1 Introduction

The ACPGBI has been at the forefront in developing guidelines, position statements and national training programs related to both common, and complex, colorectal pathology. These initiatives often serve as a global reference in this challenging field. The Association of Coloproctology of Great Britain and Ireland (ACPGBI) 2007 Colorectal Cancer Management Guidelines have been the basis for continuous evolution in the way these cancers are managed. The current update aims to clarify many recent developments on the multidisciplinary management of colorectal cancer and to provide links to relevant publications. The recommendations made within these guidelines have been graded according to the Oxford Centre for Evidence-based Medicine – levels of evidence (www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/). We hope that these guidelines will offer a framework for clinicians and MDT's to tailor treatments to suit individual patients. We also hope to direct future research and debate in a rapidly evolving field.

A substantial part of the workload of colorectal units is to not only exclude diagnosis of cancer but to manage cancer of the colon, rectum and anal canal. Access to information through technology, and particularly the internet, has changed perceptions and expectations of cancer patients, their carers and clinicians. The general public and healthcare providers continue to shift focus towards cancer prevention and early diagnosis. At the other end of the spectrum, patients with locally advanced, recurrent or metastatic cancer are increasingly being considered for tailored multimodal therapy, based on molecular biology and pharmaceutical advances.

In the UK, through the NCRI Colorectal Cancer Clinical Trials Group and numerous other research organizations, we are proud of our record of being at the forefront of designing and completing many internationally acclaimed oncological and surgical trials. These have been instrumental in shaping our current clinical practice. We must continue to build on this foundation by developing and recruiting into new trials to further improve treatment.

1.1 Multidisciplinary teams

Over the last few decades, multidisciplinary teams (MDTs) have evolved, and consolidated, in individual units to manage colorectal cancer. At the MDT meeting, the clinical nurse specialist, with the attending surgeon, are best positioned to act as the patients’ advocates and ensure crucial decisions are made with a first-hand knowledge of the patient and their wishes. It is pertinent that MDT recommendations are based on the available information and recommendations may, or may not be appropriate, or acceptable to the individual patient. Clinicians should support patients requesting second opinions and guide them with appropriate pathways. Current MDTs should look to extend their role in training junior surgeons, radiologists, histopathologists and oncologists, and mentoring new members of the core team. Personal-audits and regular feedback between core members should be an integral part of the development of the MDT.

Ongoing sub-specialization has encouraged development of specialist MDTs in a number of areas including anal cancer, early rectal cancer, ‘beyond’-TME and recurrent pelvic cancers, and cytoreductive surgery.
Teams treating colorectal disease need to recognize the spectrum of disease, diversity of treatments and develop care pathways to access specialist MDT’s.

1.2 Prevention and earlier diagnosis
Public awareness campaigns and the NHS Bowel Cancer Screening Program have impacted positively on the diagnosis of early stage disease, and polyp detection and clearance are likely to reduce colorectal cancer incidence. Introduction of Faecal Immunochemical Test and Bowel Scope Screening will further improve the stage at diagnosis of colon and rectal cancer.

Bowel cancer screening has added to the challenge of treating polyp cancers and early rectal cancer; oncological adequacy of minimally invasive interventions (polypectomy and local excisions) vs morbidity and mortality risk of resection surgery. The ongoing SPECC (Significant Polyp Early Colorectal Cancer) Pelican/ACPGBI Program aims to stimulate discussion and training in these areas. Robust risk stratification tools to help MDTs and patients make informed decisions, especially in an older and frailer population, are needed. Clinical trials, such as the recently completed NCRI TREC-1 and the new NCRI STAR-TREC in early rectal cancer will add to this knowledge.

1.3 Laparoscopic Surgery and Enhanced Recovery After Surgery (ERAS)
The Laparoscopic Colorectal Surgery (LAPCO) program, which was a joint initiative between the ACPGBI and NHS England, delivered high quality accreditation training in laparoscopic surgery to NHS colorectal surgeons. This initiative, together with increasing public awareness of laparoscopic surgery, has resulted in a steady year-on-year increase in the proportion of cases treated by minimal access, whilst achieving good oncological outcomes in addition to the short-term early benefits, particularly in colon cancer but less so in rectal cancer.

