Colorectal cancer: management

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Abstract

Colorectal cancer is common with a lifetime risk of 5% and remains the second most common cause of cancer death, with low 5-year survival (55%). Early detection through bowel screening and surveillance of high-risk groups aims to identify early disease. Specialist surgery, despite the associated morbidity and mortality, offers the best chance of cure. Isolated multiorgan metastatic disease is increasingly resected, with good results. This article summarizes management of colorectal cancer, with a focus on early rectal and polyp cancers, which can pose management dilemmas.

Keywords Colorectal; early rectal; MRCP; neoadjuvant; polyp; surgery

Key points

- History and clinical examination are essential in assessment
- Multidisciplinary team working facilitates the personalization of treatment to the individual patient
- Resectional surgery remains the core treatment modality for effecting cure
- Oncological principles of clear resection margins and tumour excision are critical

Preoperative assessment and staging

Comprehensive preoperative assessment of colorectal cancer (CRC) patients is essential to determine appropriate treatment. Careful history-taking uncovers symptoms suggestive of impending obstruction or symptomatic anaemia, and helps determine surgical fitness. Any family history of CRC, polyps or other cancers that might indicate a genetic predisposition should be sought. Physical examination, digital rectal examination and sigmoidoscopy should be performed by the operating surgeon. Rectal examination should assess the distance of the tumour from the anal verge, sphincter complex involvement and the degree of tethering or fixity. Rigid sigmoidoscopy assesses luminal circumferential involvement and narrowing in addition to distance from the anal verge.

Staging investigations assess the extent of local, regional and distant disease; they also identify synchronous lesions and other prognostic factors, helping to optimize management. All patients should undergo computed tomography (CT) of the chest, abdomen and pelvis. CT assesses the primary tumour and metastatic disease but is poor at assessing nodal disease. Rectal cancer magnetic resonance imaging (MRI) can identify poor prognostic features such as mesorectal invasion, nodal disease and extramural venous invasion, and hence the potential for local recurrence (Figure 1).

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Endorectal ultrasound can enhance early rectal tumour assessment (T1/2 versus T3 stage). Synchronous lesions should be excluded in patients without obstructive symptoms by colonoscopy or CT colonography. Positron emission tomography (PET) should be reserved for identifying occult disease when primary exenterative (eviscerative) or re-do surgery for recurrence is planned. At present, no imaging modalities accurately predict the presence of small-size peritoneal disease.

All patients should meet a colorectal specialist nurse who should be accessible to explain the management plan in detail and address concerns. Where relevant, the stoma team should make early contact to discuss common stoma-related anxieties. Current trials are exploring the role of prehabilitation before surgery with respect to complications and oncological outcomes.

The demonstration of superior surgical and oncological outcomes when surgery is performed by specialist surgeons in high-volume hospitals has led to a centralization of services.[1] All staging investigations are discussed by the multidisciplinary team (MDT: surgeon, pathologist, radiologist, nurse, oncologist) to tailor patient-specific management. Staging determines the surgical strategy, from transanal endoscopic microsurgery (TEM) to abdominoperineal resection (APR), and the rationale for neoadjuvant treatment in the context of patient-specific disease and co-morbidity. Further management, discussed below, depends on disease stage.

Early colorectal cancer

Polyp cancer

Polyp cancers account for 0.75–5.6% of colorectal polyps excised at colonoscopy.[2] Bowel cancer screening has increased detection, and 10% of screen-detected cancers are malignant polyps. Polyp cancer management is a complex balance between residual disease risk versus potential morbidity and mortality, and requires thoughtful discussion with the patient. The chief objectives are identifying potentially malignant polyps, predicting residual disease risk and tailoring management appropriately.

Several endoscopic features aid identification of malignant polyps, including size, flatness, ulceration, consistency, stalk broadening and lack of lifting.[2] Invasive cancer risk increases with adenoma size. The Kudo and Paris classifications also account for flat or depressed lesions, which have significant malignant potential.[2] The Kudo polyp pit pattern can indicate likelihood of malignancy. Polyps >1 cm should be tattooed

