COLORECTAL CANCER STRUCTURED REPORTING PROTOCOL

(3nd Edition 2016)

Core Document versions:

- AJCC Cancer Staging Manual 7th edition (including errata corrected with 5th reprint 10th Aug 2010).
- World Health Organization Classification of Tumours Pathology and Genetics of Tumours of the Digestive System, 2010, 4th edition

ISBN: 978-1-76000-434-7

Publications number (SHPN): (CI) 160179

Online copyright

First published: May 2016, 3rd Edition (Version 3.0)

Disclaimer

The Royal College of Pathologists of Australasia ("College") has developed these protocols as an educational tool to assist pathologists in reporting of relevant information for specific cancers. Each protocol includes "standards" and "guidelines" which are indicators of 'minimum requirements' and 'recommendations', which reflect the opinion of the relevant expert authoring groups. The use of these standards and guidelines is subject to the clinician's judgement in each individual case.

The College makes all reasonable efforts to ensure the quality and accuracy of the protocols and to update the protocols regularly. However subject to any warranties, terms or conditions which may be implied by law and which cannot be excluded, the protocols are provided on an "as is" basis. The College does not warrant or represent that the protocols are complete, accurate, error-free, or up to date. The protocols do not constitute medical or professional advice. Users should obtain appropriate medical or professional advice, or where appropriately qualified, exercise their own professional judgement relevant to their own particular circumstances. Users are responsible for evaluating the suitability, accuracy, currency, completeness and fitness for purpose of the protocols.

Except as set out in this paragraph, the College excludes: (i) all warranties, terms and conditions relating in any way to; and (ii) all liability (including for negligence) in respect of any loss or damage (including direct, special, indirect or consequential loss or damage, loss of revenue, loss of expectation, unavailability of systems, loss of data, personal injury or property damage) arising in any way from or in connection with; the protocols or any use thereof. Where any statute implies any term, condition or warranty in connection with the provision or use of the protocols, and that statute prohibits the exclusion of that term, condition or warranty, then such term, condition or warranty is not excluded. To the extent permitted by law, the College's liability under or for breach of any such term, condition or warranty is limited to the resupply or replacement of services or goods.

Contents

Scope

This protocol contains standards and guidelines for the preparation of structured reports for colorectal cancer. It is not intended to apply to tumours of the appendix, small bowel and anus. Local excisions of colorectal carcinomas will be dealt with in a subsequent 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.

This document is based on information contained within multiple international publications and datasets and has been developed in consultation with local practising pathologists, oncologists, surgeons, radiologists and interested national bodies.

Abbreviations

AJCC	American Joint Committee on Cancer
CRC	colorectal cancer
CRM	circumferential resection margin
HNPCC	hereditary nonpolyposis colorectal cancer
IEL	intraepithelial lymphocytes
LIS	laboratory information system
MMRD	mismatch repair deficient
MSI	microsatellite instability
PBS	Pharmaceutical Benefits Scheme
R	residual tumour status
RCPA	Royal College of Pathologists of Australasia
TME	total mesorectal excision
TNM	tumour-node-metastasis
WHO	World Health Organization

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.

Ancillary study	An ancillary study is any pathology investigation that may form part of a cancer pathology report but is not part of routine histological assessment.
Clinical information	Patient information required to inform pathological assessment, usually provided with the specimen request form. Also referred to as 'pretest information'.
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 (eg 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 (eg 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 not essential for clinical management, staging or prognosis of a cancer, but are recommended. Guidelines include key observational and interpretative findings that are fundamental to the diagnosis and conclusion. 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 (eg G1.10).
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.
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 histo-morphological assessment.
Standard	Standards are mandatory, as indicated by the use of the term 'must'. Their use is reserved for core items essential for the clinical management, staging or prognosis of the cancer and key information (including observations and interpretation) which is fundamental to the diagnosis and conclusion. 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 (eg **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 pre-existing 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

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.[1] 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

Structured pathology reports with standardised definitions for each component have been shown to significantly improve the completeness and quality of data provided to clinicians, and have been recommended both in North America and the United Kingdom.[2-5]

Several studies have highlighted deficiencies in the content of colorectal cancer resection reports, including elements that are considered crucial for patient management.[6] Many studies have shown that adherence to a checklist for colorectal cancer reporting significantly improves the rate of inclusion of these crucial features.[2]

The College of American Pathologists and the Royal College of Pathologists (United Kingdom) have recently published useful protocols for the reporting of cancer.[7] These have been widely used in recent years in Australia and New Zealand, usually in modified formats to suit local requirements and preferences. A protocol endorsed by the Royal College of Pathologists of Australasia and other local organisations involved in the management of colorectal cancer is therefore needed. The authors have not attempted to 're-invent the wheel' but have borrowed freely from pre-existing publications. The intention is to provide pathologists with a minimum dataset and guidelines that are comprehensive, easy to use, and in keeping with local capacity and practice.

Design of this protocol

This protocol defines the relevant information to be assessed and recorded in a pathology report for colorectal cancer. Mandatory elements (standards) are differentiated from those that are not mandatory but are recommended (guidelines). Also, items suited to tick boxes are distinguished from more complex elements requiring free text or narrative. 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 representing information from this protocol, organised and formatted differently to suit their respectively different purposes.

It should be noted that if the resection specimen contains two or more primary carcinomas (as indicated by the term 'synchronous carcinomas' on the reporting checklist) then a separate reporting checklist must be completed for each primary carcinoma.

Key documentation

- Tumours of the colon and rectum. In: *Pathology and Genetics of Tumours of the Digestive System.* World Health Organization Classification of Tumours, 2011[8]
- *AJCC Cancer Staging Manual,* 7th edition, American Joint Committee on Cancer, 2010[9]
- *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols,* Royal College of Pathologists of Australasia, 2009[10]
- *The Pathology Request–Test–Report Cycle — Guidelines for Requesters and Pathology Providers,* Royal College of Pathologists of Australasia, 2004[11]
- *Minimum Dataset for Colorectal Cancer,* Cancer Council of NSW, 2007[12]

Changes since last edition

- Update to G4.02 to expand the context from just the reporting of KRAS mutation to the reporting of extended RAS testing. Commentary has been expanded. Checklist has been revised.

Authority and development

This section provides details of the committee involved in developing this protocol and the process by which it was developed.

This document is based on the *Minimum Dataset for Colorectal Cancer*, 1st Edition, June 2007[12] and was developed in collaboration with Dr Jill Farmer, the NSW Oncology Group for Colorectal Cancer and local pathologists.

Protocol developers

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

Expert committee

Associate Professor Robert Eckstein (Chair and lead author 1st edition), Pathologist

Conjoint Professor Stephen Ackland, Medical Oncologist

Dr Ian Brown (Chair and lead author 2nd and 3rd edition), Pathologist

Associate Professor David Ellis, Pathologist

Professor 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

Acknowledgements

The Colorectal expert committee wish to thank all the pathologists and clinicians who contributed to the discussion around this document.

Stakeholders

ACT Health
Anatomical Pathology Advisory Committee (APAC)
Australian Association of Pathology Practices Inc (AAPP)
Australian Cancer Network
Australian Commission on Safety and Quality in Health Care
Cancer Australia
Cancer Council ACT
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
Colorectal Cancer Research Consortium
Clinical Oncology Society of Australia (COSA)
Colorectal Surgical Society of Australia and New Zealand (CSSANZ)
Department of Health and Ageing
Grampians Integrated Cancer Services (GICS)
Health Informatics Society of Australia (HISA)
Independent Review Group of Pathologists
Medical Software Industry Association (MSIA)
National Breast and Ovarian Cancer Centre (NBOCC)
National E-Health Transition Authority (NEHTA)
National Pathology Accreditation Advisory Council (NPAAC)
National Round Table Working Party for Structured Pathology Reporting of Cancer.
New Zealand Guidelines Group (NZGG)
NSW Department of Health
NZ Ministry of Health
Peter MacCallum Cancer Institute
Public Pathology Australia
Queensland Cooperative Oncology Group (QCOG)
Representatives from laboratories specialising in anatomical pathology across Australia
Royal Australasian College of Physicians (RACP)
Southern Cancer Network, Christchurch, New Zealand
Southern Melbourne Integrated Cancer Service (SMICS)
Standards Australia
The Australasian Gastro-Intestinal Trials Group (AGITG)
The Medical Oncology Group of Australia
The Royal Australasian College of Surgeons (RACS)
The Royal Australian and New Zealand College of Radiologists (RANZCR)
The Royal Australian College of General Practitioners (RACGP)
The Royal College of Pathologists of Australasia (RCPA)
Victorian Cooperative Oncology Group (VCOG)
Western Australia Clinical Oncology Group (WACOG)

Secretariat

Meagan Judge, Royal College of Pathologists of Australasia

Development process

This protocol has been developed following the seven-step process set out in *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols*.[10]

Where no reference is provided, the authority is the consensus of the expert group.

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.[11] This document specifies the minimum information to be provided by the requesting clinician for any pathology test.

CS1.01b The patient's ethnicity must 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.

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 Medicare number (Australia), Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Identifier (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 atomically.

S1.03 The pathology accession number of the specimen must be recorded.

G1.01 Any clinical information received in other communications from the requestor or other clinician should be recorded together with the source of that information.

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.

Specimen imaging

- 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:** Specimens are best received fresh and without delay. The subsequent 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 vital for high quality pathology. 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.

    - **Specimen inspection:** The specimen needs to be thoroughly examined before opening and areas of possible serosal involvement, possible distant tumour deposits and possible lymph nodes deposits 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

colorectal 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 pre-operative 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.

  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 S2.03). However it is often useful to have normal tissue for control purposes and uninvolved margins can provide this.

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 non-peritonealised 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 non-peritonealised 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.

  - 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 non-peritonealised 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 specimen length must be recorded.

CS2.01a This and all other measurements in this protocol should be made in millimetres unless otherwise stated.

S2.02 The site of the tumour must be recorded.

CS2.02a 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 non-peritonealised (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.

CS2.02b 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[13] but it is generally agreed by surgeons that the rectum starts at the sacral promontory[14]. It was agreed by an international expert advisory committee[10] 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.

S2.03 The maximum tumour diameter must be recorded.

CS2.03a The prognostic significance of maximum tumour size is not established.[15-16]

CS2.03b Tumour size must be recorded for correlation with subsequent microscopic examination and to allow correlation with imaging

undertaken prior to surgery.

CS2.03c If possible, distinguish carcinoma from inflammatory changes, as the latter may account for a considerable volume of tumour in some cases.

S2.04 The distance of the tumour to the nearer proximal or distal 'cut end' margin must be recorded.

CS2.04a This is the measurement from the nearer cut end of the specimen and not the non-peritonealised (circumferential, radial) margin.

CS2.04b Tumour at a longitudinal margin has always been considered a poor prognostic feature but it occurs very rarely.[17-18] The necessity of sampling this margin has therefore been questioned.[19-21] 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.[21]

CS2.04c If included, doughnuts must be embedded for histological examination.

CS2.04d 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.

S2.05 The distance of the tumour to the circumferential margin must be recorded.

CS2.05a This is the measurement to the nonperitonealised (ie the circumferential or radial) margin.