Introduction of ERAS on the background of minimally invasive surgery has improved short-term outcomes including length of stay. Optimal results have been reported using a combination of ERAS and minimal access techniques. The concepts from colorectal surgical ERAS programs have been adopted by other surgical fields and have benefited a wider group of patients.

1.4 Low Rectal Cancer
The Low Rectal Cancer Development (LOREC) program is another joint initiative between the ACPGBI and NHS England, providing training to MDTs on the overall management of cancers arising at, or below, the level of the insertion of the levator muscles, including the appropriate use of extralevator abdominoperineal excision (ELAPE). The longer-term oncological outcomes and the associated morbidity of this initiative are yet to be reported.

1.5 Radiology and Histopathology
High quality radiology and detailed histopathology reporting is crucial, as it underpins MDT decision making. This provides quality assurance to patients and clinicians on management decisions. Radiology and pathology provide valuable prognostic indicators in colon and rectal cancer, which helps to determine further management. Advances in imaging and use of biomarkers have initiated individualized treatment strategies to be developed in all stages of disease. We predict that these advances will expand exponentially in the next decade.

1.6 Chemotherapy and Radiotherapy
The use of preoperative radiotherapy, with or without chemotherapy in addition to surgery in ‘operable’ rectal cancer reduces local recurrence rates, but much of the published evidence predates modern imaging, making it difficult to quantify the exact benefits. Together with ongoing improvements in surgical techniques, such as ELAPE for advanced low rectal cancer, and an increasing awareness of immediate and long-term toxicity, the risk-benefit of using radiotherapy in rectal cancer, either to downstage disease or to reduce local recurrence needs careful consideration on an individual basis. There remains significant variation in the use of radiotherapy nationally, but with further refinements in imaging and expansion of knowledge, this will allow more selective utilization. However the role of optimal surgery remains crucial.

Further advances in the use of adjuvant chemotherapy, with the addition of new targeted agents have failed to materialize. The focus has shifted to earlier use of systemic therapy in the neoadjuvant setting for colon and rectal cancers, as well as reducing the duration and toxicity of adjuvant therapies.

There is increasing worldwide interest in the potential for non-operative management of rectal cancers of all stages. Ongoing trials to improve pathological complete response rates (pCR) and translational studies to develop new predictive markers, together with high-quality observational trials such as the NCRI Deferral of Surgery, may allow for safe deferral and hopefully,
complete avoidance of surgery in selected patients who have potentially achieved pCR after preoperative chemoradiotherapy (CRT).

1.7 Outcomes and Survivorship

The National Bowel Cancer Audit (NBOCA) has evolved from being a voluntary audit when first launched in 2000, to currently being a quality assurance tool for individual surgeons and NHS Trusts. Although it has provided invaluable data to drive up the standards of care delivered nationally, there remain opportunities to further improve the quality of data collected.

Through NBOCA, the publication of individual colorectal surgeons’ outcomes has empowered patients, by providing online information about volumes and outcomes of individual surgeons and NHS Trusts. Individual surgeon outcome reporting is contentious and unit data may be more meaningful and is the subject of ongoing discussion.

1.8 Person-centred care

Most importantly, treatment of colorectal cancer should take into account individual preferences, and be delivered with dignity, compassion and respect. Patients need to understand that the management of their cancer is individualized and complex. They should be given an explanation for the perceived delays in commencing treatment, such as the need for further investigations or MDT discussion. Response to treatment is often unpredictable, as are many of the acute and late toxicities. These uncertainties should be openly discussed and patients should be able to make informed choices about their care, in partnership with their healthcare professionals. These decisions should be subject to regular review at appropriate key points during treatment, to accommodate any changes in circumstances and to allow the patient the opportunity for further discussion or reconsideration.

