COLORECTAL CANCER STRUCTURED REPORTING PROTOCOL


Incorporating the:
International Collaboration on Cancer Reporting (ICCR)
Colorectal cancer Dataset
www.ICCR-Cancer.org
Core Document versions:

- AJCC Cancer Staging Manual 8th edition, American Joint Committee on Cancer, 2016¹
- World Health Organization Classification of Tumours, Digestive System Tumours. 5th Edition, 2019²
- ICCR dataset: Colorectal cancer 1st edition v1.0
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Scope

This protocol contains standards and guidelines for the preparation of structured reports for surgical resection specimens from patients with primary carcinomas of the colon and rectum, including neuroendocrine carcinomas (NECs) and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs). It is not intended to apply to tumours of the appendix, small bowel and anus. Local excisions of colorectal carcinomas (polypectomies) are dealt with in a separate protocol. Neuroendocrine tumours are to be included in a separate protocol.

Synchronous primary tumours should have separate protocols recorded for each tumour.

Structured reporting aims to improve the completeness and usability of pathology reports for clinicians and improve decision support for cancer treatment. The protocol provides the framework for the reporting of any colorectal cancer, whether as a minimum data set or fully comprehensive report.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AGPS</td>
<td>Australasian Gastrointestinal Pathology Society</td>
</tr>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>CRC</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>CRM</td>
<td>Circumferential resection margin</td>
</tr>
<tr>
<td>HNPCC</td>
<td>Hereditary nonpolyposis colorectal cancer</td>
</tr>
<tr>
<td>ICCR</td>
<td>International Collaboration on Cancer Reporting</td>
</tr>
<tr>
<td>LIS</td>
<td>Laboratory information system</td>
</tr>
<tr>
<td>LN</td>
<td>Lymph node</td>
</tr>
<tr>
<td>MiNEN</td>
<td>Mixed neuroendocrine-non-neuroendocrine neoplasm</td>
</tr>
<tr>
<td>MMR</td>
<td>Mismatch repair</td>
</tr>
<tr>
<td>MMRD</td>
<td>Mismatch repair deficient</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MSI</td>
<td>Microsatellite instability</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>NEC</td>
<td>Neuroendocrine carcinoma</td>
</tr>
<tr>
<td>NET</td>
<td>Neuroendocrine tumour</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>PBS</td>
<td>Pharmaceutical Benefits Scheme</td>
</tr>
<tr>
<td>R</td>
<td>Residual tumour status</td>
</tr>
<tr>
<td>RCPA</td>
<td>Royal College of Pathologists of Australasia</td>
</tr>
<tr>
<td>TME</td>
<td>Total mesorectal excision</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumour-node-metastasis</td>
</tr>
<tr>
<td>UICC</td>
<td>Union for International Cancer Control</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
## Definitions

The table below provides definitions for general or technical terms used in this protocol. Readers should take particular note of the definitions for ‘standard’, ‘guideline’ and ‘commentary’, because these form the basis of the protocol.

<table>
<thead>
<tr>
<th><strong>Ancillary study</strong></th>
<th>An ancillary study is any pathology investigation that may form part of a cancer pathology report but is not part of routine histological assessment.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical information</strong></td>
<td>Patient information required to inform pathological assessment, usually provided with the specimen request form. Also referred to as ‘pretest information’.</td>
</tr>
</tbody>
</table>
| **Commentary** | Commentary is text, diagrams or photographs that clarify the standards (see below) and guidelines (see below), provide examples and help with interpretation, where necessary (not every standard or guideline has commentary). Commentary is used to:  
  - define the way an item should be reported, to foster reproducibility  
  - explain why an item is included (e.g. how does the item assist with clinical management or prognosis of the specific cancer).  
  - cite published evidence in support of the standard or guideline  
  - clearly state any exceptions to a standard or guideline.  
In this document, commentary is prefixed with ‘CS’ (for commentary on a standard) or ‘CG’ (for commentary on a guideline), numbered to be consistent with the relevant standard or guideline, and with sequential alphabetic lettering within each set of commentaries (e.g. CS1.01a, CG2.05b). |
| **General commentary** | General commentary is text that is not associated with a specific standard or guideline. It is used:  
  - to provide a brief introduction to a chapter, if necessary  
  - for items that are not standards or guidelines but are included in the protocol as items of potential importance, for which there is currently insufficient evidence to recommend their inclusion. (Note: in future reviews of protocols, such items may be reclassified as either standards or guidelines, in line with diagnostic and prognostic advances, following evidentiary review). |
Guideline

Guidelines are recommendations; they are not mandatory, as indicated by the use of the word ‘should’. Guidelines cover items that are unanimously agreed should be included in the dataset but are not supported by the National Health and Medical Research Council (NHMRC) level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Guidelines include key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g. macroscopic tumour details, block identification key, may be included as either required or recommended elements by consensus of the expert committee. Such findings are essential from a clinical governance perspective, because they provide a clear, evidentiary decision-making trail.

Guidelines are not used for research items.

In this document, guidelines are prefixed with ‘G’ and numbered consecutively within each chapter (e.g. G1.10).

Macroscopic findings

Measurements, or assessment of a biopsy specimen made by the unaided eye.

Microscopic findings

In this document, the term ‘microscopic findings’ refers to histomorphological assessment.

Predictive factor

A predictive factor is a measurement that is associated with response or lack of response to a particular therapy.

Prognostic factor

A prognostic factor is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy. It can be thought of as a measure of the natural history of the disease.

Standard

Standards are mandatory, as indicated by the use of the term ‘must’. Standards are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the NHMRC levels of evidence document). In rare circumstances, where level III-2 evidence is not available an element may be made a Standard where there is unanimous agreement in the expert committee. An appropriate staging system e.g. Pathological Tumour-node-metastasis (TNM) staging would normally be included as a required element. These elements must be recorded and at the discretion of the pathologist included in the pathology report according to the needs of the recipient of the report.

The summation of all standards represents the minimum dataset for the cancer.

In this document, standards are prefixed with ‘S’ and numbered consecutively within each chapter (e.g. S1.02).
Structured report  A report format which utilises standard headings, definitions and nomenclature with required information.

Synoptic report  A structured report in condensed form (as a synopsis or precis).

Synthesis  Synthesis is the process in which two or more preexisting elements are combined, resulting in the formation of something new.

The Oxford dictionary defines synthesis as ‘the combination of components or elements to form a connected whole’.

In the context of structured pathology reporting, synthesis represents the integration and interpretation of information from two or more modalities to derive new information.
Introduction

Colorectal cancer is currently one of the most common cancers diagnosed in Australia and has the second highest incidence of cancer-related deaths after lung cancer. Recent advances have been made in the biological understanding of this disease, which have resulted in new surgical, chemotherapeutic and radiotherapeutic strategies.

Pathological reporting

Pathological reporting of resection specimens for colorectal cancer provides important information both for the clinical management of the affected patient and for the evaluation of health care systems as a whole. For the patient, it confirms the diagnosis and describes the variables that will affect prognosis, which will inform future clinical management. For health care evaluation, pathology reports provide information for cancer registries and clinical audit, for ensuring comparability of patient groups in clinical trials, and for assessing the accuracy of new diagnostic tests and preoperative staging techniques. In order to fulfil all of these functions, the information contained within the pathology report must be accurate and complete.

Benefits of structured reporting

The pathology report lays the foundation for a patient’s cancer journey and conveys information which:

- Provides the definitive diagnosis
- Includes critical information for TNM staging
- Evaluates the adequacy of the surgical excision
- Provides morphological and biological prognostic markers which determine personalised cancer therapy

However, the rapid growth in ancillary testing such as immunohistochemistry, flow cytometry, cytogenetics, and molecular studies, have made the task of keeping abreast of advances on specific cancer investigations extremely difficult for pathologists. The use of structured reporting checklists by pathologists ensures that all key elements are included in the report specifically those which have clinical management, staging or prognostic implications. Consequently minimum or comprehensive datasets for the reporting of cancer have been developed around the world. Both the United Kingdom and United States have produced standardised cancer reporting protocols or ‘datasets’ for national use for many years.

The use of cancer reporting checklists improves completeness and quality of cancer reporting and thereby ensures an improved outcome for cancer patients. This has long term cost implications for public health by ensuring the most effective and timely treatment based on accurate and complete information.

The use of a structured reporting format also facilitates easy extraction of the necessary information by secondary users of the information i.e. cancer registries.

International Collaboration on Cancer Reporting

The International Collaboration on Cancer Reporting (ICCR), founded in 2011 by the Australasian (RCPA), United States College of American Pathologists (US CAP) and Royal College of Pathologists United Kingdom (RCPath UK) and the Canadian Association of Pathology - Association Canadienne des Pathologistes (CAP-ACP) in association with the Canadian Partnership Against Cancer (CPAC), was established to explore the possibilities of a collaborative approach to the development of common, internationally standardised and evidence-based cancer reporting protocols for surgical pathology specimens.

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The ICCR, recognising that standardised cancer datasets have been shown to provide significant benefits for patients and efficiencies for organisations through the ease and completeness of data capture\(^9\)\(^-\)\(^12\) undertook to use the best international approaches and the knowledge and experience of expert pathologists, and produce cancer datasets which would ensure that cancer reports across the world will be of the same high quality – ensuring completeness, consistency, clarity, conciseness and above all, clinical utility.

Representatives from the four countries participating in the initial collaboration undertook a pilot project in 2011 to develop four cancer datasets - Lung, Melanoma, Prostate (Radical Prostatectomy), and Endometrium. Following on from the success of this pilot project, the ICCR was joined by the European Society of Pathology (ESP) in 2013, and in 2014 incorporated a not-for-profit organisation focussed on the development of internationally agreed evidence-based datasets developed by world leading experts. The ICCR Datasets are made freely available from its website www.ICCR-Cancer.org

**Design of this protocol**

This structured reporting protocol has been developed using the ICCR dataset on Colorectal cancer as the foundation.

This protocol includes all of the ICCR cancer dataset elements as well as additional information, elements and commentary as agreed by the RCPA expert committee. It provides a comprehensive framework for the assessment and documentation of pathological features of colorectal cancers.

ICCR dataset elements for colorectal cancer are included verbatim. ICCR Required elements are mandatory and therefore represented as standards in this document. ICCR recommended elements, that is, those which are not mandatory but are recommended, may be included as guidelines or upgraded to a standard based on the consensus opinion of the local expert committee.

The ICCR elements are identified in each chapter with the ICCR logo placed before the Standard or Guideline number or bullet and the ICCR element description and commentary is boarded by a grey box as shown below:

<table>
<thead>
<tr>
<th>G3.02</th>
<th>The intraglandular extent should be recorded as a percentage.</th>
</tr>
</thead>
</table>

Additional commentary by the RCPA expert committee may be added to an ICCR element but is not included in the grey bordered area e.g.

<table>
<thead>
<tr>
<th>G2.03</th>
<th>If present, the laterality of the lymph nodes submitted may be recorded as left, right or bilateral.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS2.03a</td>
<td>If present, record site and number. All lymph node tissue should be submitted for histological examination.</td>
</tr>
</tbody>
</table>

Further information on the ICCR is available at www.iccr-cancer.org

**Checklist**

Consistency and speed of reporting is improved by the use of discrete data elements recorded from the checklist. Items suited to tick boxes are distinguished from more complex elements requiring free text or narrative. A structured or discrete approach to responses is favoured, however the pathologist is encouraged to include free text or
narrative where necessary to document any other relevant issues, to give reasons for coming to a particular opinion and to explain any points of uncertainty.

**Report format**

The structure provided by the following chapters, headings and subheadings describes the elements of information and their groupings but does not necessarily represent the format of either a pathology report (Chapter 7) or checklist (Chapter 6). These, and the structured pathology request form (Appendix 1) are templates that represent information from this protocol, organised and formatted differently to suit different purposes.

**Key documentation**

- Guidelines for Authors of Structured Cancer Pathology Reporting Protocols, Royal College of Pathologists of Australasia, 2009
- The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Provider
- World Health Organization Classification of Tumours, Digestive System Tumours. 5th Edition, 2019
- ICCR dataset: Colorectal cancer 1st edition v1.0

**Changes since last edition**

Inclusion of ICCR Core and Non-core elements.
Authority and development

This section provides information about the process undertaken to develop this protocol.

This 4th edition of the protocol is an amalgam of three separate processes:

1. This protocol is based on the ICCR dataset – Colorectal cancer 1st edition v1.0. All ICCR elements from this dataset, both core (mandatory) and non-core (optional), are included in this protocol, verbatim. (It should be noted that RCPA feedback from all Anatomical Pathology fellows and specifically the local expert committee was sought during the development process of the ICCR dataset.) Details of the ICCR development process and the international expert authoring committee responsible for the ICCR dataset are available on the ICCR website: iccr-cancer.org.

2. Additional elements, values and commentary have been included as deemed necessary by the local expert committee. In addition, the standard inclusions of RCPA protocols e.g. example reports, request information etc, have also been added.

3. This protocol was developed by an expert committee, with assistance from relevant stakeholders.


Dr Ian Brown (Lead author 2nd, 3rd and 4th editions), Pathologist
Prof Priyanthi Kumarasinghe (GI Series Chair), Pathologist
A/Prof Christophe Rosty, Pathologist
A/Prof David Ellis, Pathologist
A/Prof Andrew Ruszkiewicz, Pathologist
Dr Julie Lokan, Pathologist
Dr Duncan McLeod, Pathologist
Dr Nicole Kramer, Pathologist
Conjoint Prof Stephen Ackland, Medical Oncologist
Dr Spiro Raftopoulos, Gastroenterologist

Authorship – 1st-3rd editions

Dr Ian Brown (Chair and lead author 2nd, 3rd and 4th editions), Pathologist
A/Prof Robert Eckstein (Chair and lead author 1st edition), Pathologist
Conjoint Prof Stephen Ackland, Medical Oncologist
A/Prof David Ellis, Pathologist
Prof Nicholas Hawkins, Pathologist
Dr Sian Hicks, Medical Scientist
Dr Andrew Hunter, Colorectal Surgeon
Dr Andrew Kneebone, Radiation Oncologist
Dr Andrew Ruszkiewicz, Pathologist
Dr Mee Ling Yeong, Pathologist

Editorial manager
Christina Selinger, PhD, Royal College of Pathologists of Australasia

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Stakeholders

ACT Cancer Registry
ACT Health
Anatomical Pathology Advisory Committee (APAC)
Australasian Gastro-Intestinal Trials Group (AGITG)
Australian Commission on Safety and Quality in Health Care
Australian Digital Health Agency (ADHA)
Australian Gastrointestinal Pathology Society (AGPS)
Australian Institute of Health and Welfare (AIHW)
Australian Pathology
Cancer Australia
Cancer Council ACT
Cancer Council Australia and Australian Cancer Network (ACN)
Cancer Council NSW
Cancer Council Queensland
Cancer Council SA
Cancer Council Tasmania
Cancer Council Victoria
Cancer Council Western Australia
Cancer Institute NSW
Cancer Services Advisory Committee (CanSAC)
Cancer specific expert groups – engaged in the development of the protocols
Cancer Voices Australia
Cancer Voices NSW
Clinical Oncology Society of Australia (COSA)
Colorectal Surgical Society of Australia and New Zealand (CSSANZ)
Department of Health, Australian Government
Gastroenterological Society of Australia (GESA)
Health Informatics Society of Australia (HISA)
Independent Review Group of Pathologists
Medical Oncology Group of Australia (MOGA)
Medical Software Industry Association (MSIA)
National Pathology Accreditation Advisory Council (NPAAC)
New Zealand Cancer Control Agency
New Zealand Cancer Registry
New Zealand Committee of Pathologists
New Zealand Society of Gastroenterology (NZSG)
Northern Territory Cancer Registry
Public Pathology Australia
Queensland Cooperative Oncology Group (QCOG)
Representatives from laboratories specialising in anatomical pathology across Australia
Royal Australasian College of Physicians (RACP)
Royal Australasian College of Surgeons (RACS)
Royal Australian and New Zealand College of Radiologists (RANZCR)
Royal Australian College of General Practitioners (RACGP)
Royal College of Pathologists of Australasia (RCPA)
South Australia Cancer Registry
Southern Cancer Network, Christchurch, New Zealand
Standards Australia
Tasmanian Cancer Registry
Victorian Cancer Registry
Western Australia Clinical Oncology Group (WACOG)
Western Australian Cancer Registry

**Development process**

This protocol has been developed following the process set out in *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols*.\(^\text{13}\)

Where no reference is provided, the authority is the consensus of the local expert group for local inclusions, and the ICCR Dataset Authoring Committee for ICCR components denoted with the ICCR logo.
1 Pre-analytical

This chapter relates to information that should be recorded on receipt of the specimen in the laboratory.

The pathologist is reliant on the quality of information received from the clinicians or requestor. Some of this information may be received in generic pathology request forms, however, the additional information required by the pathologist specifically for the reporting of colorectal cancer is outlined in Appendix 1. Appendix 1 also includes a standardised request information sheet that may be useful in obtaining all relevant information from the requestor.

Surgical handling procedures affect the quality of the specimen and recommendations for appropriate surgical handling are included in Appendix 1.

S1.01 All demographic information provided on the request form and with the specimen must be recorded.

CS1.01a The Royal College of Pathologists of Australasia (RCPA) The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers must be adhered to. This document specifies the minimum information to be provided by the requesting clinician for any pathology test.

CS1.01b Ideally the laboratory information system (LIS) should include documentation as to whether or not the patient identifies as Aboriginal and/or Torres Strait Islander in Australia, or Māori in New Zealand. This is in support of government initiatives to monitor the health of those who identify as indigenous, particularly in relation to cancer.

CS1.01c The patient’s health identifiers may include the patient’s Medical Record Number as well as a national health number such as a patient’s Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Index (New Zealand).