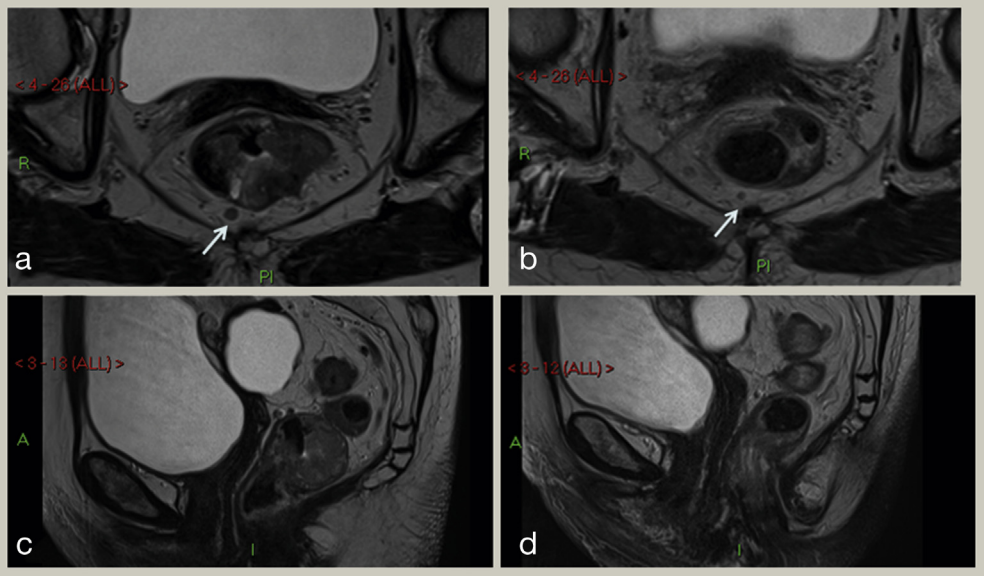

Figure 1 MRI of rectal cancer before long-course chemoradiation. (**a, c**) showing mesorectal lymph node (arrow), which is reduced in size after treatment (**b**). Sagittal sections show an overall reduction in tumour bulk from before (**c**) to after (**d**) treatment. Images courtesy of Dr Stephen Glancy, Consultant Radiologist, Western General Hospital, Edinburgh, UK.

submucosally 1–2 cm distal to the polyp site (i.e. the anal side of the lesion) to allow follow-up and identification at surgery. Polypectomy techniques, aiming for complete resection, comprise snare polypectomy, endoscopic mucosal resection and endoscopic submucosal dissection. Importantly, piecemeal resection should not be undertaken when malignancy is likely unless as definitive palliative management.

Pathology helps to determine management, as several histological features are prognostic indicators (Figure 2). Malignant polyps are defined as an invasion of malignant cells into the submucosa and must be differentiated from epithelial displacement, which has no malignant potential. The risk of malignancy is greater in polyps with villous morphology. Patients with serrated polyps have a 2.5-fold increased risk of CRC, but the serrated polyp itself may not progress to malignancy. Poorly differentiated polyp cancers (7.2%) should be resected given the 10% risk of distant disease and 23% risk of nodal disease. Other adverse prognostic markers are mucinous, signet-ring and tumour-budding morphology.

The decision to offer surgical resection relies on combining these factors to predict loco-regional disease. Risk of loco-regional recurrence depends on polyp size, morphology, resection margin, degree of differentiation and lymphovascular invasion, which is an independent predictor of nodal involvement. Nodal disease increases from 7% if there is no lymphovascular invasion to 35% if present. Risk of nodal disease is greater with sessile than pedunculated polyps. A positive resection margin ($\leq$1 mm) is an indication for completion resection, but assessment can be difficult because of diathermy artefacts and piecemeal excision. The risk of nodal disease increases from 2% if the margin is >1 mm and there are no other poor prognostic indicators, to 33% if the margin is <1 mm. Submucosal invasion of the polyp also indicates nodal involvement. The Haggitt pathological classification suggests a 6.2% risk of nodal disease if the polyp stalk is involved, and less if invasion is confined to the polyp head. Kikuchi levels of submucosal infiltration, which rely on the presence of muscularis propria within the biopsy, assess the depth of sessile polyp invasion if lesions are removed *en bloc*. Deeper submucosal layer invasion (Kikuchi sm3) is associated with nodal disease in 14.4–23%. Surgery is indicated for cancer at the polyp base, a Haggit 4 lesion or Kikuchi Sm3 in sessile polyps.

MDT decision-making involves combined assessment of all features to estimate whether risk is low, intermediate or high, and balance this against morbidity/mortality. Guidelines regarding residual disease scoring with recommendations for surgery versus surveillance are available.2 High-risk patients should be offered surgery providing adequate fitness is present, but most have no residual disease either locally or nodally. No imaging modality reliably detects nodal disease. Patients with polyp cancers who do not undergo surgery require follow-up surveillance with regular colonoscopy and CT imaging. MRI can be useful for surveillance after TEM.