Healthcare professionals must not underestimate the psychological and social impact of a diagnosis of colorectal cancer on the individual as well as family, carers and supporters. There is wide variation in their reactions, their ability to cope and their recall of information received, which may be subject to strong emotions and anxiety. Communication and listening skills for such patients need to be exemplary as they form a vital part of the patient journey, from undergoing treatment, to recovery and eventual readjustment to life beyond hospital.

1.9 Summary

These guidelines offer an updated framework for colorectal cancer clinicians and MDTs. They will continue to evolve and require updating in light of ongoing developments and emerging evidence.

Conflicts of interest

None of the authors have any conflicts to declare.
2 Diagnosis, Investigations and Screening

2.1 Initial diagnosis

2.1.1 Process of referral and investigation

Concern over a diagnosis of colorectal cancer should prompt urgent referral, in most cases within general practice through a ‘two week wait rule’. Criteria for two-week wait referral (National Institute for Health and Clinical Excellence, 2015) should be satisfied and in many institutions, patients are offered a ‘direct to test service’. Initial investigations are planned on the basis of presenting symptoms (anaemia, change in bowel habit, rectal or abdominal mass), age and co-morbidity, as well as available local expertise and resources. A typical investigation algorithm is shown in Table 2.1. Patients presenting via a non-urgent route should also be investigated along similar lines. The NICE guidance (NG 12) for suspected colorectal cancer (National Institute for Health and Clinical Excellence, 2015) recommends using faecal occult blood testing for a subset of patients without rectal bleeding. This remains contentious due to equivocal evidence in symptomatic patients. Its practical implementation remains challenging in most regions.

2.1.2 Choice of investigations

The recent UK Special Interest Group in Gastrointestinal and Abdominal Radiology (SIGGAR) trials (Atkin et al., 2013; Halligan et al., 2013) provides level 1 evidence on the choice for whole colon imaging in patients with symptoms suggestive of colorectal cancer. The trial comprised a composite single endpoint incorporating:

1. CT colonography (CTC) vs double contrast barium enema (DCBE), with detection rates of cancer and large polyps (≥1 cm).
2. CTC vs optical colonoscopy (OC), powered to measure the requirement for additional colonic tests following the randomized investigation. The rationale is
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Age</th>
<th>2WW Indication</th>
<th>Please tick*</th>
<th>Direct to test</th>
<th>Results</th>
</tr>
</thead>
</table>
| Change in bowel habit         | Over 55 | **Looser and/or more frequent stools, persistently for more than 6 weeks without rectal bleeding** | Colonscopy   | *Fit for bowel prep?:*  
Y { } N { }  
Positive test (cancer) – direct referral to MDT via colorectal nurse specialists  
Or to other MDT if non-GI cancer e.g. ovarian  
Negative test (no major pathology) – Once cancer has been excluded, patient will be referred back to GP e.g. coeliac disease, gallstones, hernias etc.  
Only in exceptional circumstances where immediate onward referral is deemed clinically necessary will onward referral be made by the secondary care clinician see OTHER below:  
**Other** - Any condition detected on investigation that poses imminent danger of deterioration or serious harm to the patient e.g. AAA >= 5 cm, Inflammatory bowel disease, decompensated cirrhosis, colonic polyp >= 1 cm, will be referred directly to the appropriate service. |

| Rectal bleed                  | Over 40 | **Change in bowel habit** – rectal bleeding with a change in bowel habit to looser and/or more frequent stools persistently for 6 weeks | Colonscopy   | *Fit for bowel prep?:*  
Y { } N { }  
Flexible sigmoidoscopy |
|                               | Over 55 | **No change in bowel habit** Rectal bleeding persistently for >6 weeks without a change in bowel habit & without anal symptoms | Flexible sigmoidoscopy |

| Mass                          | All ages | Rectal – A definite palpable rectal (not pelvic) mass                           | Flexible sigmoidoscopy |
| All ages                      |         | Abdominal – A definite palpable abdominal mass                                    | CT colonography or colonoscopy |