S1.02 All clinical information as documented on the request form must be recorded verbatim.

CS1.02a The request information may be recorded as a single text (narrative) field or it may be recorded in a structured format.

CS1.02b In most cases all clinical information should be transcribed: however, in a small number of cases the pathologist may exercise discretion regarding the inclusion of provided clinical information, for instance, possibly erroneous information or information that may impact on patient privacy. In such case reference should be made as to the location of the complete clinical information e.g. ‘Further clinical information is available from the scanned request form.’

G1.01 The copy doctors requested on the request form should be recorded.

S1.03 The pathology accession number of the specimen must be recorded.
**S1.04** The principal clinician involved in the patient's care and responsible for investigating the patient must be recorded.

**CS1.04a** The principal clinician should provide key information regarding the clinical presentation of the patient. Follow up may be required with the principal clinician for a number of reasons:

- The clinical assessment and staging may be incomplete at the time of biopsy.
- The pathology request is often authored by the clinician performing the surgical excision/biopsy rather than the clinician who is investigating and managing the patient.
- The identity of this clinician is often not indicated on the pathology request form.

In practice therefore, it is important in such cases that the reporting pathologist should be able to communicate with the managing clinician for clarification.

**CS1.04b** The Australian Healthcare identifiers i.e. Healthcare Provider Identifier - Individual (HPI-I) and Healthcare Provider Identifier - Organisation (HPI-O) should be included, where possible, to identify the principal clinician involved in the patient's care.

**G1.02** Any clinical information received in other communications from the requestor or other clinician should be recorded together with the source of that information.

**CG1.02a** There should be a free text field so that the referring doctor can add anything that is not addressed by the above points, such as previous cancers, risk factors, investigations, treatments and family history.
2 Specimen handling and macroscopic findings

This chapter relates to the procedures required after the information has been handed over from the requesting clinician and the specimen has been received in the laboratory.

Tissue banking

➢ Pathologists may be asked to provide tissue samples from fresh specimens for tissue banking or research purposes. The decision to provide tissue should only be made if the pathologist is sure that the diagnostic process will not be compromised. As a safeguard, research use of the tissue samples may be put on hold until the diagnostic process is complete.

➢ If tissue is sampled for banking or research then this should be done in consultation with a pathologist and recorded in the report. It is good practice to specify a paraffin block that is ideal for future ancillary testing or research purposes, if possible.

Specimen imaging

➢ Detailed fixation and specimen handling instructions are available from the RCPA online Cut-up Manual:


➢ Images of the gross specimen showing the overall conformation of the tumour and, especially in the case of rectal resections, images showing the relation of the tumour to the resection margins, are desirable, and useful for multidisciplinary meetings.

Specimen handling

➢ The specimen must be handled in a systematic and thorough fashion to ensure completeness and accuracy of pathological data.

• Specimen reception: Specimen fixation, macroscopic assessment and sampling for histology are crucial. The aim is to make a diagnosis, assess resection status and glean all other prognostic information.

  The opened, cleaned specimen should be fixed, at least overnight, in an adequate volume of formalin.

  Despite the pressure by clinicians on the pathologist for rapid turnaround, adequate fixation and processing of colorectal specimens is highly important. Full fixation facilitates obtaining thin transverse slices through the tumour and it has also been shown to increase lymph node yield. Slices can be made into mesocolic adipose tissue to aid fixation.

  In addition, the experience of the person cutting up and reporting the specimen, is probably an important determinant of quality pathology, however further studies in this area are warranted.
- **Specimen inspection:** The specimen needs to be thoroughly examined before opening. Areas of possible serosal involvement - often located at the junction of the mesenteric reflection on the antimesenteric portion of the bowel - possible distant tumour and lymph node deposits should be identified. Serosal nodules away from the primary tumour are regarded as distant metastases in the TNM classification. Assessment of tumour perforation is best made in the freshly received and unopened specimen.

- **Tumour inspection:** There are two recommended methods of opening a colon resection specimen.

  The first method involves opening the specimen with scissors anteriorly up and down to the level of the tumour, which is left unopened. A wick of formalin soaked paper or gauze is then inserted into the unopened lumen to aid exposure of the tumour to the fixative. The entire specimen is then placed in formalin for complete fixation.

  The second method involves opening the specimen along its length. If the tumour is not circumferential, then the specimen should be opened through an area not involved by tumour. If the tumour is circumferential then it will have to be cut through at some point, but this should avoid areas of possible serosal or nonperitonealised resection margin involvement. Again, the entire specimen should then be placed in an adequate amount of formalin for complete fixation.

  For rectal tumours, leaving the tumour intact and bread-slicing it when fixed is recommended. This method facilitates assessment of the very important nonperitonealised resection margin. The relationship of the tumour, nodes, or extramural tumour deposits to the nonperitonealised resection margin must be assessed and measured (see S2.04 below). This facilitates correlation with preoperative imaging and subsequent microscopic examination.

- **Marking of resection margins:** The nonperitonealised resection margin of the rectum or colon needs to be inked. Other cut surgical resection margins can be inked if the tumour is nearby.

  The serosal surface is not a resection margin and is therefore not inked. Inking of the serosa may result in misinterpretation of serosal surface involvement as representing margin involvement. It can also mask the presence of tumour cells on the serosal surface.

- **Block selection:** The tumour needs to be sliced transversely at 3–4 mm intervals and the tumour slices laid out sequentially. Block selection must target the prognostic questions that need to be answered. It is not possible to give an absolute number. Sufficient blocks (generally at least 4) should be taken to enable the pathologist to fully assess all the necessary parameters for staging and prognosis. The likelihood of identifying prognostically useful features, such as extramural venous invasion and serosal penetration, increases with the number of blocks taken.

  Select blocks that show the greatest depth of tumour invasion. Select blocks that show tumour close to or at a serosal surface. Serosal involvement is especially prone to occur at or adjacent to peritoneal reflections, especially in the clefts adjacent to the bowel wall, and should be suspected in any areas of serosa that appear granular, dull or haemorrhagic.
Rectal tumours previously treated with neoadjuvant therapy show varying degrees of regression, altering their appearance, and tumour may be difficult to recognise grossly. Blocking of the whole area of abnormality may be required to confirm the presence of tumour, and to evaluate tumour regression grade.

Tumour at a longitudinal margin occurs only very rarely and several studies have questioned the necessity of sampling the cut end margins. If the tumour is >30 mm from the cut end it is not always necessary to examine the margin microscopically (see below S2.07). However, it is often useful to have normal tissue for control purposes and uninvolved margins can provide this. It is also useful to examine for potential background disease, such as inflammatory bowel disease, or unrelated disease processes, such as lymphocytic or collagenous colitis.

The relationship of rectal tumours to the circumferential margin must be assessed with appropriate blocks (see S2.05). Most of the colon has a long mesentery, so the assessment of this resection margin is rarely an issue. However, the cut margin of the mesentery is a surgical margin and if the tumour is advanced, it may potentially be involved, either by direct spread, or by involved nodes, at its apex. The caecum and the proximal ascending colon do not have a mesentery and posteriorly have a nonperitonealised bare area of variable size which is potentially an area of surgical margin involvement, especially in tumours arising from the posterior wall or in circumferential tumours. Involvement of the nonperitonealised resection margin in tumours at these sites should be sought and recorded when present.

Lymph node sampling is described below (see below).

Sampling should be performed on any background abnormalities, and in particular polyps or inflammatory bowel disease.

If there is tumour perforation, then a block should be taken for histological record.

➢ All regional lymph nodes must be harvested from the specimen and examined histologically.

The finding of positive lymph nodes is a major determinant of whether a patient receives adjuvant therapy. The probability of finding a positive lymph node increases with the number of nodes found, although this probability curve flattens out after finding 12–15 nodes. The number of nodes present depends on a number of factors, including the size of the specimen, the amount of mesenteric tissue present and whether the patient has received neo-adjuvant therapy. Whilst for purposes of audit an average of 12 lymph nodes should be found, lesser numbers of nodes are present in individual cases.

Pending further evidence, it is prudent to approach lymph node retrieval as follows

- all identifiable lymph nodes should be retrieved and examined
- if twelve or fewer lymph nodes are found then the specimen should be re-examined for lymph nodes as a longer period of fixation in formalin can improve lymph node detection; this is particularly important in stage II (pN0) tumours
- alternative fixatives and fat clearance methods can be used to increase lymph node yield but the evidence is most robust in
studies where the yield was low to begin with\textsuperscript{15}

- the greatest yield for positive lymph nodes in a second search is the region of the tumour bed\textsuperscript{16}

- if 12 or fewer lymph nodes are retrieved a note should be made in the pathology report, describing how this has been addressed

- assessment of a laboratories average lymph node yield can be used as a quality indicator but may reflect a particular surgical or patient cohort, rather than a particular laboratories practice

- Lymph nodes are difficult to find in a poorly fixed specimen. The lymph node bearing tissue needs to be methodically palpated and sliced at small intervals. All macroscopically uninvolved nodes need to be embedded completely. Macroscopically involved nodes require only 1 block for confirmation. To aid in accurate microscopic examination, strip the lymph nodes of fat; nodes of dissimilar size should not be embedded in the same block.

In the case of extended or total colectomy specimens, it may not be necessary to examine all non regional lymph nodes. All lymph nodes received in the form of separately identified specimens must be examined microscopically.

- Any lymph nodes lying close to the nonperitonealised resection margin need to be sampled in continuity with that margin. If there is tumour in any of the lymph nodes then it is the measurement from the involved lymph node to the nonperitonealised resection margin, if it is closer, rather than from the primary tumour, that is important. This is also true for any isolated tumour deposit in the perirectal or pericolic fat.

- It is good practice that the apical lymph node should be identified as it is commonly used in clinical staging.

- In the case of two synchronous primary carcinomas, where appropriate, lymph nodes need to be assigned and assessed for each cancer separately.

➢ A block containing tumour should be nominated for further ancillary studies.

### Macroscopic findings

#### S2.01 The labelling of the specimen(s) must be clearly recorded.

<table>
<thead>
<tr>
<th>EC</th>
<th>CR</th>
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<tbody>
<tr>
<td><strong>S2.02</strong></td>
<td><strong>Clinical information must be recorded.</strong></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>EC</th>
<th>CR</th>
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<tbody>
<tr>
<td><strong>CS2.02a</strong></td>
<td>Clinical information can be provided by the clinician on the endoscopy report or the pathology request form. Pathologists could search for additional information from possible previous pathology reports. The presence of a known polyposis syndrome, Lynch syndrome, chronic inflammatory bowel disease or any other relevant gastrointestinal disorder should be recorded and provided to the pathologist, as awareness of such underlying conditions may influence both specimen sampling and</td>
</tr>
</tbody>
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The operative procedure must be recorded.

Information regarding the nature of the operative procedure should be provided, with any refinements as necessary, for example the attempted dissection plane in an abdominoperineal resection. Should the operative specimen include any tissue or organ not typically submitted within that specimen type, for example en bloc resection of a segment of intestine or abdominal wall connective tissue, this should be clearly indicated. Inclusion of the peritoneal reflection within an anterior resection specimen distinguishes a low anterior resection from a high anterior resection.

The specimen length must be recorded.

This and all other measurements in this protocol should be made in millimetres unless otherwise stated.

The site of the tumour must be recorded.

If multiple primary tumours are present, separate protocols should be used to record tumour site and all following elements for each primary tumour. Determination of tumour site is based on clinical information provided on the pathology request form combined with specimen assessment by the pathologist. Any significant discrepancy should be discussed with the clinical team and the tumour site clearly documented by specimen photography. Recording the anatomical site of tumour allows correlation with prior endoscopic and radiological investigations, indicates whether or not a nonperitonealised margin is likely to be present and defines the presence of regional versus non-regional lymph nodes. In particular, distinction of colonic from rectal origin is of importance, given different biologies, clinical features and management. Every effort should be made, therefore, to accurately classify a tumour as colonic or rectal in origin.

If a tumour straddles two sites, the site with the greatest tumour bulk should be recorded. The three taeniae coli of the sigmoid colon fuse to form the circumferential longitudinal muscle of the rectal wall, marking the rectosigmoid boundary. If distinction between the sigmoid colon and rectum is not possible by pathological assessment, for example owing to advanced tumour stage obliterating anatomical landmarks, the tumour site can be recorded based on clinical information available.

Classification as rectosigmoid should be reserved for cases in which an accurate determination between rectum and sigmoid cannot be made by pathological assessment and clinical information regarding site is not available.

The determination of the site is based on the assessment by the pathologist and the information provided by the surgeon on the request form. The anatomical site of the tumour is
relevant for the following reasons:

- It provides correlation with previous investigations.
- It indicates whether a nonperitonealised (circumferential) margin is likely to be present.
- The natural history and treatment of rectal cancer differs significantly from colonic cancer.
- It defines the presence of regional lymph nodes versus non-regional lymph nodes.

CS2.05c  Strictly the rectum is that part of the large bowel distal to the sigmoid colon and its upper limit is indicated by the end of the sigmoid mesocolon. Standard anatomical texts put this at the level of the 3rd sacral vertebra but it is generally agreed by surgeons that the rectum starts at the sacral promontory. It was agreed by an international expert advisory committee that any tumour whose distal margin is seen at 15 cm or less from the anal verge using a rigid sigmoidoscope should be classified as rectal. The pathologist can identify the upper end of the rectum as the point where the colonic taeniae coli merge to form a single external muscle layer.

**S2.06** The maximum tumour diameter must be recorded.

CS2.06a  No prognostic significance has been attached to tumour size for colorectal cancer and size does not directly influence tumour staging. Recording of size, based on a combination of macroscopic and microscopic assessment, allows correlation with preoperative imaging, endoscopic and surgical assessments. Assessment of tumour dimensions should, if possible, exclude any inflammatory component or preinvasive lesion, a separate measurement of which may be provided.

**S2.07** The distance of the tumour to the nearer proximal or distal ‘cut end’ margin must be recorded.

CS2.07a  This is the measurement from the nearer cut end of the specimen and not the nonperitonealised (circumferential, radial) margin.

CS2.07b  Tumour at a longitudinal margin has always been considered a poor prognostic feature but it occurs very rarely. The necessity of sampling this margin has therefore been questioned. It is essential to sample this margin and examine it histologically if the tumour is close to the margin (within 30 mm), or if the tumour is found by histology to have an exceptionally infiltrative growth pattern, to show extensive blood vascular or lymphatic permeation, or to be a signet-ring, small cell or undifferentiated carcinoma.

CS2.07c  If included, doughnuts must be embedded for histological examination.
The difficulty presented by staples is recognised. In this situation, it is important for blocks taken immediately adjacent to the line of staples along the plane of the staple line to be examined.

### S2.08 The distance of the tumour to the circumferential margin must be recorded.

**CS2.08a** This is the measurement to the nonperitonealised (i.e. the circumferential or radial) margin.

**CS2.08b** This measurement is useful for comparison with and validation of the microscopic measurement.

**CS2.08c** It is not only the continuous spread of the primary tumour that is important for this measurement, but also discontinuous spread in the form of lymph node metastases, extramural deposits, and tumour in vessels and lymphatics. Even if the main tumour appears ‘well clear’ of this margin, it is important to block the tissue between the nearest tumour edge and the nonperitonealised resection margin to ensure picking up any discontinuous areas of spread. It may be that the tissue has to be embedded in two or more sequential blocks but this margin must be well sampled.

**CS2.08d** This combined with the clinical and microscopic findings is used to define the R code status (see Chapter 5).

### S2.09 The presence or absence of tumour perforation must be recorded.

**CS2.09a** Perforation through the tumour into the peritoneal cavity is a well-established adverse prognostic factor in colonic and rectal cancer and should be recorded. Tumour perforation is defined as a macroscopically visible full thickness defect through the tumour, such that the bowel lumen within the segment involved by tumour is in communication with the external surface of the resection specimen or with the lumen of another organ. Such cases are regarded as pT4a in the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) 8th edition Staging Systems. The term perforation should be reserved for the biological setting and, for clarity, different descriptive terminology applied should a full thickness defect in the specimen arise intra-operatively. Such clinical information should be conveyed to the reporting pathologist to assist pathological interpretation. If an iatrogenic full thickness defect in the tumour occurs whilst the specimen is in situ within the abdominal cavity, this is best regarded as pT4a disease, given the risk of tumour seeding the peritoneal cavity. This interpretation is however offered without good evidence. If such an iatrogenic defect occurs once the specimen is outside the abdominal cavity, the defect should not influence pT classification. An explanatory note regarding interpretation should be provided in the pathology report. Peritumoural abscess cavity, for example within the
mesentery, that is contained and does not demonstrate breach of the serosal surface, should not be considered perforation and is considered pT3 rather than pT4a. Perforation of the colon as a result of a more distal obstructing tumour is distinct from tumour perforation and does not indicate pT4 disease, but nevertheless should be recorded as it is associated with high mortality risk.

**CS2.09b** Perforation of the proximal bowel as a result of a distal obstructing tumour must not be recorded as tumour perforation, but should be noted (see below).

**CS2.09c** It is important to distinguish, where possible, between perforation occurring at the time of surgery and perforation before surgery.

**S2.10** For rectal tumours, the relationship of the tumour to the anterior peritoneal reflection must be recorded (refer to Figure 1).

**CS2.10a** For rectal tumours only, the relationship of the tumour to the anterior peritoneal reflection must be recorded, as this predicts the risk of local recurrence in addition to peritoneal recurrence (Figure 1).27 The anterior aspect of the rectum is covered by peritoneum down to level of the peritoneal reflection. Posteriorly, the nonperitonealised margin extends upwards as a triangular shaped bare area containing the rectal arteries. Superiorly this area is continuous with the sigmoid mesocolon.

