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Article title

What you need to know about: Histopathology: Improving outcomes in bowel cancer

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Abstract

Histopathologists play a major role in the assessment of cancer specimens by feeding back various prognostic factors identified through meticulous macroscopic and microscopic examination to the multidisciplinary team at the weekly meetings. In rectal cancer, histopathologists identified the importance of avoiding tumour involvement at the circumferential resection margin, which along with total mesorectal excision surgery has led to a marked improvement in outcomes for rectal cancer patients. We also described grading systems for the assessment of the plane of surgery in the mesorectum, anal sphincters and mesocolon, which along with specimen photographs provide feedback on the quality of the surgery to the surgical team and promote improvements in surgical treatment. This article will discuss how the histopathological assessment of colorectal cancer specimens is undertaken and how it has led to direct improvements in patient outcomes.

Introduction

Meticulous histopathological examination of surgical resection specimens is central to the management of patients with cancer. From an accurate histopathology report, the multidisciplinary team can determine whether further surgical, radiological or oncological input is required. In addition, histopathologists have played a major role in the evolution of surgical techniques. The basic principles of optimal cancer surgery have been acknowledged for over a century and include the correct plane of dissection, clean cutting and atraumatic surgery. These principals ensure resection of the cancer and all of the pathways of metastatic spread in an intact package. Recognition of the importance of meticulous surgical planes in colorectal cancer was not widely appreciated until relatively recently. This article will discuss how the assessment of colorectal cancer specimens and subsequent feedback to surgical teams has led to direct improvements in patient outcomes.

The introduction of total mesorectal excision

In the early 1980s, the standard surgical practice when performing anterior resection (AR) for rectal cancer was to incise the mesorectal fascia and bluntly dissect through the mesorectal fat producing a cone shaped specimen. During this period, local recurrence of the cancer occurred in up to 35% of cases (Lasson et al, 1984) and the five-year survival was significantly worse when compared to more proximal colon

cancers. Professor Bill Heald and colleagues in Basingstoke (1982) described a technique whereby the rectum and mesorectum were excised in full by dissecting along the outside of the mesorectal fascia down to the pelvic floor. The technique became known as total mesorectal excision (TME) and removed a greater volume of tissue around the cancer within an intact fascial-lined package. Heald reported no local recurrences in the study follow-up period, which represented a major improvement on standard practice.

The importance of the circumferential resection margin

At the same time as TME was being described in Basingstoke, Professor Phil Quirke, a histopathologist at the University of Leeds, described for the first time the importance of avoiding tumour involvement of the circumferential resection margin (CRM), the lateral surgically created margin on the outside of the mesorectum. Quirke et al (1986) showed that if tumour cells were present one millimetre or less from the CRM, the risk of local recurrence increased twelve fold. It soon became apparent that the introduction of TME surgery resulted in a specimen that had a much lower risk of CRM involvement by tumour. Locally advanced tumours which threatened or invaded through the mesorectal fascia could now be detected pre-operatively using magnetic resonance imaging and radiotherapy could be used prior to surgery to shrink the tumour and improve the chances of a complete resection.

Histopathologists within the United Kingdom (UK) now routinely assess the status of the CRM in all cases of rectal cancer by applying black ink to the bare mesorectal surface at the time of specimen receipt so that an accurate distance of the tumour to the margin can be reported histologically. The specimen is serially sliced after inking so that the tumour and the CRM can be observed in detail and the most relevant areas are then selected for histological examination (figure 1). This information is fed back to the multidisciplinary team and is used to audit the accuracy of pre-operative imaging, the effectiveness of radiotherapy and the quality of the surgery.

The importance of assessing surgical planes

Quirke and colleagues soon realised that the risk of local recurrence was not just related to the status of the CRM, but also to how carefully the surgeon had stayed within the mesorectal fascial plane. A three point quality grading system was

developed (table 1) and was prospectively shown to predict the risk of local recurrence independently of whether pre-operative radiotherapy was given (Quirke et al, 2009). These results have now been replicated in a number of other studies around the world and the grading system is mandatory for all rectal cancer specimens in the United Kingdom as specified in the Royal College of Pathologists guidelines for reporting colorectal cancer specimens (Williams et al, 2007).