CS2.05b This measurement is useful for comparison with and validation of the microscopic measurement.

CS2.05c 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.

CS2.05d This combined with the clinical and microscopic findings is used to define the R code status (see Chapter 5).

S2.06 The presence or absence of tumour perforation must be recorded.

CS2.06a Perforation through the tumour into the peritoneal cavity is a well established adverse prognostic factor in colonic[22] and rectal cancer.[23] It is suggested that a block be taken from the area of

perforation for histological confirmation. If perforation is present, then this is regarded as pT4 in the TNM staging system, regardless of other factors.[9]

CS2.06b 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).

CS2.06c It is important to distinguish, where possible, between perforation occurring at the time of surgery and perforation before surgery.

S2.07 For rectal tumours the relationship of the tumour to the anterior peritoneal reflection must be recorded (refer to Figure S2.07a).

CS2.07a 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.

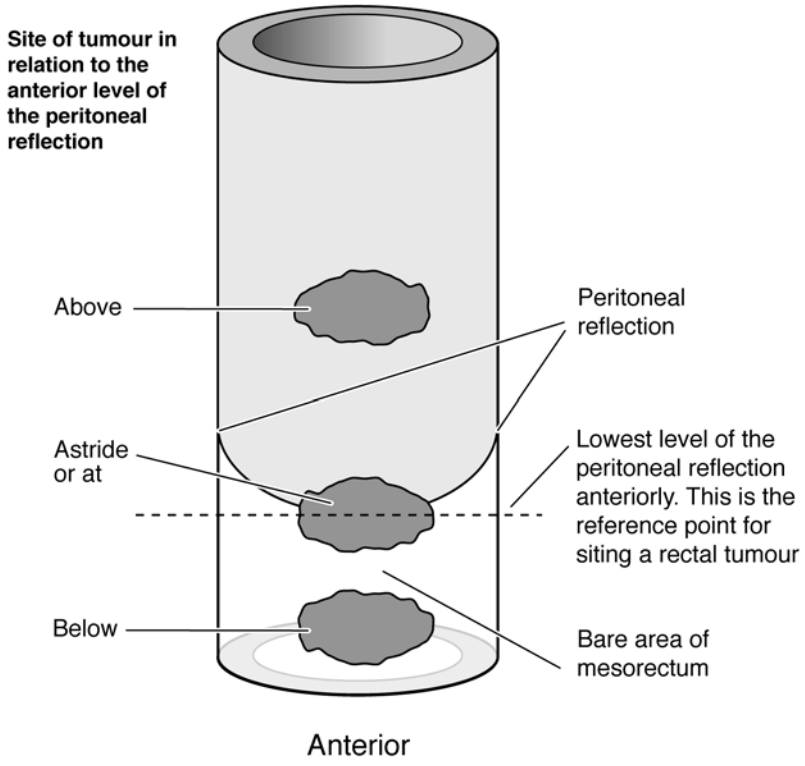


Figure S2.07a Site of tumour in relation to the anterior level of the peritoneal reflection

CS2.07b 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 S2.07b).

CS2.07c 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 S2.07b). Low rectal tumours will be completely surrounded by a non-peritonealised margin (the circumferential margin), while upper rectal tumours have a non-peritonealised margin posterolaterally and a peritonealised (serosal) surface anteriorly. Tumours below the peritoneal reflection have the highest rates of local recurrence.[23-26]

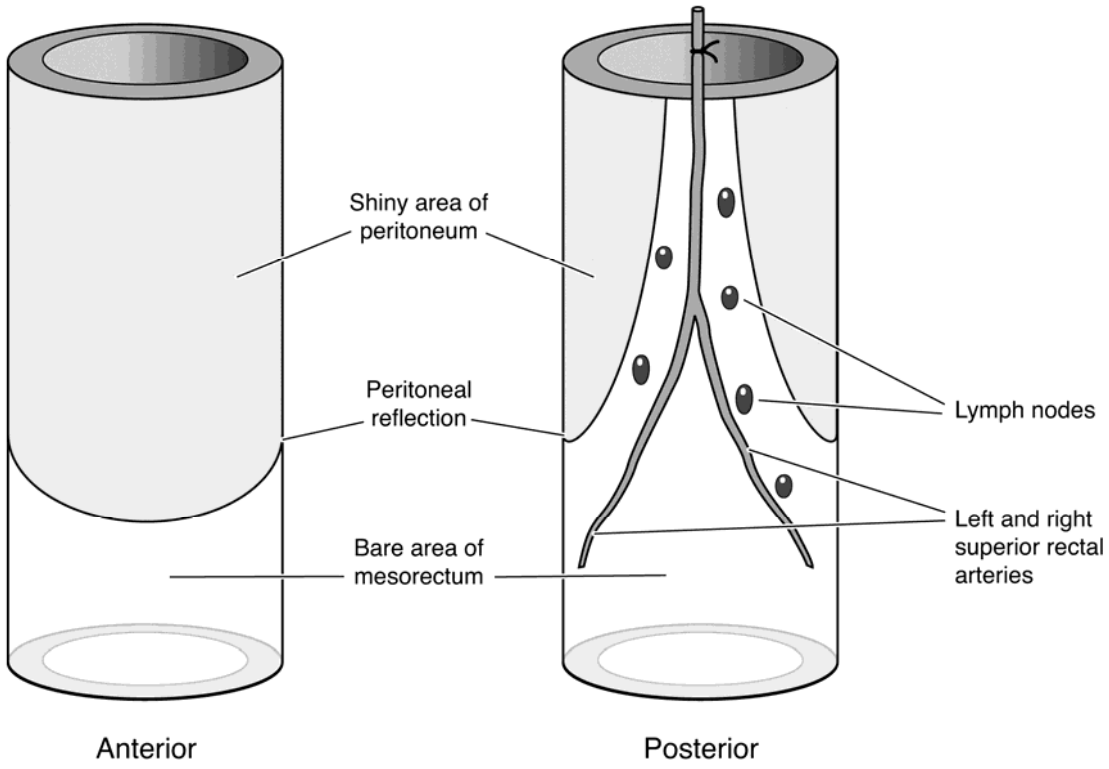


Figure S2.07b Site of non-peritonealised margin (bare area of mesorectum) in relation to the peritoneal reflection

S2.08 For rectal resections the intactness of the mesorectum must be recorded.

CS2.08a The prognosis of rectal carcinoma has significantly improved with the use of total mesorectal excision (TME). Gross pathological assessment of the intactness of the mesorectum has been shown to correlate with patient outcome.

CS2.08b The intactness of the specimen is recorded as one of the following:[27]

- **Incomplete:** little bulk to the rectum, defects in the mesorectum down to the muscularis propria, after transverse sectioning the circumferential margin appears very irregular.
- **Nearly complete:** moderate bulk to the mesorectum,

irregularity of the mesorectal surface with defects greater than 5 mm but none extending to the muscularis propria, no areas of visibility of the muscularis propria except at the insertion site of the levator ani muscles.

- **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, after circumferential sectioning the circumferential margin appears smooth.

- The intactness may be graded as follows:

  – Incomplete (grade 1)

  – Nearly complete (grade 2)

  – Complete (grade 3)

G2.01 Any involvement of the peritoneum should be recorded.

CG2.01a 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

CG2.01b Tumour involvement of the serosa discontinuous from the site of the main tumour is to be recorded as a metastasis.

G2.02 The number of lymph nodes placed in each cassette should be recorded.

CG2.02a The number of lymph nodes placed in each cassette should be recorded as a quality measure.

G2.03 The number, diameter and gross configuration of polyps should be summarised.

CG2.03a The pathologist should be cognisant of the presence of polyposis syndromes. These include:

- Familial Adenomatous Polyposis (FAP)

- Serrated

- MutYH

- Juvenile

- Peutz–Jeghers

CG2.03b At the present time the criteria for hyperplastic (serrated) polyposis syndrome:

1. At least five histologically confirmed hyperplastic (serrated) polyps proximal to the sigmoid colon, of which two are greater

than 1 cm in diameter

2. Any number of hyperplastic (serrated) polyps proximal to the sigmoid colon in a subject with a first-degree relative with hyperplastic polyposis

3. More than 20 hyperplastic (serrated) polyps of any size distributed evenly throughout the colon.[28-29]

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 dataset. 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).

CG2.03e 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.

S2.09 The nature and sites of all blocks must be recorded.

3 Microscopic findings

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

S3.01 The tumour type must be recorded.

CS3.01a The description must be based on the WHO *Histological Classification of Tumours of the Colon and Rectum* (refer to Appendix 4).[8] This publication, as well as a current version of the American Joint Commission on Cancer (AJCC) *Cancer Staging Manual*[9] should be readily accessible to the reporting pathologist.

CS3.01b Virtually all colorectal cancers are adenocarcinomas. The term 'Adenocarcinoma NOS' on the reporting checklist is used to indicate conventional adenocarcinoma without any of the special features of the tumour types listed below it.

CS3.01c For most tumours, histological type is not prognostically significant. Exceptions include tumour types that are, by definition, high grade (ie 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.[8] Note that well differentiated neuroendocrine (carcinoid) tumours are listed separately to carcinoma in the WHO histological classification.[8]

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

CS3.02a The practical difficulties of the application of grading criteria and the reproducibility of grading are widely recognised, and reflected in the commentary below.[30]

CS3.02b In the WHO histological classification,[8] grading is based on the percentage of tumour showing formation of gland-like structures:

- **Well differentiated** adenocarcinoma shows glandular structures in >95% of the tumour.
- **Moderately differentiated** adenocarcinoma show 50–95% glandular structures.
- **Poorly differentiated** adenocarcinoma show 0-49% glandular structures.

CS3.02c Medullary carcinoma needs to be recognised separately and not graded[31-32] Mucinous carcinomas are generally not graded, but there is recent evidence that grading has prognostic significance.[33] The 4th edition of the WHO suggests that mucinous carcinomas that are MSI-high should be regarded as low grade.[8]

CS3.02d Histological grade is a stage-independent prognostic factor.[24,34] Multiple grading systems with variation in the number of strata

within them have been suggested over the years. The distinction between well- and moderately differentiated adenocarcinoma (low grade) versus poorly differentiated or undifferentiated carcinoma (high grade) has been shown to be prognostically useful.[32] The terms well, moderately, poorly differentiated and undifferentiated are equivalent to Grades 1–4 in the TNM staging system.[35]

CS3.02e For the most part a pathological distinction between low-grade and high-grade carcinomas can be made with acceptable interobserver variability. Distinction between well and moderately differentiated carcinomas is less reproducible and associated with significant interobserver variability.[32] The majority of carcinomas are well or moderately differentiated, having a 'conventional' appearance, and should be placed in the low-grade category. Jass et al[31]defined 'well differentiated' as showing 'simple or complex tubules, easily discerned nuclear polarity, uniformity of nuclear size, and close resemblance to benign precursor lesion' and 'moderately differentiated' as showing 'less regular glandular differentiation and nuclear polarity poorly discerned or lost'. High-grade tumours are poorly differentiated or undifferentiated; Jass et al[31]described 'poorly differentiated' as showing 'highly irregular glands or loss of glandular differentiation and loss of nuclear polarity.'

