

REVIEW

Reporting colorectal cancer

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The management of colorectal cancer is a team process. High-quality reporting of colorectal cancer is very important as the whole team relies upon the skill of the pathologist. Failure to report key features can lead to undertreatment of this disease. The use of a proforma has been demonstrated to be beneficial and we recommend staying with TNM5 due to scientific and reproducibility issues with TNM6. Important features in stage II/Dukes' B cases are extramural vascular invasion, peritoneal involvement, extent of extramural spread, incomplete resection and perfor-

ation. All of these may lead to adjuvant therapy being administered. The surgically created circumferential resection margin (CRM) and the mode of its creation are important features and the CRM retains its value after preoperative therapy. Regression grading should be applied only to fully resected tumours and the dissection and sampling must be standardized to allow comparison of results between trials and centres. When reporting local resections of early-stage cancers we need to look for features that predict spread to local lymph nodes to allow a full resection to be considered.

Keywords: circumferential resection margin, colon cancer, colorectal cancer, histopathology, pathology, TNM staging

Abbreviations: 5FU, 5-fluorouracil; CRC, colorectal cancer; CRM, circumferential resection margin; κ, kappa; MRC, Medical Research Council; TME, total mesorectal excision; TNM, tumour, nodes and metastasis; UK, United Kingdom

Introduction

Colorectal cancer (CRC) is an important and common disease but it remains badly reported with many pathologists ignorant of the importance of their role and the benefits that good reporting brings to the patient and the multidisciplinary team. Thanks to the recognition of the importance of the pathologist in the UK and investment by the National Health Service, we have gone part way to changing this situation, but

even here there is much that can still be improved upon.

The multidisciplinary team

Pathologists should report CRC in the context of a specialist team who care for these patients. Key members include pathologists but also surgeon(s), radiologist(s), medical and clinical oncologists as well as specialized nurses. If such a team does not exist in your institution then you must ensure that protocols for management exist, that your communication pathways are excellent and that you audit your work to enable yourself to demonstrate that you are performing to the highest standards. There is no doubt that the standard of practice of each individual team member affects outcomes. Poor

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practice costs lives that otherwise may have been saved. The role of the pathologist in the team varies with respect to each professional group. For the surgeon we must feedback on completeness of excision, the plane of surgery that the surgeon has achieved and generate an accurate prognosis from dissection and microscopy. For the radiologist it is to confirm the accuracy of preoperative staging and their prediction of completeness of excision in rectal cancer. For the oncologist it is to describe the effectiveness of neoadjuvant therapy, to identify patients in need of adjuvant therapy and in future, if possible, suggest the most appropriate therapy using appropriate molecular tests.

Completeness of reporting and the minimum dataset

Many studies report the frequency with which incomplete reports are issued.^{1–5} There are three reasons for this: first, ignorance of the importance of certain features for management; second, the large number of possible prognostic features that can be reported; and third, the obsession with free text reports. The first can be overcome only by standards, education, routine audit and feedback from other members of the team. The second and third can be overcome by the adoption of a minimum dataset such as that developed by the Royal College of Pathologists⁶ and shown in Figure 1. The first step is the identification of the high level evidence, preferably grade 1, derived from metaanalyses or clinical trials.^{7,8} Second, the coming together of interested parties to discuss and debate the evidence and settle on those features valuable to the patient and team performance. These should then be drafted into a proforma, preferably of one page, and then widely circulated for comment. National bodies should mandate their use and preferably they should be returned to cancer registries so that audit can occur of pathological/surgical performance. In the UK all the professional bodies concerned with treating CRC have agreed the College proforma. The adoption of proforma reporting has shown the improvement of completeness of datasets from 0% to 96% by its use within a single department³ and a 28.4% increase in completed data items when compared with non-proforma reporting when studied within Wales.¹ When items are omitted, is this because the feature is absent or is it because it has not been assessed? When analysing over 5000 Yorkshire minimum dataset proforma returns, the survival curves for omissions lie intermediate between the feature-positive and feature-negative curves, suggesting it is a lack of assessment rather than a failure to tick the positive box.