Early rectal cancer

The term 'early' rectal cancer describes an adenocarcinoma that has not invaded beyond the submucosa or muscularis propria (T1/2, N0). Early rectal cancer is present in 10–15% of symptomatic patients and 30% of screen-detected cancers. Data from the UK bowel cancer screening programme show an increase from stage I cancers in unscreened populations (14.7%) to screen-detected populations (49.9%). Conventionally, to ensure oncological clearance, all rectal cancer patients are offered resectional surgery in the form of anterior resection or APR, but there has been a recent trend towards so-called 'organ preservation'. Hence, surgical options range from polypectomy/TEM/per-anal excision to resectional surgery. As with polyp cancers, it is important to balance nodal disease and local recurrence risk against co-morbidity and the risk of surgery.

Total mesorectal excision (TME) aims to ensure removal of the tumour and associated nodal disease within the mesorectum,

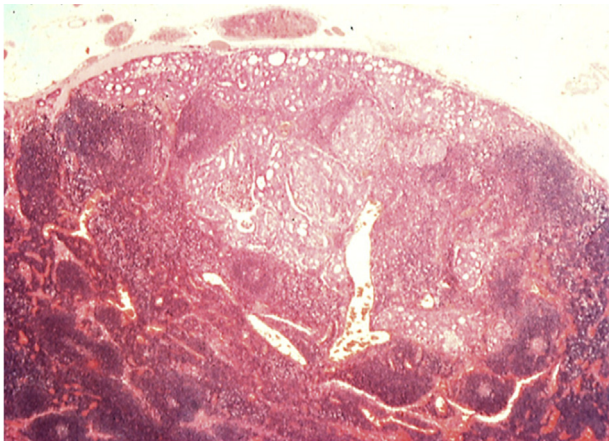

Figure 2 Mesenteric lymph node from a patient with Dukes' C colorectal cancer showing infiltration with adenocarcinoma cells. Image courtesy of Professor Mark Arends, Professor of Pathology, Western General Hospital, Edinburgh, UK.

and is associated with a 3% rate of local recurrence. The current trend towards 'organ preservation' aims to avoid the potential mortality and morbidity of major resectional surgery, including poor function and permanent stoma, without compromising oncological clearance. Multimodality staging is critical for appropriate decision-making. Endorectal ultrasound stages early disease with an accuracy of 55–97% but does not aid decision-making. MRI is essential to assess bulky lesions (>5 mm) and extramural vascular invasion but cannot predict nodal disease. Baseline MRI is also useful for follow-up after local excisional surgery.

TEM now plays an increasing part in early rectal cancer management. TEM does not treat nodal disease and has an associated risk of local recurrence. Nonetheless, early T-stage disease patients with no nodal disease are cured, so patient selection is critical. The UK TEM study found that depth of tumour invasion, maximum tumour diameter and presence of lymphovascular invasion independently predicted local recurrence.[3] Risk of local recurrence increases in patients with Sm2–3 and pT2 cancers, who should be offered salvage surgery if fit. Hence, if pathology indicates there is a high-risk of nodal disease/local recurrence, it is important to undertake completion surgery, but this is carefully balanced against co-morbidity, life expectancy and patient choice (i.e. stoma).

The key issue, as with polyp cancers, is the inability to stage nodal disease, which increases with invasion depth and tumour size. In a review of 3621 patients, the overall risk of nodal disease with T1 rectal cancers was 11.4%. Features predicting nodal disease are similar to those for polyp cancers: submucosal invasion and poorly differentiated signet cell and mucinous morphology. TEM is limited for lower-third rectal cancers given the relative lack of mesorectal tissue. A recent study examined outcome after re-do surgery and found that full-thickness TEM, distal lesions and those with an interval to TME surgery of >7 weeks had inferior TME specimens.

The surge of interest in organ preservation has triggered debate regarding the role of neoadjuvant therapy before TEM. The Lezoche group has suggested that there is no difference in long-term survival with chemo-radiation followed by TEM compared with resectional surgery. This must be balanced against considerable morbidity from radiotherapy to which early rectal cancer patients would not usually be subjected, and increased TEM complication rates after chemo-radiation. Neoadjuvant treatment should currently not be offered outside trial settings. Adjuvant radiotherapy after TEM was shown to reduce local recurrence in a small series. There are limited data on the duration of follow-up after TEM, but surveillance should probably continue for 5–10 years.

Advanced colorectal cancer

Locally advanced colon cancer

The need for complete resection in locally advanced colon cancer (T4) depends upon the degree of invasion into surrounding structures and whether these are resectable *en bloc*. Staging is critical to both planning and consent for multivisceral resection. The role of neoadjuvant chemotherapy in locally advanced resectable colon cancer is under investigation, but concerns remain regarding increased complication rates. Although the pilot phase results report 'acceptable' toxicity, concerns remain regarding the over-treatment of stage II patients. Locally recurrent colon cancer, less common than distant relapse, accounts for 10–20% of recurrences and usually occurs within 3 years of resection.