It is recommended that histopathologists take photographs of rectal cancer resection specimens to provide a permanent record of the quality of surgery that can be shown to surgeons at multidisciplinary meetings in order to provide feedback and promote continued learning. Photographs should also be taken of the cross-sectional slices to demonstrate the depth of any mesorectal defects and to provide feedback to radiologists about their pre-operative staging including the predicted status of the CRM, extramural vascular invasion and lymph node involvement.

The importance of multidisciplinary education programmes

Following the recognition that reporting the status of the CRM and surgical planes improved the quality of the surgery, a number of multidisciplinary education programmes focusing on the quality of surgery, pathology, radiology and pre-operative treatment strategies took place around the world. One such training programme at the Karolinska hospital in Stockholm, Sweden included workshops incorporating video-based surgical sessions and histopathology workshops focusing on the importance of the CRM. This resulted in improvement in the quality of the specimens produced, recurrence rates and overall survival, which were superior when compared to surgeons who had not undergone focused training (Martling et al, 2000). Similar results were replicated in programmes across the UK, Norway and the Netherlands, and a recent Spanish programme showed that in over 10,000 patients treated between 2006 and 2012, the local recurrence rate has reduced in curative disease to 7.7% (Ortiz et al, 2013).

The problem with low rectal cancer

Whilst education and audit provided improvements in outcomes for many rectal cancer patients, tumours within the low rectum requiring an abdominoperineal excision (APE) carried a higher rate of local recurrence (15% vs. 10%) and lower

five-year survival (59% vs. 69%) (Wibe et al, 2004).

This was discovered to be due to a combination of a reduction in protective mesorectal fat towards the pelvic floor when following the mesorectal tissue plane and the poor visualisation in the deep pelvis with the conventional supine position resulting in surgeons deviating into the sphincter muscles. Both of these factors led to a higher rate of CRM involvement and intraoperative tumour perforation when compared to AR for higher tumours. A similar three point quality grading system was therefore developed by Professor Quirke to describe the plane of surgery undertaken in the distal part of the APE in the region of the anal sphincters (table 2).

A study of 374 APE specimens from a multicentre rectal cancer trial in the Netherlands showed that two thirds of cases were resected in the sphincteric plane and one third in the intrasphincteric plane (Nagtegaal et al, 2005). There were no extralevator plane excisions. APE was associated with a significantly higher rate of CRM involvement when compared to the patients who had undergone AR in the same trial (30.4% vs. 17.1%).

The solution to the low rectal cancer problem

The extralevator plane APE was proposed as the solution to these problems in advanced low rectal cancers. This more extensive resection involves removal of the levator ani muscles en-bloc with the mesorectum and sphincter muscles to increase the amount of tissue removed around the tumour and produce a more cylindrical rather than a waisted specimen (Holm et al, 2007). The perineal portion of this operation is preferably performed with the patient in a prone, rather than supine, position to allow improved visualisation of the operative field. West et al (2010a) confirmed the increased volume of tissue resected and demonstrated a reduction in both CRM involvement (58% to 20%) and intraoperative perforations (28% to 8%) when compared to a conventional APE. Surgeons who changed technique during the study period showed significant improvements in their short term oncological outcomes.

Multidisciplinary training programmes focussing on low rectal cancer treatment were funded by the UK government and organised by the Pelican Cancer Foundation and

were held between 2011 and 2013. The Low Rectal Cancer National Development Programme (www.lorec.nhs.uk) included sessions focussing on the importance of histopathologists assessing low rectal cancer specimens and it is now expected that a careful assessment of the CRM will take place along with mesorectal and sphincter grading backed up by routine specimen photography. It is hoped that this programme will improve the treatment and therefore outcomes for patients with low rectal cancer towards those reported for higher tumours.

Translating these improvements into colon cancer

Whilst rectal cancer has been the focus of extensive study, audit and education over the past twenty five years, colon cancer has been relatively neglected leading to a reversal in outcomes with rectal cancer patients now being more likely to survive long term compared to those with colon cancer in several European countries. Recent studies using histopathological assessment of the surgical specimen have shown marked variation in surgical techniques for colon cancer. A three point quality grading system was developed by West and Quirke (table 3) who showed in 399 cases from Leeds that only 32% were resected in the optimal mesocolic plane and 24% had major defects going down to the muscle tube (West et al, 2008). Mesocolic plane surgery was associated with a 15% greater five year overall survival in all cases and 27% greater in cases with stage III (lymph node positive) disease.