For example, in Dukes' stage B patients with extramural vascular invasion, 54.6% survived 5 years compared with 69.8% of those with no extramural vascular invasion (EMVI). Those where the box was not ticked had an intermediate survival of 61.7%. This was less marked for peritoneal involvement with figures of 52.0%, 70.4% and 67.2%. Movement to a computer proforma would remove the option of failure to consider a feature as it forces a statement and should have a positive impact on patient outcomes.

Which staging system?

The creation of the TNM system undoubtedly improved staging of CRC. It allowed for improved international communication and better management of patients. However, it has failed to move with the times. Modern medical practice demands evidence-based standards that are generated on the basis of first-class evidence and wide debate. Since staging in CRC is used to determine treatment, it too should require evidence from good-quality prospective randomized clinical trials. Usually two trials with similar findings from different populations will sway the clinical community into changing its practice. Unfortunately, such 'modern practice' has not developed within TNM. Regular revision of staging systems is a good idea but they should change only when there is such evidence. All too often TNM has changed critical features that direct therapy in the absence of such evidence. In TNM5⁹ the creation of the 3-mm rule that called an isolated tumour deposit a tumour-positive lymph node if it was > 3 mm in size was not based on trial or even survival data as stated by Goldstein *et al.*¹⁰ and, as such, should not have been introduced. In TNM6 there has been a further change to lymph node definitions and also to the definition of a further high-risk feature, venous invasion. TNM6¹¹ states, 'smooth metastatic nodules in the pericolic or perirectal fat are considered as lymph node metastases and will be counted in the N staging'. This gives rise to the questions of how smooth is 'smooth' and what is the minimum size of a nodule. In the quoted references they use grossly palpable¹⁰ as the definition, but this is not stated in TNM6. This would lead to having to ignore deposits that might not have been palpable, adding yet more confusion. Whilst the 3-mm rule lacked clinical trial evidence and survival data, at least it had the advantage of being quantitative and could be used as a starting point to test these hypotheses in clinical trials. This error over nodes is compounded by the change of the definition of venous invasion to another poorly defined statement: 'in

NATIONAL MINIMUM DATA SET
COLORECTAL CANCER HISTOPATHOLOGY REPORT

Surname..... Forenames..... Date of birth..... Sex.....
 Hospital..... Hospital No..... NHS No.....
 Date of receipt..... Date of reporting..... Report No.....
 Pathologist..... Surgeon.....

