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Dataset for pathology reporting of colorectal cancer: recommendations from the International Collaboration on Cancer Reporting (ICCR)

Maurice B Loughrey[a,b], Fleur Webster[c], Mark J Arends[d], Ian Brown[e], Lawrence J Burgart[f], Chris Cunningham[g], Jean-Francois Flejou[h], Sanjay Kakar[i], Richard Kirsch[j], Motohiro Kojima[k], Alessandro Lugli[l], Christophe Rosty[m,n,o], Kieran Sheahan[p], Nicholas P West[q], Richard H. Wilson[r], Iris D Nagtegaal[s]

a. Centre for Public Health, Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, Northern Ireland, UK.

b. Department of Cellular Pathology, Belfast Health and Social Care Trust, Belfast, Northern Ireland, UK.

c. International Collaboration on Cancer Reporting, Sydney, NSW, Australia.

d. Division of Pathology, Institute of Genetics & Molecular Medicine, University of Edinburgh, Edinburgh, UK.

e. Envoi Pathology, Kelvin Grove, QLD, Australia.

f. Department of Pathology, Virginia Piper Cancer Institute, Abbott Northwestern Hospital, Minneapolis, MN, USA.

g. Department of Colorectal Surgery, Churchill Hospital, Oxford University Hospitals NHSFT, Oxford, UK.

h. Department of Pathology, Saint-Antoine Hospital, Sorbonne University, Paris, France.

i. Department of Pathology, University of California San Francisco, San Francisco, CA, USA.

j. Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada.

k. Division of Pathology, Research Center for Innovative Oncology, National Cancer Center, Chiba, Kashiwa, Japan.

l. Institute of Pathology, University of Bern, Bern, Switzerland.

m. Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia.

n. Envoi Specialist Pathologists, Brisbane, QLD, Australia.

o. Department of Pathology, University of Melbourne, Melbourne, VIC, Australia.

p. Department of Pathology, St Vincent's University Hospital & University College, Dublin, Ireland.

q. Pathology and Data Analytics, Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK.

r. Institute of Cancer Sciences, University of Glasgow, Glasgow, UK.

s. Department of Pathology, Radboud University Medical Centre, Nijmegen, The Netherlands.

Corresponding author:
Prof. Iris Nagtegaal
Department of Pathology
Radboud University Medical Center
PO Box 9101, 6500 HB
Nijmegen
The Netherlands
Telephone: +31 (0)24 361 02 29
E-mail: Iris.Nagtegaal@radboudumc.nl

Mini-abstract: Description of the new International Collaboration on Cancer Reporting (ICCR) dataset for pathology reporting of colorectal cancer surgical resection specimens. This first internationally agreed dataset for colorectal cancer pathology reporting promotes standardization of pathology reporting and enhanced clinicopathological communication between colorectal surgeon and pathologist.

Running title: ICCR Colorectal Cancer dataset

Abstract

Objective: To describe a new, international dataset for pathology reporting of colorectal cancer surgical specimens, produced under the auspices of the International Collaboration on Cancer Reporting (ICCR).

Summary Background Data: Quality of pathology reporting and mutual understanding between colorectal surgeon, pathologist and oncologist are vital to patient management. Some pathology parameters are prone to variable interpretation, resulting in differing positions adopted by existing national datasets.

Methods: The ICCR, a global alliance of major pathology institutions with links to international cancer organizations, has developed and ratified a rigorous and efficient process for the development of evidence-based, structured datasets for pathology reporting of common cancers. Here we describe the production of such a dataset for colorectal cancer surgical resection specimens by a multidisciplinary panel of internationally recognized experts.

Results: The agreed dataset comprises eighteen core (essential) and seven non-core (recommended) elements identified from a review of current evidence. Areas of contention are addressed, some highly relevant to surgical practice, with the aim of standardizing multidisciplinary discussion. The summation of all core elements is considered to be the minimum reporting standard for individual cases. Commentary is provided, explaining each element's clinical relevance, definitions to be applied where appropriate for the agreed list of value options and the rationale for considering the element as core or non-core.

Conclusions: This first internationally agreed dataset for colorectal cancer pathology reporting promotes standardization of pathology reporting and enhanced clinicopathological communication. Widespread adoption will facilitate international comparisons, multinational clinical trials and help to improve the management of colorectal cancer globally.

Introduction

Pathology reporting of cancer resection specimens, through provision of histological subtype, grade, stage and other clinically relevant information, impacts on individual patient management and prognosis. At a population level, it provides raw data for cancer registration purposes, and is used for epidemiological audit and research.[1] Tissue-based cancer research, including that conducted within clinical trials,[2] may also be stratified based on histopathological stage, the presence or absence of other high risk morphological features or molecular pathological subtypes. Standardization of approach to pathology evaluation of cancer resection specimens and reporting of individual features is of utmost importance therefore, to allow valid comparison of data between cohorts and between countries, to allow assessment of the impact of new screening programs and to allow participation in multicenter trials which require a minimum standard of pathology reporting or target a specific subset of cancer. However, some pathology parameters are prone to variable or evolving interpretation, resulting in differing positions adopted by various national datasets in existence or an inability to reach consensus, manifest as a lack of clearly expressed guidance for certain contentious areas. This is evidenced by regular changes made to TNM staging systems as new evidence and new interpretations emerge. For some issues, clear guidance is simply unavailable.

All of these principles apply to colorectal cancer and some such issues impact directly on surgical practice and staging. For example, the minimum distance of tumor from a margin required to label as 'clear', the interpretation of regional, discontinuous 'tumor deposits' and the interpretation of surgical resection margin status when this is involved by tumor not continuous with the primary tumor.[3] As guidance must be offered on the basis of available evidence, some discordance is inevitable where the evidence base is limited, but nevertheless

in this scenario a consensus position based on best available evidence and expert opinion is helpful to assist pathologists in case by case reporting and surgeons and oncologists in clinical management of their patients. Close liaison between surgeon and pathologist, and good surgical understanding of pathology reporting guidelines and practice are key to maximizing the quality of pathology reports and their value to the surgeon and ultimately the patient.

Pathology protocols and datasets are well established in some countries and have been independently developed at national level by organizations including the College of American Pathologists (CAP), USA, the Royal College of Pathologists (RCPath), United Kingdom (UK), and the Royal College of Pathologists of Australasia (RCPA). Although these organizations' protocols broadly align, there are significant differences in structure, content and terminology and some subtle differences in interpretation that could hinder international comparison. Standardization of existing national cancer reporting datasets would also have the added benefits of reducing the global burden of regular dataset production and of providing a single benchmarking reference available to other countries.

With this in mind, in 2011, a number of pathology organizations including the CAP, RCPath and RCPA formed the International Collaboration on Cancer Reporting (ICCR) and successfully piloted the development of datasets for pathology reporting of a select number of cancers. The subsequent ICCR development has been described previously in detail.[4,5] The ICCR has developed important strategic alliances with other international cancer organizations including the International Agency for Research on Cancer (IARC) which is responsible for producing the World Health Organization (WHO) monographs or 'Blue Books' on tumor classification and the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC). These partnerships facilitate the co-ordination

of dataset production with new tumor classifications and staging systems. The ICCR datasets are freely available from the ICCR website (http://www.iccr-cancer.org/datasets). Here we describe the production of such a dataset for colorectal cancer surgical resection specimens by a panel of internationally recognized expert pathologists and other clinicians, supported by the ICCR. Areas of contention or divergence are addressed, with the aim of offering a consensus position to standardize interpretation and multidisciplinary discussion.

Methods

The ICCR has developed a rigorous process for the production of individual datasets (http://www.iccr-cancer.org/datasets/dataset-development). This process has been described in detail in previous publications (http://www.iccr-cancer.org/articles/publications). The ICCR quality framework dictates both content and presentation and the roles and responsibilities of all involved are clearly outlined. In brief, the Dataset Steering Committee (DSC) of the ICCR appointed a 'Series Champion' (IN) to coordinate the simultaneous development of a related suite of five datasets all pertaining to gastrointestinal and pancreaticobiliary tract cancers, and a Chair (MBL) to oversee production of the colorectal cancer resection dataset. A further eleven expert gastrointestinal pathologists, comprising two each from the USA (LB, SK), UK (MA, NW) and Australia (IB, CR) and one each from Canada (RK), Japan (MK), France (JF), Ireland (KS) and Switzerland (AL), together with a colorectal surgeon (CC) and a colorectal oncologist (RW) comprised the fifteen members of the Dataset Authoring Committee (DAC). Lead authors of the current CAP, RCPath and RCPA colorectal cancer datasets were included.[6-8] The group was coordinated by an ICCR Project Manager (FW), assuring optimal communication within the international group and adherence to agreed timelines.

Regarding scope, this dataset was developed for the reporting of pathology specimens resulting from major surgical resection of primary carcinomas arising within the colon and rectum. This includes neuroendocrine carcinomas (NECs) and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs).[9] It is not applicable to carcinomas of the small intestine, appendix or anus, nor to neuroendocrine tumors (NETs) or non-epithelial

malignancies, as these are subject to different tumor classifications and staging systems. Furthermore, primary colorectal carcinomas treated by local excision are the subject of a separate ICCR dataset, as specimen handling and reporting of these differ from major surgical resection specimens.

An initial draft document was produced by the Project Manager and Chair after scrutiny of core and non-core data items within existing CAP, RCPath and RCPA colorectal cancer datasets and review of current published evidence. This draft was circulated and individual dataset items discussed amongst the DAC at a coordinated series of teleconferences, following which an agreed draft dataset was posted for open international consultation on the ICCR website for a period of two months. All comments received were discussed by the DAC and, where agreed, resultant changes incorporated into the final dataset, which was ratified by the DSC prior to publication. The final agreed dataset is available at http://www.iccr-cancer.org/datasets/published-datasets/digestive-tract/colorectal.

The ICCR dataset style lists a set of reporting elements and value lists (responses) accompanied by a commentary for each, explaining the element and categorization, offering guidance for reporting, citing relevant evidence and, where applicable, definitions for the value lists. Each element is categorized as either core or non-core. Core elements are those unanimously agreed by the expert panel to be essential for diagnosis, prognostication and/or patient management. These generally required evidentiary support at Level III-2 or above [based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence document, and defined as 'Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial'].[10] Non-core elements were those that did not meet the above criterion but were considered by the panel to be clinically important,

representing good practice but not currently fully validated for routine clinical practice. Specific levels of evidence were not assigned to each core or non-core element. The summation of all core elements is considered to be the minimum reporting standard for individual cases.

