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

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Authorship justification: This manuscript describes the creation of a new International Collaboration on Cancer Reporting dataset for pathology reporting of colorectal cancer surgical resection specimens. This first internationally agreed dataset for colorectal cancer pathology reporting represents the culmination of a series of web meetings and protracted e-mail exchanges over several years discussing, agreeing and finalising content amongst an international authorship, representing four continents and nine countries. All authors were deeply involved in this process, (a) making substantial contributions to one or more dataset items (b) participating in either drafting specific manuscript sections or reviewing critically for intellectual content; and (c) approving the final version for publication.

Running title: ICCR Colorectal Cancer dataset

Min 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.

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).

Background: 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 a dataset for colorectal cancer 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.

Keywords: dataset, protocol, structured report, synoptic report, ICCR, guidelines, colorectal cancer

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 data for cancer registrations, epidemiological audits and research including clinical trials.[1,2] Tissue-based cancer research also partly relies on histopathological stage, the presence high risk features and molecular pathological subtypes. Standardization of pathology evaluation of cancer resection specimens and reporting of individual features is essential, to allow valid comparison of data between cohorts and countries, to allow assessment of the impact of new screening programs and to allow participation in multicenter trials. 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 (CRC) 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] If there is limited evidence, clear consensus-based guidelines, based on best available evidence and expert opinion, are 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] 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 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 CRC 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 CRC 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 CRC datasets were included.[5-7] 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).[2] 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 classifications and staging systems. Furthermore, primary CRC 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 CRC 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'].[8] 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 essential for optimal specimen sampling and histological interpretation. 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 on neoadjuvant therapy, including type 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. Staging should be provided with a 'y' prefix.

Secondly, the nature of the operative procedure is 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. If the operative specimen includes any additional tissue or organs, 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 tumors, these should all be documented individually and separate datasets completed for each. Tumor location is a core item, 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 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 biology, clinical features, management and risks of peritoneal versus local 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 growth obliterates these anatomical landmarks, the tumor site should be retrieved from available clinical and radiological information.[9] 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

Tumor size has no prognostic significance for CRC and does not directly influence staging. Despite this, maximum 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 CRC [10,11] and its presence or absence should be recorded as a core item. Tumor perforation is defined as a macroscopically visible full thickness defect, 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.[12,13] 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 CRC. 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. 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).[14] 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%.[15,16] Furthermore, objective macroscopic assessment by pathologists of the surgical plane of excision predicts margin involvement, local recurrence and survival.[14,17] 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.[18] More radical surgery to

remove more tissue around low rectal tumors by *en bloc* resection of the levator muscles, extralevator abdominoperineal excision, reduces the risk of CRM involvement and intraoperative full thickness defects leading to better long term outcomes.[19, 20] Using staging magnetic resonance imaging (MRI), radiologists are able to predict the optimal dissection plane for abdominoperineal excision surgery.[21] 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 CRC dataset,[6] 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.[11] 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.[22] 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.[23] 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.[22]

Histological tumor type

The WHO Classification of Tumors of the Digestive System is recommended for tumor typing as a core item.[2] Almost all CRC are adenocarcinomas, most of which are of no specific type or 'not otherwise specified' (NOS). Specific subtypes of adenocarcinoma are recognized 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, 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.[2] Like mucinous adenocarcinoma, there is a strong association with microsatellite instability and *BRAF* V600E mutation.[2]

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.[2]

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.[2] *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.[2]

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.[2] 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.[2] 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.[24] Grade 3 NETs are better differentiated than NECs and the primary distinction is morphological. 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,[25] histological grade of CRC, based on gland formation, is an independent prognostic factor and is a core item.[26,27] A two-tiered

grading system is more reproducible and favoured over a four-tiered grading system. Aligning with the latest WHO classification,[2] grading is based on the least differentiated 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 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.[28]

According to the latest WHO classification, only adenocarcinoma NOS and mucinous adenocarcinoma should be graded.[2] 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.[2]

Extent of invasion

Local invasion depth of CRC is categorised by the pT classification. This is the most important prognostic factor in CRC and is a core data item, using UICC and AJCC 8th edition criteria.[12,13] 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,[29] 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 the low rectum, where complexities of sphincter anatomy make accurate assessment of level of invasion 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.