<p>Gross Description</p> <p>Site of tumour</p> <p>Maximum tumour diameter</p> <p>Distance of tumour to nearer margin (cut end)</p> <p>Presence of tumour perforation (pT4) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>For rectal tumours</p> <p>Tumour is <input type="checkbox"/> above <input type="checkbox"/> at <input type="checkbox"/> below the peritoneal reflection</p> <p>Distance from the dentate line.....</p> <hr/> <p>Histology</p> <p>Type</p> <p>Adenocarcinoma <input type="checkbox"/> Yes <input type="checkbox"/> No (to include mucinous and signet ring adenocarcinomas)</p> <p>If No, other</p> <p>Differentiation by predominant area</p> <p><input type="checkbox"/> Well/moderate <input type="checkbox"/> Poor</p> <p>Local Invasion</p> <p><input type="checkbox"/> Submucosa (pT1)</p> <p><input type="checkbox"/> Muscularis propria (pT2)</p> <p><input type="checkbox"/> Beyond muscularis propria (pT3)</p> <p><input type="checkbox"/> Tumour cells have breached the peritoneal surface or invaded adjacent organs (pT4)</p> <p>Margins</p> <table border="0"> <tr> <td>Tumour Involvement</td> <td>N/A</td> <td>Yes</td> <td>No</td> </tr> <tr> <td>Doughnut</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Margin (cut end)</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table> <p>For rectal tumours</p> <p>Circumferential margin involvement <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>Histological measurement from tumour to circumferential margin.....mm</p>	Tumour Involvement	N/A	Yes	No	Doughnut	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Margin (cut end)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>Metastatic Spread</p> <p>No of lymph nodes examined</p> <p>No of positive lymph nodes</p> <p>(pN1 1–3 nodes, pN2 4 + nodes involved)</p> <table border="0"> <tr> <td></td> <td>Yes</td> <td>No</td> </tr> <tr> <td>Apical node positive (Dukes C2)</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Extramural vascular invasion</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table> <p>Background Abnormalities</p> <table border="0"> <tr> <td></td> <td>Yes</td> <td>No</td> </tr> <tr> <td>Adenoma(s)</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Synchronous carcinomas(s) (Complete a separate form for each cancer)</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Ulcerative colitis</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Crohn's disease</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Familial adenomatous polyposis</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Other comments</td> <td></td> <td></td> </tr> </table> <hr/> <p>Pathological Staging</p> <p>Complete resection at all margins <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>TNM</p> <p><input type="checkbox"/> T <input type="checkbox"/> N <input type="checkbox"/> M</p> <p>Dukes</p> <p><input type="checkbox"/> Dukes A (Growth limited to wall, nodes negative)</p> <p><input type="checkbox"/> Dukes B (Growth beyond wall, nodes negative)</p> <p><input type="checkbox"/> Dukes C1 (Nodes positive and apical node negative)</p> <p><input type="checkbox"/> Dukes C2 (Apical node positive)</p> <p>Histologically confirmed liver mets <input type="checkbox"/> Yes <input type="checkbox"/> No</p>		Yes	No	Apical node positive (Dukes C2)	<input type="checkbox"/>	<input type="checkbox"/>	Extramural vascular invasion	<input type="checkbox"/>	<input type="checkbox"/>		Yes	No	Adenoma(s)	<input type="checkbox"/>	<input type="checkbox"/>	Synchronous carcinomas(s) (Complete a separate form for each cancer)	<input type="checkbox"/>	<input type="checkbox"/>	Ulcerative colitis	<input type="checkbox"/>	<input type="checkbox"/>	Crohn's disease	<input type="checkbox"/>	<input type="checkbox"/>	Familial adenomatous polyposis	<input type="checkbox"/>	<input type="checkbox"/>	Other comments		
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Figure 1. National minimum dataset for colorectal cancer issued by the Royal College of Pathologists. This is currently under revision (Royal College of Pathologists. Reproduced with permission).

contrast irregularly contoured metastatic nodules in the peritumoral fat are considered vascular invasion and will be coded as an extension of the T category as either V1 (microscopic vascular invasion) if only microscopically visible or a V2 (macroscopic vascular invasion) if grossly visible'. There is no mention of venous wall or endothelium only irregularity. From first principles, early venous invasion prior to destructive invasion of the venous wall by the tumour would of necessity be smooth. Most venous invasion that we report is smooth walled and not irregular, so we fail to understand this particular change. The evidence base for the changes is poor. The quoted papers did not intend to change the TNM classification. Goldstein¹⁰ says that 'the optimum TNM classification for PTDs (pericolonic tumour deposits) remains to be defined'. The papers of Harrison *et al.*^{12,13} did not find PTDs to have independent statistical significance. Evidence is starting to accrue for ignoring TNM6. The important study from Cardiff¹⁴ asked 23 pathologists to characterize extramural nodules into smooth and round or irregular, as recommended in TNM6 in 80 cases. The κ agreement was 0.36 and no difference was seen between specialists and non-specialists or between consultants and trainees, suggesting that expertise does not improve consistency. Not only does it have poor reproducibility, but also five of 80 (6%) cases were upstaged from N0 to N1. These may not have been offered therapy under TNM5 but would be under TNM6. Would they benefit? Since TNM6 was not tested in a randomized trial of treatment, it is impossible to know. Thus we have evidence from Wales that these changes to TNM6 are unreliable and this is a common message from many colleagues as well as in our own practice.