CS3.02f Whether grading should be based on the predominant pattern of differentiation or the area of worst differentiation is controversial.[31,36] 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.[37]

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).

CS3.02g 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.

CS3.02h There is considerable attention being paid to the process of 'tumour budding' (ie dedifferentiation at the advancing margin of the carcinoma, giving rise to single tumour cells and small clusters of up to four cells). There is increasing evidence that this has adverse prognostic significance.[38] However, this is not yet sufficiently established or standardised to justify its inclusion as an item for routine reporting.

S3.03 The maximum degree of local invasion into or through the bowel wall must be recorded.

CS3.03a This is based on the T component of the TNM staging system, as outlined in the AJCC Cancer Staging Manual.[9]

Table CS3.03a **Pathological tumour (T) classification for colorectal cancer.** 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, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com.

pTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour
pTis	Carcinoma in-situ: intraepithelial or invasion of lamina propria
pT1	Tumour invades submucosa
pT2	Tumour invades muscularis propria
pT3	Tumour invades through muscularis propria into pericolorectal tissues
pT4a	Tumour penetrates to the surface of the visceral peritoneum
pT4b	Tumour directly invades or is adherent to other organs or structures

Comments on T stages:

- **pTis:** This category is included to help achieve a uniform staging system across all organ systems and represents either in situ carcinoma or carcinoma showing invasion of the lamina propria (intramucosal carcinoma). However, colorectal neoplasia has not been shown to have metastatic potential until it has invaded through the muscularis mucosae. Therefore, the term pTis is generally avoided in the colorectum and the term high grade dysplasia is preferred. pTis tumours should be regarded as adenomas and not as carcinomas for the purpose of diagnosis and cancer registration.

- **pT3:** Tumour invades through muscularis propria into pericolorectal tissues.
  pT3 indicates spread in continuity beyond the bowel wall. The microscopic presence of tumour cells confined within the lumen of lymph vessels or veins does not qualify as local spread in the T classification.[9] Occasionally cancer has spread as far as the outer edge of the muscularis propria but not beyond. If no muscle separates the cancer from the mesenteric tissue then the muscle coat should be interpreted as breached (pT3)[31] Whilst the subdivision of pT3 into T3a, b, c and d has been dispensed with in the current TNM staging, the subdivision has been shown to have prognostic significance as well as being useful in the planning of further therapy.[39-40] If desired, as an alternative, the distance of tumour invasion beyond the muscularis propria may be given as a measurement in

millimetres.

- **pT4:** Note the reversal of T4a and T4b that has occurred between the 6th and 7th editions of the AJCC cancer staging manual. T4b includes cases in which tumour is adherent to other organs or structures, and tumour cells are histologically demonstrated in the adhesions. Stage pT4b also includes direct invasion of other segments of the colorectum by way of the serosa; for example, invasion of sigmoid colon by a carcinoma of the caecum.[9,35,41] By contrast, intramural or longitudinal extension of tumour into an adjacent part of the bowel (eg extension of a caecal tumour into the terminal ileum) does not affect the pT stage. Stage pT4a indicates that tumour invades through serosa with tumour cells visualised on the serosal surface or free in the peritoneal cavity. The adverse prognostic significance of involvement of the serosal surface has been emphasised and this should be sought by careful microscopic examination.

  Recent studies and commentaries[42-43] have drawn attention to the fact that tumour near the serosa may in fact have breached the serosal elastic lamina but not appear on the surface of the colon as it elicits a fibroblastic reaction that forms a cap over the tumour. This finding appears to have adverse significance and tumours showing this feature may have the significance of a pT4a stage. An elastic tissue stain such as VVG or orcein can highlight invasion of the serosal elastic lamina and should be considered in all cases where tumour is close to the colon surface.

  Serosal involvement through direct continuity with the primary tumour (pT4) is recorded differently from peritoneal tumour deposits that are separate from the primary. These latter deposits are regarded as distant metastases (pM1). These peritoneal deposits may involve the surface of the colon away from the region of the tumour.

- Cases showing perforation through the tumour should be classified as pT4a, but not cases where perforation is at a site distant to the tumour.

S3.04 Involvement of the proximal or distal resection margins ('cut-end' margins) by tumour must be recorded. If the margin is less than 10 mm, the clearance must be recorded.

CS3.04a See commentary relating to this in Chapter 2 (Macroscopic findings S2.07).

S3.05 The status of the nonperitonealised circumferential margin in rectal tumours must be recorded.

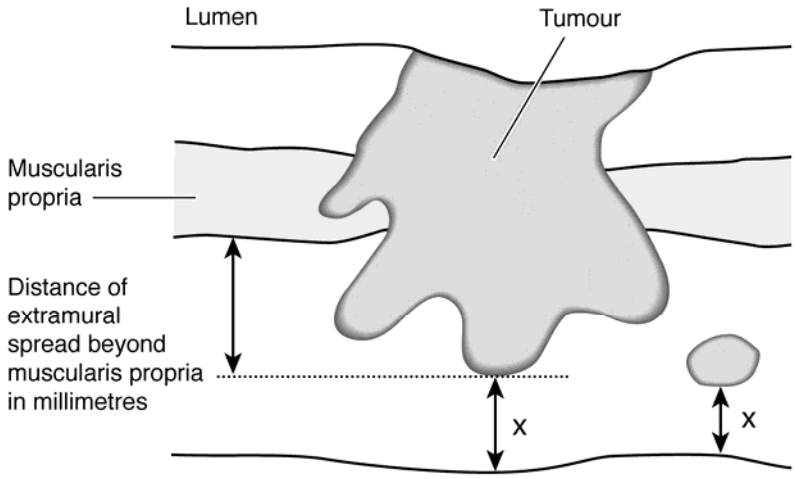
CS3.05a In rectal tumours, the minimum distance in millimetres between the tumour and the nonperitonealised (circumferential, radial) margin must be recorded from the histological slides.

CS3.05b Rectal tumours frequently (5–36%) involve the nonperitonealised surgical circumferential resection margin (CRM) and this is

associated with significantly higher rates of local recurrence and cancer-related death.[44-51]

CS3.05c 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.[52] The vast majority of studies, including clinical trials and population studies, have used a cutoff of 1 mm or less to define margin involvement.

CS3.05d 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 S3.05). All types of involvement confer a poor prognosis.[45,48]



x = minimum clearance in mm of primary tumour, extramural or nodal deposit or tumour in vessel etc, whichever is the closest.

Figure S3.05 Measurement of the distance of tumour to the circumferential resection margin (CRM)

CS3.05e Confusingly, the residual tumour status (R) used in the TNM staging system requires that tumour be identified at the actual resection margin for the margin to be considered involved.[35] Thus, in TNM staging if tumour is not actually seen at this margin it is coded as R0. Therefore, recording the distance between the tumour and the CRM will alert the clinician to those patients who may benefit from being treated as though they were margin positive.

S3.06 Results of lymph node histopathology must be recorded.

CS3.06a The finding of positive lymph nodes is a major determinant of whether the patient receives adjuvant therapy. The probability of finding a positive node increases with the number of nodes found.[53-54] Although this probability curve flattens out after finding

12–15 nodes[54], all identified lymph nodes must be microscopically examined. In general, a minimum of 10-12 lymph nodes should be identified and examined.[7 35]

CS3.06b The AJCC recommendations state that if the examined lymph nodes are negative, even if only a small number of nodes has been found, the case should nevertheless be classified as pN0 rather than pNX.[35]

CS3.06c 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.[35]

CS3.06d 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.[31-32]

CS3.06e 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.[55-57]

- The AJCC TNM 7th 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.[9] Optional designation as pN0(i+) may be used in this situation,[41]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.[31]

CS3.06f 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.[58]

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.[9]

G3.01 Involvement of the apical lymph node should be recorded, if required where staging systems additional to TNM staging are in use.

CG3.01a 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.[59]

S3.07 For all tumours, venous and small vessel invasion must be reported and its anatomic location specified as intramural or extramural.

CS3.07a Venous invasion by tumour has been repeatedly shown by multivariate[24,60-61] 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.[61-63] Similar disparate results have also been reported for lymphatic invasion.[63] 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 (eg extramural veins) were both considered strong determinants of prognostic impact.[32,64] 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.

CS3.07b Some groups have recommended that only extramural venous invasion be recorded,[21] while others have recommended that the site of any venous invasion should be recorded, along with its location, intra or extramural.[32] In one study, intramural and extramural vascular invasion were shown to have similar prognostic value.[22] It is recommended that extramural and intramural venous invasion be recorded separately.

CS3.07c 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.[65] Assessment should be concentrated at the invasive edge of the tumour. It is an observation of the Royal College of Pathologists colorectal reporting database that extramural venous invasion should be detected in at least 25% of colectomy specimens.[66]

CS3.07d 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.[67]

G3.02 Perineural invasion should be assessed using routine histology and reported.

CG3.02a 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.[68]

S3.08 The presence of histologically confirmed distant metastases and their site must be recorded.

CS3.08a Disease classifiable as distant metastasis may sometimes be present within the primary tumour resection specimen (eg a serosal or mesenteric or greater omental deposit that is distant from the primary tumour mass).

CS3.08b Metastatic deposits in lymph nodes distant from those surrounding the main tumour or its main artery in the specimen will usually be submitted separately by the surgeon. Metastatic deposits in lymph nodes distant from the tumour or its main artery (ie nonregional nodes) may be seen in extended colectomy specimens and are regarded as distant metastases (pM1).[41]

S3.09 The presence of any relevant coexistent pathological abnormalities in the bowel must be recorded.

CS3.09a The presence of polyps (type, number, and whether having the criteria of a polyposis syndrome), presence and type of chronic inflammatory bowel disease, with or without dysplasia, and any other clinically relevant pathology is important information that needs to be recorded.

S3.10 The microscopic residual tumour status must be recorded (ie the completeness of resection).

CS3.10a 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).

S3.11 The response of the tumour to neoadjuvant treatment must be recorded.

CS3.11a 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:[69]

- **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

CS3.11b 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.

CS3.11c 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.[41]

G3.03 Any additional relevant information should be recorded.

CG3.03a There must be a free text field so that the pathologist can add any essential information that is not addressed by the above points.

4 Ancillary studies 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.

G4.01 Immunohistochemistry tests should be performed to test mismatch repair deficiency status and the results recorded in the pathology report.

CG4.01a 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 mismatch repair deficient (MMRD). MMRD cancers occur either sporadically (~12% of all colorectal cancers, usually as a result of methylation of the MLH1 gene), or less commonly (~2%) associated with Lynch syndrome (hereditary nonpolyposis colorectal cancer or HNPCC syndrome) because of changes in the DNA sequence of the genes.

CG4.01b Immunohistochemical analysis of mismatch repair proteins is used to detect MMRD in colorectal cancer, with an absence of one or more of the mismatch repair proteins considered an abnormal result.[70-71] The absence should be a complete absence of nuclear staining of all the carcinomatous epithelium with unequivocal positive staining of the nuclei of non-neoplastic epithelium and intratumoral lymphocytes. As PMS2 is an obligate partner of MLH1 and MSH6 is an obligate partner of MSH2, it is adequate to screen for MMRD by using only MSH6 and PMS2 in the first instance. MLH1 and MSH2 can be studied subsequently if either MSH6 or PMS2 is absent.[72-73] This limited approach may not be adequate for archival tissue where the intensity of immunoreactions is often reduced.