| Anaemia                       | All ages | Men – of any age with unexplained iron deficiency 110 g/l or below               | CT colonography or colonoscopy + OGD |
| All ages                      |         | Women – non-menstruating women with unexplained iron deficiency anaemia 100 g/l or below | CT colonography or colonoscopy + OGD |
| Any of above                  | >75 years | As above (please tick) BUT aged >75 years or symptoms not covered in above       | 2WW Outpatient clinic Clinic then Direct-to-Test and as above |
that subsequent OC with biopsy will usually be required for CTC-suspected cancer or significant polyp, and that any benefit in avoiding an endoscopic procedure would be cancelled out if a CTC precipitates a large number of subsequent unnecessary colonoscopies. Conversely, OC is more often suboptimal, limited or incomplete in the more elderly symptomatic population, which may lead to further colonic investigations.

The principal finding was that CTC detected significantly more cancers and large polyps than DCBE (7.3% vs 5.6%; P = 0.039). Patients randomized to CTC were diagnosed with fewer post-test colorectal cancers than DCBE during a 3-year follow up period (3/45 vs 12/85). No significant difference was found in detection rates between CTC and OC (10.7% vs 11.4%) but CTC generated more colonic investigations than OC (relative risk 3.65). Post-test colorectal cancers during 3-year follow up were 1/29 for CTC and 0/55 for OC, confirming prior meta-analysis suggesting no significant difference in sensitivity of the two tests for colorectal cancer (Pickhardt et al., 2011).

Patients with suspected colorectal cancer should be offered either optical colonoscopy or CT colonography.

**Recommendation grade A**

CT colonography should replace double contrast barium enema.

**Recommendation grade A**

2.1.3 **Quality of investigations**

Regardless of whether OC or CTC is used, certain levels of Quality Assurance should be achieved by these investigations.

- Colonoscopy
  Colonoscopy should be performed by an experienced colonoscopist, or a colonoscopist who has been certified by the Joint Advisory Group (JAG), or by trainees supervised by one of the above. National quality and safety standards for endoscopy have been set by the Department of Health using a Global Rating Scale (GRS) (www.grs.nhs.uk) and by the British Society for Gastroenterology (www.BSG.org.uk). The quality and safety indicators underpin the respective items using GRS.

- CT Colonography (CTC)
  There are several international consensus recommendations regarding acquisition of CTC images (Burling, 2010; McFarland et al., 2009; Neri et al., 2013). The examination may be performed following full purgative bowel preparation and administration of a faecal tagging agent (oral contrast medium administered several hours prior to the investigation). Some faecal tagging agents such as sodium amidotrizoate/meglumine amidotrizoate (Gastrografin) also have a laxative effect and can be used as a combined cleansing/tagging agent. Although some oral faecal tagging agents have a laxative effect, others do not, and in particularly frail patients a combination of dietary manipulation and non-laxative faecal tagging (such as low-dose iso-osmolar iodinated contrast media, or certain barium sulphate preparations) may achieve adequate image quality to exclude clinically relevant neoplasia. In all cases (with or without purgation), faecal tagging is now regarded as mandatory when performing CTC.

  Mechanical insufflation with CO₂ reduces patient discomfort and improves colonic distension, when compared with room air. Intravenous antispasmodic, typically hyoscine butylbromide (Buscopan), also improves distension and may reduce pain. The use of intravenous contrast medium is not essential for colonic lesion detection, but may be an efficient strategy in patients in whom the pre-test probability of either colorectal cancer or important extracolonic pathology is high, and is invariably given when whole colon imaging and staging is required following detection of a cancer where OC failed to evaluate the proximal colon.

  All reporting radiologists must meet the recommended standards for competency, and be actively involved in audit of their practice and performance (British Society of Gastrointestinal and Abdominal Radiology (BSGAR), The Royal College of Radiologists, 2014). There are specific stipulations for radiologists involved in the National Bowel Cancer Screening Program (NHS Bowel Cancer Screening Programme, 2012).