Results

A summary of the agreed core and non-core elements is presented in Table 1 and each is described in further detail below:

Clinical information

Knowledge of relevant clinical information, such as an underlying polyposis syndrome, Lynch syndrome or chronic inflammatory bowel disease, is very important to the reporting pathologist as this may influence both specimen sampling and histological interpretation. Such history may be discernible from the pathology information management system or hospital electronic clinical record. However, as it is beyond the control of the pathologist to ensure this information is available, it is considered a non-core rather than a core item. Two specific items represent exceptions to this rule, given their importance, and are considered core.

Firstly, information regarding administration of neoadjuvant therapy, including its nature and duration, is a core item and must always be provided to the pathologist, as response to therapy can influence stage and tumor morphology, potentially altering interpretation. If this information is not provided to the pathologist, it may be suspected upon histological examination if features of regression are evident, and clarity sought prior to reporting the case. Staging should be provided with a 'y' prefix.

Secondly, the nature of the operative procedure is considered a core item (Table 1), and additional information may be provided clinically, such as the attempted dissection plane in an abdominoperineal excision. Distinction of high from low anterior resection, the latter

defined by inclusion of the peritoneal reflection within the specimen, is considered non-core, but may represent useful data for clinical audit. If the operative specimen includes any tissue or organ not typically present within that specimen type, for example *en bloc* resection of a separate segment of intestine or abdominal wall connective tissue or a more extensive anterior exenteration specimen (Figure 1), details of all organs present within the submitted specimen should be clearly stated on the specimen request form.

Tumor site

If a specimen contains multiple synchronous primary tumors, these should all be documented individually and separate datasets completed for each. Tumor location is a core item, is usually obvious, stated in the clinical information provided and confirmed by macroscopic specimen examination. It can be difficult to identify specific location in the colon within an *ex vivo* specimen, particularly in relation to the flexures. If clinical and pathological tumor locations are discordant, this should be documented by photography and discussed with the clinical team. Recording the anatomical site of tumor allows correlation with prior endoscopic and radiological investigations, indicates whether or not a non-peritonealised margin is likely to be present and permits classification of lymph nodes as regional versus non-regional. Distinction of colonic from rectal origin is of importance, given different biologies, clinical features, management and risks of peritoneal versus local tumor bed recurrence. This classification can be subjective, especially for more advanced stage tumors. If a tumor straddles two sites, the site with the greatest tumor bulk should be recorded. The rectosigmoid boundary is marked by fusion of the three taeniae coli of the sigmoid colon to form the circumferential longitudinal muscle of the rectal wall. If advanced tumor obliterates these anatomical landmarks, the tumor site can be informed by available clinical and radiological

information.[11] Classification as rectosigmoid should be reserved for cases in which an accurate determination between rectum and sigmoid cannot be made by above methods.

Tumor dimensions

Unlike many other tumors, size has no prognostic significance for colorectal cancer and does not directly influence tumor staging. Despite this, an indication of maximum tumor dimension is considered a core data item, as it is baseline information which allows correlation with pre-operative clinical, endoscopic and radiological assessments. It should be based on a combination of macroscopic and microscopic assessment and, if possible, exclude any associated inflammatory component or pre-invasive lesion, which may be noted in a comment for clinicopathological correlation. Additional tumor dimensions may be provided as non-core data.

Perforation

Tumor perforation into the peritoneal cavity is a well-established adverse prognostic factor in colonic[12] and rectal[13] cancer and its presence or absence should be recorded as a core item. This is defined as a macroscopically visible full thickness defect through the tumor, such that the bowel lumen within the segment involved by tumor is in communication with the external surface of the resection specimen or with the lumen of another organ. Cases with tumor perforation are regarded as pT4a in the UICC/AJCC/ 8th edition Staging Systems.[14,15] Note that tumor perforation requires penetration of the serosal surface. Peritumoral abscess cavity, for example within the mesentery, that is contained and does not demonstrate breach of the serosal surface, is not considered perforation and is considered pT3 rather than pT4a. This may be commonly encountered in the setting of sigmoid diverticular disease complicated by tumor. Perforation of the colon resulting from a more distal obstructing tumor is distinct from

tumor perforation and is not interpreted as pT4 disease. However, this should still be recorded as non-tumor perforation is associated with higher mortality risk.

Some confusion can be introduced when using the term perforation for other settings, such as when a full thickness defect arises intraoperatively. It is important that such clinical information is conveyed to the reporting pathologist and, for clarity, it is advised that different descriptive terminology is applied. We consider the term perforation is best reserved for the biological setting, as the clinical impact is likely different depending on the scenario. If an iatrogenic full thickness tumor defect arises whilst the specimen is *in situ* within the abdominal cavity, there is likely some risk of tumor seeding the peritoneal cavity and we consider this is best regarded as pT4a disease. This interpretation is however offered without good evidence. In contrast, if such an iatrogenic defect occurs once the specimen is outside the abdominal cavity, this should not influence pT classification. Interpretation therefore requires close clinicopathological correlation and this should always be explained in the pathology report.

Relation of tumor to anterior peritoneal reflection

For rectal cancers, the relationship of the tumor to the anterior peritoneal reflection is reported as a core item, as this predicts the risk of local recurrence in addition to peritoneal recurrence (Figure 2).[16] The anterior aspect of the rectum has a peritoneal covering to the level of the peritoneal reflection. Posteriorly, the non-peritonealised margin is represented by a triangular-shaped bare which extends superiorly in continuity with the mesentery of the sigmoid colon.

Plane of mesorectal excision

Prospective randomised controlled trials have demonstrated that, in patients with rectal cancer, use of total mesorectal excision (TME) surgery improves local recurrence rates and the survival by up to 20%.[17,18] Furthermore, objective macroscopic assessment by pathologists of the surgical plane of excision predicts margin involvement, local recurrence and survival.[16,19] This grading is therefore considered a core item for reporting. The optimal plane is that of the mesorectal fascia (complete TME) whilst excision extending onto the muscularis propria (incomplete TME) is associated with the worst outcomes. Overall macroscopic assessment of the intact specimen, with grading based on the worst area, is as described in Table 2 and illustrated in Figure 3.

Plane of sphincter excision

In considering management of rectal cancer, abdominoperineal excision for lower tumors has been associated with poorer outcomes compared to anterior resection for higher tumors, due to increased rates of circumferential resection margin (CRM) involvement and intraoperative full thickness defects, referred to as perforation in this literature.[20] More radical surgery to remove more tissue around low rectal tumors by *en bloc* resection of the levator muscles, extralevator abdominoperineal excision, has been shown by meta-analysis to reduce the risk of CRM involvement and intraoperative full thickness defects leading to better long term outcomes.[21, 22] Using staging magnetic resonance imaging (MRI), radiologists are able to predict the optimal dissection plane for abdominoperineal excision surgery.[23] Subsequent correlation with pathological assessment of the intact surgical excision specimen allows surgical audit of the plane of dissection achieved around the sphincters. As this assessment is currently a core data item in only one national colorectal cancer dataset,[7] and not in routine use in many other countries, it has been included as a non-core item. The overall assessment

is based on the worst area, as described in Table 2 and illustrated in Figure 3.[13] This grading should be performed in addition to mesorectal grading for abdominoperineal excision specimens.

Plane of mesocolic excision

Beyond assessment of rectal cancer surgery, the quality of surgical technique for colonic cancer, evaluating the plane of mesocolic excision, has been shown, in retrospective observational studies and one randomised clinical trial, to predict outcomes.[24,25] Surgery in the mesocolic plane is associated with a lower rate of local recurrence and better survival when compared to surgery in the muscularis propria plane. Complete mesocolic excision, where surgery occurs in the mesocolic plane with a high vascular ligation, is associated with better plane of surgery and higher lymph node yield, although the effect of the high ligation on long term outcomes is uncertain and subject to further study.[26] Pathological evaluation of mesocolic surgery is considered a non-core data item, as its application requires further validation in clinical practice. Overall assessment is based on the worst area, as described in Table 2 and illustrated in Figure 3.[25]

Histological tumor type

The WHO Classification of Tumors of the Digestive System, 5th edition, 2019, is recommended for tumor typing and is a core item.[9] Almost all colorectal cancers are adenocarcinomas, most of which are of no specific type or 'not otherwise specified' (NOS). Specific subtypes of adenocarcinoma are recognised and defined as follows:

Mucinous adenocarcinoma has greater than 50% of the tumor comprised of pools of extracellular mucin, containing malignant glands or individual tumor cells. Microsatellite

instability is more common in mucinous adenocarcinomas compared to adenocarcinoma, NOS, as is the presence of an activating *BRAF* V600E mutation.

Signet-ring cell adenocarcinoma has greater than 50% of the tumor demonstrating signet-ring cell morphology, in the form of malignant cells with intracytoplasmic mucin, displacing and typically indenting the nuclei. Signet-ring cell adenocarcinoma is associated with worse stage-for-stage survival relative to conventional adenocarcinoma.[27] Like mucinous adenocarcinoma, there is a strong association with microsatellite instability and *BRAF* V600E mutation.[28]

Medullary carcinoma demonstrates solid sheets of malignant cells with indistinct cell boundaries, vesicular nuclei, prominent nucleoli, abundant eosinophilic cytoplasm and prominent intratumoral and peritumoral inflammatory infiltrates. Almost invariably these tumors demonstrate microsatellite instability and are associated with a good prognosis.[29]

Serrated adenocarcinoma by definition demonstrates glandular serrations, often slit-like, and tumor cells usually have low nuclear to cytoplasmic ratio with abundant eosinophilic or clear cytoplasm and sometimes accompanied by areas of mucinous differentiation.[30] *BRAF* or *KRAS* activating mutations are common.

Micropapillary adenocarcinoma is characterised by small, rounded clusters of tumor cells lying within stromal spaces mimicking vascular channels. At least 5% of the tumor should demonstrate this feature for this classification. There is an association with adverse pathological features including extramural venous invasion and lymph node metastatic disease.[31]

Adenoma-like adenocarcinoma is a subtype of adenocarcinoma in which at least 50% of the invasive tumor has an adenoma-like appearance with villous architecture, low grade cytology, a pushing growth pattern and minimal desmoplastic stromal reaction.[32] Demonstration of invasion is difficult on endoscopic biopsy. This subtype is associated with a good prognosis.