In the UK the minimum dataset was widely debated and agreed on the basis of TNM5. The evidence base for the changes in TNM6 does not warrant adoption and UK practice will be to remain with TNM5 with a call for TNM to move with the times and adopt an evidence-based approach to developing this staging system. By stating this we must also call for the routine introduction of a pathology proforma into all clinical trials of CRC. It is only the testing of new pathological (prognostic and treatment-related) and molecular pathological features alongside standard pathological features that will enable progress to be made and better staging systems to be developed.

Key reporting features

Staging of a cancer should be focused on treatment and prognosis.

TREATMENT

Key treatment features are those that trigger adjuvant therapy, those that suggest further therapy is required and factors that might lead to improvements in treatment in future patients.

To deal with adjuvant therapy first. The early Moertel studies^{15–17} reported that node-positive patients with colon cancer improved their survival when treated with 5 fluorouracil (5FU) and there was a non-significant trend in stage II node-negative cases.¹⁶ This has been extensively supported by other studies. There is also strong evidence to support its use in node-positive rectal cancer.¹⁸ Equivalent efficacy with intravenous 5FU has been demonstrated with the use of the oral agent capecitabine in the X-ACT study.¹⁹ Recent studies such as MOSAIC²⁰ and NSABP C-07²¹ have shown that the addition of oxaliplatin to 5FU/folinic acid further improves outcomes in node-positive disease by around 5% over 5FU/folinic acid alone (7–9% stage III and 3–4% stage II). 5FU alone enhances 5-year survival by around 5–7% with 5FU/oxaliplatin doubling the benefit to 10–15% in stage III disease. Thus, a failure to find positive lymph nodes and a patient being defined as node negative loses an individual up to 15% additional 5 years' survival. These figures may improve further with the addition of anti-vascular endothelial growth factor therapies, as they have done with advanced disease. The chance of a patient being called node positive depends on the number of lymph nodes found by the pathologist. There is no minimum number of nodes to be found and as many as possible should be retrieved. Pathology practice in the early 1990s retrieved an average of six nodes. This has substantially improved in the UK. The best centres now routinely obtain 15–18 nodes and all should aspire to this. Small lymph nodes need to be found as small metastatic deposits do occur and, if reported, will trigger treatment in appropriate patients. However, TNM do not consider micrometastases under 0.2 mm as nodal involvement. We have also found a strong association between the finding of a low median number of lymph nodes by a hospital and a low frequency of reporting of other high-risk features, suggesting that low lymph node counts identify overall poor performance and significant understaging of patients.

Stage II, node-negative Dukes' B patients

Many oncologists will treat high-risk node-negative patients with adjuvant chemotherapy. There is evidence available from the Quasar study group¹⁸

suggesting that stage II patients can also benefit from adjuvant therapy with a 3% improvement in 5-year survival and a further 3.5% with the addition of oxaliplatin from the MOSAIC²⁰ and NSABP CO-7²¹ trials. With high-risk stage II patients having an increased risk of relapse, many are being offered treatment. What defines high risk? This is a difficult question, as there are no trials with a pathology proforma that prospectively sought to answer which subsets of cases benefited from treatment. In the absence of trial data, if we use retrospective non-trial data then it would seem reasonable to treat patients who have a worse prognosis than patients who have a single positive node, since the latter is a definite indication for treatment. In our population-based series there are several features that appear to confer a worse prognosis, namely peritoneal invasion, perforation, extramural venous invasion, incomplete resection and extensive extramural spread.²² Treatment by oncologists can either be triggered by the finding of a single high-risk feature or according to a formula such as Petersen's,²³ where each feature is given a score.

Unfortunately, the reporting of such features is highly variable amongst pathologists and they are widely under reported, again reducing the frequency of treatment and potentially reducing the survival of CRC patients. On average we would expect a careful pathologist to find extramural vascular invasion in around 30% of cases and peritoneal involvement in 30% of the colon cancers and 10% in the rectum. Unfortunately, in practice these figures are highly variable between pathologists and in routine practice EMVI is usually nearer 10%. The important message is that we need to look carefully, since if we miss these features patients may lose out on being offered increasingly effective treatments.