CG4.01c Certain histological features suggest the presence of MMRD, including:

- increased tumour infiltrating lymphocytes
- medullary or micro-glandular morphology
- mucinous or signet ring cell morphology in 50% or more of the tumour.

Intraepithelial lymphocytes (IELs) are those that are in direct contact with tumour cells or are located directly between tumour cell clusters. Only a high density of lymphocytes (≥5 per high-powered field) (× 40 objective) should be considered significant. While the extent of lymphocytic infiltrates at the margins of the tumour (peritumoural lymphocytes) and the prominence of lymphoid follicles (Crohn's-like reaction) in adjacent tissues are also features of MMRD tumours, most studies have found the strongest correlation between IELs and MMRD.[74-75] IEL counts are not necessary if MMR deficiency status is to be assessed formally, by MMRD immunohistochemistry or microsatellite instability (MSI)

testing (see CG4.01d).

Medullary carcinomas have a strong association with MMRD, and both medullary and mucinous carcinomas with MMRD have been shown to have a more favourable prognosis. Most mucinous carcinomas however, are not MMRD and these tend to have a poorer prognosis. Thus the prognostic significance of a mucinous carcinoma diagnosis is uncertain without knowledge of MMRD status.

CG4.01d Tumours that show loss of MMR proteins are almost always characterised by MSI. Although microsatellite analysis, which involves the amplification and analysis of selected microsatellite loci within the genome of the tumour cells, is used less commonly in the diagnostic pathology setting, it continues to have a role in problematic cases.

CG4.01e The finding of MMRD and/or MSI is important in colorectal cancer for the following reasons:

- MMRD has been shown to be a favourable prognostic factor in colorectal cancer, in terms of both recurrence-free survival and overall survival.[74,76-77]
- There is increasing evidence to support the observations that MMRD tumours are less responsive to 5FU-based adjuvant chemotherapy[30,78-79] although this has not been shown conclusively in all studies.[58,80-81]
- In ~20% of cases with MMRD, this abnormality will be associated with underlying Lynch syndrome, which raises cancer issues for all family members.

CG4.01f For the purposes of detecting individuals with Lynch syndrome (HNPCC), MMR testing is currently recommended as the initial screening procedure. At a minimum all cases of colorectal cancer arising in individuals less than 50 years of age should be tested. In addition, all cases meeting the revised Bethesda guidelines (below) should be tested.

- patients with synchronous, metachronous colorectal, or other HNPCC-associated tumours regardless of age
- colorectal cancer with MSI-H histology in patients under age of 60
- colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under age 50 years
- colorectal cancer diagnosed in two or more first or second-degree relatives with HNPCC-related tumours, regardless of age

NB HNPCC-associated tumours include endometrial, gastric, ovarian, pancreatic, upper urinary tract, biliary, small bowel, and brain tumours, and sebaceous adenomas and keratoacanthomas in Muir-Torre syndrome.

It is increasingly recognised that many patients with Lynch syndrome fall outside of the Bethesda screening guidelines. This is mainly because as many as 50% of patients with Lynch syndrome develop their first colorectal carcinoma >50 years of

age.[82] and because a family history is often not evident. In view of this, at least some laboratories now perform routine testing of all colorectal carcinomas. There is also good data to support extending routine MMRD testing at least to a patient age of 70 years.[82]

MMRD staining can be performed on either biopsy or resection specimen material. Biopsy material has been shown to be as reliable as resection specimen material in detecting a defect in MMR expression.[83] Biopsy material has the added advantage of allowing preoperative decision making if Lynch syndrome is suspected.

The following situations deserve further commentary:

1) Lynch syndrome arising due to MSH6 deficiency typically occurs at a later age (median, 56 y) at diagnosis and is found in larger proportion (25%) of rectal cancers than the other MMRD enzymes. However, MMRD testing of rectal cancers post adjuvant chemo/radiotherapy will typically reveal a loss of MSH-6 staining which is an effect of the treatment and does not indicate underlying MMRD.[84] In post chemo/radiotherapy cases displaying MSH6 loss, it is advisable that the MMR stains are performed on the pre-treatment biopsy.

2) Recently it has been discovered that a subset of MSH2 deficiency related Lynch syndrome is due to an inherited epigenetic defect of EPCAM. While not routinely available at present, pathologists may be able to perform immunohistochemical testing for this protein in the future.[85]

3) Loss of expression of all mismatch repair markers ('null pattern')

    - Sporadic methylation of MLH-1 promotor region with secondary mutation related loss of MSH-2 can rarely occur.[86]

Pathologists should be aware that preservation of staining for MMR does not exclude Lynch syndrome since truncating mutations of MMR genes may produce a protein that is immunoreactive but non functional.[87] MSH6 gene defects may be particularly prone to this phenomonen.[88]

CG4.01g Testing for somatic mutations of the *BRAF* gene may be used in conjunction with MMRD tests as a surrogate indicator for Lynch syndrome. Mutations of the *BRAF* gene are rare in tumours arising from a Lynch syndrome background, yet are very common in MMRD tumours that occur sporadically because of methylation of MLH1.[61-64,67-68,70-71,74-75,80,89-90] As a consequence, when present, *BRAF* mutations can be useful in helping to distinguish between sporadic tumours arising through hypermethylation, and Lynch syndrome-associated tumours arising from a germline mutation. As the test results may indicate possible familial cancer cases, there are ethical implications that need to be taken into account before *BRAF* testing. Note: The usefulness of the BRAF V600E test is in tumours exhibiting loss of MLH1 expression – the presence of the mutation effectively excludes Lynch syndrome, whereas its absence is unhelpful (ie could be either sporadic or

familial). An immunohistochemical stain for detection of BRAF V600E has recently become commercially available and may supplant the need for PCR based testing.

G4.02 The result of extended RAS mutation testing should be recorded.

CG4.02a 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.

CG4.02b 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).[91-93] 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.

CG4.02c *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.

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).

S5.01 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* (7th Edition).[9]
(See Tables S5.01a and S5.01b below.)

Table S5.01a **AJCC/UICC colorectal cancer TNM classification.** 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, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com.

T classification	**Primary tumour**
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into pericolorectal tissues
T4a	Tumour penetrates to the surface of the visceral peritoneum
T4b	Tumour directly invades or is adherent to other organs or structures
N classification	**Regional lymph nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumour deposit(s) in the subserosa, mesentery, or nonperitonealised pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
M classification	**Distant metastasis**
M0	No distant metastasis

M1	Distant metastasis
M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

Table S5.01b **AJCC/UICC pathological stage grouping for colorectal cancer**[9] 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, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com.

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

CS5.01a The allocation of the TNM stage relies upon synthesis of information provided in the clinical request form and following macroscopic and microscopic examination.

CS5.01b The y prefix must be used if there has been prior chemotherapy or radiotherapy.

CS5.01c 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 (ie 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 year of publication and/or edition of the cancer staging system used in S5.01 must be included in the report.

S5.03 The residual tumour status must be recorded according to the AJCC *Cancer Staging Manual* (7th Edition)[9]

CS5.03a 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, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com.)

- R0: Complete resection, margins histologically negative, no residual tumour left after resection (primary tumour, regional nodes)
- R1: Incomplete resection, margins histologically involved, microscopic tumour remains after resection of gross disease (primary tumour, regional nodes)
- R2: Incomplete resection, margins macroscopically involved or gross disease remains after subtotal resection (eg primary tumour, regional nodes, or liver metastasis).

CS5.03b Residual tumour classification (R status) is not limited to the primary tumour. The R classification not only considers locoregional residual tumour, but also distant residual tumour in the form of unresected or incompletely resected metastases (R2)[94] For example, a metastasis in the liver from a primary colorectal carcinoma would be M1 and R0 if the metastasis was solitary and resected with tumour-free margins. This case would be M1 and R2 if the metastasis was not resected.

CS5.03c The resection status rule also applies to lymph nodes. If a positive lymph node is left behind it is classified as R2.

CS5.03d Tumour cells that are confined to the lumen of blood vessels or lymphatics at the resection margin are classified as R0.[94]

CS5.03e Peritoneal involvement alone is not a reason to categorise the tumour as incompletely excised.

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

a. specimen type (S1.02)
b. tumour site (S2.02)
c. tumour type (S3.01)
d. tumour stage (S5.01)
e. completeness of excision (S5.03).

S5.04 Record if this is a new primary cancer or a recurrence of a previous cancer, if known.

CS5.04a 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 metastasis 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.

CS5.04b 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.

S5.05 A field for free text or narrative in which the reporting pathologist can give overarching case comment must be provided.

CS5.05a 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.

CS5.05b Use of this field is at the discretion of the reporting pathologist.

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 laboratory information system (LIS) capabilities and as described in *Functional Requirements for Structured Pathology Reporting of Cancer* Protocols.{Royal College of Pathologists of Australasia, 2011 #790}

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.

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.

Values in italics are conditional on previous responses.

Values in all caps are headings with sub values.

S/G	Item description	Response type	Conditional
Pre-analytic			
S1.01	**Demographic information provided**		
S1.02	**Clinical information provided on request form**	**Text** OR **Structured entry as below:**	
	Operating surgeon name & contact details	**Text**	
	Perforation	**Single selection value list:** • Absent • Present	**If present, record the nature of perforation**
	Nature of perforation	***Multi select value list (select all that apply):*** • *Through tumour prior to surgery* • *Through tumour during surgery mobilisation* • *Away from tumour*	

S/G	Item description	Response type	Conditional
	Clinical obstruction	**Single selection value list:** • Absent • Present	
	Tumour location	**Single selection value list:** • Caecum • Ascending colon • Hepatic flexure • Transverse colon • Splenic flexure • Descending colon • Sigmoid colon • Rectosigmoid junction • Rectum	
	For synchronous tumours indicate each other site	**Text** Note: Synchronous tumours should be reported separately – this serves only to identify the presence of other synchronous tumours for which separate reports will be submitted.	
	Distance from the anal verge	***Numeric: ___cm*** *Note: Measured in cm by longstanding surgical convention*	***Conditional on rectum being selected***

S/G	Item description	Response type	Conditional
	Type of operation	**Single selection value list:** • Right hemicolectomy • Extended right hemicolectomy • Transverse colectomy • Left hemicolectomy • Anterior resection • Abdominoperineal resection • Proctocolectomy • Total colectomy with ileorectal anastomosis • Hartmann's procedure • Other procedure(s)	**If other procedure(s) is selected, record type of procedure.** **If anterior resection is selected, record anterior resection type.**
	Type of procedure	***Text***	
	Anterior resection type	***Single selection value list:*** • *High* • *Low* • *Ultralow*	
	Pre-operative radiotherapy	**Single selection value list:** • No • Yes	**If yes, record type of course**