**CS2.10b** 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.
Figure 1. Site of tumour in relation to the anterior level of the peritoneal reflection

CS2.10c The anterior aspect of the rectum is covered by peritoneum down to the peritoneal reflection. On the posterior aspect the nonperitonealised margin extends upwards as a triangular shaped bare area containing the rectal arteries, which then continues up to the start of the sigmoid mesocolon (see Figure 2).

CS2.10d The nonperitonealised margin is also known as the radial or circumferential resection margin. It consists of a ‘bare’ area of connective tissue at the surgical plane of excision that is not covered by serosa (see Figure 5). Low rectal tumours will be completely surrounded by a nonperitonealised margin (the circumferential margin), while upper rectal tumours have a nonperitonealised margin posterolaterally and a peritonealised (serosal) surface anteriorly. Tumours below the peritoneal reflection have the highest rates of local recurrence.28-31
Figure 2. Site of nonperitonealised margin (bare area of mesorectum) in relation to the peritoneal reflection

S2.11 For rectal cancer, the plane of mesorectal excision must be recorded.

CS2.11a The quality of surgical technique has been shown by prospective randomised controlled trials to predict outcome following surgical treatment for rectal cancer. Total mesorectal excision (TME) surgery improves local recurrence rates and the corresponding survival by up to 20%.\textsuperscript{32,33} Macroscopic evaluation of the completeness of the mesorectum, by objective assessment of the surgical plane of excision, predicts margin involvement, local recurrence and survival.\textsuperscript{27,34,35} Excision in the mesorectal plane (complete TME) has the best outcome while excision extending onto the muscularis propria (incomplete TME) has the worst.

Assessment requires examination of the intact specimen and overall assessment is based on the worst area, as described below:

Mesorectal fascia (complete)
- Intact bulky mesorectum with a smooth surface
- Only minor irregularities of the mesorectal surface
- No surface defects greater than 5 mm in depth
- No coning towards the distal margin of the specimen

Intramesorectal (near complete)
- Moderate bulk to the mesorectum
- Irregularity of the mesorectal surface with defects greater
than 5 mm, but none extending to the muscularis propria

- Moderate coning may be evident distally
- No areas of visibility of the muscularis propria except at the insertion site of the levator ani muscles

Muscularis propria (incomplete)

- Little bulk to the mesorectum
- Defects in the mesorectum down to the muscularis propria
- After transverse sectioning, the circumferential margin appears very irregular and is formed by muscularis propria in areas.

CS2.11b The intactness of the specimen may be graded as follows:
- Incomplete (grade 1)
- Nearly complete (grade 2)
- Complete (grade 3)

For abdominoperineal excision specimens, the plane of sphincter excision should be recorded.

Abdominoperineal excision for low rectal cancer has been associated with poorer outcomes compared to anterior resection for higher tumours due to increased rates of circumferential resection margin (CRM) involvement and intraoperative full thickness defects (“perforations”). Extralevator abdominoperineal excision has been shown in meta-analyses to reduce CRM involvement and intraoperative full thickness defects leading to better long term outcomes. This is due to the removal of more tissue around the tumour. Radiologists are able to predict the optimal dissection plane in abdominoperineal excision from the staging magnetic resonance imaging (MRI). This should be correlated with the plane of dissection achieved on the resection specimen around the sphincters (below the mesorectum). The plane of surgery in the mesorectum should be assessed separately.

Assessment requires examination of the intact specimen and overall assessment is based on the worst area, as described below:

Extralevator plane
- Dissection plane lies external to the external sphincter and levator ani muscles, which are removed en bloc with the mesorectum and anal canal
- Cylindrical-shaped specimen with the levators forming an extra protective layer above the sphincters
- No significant defects into the sphincter muscles or levators

Sphincteric plane
- Dissection plane lies on the surface of the sphincter muscles
- No levator ani muscle attached or only a very small cuff
leading to coning or surgical waisting at the level of puborectalis
- No significant defects into the sphincter muscles

Intrasphincteric plane
- Dissection plane lies within the sphincter muscles or even deeper into the submucosa
- Full thickness iatrogenic defect of the specimen at any point below the peritoneal reflection

<table>
<thead>
<tr>
<th>G2.02</th>
<th>For colon cancer specimens, the plane of mesocolic excision should be recorded.</th>
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</table>
| G2.02a| The quality of surgical technique in the mesocolon has been shown, in retrospective observational studies and one randomised clinical trial, to predict outcome following surgical treatment for colon cancer in a similar way to that seen in rectal cancer.\(^{41-43}\) Surgery in the mesocolic plane is associated with a lower rate of local recurrence and better survival when compared to surgery in the muscularis propria plane. Complete mesocolic excision, where surgery occurs in the mesocolic plane with a high vascular ligation, is associated with better plane of surgery and more lymph nodes, although the effect of the high ligation on long term outcomes remains debated.\(^{44}\) The height of the vascular ligation is not taken into consideration during the plane of mesocolic excision assessment.

Assessment requires examination of the intact specimen and overall assessment is based on the worst area, as described below:

Mesocolic plane
- Smooth surface to the mesocolon (mesocolic fascia and peritoneum)
- Only minor irregularities
- No surface defects greater than 5 mm in depth

Intramesocolic plane
- Irregularity of the mesocolic surface with defects greater than 5 mm, but none extending to the muscularis propria

Muscularis propria plane
- Defects in the mesocolon down to the muscularis propria
- After transverse sectioning, the mesocolic margin is irregular and formed by muscularis propria in areas

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<thead>
<tr>
<th>G2.03</th>
<th>Any involvement of the peritoneum should be recorded.</th>
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| CG2.03a| This should be recorded as one of the following:
- Tumour invades to the peritoneal surface
- Tumour has formed nodule(s) discrete from the tumour mass along the serosal surface

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CG2.03b Tumour involvement of the serosa discontinuous from the site of the main tumour is to be recorded as a metastasis.

G2.04 A descriptive or narrative field should be provided to record any macroscopic information that is not recorded in the above standards and guidelines, and that would normally form part of the macroscopic description.

CG2.04a Examples include the presence of tissues and organs adherent to the colon, the presence of tumours other than primary adenocarcinoma, and coexistent chronic inflammatory bowel disease.

CG2.04b Other information related to the primary tumour may also be recorded here such as gross configuration of the tumour and lymph nodes, appearance of the serosa over the tumour, etc.

CG2.04c The traditional macroscopic narrative recorded at the time of specimen dissection is often reported separately from the cancer protocol. Although this remains an option, it is recommended that macroscopic information be recorded within the overall structure of this protocol.

CG2.04d Some of these elements are formally recorded in the 'Microscopic findings' (see Chapter 3).

CG2.04e Much of the information recorded in a traditional macroscopic narrative is covered in the standards and guidelines above and in many cases, no further description is required.
3 Microscopic findings

Microscopic findings relate to purely histological or morphological assessment. Information derived from more than one type of investigation (e.g. clinical, macroscopic and microscopic findings), are described in Chapter 5.

<table>
<thead>
<tr>
<th>EC3.01</th>
<th>The histological tumour type must be recorded.</th>
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<tbody>
<tr>
<td>CS3.01a</td>
<td>Colorectal cancers should be typed according to the World Health Organization (WHO) Classification of Tumours of the Digestive System, 5th edition, 2019. Almost all are adenocarcinomas. Most colorectal adenocarcinomas are of no specific type (not otherwise specified (NOS)) but some subtypes of adenocarcinoma are defined as follows:</td>
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</table>

- **Mucinous adenocarcinoma** classification requires greater than 50% of the tumour to comprise pools of extracellular mucin containing malignant glands or individual tumour cells. Microsatellite instability is present in a higher proportion compared to adenocarcinoma, NOS. Tumours with less than 50% mucinous content are described as having a mucinous component.

- **Signet-ring cell adenocarcinoma** classification requires greater than 50% of the tumour to demonstrate single malignant cells with intracytoplasmic mucin, displacing and typically indenting the nuclei, imparting signet-ring cell morphology. Signet-ring cell carcinoma has stage-independent adverse prognostic significance relative to conventional adenocarcinoma. There is a strong association with microsatellite instability and with Lynch syndrome. Tumours with less than 50% signet-ring cell content are described as having a signet-ring cell component.

- **Medullary carcinoma** is characterised by sheets of malignant cells with indistinct cell boundaries, vesicular nuclei, prominent nucleoli, abundant eosinophilic cytoplasm and prominent intratumoural lymphocytes and neutrophils. These tumours almost invariably demonstrate microsatellite instability and are associated with a good prognosis.

- **Serrated adenocarcinoma** shares morphological similarities with precursor serrated polyps, demonstrating glandular serrations, which are often slit-like, abundant eosinophilic or clear cytoplasm, minimal necrosis and sometimes areas of mucinous differentiation.

- **Micropapillary adenocarcinoma** is characterised by small, rounded clusters of tumour cells lying within stromal spaces mimicking vascular channels. At least 5% of the tumour should demonstrate this feature to classify as micropapillary adenocarcinoma. This pattern is most frequently encountered alongside adenocarcinoma, NOS. There is a strong association with adverse pathological features including a high risk of lymph node metastatic disease.

- **Adenoma-like adenocarcinoma** is defined as an invasive adenocarcinoma in which at least 50% of the invasive tumour...
has an adenoma-like appearance with villous architecture, low grade cytology, a pushing growth pattern and minimal desmoplastic stromal reaction. Diagnosis of adenocarcinoma on endoscopic biopsy is exceedingly difficult. This variant is associated with a good prognosis.

Neuroendocrine neoplasms are classified into NETs, NECs and MiNENs. NETs are graded 1-3 using the mitotic count and Ki-67 proliferation index. Pure NETs are not considered within the scope of this protocol. NECs show marked cytological atypia, brisk mitotic activity, and are subclassified into small cell and large cell subtypes. NECs are considered high-grade by definition. A Ki-67 proliferation index <55% is associated with better overall survival. MiNENs are usually composed of a poorly differentiated NEC component and an adenocarcinoma component.

While it is convention to only include those tumours with at least 30% or more of each component in the MiNEN group, any component of small cell neuroendocrine carcinoma, even if <30% of the tumour, should be reported in the diagnosis because of the significant clinical implication, even if the tumour is not designated to be a MiNEN.

Other epithelial tumours rarely encountered include adenosquamous carcinoma, carcinoma with sarcomatoid components, undifferentiated carcinoma, squamous cell carcinoma, and non-signet-ring cell poorly cohesive adenocarcinoma,. Many of these are extremely rare. Refer to ICCR dataset for full commentary.

| CS3.01b | It is important to note, that a small component of neuroendocrine cells interspersed within a glandular tumour does not fall into the category of MiNEN. This category should be reserved for tumours displaying two distinct morphologic and immunohistochemically identifiable areas. Because the category of ‘MiNEN’ reflects a range of combinations of tumours, ideally the specific category for the site should be used e.g. mixed adenocarcinoma-NEC or mixed adenocarcinoma-NET. |
| CS3.01c | Serrated adenocarcinoma typically arises from a precursor serrated polyp (sessile serrated lesion or traditional serrated adenoma), which may be evident at the edge of the invasive carcinoma in some cases. They are characterised by mutations in the MAPK signalling pathway (i.e. BRAF or KRAS).

Micropapillary adenocarcinoma represents an evolving subtype. In these lesions, epithelial membrane antigen EMA (MUC1) immunohistochemistry demonstrates an ‘inside-out’ pattern of staining with expression on the external aspect of the epithelial nests rather than the luminal aspect.

While the WHO states that rounded clusters of tumour cells lying within stromal spaces mimicking vascular channels should represent at least 5% of the tumour to classify as a micropapillary lesion, it more likely represents a component of conventional adenocarcinoma. Nonetheless, these features
should be reported.

It is the opinion of the RCPA colorectal cancer (CRC) expert panel that serrated and micropapillary adenocarcinomas are relatively uncommon, and current guidelines are not yet sufficient to adequately describe these lesions.

See Appendix 5 for example representative images of histological tumour types.

CS3.01d Additional histological tumour types not included in the WHO *Histological Classification of Tumours of the Colon and Rectum* (refer to Appendix 4) include choriocarcinoma, clear cell carcinoma, microglandular goblet cell carcinoma, carcinomas with melanin production.

CS3.01e The description should be based on the WHO *Histological Classification of Tumours of the Colon and Rectum* (refer to Appendix 4). This publication, as well as a current version of the *AJCC Cancer Staging Manual* should be readily accessible to the reporting pathologist.

CS3.01f For most tumours, histological type is not prognostically significant. Exceptions include tumour types that are, by definition, high grade (i.e. signet-ring cell carcinoma); and the medullary subtype, which is invariably associated with mismatch repair gene deficiency and has a favourable prognosis when compared to other poorly differentiated and undifferentiated colorectal carcinomas. Note that well differentiated neuroendocrine (carcinoid) tumours are listed separately to carcinoma in the WHO histological classification and are staged and graded differently.

**S3.02** The histological grading of the tumour must be recorded.

CS3.02a Despite low level of interobserver agreement, histological grade is an independent prognostic factor used in risk assessment models for colorectal carcinoma. Various grading systems have been used over the years. A two-tiered grading system is more reproducible and more prognostically relevant than a four-tiered grading system. For consistency with the latest WHO Classification, grading should be based on the least differentiated component of the tumour, although there is no good evidence to support this stance and a minimum area of high grade tumour required for this classification has not been defined. Tumour buds or poorly differentiated clusters, most commonly seen at the invasive tumour front, should not be considered in the evaluation of grade. However, emerging data suggests that grading based on poorly differentiated clusters is superior to conventional grading with respect to both prognostic value and reproducibility.

Only adenocarcinoma, NOS, and mucinous adenocarcinoma should be graded. Grading is not applicable to other subtypes of adenocarcinoma, as grading by gland formation is difficult to apply to subtypes and most of these are associated with their own clinical prognosis e.g. bad for signet-ring cell
adenocarcinoma and good for adenoma-like adenocarcinoma. Mucinous adenocarcinoma should be graded on glandular formation and epithelial maturation. \(^45\) Tumour mismatch repair status is likely to influence clinical behaviour of some histological tumour types, including mucinous adenocarcinoma, but some studies have found morphological grading superior to mismatch repair status for prognostication of mucinous adenocarcinomas. \(^53,64\)

**CS3.02b** Whether grading should be based on the predominant pattern of differentiation or the area of worst differentiation is controversial. \(^65,66\) In this protocol, it is recommended that, ‘when a carcinoma has heterogeneity in differentiation, grading should be based on the least differentiated component, not including the leading front of invasion’, as stated in the WHO classification. \(^67\)

Small foci of apparent poor differentiation may be seen at the advancing edge of tumours but these should not be used to classify the tumour as poorly differentiated (see also ‘tumour budding’ below).

**CS3.02c** A two tiered grading system is recommended, based on the WHO classification:

- **Low grade** — well differentiated and moderately differentiated
- **High grade** — poorly differentiated and undifferentiated

The two tiered grading system is much more reproducible and more prognostically representative.

**S3.03** The maximum degree of local invasion must be recorded.

**CS3.03a** The anatomic extent of tumour invasion, based on a combination of macroscopic and microscopic assessment of an excision specimen, is the most important prognostic factor in colorectal cancer. pT classification indicates the extent of invasion of the primary tumour in the absence of application of neoadjuvant therapy. Criteria of the UICC and AJCC \(^8\)th editions\(^1,26\) are applied, with the exception that pT in situ is not recognised. Rare cases of colorectal neoplasia confined to invasion of the lamina propria (intramucosal invasive neoplasia or intramucosal carcinoma) are acknowledged but, given the negligible metastatic potential of such neoplasms, \(^68\) these should be classified under the same category with high grade dysplasia/high grade non-invasive neoplasia.

pT1 indicates tumour extension beyond muscularis mucosae into submucosa, but without involvement of muscularis propria. Further consideration of pT1 colorectal carcinoma is provided in a separate local excision protocol.

pT2 indicates extension into muscularis propria but not beyond. In the low rectum, the internal sphincter represents a continuation of the muscularis propria and invasion of this also constitutes pT2. Note that skeletal muscle fibres can cross over from external to internal sphincter and invasion of skeletal muscle fibres of the internal sphincter is also classified as pT2.
Such complexities of sphincter anatomy make accurate assessment of level of invasion in this region challenging.

pT3 indicates tumour spread beyond muscularis propria in continuity with the primary tumour and excluding tumour confined to the lumen of veins or lymphatic channels. Distinction from pT2 may be difficult if tumour extends to the outer edge of the muscularis propria. If no muscle separates tumour cells from mesenteric connective tissue, the tumour should be classified as pT3. Invasion beyond internal sphincter into the intrasphincteric plane, but not involving the external sphincter, is considered pT3.

pT4 encompasses either tumour infiltration of the peritoneal surface (pT4a) or tumour involvement of an adjacent organ (pT4b). Peritoneal involvement has been demonstrated by multivariate analysis to have a negative impact on prognosis. Although some small studies have suggested that peritoneal involvement was associated with worse outcome than invasion of adjacent organs, data from a large cohort of more than 100,000 colon cancer cases indicate that penetration of the visceral peritoneum carries a 10-20% better 5-year survival than locally invasive carcinomas for each pN category.

Involvement of the peritoneal surface (pT4a) is defined as tumour breaching the serosa with tumour cells visible either on the peritoneal surface, free in the peritoneal cavity or separated from the peritoneal surface by inflammatory cells only. Should tumour pass close to the serosal surface and elicit a mesothelial reaction but no clear invasion, additional sections and/or multiple levels should be examined. If tumour does not demonstrate serosal involvement after additional evaluation, it should be categorised as pT3. Assessment of this scenario remains prone to interobserver variation. Several studies advocate the application of elastic stains to evaluate peritoneal elastic lamina invasion, as a staging or prognostic tool, but others have not found this useful. Cases with perforation through tumour should also be classified as pT4a, even in the absence of microscopic documentation of tumour cells on the peritoneal surface. This does not apply to colonic or rectal perforation distant from the tumour, for example secondary to distal obstruction.