Hohenberger et al (2009) from Erlangen, Germany reported some of the best outcomes for colon cancer surgery in the literature to date and described a more extensive operation termed complete mesocolic excision (CME). This utilised the same oncological principles as TME surgery for rectal cancer with surgeons meticulously operating within embryological tissue planes and producing an intact fascial and peritoneal-lined specimen. Additionally the supplying artery is ligated at its origin and resected with the central lymph nodes, which is considerably more radical than many colon cancer surgeons practice worldwide. West et al (2010b) were able to show that surgeons in Erlangen removed more tissue between the tumour and high vascular tie (131 vs. 90mm) and more lymph nodes (30 vs. 18) when compared to conventional colon cancer surgery undertaken in Leeds. CME is therefore considered as the optimal operation for patients with advanced colon cancer, although the oncological benefits need to be weighed up against the

possible risk of greater morbidity when undertaking more radical surgery.

Multidisciplinary education programmes focussing on the importance of optimal colon cancer surgery, imaging and histopathology have been undertaken across Europe. One such programme in Denmark has shown that focussed training on CME surgery significantly improved the plane of surgery, the amount of tissue taken out around the tumour and the lymph node yield (West et al, 2010c). It is expected that these improvements will translate into a significant survival benefit for patients with colon cancer.

It is therefore recommended that histopathologists carefully assess the quality of colon cancer specimens in the same way as happens for rectal cancer, and feed this back to the surgical team at the multidisciplinary meetings. Photographs should be taken of the whole specimen and cross-sectional slices in order to demonstrate the site and depth of any mesocolic defects. The importance of specimen photography and histopathological quality grading is being prospectively tested in the UK FOxTROT trial, an assessment of the benefit of pre-operative chemotherapy in advanced colon cancer.

Other important histopathological prognostic factors

Following meticulous dissection of the specimen and microscopic examination of selected tissue blocks, the final histopathology report will be issued and should contain other important prognostic information that is used to influence subsequent management (Williams et al, 2007). One of the most important outcome predictors is the stage of disease, which in the UK is currently determined using the 5th edition of TNM staging (Sobin et al, 1997). Patients with tumour deposits in lymph nodes (stage III disease) are commonly offered adjuvant chemotherapy in order to improve the chances of long term survival. For this reason, all of the lymph nodes within the specimen should be meticulously dissected and examined, and the Royal College of Pathologists recommend regular audit to ensure that lymph node yields remain in excess of twelve (Williams et al, 2007). Lymph node involvement is often preceded by lymphatic vessel invasion, which should be looked for and reported by histopathologists (figure 2, Bosch et al, 2013).

Other high risk features in stage II disease that may indicate potential benefit from adjuvant chemotherapy include extramural venous invasion (EMVI), peritoneal involvement and extension of tumour five millimetres or more beyond the outer edge of the muscularis propria. EMVI is a well recognised predictor of distant recurrence but is frequently missed by pathologists (figure 3, Morris et al, 2007). Macroscopically it appears as serpigenous extensions of tumour at right angles to the muscularis propria and special stains may be necessary to definitively identify residual vascular structures. Failure of the histopathologist to identify any of these high risk features may result in patients not being offered adjuvant chemotherapy from which they could potentially benefit.

Conclusion

Histopathologists have greatly contributed to the identification of optimal surgical techniques in colorectal cancer by meticulously assessing resection specimens and feeding back to multidisciplinary teams. Major histopathological advances have included the identification of the importance of the CRM in rectal cancer and the description of grading systems for the quality of surgery in the mesorectum, the anal sphincters and the mesocolon. These advances have played a major role in the marked improvements noted in long term outcomes for colorectal cancer patients over recent years and have helped to promote the importance of histopathologists in the multidisciplinary care of cancer patients across the world.