S/G	Item description	Response type	Conditional
	Type of course	***Single selection value list:*** • *Short course* • *Long course*	
	Surgeon's opinion on the existence of local residual cancer postsurgery	**Text**	
	Involvement of adjacent organs	**Text**	
	New primary cancer or recurrence	**Single selection value list:** • New primary • Regional (local) recurrence • Distant metastases	**If regional (local) recurrence or distant metastasis describe.**
	Describe	***Text***	
S1.03	**Pathology accession number**	**Alpha-numeric**	
G1.01	Other relevant details	**Text**	
Macroscopic findings			
S2.01	**Specimen length**	**Numeric:___mm**	

S/G	Item description	Response type	Conditional
S2.02	**Tumour site**	**Single selection value list:** • Caecum • Ascending colon • Hepatic flexure • Transverse colon • Splenic flexure • Descending colon • Sigmoid colon • Rectosigmoid junction • Rectum	
S2.03	**Maximum tumour diameter**	**Numeric: ___mm**	
S2.04	**Distance of tumour to the nearer proximal or distal 'cut end'**	**Numeric: ___mm**	
S2.05	**Distance of tumour to the nonperitonealised circumferential margin**	**Numeric: ___mm**	
S2.06	**Tumour perforation**	**Single selection value list:** • Absent • Present	

S/G	Item description	Response type	Conditional
S2.07	***Relationship to anterior peritoneal reflection***	***Single selection value list:*** • *Entirely above* • *Astride* • *Entirely below*	***Conditional on rectum being selected in S2.02***
S2.08	***Intactness of mesorectum***	***Single selection value list:*** • *Incomplete (grade 1)* • *Nearly complete (grade 2)* • *Complete (grade 3)*	***Conditional on rectum being selected in S2.02***
G2.01	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	
G2.02	Lymph nodes	**Single selection value list:** • Not received • Received	***If received, record the number of nodes***
	Number of lymph nodes per cassette	***Numeric: ___ in cassette: ___*** <u>Note</u>: *repeat for each cassette with lymph nodes.*	
G2.03	Polyps	**Single selection value list:** • Absent • Present	***If present, provide a polyp summary.***

S/G	Item description	Response type	Conditional
	Polyp summary	***Text*** *<u>Note</u>: the polyp summary should include the numbers, diameter range and gross appearance*	
G2.04	Other macroscopic comments	**Text**	
S2.09	**Nature and site of blocks**	**Text**	
Microscopic findings			
S3.01	**Tumour type**	**Single selection value list from WHO Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System (2010).**	
S3.02	**Histological grade**	**Single selection value list:** • Low grade – well and moderately differentiated • High grade - poorly and undifferentiated	

S/G	Item description	Response type	Conditional
S3.03	**Maximum degree of local invasion into or through the bowel wall**	**Single selection value list:** • pT1 Tumour invades submucosa • pT2 Tumour invades muscularis propria • pT3 Tumour invades through muscularis propria into pericolorectal tissues • pT4a Tumour penetrates to the surface of the visceral peritoneum • pT4b Tumour directly invades or is adherent to other organs or structures	
S3.04	**Involvement of the proximal or distal resection ('cut-end') margins**	**Single selection value list:** • Not involved • Involved	**If involved is selected, record involved margin(s)** **If not involved is selected, record microscopic clearance.**
	Involved margin(s)	***Multi select value list (select all that apply):*** • *Distal* • *Proximal*	
	Microscopic clearance	***Numeric: ___mm*** (if the margin is less than 10 mm) ***OR Clearance is ≥10mm***	

S/G	Item description	Response type	Conditional
S3.05	***Status of the nonperitonealised circumferential margin (rectal tumours)***	**Single selection value list:** • Not involved • Involved	***Conditional on rectum being selected in S2.02*** ***If not involved is selected, record microscopic clearance.***
	Microscopic clearance	***Numeric: ___mm***	
S3.06	***Lymph node involvement***	***Single selection value list:*** • *Absent* • *Present*	***Conditional on nodes being received in G2.02. If G2.02 has been recorded as "not received" this standard is not required.*** ***If present, record site(s) and number of lymph nodes***
	Site(s) and numbers of lymph nodes	***Text:*** *Site of lymph node* ***AND*** ***Numeric: _____/_____*** *(Number of positive nodes/ Total number of nodes from this site)* *Notes:* *Site is the LN drainage relevant to the site of tumour being reported.*	

S/G	Item description	Response type	Conditional
	Isolated extra-mural tumour deposits	**Single selection value list:** • Absent • Present	
G3.01	Apical node involvement	**Single selection value list:** • Not applicable • Absent • Present	
S3.07	**VENOUS AND SMALL VESSEL INVASION**		
	Intramural vein invasion	**Single selection value list:** • Not identified • Present	
	Extramural vein invasion	**Single selection value list:** • Not identified • Present	
	Small vessel invasion	**Single selection value list:** • Not identified • Present • Present and extensive	

S/G	Item description	Response type	Conditional
G3.02	Perineural invasion	**Single selection value list:** • Not identified • Present • Present and extensive	
S3.08	**Histologically confirmed distant metastases**	**Single selection value list:** • Absent • Present	**If present, record sites**
	Site(s)	***Text***	
S3.09	**Relevant coexistent pathological abnormalities**	**Multi select value list (select all that apply):** • None noted • Polyps • Ulcerative colitis • Crohn's disease • Other	**If Polyps is selected provide details** **If Ulcerative colitis or Crohn's disease is selected record dysplasia** **If other is selected, provide details in "other abnormality"**
	Polyp details (type, number, polyposis syndrome criteria met etc)	***Text***	
	Dysplasia	**Single selection value list:** • With dysplasia • Without dysplasia	
	Other abnormality	***Text***	

S/G	Item description	Response type	Conditional
S3.10	**Microscopic residual tumour status (completeness of resection)**	**Text**	
S3.11	**Response to neoadjuvant therapy**	**Single selection value list:** • **No prior treatment** • **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.	
G3.03	Microscopic comments	**Text**	
Ancillary test findings			
G4.01	MISMATCH REPAIR ENZYMES		
	MLH-1	**Single selection value list:** • Not tested • Normal staining • Loss of staining	

S/G	Item description	Response type	Conditional
	PMS-2	**Single selection value list:** • Not tested • Normal staining • Loss of staining	
	MSH-2	**Single selection value list:** • Not tested • Normal staining • Loss of staining	
	MSH-6	**Single selection value list:** • Not tested • Normal staining • Loss of staining	
	Comments	**Text**	
	Microsatellite instability (MSI)	**Single selection value list:** • Unstable • Stable • Not tested	**If unstable or stable, record laboratory performing test and report number**
	Comments	**Text**	
	Laboratory performing test and report number	***Text***	

S/G	Item description	Response type	Conditional
	BRAF (V600E mutation)	**Single selection value list:** • Mutated • Wild type • Not tested	**If mutated or wild type, record laboratory performing test and report number**
	Comments	**Text**	
	Laboratory performing test and report number	***Text***	
G4.02	*RAS* gene mutation testing *(KRAS exons 2,3,or 4, NRAS exons 2,3 or 4 or RAS mutation)*	**Single selection value list:** • Mutated • Wild type • Not tested	**If mutated or wild type, record laboratory performing test and report number**
	Comments	**Text**	
	Laboratory performing test and report number	***Text***	
Synthesis and overview			
S5.01	**TUMOUR STAGE**		
	T	**Single selection value list:** TX Primary tumour cannot be assessed T0 No evidence of primary tumour Tis Carcinoma in situ: intraepithelial or invasion of lamina propria T1 Tumour invades submucosa	

S/G	Item description	Response type	Conditional
		T2 Tumour invades muscularis propria T3 Tumour invades through the muscularis propria into pericolorectal tissues T4a Tumour penetrates to the surface of the visceral peritoneum T4b Tumour directly invades or is adherent to other organs or structures	
	N	**Single selection value list:** NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Metastasis in 1-3 regional lymph nodes N1a Metastasis in one regional lymph node N1b Metastasis in 2-3 regional lymph nodes N1c Tumour deposit(s) in the subserosa, mesentery, or nonperitonealised pericolic or perirectal tissues without regional nodal metastasis N2 Metastasis in 4 or more regional lymph nodes N2a Metastasis in 4-6 regional lymph nodes N2b Metastasis in 7 or more regional lymph nodes	

S/G	Item description	Response type	Conditional
	M	**Single selection value list:** M0 No distant metastasis M1 Distant metastasis M1a Metastasis confined to one organ or site (e.g. liver, lung, ovary, nonregional node) M1b Metastases in more than one organ/site or the peritoneum	
	Stage grouping	**Single selection value list:** **Stage** **T** **N** **M** 0 Tis N0 M0 I T1 N0 M0 T2 N0 M0 IIA T3 N0 M0 IIB T4a N0 M0 IIC T4b N0 M0 IIIA T1-T2 N1/N1c M0 T1 N2a M0 IIIB T3-T4a N1/N1c M0 T2-T3 N2a M0 T1-T2 N2b M0 IIIC T4a N2a M0 T3-T4a N2b M0 T4b N1-N2 M0 IVA Any T Any N M1a IVB Any T Any N M1b	

S/G	Item description	Response type	Conditional
S5.02	**Year and/or edition of staging system**	**Numeric:** year **AND/OR** **Text:** Edition eg 1st, 2nd etc	
S5.03	**Residual tumour status**	**Single selection value list:** R0: Complete resection, margins histologically negative, no residual tumour left after resection (primary tumour, regional nodes) R1: Incomplete resection, margins histologically involved, microscopic tumour remains after resection of gross disease (primary tumour, regional nodes) R2: Incomplete resection, margins macroscopically involved or gross disease remains after subtotal resection (eg primary tumour, regional nodes, or liver metastasis).	
G5.01	Diagnostic summary Include: a. specimen type b. tumour site c. tumour type d. tumour stage e. completeness of excision	**Text**	

S/G	Item description	Response type	Conditional
S5.04	**New primary cancer or recurrence**	**Single selection value list:** • New primary • Regional (local) recurrence • Distant metastases • Indeterminate	**If regional (local) recurrence or distant metastasis describe.**
	Describe	***Text***	
S5.05	**Overarching comment**	**Text**	

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.

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 should 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

- **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 location should be recorded.**
  - Choose from one of the following:
    - caecum
    - ascending colon
    - hepatic flexure
    - transverse colon
    - splenic flexure
    - descending colon
    - sigmoid colon
    - rectosigmoid junction
    - rectum.
  - 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.
- **The type of operation performed should be recorded.**
  - Choose from one of the following:
    - right hemicolectomy
    - extended right hemicolectomy
    - transverse colectomy
    - left hemicolectomy
    - anterior resection (specify whether high, low or ultralow)
    - abdominoperineal resection
    - proctocolectomy
    - total colectomy with ileorectal anastomosis
    - Hartmann's procedure
    - other (specify).
- **If pre-operative radiotherapy has been administered, this should be recorded.**

- In general, this applies to rectal cancer only. Pre-operative 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 (ie 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.