Note pT4a implies peritoneal involvement through direct contact with the primary tumour whereas peritoneal deposition of tumour discontinuous from the primary tumour is regarded as distant metastatic disease (pM1c). It is also important to carefully distinguish involvement of a peritoneal surface from involvement of a nonperitonealised 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.

Tumour involvement of an adjacent organ (pT4b) may follow peritoneal invasion or represent direct extraperitoneal invasion, for example in low rectal tumours. Tumours adherent to other organs must be demonstrated microscopically to show invasion into the adjacent organ, rather than inflammatory adherence,
to be classified as pT4b. Intramural (longitudinal) tumour extension into an adjacent part of the intestine does not influence pT classification, for example intramural extension of a caecal tumour into the terminal ileum or of a rectal tumour into the anal canal. Tumour involvement of greater omentum is considered pT4b if it follows transperitoneal invasion. Rarely, a transverse colonic tumour can invade greater omentum directly without breaching the serosa, meriting classification as pT3 rather than pT4b. For rectal tumours, invasion of skeletal muscle of the external sphincter and/or levator ani is classified as pT4b.

CS3.03b In the rare situation where discontinuous tumour deposits in the omentum arise from a directly invading transverse colon cancer, gross appearance and macroscopic assessment is important. Recording how the omentum was adherent, and the location of the mesentry, can be helpful. If the transverse colon is attached and appears to be involved, then the gross appearance may be very important in staging.

G3.01 The measurement of invasion beyond muscularis propria should be recorded.

CG3.01a Tumours classified as pT3 can be prognostically stratified accordingly to their extent of invasion beyond muscularis propria, with 5 mm an important cut-off in some studies.\(^\text{78,79}\) This distance should be measured to the nearest millimetre from the outer margin of the muscularis propria, reconstructing this margin if necessary in the event of destruction by tumour. Note this measurement applies only to the primary tumour and any discontinuous tumour foci, of any form, should be discounted in this assessment.

G3.02 The inflammatory cell infiltrate may be assessed.

CG3.02a Inflammatory and immune reactions to CRC are generally associated with improved outcome.\(^\text{80-82}\) They are classified as follows:

Lymphocytic immune reactions. These have several patterns: tumour-infiltrating lymphocytes, peritumoural lymphocyte infiltration, and peritumoural lymphoid aggregates

Tumour-infiltrating lymphocytes are associated with mismatch repair-deficient (MMRD) CRCs.\(^\text{83}\)

There is an evolving role in predicting for a good response to immunotherapy treatment.\(^\text{84,85}\)

Tumour-infiltrating lymphocytes are an independent predictor of improved prognosis. They are associated with less aggressive features including a decreased likelihood of venous invasion.\(^\text{86-88}\) The improved outcomes seen in MMRD cancers are likely the result of the tumour-infiltrating lymphocytic response seen in these tumours.

Other inflammatory cell reactions that have been shown to have prognostic relevance include prominent neutrophil and eosinophil infiltration.\(^\text{89-92}\)
The presence of lymphovascular invasion must be recorded.

**CS3.04a**

For colorectal cancer, it is important to report the presence or absence of lymphovascular invasion and to classify this further according to the type of vessels involved and, for veins, their intramural or extramural location, as these features may have different clinical and prognostic implications. Extramural (beyond muscularis propria) venous invasion has been demonstrated on multivariate analysis by multiple studies to be a stage independent adverse prognostic factor for colonic and rectal cancer. There is also evidence from several studies that intramural (intramuscular or submucosal) venous spread is also of prognostic importance but the evidence is much weaker than for extramural venous invasion.

Venous invasion is defined as tumour present within an endothelium-lined space that is either surrounded by a rim of muscle or contains red blood cells. It should be suspected in the presence of a rounded or elongated deposit of tumour beside an artery. Interpretation of such features is subjective and can be improved by the application of immunohistochemical and histochemical stains, in particular elastic staining to identify venous elastic lamina. A circumscribed tumour nodule surrounded by a smooth muscle wall or an identifiable elastic lamina, evident on hematoxylin and eosin or elastic stains, is considered sufficient to classify as venous invasion. Examination of multiple levels in blocks showing features suspicious of venous invasion can also be helpful in borderline cases.

Small vessel invasion should be reported separately from venous (large vessel) invasion. Small vessel invasion is defined as tumour involvement of thin-walled structures lined by endothelium, without an identifiable smooth muscle layer or elastic lamina. Small vessels may represent lymphatics, capillaries or post-capillary venules. Lymphatics and venules may be distinguished by D2-40 immunohistochemistry, which only stains lymphatic endothelial cells, not venular, but this is not routinely recommended in reporting surgical resection specimens. All forms of small vessel invasion are considered under the ‘L’ classification under UICC/AJCC TNM 8th editions. Small vessel invasion is associated with lymph node metastatic disease and has been shown to be an independent indicator of adverse outcome in some but not all studies. A higher prognostic significance of extramural small vessel invasion has been suggested, but the importance of anatomic location in small vessel invasion is not well established.

**CS3.04b**

Venous invasion by tumour has been repeatedly shown by multivariate and univariate analyses to be a stage independent adverse prognostic factor. However some studies identifying venous invasion as an adverse factor on univariate analysis have failed to confirm its independent impact on prognosis on multivariate breakdown. Similar disparate results have also been reported for lymphatic invasion. In other reports, vascular invasion as a general feature was...
prognostically significant, but no distinction between lymphatic and venous vessels was made. In a few studies the location as well as the type of the involved vessels (e.g. extramural veins) were both considered strong determinants of prognostic impact.\textsuperscript{109,110} Data from the many studies are difficult to amalgamate but nevertheless, the importance of venous and small vessel (lymphovascular) invasion by tumour is generally accepted, and it is considered that venous and small vessel invasion must be sought and separately recorded.

CS3.04c Some groups have recommended that only extramural venous invasion be recorded,\textsuperscript{23} while others have recommended that the site of any venous invasion should be recorded, along with its location, intra or extramural.\textsuperscript{109} In one study, intramural and extramural vascular invasion were shown to have similar prognostic value.\textsuperscript{111} It is recommended that extramural and intramural venous invasion be recorded separately.

CS3.04d There should be a high index of suspicion of involvement of a vein if an isolated elongated deposit of tumour is seen alongside an artery. Examination of multiple levels in blocks showing features suspicious of vascular invasion can be helpful and there may be a role for the use of immunohistochemical stains for endothelium and smooth muscle. An elastic tissue stain such as an orcein histochemical stain is also useful to aid detection of venous invasion.\textsuperscript{112} Assessment should be concentrated at the invasive edge of the tumour. It is an observation of the Royal College of Pathologists colorectal reporting protocol that intramural and/or extramural venous invasion should be detected in at least 30% of colectomy specimens.\textsuperscript{113}

CS3.04e The prognostic importance of involvement of small (thin-walled, presumably lymphatic) vessels in the submucosa has been well documented with respect to polypectomies of malignant polyps. Such involvement has been shown to be associated with an increased risk of regional lymph node metastasis.\textsuperscript{114}

<table>
<thead>
<tr>
<th>S3.05</th>
<th>The presence of perineural invasion must be recorded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3.05a</td>
<td>Multiple independent studies and one meta-analysis have demonstrated the adverse prognostic implication of perineural invasion in colorectal cancer, particularly in stage II disease.\textsuperscript{102,115-118} One large multicentre study reported adverse prognostic significance of both intramural and extramural perineural invasion.\textsuperscript{115} However the importance of anatomic location in perineural invasion is not well established.</td>
</tr>
<tr>
<td>S3.05b</td>
<td>There is some evidence that perineural infiltration by tumour is an important indicator of spread, particularly in rectal tumours where it may involve the sacral plexus and this may be an indication for radiotherapy.\textsuperscript{119}</td>
</tr>
</tbody>
</table>

| S3.06 | Results of lymph node histopathology must be recorded. |
The regional lymph node status is a major determinant of whether or not a patient receives adjuvant chemotherapy. Non-regional lymph node involvement by tumour, within large resection specimens, should be recorded separately, as this indicates distant metastatic (pM1) disease. In the case of two synchronous primary tumours in distinct anatomic regions, lymph nodes need to be assigned by regional status and assessed for each cancer separately.

The number of nodes present depends on the length of the resection specimen, the amount of attached mesenteric tissue, the age of the patient and whether or not the patient has received neoadjuvant therapy. Diligent pathology dissection is crucial as many positive lymph nodes are less than 5 mm in size. Some cases contain only a small number of nodes, but dissectors and departments should aim for a median lymph node yield of at least twelve per case. In stage II disease, low lymph node harvest is an adverse prognostic factor.

With respect to small nodal tumour deposits, a systematic review and meta-analysis found higher risk of disease recurrence in stage I/II colorectal cancer cases in the presence of only micrometastatic disease in lymph nodes (one or more deposit ≥0.2 mm and <2 mm) compared to those with tumour-negative nodes, but no increased risk of disease recurrence in cases in the presence of only ‘isolated tumour cells’ in lymph nodes (single tumour cells or groups <0.2 mm in maximum dimension) compared to those with tumour-negative nodes. Therefore, cases in which isolated tumour cells, identified on haematoxylin and eosin or immunohistochemical staining, represent the only form of nodal involvement should be classified as pN0, with a comment on the presence of the isolated tumour cells and optional designation as pN0(i+). Any lymph node containing tumour measuring ≥0.2 mm in diameter is counted as a positive node.

If neoadjuvant therapy has been received, designation as nodal involvement (ypN1/2) is based only on the presence of viable tumour. Assessment of lymph nodes in this setting should ideally include a descriptive comment on the presence or absence of signs of regression (fibrosis, necrosis or mucin) within nodal tissue, to allow correlation with initial staging MRI.

Although it is now accepted terminology to describe cases as pN0 - in which isolated tumour cells represent the only form of nodal involvement, in practice many pathologists and clinicians often view these nodes as positive.

Accurate identification of positive lymph nodes is key to accurate staging and a major determinant of whether a patient receives adjuvant therapy. The probability of finding a positive node increases with the number of nodes found and increased lymph node retrieval is also independently associated with improved survival.

Early studies suggested the likelihood of detecting a positive lymph node flattened out after finding 12–15 nodes, leading to many guidelines recommending a minimum of 12 lymph nodes.
nodes be retrieved. However, there is a lack of consensus on what a minimum retrieval number should be and the reason is likely to be that lymph node yield is multifactorial. Lymph node retrieval is affected by a number of factors which can be categorised into surgical (length of specimen, type of procedure), patient (location, size) and laboratory (experience, caseload) factors.\textsuperscript{129} Some factors are modifiable, such as pathologist or surgical experience, while others are not and in the future it may be that the cut-off is adjusted by patient or tumour-specific factors.\textsuperscript{127}

Pending further evidence, it is prudent to approach lymph node retrieval as follows

- all identifiable lymph nodes should be retrieved and examined
- if twelve or fewer lymph nodes are found then the specimen should be re-examined for lymph nodes as a longer period of fixation in formalin can improve lymph node detection; this is particularly important in stage II (pN0) tumours
- alternative fixatives and fat clearance methods can be used to increase lymph node yield but the evidence is most robust in studies where the yield was low to begin with\textsuperscript{15}
- the greatest yield for positive lymph nodes in a second search is the region of the tumour bed\textsuperscript{16}
- if 12 or fewer lymph nodes are retrieved a note should be made in the pathology report, describing how this has been addressed
- assessment of a laboratory's average lymph node yield can be used as a quality indicator but may reflect a particular surgical or patient cohort, rather than a particular laboratory's practice

CS3.06d Direct extension of a colorectal tumour into a lymph node is considered nodal metastasis. Metastasis in any lymph nodes other than regional nodes is classified as distant metastasis.\textsuperscript{130}

CS3.06e There is no consensus that occult metastatic disease detected by immunohistochemistry or other methods discriminates between high- and low-risk groups of patients. Data are thus insufficient to recommend routine use of tissue levels or ancillary special techniques.\textsuperscript{65,109}

CS3.06f Recording small tumour deposits in lymph nodes needs to take account of the following issues:

- Isolated tumour cells are defined as ‘single malignant cells or a few tumour cells in microclusters’, not more than 0.2 mm in diameter, present within a lymph node. They may be single or multiple. They may be visible in H&E stained sections or detected by immunohistochemistry. The literature suggests that the finding of such cells is not a marker of an adverse prognosis for the patient.\textsuperscript{131-133}
- The AJCC TNM 8th edition recommends that cases in which isolated tumour cells are the only form of nodal involvement should be classified as pN0, although the presence of the isolated tumour cells should be noted. Optional designation as pN0(i+) may be used in this situation, although a free-text description might provide clearer communication.

- It has been argued that very small nodal deposits that show evidence of growth, for example glandular differentiation, distension of the sinus or a stromal reaction, should be regarded as metastases irrespective of size.

**CS3.06g** The assessment of isolated deposits of tumour within the mesocolic and mesorectal fat, in particular whether they represent nodal metastases, can be difficult.

Isolated tumour deposits may derive from nodes, vascular invasion, perineural invasion or a combination of these within a single case. Such deposits are conveniently described as discontinuous extramural tumour deposits or satellite nodules. Most examples occur in situations where there are unequivocally involved nodes anyway (in a literature review of 1520 patients, only 8% of cases were not associated with lymph node deposits). However even where present without definite nodal metastasis, they are associated with an adverse prognosis.

This difficulty has been neatly addressed in the AJCC TNM 7th edition by the placing of cases with extramural tumour deposits within the N category. In the absence of co-existent definite lymph node metastases (defined in the 7th edition as having identifiable residual lymph node tissue), these cases are categorised as N1c.

**G3.03** Involvement of the apical lymph node should be recorded, if required, where staging systems additional to TNM staging are in use.

**CG3.03a** Both the Australian Clinicopathological Staging System and the Dukes staging system are in use in some institutions in Australasia. These require the status of the apical lymph node to be recorded.

**G3.04** The ratio of involved lymph nodes to the total number of nodes ('lymph node ratio') should be recorded.

**CG3.04a** The ratio of involved nodes to the total number of nodes has emerged as a potential prognostic factor. Lymph node ratio is defined as the ratio of the number of positive nodes to the total number of harvested nodes. It is a significant prognostic feature in stage III colorectal carcinoma where a high ratio predicts both poor overall survival and disease-free survival. The predictive value of this factor appears to be higher than the nodal stage alone.

**S3.07** The presence of tumour deposits must be recorded.
| **CS3.07a** | Under the UICC/AJCC TNM 8th editions definition, tumour deposits (satellites) are discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissue’s lymph drainage area of a primary carcinoma that are discontinuous from the primary and without histological evidence of residual lymph node or identifiable vascular or neural structures. The definition does not specify any minimum size of deposit or minimum distance of separation from the primary tumour. If a vessel wall is identifiable on H&E, elastic or other stains, it should be classified as venous invasion or lymphatic invasion. Similarly, if neural structures are identifiable, the lesion should be classified as perineural invasion. Identification of venous, lymphatic or perineural invasion does not change the T category. The presence of tumour deposits, as defined, also does not change the primary tumour T category, but changes the node status (N) to pN1c if all regional lymph nodes are negative on pathological examination. Therefore, pN1c is only applied in the setting of node-negative disease and, if any nodes contain metastatic tumour, the number of tumour deposits is not added to the involved node count in determining final pN category. However, as there is evidence from meta-analysis of the adverse prognostic significance of tumour deposits, albeit based on a previous definition, the presence and number of identified tumour deposits should be recorded regardless of pN status.

A mesenteric focus of tumour, without evidence of origin, which is discontinuous from the primary tumour, located within its lymphatic drainage area and predominantly subserosal in location but which penetrates the serosal surface of the mesentry, should be classified as a tumour deposit rather than distant metastatic (pM1c) disease. This finding does not influence the pT category, which should be based on extent of invasion of the primary tumour only, but a comment may be added that, given serosal involvement by the tumour deposit, behaviour may equate to pT4a disease. Guidance on this interpretation is offered without good evidence. pM1c disease should be reserved for tumour which appears to have arisen from metastatic spread via the peritoneal cavity.

Assessment of discontinuous tumour foci is difficult following administration of neoadjuvant therapy and evident tumour regression. This setting requires consideration of tissue separating the primary tumour site from the discontinuous tumour foci. Designation of such foci as tumour deposits should require the presence of intervening normal tissue, not just fibrosis. |
| **G3.05** | Tumour budding should be recorded. |
| **CG3.05a** | Tumour budding is defined as single cells or clusters of up to four tumour cells at the invasive front of carcinomas. It is considered to be the morphological manifestation of epithelial mesenchymal transition. Tumour budding is different from tumour grade (based on gland formation away from the invasive front) and poorly differentiated clusters (≥5 cells). There is increasing evidence that tumour budding is an |
independent adverse prognostic factor in colorectal carcinoma. Several studies have shown that stage pT1 colorectal carcinomas with tumour budding score Bd2 and Bd3 (≥5 buds) are associated with an increased risk of lymph node metastasis. For stage II colorectal carcinomas, tumour budding score Bd3 is associated with increased risk of recurrence and mortality.

Tumour budding is reported as the number of buds and scored using a three-tier system. According to the recommendations from a consensus conference on tumour budding, the number of tumour buds is the highest count after scanning ten separate fields (at 20x objective lens) along the invasive front of the tumour or the entire lesion for malignant polyps (‘hotspot’ approach). The number of tumour buds is counted on H&E. If the invasive front of the tumour is obscured by inflammatory cells, immunohistochemistry using pan-cytokeratin can be used to help identify the buds, but the final count is performed on H&E. Depending on the eyepiece field diameter of the microscope used, the number of buds may need to be normalised to represent the number for a field of 0.785 mm² (objective lens 20x with eyepiece diameter of 20 mm). Refer to ICCR dataset for full commentary.