Key points

- Histopathologists play a major role in the assessment of cancer specimens by feeding back to multidisciplinary teams.
- Histopathologists identified the importance of avoiding tumour involvement at the circumferential resection margin, which along with total mesorectal excision surgery has led to a marked improvement in outcomes for rectal cancer patients.
- Histopathologists have described grading systems for the assessment of the plane of surgery in the mesorectum, anal sphincters and mesocolon.

- Histopathologists take photographs of colorectal cancer resections in order to provide feedback on the quality of the specimen to the surgical team and promote improvements in surgical treatment.
- Histopathologists have played a major role in multidisciplinary education programmes for colorectal cancer treatment resulting in major advances in outcomes for patients.

Conflicts of interest

Both authors declare no conflicts of interest.

References

Bosch SL, Teerenstra S, de Wilt JH, Cunningham C, Nagtegaal ID (2013) Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy **45**(10): 827–34.

Heald RJ, Husband EM, Ryall RD (1982) The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg **69**(10): 613–6.

Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S (2009) Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. Colorectal Dis **11**(4): 354–64.

Holm T, Ljung A, Haggmark T, Jurell G, Lagergren J (2007) Extended abdominoperineal resection with gluteus maximus flap reconstruction of the pelvic floor for rectal cancer. Br J Surg **94** (2): 232–8.

Lasson ALL, Ekelund GR, Lindstrom CG (1984) Recurrence risk after stapled anastomosis for rectal carcinoma. Acta Chir Scand **150**(1): 85–9.

Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B (2000) Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Lancet **356**(9224): 93–6.

Morris EJ, Maughan NJ, Forman D, Quirke P (2007) Who to treat with adjuvant therapy in Dukes B/stage II colorectal cancer? The need for high quality pathology. Gut **56**(10): 1419–25.

Nagtegaal ID, van de Velde CJ, Marijnen CA, van Krieken JH, Quirke P (2005) Low rectal cancer: a call for a change of approach in abdominoperineal resection. J Clin Oncol **23**(36): 9257–64.

Ortiz H, Codina A on behalf of Viking Project Collaborative Group (2013) The Spanish Association of Surgeon's audited teaching programme for rectal cancer. Results after six years. Cir Esp **91**(8): 496–503.

Quirke P, Durdey P, Dixon MF, Williams NS (1986) Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet **2**(8514): 996–9.

Quirke P, Steele R, Monson J, Grieve R, Khanna S, Couture 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): 821–8.

Sobin LH, Wittekind C, eds (1997) TNM Classification of Malignant Tumours. Edition 5. Wiley-Liss, New York: 66-69.

West NP, Morris EJ, Rotimi O, Cairns A, Finan PJ, Quirke P (2008) Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. Lancet Oncol **9**(9): 857–65.

West NP, Anderin C, Smith KJ, Holm T, Quirke P (2010a) Multicentre experience with extralevator abdominoperineal excision for low rectal cancer. Br J Surg **97**(4): 588–99.

West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P (2010b) Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J Clin Oncol **28**(2): 272–8.

West NP, Sutton KM, Ingeholm P, Hagemann-Madsen RH, Hohenberger W, Quirke P (2010c) Improving the quality of colon cancer surgery through a surgical education program. Dis Colon Rectum **53**(12): 1594–603.

Wibe A, Syse A, Andersen E, Tretli S, Myrvold HE, Soreide O (2004) Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior vs. abdominoperineal resection. Dis Colon Rectum **47**(1): 48–58.

Williams GT, Quirke P, Shepherd N (2007) Standards and datasets for reporting cancers: Dataset for colorectal cancer. 2nd edn. The Royal College of Pathologists, London.