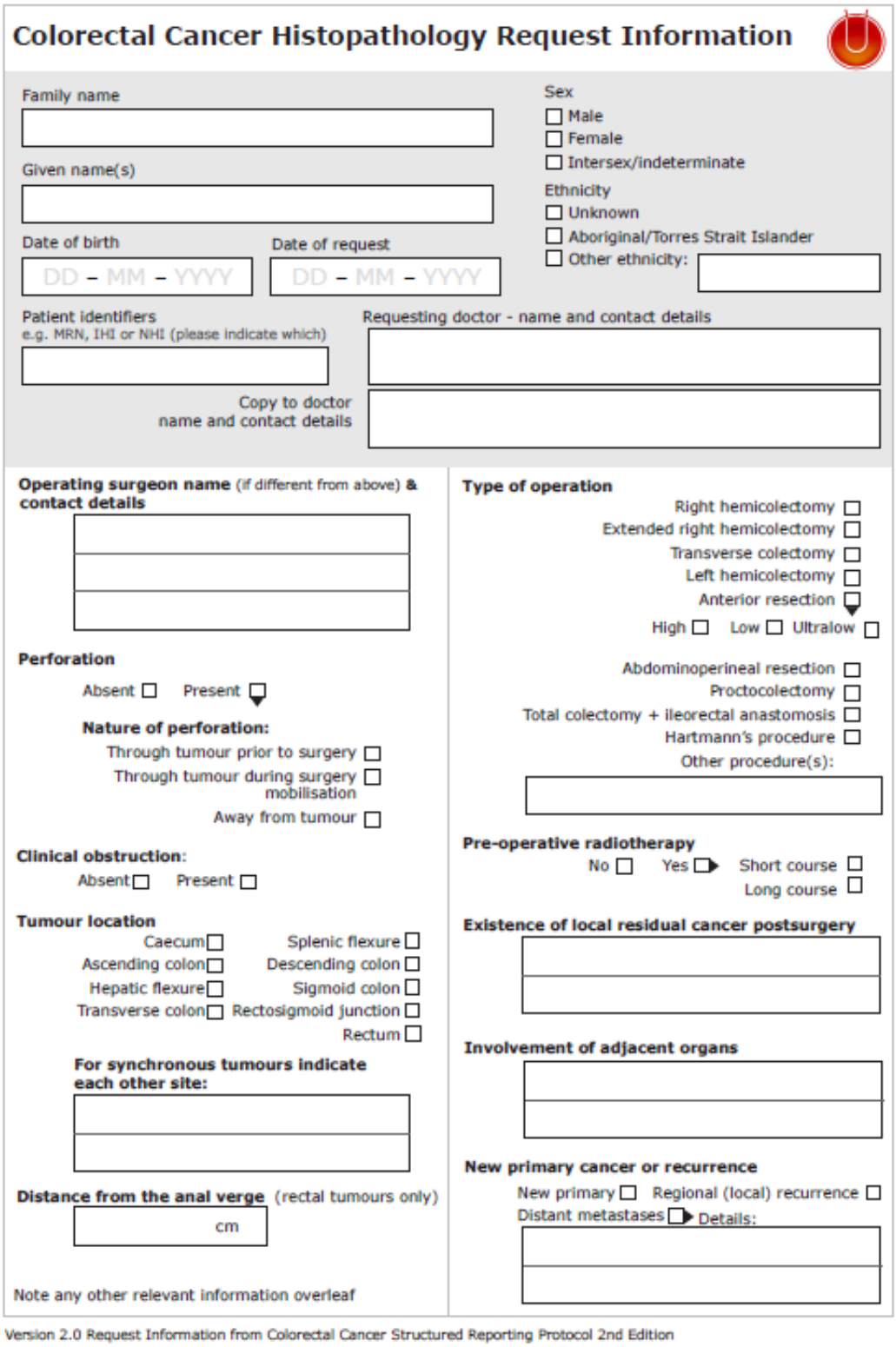
- The reporting of metastatic deposits, either resected or not resected, is required for assessment of the metastatic (M) stage of the tumour.

- 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.

Example Request Information Sheet



Colorectal Cancer Histopathology Request Information

Family name

Given name(s)

Date of birth DD – MM – YYYY

Date of request DD – MM – YYYY

Sex
- Male
- Female
- Intersex/indeterminate

Ethnicity
- Unknown
- Aboriginal/Torres Strait Islander
- Other ethnicity:

Patient identifiers
e.g. MRN, IHI or NHI (please indicate which)

Requesting doctor - name and contact details

Copy to doctor name and contact details

Operating surgeon name (if different from above) **& contact details**

Perforation

Absent ☐ Present ☐

Nature of perforation:
- Through tumour prior to surgery ☐
- Through tumour during surgery mobilisation ☐
- Away from tumour ☐

Clinical obstruction:

Absent ☐ Present ☐

Tumour location
- Caecum ☐
- Ascending colon ☐
- Hepatic flexure ☐
- Transverse colon ☐
- Splenic flexure ☐
- Descending colon ☐
- Sigmoid colon ☐
- Rectosigmoid junction ☐
- Rectum ☐

For synchronous tumours indicate each other site:

Distance from the anal verge (rectal tumours only)

cm

Note any other relevant information overleaf

Type of operation
- Right hemicolectomy ☐
- Extended right hemicolectomy ☐
- Transverse colectomy ☐
- Left hemicolectomy ☐
- Anterior resection ☐
  - High ☐ Low ☐ Ultralow ☐
- Abdominoperineal resection ☐
- Proctocolectomy ☐
- Total colectomy + ileorectal anastomosis ☐
- Hartmann's procedure ☐
- Other procedure(s):

Pre-operative radiotherapy

No ☐ Yes ☐ Short course ☐ Long course ☐

Existence of local residual cancer postsurgery

Involvement of adjacent organs

New primary cancer or recurrence

New primary ☐ Regional (local) recurrence ☐
Distant metastases ☐ Details:

Version 2.0 Request Information from Colorectal Cancer Structured Reporting Protocol 2nd Edition

The above Request Information Sheet is published to the RCPA website.

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 like data elements under headings and using 'white space' assists in rapid transfer of information.[95]

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.[95]
- Reduce 'clutter' to a minimum.[95] Thus, information that is not part of the protocol (eg billing information or Snomed codes) should not appear on the reports or should be minimised.
- Reduce the use of formatting elements (eg 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

Citizen, George W.
C/O Paradise Close
Nar Nar Goon East, 3181
Tasmania

Male

DOB 1/7/1964
MRN FMC1096785

Lab Ref: **11/P28460**
Referred: 30/2/2011

Copy to: Dr G. Gleason
Rainforest Cancer Centre.
46 Smith Road,
Woop Woop, 3478

Referred by: Dr V. Smith
Suite 3, AJC Medical Centre,
Bunyip Crescent
Nar Nar Goon East, 3182

COLORECTAL CANCER STRUCTURED REPORT

Diagnostic Summary

Low anterior resection:

Rectal adenocarcinoma, excision complete, ypT3,pN1b,cM0, Stage IIIB.

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

Supporting Information

CLINICAL

Perforation	Absent
Clinical obstruction	Absent
Tumour location:	Rectum, 6cm from anal verge
Pre-operative radiotherapy:	Yes. Short course
Residual cancer postsurgery:	None noted
Involvement of adjacent organs:	None noted
New primary cancer or recurrence:	New primary. No metastatic lesions

MACROSCOPIC

Tissue banking:	No
Specimen images:	Yes
Specimen length:	130mm
Tumour site:	Rectum
Anterior peritoneal reflection:	Astride
Tumour perforation:	Absent
Intactness of mesorectal:	Complete (grade 3)
Maximum tumour diameter:	50mm
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.
Distance from margins:	
Proximal-	20mm
Distal-	15mm
Circumferential-	15mm
Lymph nodes:	Received 3 in cassette 1 4 in cassette 2 7 in cassette 3
Polyps:	Present. Two 5mm polyps are noted.

Macroscopic comments:	Tumour appears ulcerated and scarred. Overlying serosa appears normal. Extramuscular spread to 15mm
Nature and site of blocks:	Blocks 1 to 6: tumour. Block 7: distal margin. Blocks 8 & 9 : circumferential margin. Blocks 10 to 16: 14 lymph nodes (2 in each block).

MICROSCOPIC

Tumour type (WHO):	Adenocarcinoma
Histological grade:	Low grade – well differentiated and moderately differentiated
Depth of invasion:	pT3 Tumour invades through muscularis propria into pericolorectal tissues
Small vessel invasion:	Not identified
Intramural vein invasion:	Present
Extramural vein invasion:	Not identified
Perineural invasion:	Not identified
Margins:	Not involved
Proximal -	Microscopic clearance is >10mm
Distal -	9mm
Circumferential -	13mm
Lymph node involvement:	Present
Number positive:	Perirectal LN basin: 2/14
Isolated extra-mural deposits:	Absent
Apical node involvement:	Absent
Distant metastases:	Absent
Coexisting abnormalities:	Polyps
Polyp details:	Two tubular adenomata confirmed.
Completeness of resection:	Complete resection
Response to Rx:	Grade 2 (minimal response) Residual cancer outgrown by fibrosis
Microscopic comment:	The submucosal nodule 20mm from the distal margin is a well differentiated carcinoid tumour, completely excised.

ANCILLARY STUDIES	Immunohistochemistry for mismatch repair gene products: staining of carcinoma cells for MLH-1, PMS-2, MSH-2 and MSH-6 is present.

SYNTHESIS

Tumour stage (AJCC 7th edition):	ypT3, pN1b, cM0
Stage group:	IIIB
Residual tumour status :	0
New primary cancer or recurrence:	New primary
Comment:	Mismatch repair gene deficiency is not identified.

Reported by Dr Robert Beckstein Authorised 4 /3/2011

Appendix 4 WHO Classification[a] of tumours of the colon and rectum 4th edition.

Epithelial tumors	
Premalignant lesions	
Adenoma, NOS	8140/0
Tubular adenoma, NOS	8211/0
Villous adenoma, NOS	8261/0
Tubulovillous adenoma, NOS	8263/0
Glandular intraepithelial neoplasia, low grade	8148/0
Glandular intraepithelial neoplasia, high grade	8148/2
Serrated lesions	
Sessile serrated adenoma/polyp	8213/0
Serrated polyposis	8213/0
Traditional serrated adenoma	8213/0
Carcinomas	
Adenocarcinoma, NOS	8140/3
Cribriform comedo-type adenocarcinoma	8201/3
Medullary carcinoma, NOS	8510/3
Micropapillary carcinoma	8265/3
Colloid carcinoma	8480/3
Serrated adenocarcinoma	8213/3
Signet ring cell carcinoma	8490/3
Adenosquamous carcinoma	8560/3
Spindle cell carcinoma, NOS	8032/3
Squamous cell carcinoma, NOS	8070/3
Undifferentiated carcinoma	8020/3
Neuroendocrine neoplasms	
Neuroendocrine tumor G1 (NET G1) / Carcinoid	8240/3
Neuroendocrine tumor G2 (NET G2)	8249/3
Neuroendocrine carcinoma, NOS	8246/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3
Mixed adenoneuroendocrine carcinoma	8244/3
Enterochromaffin cell (EC), serotonin-producing neuroendocrine tumour (NET)	8241/3
L cell, Glucagon-like peptide-producing and PP/PYY-producing NETs	8152/1
Mesenchymal tumors	
Leiomyoma, NOS	8890/0
Lipoma, NOS	8850/0
Angiosarcoma	9120/3
Gastrointestinal stromal tumor, malignant	8936/3
Kaposi sarcoma	9140/3
Leiomyosarcoma, NOS	8890/3
Schwannoma, NOS	9560/0
Perineurioma, NOS	9571/0
Ganglioneuroma	9490/0
Granular cell tumor, NOS	9580/0

Malignant lymphomas

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
Mantle cell lymphoma	9673/3
Diffuse large B-cell lymphoma (DLBCL), NOS	9680/3
Burkitt lymphoma, NOS	9687/3
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma	9680/3

References

1 AIHW (Australian Institute of Health and Welfare) and AACR (Australasian Association of Cancer Registries) (2004). *Cancer in Australia 2001*. Cancer Series No.28 (AIHW cat. no. CAN 23). AIHW, Canberra.