Neuroendocrine neoplasms of the gastrointestinal tract are currently classified into NETs, NECs and MiNENs.[9] The term MiNEN incorporates the prior term mixed adenoneuroendocrine carcinoma (MANEC), in recognition that occasionally the non-neuroendocrine component of mixed tumors may not be an adenocarcinoma. NETs are now graded 1-3 on the basis of mitotic count and Ki-67 proliferation index, with NET grade 3 recognizing a subset of tumors previously meeting criteria for NEC, but found to be less responsive to platinum-based chemotherapy, yet have better survival compared to other NECs.[33] Grade 3 NETs are better differentiated than NECs and the primary distinction is morphological. They tend to have a lower Ki-67 proliferation index, though above the definitional threshold of 20%. NECs show marked cytological atypia, brisk mitotic activity, are subclassified into small cell and large cell subtypes and are considered high-grade by definition so are not graded. A Ki-67 proliferation index of less than 55% is associated with better overall survival.[34] A recent study of 25 NECs revealed frequent dysregulation of the Rb/E2F pathway, with distinct molecular subgroups characterized by loss of Rb immunoexpression, p53 alteration or p16 overexpression.[35] MiNENs are usually composed of a poorly differentiated NEC component and a conventional adenocarcinoma NOS component and each should arbitrarily constitute 30% of the tumor for this designation. This dataset is applicable to NECs and MiNENs but, given different staging and grading systems applied, NETs should not be reported using this dataset.

Other epithelial tumors rarely encountered include adenosquamous carcinoma, carcinoma with sarcomatoid components, undifferentiated carcinoma, squamous cell carcinoma and non-signet-ring cell poorly cohesive adenocarcinoma.

Histological tumor grade

Although subject to poor interobserver agreement,[36] histological grade of colorectal cancer, based on gland formation, is an independent prognostic factor and is considered a core data item.[37-39] A two-tiered grading system is more reproducible and favoured over a four-tiered grading system. Aligning with the latest WHO classification,[9] grading is based on the least differentiated tumor component, rather than predominant pattern, although this is recommended without good evidence and a minimum area of high grade tumor required for classification as high grade has not been defined. Tumor buds or poorly differentiated clusters, most commonly seen at the invasive tumor front, should not be considered in the evaluation of grade. Grading based on poorly differentiated clusters may be superior to conventional grading with respect to both prognostic value and reproducibility but further studies are required in this regard.[40,41]

According to the latest WHO classification, only adenocarcinoma NOS and mucinous adenocarcinoma should be graded.[9] Grading is not applicable to other subtypes of adenocarcinoma, as assessment of gland formation is difficult to apply to subtypes and most subtypes are associated with their own clinical prognosis independent of grade. Mucinous adenocarcinoma should be graded on glandular formation and epithelial maturation.[9] Mismatch repair status is likely to influence the clinical behaviour of some histological tumor types, including mucinous adenocarcinoma. However, some studies have found that

morphological grading outperforms mismatch repair status with respect to prognostication of mucinous adenocarcinomas.[42,43]

Extent of invasion

In the absence of application of neoadjuvant therapy, pT classification indicates the anatomic extent of invasion of the primary tumor. This is the most important prognostic factor in colorectal cancer and is a core data item. It is assessed on a combination of macroscopic and microscopic features within an excision specimen, applying UICC and AJCC 8th edition criteria.[14,15] The only exception is that pT *in situ* is not recognized in this dataset. This is somewhat contentious and rare cases of colorectal neoplasia confined to invasion of the lamina propria (intramucosal invasive neoplasia or intramucosal carcinoma) are acknowledged but, given the negligible metastatic potential of such neoplasms,[44] the consensus position of the DAC was that these should be classified under the same category as high grade dysplasia/high grade non-invasive neoplasia.

Given the clear anatomical delineation of the muscularis propria at most sites, defining pT1-pT3 tumors, classification of this extent of invasion is not often problematic. An exception is in tumors of the low rectum, where complexities of sphincter anatomy make accurate assessment of level of invasion in this region challenging. The internal sphincter represents a continuation of the muscularis propria and invasion of this also constitutes pT2. Skeletal muscle fibres can cross over from external to internal sphincter and therefore invasion of skeletal muscles fibres may only represent pT2 disease if these fibres are from the internal sphincter. Invasion beyond internal sphincter into the intrasphincteric plane, but not involving the external sphincter, is considered pT3. Note that in some areas of the sphincter complex the internal and external sphincter muscles are directly apposed with only a theoretical space

between. Distinction of pT2 from pT3 in the colon is usually straightforward. If tumor extends to the outer edge of the muscularis propria, or any invasion beyond, such that no muscle bundles separate tumor cells from mesenteric connective tissue the tumor should be classified as pT3.[45]

pT4 includes tumor infiltration of the peritoneal surface (pT4a) or involvement of an adjacent organ or structure (pT4b). Peritoneal involvement has been demonstrated by multivariate analysis to have a negative impact on prognosis.[46,47] Data from a cohort of more than 100,000 colon cancer cases indicate that pT4a carcinomas have on average a 10-20% better 5-year survival than pT4b carcinomas for each pN category.[48] Involvement of the peritoneal surface requires tumor breaching the serosa with tumor cells visible either on the peritoneal surface, free in the peritoneal cavity or separated from the peritoneal surface by inflammatory cells only.[12] If tumor passes close to the serosal surface and elicits a mesothelial reaction without clear invasion, this is categorised as pT3, although additional sections and/or multiple levels should be examined to look deeper invasion. This setting is prone to interobserver variation however.[49] Elastic stains to identify peritoneal elastic lamina invasion are advocated in some studies, as a staging or prognostic tool, but others studies have not found this adjunct useful.[50-53] Cases with tumor perforation are classified as pT4a, without the need to document tumor cells on the peritoneal surface.

It is important to distinguish peritoneal involvement through direct continuity with the primary tumor from peritoneal deposition of tumor discontinuous from the primary tumor. The former indicates pT4a disease whilst the latter is regarded as distant metastatic disease, pM1c. It is also important, through careful macroscopic specimen assessment, to carefully distinguish tumor involvement of a peritoneal surface from tumor involvement of a non-

peritonealised surgical resection margin. Peritoneal involvement is a risk factor for recurrent intraperitoneal metastatic disease whilst margin involvement is a risk factor for local recurrence.

Adjacent organ involvement by tumor (pT4b) may follow peritoneal invasion or, for example in low rectal tumors, represent direct extraperitoneal invasion. If a tumor is macroscopically adherent to another organ, microscopic invasion must be demonstrated to classify as pT4b, otherwise the adherence is considered inflammatory in nature. Longitudinal tumor extension into the wall of an adjacent segment of the intestine does not influence pT classification. Rectal tumors invading skeletal muscle of the external sphincter and/or levator ani are classified as pT4b.

Measurement of invasion beyond muscularis propria

Prognosis of patients with pT3 tumors can be stratified accordingly to their extent of invasion of the primary tumor beyond the muscularis propria, with ≥5 millimeter (mm) an accepted cut-off for higher risk in some studies.[44,45] Based on the level of existing evidence, this is considered a non-core item for reporting. The distance beyond the muscularis propria is measured to the nearest mm from the outer margin of the muscularis propria. In the event of local tissue destruction by tumor, reconstruction of this outer margin may be required for the purposes of measurement. The measurement should be performed macroscopically and refined microscopically if appropriate.

Lymphatic and venous invasion

As with many other cancers, the presence or absence of lymphovascular invasion has strong prognostic implications for colorectal cancer and this should be reported as a core item.

Classification is required according to the type of vessels involved (Figure 4) and, for veins, their intramural or extramural location, as the vessel type and location have different clinical and prognostic implications. Extramural venous invasion, present beyond the muscularis propria, has the greatest clinical significance, having been demonstrated on multivariate analysis in multiple studies to be a stage-independent adverse prognostic factor for both colonic and rectal cancer.[54] Intramural venous invasion, identified within the submucosa or muscularis propria but not beyond, is also of prognostic importance but the evidence is much weaker than for extramural venous invasion.[12,55,56]

The minimum criteria for calling venous invasion is debatable. The longstanding definition of Talbot *et al* (1981) is approved, whereby venous invasion is defined as tumor present within an endothelium-lined space that is either surrounded by a rim of muscle or contains red blood cells.[57] Proximity of a rounded or elongated deposit of tumor beside an artery should raise suspicion of venous invasion but is not diagnostic without identification of a residual venous wall. Examination of further levels and immunohistochemical and/or histochemical stains may help interpretation, in particular the application of elastic staining to identify venous elastic lamina.[56,58-62] A circumscribed tumor nodule surrounded by a smooth muscle wall or an identifiable elastic lamina is considered sufficient to classify as venous invasion.

Small vessel invasion is defined as tumor involvement of thin-walled structures lined by endothelium, without an identifiable smooth muscle layer or elastic lamina. Small vessels may represent lymphatics, capillaries or post-capillary venules and invasion of these should be distinguished from large vessel (venous) invasion. D2-40 immunohistochemistry, which only stains lymphatic endothelial cells, not venular, can be used to classify small vessel invasion further but this is not in routine use in this setting. Small vessel invasion of all forms

is considered under the 'L' classification under UICC/AJCC TNM 8th editions.[14,15] The identification of small vessel invasion has been reported in some but not all studies to be associated with lymph node metastatic disease and represent an independent prognostic factor.[55,63-65] The relative importance of intramural and extramural anatomic location with respect to small vessel invasion has not been well established.[55]

Perineural invasion

The presence of perineural invasion in colorectal cancer (Figure 4) has been reported in multiple independent studies and one meta-analysis to have adverse prognostic implication, particularly in stage II disease.[63,66-69] Although the importance of anatomic location in perineural invasion is not well established, one large multicenter study, reported adverse prognostic significance for both intramural and extramural locations.[66] The presence or absence of any perineural invasion is therefore considered a core item but it is not necessary to specify anatomical location.

Lymph node status

Regional lymph node status is a major determinant of whether or not a patient with colorectal cancer receives adjuvant chemotherapy and is a core item. Distinction from non-regional lymph node involvement by tumor is important as the latter indicates distant metastatic (pM1) disease. If a specimen contains two or more synchronous primary tumors in distinct anatomic regions, attempt should be made to assign lymph nodes by regional status and each cancer assessed for nodal status separately.

The age and gender of the patient, the length of the resection specimen, the amount of attached mesenteric tissue, tumor stage, tumor mismatch repair status and whether or not the

patient has received neoadjuvant therapy are all factors which influence the number of lymph nodes present in a surgical resection specimen.[70] It is important to perform a diligent pathological dissection to identify all lymph nodes in a specimen as lymph nodes containing metastatic disease may be very small. Individual dissectors and departments should aim for a median lymph node yield of at least twelve per case. Low lymph node harvest is an adverse prognostic factor in stage II disease.[71] This reflects a combination of inadequate nodal retrieval and unfavorable patient immunology.