Tumour budding should only be reported in non-mucinous and non-signet-ring cell adenocarcinoma areas. Furthermore, for colonic or rectal adenocarcinomas resected after neoadjuvant therapy, tumour budding should not be reported.

See Table 1 for International Tumour Budding Consensus Conference (ITBCC) 2016 conversion table and Figure 3 for the procedure proposed by the ITBCC 2016 for reporting tumour budding in colorectal cancer in daily diagnostic practice.

Response to neoadjuvant therapy must be recorded.

Patients with completely excised rectal carcinomas, who have received preoperative chemoradiotherapy that has resulted in complete or marked regression of tumour and replacement by fibrosis, necrosis or acellular mucin, have a better prognosis than those without significant regression. A four tier system of grading regression is recommended, based on a modification of that described by Ryan et al (2005). This should be applied when any form of neoadjuvant therapy is administered, to rectal or colonic tumours. Tumour regression assessment is based on evaluation of the primary tumour site, but a descriptive comment should be added if any such features are evident in regional lymph nodes, or at any distant metastatic sites. Designation as complete pathological response implies the absence of viable tumour locally (ypT0) and in lymph nodes (ypN0) and requires processing of the entire tumour bed for histological examination.

See Appendix 6 Table 6 for a comparison of regression grading systems.
Chemotherapy and/or radiotherapy before resection is associated with significant downstaging, and improved prognosis. These specimens require close gross examination and additional blocking to demonstrate tumour. The degree of tumour regression has been shown to correlate with prognosis. The classification of the AJCC, based on that of Ryan et al, is recommended:\(^{155}\)

- **Grade 0: (complete response):** No viable cancer cells
- **Grade 1: (moderate response):** Single cells or small groups of cancer cells.
- **Grade 2: (minimal response):** Residual cancer outgrown by fibrosis
- **Grade 3: (poor response):** Minimal or no tumour kill; extensive residual cancer

Note that acellular mucin pools seen in patients after therapy are regarded as indicators of complete regression. They do not contribute to T staging, and when seen in lymph nodes do not count as positive nodes. It is advisable to comment upon their presence in a free text comment for the purpose of correlation with pre-operative imaging.

If neoadjuvant 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. Tumour remaining in a resection specimen following neoadjuvant therapy should always be classified by ypTNM to distinguish it from untreated tumour.\(^{134}\)

The margin status must be recorded.

| CS3.09a | Assessments of longitudinal and circumferential resection margins may require macroscopic or microscopic measurement, depending on proximity of tumour to margins. Separately submitted anastomotic rings (‘doughnuts’) should be taken into consideration for longitudinal margin assessment. Unless a tumour has particularly aggressive morphological features, for example signet-ring cell carcinoma, it is generally only necessary to histologically examine longitudinal margins if the tumour extends macroscopically to within 30 mm.\(^{156}\) For tumours further than this, it can be assumed that the longitudinal margins are not involved. The circumferential (radial or nonperitonealised) margin represents the adventitial soft tissue margin closest to the deepest penetration of tumour and is created surgically by blunt or sharp dissection of the retroperitoneal or subperitoneal aspect, depending on the nature of the surgical resection. This margin must be assessed for any tumour either unencased or incompletely encased by peritoneum. Rectal tumours below the peritoneal reflection will be completely encased by a circumferential, nonperitonealised margin, while upper rectal tumours, and often proximal colonic tumours, have a nonperitonealised margin posteriorly and a peritonealised surface anteriorly (Figure 4). Transverse and sigmoid colonic
tumours generally only have a narrow, readily identifiable, nonperitonealised margin, representing the level of surgical dissection of the mesentery. The term circumferential margin is favoured, even though the nonperitonealised margin is not always circumferential.

Circumferential margin involvement, typically defined as tumour ≤1 mm from the margin, is predictive of local recurrence and poor survival in rectal tumours.\textsuperscript{157-161} The importance of circumferential margin involvement in proximal colonic tumours has been recognised but less evidence is available.\textsuperscript{162,163} Any circumferential margin ≤1 mm from tumour should be recorded as involved, but the precise distance recorded, to the nearest 0.1 mm must be included. If the tumour is clear by <10 mm, the specific distance of clearance should also be recorded, to the nearest 1 mm.

There is limited outcome data with respect to mode of circumferential margin involvement by tumour, but this limited data suggest that cases with margin involvement by discontinuous or intravascular (blood vessel or lymphatic vessel) tumour behave similarly to those with margin involvement by direct tumour spread with respect to local recurrence.\textsuperscript{157,158} However, margin involvement by tumour confined to a lymph node was not associated with a significant risk of local recurrence in one study.\textsuperscript{158} Therefore, assuming the involved lymph node has an intact capsule and has not been transected at surgery, identification of an involved node at the circumferential margin should not be interpreted as margin involvement. An explanatory comment should be added to the pathology report to this effect. If a margin is designated as involved by tumour other than the primary mass, this should be clearly described and a separate measurement provided with respect to clearance from the margin of the primary tumour.

CS3.09b Rectal tumours frequently (5–36%) involve the nonperitonealised surgical CRM and this is associated with significantly higher rates of local recurrence and cancer-related death.\textsuperscript{164-171}

CS3.09c The frequency of involvement of the CRM depends on the quality of surgery, advancing TNM stage and whether the patient has undergone preoperative neoadjuvant therapy. The closer the tumour is to the CRM, the worse the prognosis.\textsuperscript{172} The vast majority of studies, including clinical trials and population studies, have used a cutoff of 1 mm or less to define margin involvement.

CS3.09d CRM involvement may be through direct continuity with the main tumour, by tumour deposits discontinuous from the main tumour, or by tumour in veins, lymphatics or lymph nodes (Figure 4).\textsuperscript{165,166,173} Some surgeons like to know whether the tumour is contained within the lymph node or invades beyond the lymph node, as the latter is associated with a worse prognosis.

S3.10 The presence of histologically confirmed distant metastases and their site must be recorded.

CS3.10a Tumour classifiable as distant metastatic disease may
sometimes be present within the primary tumour resection specimen, for example a peritoneal or omental deposit that is discontinuous from the primary mass. Metastatic deposits in ‘non-regional’ lymph nodes distant from those surrounding the main tumour will usually be submitted separately by the surgeon but may be present within an extended colectomy specimen.

Given different prognostication associated with the pattern of organ involvement by distant metastatic disease, UICC/AJCC 8th edition Staging Manuals have subclassified pM1 into pM1a indicating metastatic disease in one distant organ (excluding metastatic peritoneal disease), pM1b indicating metastatic disease in two or more distant organs and pM1c indicating metastatic peritoneal disease (regardless of other organ involvement).\(^1\)\(^,\)\(^2\)\(^,\)\(^6\) Note, pathologists can only base assessment of distant metastatic disease on submitted specimens and therefore should not use the terms ‘pM0’ or ‘pMX’. cM1 and cM0 are used when clinical, usually radiological, evidence suggests the presence or absence respectively of distant metastatic disease.

| G3.06 | The presence of any relevant coexistent pathological abnormalities in the bowel should be recorded. |
| CG3.06a | The presence of any pathological abnormalities in the background colon or rectum should be recorded. These include polyps (type, number and whether meeting criteria for any polyposis syndrome), chronic inflammatory bowel disease (distribution and specify with or without dysplasia), effects of any neoadjuvant therapy on non-neoplastic tissue, diverticular disease and/or changes related to obstruction. Synchronous carcinomas should have individual protocols completed for all appropriate elements. |

**S3.11 The microscopic residual tumour status must be recorded (i.e. the completeness of resection).**

| CS3.11a | As the assessment of residual tumour status requires the input of the surgeon, as well as macroscopic and microscopic assessment; it is further dealt with in Chapter 5 (Synthesis and overview). |

| G3.07 | Any additional relevant information should be recorded. |
| CG3.07a | There must be a free text field so that the pathologist can add any essential information that is not addressed by the above points. |
Table 1. International Tumour Budding Consensus Conference (ITBCC) 2016 conversion table to adjust and standardise the tumour bud count for different microscope types

<table>
<thead>
<tr>
<th>Eyepiece FN Diameter (mm)</th>
<th>Specimen Area (mm²)</th>
<th>Normalisation Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>0.636</td>
<td>0.810</td>
</tr>
<tr>
<td>19</td>
<td>0.709</td>
<td>0.903</td>
</tr>
<tr>
<td>20</td>
<td>0.785</td>
<td>1.000</td>
</tr>
<tr>
<td>21</td>
<td>0.866</td>
<td>1.103</td>
</tr>
<tr>
<td>22</td>
<td>0.950</td>
<td>1.210</td>
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<tr>
<td>23</td>
<td>1.039</td>
<td>1.323</td>
</tr>
<tr>
<td>24</td>
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<tr>
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<td>1.563</td>
</tr>
<tr>
<td>26</td>
<td>1.327</td>
<td>1.690</td>
</tr>
</tbody>
</table>


[https://doi.org/10.1038/modpathol.2017.46](https://doi.org/10.1038/modpathol.2017.46)
Figure 3. Procedure proposed by the International Tumour Budding Consensus Conference (ITBCC) 2016 for reporting tumour budding in colorectal cancer in daily diagnostic practice.

1. Define the field (specimen) area for the 20x objective lens of your microscope based on the eyepiece field number (FN) diameter

<table>
<thead>
<tr>
<th>Eyepiece FN Diameter (mm)</th>
<th>Specimen Area (mm²)</th>
<th>Normalization Factor</th>
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</thead>
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<tr>
<td>18</td>
<td>0.30</td>
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<tr>
<td>19</td>
<td>0.750</td>
<td>0.963</td>
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<tr>
<td>20</td>
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<td>23</td>
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<td>1.227</td>
<td>1.563</td>
</tr>
<tr>
<td>26</td>
<td>1.327</td>
<td>1.680</td>
</tr>
</tbody>
</table>

2. Select the H&E slide with greatest degree of budding at the invasive front

3. Scan 10 individual fields at medium power (10x objective) to identify the “hotspot” at the invasive front

For surgical resection specimens, scan 10 fields

For pT1 endoscopic resections (usually <10 fields available), scan all

4. Count tumor buds in the selected “hotspot” (20x objective)

Selected hotspot indicated in red

5. Divide the bud count by the normalization factor (figure 2) to determine the tumor bud count per 0.785mm²

\[
\frac{\text{Tumor bud count}}{\text{Normalization factor}} \times \frac{1}{0.785 \text{mm}^2} = \text{Bud count (20x objective per 0.785 mm}^2\text{)}
\]

Select the budding [Bd] category based on bud count and indicate the absolute count per 0.785mm² (see reporting example)

<table>
<thead>
<tr>
<th>Bd1 (low)</th>
<th>0-4 buds</th>
<th>per 0.785 mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bd2 (intermediate)</td>
<td>5-9 buds</td>
<td>per 0.785 mm²</td>
</tr>
<tr>
<td>Bd3 (high)</td>
<td>≥10 buds</td>
<td>per 0.785 mm²</td>
</tr>
</tbody>
</table>

Reporting example:

Tumor budding: Bd3 (high), count 14 (per 0.785 mm²)


https://doi.org/10.1038/modpathol.2017.46
Figure 4. Measurement of the distance of tumour to the circumferential resection margin

\[ x = \text{minimum clearance in mm of primary tumour, extramural or nodal deposit or tumour in vessel etc, whichever is the closest.} \]
4 Ancillary findings

Ancillary studies of colorectal carcinoma are being increasingly used as prognostic biomarkers, to aid detection of an underlying genetic basis and to indicate the likelihood of patient response to specific biologic therapies.

<table>
<thead>
<tr>
<th>CG4.01</th>
<th>Screening for Lynch syndrome should be performed.</th>
</tr>
</thead>
</table>

CG4.01a Lynch syndrome is the most common inherited cause of colorectal carcinoma and is defined by an inherited loss of mismatch repair (MMR) gene function.\textsuperscript{174,175} Mismatch repair enzymes are important proteins that fix small errors in the gene code following DNA synthesis. The four most common enzymes are MLH1, MSH2, PMS2, MSH6. Defects in the genes coding for these enzymes can result in loss of the protein, as well as loss of this important function. Tumours showing this loss are said to be MMR deficient. MMRD cancers occur either sporadically (~15-20% of all colorectal cancers, usually as a result of methylation of the \textit{MLH1} gene), or less commonly (~3%) associated with Lynch syndrome (formerly called hereditary nonpolyposis colorectal cancer or HNPCC syndrome) because of changes in the DNA sequence of the genes (Table 2). The IHC stains can be performed on diagnostic biopsy material or on the resection specimen.

In a small number of cases, MMR gene function is silenced by a mutation in an adjacent gene e.g. \textit{EPCAM} gene which is immediately upstream of the \textit{MSH2} gene and prevents transcription of the \textit{MSH2} gene and \textit{LRRFIP2} gene which is adjacent to \textit{MLH1}.

Not all MMR genes portend the same risk for CRC.\textsuperscript{174,175} Table 3 presents current data on the cumulative lifetime risk of CRC and all cancers in patients with Lynch syndrome. Table 4 outlines a suggested multigene panel for assessment of CRC with high genetic/familial risk.\textsuperscript{176}

Screening for MMRD serves 2 useful clinical purposes: 1) detection of Lynch syndrome and 2) Identification of microsatellite instability in the colorectal carcinoma.

CG4.01b If stains have been done on the preoperative biopsy, these results should be copied into the structured report, with acknowledgement that they were performed on the biopsy material.

CG4.01c Lynch-like syndrome refers to cases clinically suspected to represent Lynch syndrome on the basis of MSI and deficiency of immunohistochemical staining for a MMR protein, however a germline mutation is not able to be identified (Figure 5). Potential causes include biallelic somatic inactivation of mismatch repair function or an as yet undetectable germline abnormality. The latter is believed to be most common. Currently, follow up is the same as if the patient had confirmed Lynch syndrome.
In surgical resections there may be zones of poor fixation or tumour hypoxia, so it is allowable to have up to 10% of the tumour cells exhibiting equivocal or weak expression for mismatch repair markers, so long as other areas of the tumour show uniform strong expression.

See Table 2 for patterns of MMR expression and their clinical significance.

**BRAF** testing and/or **MLH1** methylation testing should be performed where appropriate.

**BRAF** mutation testing and **MLH1** promoter methylation analysis are performed to help distinguish sporadic **MLH1**-deficient colorectal carcinomas from Lynch-syndrome associated tumours caused by constitutional **MLH1** mutation. The presence of either **BRAF** V600E mutation or **MLH1** promoter methylation effectively excludes Lynch syndrome. **BRAF** mutation status may also have predictive/therapeutic value.

Screening for mismatch repair deficiency as a marker of microsatellite instability should be performed.

Testing colorectal carcinoma for MMR protein deficiency is used for Lynch syndrome screening and provides therapeutic decision information for patient management. MMR deficiency is associated with good prognosis, poor response to 5-fluorouracil-based chemotherapy and predicts response to immune checkpoint blockade therapy.

The result of extended **RAS** mutation testing should be recorded.

Testing for the presence of mutations in the **RAS** gene family is typically requested by the clinician when metastatic disease is present. Therefore, such testing will most often be performed after the colorectal resection. In this situation, the result should be appended to the initial pathology report.

Some studies suggest that individuals with **RAS** mutant colorectal cancers have a reduced progression-free survival and overall survival. More recently **RAS** mutation status has been shown to predict response to drugs that specifically target the epidermal growth factor receptor (EGFR). Tumours that harbour mutations in **RAS** are resistant to the effects of these medications. Thus, testing for **RAS** mutations will become increasingly important as the activity of anti EGFR compounds is confined to only those patients with wild type **RAS** mutations. Anti-EGFR treatments are often used in individuals with metastatic disease, but the status of **RAS** family genes in the primary tumour is usually the same as that of metastases, and thus the findings from the primary tumour block can be used to predict treatment response in metastatic settings.

**RAS** mutation status is currently determined by a variety of genetic methods that are not routine in most diagnostic
laboratory settings. The majority of these tests can be performed on formalin fixed paraffin embedded tissue and requests for blocks containing tumour for extended RAS panel testing may be received many years after the primary cancer has been resected. For this reason, for possible subsequent mutation testing, it is desirable to designate a block from all colorectal cancer resections that contains a high proportion (preferably over 70%) of cancer. Ideally, the best block for molecular testing and the percentage of viable tumour should be documented in the histopathology report.