Locally advanced rectal cancer

Surgery for rectal cancer remains essential if a cure is to result. Strict adherence to oncological principles of TME has led to a decrease in local recurrence rates. Nonetheless, given the well-recognized impact of clear margins (R0 resection) on local recurrence and survival, there has been a rapid introduction of neoadjuvant chemo-radiation therapy (CRT) as standard in patients undergoing rectal cancer surgery, to decrease local recurrence. Short-course radiotherapy (SCRT) led to reduced local recurrence (11% versus 27%) and increased 5-year survival (58% versus 48%). Combining SCRT with optimal TME surgery reduced local recurrence further (2.4% versus 8.2%) but did not affect overall survival. As CRT becomes increasingly standard, concerns are escalating regarding long-term effects of radiotherapy on pelvic function.[4]

Poorer low rectal cancer outcomes have led to increased use of CRT to allow 'sphincter-saving surgery' and widespread adoption of extra-levator abdominoperineal excision surgery for APR. Recent data suggest that extra-levator abdominoperineal excision does not improve short-term oncological outcome. There is still concern regarding the liberal use of radiotherapy and its associated long-term toxicity. Low local recurrence rates are achievable without neoadjuvant therapy in carefully selected stage II/III patients. Pelvic exenteration for locally advanced T4 rectal cancers have an R0 resection rate as high as 87% in selected cases. In summary, patient selection is critical and best determined by the operating surgeon; digital rectal examination, often during examination under anaesthetic, will identify the degree of margin involvement and the place for neoadjuvant radiotherapy.

Complete pathological response, where no tumour is found in the pathological specimen after CRT, has been reported in 15–20% of patients with locally advanced rectal cancer and is

associated with better overall survival. An interval ≥8 weeks between completion of CRT and surgery is associated with increased complete pathological response rates.[5] Hence, much debate surrounds the interval between CRT completion and timing of surgery. A systematic review of 15 studies concluded that a longer interval would maximize the benefit of down-staging. Maximal response is more likely with intervals of 12 weeks. 'Watch-and-wait' strategies are increasingly being evaluated, and rectal preservation has to be balanced against the risk of local regrowth and distant progression.

Recurrent cancer

Despite the advances described in surgical technique and the selective use of neoadjuvant regimens for rectal cancer, local relapse occurs in around 5–10% patients, usually within first 2 years of surgery. Risk factors for recurrence include locally advanced T3/T4 tumours, anastomotic failure, positive mesorectal nodes and adverse pathological features such as lymphovascular invasion. Management depends on the extent and position of recurrence and the presence of distant disease. Salvage surgery is an option if recurrence is localized, there is no distant disease and the probability of R0 resection is high. This has to be offset against the considerable morbidity of pelvic exenteration. The key is patient selection, along with candid discussion with the patient and family regarding both cancer and disability outcomes. The location of recurrence and the relationship to surrounding structures determines the probability of R0 resection.

The classification of recurrence in a systematic manner permits the comparison of outcomes. Patterns of recurrence are classified as axial or central (not involving bone or side wall), anterior (which can involve genitourinary organs), posterior (which can involve sacrum) and lateral (invading iliac vessels, pelvic autonomic nerves or ureters, or extending into the greater sciatic foramen). Complete restaging, with CT/MR and PET imaging for distant disease, followed by discussion in the MDT, is essential. Five-year survival averages are around 19% but better outcomes (55–90%) result from R0 resection and careful patient selection. There is no survival difference between R2 resection and non-operative management.

Metastatic colorectal cancer

The liver is the most common site of CRC metastases, which are present in around 20–25% of patients at diagnosis; about 25% will develop them later. Liver-only metastatic disease should be discussed by the hepatic MDT, so hepatic surgeons can assess resectability and the value of neoadjuvant chemotherapy. Five-year survival is reported as 28–47% in studies with >400 cases. Reported independent predictors of poor long-term outcome are >3 hepatic metastases, node positivity or a poorly differentiated primary, extrahepatic disease, tumour diameter >5 cm, raised serum carcino embryonic antigen (CEA) and a positive resection margin. Other factors associated with poor prognosis are a short disease-free interval between primary resection and lung metastases, multiplicity, high CEA values and involved hilar/or mediastinal lymph nodes. It is important that symptom control remains the priority but that aggressive management is sought where appropriate.