Regarding small tumor foci within lymph nodes, a systematic review and meta-analysis found higher risk of disease recurrence in stage I/II colorectal cancer cases in micrometastatic disease (one or more deposit ≥0.2 mm and <2 mm) compared to those with tumor-negative nodes, but no increased risk of disease recurrence in the presence of only 'isolated tumor cells' (single tumor cells or groups <0.2 mm in maximum dimension) compared to tumor-negative nodes.[72] Therefore, any lymph nodes containing micrometastatic or larger tumor foci are considered as positive nodes whereas isolated tumor cells, identified on H&E or immunohistochemical staining, when representing the only form of nodal involvement should be classified as pN0, with a comment indicating the presence of isolated tumor cells and optional designation as pN0(i+).

Following neoadjuvant therapy, only the identification of viable tumor constitutes nodal involvement (ypN1/2). Necrosis, fibrosis or acellular mucin within lymph nodes in this setting is not considered nodal tumor involvement. Nevertheless a descriptive comment of these findings indicates likely response to therapy and allows correlation with initial staging MRI.

Tumor deposits

The term tumor deposit, or satellite, was introduced in the UICC/AJCC TNM 7th editions[73,74] and the concept refined in UICC/AJCC TNM 8th editions, to define tumor deposits as discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma that are discontinuous from the primary and without histological evidence of residual lymph node or identifiable vascular or neural structures (Figure 4).[14,15] If a vessel wall is identifiable on H&E, elastic or other stains, it should be classified as venous invasion or lymphatic invasion and if neural structures are identifiable in association with the tumor, the lesion should be classified as perineural invasion rather than as a tumor deposit. A minimum size of deposit or minimum distance of separation from the primary tumor, or further other deposits, is not specified. Neither is guidance on how to classify mesenteric tumor which demonstrates lymphatic, venous or perineural invasion, but where the bulk of the tumor appears unrelated to the vascular or neural structure. The identification of a tumor deposit is considered under the node (N) rather than primary tumor (T) status for the purposes of staging and a tumor with one or more tumor deposits, but no regional lymph nodes positive for tumor, is classified as pN1c. Tumor deposits are discounted for staging purposes if any regional nodes contain tumor and the number of tumor deposits is not added to the involved node count. However, there is evidence from meta-analysis of the adverse prognostic significance of tumor deposits in the presence of lymph node metastatic disease, based on the UICC/AJCC TNM 7th editions[73,74] definition, and therefore the presence and number of identified tumor deposits should be recorded in all cases, as a core item.[75]

Mesenteric tumor, without evidence of origin, which is discontinuous from the primary tumor and predominantly subserosal in location but which penetrates the serosal surface of the mesentery, should be classified as a tumor deposit rather than as distant metastatic (pM1c)

disease. This does not influence the pT category, which should be based on extent of local invasion of the primary tumor only. However, given serosal involvement by the tumor deposit may equate clinically to pT4a disease, a comment may be usefully added to this effect. Guidance on this interpretation is offered without good evidence. pM1c disease should be reserved for cases where the tumor appears to have arisen from metastatic spread via the peritoneal cavity.

In the setting of tumor regression following administration of neoadjuvant therapy, the distinction of discontinuous residual primary tumor foci from tumor deposit is difficult and subjective. To facilitate uniform interpretation, it is recommended that designation as tumor deposit should necessitate the presence of intervening normal tissue, rather than just fibrosis or acellular mucin.

Tumor budding

There is considerable interest in the phenomenon of tumor budding, considered to be a morphological manifestation of epithelial mesenchymal transition.[76] A tumor bud is defined as a single tumor cell or cluster of up to four tumor cells usually most evident at the invasive front of carcinomas. Budding is of potential clinical relevance to colorectal cancer in two distinct settings. Firstly, multiple studies have shown that pT1 colorectal carcinomas with greater budding (tumor budding scores Bd2 and Bd3) are associated with an increased risk of lymph node metastatic disease compared to those with lesser budding (tumor budding score Bd1).[77-81] Secondly, in stage II colorectal carcinomas, tumor budding score Bd3 is associated with an increased risk of recurrence and mortality.[82-84]

As recommended from the International Tumor Budding Consensus Conference (ITBCC) of 2016,[85] tumor budding is scored using a three-tier system according to the number of buds evident in the highest count after scanning ten separate fields (at 20x objective lens) along the invasive front of the tumor or the entire lesion for malignant polyps ('hotspot' approach). The number of tumor buds is based on haematoxylin and eosin (H&E) assessment, although pan-cytokeratin immunohistochemistry can be used to help identify hotspots.[86] This may be of particular value when the invasive front is obscured by inflammatory cells. A correction for microscope eyepiece field diameter is required, the bud count normalised to a field area of 0.785 mm^2 (equivalent to an objective lens 20x with eyepiece diameter of 20 mm).

Tumor budding, applying the above system to assess tumor budding score (Bd1-Bd3) and actual number of buds, is considered a non-core item for reporting, pending the emergence of further evidence of reproducibility of assessment and clinical significance. Note that budding should only be reported in non-mucinous and non-signet-ring cell adenocarcinoma areas of tumor and budding should not be reported in cancers resected after neoadjuvant therapy.

Response to neoadjuvant therapy

Preoperative radiotherapy, chemoradiotherapy or systemic anti-cancer therapy may result in morphological tumor response in the form of fibrosis, necrosis or acellular mucin. Patients with rectal carcinomas who have had complete surgical resection following chemoradiotherapy, with morphological evidence of complete or marked tumor regression, have a better prognosis than those without significant regression.[87-91] For grading of regression, a four-tier system is recommended, based on a modification of the system described by Ryan *et al.*[92] Scoring (0-3) should be applied when any form of preoperative therapy is administered to rectal or colonic tumors, including short-course radiotherapy. In

such circumstances, this is a core item for reporting. Assessment of regression is based on evaluation of the primary tumor site. Similar features may be evident within regional lymph nodes involved by metastatic tumor, or at any distant metastatic sites. Although findings at metastatic sites do not influence tumor regression score, a descriptive comment in the pathology report is recommended to allow correlation with imaging. Overall designation as a complete pathological response requires the absence of viable tumor locally (ypT0) and in lymph nodes (ypN0). The entire tumor bed should be processed for histological examination in this situation.

Margin status

Assessment of surgical margin status has prognostic value and is considered a core item for reporting. In particular, circumferential or non-peritonealised margin involvement in rectal cancer is strongly predictive of local recurrence and poor survival.[93-97] Margin involvement in colon cancer is much less common and there is less evidence of its significance.[98,99] The definition of margin involvement is somewhat contentious but it is generally accepted that any circumferential margin ≤1 mm from tumor should be regarded as involved. The precise distance to the margin should be recorded, to the nearest 0.1 mm, if less than 1 mm, and to the nearest 1 mm, if less than 10 mm. This assessment may require a combination of macroscopic and microscopic evaluation. Any separately submitted anastomotic rings should be taken into consideration in measuring the distance to longitudinal margins.

There is some evidence to suggest that margin involvement due to discontinuous or intravascular tumor is associated with a similar risk of local recurrence to that of margin involvement by primary tumor.[93,94] Margin involvement by tumor within a lymph node, however, was reported in one study not to be associated with a significant risk of local

recurrence.[94] Therefore, if a lymph node containing tumor is present at the resection margin, and the lymph node capsule is intact, the circumferential margin should not be reported as involved (Figure 5). A comment should be added to the pathology report describing the interpretation. In the setting of margin involvement by discontinuous tumor, this should be clearly reported and a separate measurement provided of distance from the primary tumor.

Coexistent pathology

Any background colonic or rectal pathological abnormalities, such as polyps, chronic inflammatory bowel disease, effects of neoadjuvant therapy, diverticular disease or obstructive changes should be recorded as non-core information. In the event of two or more synchronous primary carcinomas, individual datasets should be completed as appropriate.

Ancillary studies

Clinical applications of ancillary testing applied to colorectal cancer are limited but expanding. Reflex testing for defective mismatch repair (MMR)/microsatellite instability (MSI) status is now widely recommended for the detection of Lynch syndrome,[100,101] caused by either a constitutional pathogenic mutation in one of the MMR genes, or sporadic MMR deficient colorectal cancers, usually caused by hypermethylation of the *MLH1* MMR gene promoter region. Defective MMR (dMMR) associated with MLH1 loss, or a MSI-high result, triggers algorithmic testing, including somatic *BRAF* mutation testing and/or *MLH1* promoter methylation testing, to distinguish between sporadic dMMR cancers and Lynch syndrome. Absence of *BRAF* V600 mutation and/or absent *MLH1* promoter hypermethylation should prompt a recommendation of referral to clinical genetics for appropriate counselling prior to germline mutation screening of the relevant MMR genes, as should loss of PMS2, MSH2

and/or MSH6 immunohistochemical expression. MMR status also informs patient management with MMR deficiency associated with good prognosis, poorer response to 5-fluorouracil-based chemotherapy and potential response to immune checkpoint blockade therapy.[102,103]

Patients with metastatic colorectal cancer should have available formalin-fixed paraffin-embedded tissue from either the primary or metastatic tumor tested for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations by either targeted assay or next generation sequencing.[101,104] The presence of a mutation in *KRAS* or *NRAS* (in exons 2, 3 or 4) is associated across stages II, III and IV with worse prognosis than matched *RAS* 'wild type' tumors and also predicts resistance to the anti-epidermal growth factor receptor (anti-EGFR) therapies cetuximab or panitumumab.[105,106] 'Wild type' *KRAS* and *NRAS* status must therefore be established before these drugs are administered. Similarly, it is likely that the presence of the V600E *BRAF* mutation confers resistance to anti-EGFR therapy, though this may be modified by addition of a BRAF and/or MEK inhibitor.[107,108] Most modern guidelines therefore recommend also testing metastatic colorectal cancers for the V600E *BRAF* mutation.[101]

Although the above indications for focused ancillary testing in colorectal cancer are now well established, facilities for such testing are not globally available. As such, these are currently considered non-core items for reporting. It is inevitable that further clinical applications of ancillary testing for colorectal cancer will emerge and this will be kept under review.

Histologically confirmed distant metastases

It is occasionally possible to designate a case as having histologically confirmed distant metastatic disease (pM1) on examination of either the main surgical resection specimen, for

example when a peritoneal or omental deposit is identified, or of a separately submitted biopsy or resection specimen, for example from the liver or a non-regional lymph node.

UICC/AJCC 8th edition staging systems recognize prognostic stratification according to the pattern of organ involvement by distant metastatic disease and have subclassified pM1 into pM1a indicating metastatic disease in one distant organ (excluding metastatic peritoneal disease), pM1b indicating metastatic disease in two or more distant organs and pM1c indicating metastatic peritoneal disease (regardless of other organ involvement).[14,15] It is therefore important for pathologists to accurately document such disease and this is considered a core item for reporting. It should be noted that pathologists can only make a positive statement regarding distant metastatic disease, their assessment based on selected specimens submitted to them for examination, and therefore the terms 'pM0' or 'pMX' should no longer be used. cM1 and cM0 can be applied according to best radiological and intraoperative evidence available.