Incomplete excision

Tumour at a longitudinal margin has always been considered a poor prognostic feature but occurs in only 1–2% of patients within clinical trials such as CLASICC.²⁴ Tumour at other surgical margins has also been investigated. It is clear that tumour frequently (5–36%) involves the surgical circumferential resection margin (CRM) in the rectum and is significantly associated with higher rates of local recurrence and a poorer survival.^{25–32} Its frequency depends on the quality of surgery [non-total mesorectal excision (TME)], advancing TNM stage and whether the patient has undergone preoperative neoadjuvant therapy. The closer the tumour is to the CRM the worse the prognosis for the patient. The vast majority of studies,

including clinical trials and population studies, have used a cut-off of 1 mm but TNM insist on tumour at the margin and the Dutch TME study suggested 2 mm. The modes of involvement, whether direct, discontinuous, venous or neural, all confer a poor prognosis.^{25,33} There is little data about tumour within a lymph node and further work is required in this area, but until this is available this mode of involvement should be considered as of the same importance.

In the colon the surgeon creates a very small mesocolic margin but in the right colon there is an area of variable size on the posterior surface of the caecum and ascending colon. The frequency of involvement is usually around 7–10%.^{34,35} At 3 years we were unable to demonstrate that this margin related to local recurrence or survival in the MRC CLASICC study.³⁵ More studies are required of this area, as it may be the case that involvement of the margin may only be prognostic in early-stage disease, as seen in the oesophagus.³⁶

Quality of surgery

A new responsibility for the pathologist has recently emerged: that of describing the plane of surgery in rectal cancer. From two prospective randomized trials^{37,38} we now have evidence that the operative plane of surgery predicts not only margin positivity but local recurrence and survival. Surgery in the mesorectal plane has the best outcome. Violation of the mesorectal fascia with surgery in the mesorectum has an intermediate outcome, with the worst being when surgery impinges on the muscularis propria. With increasing closeness of the surgical margin to the muscularis propria the rate of margin involvement increases, the frequency of local recurrence increases and survival decreases. Focusing on these features and continual feedback of these features to the multidisciplinary team should lead to improvement in the quality of surgery and better clinical outcomes. In the MRC CR07 trial the quality of surgery rates improved and margin positivity rates fell substantially over the study.³⁸

We have identified differences between the quality of surgery of anterior resections and abdomino-perineal excisions.^{39,40} However, for routine reporting only the assessment of the mesorectum has been tested in the context of randomized trials and we must await further trials before adopting the separate classification of such cases. However, one should look very carefully in the areas of the sphincters and low mesorectum for CRM involvement, as it is very frequent due to the difficulty of operating in this area. Some surgeons resect the