<table>
<thead>
<tr>
<th>CG4.05</th>
<th>Any additional studies for colorectal carcinoma should be performed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG4.05a</td>
<td>If a pure or mixed neuroendocrine neoplasm is suspected on morphology, immunohistochemistry is required to confirm neuroendocrine differentiation, usually applying synaptophysin and chromogranin A as a minimum. As with other gastrointestinal tract and pancreatic neuroendocrine neoplasms, assessment of proliferation index by Ki-67 immunohistochemistry is fundamental to grading of the neuroendocrine component. A Ki-67 proliferation index &lt;55% is associated with better overall survival in NECs.</td>
</tr>
<tr>
<td>CG4.05b</td>
<td>IHC can be performed to exclude metastatic carcinoma. The classical immunophenotype of colorectal carcinoma is CK7 negative, CK20 positive, CDX2 positive and SATB2 positive. However, it is important to be aware that Cytokeratin 20 and CDX-2 reactivity may be absent while conversely CK7 expression may be seen in microsatellite unstable colorectal carcinomas.</td>
</tr>
</tbody>
</table>
| CG4.05c| Approximately 5% of all colorectal carcinomas arise as a result of an inherited syndrome, with this prevalence being 10-15% in patients less than 50 years of age. The detection of an inherited colorectal cancer syndrome requires a high index of suspicion and knowledge of the manifestations and inheritance of the common syndromes. Table 4 is a summary of the more common syndromes. Syndromes can be divided into those associated with polyposis (serrated or adenomatous) and those not associated with significant numbers of polyps (non polyposis) (Table 5). The most common example of a non polyposis syndrome is Lynch syndrome, which fortunately can be identified in most cases via MMRD immunohistochemistry performed on the colorectal carcinoma. The polyposis syndromes are evidenced by large numbers of polyps typically developing at a younger age (<50 years). As a general guidance the NHMRC minimum requirements for referral to a genetic counselling service are those provided for MUTYH syndrome and listed in Table 5. Importantly, the polyp count is cumulative, so referral to previous pathology findings is useful. Referral to a genetics service for germline genetic testing for mutations in MUTYH is indicated for persons with a cumulative count of ≥ 20 colorectal adenomas at any age. Testing may also be considered in patients with ≥ 10
adenomas and any of the following:\textsuperscript{182,183} 

- age under 50
- synchronous colorectal cancer
- both adenomatous and serrated polyps where the adenomatous polyps dominate
- family history suggestive of recessive inheritance (e.g. consanguinity in parents or siblings with documented adenomatous polyposis or colorectal cancer).

Genetic testing is now performed via a multigene panel. Table 5 lists the National Comprehensive Cancer Network (NCCN) suggested panel for colorectal cancer.

\textbf{Figure 5. Lynch-like syndrome}

Adapted from Yozu M et al. Australasian Gastrointestinal Pathology Society (AGPS) consensus guidelines for universal defective mismatch repair testing in colorectal carcinoma. Pathology. 2019 Apr;51(3):233-239\textsuperscript{184}
### Table 2 Patterns of expression of mismatch repair immunohistochemistry and their clinical significance\(^{184,185}\)

<table>
<thead>
<tr>
<th>Pattern of IHC expression</th>
<th>Probability of Lynch Syndrome</th>
<th>Significance / further testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ + + +</td>
<td>Very unlikely</td>
<td>Normal pattern. No further testing unless a strong clinical suspicion of Lynch syndrome exists</td>
</tr>
<tr>
<td>- + + -</td>
<td>Sporadic microsatellite instability high Or Lynch syndrome</td>
<td><strong>BRAF</strong> mutation testing (PCR or immunohistochemistry) or MLH1 methylation If <strong>BRAF</strong> mutation or MLH1 methylation is present – sporadic CRC If mutation/MLH1 methylation is absent: investigate for Lynch syndrome by MLH1, followed by PMS2 germline testing</td>
</tr>
<tr>
<td>+ - - +</td>
<td>Likely</td>
<td>MSH2, followed by MSH6 germline testing required</td>
</tr>
<tr>
<td>+ + -$ +</td>
<td>Likely, unless chemotherapy/radiotherapy has been given</td>
<td>MSH6, followed by MSH2 germline testing required. No testing required if post chemoradiotherapy</td>
</tr>
<tr>
<td>+ + + -</td>
<td>Likely</td>
<td>PMS2, followed by MLH1 germline testing. This could also represent MLH1 mutation producing protein that is immunoreactive to the MLH1 immunohistochemical stains but is non-</td>
</tr>
<tr>
<td>- + - -*</td>
<td>Unlikely</td>
<td>MLH1 promoter hypermethylation with a secondary acquired mutation in a mononucleotide microsatellite of MSH6 gene</td>
</tr>
<tr>
<td>- - - -</td>
<td>Possible</td>
<td>Germline loss of <strong>MSH2</strong> and hypermethylation of MLH1 or hypermethylation silencing of both MLH1 and MSH2</td>
</tr>
<tr>
<td>+# + + -</td>
<td>Unlikely</td>
<td>MLH1 promoter hypermethylation</td>
</tr>
</tbody>
</table>

$ can have a nucleolar pattern of staining in post chemotherapy/radiotherapy setting

*(partial or complete)*

# punctate pattern of staining (false positive)

Table 3. Cumulative lifetime risk of colorectal cancer and all cancers to age 75 years in patients with Lynch syndrome\textsuperscript{174,175}

<table>
<thead>
<tr>
<th>Mismatch repair gene</th>
<th>Sex</th>
<th>Cumulative risk of all cancers (%)</th>
<th>Cumulative risk of colorectal carcinoma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>71.4</td>
<td>57.1</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>81.0</td>
<td>48.3</td>
</tr>
<tr>
<td>MLH1</td>
<td>Male</td>
<td>75.2</td>
<td>51.4</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>84.3</td>
<td>46.6</td>
</tr>
<tr>
<td>MSH2</td>
<td>Male</td>
<td>41.7</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>61.8</td>
<td>20.3</td>
</tr>
<tr>
<td>MSH6</td>
<td>Male/Female</td>
<td>34.1</td>
<td>10.4</td>
</tr>
</tbody>
</table>

Table 4. NCCN suggested multigene panel for assessment of colorectal carcinoma with high genetic/familial risk\textsuperscript{176}

<table>
<thead>
<tr>
<th>Gene</th>
<th>Risk level</th>
<th>Disease Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>High</td>
<td>FAP and attenuated FAP</td>
</tr>
<tr>
<td>ATM</td>
<td>Unclear</td>
<td>Increased risk for breast and colorectal cancer</td>
</tr>
<tr>
<td>AXIN2</td>
<td>Unclear - possibly high-risk</td>
<td>Polyposis and colorectal carcinoma, dental abnormalities</td>
</tr>
<tr>
<td>BLM heterozygotes</td>
<td>Unclear - low risk at most</td>
<td>Colorectal carcinoma</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>High</td>
<td>Juvenile polyposis syndrome</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Moderate</td>
<td>Increased risk for breast and colorectal carcinoma</td>
</tr>
<tr>
<td>EPCAM</td>
<td>High</td>
<td>Lynch syndrome</td>
</tr>
<tr>
<td>GALNT12</td>
<td>Unclear - probably low risk</td>
<td>Colorectal carcinoma</td>
</tr>
<tr>
<td>GEM1</td>
<td>Unclear - possibly high-risk</td>
<td>Hereditary mixed polyposis syndrome</td>
</tr>
<tr>
<td>MLH1</td>
<td>High</td>
<td>Lynch syndrome</td>
</tr>
<tr>
<td>MSH2</td>
<td>High</td>
<td>Lynch syndrome</td>
</tr>
<tr>
<td>MSH6</td>
<td>High</td>
<td>Lynch syndrome</td>
</tr>
<tr>
<td>MSH3</td>
<td>Unclear - possibly high-risk</td>
<td>Polyposis and colorectal carcinoma</td>
</tr>
<tr>
<td>MUTYH</td>
<td>High (biallelic mutations)</td>
<td>Polyposis and colorectal carcinoma</td>
</tr>
<tr>
<td>NTHL1</td>
<td>Unclear - possibly high-risk</td>
<td>Polyposis in colorectal carcinoma</td>
</tr>
<tr>
<td>POLD1</td>
<td>Unclear - possibly high-risk</td>
<td>Polymerase proofreading associated polyposis</td>
</tr>
<tr>
<td>POLE</td>
<td>Unclear - possibly high-risk</td>
<td>Polymerase proofreading associated polyposis</td>
</tr>
<tr>
<td>PMS2</td>
<td>high</td>
<td>Lynch syndrome</td>
</tr>
<tr>
<td>PTEN</td>
<td>Moderate to high</td>
<td>Cowden syndrome/PTEN hamartoma syndrome</td>
</tr>
<tr>
<td>SMAD4</td>
<td>High</td>
<td>Juvenile polyposis syndrome</td>
</tr>
<tr>
<td>STK11</td>
<td>High</td>
<td>Peutz-Jeghers syndrome</td>
</tr>
<tr>
<td>TP53</td>
<td>High</td>
<td>Li Fraumeni syndrome</td>
</tr>
</tbody>
</table>

### Table 5. Familial syndromes associated with increased risk of colorectal cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene responsible</th>
<th>Inheritance</th>
<th>Typical phenotype</th>
<th>Extracolonic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch syndrome*</td>
<td><em>EPCAM</em> deletion leading to epigenetic silencing of MSH2, MLH1, MSH6 or PMS2</td>
<td>Autosomal dominant</td>
<td>Early onset colorectal cancer, particularly in the proximal colon&lt;br&gt; The incidence of adenomas is not high but those that do arise have a high risk of rapidly progressing to malignancy; Cancers display microsatellite instability</td>
<td>Endometrial, ovarian, gastric, pancreatic, urothelial, renal pelvic, small intestine, biliary tract, brain, sebaceous gland adenomas and keratoacanthomas</td>
</tr>
<tr>
<td>Familial adenomatous polyposis (FAP)*</td>
<td><em>APC</em></td>
<td>Autosomal dominant</td>
<td>&gt; 100 adenomas</td>
<td>Duodenal, gastric, desmoid, brain, thyroid, hepatoblastoma</td>
</tr>
<tr>
<td>Attenuated FAP (AFAP)</td>
<td><em>APC</em></td>
<td>Autosomal dominant</td>
<td>&gt; 10 adenomas before age 30 years or 20–100 adenomas</td>
<td>Duodenal, gastric</td>
</tr>
<tr>
<td>MUTYH-associated polyposis</td>
<td><em>APC</em></td>
<td>Autosomal dominant</td>
<td>Usually 20–100 adenomas but may have &gt; 100</td>
<td>Duodenal, gastric</td>
</tr>
<tr>
<td>Polymerase proofreading-associated polyposis (PPAP)</td>
<td><em>POLD1</em> or <em>POLE</em></td>
<td>Autosomal dominant</td>
<td>10–100 adenomas and variable number of serrated polyps</td>
<td>Endometrial</td>
</tr>
<tr>
<td>MUTYH-associated polyposis</td>
<td><em>NTHL1</em></td>
<td>Autosomal recessive</td>
<td>8–50 adenomatous polyps</td>
<td>Endometrial</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td><em>STK11</em></td>
<td>Autosomal dominant</td>
<td>Histologically characteristic hamartomatous polyps throughout gastrointestinal tract and mucocutaneous pigmentation</td>
<td>Upper gastrointestinal and small intestine, breast, gynaecological, pancreas</td>
</tr>
<tr>
<td>Juvenile polyposis syndrome</td>
<td><em>SMAD4</em> or <em>BMPR1A</em></td>
<td>Autosomal dominant</td>
<td>Histologically characteristic hamartomatous polyps throughout gastrointestinal tract; polyps of mixed histology may also be present</td>
<td>Upper gastrointestinal and small intestine but no evidence of excess risk for extra-gastrointestinal cancers</td>
</tr>
<tr>
<td>Serrated polyposis syndrome</td>
<td>Unknown</td>
<td>Unclear and low penetrance</td>
<td>At least 5 serrated polyps proximal to the sigmoid with ≥ 2 of these &gt; 10 mm or &gt; 20 serrated polyps of any size but distributed throughout the colon</td>
<td>Nil known</td>
</tr>
</tbody>
</table>
Some patients develop adenomas and hyperplastic polyps in addition to colonic hamartomas. There is no evidence that all families with PTEN are at high risk of bowel cancer. Families with a history of colorectal cancer should follow screening guidelines based on their family history.

Breast, endometrial, thyroid, renal, skin lesions (trichilemmoma, papilloma).
Cowden Syndrome is often associated with macrocephaly.

**Table:**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Inheritance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowden syndrome</td>
<td>PTEN</td>
<td>Autosomal dominant</td>
<td>Some patients develop adenomas and hyperplastic polyps in addition to colonic hamartomas. There is no evidence that all families with PTEN are at high risk of bowel cancer. Families with a history of colorectal cancer should follow screening guidelines based on their family history.</td>
</tr>
</tbody>
</table>

*Note on nomenclature*

Historically, eponymous names were used to refer to specific clinical phenotypes in an individual patient, but now that the genetic basis of FAP and LS is known they should be avoided.

- **Gardner Syndrome** refers to classic FAP where intestinal polyposis is associated with extra-intestinal manifestations including osteomas (typically of the skull), fibromas, epidermoid cysts and desmoid tumours.
- **Muir-Torre syndrome** refers to Lynch syndrome associated with sebaceous gland tumours such as sebaceous epitheliomas, sebaceous adenomas, sebaceous carcinomas and keratoacanthomas.
- **Turcot syndrome** (brain tumour – polyposis syndrome) refers to the occurrence of multiple colorectal adenomas and a primary brain tumour. It can also be associated with cafe-au-lait spots. Turcot syndrome is associated with at least 2 distinct types of germline defects:
  - Type 1 is associated with a mutation in one of the mismatch repair genes and gliomas (predominantly astrocytomias) and accounts for about one third of cases.
  - Type 2, which accounts for two thirds of cases, is associated with a mutation in the APC gene (FAP variant) and medulloblastoma is the most common type of brain tumour.

# any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis syndrome.

5 Synthesis and overview

Information that is synthesized from multiple modalities and therefore cannot reside solely in any one of the preceding chapters is described here. For example, tumour stage is synthesized from multiple classes of information – clinical, macroscopic and microscopic. Overarching case comment is synthesis in narrative form. Although it may not necessarily be required in any given report, the provision of the facility for overarching commentary in a cancer report is essential.

By definition, synthetic elements are inferential rather than observational, often representing high-level information that is likely to form part of the ‘Diagnostic summary’ section in the final formatted report (see G5.01).

<table>
<thead>
<tr>
<th>S5.01</th>
<th>The tumour stage and stage grouping must be recorded, incorporating clinical and pathological data, based on the TNM staging system of the AJCC Cancer Staging Manual (8th Edition).</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS5.01a</td>
<td>TNM staging should be assessed according to the agreed criteria of the UICC and AJCC 8th editions. The only exception is that pT in situ is not recognised for colorectal cancer in this protocol. Rare cases of colorectal neoplasia confined to invasion of the lamina propria (intramucosal invasive neoplasia or intramucosal carcinoma) are acknowledged but, given the negligible metastatic potential of such neoplasms,68 these should be classified under the same category with high grade dysplasia/high grade non-invasive neoplasia. Note in the setting of completion surgery following a diagnosis of carcinoma in a local excision specimen, an overall tumour stage should be provided based on the pathological findings within both specimens, usually taking into consideration extent of local invasion in the local excision specimen and any residual local or nodal metastatic tumour in the subsequent surgical resection specimen. Regarding synchronous carcinomas, whilst individual protocols should be completed for each tumour, a single overarching stage should be provided, following the conventions of TNM and applying the ‘m’ suffix.</td>
</tr>
<tr>
<td>CS5.01b</td>
<td>The allocation of the TNM stage relies upon synthesis of information provided in the clinical request form and following macroscopic and microscopic examination.</td>
</tr>
<tr>
<td>CS5.01c</td>
<td>The y prefix must be used if there has been prior chemotherapy or radiotherapy.</td>
</tr>
</tbody>
</table>
| CS5.01d | The terminology pM1 (distant metastases present) should only be used by pathologists on the basis of pathological assessment of a relevant tissue sample. However, pathologists are strongly encouraged to use clinical terminology (cM0, cM1) in their final report on the basis of information provided to them on the surgical request form. It may advisable to make this clear in a comment (i.e. cM1 – based on clinical
evidence of liver metastases). Under this scenario, the hierarchy of M stage reports available to the pathologist would be as follows:

- pM1 in the presence of pathologically proven metastatic disease
- cM1 where clinical information stated metastases were present but where there was no pathological evidence of this
- cM0 where there was a clinical statement of no metastases and no pathological evidence of metastases.

**S5.02 The residual tumour status must be recorded according to the AJCC Cancer Staging Manual (8th Edition)**

CS5.02a The R codes are as follows. (Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, 8th Edition (2017) published by Springer Science and Business Media LLC, [www.springerlink.com](http://www.springerlink.com).)

- RX: Presence of residual tumour cannot be assessed
- R0: No residual tumour
- R1: Microscopic residual tumour
- R2: Macroscopic residual tumour at the primary cancer site or regional nodal sites (This designation is not used to indicate metastatic disease identified but not resected at surgical exploration.)

CS5.02b Residual tumour classification (R status) is not incorporated into TNM8 staging.\(^1\) However, the absence or presence of residual tumour and status of the margins may provide important information that affects subsequent treatment and prognosis and may be recorded in the medical record and cancer registry.\(^1\)

CS5.02c The resection status rule also applies to lymph nodes. If a positive lymph node is left behind it is classified as R2.

CS5.02d Tumour cells that are confined to the lumen of blood vessels or lymphatics at the resection margin are classified as R0.\(^187\)

CS5.02e Peritoneal involvement alone is not a reason to categorise the tumour as incompletely excised.

**S5.03 The year of publication and/or edition of the cancer staging system used in S5.01 must be included in the report.**

G5.01 The 'Diagnostic summary' section of the final formatted report should include:

a. specimen label
b. tumour site
c. histological tumour type
d. margin status

e. tumour stage

**S5.04** A field for free text or narrative in which the reporting pathologist can give overarching case comment must be provided.

CS5.04a This field may be used, for example, to:

- list any relevant ancillary tests
- document any noteworthy adverse gross and/or histological features
- express any diagnostic subtlety or nuance that is beyond synoptic capture
- document further consultation or results still pending.

CS5.04b Use of this field is at the discretion of the reporting pathologist.

**G5.02** The edition/version number of the RCPA protocol on which the report is based should be included on the final report.

CG5.02a For example, the pathology report may include the following wording at the end of the report: 'the data fields within this formatted report are aligned with the criteria as set out in the RCPA document ‘XXXXXXXXXX’ XXXX Edition dated XXXXXXX.'
6 Structured checklist

The following checklist includes the standards and guidelines for this protocol which must be considered when reporting, in the simplest possible form. The summation of all 'standards' is equivalent to the ‘minimum dataset’ for colorectal cancer. For emphasis, standards (mandatory elements) are formatted in bold font.