Pathological staging

The agreed criteria of the UICC and AJCC 8th editions are applied to derive TNM stage.[14,15] The only exception is that this dataset does not advocate the use of pT *in situ* for colorectal cancer, as discussed above.

If completion surgery follows a diagnosis of carcinoma made in a local excision specimen, the pathological findings within both specimens should be considered in providing a single, overall TNM stage. Similarly, if a resection specimen contains synchronous primary carcinomas, each should be separately assessed and individual datasets completed, but a single overarching stage provided, following the conventions of TNM.

Discussion

Quality of pathology reporting and mutual understanding between colorectal surgeon and pathologist is vital to management and outcomes of patients with colorectal cancer. It is well established that adoption of structured pathology reporting is associated with greater clinician satisfaction and improved access to pathology information relevant to patient management, as well ease of returning pathology data for central registration purposes.[109,110] Adoption of structured reporting helps ensure data is complete and it has been demonstrated for colorectal cancer to reduce the risk of missing assessment of important pathology features when compared to narrative reporting, especially for non-specialist pathologists, thereby impacting patient care.[110,111] There remains an important role however for a narrative component to pathology reports, explaining any areas of uncertainty or unusual pathological findings which may be pertinent to individual patient management and offer useful feedback to the surgeon.

Herein we have described the process of creation of such a dataset for colorectal cancer surgical resection specimens, involving an international panel of expert gastrointestinal pathologists from nine countries and with representation from colorectal surgery and oncology. There was strong representation of authors of equivalent existing colorectal cancer datasets from the US, UK and Australasia. A key aim of ICCR is to minimize the workload involved in production and regular update of such datasets in addition to standardization of reporting to facilitate international comparisons. Scrutiny of these existing national datasets illustrates the current problem of lack of uniformity.[6-8] Whilst most of the content is uniform between datasets, there are subtle but important differences pertaining to numerous data items, which would hinder comparison. This is the first agreed international dataset for

colorectal cancer pathology reporting. It is hoped that the various national datasets align with this ICCR version in the future.

This dataset is more extensive than the UICC/AJCC TNM cancer staging systems, which provide primarily a classification of anatomical extent of disease and represent the most powerful predictor of clinical outcome for many cancers. Incorporation of additional prognostically relevant morphological features into TNM staging is challenging. Some, specifically venous, lymphatic invasion and perineural invasion, can already be optionally recorded under the UICC/AJCC systems, not impacting the summary stage. However, as a result the prognostic impact of these features may not be fully considered in the clinical management of individual cases. More prominent integration of newly-defined prognostic features into the TNM system will be complex, for example as described above for tumor deposits. Nevertheless, international discussion of such features is necessary to further the goals of reproducible consensus definitions and standardization of interpretation.

The ICCR aspires to widespread uptake of this freely available dataset by those countries currently lacking such a strategy, to improve the standard of pathology reporting of colorectal cancer globally. The greatest impact may be in low- and middle-income countries, where incidence of colorectal cancer has risen significantly.[112-114] Standardized reporting will allow comparison of relative proportions of colorectal cancer subtypes between countries, assessment of the impact of new screening programs and participation in international trials targeting a specific molecular subset of colorectal cancer and requiring a minimum standard of pathology reporting.

To conclude, this internationally agreed freely available dataset provides a structured template for the pathological reporting of colorectal cancer surgical resection specimens. The ICCR initiative streamlines the dataset production process, both for new datasets and for regular updates as new evidence emerges. Such international collaborative efforts become more important with rapid progress in the fields of molecular pathology, digital pathology and image analysis, allowing rapid translation of new developments, many relevant to surgical practice, into routine pathology reporting.

Acknowledgement

References

1   Manser MD, Levine DF, Pheby DF, et al (2000). Colorectal cancer registration: the central importance of pathology. *J Clin Pathol* 53(11):875-877.

2   Nagtegaal ID, West NP, van Krieken JH, et al (2014). Pathology is a necessary and informative tool in oncology clinical trials. *J Pathol* 232(2):185-189.

3   Quirke P, Williams GT, Ectors N, et al (2007). The future of the TNM staging system in colorectal cancer: time for a debate? *Lancet Oncol* 8(7):651-657.

4   Williams MD, DeLellis RA, Erickson LA, et al (2020). Pathology data set for reporting parathyroid carcinoma and atypical parathyroid neoplasm: recommendations from the International Collaboration on Cancer Reporting. *Hum Pathol* DOI:10.1016/j.humpath.2020.07.008

5   Kench JG, Judge M, Delahunt B, et al (2019). Dataset for the reporting of prostate carcinoma in radical prostatectomy specimens: updated recommendations from the International Collaboration on Cancer Reporting. *Virchows Arch* 475(3):263-277.

6   College of American Pathologists (2020). *Protocol for the examination of excisional biopsy specimens from patients with primary carcinoma of the colon and rectum*. Available from: https://documents.cap.org/protocols/cp-gilower-colonrectum-biopsy-20-4100.pdf (Accessed 28th August 2020).

7   The Royal College of Pathologists (2018). *Dataset for histopathological reporting of colorectal cancer*. Available from: Available from: https://www.rcpath.org/uploads/assets/c8b61ba0-ae3f-43f1-85ffd3ab9f17cfe6/G049-Dataset-for-histopathological-reporting-of-colorectal-cancer.pdf (Accessed 22nd April 2020).

8   Royal College of Pathologists of Australasia (2016). *Colorectal cancer structured reporting protocol*. Available from: Available from: https://www.rcpa.edu.au/getattachment/730b9fad-3228-4601-9009-b3d671818bd6/Protocol-colorectal-cancer.aspx (Accessed 22nd April 2020).

9   Nagtegaal ID, Arends MJ, Odze RD and Lam AK (2019). Tumours of the colon and rectum. In: *Digestive System Tumours. WHO Classification of Tumours, 5th Edition*, Lokuhetty D, White V, Watanabe R and Cree IA (eds), IARC Press, Lyon, France.

10   Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.

11   D'Souza N, de Neree Tot Babberich MPM, d'Hoore A, et al (2019). Definition of the Rectum: An International, Expert-based Delphi Consensus. *Ann Surg* 270(6):955-959.

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

13   Nagtegaal ID, van de Velde CJ, Marijnen CA, et al (2005). Low rectal cancer: a call for a change of approach in abdominoperineal resection. *J Clin Oncol* 23(36):9257-9264.

14   Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *Union for International Cancer Control. TNM Classification of Malignant Tumours, 8th Edition*, Wiley-Blackwell, USA.

15   Amin MB, Edge SB, Greene FL, et al (2017). *AJCC Cancer Staging Manual. 8th ed.*, Springer, New York.

16   Quirke P, Steele R, Monson J, et al (2009). Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet* 373(9666):821-828.

17   Arbman G, Nilsson E, Hallbook O, et al (1996). Local recurrence following total mesorectal excision for rectal cancer. *Br J Surg* 83(3):375-379.

18   Kapiteijn E, Marijnen CA, Nagtegaal ID, et al (2001). Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 345(9):638-646.

19   Nagtegaal ID, van de Velde CJ, van der Worp E, et al (2002). Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol* 20(7):1729-1734.

20   den Dulk M, Putter H, Collette L, et al (2009). The abdominoperineal resection itself is associated with an adverse outcome: the European experience based on a pooled analysis of five European randomised clinical trials on rectal cancer. *Eur J Cancer* 45(7):1175-1183.

21   Stelzner S, Koehler C, Stelzer J, et al (2011). Extended abdominoperineal excision vs. standard abdominoperineal excision in rectal cancer-a systematic overview. *Int J Colorectal Dis* 26(10):1227-1240.

22   West NP, Anderin C, Smith KJ, et al (2010). Multicentre experience with extralevator abdominoperineal excision for low rectal cancer. *Br J Surg* 97(4):588-599.

23   Battersby NJ, How P, Moran B, et al (2016). Prospective validation of a low rectal cancer magnetic resonance imaging staging system and development of a local recurrence risk stratification model: the MERCURY II study. *Ann Surg* 263(4):751-760.

24   Quirke P, Thorpe H, Dewberry S, et al (2008). *Prospective assessment of the quality of surgery in the MRC CLASICC trial evidence for variation in the plane of surgery in colon*

cancer, local recurrence and survival. Available from: Available from: http://abstracts.ncri.org.uk/abstract/prospective-assessment-of-the-quality-of-surgery-in-the-mrc-clasicc-trial-evidence-for-variation-in-the-plane-of-surgery-in-colon-cancer-local-recurrence-and-survival-4/ (Accessed 22nd April 2020).

25   West NP, Morris EJ, Rotimi O, et al (2008). Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. *Lancet Oncol* 9(9):857-865.

26   Gouvas N, Agalianos C, Papaparaskeva K, et al (2016). Surgery along the embryological planes for colon cancer: a systematic review of complete mesocolic excision. *Int J Colorectal Dis* 31(9):1577-1594.

27   Kang H, O'Connell JB, Maggard MA, et al (2005). A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. *Dis Colon Rectum* 48(6):1161-1168.

28   Kakar S, Deng G, Smyrk TC, et al (2012). Loss of heterozygosity, aberrant methylation, BRAF mutation and KRAS mutation in colorectal signet ring cell carcinoma. *Mod Pathol* 25(7):1040-1047.

29   Pyo JS, Sohn JH and Kang G (2016). Medullary carcinoma in the colorectum: a systematic review and meta-analysis. *Hum Pathol* 53:91-96.

30   Garcia-Solano J, Perez-Guillermo M, Conesa-Zamora P, et al (2010). Clinicopathologic study of 85 colorectal serrated adenocarcinomas: further insights into the full recognition of a new subset of colorectal carcinoma. *Hum Pathol* 41(10):1359-1368.

31   Haupt B, Ro JY, Schwartz MR, et al (2007). Colorectal adenocarcinoma with micropapillary pattern and its association with lymph node metastasis. *Mod Pathol* 20(7):729-733.

32   Gonzalez RS, Cates JM, Washington MK, et al (2016). Adenoma-like adenocarcinoma: a subtype of colorectal carcinoma with good prognosis, deceptive appearance on biopsy and frequent KRAS mutation. *Histopathology* 68(2):183-190.

33   Sorbye H, Strosberg J, Baudin E, et al (2014). Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer* 120(18):2814-2823.