**Radiological and endoscopic investigations should meet national standards and be subjected to regular Quality Assurance.**

**Recommendation grade C**

2.1.4 **Diagnosis of colorectal cancer**

Colon cancer should ideally be confirmed histologically, but when a lesion with high probability of malignancy has been detected by CTC, histology prior to surgery is not essential if the segment cannot be reached endoscopically. Conversely, histological confirmation of malignancy should be considered mandatory in all rectal cancers when surgery might result in either a permanent stoma or an ultra-low anterior resection, or when neoadjuvant therapy is being considered. Exception to this may be a large endoluminal lesion where biopsies have been inconclusive and the lesion is not amenable to endoscopic surgery.
Preoperative histological confirmation of colonic cancer is desirable but not essential in cases with high probability of malignancy based on clinical presentation and optimal imaging.

Recommendation grade D

Pre-treatment histological confirmation of rectal cancer is considered essential. Exceptions should be rare and are usually large lesions not amenable to endoscopic removal and inconclusive biopsies.

Recommendation grade D

2.2 Staging of Colorectal Cancer

Staging investigations for colorectal cancer should address three areas:

a) Assessment of local disease
b) Metastatic disease
c) Synchronous colonic disease

2.2.1 Assessment of local disease

Local extent of colonic disease is assessed by abdominal and pelvic computed tomography (CT) to provide information on extent of spread in relation to the bowel wall and adjacent organs. This is essential to the planning of surgery (e.g. non-anatomical resection) and to allow consideration of neoadjuvant therapy when the disease is locally very advanced or unresectable.

CT has limited ability to differentiate the individual layers of the bowel wall, making the distinction between T1 and T2 disease challenging. Although certain tumour morphology features seen on CT colonography, namely an arc-shaped or trapezoidal tumour configuration, may suggest T1 or T2 status, these are yet to be validated in a prospective, multicentre setting. Similarly, the distinction between T3 and T4 disease can be challenging because the latter may be contingent only on sub-millimetre spread through the serosa for peritonealized colon (T4a by TNM 7th edition; T4b by TNM 5th edition).

Conversely, because of the naturally high contrast at CT between the bowel wall and the adjacent fat, T3 disease can usually be discriminated from earlier-stage lesions, which is removed with the primary. Meta-analysis suggests that CT is approximately 70% sensitive for the detection of nodal involvement for colonic cancers (Dighe et al., 2010), similar to prior meta-analysis for rectal cancers.

Magnetic resonance imaging (MRI), with few exceptions such as patients with contra-indications to MRI or unwilling due to phobia, is recommended for local staging of rectal cancers, particularly to determine the risk of the circumferential margin (CRM) being involved or threatened by tumour. The ability of MRI to predict a clear (>1 mm) CRM in rectal cancer is very good (>90%) (MERCURY Study Group, 2006). However, staging of lymph nodes is less accurate.

Cancers of the lower third of the rectum are defined on MRI as an adenocarcinoma with its lower edge, at or below the level of origin of the levator muscle on the pelvic side-wall (Moran 2014). Patients with low rectal cancers have generally worse outcomes in terms of survival compared to mid and upper rectal cancers. Specific management issues have been identified and addressed through the LOREC program, in order to try to improve outcomes in this group.

Rectal cancer requires specifically tailored locoregional staging since this affects the feasibility and timing of radical surgery, and this will be discussed further in Chapter 4.

Since introduction of the UK NHS Bowel Cancer Screening Program, increasing numbers of early colon and rectal cancers are being diagnosed. Suspected early stage rectal cancers should be assessed with endorectal ultrasound for more accurate local staging if considering the patient for an organ preserving approach. A Significant Polyp Early Colorectal Cancer (SPECC) Program is currently underway to improve definition, recognition, documentation, strategic planning and treatment of these lesions (Pelicanancer.org.uk).