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.[30] 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.[31] 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.[10] If tumor passes close to the serosal surface and elicits a mesothelial reaction without clear invasion, this is categorized as pT3, although additional sections and/or multiple levels should be examined to look deeper invasion. This setting is prone to interobserver variation however.[32] Elastic stains to identify peritoneal elastic lamina invasion are advocated in some studies, as a staging or prognostic tool.[33,34] 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 discontinuous peritoneal deposition. The former indicates pT4a disease whilst the latter is regarded as distant metastatic disease, pM1c. It is also important to distinguish involvement of a peritoneal surface from involvement of a non-peritonealised resection margin. Peritoneal involvement is a risk factor for peritoneal metastases 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.[29] 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

The presence or absence of lymphovascular invasion has strong prognostic implications for CRC 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.[35] 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.[10,36,37]

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.[38] 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 additional stains may help interpretation.[39,40] 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 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.[12,13] 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.[36,41-43] The relative importance of intramural and extramural anatomic location with respect to small vessel invasion has not been well established.[36]

Perineural invasion

The presence of perineural invasion in CRC (Figure 4) has adverse prognostic implication, particularly in stage II disease.[41,44,45] 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.[44] 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 determines the need for adjuvant chemotherapy and is a core item. Non-regional lymph node involvement is 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.

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.[46] This reflects a combination of inadequate nodal retrieval and unfavorable patient immunology.

Micrometastases (size between 0.2 mm and 2 mm) are associated with recurrence in stage I/II CRC compared to tumor-negative nodes, but there is no increased risk of disease recurrence in the presence of 'isolated tumor cells' (single tumor cells or groups <0.2 mm in maximum dimension) compared to tumor-negative nodes.[47] 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[48,49] and the concept refined in UICC/AJCC TNM 8th editions: 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).[12,13] 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 tumor deposits in the absence of lymph node metastases are classified as pN1c. In the presence of lymph node metastases, tumor deposits are discounted for staging purposes. 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[48,49] definition, and therefore the presence and number of identified tumor deposits should be recorded in all cases, as a core item.[50]

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 tumor budding, considered to be a morphological manifestation of epithelial mesenchymal transition.[51] A tumor bud is defined as a single tumor cell or cluster of up to four tumor cells at the invasive front of carcinomas. Budding is of potential clinical relevance to CRC in two distinct settings. Firstly, multiple studies have shown that pT1 CRC 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).[52-54] Secondly, in stage II CRC, tumor budding score Bd3 is associated with an increased risk of recurrence and mortality.[55]

As recommended from the International Tumor Budding Consensus Conference (ITBCC) of 2016,[56] 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.[57] 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

Any form of neoadjuvant therapy may result in morphological tumor response in the form of fibrosis, necrosis or acellular mucin. The presence of complete or marked tumor regression in rectal cancer resection specimen is associated with a better outcome.[58,59] For grading of regression, a four-tier system is recommended, based on a modification of the system described by Ryan *et al.*[60] 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 is a core item. In particular, circumferential or non-peritonealised margin involvement in rectal cancer is strongly predictive of local recurrence and poor survival.[61,62] Margin involvement in colon cancer is much less common and there is less evidence of its significance.[63,64] The definition of margin involvement is somewhat contentious but it is generally accepted that any circumferential margin ≤1 mm 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.[61,62] 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.[62] 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 CRC 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,[65,66] caused by either a constitutional pathogenic mutation in one of the MMR genes, or sporadic MMR deficient CRC, 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.[67]

Patients with metastatic CRC should be tested for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations when treatment with anti-epidermal growth factor receptor (anti-EGFR) therapy is considered.[66,68] 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.[69,70] Most modern guidelines therefore recommend also testing metastatic CRC for the V600E *BRAF* mutation.[66]