34   Milione M, Maisonneuve P, Spada F, et al (2017). The Clinicopathologic Heterogeneity of Grade 3 Gastroenteropancreatic Neuroendocrine Neoplasms: Morphological Differentiation and Proliferation Identify Different Prognostic Categories. *Neuroendocrinology* 104(1):85-93.

35   Shamir ER, Devine WP, Pekmezci M, et al (2019). Identification of high-risk human papillomavirus and Rb/E2F pathway genomic alterations in mutually exclusive subsets of colorectal neuroendocrine carcinoma. *Mod Pathol* 32(2):290-305.

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   Chapuis PH, Dent OF, Fisher R, et al (1985). A multivariate analysis of clinical and pathological variables in prognosis after resection of large bowel cancer. *Br J Surg* 72(9):698-702.

38   Renfro LA, Grothey A, Xue Y, et al (2014). ACCENT-based web calculators to predict recurrence and overall survival in stage III colon cancer. *J Natl Cancer Inst* 106(12):1-9.

39   Weiser MR, Gonen M, Chou JF, et al (2011). Predicting survival after curative colectomy for cancer: individualizing colon cancer staging. *J Clin Oncol* 29(36):4796-4802.

40   Konishi T, Shimada Y, Lee LH, et al (2018). Poorly differentiated clusters predict colon cancer recurrence: an in-depth comparative analysis of invasive-front prognostic markers. *Am J Surg Pathol* 42(6):705-714.

41   Ueno H, Kajiwara Y, Shimazaki H, et al (2012). New criteria for histologic grading of colorectal cancer. *Am J Surg Pathol* 36(2):193-201.

42   Kakar S, Aksoy S, Burgart LJ and Smyrk TC (2004). Mucinous carcinoma of the colon: correlation of loss of mismatch repair enzymes with clinicopathologic features and survival. *Mod Pathol* 17(6):696-700.

43   Yoshioka Y, Togashi Y, Chikugo T, et al (2015). Clinicopathological and genetic differences between low-grade and high-grade colorectal mucinous adenocarcinomas. *Cancer* 121(24):4359-4368.

44   Kojima M, Shimazaki H, Iwaya K, et al (2017). Intramucosal colorectal carcinoma with invasion of the lamina propria: a study by the Japanese Society for Cancer of the Colon and Rectum. *Hum Pathol* 66:230-237.

45   Jass JR, O'Brien MJ, Riddell RH, et al (2007). Recommendations for the reporting of surgically resected specimens of colorectal carcinoma. *Hum Pathol* 38(4):537-545.

46   Puppa G, Maisonneuve P, Sonzogni A, et al (2007). Pathological assessment of pericolonic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging. *Mod Pathol* 20(8):843-855.

47   Shepherd NA, Baxter KJ and Love SB (1997). The prognostic importance of peritoneal involvement in colonic cancer: a prospective evaluation. *Gastroenterology* 112(4):1096-1102.

48   Gunderson LL, Jessup JM, Sargent DJ, et al (2010). Revised TN categorization for colon cancer based on national survival outcomes data. *J Clin Oncol* 28(2):264-271.

49   Kirsch R, Messenger DE, Shepherd NA, et al (2018). Wide variability in assessment and reporting of colorectal cancer specimens among North American pathologists: results of a Canada-US Survey. *Can J of Pathol* 11(1):58-69.

50   Liang WY, Chang WC, Hsu CY, et al (2013). Retrospective evaluation of elastic stain in the assessment of serosal invasion of pT3N0 colorectal cancers. *Am J Surg Pathol* 37(10):1565-1570.

51   Kojima M, Nakajima K, Ishii G, et al (2010). Peritoneal elastic laminal invasion of colorectal cancer: the diagnostic utility and clinicopathologic relationship. *Am J Surg Pathol* 34(9):1351-1360.

52   Grin A, Messenger DE, Cook M, et al (2013). Peritoneal elastic lamina invasion: limitations in its use as a prognostic marker in stage II colorectal cancer. *Hum Pathol* 44(12):2696-2705.

53   Puppa G, Shepherd NA, Sheahan K, et al (2011). Peritoneal elastic lamina invasion in colorectal cancer: the answer to a controversial area of pathology? *Am J Surg Pathol* 35(3):465-468.

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

55   Betge J, Pollheimer MJ, Lindtner RA, et al (2012). Intramural and extramural vascular invasion in colorectal cancer: prognostic significance and quality of pathology reporting. *Cancer* 118(3):628-638.

56   Roxburgh CS, McMillan DC, Anderson JH, et al (2010). Elastica staining for venous invasion results in superior prediction of cancer-specific survival in colorectal cancer. *Ann Surg* 252(6):989-997.

57   Talbot IC, Ritchie S, Leighton M, et al (1981). Invasion of veins by carcinoma of rectum: method of detection, histological features and significance. *Histopathology* 5(2):141-163.

58   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(11):1021-1025.

59   Kirsch R, Messenger DE, Riddell RH, et al (2013). Venous invasion in colorectal cancer: impact of an elastin stain on detection and interobserver agreement among gastrointestinal and nongastrointestinal pathologists. *Am J Surg Pathol* 37(2):200-210.

60   Roxburgh CS and Foulis AK (2011). The prognostic benefits of routine staining with elastica to increase detection of venous invasion in colorectal cancer specimens. *J Clin Pathol* 64(12):1142.

61   Messenger DE, Driman DK and Kirsch R (2012). Developments in the assessment of venous invasion in colorectal cancer: implications for future practice and patient outcome. *Hum Pathol* 43(7):965-973.

62   Kojima M, Shimazaki H, Iwaya K, et al (2013). Pathological diagnostic criterion of blood and lymphatic vessel invasion in colorectal cancer: a framework for developing an objective pathological diagnostic system using the Delphi method, from the Pathology Working Group of the Japanese Society for Cancer of the Colon and Rectum. *J Clin Pathol* 66(7):551-558.

63   Santos C, Lopez-Doriga A, Navarro M, et al (2013). Clinicopathological risk factors of Stage II colon cancer: results of a prospective study. *Colorectal Dis* 15(4):414-422.

64   Lim SB, Yu CS, Jang SJ, Kim TW, Kim JH and Kim JC (2010). Prognostic significance of lymphovascular invasion in sporadic colorectal cancer. *Dis Colon Rectum* 53(4):377-384.

65   van Wyk HC, Roxburgh CS, Horgan PG, et al (2014). The detection and role of lymphatic and blood vessel invasion in predicting survival in patients with node negative operable primary colorectal cancer. *Crit Rev Oncol Hematol* 90(1):77-90.

66   Ueno H, Shirouzu K, Eishi Y, et al (2013). Characterization of perineural invasion as a component of colorectal cancer staging. *Am J Surg Pathol* 37(10):1542-1549.

67   Liebig C, Ayala G, Wilks J, et al (2009). Perineural invasion is an independent predictor of outcome in colorectal cancer. *J Clin Oncol* 27(31):5131-5137.

68   Knijn N, Mogk SC, Teerenstra S, et al (2016). Perineural invasion is a strong prognostic factor in colorectal cancer: a systematic review. *Am J Surg Pathol* 40(1):103-112.

69   Huh JW, Kim HR and Kim YJ (2010). Prognostic value of perineural invasion in patients with stage II colorectal cancer. *Ann Surg Oncol* 17(8):2066-2072.

70   Wijesuriya RE, Deen KI, Hewavisenthi J, et al (2005). Neoadjuvant therapy for rectal cancer down-stages the tumor but reduces lymph node harvest significantly. *Surg Today* 35(6):442-445.

71   Chang GJ, Rodriguez-Bigas MA, Skibber JM, et al (2007). Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst* 99(6):433-441.

72   Sloothaak DA, Sahami S, van der Zaag-Loonen HJ, et al (2014). The prognostic value of micrometastases and isolated tumour cells in histologically negative lymph nodes of patients with colorectal cancer: a systematic review and meta-analysis. *Eur J Surg Oncol* 40(3):263-269.

73   Sobin LH, Gospodarowicz MK and Wittekind C (eds) (2009). *Union for International Cancer Control. TNM Classification of Malignant Tumours, (7th ed)*, Wiley-Blackwell, USA.

74   Edge SE, Byrd DR, Compton CC, et al (eds) (2010). *AJCC Cancer Staging Manual 7th ed.*, Springer, New York.

75   Nagtegaal ID, Knijn N, Hugen N, et al (2017). Tumor deposits in colorectal cancer: improving the value of modern staging-a systematic review and meta-analysis. *J Clin Oncol* 35(10):1119-1127.

76   Zlobec I and Lugli A (2010). Epithelial mesenchymal transition and tumor budding in aggressive colorectal cancer: tumor budding as oncotarget. *Oncotarget* 1(7):651-661.

77   Pai RK, Cheng YW, Jakubowski MA, et al (2017). Colorectal carcinomas with submucosal invasion (pT1): analysis of histopathological and molecular factors predicting lymph node metastasis. *Mod Pathol* 30(1):113-122.

78   Beaton C, Twine CP, Williams GL et al (2013). Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. *Colorectal Dis* 15(7):788-797.

79   Ueno H, Hase K, Hashiguchi Y, et al (2014). Novel risk factors for lymph node metastasis in early invasive colorectal cancer: a multi-institution pathology review. *J Gastroenterol* 49(9):1314-1323.

80   Suh JH, Han KS, Kim BC, Hong CW, Sohn DK, Chang HJ, Kim MJ, Park SC, Park JW, Choi HS and Oh JH (2012). Predictors for lymph node metastasis in T1 colorectal cancer. *Endoscopy* 44(6):590-595.

81   Tateishi Y, Nakanishi Y, Taniguchi H, et al (2010). Pathological prognostic factors predicting lymph node metastasis in submucosal invasive (T1) colorectal carcinoma. *Mod Pathol* 23(8):1068-1072.

82   van Wyk HC, Park J, Roxburgh C, et al (2015). The role of tumour budding in predicting survival in patients with primary operable colorectal cancer: a systematic review. *Cancer Treat Rev* 41(2):151-159.

83   Petrelli F, Pezzica E, Cabiddu M, et al (2015). Tumour budding and survival in stage II colorectal cancer: a systematic review and pooled analysis. *J Gastrointest Cancer* 46(3):212-218.

84   Rogers AC, Winter DC, Heeney A, et al (2016). Systematic review and meta-analysis of the impact of tumour budding in colorectal cancer. *Br J Cancer* 115(7):831-840.

85   Lugli A, Kirsch R, Ajioka Y, Bosman F, Cathomas G, Dawson H, El Zimaity H, Flejou JF, Hansen TP, Hartmann A, Kakar S, Langner C, Nagtegaal I, Puppa G, Riddell R, Ristimaki A, Sheahan K, Smyrk T, Sugihara K, Terris B, Ueno H, Vieth M, Zlobec I and Quirke P (2017). Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. *Mod Pathol* 30(9):1299-1311.