Adjuvant chemotherapy

After surgery with curative intent, the aim of adjuvant chemotherapy is to reduce systemic micro-metastases. The MDT discusses all patients to specify management depending on likelihood of recurrence, fitness for chemotherapy and overall life expectancy. Current recommendations suggest that stage III (lymph node positive) patients might benefit from adjuvant chemotherapy, with a 30% decrease in recurrence. Given that the absolute increase in 5-year survival is only 5% in stage II disease, adjuvant chemotherapy can be considered in those with high-risk features, such as poor differentiation, perforation, perineural or lymphovascular invasion, or involved margins. The absolute benefit of adjuvant chemotherapy clearly has to be balanced against the potential for serious and life-threatening toxicity.

Follow-up and surveillance

The aim of post-treatment surveillance is to identify disease recurrence early. There is debate regarding the optimal follow-up regimen and the impact this might have on overall survival. A recent randomized controlled trial reviewed CEA only, CT only, CEA and CT, and minimum follow-up: CT or CEA screening increased the rate of surgical treatment for recurrence compared with minimal follow-up, but there was no advantage to combining CEA and CT. Current recommendations are colonoscopy and CT at 1 year and continuing surveillance thereafter, with regular CEA measurement at 6-monthly intervals.

Recent developments

Laparoscopic surgery is increasingly accepted as an alternative to open surgery, with decreased length of stay and earlier recovery as key benefits. However, there remains limited evidence on both immediate and longer term oncological outcomes. A recent Cochrane review of several randomized controlled trials concluded there was moderate quality evidence that laparoscopic TME has similar long-term survival outcomes to open surgery in rectal cancer. The key long-term contribution of laparoscopic surgery might be a reduction in small bowel obstruction caused by adhesions and incisional herniae. Other perceived technological advances, including single-incision laparoscopic surgery and robotic surgery, continue to be championed; however, there as yet no proven health- or cost-related advantages of these techniques. The results of the Robotic versus Laparoscopic Resection for Rectal Cancer (ROLARR) trial, comparing robotically assisted and standard laparoscopic rectal cancer surgery, are awaited.

As discussed earlier, lymph node staging is critical but inaccurate with current imaging modalities. Sentinel lymph node identification in CRC, using markers such as indocyanine green, has shown renewed interest and could contribute to improved lymph node resection. Considerable research efforts are being concentrated on characterizing the genetic and molecular biology of CRC, and tangible clinical benefits, in terms of improving outcomes, are foreseen in the near future. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 50-year-old man presented with a 6-week history of intermittent rectal bleeding and some tenesmus. On clinical examination the abdomen was unremarkable with no groin lymphadenopathy but on rectal examination there was a mass 4 cm from the anal verge which felt fixed posteriorly. It encompassed less than one-third of the lumen.

What is the next best step in this patient's management?

A Biopsy of rectal lesion
B CT scan chest, abdomen and pelvis
C MR scan chest, abdomen and pelvis
D Multidisciplinary team discussion
E Long-course radiotherapy

Question 2

A 75-year-old woman was reviewed following transanal endoscopic microsurgery (TEMS). She had previously been found to have a 2.5 cm mobile rectal adenomatous lesion located at 3 cm from the anal verge. This was thought to be a tubulovillous adenoma on biopsy. Staging scans had been normal. Colonoscopy had not shown metachronous lesions. She also had chronic obstructive pulmonary disease and ischaemic heart disease. She had a 60 pack-year smoking history.

Investigation

Pathology of the TEMS resection showed T2 cancer with Kikuchi level sm2. The margin was clear with no evidence of extramural lympho-vascular invasion.

What is the best next step in this patient's management?

A Multidisciplinary team discussion
B Proceed to anterior resection to stage lymph nodes
C Re-excise the rectal scar
D Repeat staging CT scan and MR scan pelvis
E Monitor for recurrence using carcino-embryonic antigen (CEA)

Question 3

A 44-year-old woman was reviewed at an MDT meeting. She had presented with rectal bleeding and on colonoscopy was found to have a 2 cm pedunculated polyp in the sigmoid colon and 11 other smaller polyps throughout the colon which were all excised.

Investigation

Pathology from the largest polyp showed a focus of adenocarcinoma within the polyp with the margin <1 mm from the diathermised edge. The remainder of the polyps were tubulovillous adenomas.

What is the most likely advice following the MDT meeting?

A Proceed to total colectomy
B Proceed to anterior resection to remove remainder of sigmoid colon and stage nodal disease
C Repeat colonoscopy in 1 months
D Take blood for genetic testing
E Discuss management options with patient to explain risk of recurrence versus risk of surgery