Figures

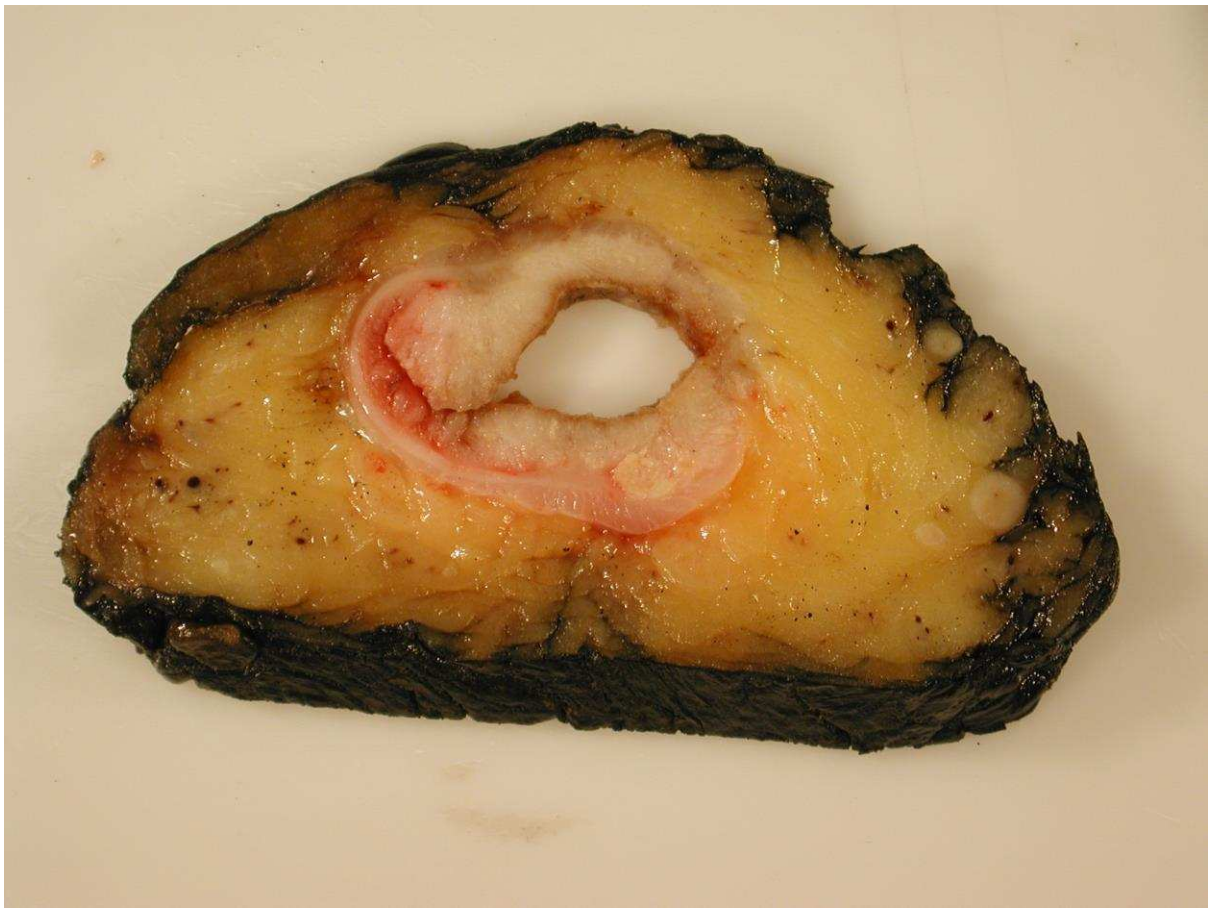

Figure 1: A cross-sectional slice of an anterior resection specimen for rectal cancer. The circumferential resection margin has been inked black so that a histological measurement of the tumour to the nearest margin can be determined. The tumour is almost circumferential and does not appear to have invaded beyond the muscularis propria. Some lymph nodes can be noted at the right side of the slice near to the margin.