86   Koelzer VH, Assarzadegan N, Dawson H, et al (2017). Cytokeratin-based assessment of tumour budding in colorectal cancer: analysis in stage II patients and prospective diagnostic experience. *J Pathol Clin Res* 3(3):171-178.

87   Maas M, Nelemans PJ, Valentini V, et al (2010). Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 11(9):835-844.

88   Rodel C, Martus P, Papadoupolos T, et al (2005). Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol* 23(34):8688-8696.

89   Hermanek P, Merkel S and Hohenberger W (2013). Prognosis of rectal carcinoma after multimodal treatment: ypTNM classification and tumor regression grading are essential. *Anticancer Res* 33(2):559-566.

90   Gavioli M, Luppi G, Losi L, et al (2005). Incidence and clinical impact of sterilized disease and minimal residual disease after preoperative radiochemotherapy for rectal cancer. *Dis Colon Rectum* 48(10):1851-1857.

91   Ruo L, Tickoo S, Klimstra DS, et al (2002). Long-term prognostic significance of extent of rectal cancer response to preoperative radiation and chemotherapy. *Ann Surg* 236(1):75-81.

92   Ryan R, Gibbons D, Hyland JM, et al (2005). Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology* 47(2):141-146.

93   Nagtegaal ID and Quirke P (2008). What is the role for the circumferential margin in the modern treatment of rectal cancer? *J Clin Oncol* 26(2):303-312.

94   Birbeck KF, Macklin CP, Tiffin NJ, et al (2002). Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg* 235(4):449-457.

95   Ng IO, Luk IS, Yuen ST, et al (1993). Surgical lateral clearance in resected rectal carcinomas. A multivariate analysis of clinicopathologic features. *Cancer* 71(6):1972-1976.

96   Adam IJ, Mohamdee MO, Martin IG, et al (1994). Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 344(8924):707-711.

97   Quirke P, Durdey P, Dixon MF, et al (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.

98   Scott N, Jamali A, Verbeke C, et al (2008). Retroperitoneal margin involvement by adenocarcinoma of the caecum and ascending colon: what does it mean? *Colorectal Dis* 10(3):289-293.

99   Bateman AC, Carr NJ and Warren BF (2005). The retroperitoneal surface in distal caecal and proximal ascending colon carcinoma: the Cinderella surgical margin? *J Clin Pathol* 58(4):426-428.

100   National Institute for Health and Care Excellence (2017). *Molecular testing strategies for Lynch syndrome in people with colorectal cancer*. Available from: https://www.nice.org.uk/guidance/dg27 (Accessed 28th August 2020).

101   National Comprehensive Cancer Network (2020). *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer*. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf (Accessed 28th August 2020).

102   Le DT, Durham JN, Smith KN, et al (2017). Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 357(6349):409-413.

103   Le DT, Uram JN, Wang H, et al (2015). PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 372(26):2509-2520.

104   National Institute for Health and Care Excellence (2017). *Cetuximab and panitumumab for previously untreated metastatic colorectal cancer. Technology appraisal guidance*. Available from: https://www.nice.org.uk/guidance/ta439/chapter/1-Recommendations (Accessed 28th August 2020).

105   Amado RG, Wolf M, Peeters M, et al (2008). Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 26(10):1626-1634.

106   Lièvre A, Bachet JB, Boige V, et al (2008). KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol* 26(3):374-379.

107   Pietrantonio F, Petrelli F, Coinu A, et al (2015). Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. *Eur J Cancer* 51(5):587-594.

108   Morris VK and Bekaii-Saab T (2020). Improvements in Clinical Outcomes for BRAF(V600E) -Mutant Metastatic Colorectal Cancer. *Clin Cancer Res* DOI:10.1158/1078-0432.CCR-19- 3809.

109   Lankshear S, Srigley J, McGowan T, et al (2013). Standardized synoptic cancer pathology reports - so what and who cares? A population-based satisfaction survey of 970 pathologists, surgeons, and oncologists. *Arch Pathol Lab Med* 137(11):1599-1602.

110   Srigley JR, McGowan T, Maclean A, et al C (2009). Standardized synoptic cancer pathology reporting: a population-based approach. *J Surg Oncol* 99(8):517-524.

111   Messenger DE, McLeod RS and Kirsch R (2011). What impact has the introduction of a synoptic report for rectal cancer had on reporting outcomes for specialist gastrointestinal and nongastrointestinal pathologists? *Arch Pathol Lab Med* 135(11):1471-1475.

112   Arnold M, Abnet CC, Neale RE, et al (2020). Global Burden of 5 Major Types of Gastrointestinal Cancer. *Gastroenterology* 159(1):335-349.e315.

113   Kamaraju S, Drope J, Sankaranarayanan R, et al (2020). Cancer Prevention in Low-Resource Countries: An Overview of the Opportunity. *Am Soc Clin Oncol Educ Book* 40:1-12.