2 Cross SS, Feeley KM and Angel CA (1998). The effect of four interventions on the informational content of histopathology reports of resected colorectal carcinomas. *J Clin Oncol* 51(6):481–482.

3 Mathers M, Shrimankar J, Scott D, Charlton F, Griffith C and Angus B (2001). The use of a standard proforma in breast cancer reporting. *J Clin Pathol* 54(10):809–811.

4 Srigley JR, McGowan T, MacLean A, Raby M, Ross J, Kramer S and Sawka C (2009). Standardized synoptic cancer pathology reporting: A population-based approach. *J Surg Oncol* 99(8):517–524.

5 Gill AJ, Johns AL, Eckstein R, Samra JS, Kaufman A, Chang DK, Merrett ND, Cosman PH, Smith RC, Biankin AV and Kench JG (2009). Synoptic reporting improves histopathological assessment of pancreatic resection specimens. *Pathology* 41(2):161–167.

6 Bull AD, Biffin AH, Mella J, Radcliffe AG, Stamatakis JD, Steele RJ and Williams GT (1997). Colorectal cancer pathology reporting: a regional audit. *Journal of Clinical Pathology* 50(2):138–142.

7 RCP (Royal College of Pathologists) (2007). *Standards and Datasets for Reporting Cancers — Dataset for Colorectal Cancer*. RCP, London.

8 WHO (World Health Organization) (2010). *Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System (4th edition)*. Bosman FT, Carneiro F, Hruban RH and Theise ND. IARC Press, Lyon.

9 Edge SE, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A (eds) (2010). *AJCC Cancer Staging Manual 7th ed.*, New York, NY.: Springer.

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

11 RCPA (Royal College of Pathologists of Australasia) (2004). *Chain of Information Custody for the Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers*. RCPA, Surry Hills, NSW.

12 Farmer J, Hicks S, Ward R and Hawkins N (2007). *Minimum Dataset for Colorectal Cancer*. Cancer Council NSW, Sydney.

13 Williams P and Warwick R (eds) (1980). *Gray's Anatomy*, Churchill Livingstone, London, England.

14 UKCCCR (United Kingdom Coordinating Committee on Cancer Research) (ed) (1989). *Handbook for the Clinicopathological Assessment and Staging of Colorectal Cancer*, UKCCCR, London.

15 Miller W, Ota D, Giacco G, Guinee V, Irimura T, Nicolson G and Cleary K (1985). Absence of a relationship of size of primary colon carcinoma with metastasis and survival. *Clinical & Experimental Metastasis* 3(3):189–196.

16 Morris M, Platell C, de Boer B, McCaul K and Iacopetta B (2006). Population-based study of prognostic factors in stage II colonic cancer. *British Journal of Surgery* 93(7):866–871.

17 Guillou PJ, Quirke P, Bosanquet N, Smith A, Thorpe H, Walker J, Bell SE and Brown JM (2003). The MRC CLASICC trial: results of short term endpoints. *British Journal of Cancer* 88(Suppl. 1):S11–S24.

18 Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AMH, Heath RM and Brown JM (2005). Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 365(9472):1718–1726.

19 Compton CC (2003). Colorectal carcinoma: diagnostic, prognostic, and molecular features. *Modern Pathology* 16(4):376–388.

20 Cross SS, Bull AD and Smith JH (1989). Is there any justification for the routine examination of bowel resection margins in colorectal adenocarcinoma? *J Clin Pathol* 42(10):1040–1042.

21 Royal College of Pathologists Working Group on Cancer Services (1998). *UK Guidelines. Minimum data set for colorectal cancer histopathology reports*, Royal College of Pathologists, London.

22 Petersen VC, Baxter KJ, Love SB and Shepherd NA (2002). Identification of objective pathological prognostic determinants and models of prognosis in Dukes' B colon cancer. *Gut* 51(1):65–69.

23 Nagtegaal ID, van de Velde CJ, Marijnen CA, van Krieken JH and Quirke P (2005). Low rectal cancer: a call for a change of approach in abdominoperineal resection. *Journal of Clinical Oncology* 23(36):9257–9264.

24 Freedman LS, Macaskill P and Smith AN (1984). Multivariate analysis of prognostic factors for operable rectal cancer. *Lancet* 2(8405):733–736.

25 Bentzen SM, Balslev I, Pedersen M, Teglbjaerg PS, Hanberg-Sorensen F, Bone J, Jacobsen NO, Sell A, Overgaard J and Bertelsen K (1992). Time to loco-regional recurrence after resection of Dukes' B and C colorectal cancer with or without adjuvant postoperative radiotherapy. A multivariate regression analysis. *British Journal of Cancer* 65(1):102–107.

26 Pilipshen SJ, Heilweil M, Quan SH, Sternberg SS and Enker WE (1984). Patterns of pelvic recurrence following definitive resections of rectal cancer. *Cancer* 53(6):1354–1362.

27 Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW and van de Velde CJ (2001). Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *New England Journal of Medicine* 345(9):638–646.

28 Cancer Council Australia (December 2011). *Clinical Practice Guidelines for Surveillance Colonoscopy – in adenoma follow-up; following curative resection of colorectal cancer; and for cancer surveillance in inflammatory bowel disease.*

http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/ext0008_colonoscopy_guideline_120314.pdf, NHMRC.

29 Rosty C, Parry S and Young JP (2011). Serrated Polyposis: An EnigmaticModel of Colorectal Cancer Predisposition. *Int J Surg Pathol.* Volume 2011 Article ID 157073

30 Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, Hamilton SR, Laurent-Puig P, Gryfe R, Shepherd LE, Tu D, Redston M and Gallinger S (2003). Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *New England Journal of Medicine* 349(3):247–257.

31 Jass JR, O'Brien MJ, Riddell RH and Snover DC (2007). Recommendations for the reporting of surgically resected specimens of colorectal carcinoma. *Virchows Arch* 450(1):1–13.

32 Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, Hammond ME, Henson DE, Hutter RV, Nagle RB, Nielsen ML, Sargent DJ, Taylor CR, Welton M and Willett C (2000). Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. *Archives of Pathology and Laboratory Medicine* 124(7):979–994.

33 Egashira Y, Yoshida T, Hirata I, Hamamoto N, Akutagawa H, Takeshita A, Noda N, Kurisu Y and Shibayama Y (2004). Analysis of pathological risk factors for lymph node metastasis of submucosal invasive colon cancer. *Modern Pathology* 17(5):503–511.

34 Chapuis PH, Dent OF, Fisher R, Newland RC, Pheils MT, Smyth E and Colquhoun K (1985). A multivariate analysis of clinical and pathological variables in prognosis after resection of large bowel cancer. *British Journal of Surgery* 72(9):698–702.

35 AJCC (American Joint Committee on Cancer) (2002). *AJCC Cancer Staging Manual, 6th edition*. Springer-Verlag, New York.

36 Chandler I and Houlston RS (2008). Interobserver agreement in grading of colorectal cancers-findings from a nationwide web-based survey of histopathologists. *Histopathology* 52(4):494–499.

37 Halvorsen TB and Seim E (1988). Influence of mucinous components on survival in colorectal adenocarcinomas: a multivariate analysis. *Journal of Clinical Pathology* 41(10):1068–1072.

38 Prall F (2007). Tumour budding in colorectal carcinoma. *Histopathology* 50(1):151–162.

39 Compton CC (2006). Key issues in reporting common cancer specimens: problems in pathologic staging of colon cancer. *Archives of Pathology and Laboratory Medicine* 130(3):318–324.

40 Washington MK (2008). Colorectal carcinoma: selected issues in pathologic examination and staging and determination of prognostic factors. *Archives of Pathology and Laboratory Medicine* 132(10):1600–1607.

41 Wittekind C, Henson D, Hutter R and Sobin L (eds) (2001). *TNM Supplement: A Commentary on Uniform Use*, Wiley-Liss, New York.

42 Kojima M, Nakajima K and Ishii G et al (2010). Peritoneal elastic laminal invasion of colorectal cancer: the diagnostic utility and clinicopathologic relationship. *Am J Surg Pathol* 34:1351-1360.

43 Puppa G, Shepherd NA, Sheahan K and Stewart CJR (2011). Peritoneal Elastic Lamina Invasion in Colorectal Cancer: The Answer to a Controversial Area of Pathology? *Am J Surg Pathol* 35(3):465-468.

44 Adam IJ, Mohamdee MO, Martin IG, Scott N, Finan PJ, Johnston D, Dixon MF and Quirke P (1994). Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 344(8924):707–711.

45 Birbeck KF, Macklin CP, Tiffin NJ, Parsons W, Dixon MF, Mapstone NP, Abbott CR, Scott N, Finan PJ, Johnston D and Quirke P (2002). Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Annals of Surgery* 235(4):449–457.

46 de Haas-Kock DF, Baeten CG, Jager JJ, Langendijk JA, Schouten LJ, Volovics A and Arends JW (1996). Prognostic significance of radial margins of clearance in rectal cancer. *British Journal of Surgery* 83(6):781–785.

47 Martling A, Holm T, Bremmer S, Lindholm J, Cedermark B and Blomqvist L (2003). Prognostic value of preoperative magnetic resonance imaging of the pelvis in rectal cancer. *British Journal of Surgery* 90(11):1422–1428.

48 Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH, Pathology Review Committee and Cooperative Clinical Investigators (2002). Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 26(3):350–357.

49 Ng IO, Luk IS, Yuen ST, Lau PW, Pritchett CJ, Ng M, Poon GP and Ho J (1993). Surgical lateral clearance in resected rectal carcinomas. A multivariate analysis of clinicopathologic features. *Cancer* 71(6):1972–1976.

50 Quirke P, Durdey P, Dixon MF and Williams NS (1986). Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 2(8514):996–999.

51 Wibe A, Rendedal PR, Svensson E, Norstein J, Eide TJ, Myrvold HE and Soreide O (2002). Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *British Journal of Surgery* 89(3):327–334.

52 Quirke P and Morris E (2007). Reporting colorectal cancer. *Histopathology* 50(1):555–556.

53 Goldstein NS (2002). Lymph node recoveries from 2427 pT3 colorectal resection specimens spanning 45 years: recommendations for a minimum number of recovered lymph nodes based on predictive probabilities. *American Journal of Surgical Pathology* 26(2):179–189.

54 Pheby DFH, Levine DF, Pitcher RW and Shepherd NA (2004). Lymph node harvests directly influence the staging of colorectal cancer: evidence from a regional audit. *Journal of Clinical Pathology* 57(1):43–47.