Although the above indications for focused ancillary testing 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 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).[12,13] 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.[12,13] The only exception is that this dataset does not advocate the use of pT *in situ*, 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 CRC patients. 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 as ease of returning pathology data for central registration purposes.[71,72] Adoption of structured reporting helps ensure data is complete and it has been demonstrated for CRC 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.[72-74] 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 CRC 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 CRC 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.[5-7] 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 CRC 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 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 CRC globally. The greatest impact may be in low- and middle-income countries, where incidence of CRC has risen significantly.[75] Standardized reporting will allow comparison of relative proportions of CRC subtypes between countries, assessment of the impact of new screening programs and participation in international trials targeting a specific molecular subset of CRC 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 CRC 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.

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Figure Legends

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.

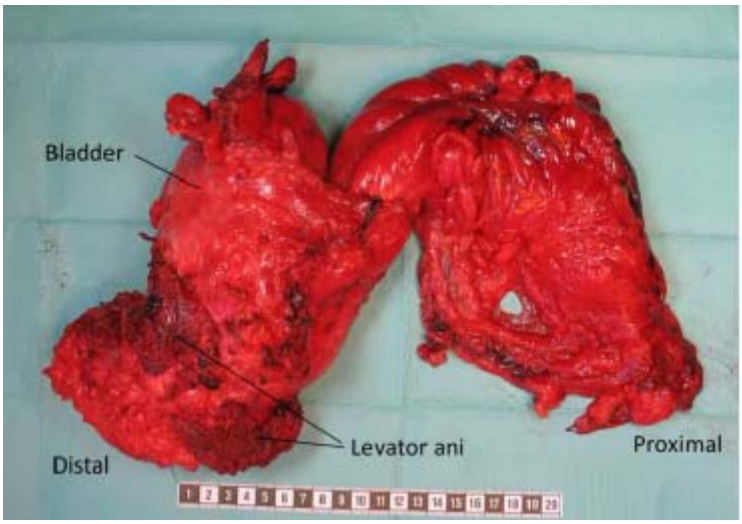

Figure 2. Rectal anatomy and possible relationships of rectal cancers to the peritoneal reflection. *Adapted by permission from Nicholas P. West and Philip Quirke: Springer Multidisciplinary Treatment of Colorectal Cancer (G. Baatrup, ed.); Quality of Surgery by Nicholas P. West and Philip Quirke (2021).*

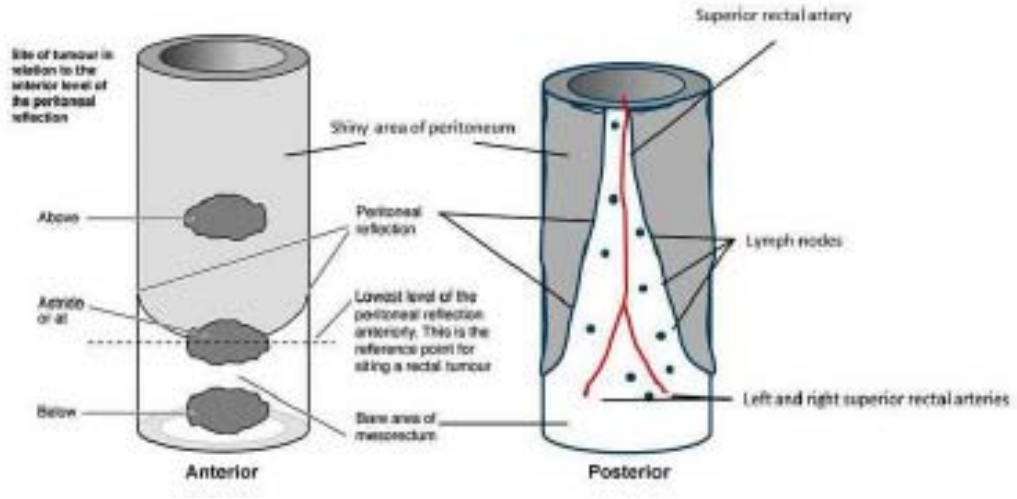

Figure 3. Planes of colorectal cancer surgery for the mesorectum (A-C), sphincters (D-F) and mesocolon (G-I). For the mesorectum, applicable to all rectal cancer specimens, the planes include the mesorectal plane, with intact mesorectum (A), intramesorectal plane, with mesorectal defect (B) and muscularis 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).*