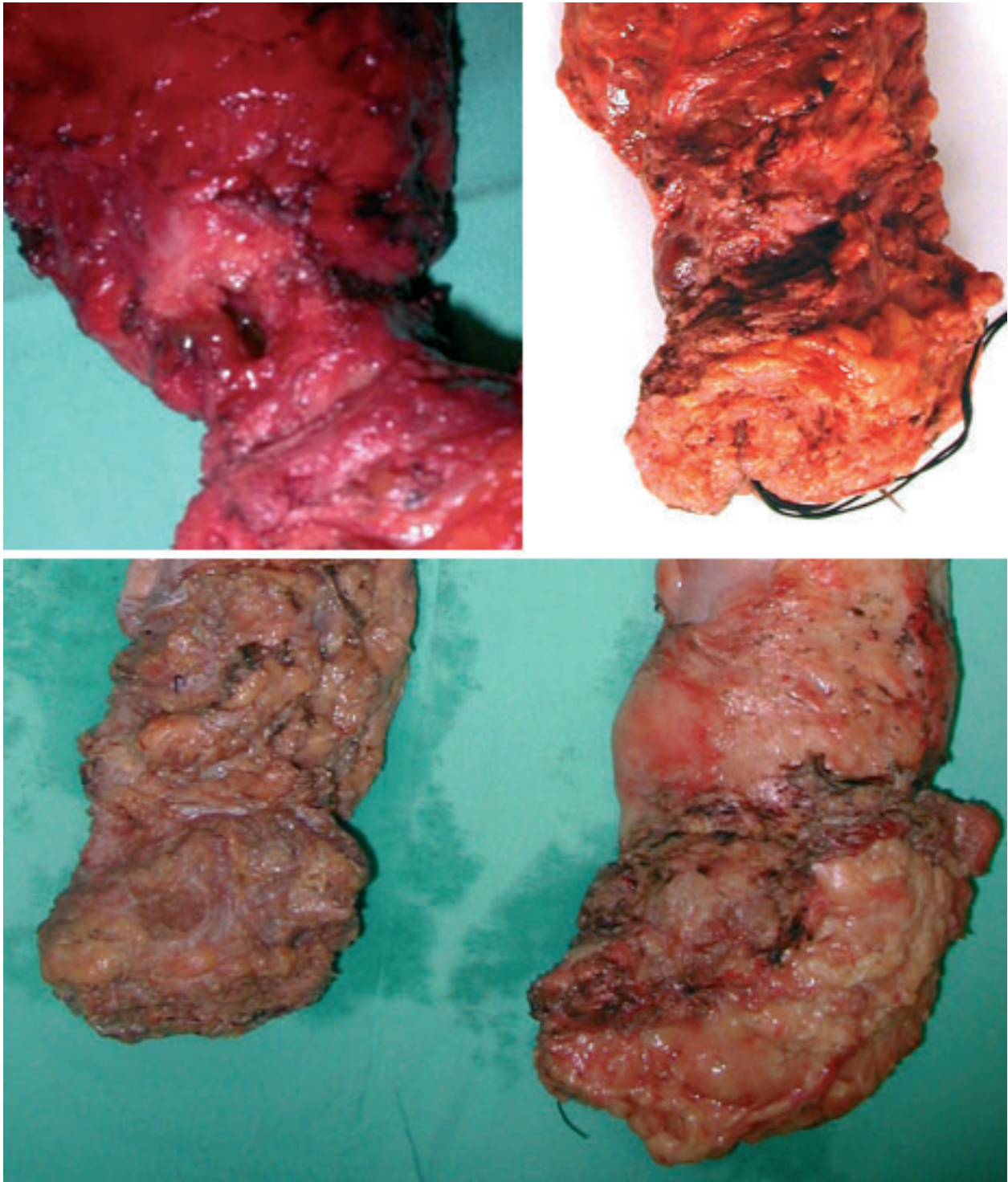


Figure 2. Examples of abdomino-perineal excision surgery. Top left shows the margin penetrating through the whole of the wall in a perforation. This has occurred at the junction of the sphincters and the base of the mesorectum. Top right shows the surgical margin to have invaded the sphincters but not penetrating into the lumen. The cross-sectional slices showed that the margin was in the submucosa. Bottom left shows a typical abdomino-perineal excision with the surgical plane on the sphincters. The mesorectal resection is irregular and would be defined as intramesorectal. Bottom right is the extralevator approach, where the levators are excised widely and left adherent to the specimen, providing an extra cushion against margin involvement by tumour. This operation was performed by Mr T. Holm of the Karolinska Hospital. The mesorectal excision is good in the mesorectal plane.



Figure 3. Three examples of dissection in the muscularis propria plane. White arrows show areas of exposed muscle. The blue dotted arrow shows a low perforation in the area of the sphincter. This plane of operation has the highest frequency of circumferential margin involvement, local recurrence and poorest survival.

levators *en bloc*, giving a more cylindrical specimen that should reduce the frequency of incomplete excision. A description of this area is helpful, stating whether the levators are attached and the position of the CRM, i.e. on the levator, sphincters or in the sphincters.

To help in making this assessment, examples of a perforation, in the sphincters, on the sphincters and an extralevator approach are shown in Figure 2.

The description defined in CR07 and adopted by the Dutch trial is given below and pictures of three cases that fall into the muscularis propria plane group that has the worst prognosis are shown in Figure 3.