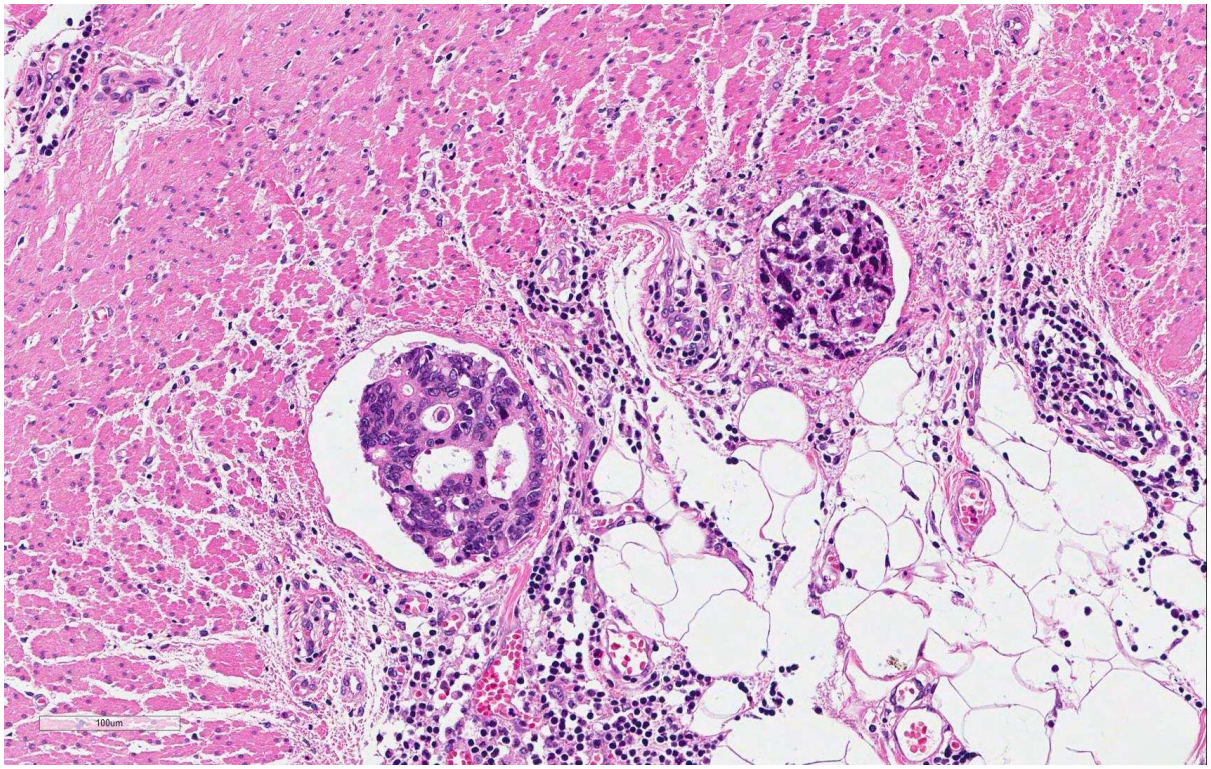

Figure 2: Lymphatic vessel invasion in a case of colonic cancer with mesenteric lymph node metastases. Two lymphatic vessels can be seen just beyond the outer limits of the muscularis propria both containing moderately differentiated adenocarcinoma.