114   Bray F, Ferlay J, Soerjomataram I, et al (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68(6):394-424.

Figures

Figure 1. A fresh anterior exenteration specimen comprising abdominoperineal excision of the rectum and anus with *en bloc* levator ani muscles, prostate, seminal vesicles and bladder.
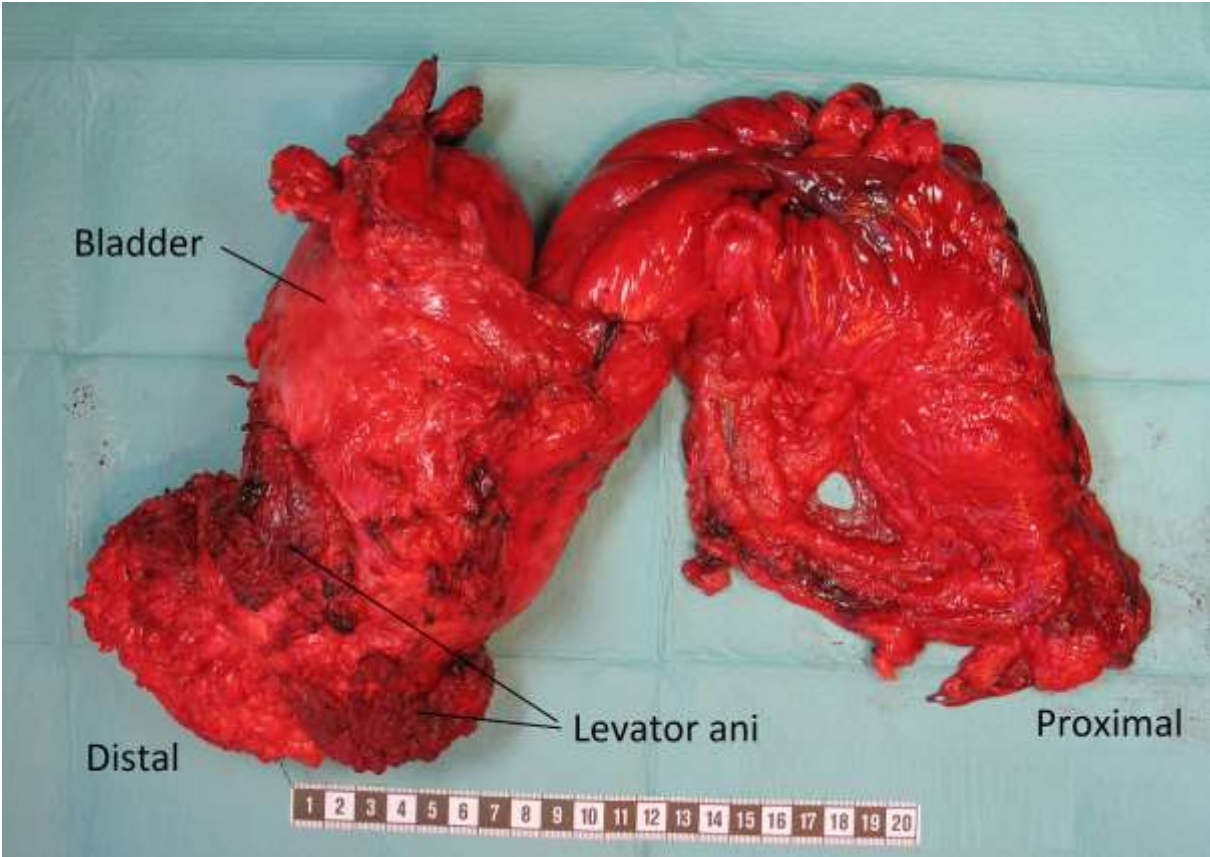
Figure 2. Rectal anatomy and possible relationships of rectal cancers to the peritoneal reflection. *Adapted by permission from Nicholas P. West and Philip Quirke: Springer Multidisciplinary Treatment of Colorectal Cancer (G. Baatrup, ed.); Quality of Surgery by Nicholas P. West and Philip Quirke (2021).*
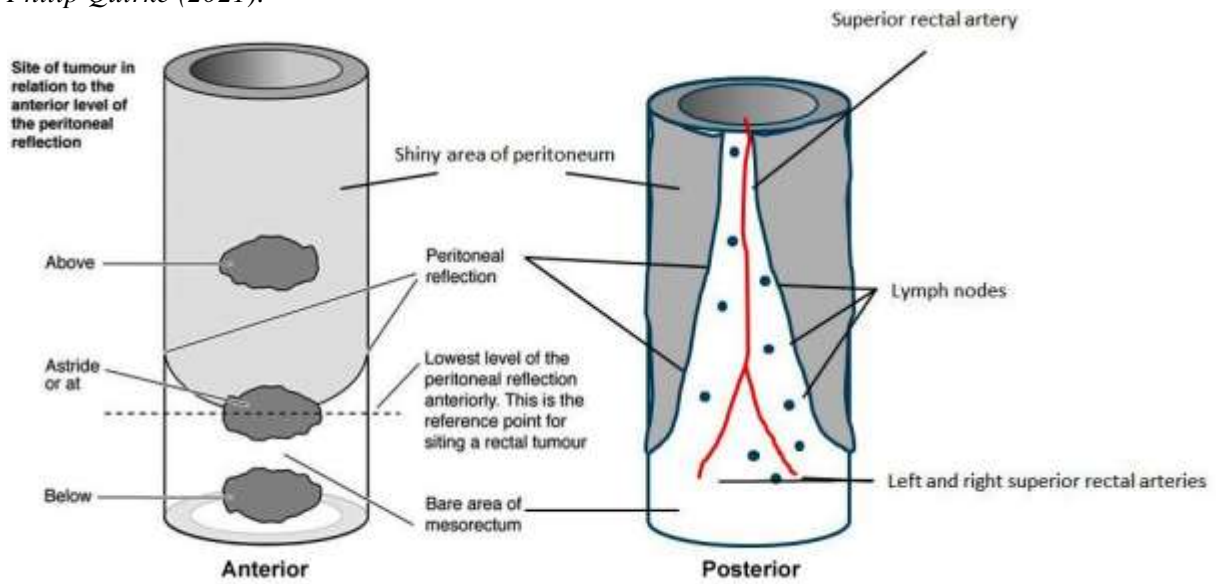
Figure 3. Planes of colorectal cancer surgery for the mesorectum (A-C), sphincters (D-F) and mesocolon (G-I). For the mesorectum, applicable to all rectal cancer specimens, the planes include the mesorectal plane, with intact mesorectum (A), intramesorectal plane, with mesorectal defect (B) and muscularis propria plane, with little bulk to mesorectum and exposure of muscularis propria (C). For the sphincters, applicable to all abdominoperineal excisions in addition to the mesorectal plane, the planes include the extralevator plane (D), sphincteric plane (E) and intrasphincteric plane (F). The extralevator specimen includes *en bloc* resection of the levator ani muscles and coccyx thus preventing the creating of a surgical waist (D). The intrasphincteric plane specimen includes a large anterior perforation (F). For the mesocolon, applicable to all colon cancer specimens, the planes include the mesocolic plane, with intact mesocolon (G), intramesocolic plane, with mesocolic defect (H) and muscularis propria plane, with ragged mesocolon and exposure of muscularis propria (I). *Adapted by permission from Nicholas P. West and Philip Quirke: Springer Multidisciplinary Treatment of Colorectal Cancer (G. Baatrup, ed.); Quality of Surgery by Nicholas P. West and Philip Quirke (2021).*
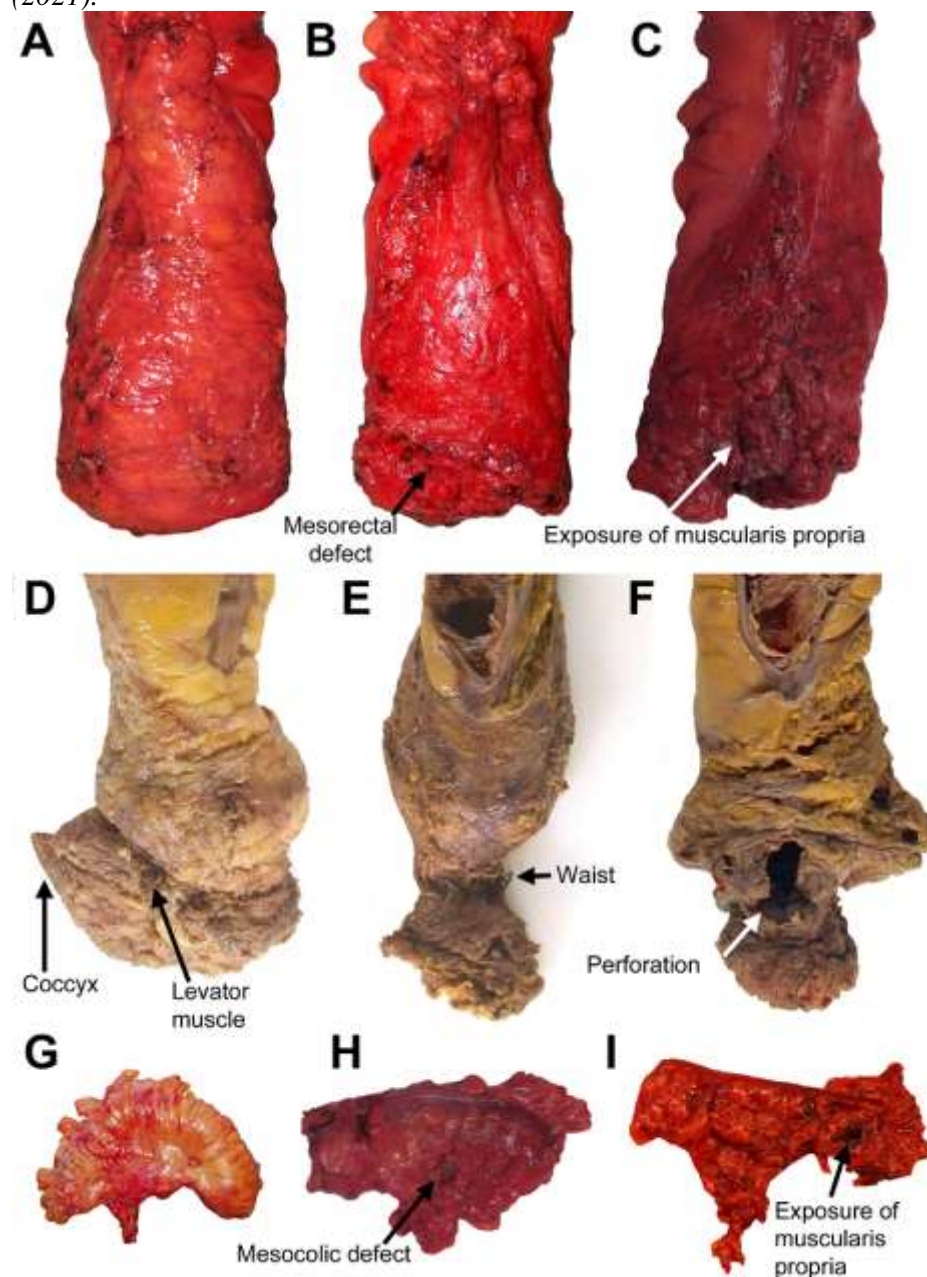
Figure 4. Metastatic pathways in colorectal cancer. A, Obvious extramural venous invasion (EMVI, black arrows), including a focus extending perpendicularly from muscularis propria (white arrow) (H&E). B, Lymph node metastatic disease (white arrows) and EMVI (black arrow,) confirmed by identification of an elastic lamina in the vein wall (inset) on histochemical staining (H&E, elastic van gieson). C, Lymphatic invasion, malignant glands (arrow) lying within a thin-walled lymphatic channel, surrounded by lymphoid cells (H&E). D, Perineural invasion, malignant glands infiltrating thickened neural bundles (arrows), highlighted by S100 immunohistochemical staining (Upper, H&E; Lower, S100). E, Tumour deposit, defined by the absence of features of any identifiable metastatic pathway (ancillary stains non-contributory).
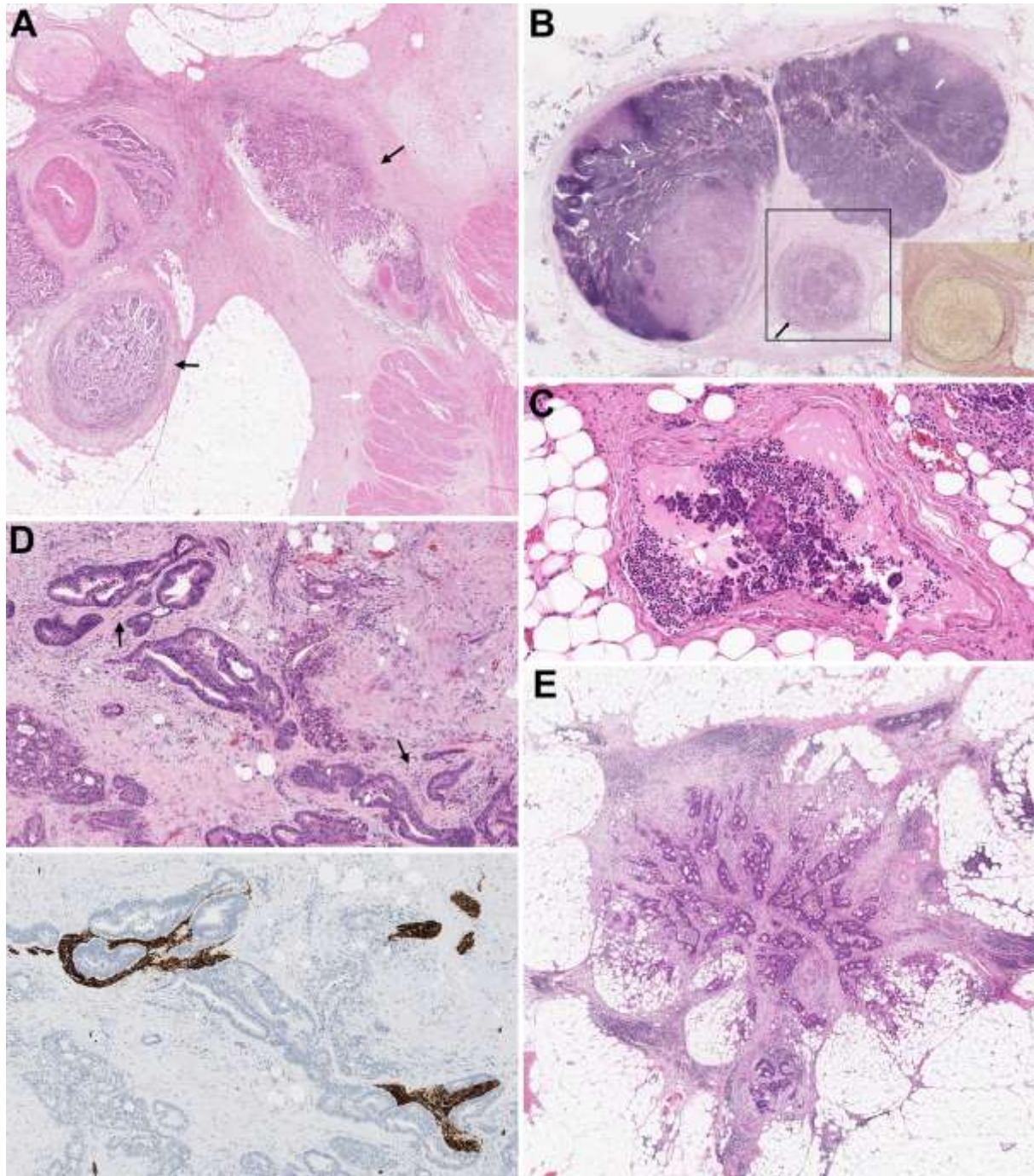
Figure 5. A, Posterior aspect of a right hemicolectomy specimen highlighting an intact, enlarged lymph node (rectangle) abutting the posterior specimen margin. B, Histology of a horizontal section through this lymph node shows metastatic mucinous adenocarcinoma. Although tumor extends to the surgical margin (painted black at base of image), tumor is confined to the intact lymph node and therefore NOT considered to represent margin involvement.