MRC CR07 definitions

MESORECTAL FASCIAL PLANE

The mesorectum should be smooth, with no violation of the fat, good bulk to the mesorectum anteriorly and posteriorly and the distal margin should appear

adequate with no coning near the tumour. No defect should be more than superficial or 5 mm deep.

INTRAMESORECTAL PLANE

Moderate bulk to mesorectum but irregularity of the mesorectal surface. Moderate coning of the specimen towards the distal margin. At no site is the muscularis propria visible with the exception of the area of insertion of levator muscles. Moderate irregularity of the CRM.

MUSCULARIS PROPRIA PLANE

There will be areas of substantial loss of mesorectal tissue. Deep cuts and tears down onto the muscularis propria will be present. On cross section there will be a very irregular CRM with little bulk to the mesorectal fat and the muscularis propria will form the CRM in places.

Post neoadjuvant assessment

The assessment of rectal cancer post-treatment needs standardization, especially in the context of clinical trials. In addition to assessing the CRM and the standard histological features it is necessary to report the degree of tumour regression.

It is becoming clear that the most important predictor of outcome in patients with locally advanced rectal cancer who undergo neoadjuvant therapy is a clear CRM.^{41–44} In patients who have a clear CRM, regression grading becomes important.⁴⁵ A number of classification variants have been proposed, but the best publication arises from this German trial⁴⁵ and as such its classification is the current gold standard. However, this factor was reported only on the R0 completely resected cases (0 mm clearance), not for the whole series including R1/R2 cases. Thus we have reliable data only in a subset of cases and thus we cannot compare the relative value of CRM versus regression grading in all cases in this trial.

For regression grading to mean anything it is necessary to standardize the assessment. This has been overlooked in the previous trials and has led to great confusion in the literature over complete response rates. The likelihood of reporting a complete response varies depending on the number of blocks of the tumour site that have been taken and the number of levels that are cut. For example, four blocks with no levels will give a much lower frequency than totally embedding of the tumour and cutting step sections through each block. The latter is impractical and what is needed is a pragmatic procedure. This was achieved for the CORE phase II study,^{46,47} when pathologists from five European countries agreed a histopathology trial protocol. In essence, it recommended five initial blocks being taken from the site of the tumour. If no tumour were present, the whole of the suspicious area would be embedded. If there were still no tumour then three levels would be cut through each block. If there were still no tumour then the patient would be reported as having had a complete response. Such a scheme combines rigorous dissection with practicality. The frequency of these specimens is rapidly increasing and in some cancer centres up to half of the cases will be post treatment.

Early colorectal cancer

Early CRC may be resected locally if polypoid, amenable to an endoscopic submucosal resection or, if low in the rectum, to a transanal resection. In these situations it is important to remember to report other features. For

polyp cancers assessment must be made of tumour spread to within 1 mm or less of the surgical resection, the presence of lymphatic or vascular invasion and poor differentiation. It is important to report these features, as well as any involvement of the muscularis propria and, if absent, the depth of invasion into the submucosa. All of these features increase the risk of the presence of nodal metastases and are likely to lead to a full resection depending on the clinical status of the patient.⁴⁸

Conclusions

The management of CRC is a team process. High-quality reporting of CRC is very important, as the whole team relies upon the skill of the pathologist. Failure to report key features can lead to undertreatment of this disease. The use of a proforma has been demonstrated to be beneficial and we recommend staying with TNM5 due to scientific and reproducibility issues with TNM6. Important features in stage II/Dukes' B cases are extramural vascular invasion, peritoneal involvement, extent of extramural spread, incomplete resection and perforation. All of these may lead to adjuvant therapy being administered. The surgically created CRM and the mode of its creation are important features and the CRM retains its value after preoperative therapy. Regression grading should be applied only to fully resected tumours and the dissection and sampling must be standardized to allow comparison of results between trials and centres. When reporting local resections of early-stage cancers, we need to look for features that predict spread to local lymph nodes to allow a full resection to be considered.

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