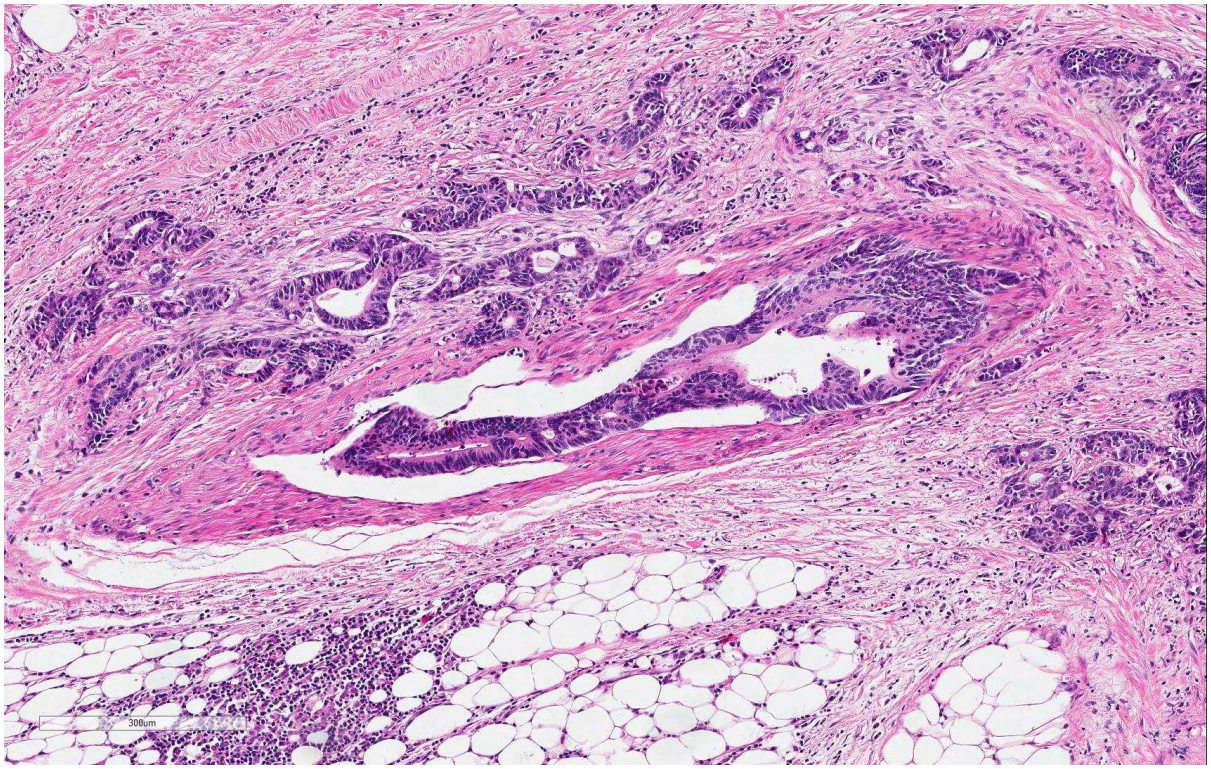

Figure 3: Extramural venous invasion in a case of stage II colonic cancer. Moderately differentiated adenocarcinoma can be seen within a muscular walled vein in the mesocolon. Further deposits of tumour can be seen in the perivascular soft tissues.

Tables

Plane	Description
Mesorectal plane	Good plane of surgery. The specimen should have a smooth surface and the mesorectal bare area should be extensively covered with mesorectal fascia. Only very minor (<5mm) defects should be seen. Distal coning should not be seen.
Intramesorectal plane	Intermediate plane of surgery. The specimen should have an irregular mesorectal surface with major defects (>5mm) and may show distal coning, although the muscularis propria should not be visible through any surgical defects.
Muscularis propria plane	Poor plane of surgery. The surgical disruptions should be large and extend down to the muscularis propria. In some cases the surgeon may have dissected into the muscularis propria resulting in the circumferential resection margin being formed by the inner layers of the bowel wall or even full thickness perforation.

Table 1: The histopathological mesorectal grading system to feed back the quality of mesorectal excisions.

Plane	Description
Extralevator plane	Good plane of surgery. The distal part of the specimen should have a smooth surface and the levator ani muscles should have been resected en-bloc with the mesorectum and sphincter muscles resulting in a non-waisted specimen. The upper part of the levator should be adherent to the distal mesorectum.
Sphincteric plane	Intermediate plane of surgery (although may be appropriate for early tumours). The levator ani should not have been resected or if present should not be adherent to the mesorectum. The distal circumferential margin should be smooth and lies on the surface of the sphincter muscles resulting in a waisted specimen. There should be no defects into the sphincter muscles.
Intrasphincteric plane	Poor plane of surgery. The surface of the specimen should be irregular with major defects seen into the sphincter muscles. Cases with perforations (full thickness defects) either within or outside of the tumour segment should be classified into this category.

Table 2: The histopathological anal sphincter grading system to feed back the quality of abdominoperineal excisions. A mesorectal grade for the upper part of the specimen should also be given (see table 1).

Plane	Description
Mesocolic plane	Good plane of surgery. The specimen should have a smooth surface and the mesocolon should be covered with either peritoneum or fascia. Only very minor (<5mm) defects should be seen.
Intramesocolic plane	Intermediate plane of surgery. The specimen should have an irregular mesocolic surface with major defects (>5mm) into the peritoneal or fascial surfaces, although the muscularis propria should not be visible through any surgical defects.
Muscularis propria plane	Poor plane of surgery. The surgical disruptions should be large and extend down to the muscularis propria. In some cases the surgeon may have dissected into the muscularis propria or even produced a full thickness perforation.

Table 3: The histopathological mesocolic grading system to feed back the quality of mesocolic excisions.