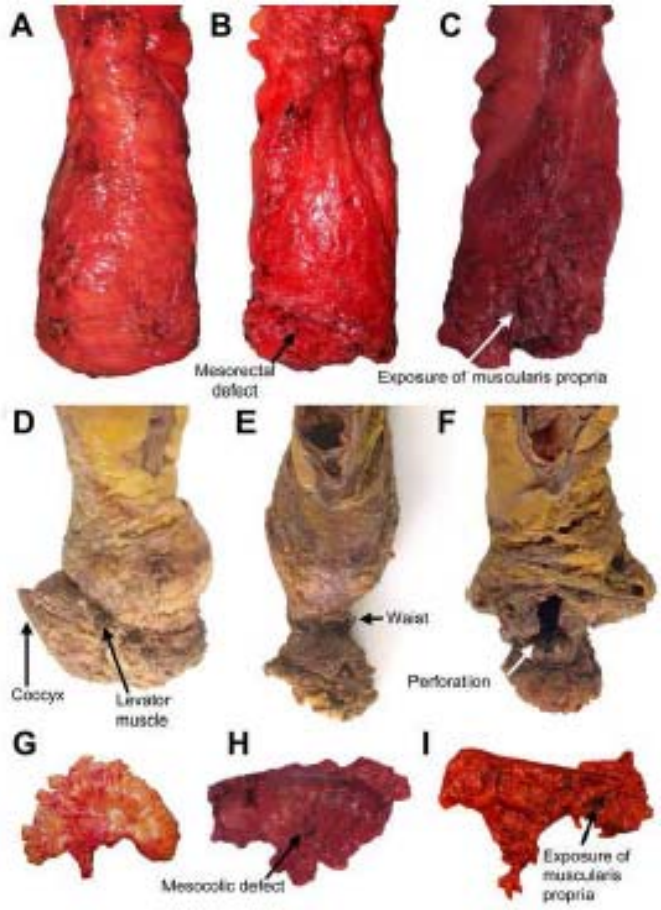

Figure 4. Metastatic pathways in colorectal cancer. A, Obvious extramural venous invasion (EMVI, black arrows), including a focus extending perpendicularly from muscularis propria (white arrow) (H&E). B, Lymph node metastatic disease (white arrows) and EMVI (black arrow,) confirmed by identification 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).

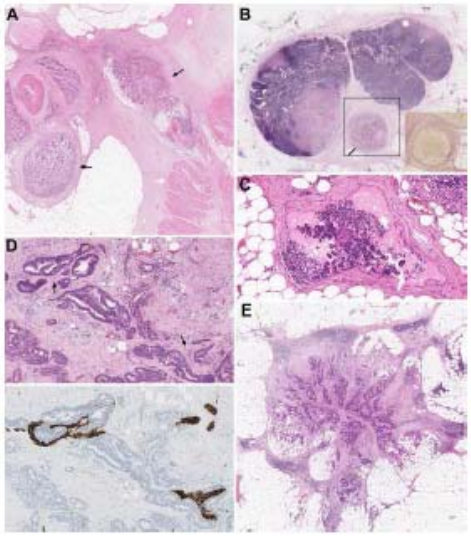

Figure 5. A, Posterior aspect of a right hemicolectomy specimen highlighting an intact, enlarged lymph node (rectangle) abutting the posterior specimen margin. B, Histology of a horizontal section through this lymph node shows metastatic mucinous adenocarcinoma. Although tumor extends to the surgical margin (painted black at base of image), tumor is confined to the intact lymph node and therefore NOT considered to represent margin involvement.