**S6.01** The structured checklist provided may be modified as required but with the following restrictions:

a. All standards and their respective naming conventions, definitions and value lists must be adhered to.

b. Guidelines are not mandatory but are recommendations and where used, must follow the naming conventions, definitions and value lists given in the protocol.

**G6.01** The order of information and design of the checklist may be varied according to the LIS capabilities and as described in *Functional Requirements for Structured Pathology Reporting of Cancer Protocols*.188

**CG6.01a** Where the LIS allows dissociation between data entry and report format, the structured checklist is usually best formatted to follow pathologist workflow. In this situation, the elements of synthesis or conclusions are necessarily at the end. The report format is then optimised independently by the LIS.

**CG6.01b** Where the LIS does not allow dissociation between data entry and report format, (for example where only a single text field is provided for the report), pathologists may elect to create a checklist in the format of the final report. In this situation, communication with the clinician takes precedence and the checklist design is according to principles given in Chapter 7.

**CG6.01c** To aide implementation of Level 6 structured reporting (where each reporting element is digitally captured using a discrete data field), some reporting elements may require repeating, such as in the case of synchronous primary tumours. For this scenario, the superscript ‘r’ is indicated next to the element ID (e.g. S2.05r) to assist with coding of the protocol template.

**G6.02** Where the checklist is used as a report template (see G6.01), the principles in Chapter 7 and Appendix 2 apply.

**CG6.02a** All extraneous information, tick boxes and unused values should be deleted.

**G6.03** Additional comment may be added to an individual response where necessary to describe any uncertainty or nuance in the selection of a prescribed response in the checklist. Additional comment is not required where the prescribed response is adequate.
**Item descriptions in italics are conditional on previous responses.**

**Values in all caps are headings with sub values.**

<table>
<thead>
<tr>
<th>S/G</th>
<th>Item description</th>
<th>Response type</th>
<th>Conditional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Pre-analytical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1.01</td>
<td>Demographic information provided</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1.02</td>
<td>Clinical information provided on request form</td>
<td><strong>Text</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Information not provided</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Structured entry as below:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Known polyposis syndrome</td>
<td><strong>Multi selection value list (select all that apply):</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>• Familial adenomatous polyposis (FAP)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>• MUTYH-associated polyposis (MAP)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>• Serrated polyposis</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>• Other, specify</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lynch syndrome</td>
<td><strong>Text</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic inflammatory bowel disease</td>
<td><strong>Multi selection value list (select all that apply):</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>• Ulcerative colitis</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>• Crohn disease</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previous polyp(s)</td>
<td><strong>Text</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previous colorectal cancer</td>
<td><strong>Text</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td><strong>Text</strong></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant therapy</td>
<td>Single selection value list:</td>
<td>Describe neoadjuvant therapy, if known</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
<td></td>
</tr>
<tr>
<td>G1.01 Copy To doctors recorded</td>
<td>Text</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1.03 Pathology accession number</td>
<td>Alpha-numeric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1.04 Principal clinician</td>
<td>Text</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1.02 Other clinical information received</td>
<td>Text</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Macroscopic findings**

<table>
<thead>
<tr>
<th>S2.01 Specimen labelled as</th>
<th>Text</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S2.02 Clinical information</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>S2.03 Operative procedure</td>
<td>Not specified</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Multi selection value list:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Total colectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Proctocolectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Right hemicolecotmy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Extended right hemicolecotmy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Transverse colectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Left hemicolecotmy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Anterior resection (specify if possible)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o High</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o Low/ultralow</td>
<td></td>
</tr>
<tr>
<td>Section</td>
<td>Description</td>
<td>Details</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>S2.04</td>
<td>Specimen length</td>
<td>Numeric: ___mm</td>
</tr>
</tbody>
</table>
| S2.05   | Tumour site | Single selection value list:  
  - Not specified  
  - Caecum  
  - Ascending colon  
  - Hepatic flexure  
  - Transverse colon  
  - Splenic flexure  
  - Descending colon  
  - Sigmoid colon  
  - Rectosigmoid*  
  - Rectum  
  - Other, specify  
  *Note: Reserved for cases in which an accurate determination between rectum and sigmoid cannot be made by pathological assessment and clinical information regarding site is not available. |
|         | Tumour dimensions | Single selection value list:  
  - Cannot be assessed, specify  
  OR  
  **Text:** Tumour identification  
  **AND**  
  **Numeric:** ___mm maximum dimension (largest |

If multiple tumours are present, separate protocols should be used to record this and all following elements for each tumour.
| S2.07<sup>a</sup> | Distance of tumour to the nearer proximal or distal 'cut end' | Additional dimensions (largest tumour) | Notes: | Repeat tumour identification and maximum dimension for each tumour identified. | **Numeric:** ____mm x ____mm |
| S2.08<sup>a</sup> | Distance of tumour to the nonperitonealised circumferential margin | | | | **Single selection value list:**
| &bull; Cannot be assessed
| OR
| **Numeric:** ____mm |
| S2.09<sup>a</sup> | Tumour perforation (defined as a macroscopically visible full thickness defect in the wall) | | | | **Single selection value list:**
| &bull; Not identified
| &bull; Present
| o Through tumour (tumour perforation)
| o Not involving tumour |
| S2.10<sup>a</sup> | Relation of tumour to anterior peritoneal reflection (rectal cancer specimens only) | | | | **Single selection value list:**
| &bull; Not applicable
| &bull; Entirely above
| &bull; Entirely below
| &bull; Astride

<p>| Applicable to any specimen containing a rectal cancer e.g. anterior resection, abdominoperineal resection, proctocolectomy |</p>
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Value List</th>
<th>Notes</th>
</tr>
</thead>
</table>
| S2.11'  | Plane of mesorectal excision (rectal cancer specimens only) | Single selection value list:  
- Not applicable  
- Mesorectal fascia (complete)  
- Intramesorectal (near complete)  
- Muscularis propria (incomplete) | Applicable to any specimen containing a rectal cancer e.g. anterior resection, abdominoperineal resection, proctocolectomy |
| G2.01'  | Plane of sphincter excision (abdominoperineal excision specimens only) | Single selection value list:  
- Extralevator plane  
- Sphincter plane  
- Intrasphincter plane | Applicable to abdominoperineal excision specimens only and should be reported in addition to the mesorectal plane |
| G2.02'  | Plane of mesocolic excision (colon cancer specimens only) | Single selection value list:  
- Mesocolic plane  
- Intramesocolic plane  
- Muscularis propria plane | Applicable to any specimen containing a colon cancer |
| G2.03'  | Peritoneum | Single selection value list:  
- Tumour invades to the peritoneal surface  
- Tumour has formed nodule(s) discrete from the tumour mass along the serosal surface | |
| G2.04   | Other macroscopic comments | Text | |
| Microscopic findings | | | |
| S3.01'  | Histological tumour type | Single selection value list from WHO Classification of Tumours of the Gastrointestinal Tract (2019). Single selection value list:  
- Adenocarcinoma, not otherwise specified (NOS) | |
<table>
<thead>
<tr>
<th>S3.02</th>
<th>Histological tumour grade</th>
<th>Single selection value list:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mucinous adenocarcinoma</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Signet-ring cell adenocarcinoma</td>
<td>Low grade $&gt;50%$ (formerly well to moderately differentiated)</td>
</tr>
<tr>
<td></td>
<td>Medullary carcinoma</td>
<td>High grade $&lt;50%$ (formerly poorly differentiated and undifferentiated)</td>
</tr>
<tr>
<td></td>
<td>Serrated adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Micropapillary adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adenoma-like adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other, specify</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only adenocarcinoma, NOS, and mucinous adenocarcinoma should be graded</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S3.03</th>
<th>Extent of invasion</th>
<th>Single selection value list:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cannot be assessed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No evidence of primary tumour</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High grade dysplasia/non-invasive neoplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Invasion into submucosa</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Invasion into muscularis propria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Invasion into subserosa or into pericolic or perirectal tissues</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Invasion onto the surface of the visceral</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Multi selection value list (select all that apply):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High grade dysplasia/non-invasive neoplasia</td>
</tr>
<tr>
<td></td>
<td>Invasion into submucosa</td>
</tr>
<tr>
<td></td>
<td>Invasion into muscularis propria</td>
</tr>
<tr>
<td></td>
<td>Invasion into subserosa or into pericolic or perirectal tissues</td>
</tr>
<tr>
<td></td>
<td>Invasion onto the surface of the visceral</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
| **G3.01** | Measurement of invasion beyond muscularis propria (for pT3 tumours) | **Single selection value list:**  
  - Cannot be assessed  
  OR |
| **Distance beyond muscularis propria** | **Numeric:** __mm | |
| **G3.02** | Inflammatory cell infiltrate | **Text**  
  Record the scoring system used |
| **S3.04** | Lymphatic and venous invasion | **Single selection value list:**  
  - Not identified  
  - Present  
    - Small vessel (lymphatic, capillary or venular)  
    - Large vessel (venous)  
    - Intramural  
    - Extramural |
| **S3.05** | Perineural invasion | **Single selection value list:**  
  - Not identified  
  - Present |
| **S3.06** | LYMPH NODE STATUS | No nodes submitted or found  
  OR |
| **Number of lymph nodes examined** | Number cannot be assessed  
  OR | **Numeric:** ___ |
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Single selection value list:</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Single selection value list:</strong></td>
<td></td>
<td>Record the number of lymph nodes (LN) examined. If involved, specify the number of positive LN</td>
</tr>
<tr>
<td>G3.03</td>
<td>Apical node involvement</td>
<td>• Not applicable</td>
<td>Not involved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Absent</td>
<td>Involved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Present</td>
<td>Not required if number cannot be determined is entered above.</td>
</tr>
<tr>
<td>G3.04</td>
<td>Ratio of involved/total lymph nodes</td>
<td>Involved lymph nodes ___ / total lymph nodes ___</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S3.07</td>
<td>Tumour deposits</td>
<td>Single selection value list:</td>
<td>If tumour deposits are present, specify number of deposits</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Not identified</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Present, specify type</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Vascular</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Number of tumour deposits</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Numeric: ___</td>
<td></td>
</tr>
<tr>
<td>G3.05</td>
<td>Tumour budding</td>
<td><strong>Cannot be assessed</strong></td>
<td>Should only be reported in non-mucinous and non-signet-ring cell adenocarcinoma areas</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Number of tumour buds</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Numeric: ___</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Note:</strong> After scanning 10 fields on a 20x objective lens, the hotspot field normalised to represent a field of 0.785 mm²</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Tumour budding score</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Single selection value list:</strong></td>
<td></td>
</tr>
</tbody>
</table>
### S3.08 Response to neoadjuvant therapy

**Single selection value list:**
- No neoadjuvant treatment
- Complete response - No viable cancer cells (score 0)
- Near complete response - Single cells or rare small groups of cancer cells (score 1)
- Partial response - Residual cancer with evident tumour regression, but more than single cells or rare small groups of cancer cells (score 2)
- Poor or no response - Extensive residual cancer with no evident tumour regression (score 3)
- Cannot be assessed, specify

### S3.09a MARGIN STATUS

**Longitudinal margin status**

**Single selection value list:**
- Cannot be assessed
- Not involved
- Involved

**Note:** Includes assessment of any separately submitted anastomotic ring(s).  

**If not involved by invasive carcinoma, estimate distance to closer margin**  
**If involved by invasive carcinoma, specify proximal or distal margin**  

<table>
<thead>
<tr>
<th>Distance to closer margin</th>
<th>Numeric: __mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal or distal margin</td>
<td>Numeric: __mm</td>
</tr>
<tr>
<td>IC</td>
<td>Description</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Circumferential margin status</td>
<td>Single selection value list:</td>
</tr>
<tr>
<td>Not involved - Distance to nearest 1 mm or $\geq 10$ mm</td>
<td></td>
</tr>
<tr>
<td>Involved ($\leq 1$ mm) – specify 0 mm or distance to nearest 0.1 mm</td>
<td></td>
</tr>
<tr>
<td>Distant metastases</td>
<td>Single selection value list:</td>
</tr>
<tr>
<td>Coexistent pathological abnormalities</td>
<td>None identified OR Multi select value list:</td>
</tr>
<tr>
<td>Microscopic residual tumour status (completeness of</td>
<td></td>
</tr>
</tbody>
</table>
### Ancillary findings

<table>
<thead>
<tr>
<th>G3.07</th>
<th>Additional microscopic comment</th>
<th>Text</th>
</tr>
</thead>
</table>

**G4.01** Ancillary studies

| **Mismatch repair (MMR) immunohistochemistry** | Not tested  
| OR | Not interpretable  
| OR | **Single select value list:**  
| • MMR proficient  
| • MMR deficient  
| o MLH1/PMS2 loss  
| o MSH2/MSH6 loss  
| o MSH6 loss  
| o PMS2 loss  
| o Other, specify |

| **BRAF (V600E) mutation testing** | Not tested  
| OR | **Single select value list:**  
| • Test failed  
| • Mutated  
| • Wild type |

| **MLH1 promoter methylation testing** | Not tested  
<p>| OR |</p>
<table>
<thead>
<tr>
<th>G4.03</th>
<th>MMR status by microsatellite instability (MSI) testing</th>
<th>Single select value list:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• Test failed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Methylated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Not methylated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inconclusive</td>
</tr>
</tbody>
</table>

**OR**

<table>
<thead>
<tr>
<th>Multi select value list:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Test failed</td>
</tr>
<tr>
<td>• MSI-high</td>
</tr>
<tr>
<td>• MSI-low</td>
</tr>
<tr>
<td>• MSI-stable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G4.04</th>
<th>RAS gene mutation testing (KRAS exons 2, 3 or 4, NRAS exons 2, 3 or 4 or RAS mutation)</th>
<th>Single selection value list:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• Mutated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Wild type</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Not tested</td>
</tr>
</tbody>
</table>

**If mutated or wild type, record laboratory performing test and report number**

<table>
<thead>
<tr>
<th>Comments</th>
<th>Text</th>
</tr>
</thead>
</table>

| Laboratory performing test and report number | Text |

| G4.05 | Neuroendocrine neoplasm neuroendocrine markers | Text |

**For neuroendocrine neoplasms only**

| Ki-67 (labelling index) | Numeric: ___ % |

<p>| Other | Text |</p>
<table>
<thead>
<tr>
<th>Synthesis and overview</th>
<th>PATHOLOGICAL STAGING (AJCC 8TH EDITION)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S5.01</strong></td>
<td></td>
</tr>
</tbody>
</table>

### TNM descriptors

**Multi select value list:**
- m - multiple primary tumours
- r - recurrent
- y - post therapy

### Primary tumour (pT)

**Single select value list:**
- **TX** Primary tumour cannot be assessed
- **T0** No evidence of primary tumour
- **Tis** Carcinoma in situ, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
- **T1** Tumour invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
- **T2** Tumour invades the muscularis propria
- **T3** Tumour invades through the muscularis propria into pericolorectal tissues
- **T4** Tumour invades* the visceral peritoneum or invades or adheres** to adjacent organ or structure

### Regional lymph node (pN)

**Single selection value list:**
- **NX** Regional lymph nodes cannot be assessed
### Lymph Node Metastasis (N)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>One to three regional lymph nodes are positive (tumour in lymph nodes measuring ≥0.2 mm), or any number of tumour deposits are present and all identifiable lymph nodes are negative</td>
</tr>
<tr>
<td>N1a</td>
<td>One regional lymph node is positive</td>
</tr>
<tr>
<td>N1b</td>
<td>Two or three regional lymph nodes are positive</td>
</tr>
<tr>
<td>N1c</td>
<td>No regional lymph nodes are positive, but there are tumour deposits in the • subserosa • mesentery • or nonperitonealized pericolic, or perirectal/mesorectal tissues.</td>
</tr>
<tr>
<td>N2</td>
<td>Four or more regional nodes are positive</td>
</tr>
<tr>
<td>N2a</td>
<td>Four to six regional lymph nodes are positive</td>
</tr>
<tr>
<td>N2b</td>
<td>Seven or more regional lymph nodes are positive</td>
</tr>
</tbody>
</table>

### Distant Metastasis (pM)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis by imaging, etc.; no evidence of tumour in distant sites or organs (This category is not assigned by pathologists.)</td>
</tr>
<tr>
<td>M1</td>
<td>Metastasis to one or more distant sites or organs or peritoneal metastasis is identified</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis to one site or organ is identified without peritoneal metastasis</td>
</tr>
<tr>
<td>M1b</td>
<td>Metastasis to two or more sites or organs is identified without peritoneal metastasis</td>
</tr>
<tr>
<td>M1c</td>
<td>Metastasis to the peritoneal surface is identified alone or with other site or...</td>
</tr>
<tr>
<td>S5.02</td>
<td>Residual tumour status</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------</td>
</tr>
<tr>
<td></td>
<td>RX:</td>
</tr>
<tr>
<td></td>
<td>R0:</td>
</tr>
<tr>
<td></td>
<td>R1:</td>
</tr>
<tr>
<td></td>
<td>R2:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S5.03</th>
<th>Year and edition of staging system</th>
<th>Numeric: year AND Text: Edition e.g. 1st, 2nd etc</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>G5.01</th>
<th>Diagnostic summary</th>
<th>Text</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Include:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. specimen label</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. tumour site</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c. histological tumour type</td>
<td></td>
</tr>
<tr>
<td></td>
<td>d. margin status</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e. tumour stage</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S5.04</th>
<th>Overarching comment</th>
<th>Text</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>G5.02</th>
<th>Edition/version number of the RCPA protocol on which the report is based</th>
<th>Text</th>
</tr>
</thead>
</table>

organ metastases
7 Formatting of pathology reports

Good formatting of the pathology report is essential for optimising communication with the clinician, and will be an important contributor to the success of cancer reporting protocols. The report should be formatted to provide information clearly and unambiguously to the treating doctors, and should be organised with their use of the report in mind. In this sense, the report differs from the structured checklist, which is organised with the pathologists’ workflow as a priority.