55 Hara M, Hirai T, Nakanishi H, Kanemitsu Y, Komori K, Tatematsu M and Kato T (2007). Isolated tumor cell in lateral lymph node has no influences on the prognosis of rectal cancer patients. *International Journal of Colorectal Disease* 22(8):911–917.

56 Hermanek P, Hutter RV, Sobin LH and Wittekind C (1999). International Union Against Cancer. Classification of isolated tumor cells and micrometastasis. *Cancer* 86(12):2668–2673.

57 Messerini L, Cianchi F, Cortesini C and Comin CE (2006). Incidence and prognostic significance of occult tumor cells in lymph nodes from patients with stage IIA colorectal carcinoma. *Human Pathology* 37(10):1259–1267.

58 Hemminki A, Mecklin JP, Järvinen H, Aaltonen LA and Joensuu H (2000). Microsatellite instability is a favorable prognostic indicator in patients with colorectal cancer receiving chemotherapy. *Gastroenterology* 119(4):921–928.

59 Davis NC and Newland RC (1983). Terminology and classification of colorectal adenocarcinoma: the Australian clinico-pathological staging system. *Australia and New Zealand Journal of Surgery* 53(3):211–221.

60 Knudsen JB, Nilsson T, Sprechler M, Johansen A and Christensen N (1983). Venous and nerve invasion as prognostic factors in postoperative survival of patients with resectable cancer of the rectum. *Diseases of the Colon & Rectum* 26(9):613–617.

61 Wiggers T, Arends JW and Volovics A (1988). Regression analysis of prognostic factors in colorectal cancer after curative resections. *Diseases of the Colon & Rectum* 31(1):33–41.

62 Chan CLH, Chafai N, Rickard MJFX, Dent OF, Chapuis PH and Bokey EL (2004). What pathologic features influence survival in patients with local residual tumor after resection of colorectal cancer? *Journal of the American College of Surgeons* 199(5):680–686.

63 Fujita S, Shimoda T, Yoshimura K, Yamamoto S, Akasu T and Moriya Y (2003). Prospective evaluation of prognostic factors in patients with colorectal cancer undergoing curative resection. *Journal of Surgical Oncology* 84(3):127–131.

64 Talbot IC, Ritchie S, Leighton M, Hughes AO, Bussey HJ and Morson BC (1981). Invasion of veins by carcinoma of rectum: method of detection, histological features and significance. *Histopathology* 5(2):141–163.

65 Howlett CJ, Tweedie EJ and Driman DK (2009). Use of an elastic stain to show venous invasion in colorectal carcinoma: a simple technique for detection of an important prognostic factor. *J Clin Pathol* 62:1021-1025.

66 Royal College of Pathologists (2007). *Dataset for Colorectal Cancer. 2nd edn.* *http://www.rcpath.org/publications-media/publications/datasets/dataset-for-colorectal-cancer-2nd-edition.htm*. (Accessed 8th May 2012).

67 Haggitt RC, Glotzbach RE, Soffer EE and Wruble LD (1985). Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology* 89(2):328–336.

68 Ueno H, Hase K and Mochizuki H (2001). Criteria for extramural perineural invasion as a prognostic factor in rectal cancer. *British Journal of Surgery* 88(7):994–1000.

69 Ryan R, Gibbons D and Hyland JMP (2005). Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology*(47):141-146.

70 Lindor NM, Burgart LJ, Leontovich O, Goldberg RM, Cunningham JM, Sargent DJ, Walsh-Vockley C, Petersen GM, Walsh MD, Leggett BA, Young JP, Barker MA, Jass JR, Hopper J, Gallinger S, Bapat B, Redston M and Thibodeau SN (2002). Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumors. *Journal of Clinical Oncology* 20(4):1043–1048.

71 Ward RL, Turner J, Williams R, Pekarsky B, Packham D, Velickovic M, Meagher A, O'Connor T and Hawkins NJ (2005). Routine testing for mismatch repair deficiency in sporadic colorectal cancer is justified. *Journal of Pathology* 207(4):377–384.

72 Hall G, Clarkson A, Shi A, Langford E, Leung H, Eckstein RP and Gill AJ (2010). Immunohistochemistry for PMS2 and MSH6 alone can replace a four antibody panel for mismatch repair deficiency screening in colorectal adenocarcinoma. *Pathology.* 42(5):409-413.

73 Shia J, Tang LH, Vakiani E, Guillem JG, Stadler ZK, Soslow RA, Katabi N, Weiser MR, Paty PB, Temple LK, Nash GM, Wong WD, Offit K and Klimstra DS (2009). Immunohistochemistry as first-line screening for detecting colorectal cancer patients at risk for hereditary nonpolyposis colorectal cancer syndrome: a 2-antibody panel may be as predictive as a 4-antibody panel. *Am J Surg Pathol.* 33(11):1639-1645.

74 Guidoboni M, Gafà R, Viel A, Doglioni C, Russo A, Santini A, Del Tin L, Macri E, Lanza G, Boiocchi M and Dolcetti R (2002). Microsatellite instability and high content of activated cytotoxic lymphocytes identify colon cancer patients with a favorable prognosis. *American Journal of Pathology* 159(1):384–385.

75 Ward RL, Cheong K, Ku S-L, Meagher A, O'Connor T and Hawkins NJ (2003). Adverse prognostic effect of methylation in colorectal cancer is reversed by microsatellite instability. *Journal of Clinical Oncology* 21(20):3729–3736.

76 Samowitz WS, Curtin K, Ma KN, Schaffer D, Coleman LW, Leppert M and Slattery ML (2001). Microsatellite instability in sporadic colon cancer is associated with an improved prognosis at the population level. *Cancer Epidemiology, Biomarkers & Prevention* 10(9):917–923.

77 Sankila R, Aaltonen LA, Jarvinen HJ and Mecklin JP (1996). Better survival rates in patients with MLH1-associated hereditary colorectal cancer. *Gastroenterology* 110(3):682–687.

78 Carethers JM, Smith EJ, Behling CA, Nguyen L, Tajima A, Doctolero RT, Cabrera BL, Goel A, Arnold CA, Miyai K and Boland CR (2004). Use of 5-fluorouracil and survival in patients with microsatellite-unstable colorectal cancer. *Gastroenterology* 126(2):394–401.

79 Claij N and te Riele H (1999). Microsatellite instability in human cancer: a prognostic marker for chemotherapy? *Experimental Cell Research* 246(1):1–10.

80 Storojeva I, Boulay J-L, Heinimann K, Ballabeni P, Terracciano L, Laffer U, Mild G, Herrmann R and Rochlitz C (2005). Prognostic and predictive relevance of microsatellite instability in colorectal cancer. *Oncology Reports* 14(1):241–249.

81 Watanabe T, Wu TT, Catalano PJ, Ueki T, Satriano R, Haller DG, Benson 3rd AB and Hamilton SR (2001). Molecular predictors of survival after adjuvant chemotherapy for colon cancer. *New England Journal of Medicine* 344(16):1196–1206.

82 van Lier MG, Leenen CH, Wagner A, Ramsoekh D, Dubbink HJ, van den Ouweland AM, Westenend PJ, de Graaf EJ, Wolters LM, Vrijland WW, Kuipers EJ, van Leerdam ME, Steyerberg EW, Dinjens WN and LIMO Study Group (2012). Yield of routine molecular analyses in colorectal cancer patients ≤70 years to detect underlying Lynch syndrome. *J Pathol.* 226(5):764-774.

83 Shia J, Stadler Z, Weiser MR, Rentz M, Gonen M, Tang LH, Vakiani E, Katabi N, Xiong X, Markowitz AJ, Shike M, Guillem J and Klimstra DS (2011). Immunohistochemical staining for DNA mismatch repair proteins in intestinal tract carcinoma: how reliable are biopsy samples? *Am J Surg Pathol.* 35(3):447-454.

84 Klarskov L, Holck S, Bernstein I, Okkels H, Rambech E, Baldetorp B and Nilbert M (2011). Challenges in the identification of MSH6-associated colorectal cancer: rectal location, less typical histology, and a subset with retained mismatch repair function. *Am J Surg Pathol.* 35(9):1391-1399.

85 Huth C, Kloor M, Voigt AY, Bozukova G, Evers C, Gaspar H, Tariverdian M, Schirmacher P, von Knebel Doeberitz M and Bläker H (2012). The molecular basis of EPCAM expression loss in Lynch syndrome-associated tumors *Mod Pathol.* 25(6):911-916.

86 Hagen CE, Lefferts J, Hornick JL and Srivastava A (2011). "Null pattern" of immunoreactivity in a Lynch syndrome-associated colon cancer due to germline MSH2 mutation and somatic MLH1 hypermethylation. *Am J Surg Pathol.* 35(12):1902-1905.

87 Shia J (2008). Immunohistochemistry versus Microsatellite Instability Testing For Screening Colorectal Cancer Patients at Risk For Hereditary Nonpolyposis Colorectal Cancer Syndrome Part I. The Utility of Immunohistochemistry. *J Mol Diagn* 10:293-300.

88 Okkels H, Lindorff-Larsen K, Thorlasius-Ussing O, Vyberg M, Lindebjerg J, Sunde L, Bernstein I, Klarskov L, Holck S and Krarup HB (2012). MSH6 Mutations are Frequent in Hereditary Nonpolyposis Colorectal Cancer Families With Normal pMSH6 Expression as Detected by Immunohistochemistry. *Appl Immunohistochem Mol Morphol.* Apr 10. [Epub ahead of print].

89 Weisenberger DJ, Siegmund KD, Campan M, Young J, Long TI, Faasse MA, Kang GH, Widschwendter M, Weener D, Buchanan D, Koh H, Simms L, Barker M, Leggett B, Levine J, Kim M, French AJ, Thibodeau SN, Jass J, Haile R and Laird PW (2006). CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer. *Nature Genetics* 38(7):787–793.

90 Loughrey MB, Waring PM, Tan A, Trivett M, Kovalenko S, Beshay V, Young MA, McArthur G, Boussioutas A and Dobrovic A (2007). Incorporation of somatic BRAF mutation testing into an algorithm for the investigation of hereditary non-polyposis colorectal cancer. *Familial Cancer* 6(3):301–310.

91 Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ, Langer C, Moore MJ and Zalcberg JR (2008). K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *New England Journal of Medicine* 359(17):1757–1765.

92 Lièvre A, Bachet J-B, Boige V, Cayre A, Le Corre D, Buc E, Ychou M, Bouché O, Landi B, Louvet C, André T, Bibeau F, Diebold M-D, Rougier P, Ducreux M, Tomasic G, Emile J-F, Penault-Llorca F and Laurent-Puig P (2008). KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *Journal of Clinical Oncology* 26(3):374–379.

93 Spano JP, Milano G, Vignot S and Khayat D (2008). Potential predictive markers of response to EGFR-targeted therapies in colorectal cancer. *Critical Reviews in Oncology/Hematology* 66(1):21–30.

94 Wittekind C, Compton CC, Greene FL and Sobin LH (2002). TNM residual tumor classification revisited. *Cancer* 94(9):2511–2516.

95 Valenstein PN (2008). Formatting pathology reports: applying four design principles to improve communication and patient safety. *Archives of Pathology and Laboratory Medicine* 132(1):84–94.