2.2.2 Metastatic disease

Colorectal cancers commonly metastasize to the liver, lungs and peritoneum. Routine staging by CT chest, abdomen and pelvis provides adequate staging in most cases. Further characterization of equivocal liver lesions may be assisted by MRI. 18-Fluorodeoxyglucose positron emission tomography/CT (18-FDG PET/CT) may be used to investigate suspicious lesions seen on CT or MRI. In addition, PET/CT provides valuable assessment to help exclude occult metastatic disease in
patients being considered for non-anatomical resection of locally advanced cancers or surgical management of liver and lung metastases, to facilitate appropriate patient selection aiming to reduce futile procedures (Adams et al., 2013).

2.2.3 Synchronous colonic disease

Synchronous colorectal cancers are present in 2–3% of patients and a further 20% have synchronous significant benign lesions (diverticular disease, colitis or polyps). Synchronous lesions should be diagnosed at colonoscopy or CTC, as this is crucial in planning complete surgical resection. The most distal significant lesion in the colon should be tattooed (Williams et al., 2013) with the proviso that the endoscopist should ensure they are in the sigmoid and not the rectum. The tattoo should be placed into a saline bleb 2–5 cm from the base of the lesion on the distal (anal) side and the estimated distance clearly documented. More than one tattoo may be applied but the endoscopist should document very carefully the number and position of tattoos in relation to the polyp or tumour. Rectal lesions should not be tattooed.

All patients with suspected colonic cancer should be staged with a CT thorax, abdomen and pelvis.

Recommendation grade B

All patients with suspected rectal cancer should be staged with a CT thorax, abdomen and pelvis. Patients being considered for curative locoregional treatment should have MRI of the pelvis.

Recommendation grade B

Synchronous lesions should be identified using colonoscopy or CTC prior to colorectal cancer resection. If complete colonoscopy is not possible, CTC should be considered. CT of the thorax can be combined with CTC to permit staging at the same hospital visit.

Recommendation grade B

2.3 Colorectal Cancer Screening

2.3.1 Screening for average risk population

2.3.1.1 NHS Bowel Cancer Screening Program (BCSP)

The NHS BCSP offers screening every 2 years to the population aged between 60–69, as over 80% of newly diagnosed colorectal cancers occur at this age and beyond. Since 2008, the screening age group has been extended to 74 years old, in accordance with the government's strategy to improve cancer outcomes.

Screening with guaiac faecal occult blood test (FOBT) has been shown to reduce colorectal cancer mortality in four large population-based randomized control trials after more than 10 years of follow up (Table 2.2) (Hewitson et al., 2008). The results from the UK and Denmark were directly comparable. The apparently superior results in the US trial were ascribed to a far higher colonoscopy rate, which in turn was due to more frequent FOB testing and a lower positive test threshold.

The guaiac FOBT is being replaced with the more accurate faecal immunochemical test (FIT) for colorectal cancer screening programs (Halloran et al., 2012). It has shown improved uptake and the ability to detect significantly more colorectal cancers and advanced adenomas (Digby et al., 2016; Moss et al., 2016). However, the higher uptake and test positivity is likely to stretch colonoscopy services even further (Tinmouth et al., 2015).

People with positive fecal occult blood tests (5 or 6 samples tested positive; or 1–4 samples positive, followed by any positive result on two subsequent screening kits) are offered a screening colonoscopy. This is carried out in endoscopy units by a JAG accredited BCSP colonoscopist. For individuals unwilling to have or who cannot tolerate colonoscopy, CTC could be considered. Follow up colonoscopies will be determined by the results of the index colonoscopy.

The NHS BCSP has had a positive impact on elective treatment of colorectal cancers by early cancer detection, increased use of minimally invasive techniques and reducing the need for emergency colorectal surgery.