Uniformity in the format as well as in the data items of cancer reports between laboratories makes it easier for treating doctors to understand the reports; it is therefore seen as an important element of the systematic reporting of cancer. For guidance on formatting pathology reports, please refer to Appendix 2. An example of a pathology report is shown in Appendix 3.
Appendix 1  Pathology request information and surgical handling procedures

This appendix describes the information that should be collected before the pathology test. Some of this information can be provided on generic pathology request forms; any additional information required specifically for the reporting of colorectal cancer may be provided by the clinician on a separate request information sheet. An example request information sheet is included below. Elements which are in bold text are those which pathologists consider to be required information. Those in non-bold text are recommended.

Also included in this appendix are the procedures that are recommended before handover of specimens to the laboratory.

Patient information

➢ Adequate demographic and request information must be provided with the specimen.

- Items relevant to cancer reporting protocols include:
  - patient name
  - date of birth
  - sex
  - identification and contact details of requesting doctor
  - date of request

- The patient’s ethnicity should be recorded, if known. In particular whether the patient is of aboriginal or Torres Strait islander origin. This is in support of a government initiative to monitor the health of indigenous Australians particularly in relation to cancer.

➢ The patient’s health identifiers should be provided.

- The patient’s health identifiers may include the patient’s Medical Record Number as well as a national health number such as a patient’s Medicare number (Australia), Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Identifier (New Zealand).

Clinical Information

<table>
<thead>
<tr>
<th></th>
<th>The presence of a known polyposis syndrome, Lynch syndrome, chronic inflammatory bowel disease or any other relevant gastrointestinal disorder should be recorded.</th>
</tr>
</thead>
</table>
| | Clinical information can be provided by the clinician on the endoscopy report or the pathology request form. Pathologists could search for additional information from possible previous pathology reports. The presence of a known polyposis syndrome, Lynch-syndrome, chronic inflammatory bowel disease or any other relevant gastrointestinal disorder should be recorded and provided to the pathologist, as awareness of such underlying conditions may influence both
specimen sampling and histological interpretation.

➢ It may be important to note the presence of previous polyps if they could indicate an undiagnosed polyposis syndrome (see Table 5).

➢ The surgeon’s identity and contact details should be recorded.
  • Name of operating surgeon, contact details, and date of operation.

➢ Perforation and/or obstruction should be recorded.
  • Perforation may be more easily appreciated by the surgeon than the pathologist. Tumour perforation is a prognostic factor in determining postoperative mortality and long-term survival. Perforation away from the tumour, related to colonic obstruction by the tumour, should be distinguished from perforation through the tumour. Perforation occurring during the course of surgery should be differentiated from the above and should be identified as such by the surgeon on the surgical request form.

The tumour site must be recorded.

• If multiple primary tumours are present, separate protocols should be used to record tumour site and all following elements for each primary tumour. Determination of tumour site is based on clinical information provided on the pathology request form combined with specimen assessment by the pathologist. Any significant discrepancy should be discussed with the clinical team and the tumour site clearly documented by specimen photography. Recording the anatomical site of tumour allows correlation with prior endoscopic and radiological investigations, indicates whether or not a nonperitonealised margin is likely to be present and defines the presence of regional versus non-regional lymph nodes. In particular, distinction of colonic from rectal origin is of importance, given different biologies, clinical features and management. Every effort should be made, therefore, to accurately classify a tumour as colonic or rectal in origin.

If a tumour straddles two sites, the site with the greatest tumour bulk should be recorded. The three taeniae coli of the sigmoid colon fuse to form the circumferential longitudinal muscle of the rectal wall, marking the rectosigmoid boundary. If distinction between the sigmoid colon and rectum is not possible by pathological assessment, for example owing to advanced tumour stage obliterating anatomical landmarks, the tumour site can be recorded based on clinical information available.

Classification as rectosigmoid should be reserved for cases in which an accurate determination between rectum and sigmoid cannot be made by pathological assessment and clinical information regarding site is not available.

• Choose from one of the following:
  • caecum
• For synchronous tumours indicate each other site for which a separate report will be submitted.

➢ The distance from the anal verge should be recorded (for rectal tumours only).

• This should be measured in centimetres (by longstanding surgical convention) using the best available information; rigid sigmoidoscopy measurements are preferred over digital rectal examination, operative findings or colonoscopy measurements.

• This measurement allows for the classification of rectal cancers into upper, mid- and lower third categories, which has a significant impact on case management.

<table>
<thead>
<tr>
<th>The operative procedure must be recorded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Information regarding the nature of the operative procedure should be provided, with any refinements as necessary, for example the attempted dissection plane in an abdominoperineal resection. Should the operative specimen include any tissue or organ not typically submitted within that specimen type, for example en bloc resection of a segment of intestine or abdominal wall connective tissue, this should be clearly indicated. Inclusion of the peritoneal reflection within an anterior resection specimen distinguishes a low anterior resection from a high anterior resection.</td>
</tr>
</tbody>
</table>

• Choose from one of the following:
  • Total colectomy (with ileorectal anastomosis)
  • Proctocolectomy
  • Right hemicolectomy
  • Extended right hemicolectomy
  • Transverse colectomy
  • Left hemicolectomy
  • Sigmoid colectomy
  • Anterior resection (specify whether high or low)
  • Hartmann procedure
  • Abdominoperineal resection
• Other, specify

<table>
<thead>
<tr>
<th>If neoadjuvant therapy has been administered, this must be recorded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Given implications for staging and interpretation of morphological features related to the primary tumour, it is important that clinical information is provided to the pathologist regarding the application of any neoadjuvant therapy, and details of such therapy, for example radiotherapy and/or chemotherapy, duration and timing in relation to surgery</td>
</tr>
</tbody>
</table>

• For rectal cancer, preoperative radiotherapy significantly alters the gross and microscopic appearance of the tumour.

• Short-course and long-course radiotherapy regimes need to be differentiated because the effects in the resected specimens are quite different.

➢ The surgeon’s opinion on the existence of local residual cancer following the operative procedure should be recorded.

• This item relates to the overall completeness of resection of the tumour, including evidence of residual disease at surgical margins or within regions in which resection has not been attempted. It allows for residual tumour status (R) to be assessed (see Chapters 2 and 3).

➢ The involvement of adjacent organs should be recorded.

• With regard to extension of disease into areas which either have or have not been resected (i.e. involvement of other organs or tissues by direct spread), it is the responsibility of the surgeon to report these deposits and, if indicated, mark these areas with a suture or other marker.

➢ Record if this is a new primary cancer or a recurrence of a previous cancer, if known.

• The term recurrence defines the return, reappearance or metastasis of cancer (of the same histology) after a disease free period.

Recurrence should be classified as distant metastases or regional (local) recurrence.

Regional (local) recurrence refers to the recurrence of cancer cells at the same site as the original (primary) tumour or the regional lymph nodes.

Distant metastasis refers to the spread of cancer of the same histologic type as the original (primary) tumour to distant organs or distant lymph nodes.

• The reporting of metastatic deposits, either resected or not resected, is required for assessment of the metastatic (M) stage of the tumour.
• The presence of involved nonregional lymph nodes stages the tumour as M1.

• This information will provide an opportunity for previous reports to be reviewed during the reporting process, which may provide valuable information to the pathologist. This information also has implications for recording cancer incidence and evidence based research.

➢ Any additional relevant information should be recorded.

• A free text field should be completed by the referring doctor to communicate anything that is not addressed by the above points, such as previous cancers, risk factors, investigations, treatments and family history.
The above Request Information Sheet is also available on the RCPA Cancer Protocols webpage.
Appendix 2 Guidelines for formatting of a pathology report

Layout

Headings and spaces should be used to indicate subsections of the report and heading hierarchies should be used where the LIS allows it. Heading hierarchies may be defined by a combination of case, font size, style and, if necessary, indentation.

Grouping similar data elements under headings and using ‘white space’ assists in rapid transfer of information.\textsuperscript{189}

Descriptive titles and headings should be consistent across the protocol, checklist and report.

When reporting on different tumour types, similar layout of headings and blocks of data should be used, and this layout should be maintained over time.

Consistent positioning speeds data transfer and, over time, may reduce the need for field descriptions or headings, thus reducing unnecessary information or ‘clutter’.

Within any given subsection, information density should be optimised to assist in data assimilation and recall. The following strategies should be used:

- Configure reports in such a way that data elements are ‘chunked’ into a single unit to help improve recall for the clinician.\textsuperscript{189}
- Reduce ‘clutter’ to a minimum.\textsuperscript{189} Thus, information that is not part of the protocol (e.g. billing information or SNOMED codes) should not appear on the reports or should be minimised.
- Reduce the use of formatting elements (e.g. bold, underlining or use of footnotes) because these increase clutter and may distract the reader from the key information.

Where a structured report checklist is used as a template for the actual report, any values provided in the checklist but not applying to the case in question must be deleted from the formatted report.

Reports should be formatted with an understanding of the potential for the information to ‘mutate’ or be degraded as the report is transferred from the LIS to other health information systems.

As a report is transferred between systems:

- text characteristics such as font type, size, bold, italics and colour are often lost
- tables are likely to be corrupted as vertical alignment of text is lost when fixed font widths of the LIS are rendered as proportional fonts on screen or in print
- spaces, tabs and blank lines may be stripped from the report, disrupting the formatting
- supplementary reports may merge into the initial report.
Appendix 3  Example of a pathology report

COLORECTAL CANCER STRUCTURED REPORT

Diagnostic Summary

Low anterior resection:

Rectum; rectal adenocarcinoma, NOS; excision complete; ypT3,pN1b,cMO, Stage IIIB (AJCC 8th edition).

Comment: Two small tubular adenomas and a well differentiated carcinoid tumour are also present. Mismatch repair gene deficiency not identified.

Supporting Information

CLINICAL

Known polyposis syndrome: None identified
Lynch syndrome: None identified
Chronic inflammatory bowel disease: None identified
Previous polyps: None identified
Previous colorectal cancer: None identified
Neoadjuvant therapy: Administered, Short course pre-operative radiotherapy
Other clinical information: Nil

MACROSCOPIC

Specimen labelled as: "Low anterior resection"
Operative procedure: Total colectomy
Specimen length: 130 mm
Tumour site: Rectum
Tumour dimensions: 50 mm
Dist. of tumour to distal ‘cut end’: 15 mm
Dist. of tumour to nonperitonealised CRM: 15 mm
Tumour perforation: Not identified
Relation of tumour to anterior peritoneal reflection: Astride
Plane of mesorectal excision: Mesorectal fascia (complete)
Peritoneum: Tumour has formed nodule(s) discrete from the tumour mass along the serosal surface. An 8mm submucosal nodule, 20mm from the distal margin is noted.
Other macroscopic comments: Tumour appears ulcerated and scarred. Overlying serosa appears normal.
MICROSCOPIC

Histological tumour type (WHO): Adenocarcinoma, NOS
Histological grade: High grade – poorly differentiated
Extent of invasion:

Distance beyond muscularis propria: Invasion through muscularis propria
Lymphatic and venous invasion: into pericolectal tissues
Perineural invasion: 4 mm
Lymph node status: Intramural vein invasion present
Number positive: Not identified

Apical node involvement: Involved
Ratio of involved/total lymph nodes: Perirectal LN basin: 2/14
Tumour deposits: Absent
Tumour budding: 2/14
Response to neoadjuvant therapy:

Not identified
Marginal status:

Cannot be assessed
Longitudinal margin - No prior treatment
Distance to closer margin - Not involved
Proximal margin - Not involved
Distal margin - 9 mm
Circumferential margin - Microscopic clearance is >10mm

Distant metastases:

Absent
Coexisting pathological abnormalities:

Polyps
Microscopic residual tumour status:

Complete resection
Microscopic comment: The submucosal nodule 20mm from
the distal margin is a well
differentiated carcinoid tumour,
completely excised.

ANCILLARY STUDIES

BRAF (V600E) mutation testing:
MLH1 promoter methylation testing:

Wildtype
MMR status by MSI testing:

Not tested
RAS gene mutation testing:

MSI-stable
Neuroendocrine neoplasm markers:

Wild type
Not applicable

Reported by Dr Robert Beckstein

Authorised 4/3/2011

Based on 4th Edition RCPA Colorectal cancer structured reporting protocol.
Appendix 4  WHO Classification of tumours of the colon and rectum 5th edition

Benign epithelial tumours and precursors

8213/0*  Serrated dysplasia, low grade
8213/2*  Serrated dysplasia, high grade
  Hyperplastic polyp, microvesicular type
  Hyperplastic polyp, goblet cell
8210/0*  Adenomatous polyp, low-grade dysplasia
8210/2*  Adenomatous polyp, high-grade dysplasia
8211/0*  Tubular adenoma, low grade
8211/2*  Tubular adenoma, high grade
8261/0*  Villous adenoma, low grade
8261/2*  Villous adenoma, high grade
8263/0*  Tubulovillous adenoma, low grade
8263/2*  Tubulovillous adenoma, high grade
  Advanced adenoma
8148/0  Glandular intraepithelial neoplasia, low grade
8148/2  Glandular intraepithelial neoplasia, high grade

Malignant epithelial tumours

8140/3  Adenocarcinoma NOS
8213/3  Serrated adenocarcinoma
8262/3*  Adenoma-like adenocarcinoma
8265/3  Micropapillary adenocarcinoma
8480/3  Mucinous adenocarcinoma
8490/3  Poorly cohesive carcinoma
8490/3  Signet-ring cell carcinoma
8510/3  Medullary adenocarcinoma
8560/3  Adenosquamous carcinoma
8020/3  Carcinoma, undifferentiated, NOS
8033/3*  Carcinoma with sarcomatoid component
8240/3  Neuroendocrine tumour NOS
8240/3  Neuroendocrine tumour, grade 1
8249/3  Neuroendocrine tumour, grade 2
8249/3  Neuroendocrine tumour, grade 3
8152/3 L-cell tumour
8152/3 Glucagon-like peptide-producing tumour
8152/3 PP/PYY-producing tumour
8241/3 Enterochromaffin-cell carcinoid
8241/3 Serotonin-producing tumour
8246/3 Neuroendocrine carcinoma NOS
8013/3 Large cell neuroendocrine carcinoma
8041/3 Small cell neuroendocrine carcinoma
8154/3 Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)

These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries. This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.

* Codes marked with an asterisk were approved by the IARC/WHO Committee for ICD-O at its meeting in April 2019.

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Appendix 5  Histological tumour types – example representative images

Micropapillary carcinoma

Medullary carcinoma (patient with Lynch syndrome)
Rhabdoid carcinoma

Mucinous carcinoma
Signet ring cell carcinoma (intramucosal)

Neuroendocrine carcinoma arising in a tubulovillous adenoma
Large cell neuroendocrine carcinoma

Undifferentiated carcinoma
Adenoma-like carcinoma
## Appendix 6  Regression grading systems

### Table 6. Comparison of regression grading systems

<table>
<thead>
<tr>
<th>Descriptive appearance</th>
<th>AJCC (Ryan)\textsuperscript{154}</th>
<th>Mandard\textsuperscript{191}</th>
<th>Becker\textsuperscript{192}</th>
<th>Dworak\textsuperscript{193}</th>
</tr>
</thead>
<tbody>
<tr>
<td>No residual tumour</td>
<td>0 (no residual tumour cells)</td>
<td>1 (no residual cancer cells)</td>
<td>1a (complete regression, 0% tumour)</td>
<td>4 (no vital tumour cells detected)</td>
</tr>
<tr>
<td>Near complete tumour regression</td>
<td>1 (single cell or small groups of cells)</td>
<td>2 (rare cancer cells)</td>
<td>1b (&lt; 10% residual tumour)</td>
<td>3 (scattered tumour cells - difficult to find)</td>
</tr>
<tr>
<td>Partial tumour regression</td>
<td>2 (residual cancer with desmoplastic response)</td>
<td>3 (fibrosis outgrowing residual cancer)</td>
<td>2 (10-50% residual tumour)</td>
<td>2 (scattered tumour cells - easy to find)</td>
</tr>
<tr>
<td>No tumour regression</td>
<td>3 (extensive residual cancer)</td>
<td>4 (residual cancer outgrowing fibrosis)</td>
<td>3 (&gt;50% residual tumour)</td>
<td>1 (predominantly tumour with significant fibrosis and/or vasculopathy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (cancer with no changes of regression)</td>
<td></td>
<td>0 (no regression)</td>
</tr>
</tbody>
</table>
Appendix 6  Practice audits

Structured reporting for colorectal carcinoma presents an ideal opportunity to perform practice audits. This is because structured pathology reports are more likely to produce consistent data on the expected range of positive findings. High frequency colorectal tumours are ideal for performing practice audits.

In some jurisdictions\textsuperscript{194-196} the following parameters have been helpful for practice audit and cross practice correlation:

1) frequency of diagnosis of the various WHO subtypes
2) frequency of serosal invasion (pT4a)
3) frequency of venous invasion\textsuperscript{197}
4) frequency of perineural invasion
5) frequency of high-level tumour budding – BD3
6) lymph node yield (how often are $\geq 12$ or more lymph nodes identified in resection specimens?)\textsuperscript{196,197}
7) MMR immunohistochemistry (how often is MMRD identified?)\textsuperscript{196}
References


RCPA (Royal College of Pathologists of Australasia) (2009). *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols*. RCPA, Surry Hills, NSW.


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Goldstein NS (2002). Lymph node recoveries from 2427 pT3 colorectal resection specimens spanning 45 years: recommendations for a minimum number of

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