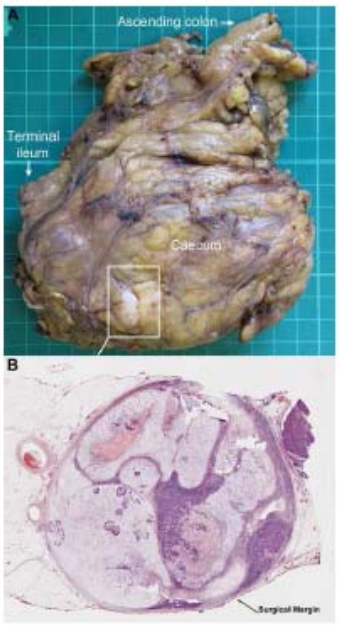

Table 1. Core and non-core elements for reporting.

Core items	**Non-core items**
Neoadjuvant therapy	Clinical information
Operative procedure	Plane of sphincter excision*
Tumor site	Plane of mesocolic excision*
Tumor dimensions (maximum)	Measurement of invasion beyond muscularis propria
Perforation	Tumor budding
Relation of tumor to anterior peritoneal reflection*	Coexistent pathology
Plane of mesorectal excision*	Ancillary studies
Histological tumor type	
Histological tumor grade	
Extent of invasion	
Lymphatic and venous invasion	
Perineural invasion	
Lymph node status	
Tumor deposits	
Response to neoadjuvant therapy	
Margin status	
Histologically confirmed distant metastases	
Pathological staging	
Ancillary studies	

*These items are only relevant to certain specimen types – see text for details

Table 2. Pathological assessment of rectal and colonic cancer surgical resection specimens.

	Optimal surgical plane	**Suboptimal surgical plane**	**Least optimal surgical plane**
Rectal cancer ***(applicable to any specimen containing a rectal cancer)***	Mesorectal fascia (complete): • Intact bulky mesorectum with a smooth surface • Only minor irregularities of the mesorectal surface • No surface defects greater than 5 millimetres (mm) in depth • No coning towards the distal margin of the specimen	Intramesorectal (near complete): • Moderate bulk to the mesorectum • Irregularity of the mesorectal surface with defects greater than 5 mm, but none extending to the muscularis propria • Moderate coning may be evident distally • No areas of visibility of the muscularis propria except at the insertion site of the levator ani muscles	Muscularis propria (incomplete): • Little bulk to the mesorectum • Defects in the mesorectum down to the muscularis propria • After transverse sectioning, the circumferential margin appears very irregular and is formed by muscularis propria in areas.
Rectal cancer treated with abdominoperineal excision	Extralevator plane: • Dissection plane lies external to the external sphincter and levator ani muscles, which	Sphincteric plane: • Dissection plane lies on the surface of the sphincter muscles • No levator ani muscle	Intrasphincteric plane: • Dissection plane lies within the sphincter muscles or even deeper

	are removed en bloc with the mesorectum and anal canal • Cylindrical-shaped specimen with the levators forming an extra protective layer above the sphincters • No significant defects into the sphincter muscles or levators	attached or only a very small cuff leading to coning or surgical waisting at the level of puborectalis • No significant defects into the sphincter muscles	into the submucosa • Full thickness iatrogenic defect of the specimen at any point below the peritoneal refection.
Colon cancer ***(applicable to any specimen containing a colon cancer)***	Mesocolic plane: • Smooth surface to the mesocolon (mesocolic fascia and peritoneum) • Only minor irregularities • No surface defects greater than 5 mm in depth	Intramesocolic plane: • Irregularity of the mesocolic surface with defects greater than 5 mm, but none extending to the muscularis propria	Muscularis propria plane: • Defects in the mesocolon down to the muscularis propria • After transverse sectioning, the mesocolic margin is irregular and formed by muscularis propria in areas.