### Table 2.2 Characteristics, Relative Risk (RR) and 95% Confidence Interval (CI) for colorectal cancer mortality of 4 randomized controlled trials using FOBT (Hewitson et al., 2008). Yr = Year.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Screening frequency</th>
<th>Age range (Yr)</th>
<th>Follow up period (Yr)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funen</td>
<td>Denmark</td>
<td>Annual</td>
<td>45–75</td>
<td>17</td>
<td>0.84</td>
<td>0.73–0.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biennial</td>
<td></td>
<td></td>
<td>0.89</td>
<td>0.78–1.01</td>
</tr>
<tr>
<td>Minnesota</td>
<td>US</td>
<td>Annual</td>
<td>50–80</td>
<td>18</td>
<td>0.67</td>
<td>0.51–0.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biennial</td>
<td></td>
<td></td>
<td>0.79</td>
<td>0.62–0.97</td>
</tr>
<tr>
<td>Nottingham</td>
<td>UK</td>
<td>Biennial</td>
<td>45–74</td>
<td>11.7</td>
<td>0.87</td>
<td>0.78–0.97</td>
</tr>
<tr>
<td>Goteberg</td>
<td>Sweden</td>
<td>Biennial</td>
<td>60–64</td>
<td>19</td>
<td>0.84</td>
<td>0.71–0.99</td>
</tr>
</tbody>
</table>
cancer resections. It also has had a positive impact on 30-day postoperative mortality and 5-year survival rates.

2.3.1.2 NHS Bowel Scope Program
A randomized controlled trial in the UK has shown that a ‘one-off’ screening flexible sigmoidoscopy reduces CRC incidence and CRC-related mortality by 23% and 31% respectively (Atkin et al., 2010) after a median follow up of 11 years. Results from the UK trial have prompted the NHS to roll out a population-based program using flexible sigmoidoscopy as screening offered at age 55 with the option to opt in up to aged 60 (http://www.cancerscreening.nhs.uk/bowel/).

Population-based NHS Bowel Cancer Screening Program will increase detection of early stage disease, improve cancer survival and reduce the need for emergency surgery. Establishment of flexible sigmoidoscopy screening is likely to reduce incidence of distal cancers as well as reducing mortality.

Recommendation grade A

Patients diagnosed through the National Bowel Cancer Screening Program should have a defined pathway into their local colorectal cancer MDT.

Recommendation grade D

2.3.2 Screening for at risk population
Approximately 5% of colorectal cancers are due to the high-risk familial conditions, Lynch syndrome and the polyposis syndromes. It is important that these familial syndromes are identified so that the index case and family members can be offered appropriate management. In a further 30% there is some familial contribution to aetiology, but the genetic factors involved remain unclear and the level of risk is heterogeneous.

Families deemed to be at high risk of colorectal cancer should be managed through clinical genetic services, which should provide a robust surveillance program ensuring appropriate use of genetic testing, timely surveillance and counseling.

2.3.2.1 Risk stratification according to family history
An accurate family history gives an empirical assessment of risk. The site and age at diagnosis of all cancers in family members should be documented, as well as the presence of related features such as colorectal adenomas. The value of risk assessment on the basis of family history is limited in small families and those with poorly defined paternity. Current BSG guidelines (Cairns et al., 2010) give a detailed evidence base for stratifying risk level according to family history, and provide screening recommendations (summarized in Table 2.3):

<table>
<thead>
<tr>
<th>Risk</th>
<th>Relative risk of CRC</th>
<th>Colonoscopy screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;2</td>
<td>None</td>
</tr>
<tr>
<td>Low moderate</td>
<td>3–6</td>
<td>One off age 55 years</td>
</tr>
<tr>
<td>High moderate</td>
<td>5 yearly from 50 years</td>
<td></td>
</tr>
</tbody>
</table>

Low risk
Individuals in this group have one of the following:
- No confirmed family history of colorectal cancer
- No first-degree relative (i.e. parent, sibling or child) with colorectal cancer
- Only one first-degree relative with colorectal cancer, diagnosed at age 50 years or older

Low risk individuals should be reassured, informed of the symptoms of colorectal cancer and encouraged to participate in the NHS Bowel Cancer Screening Program.

Recommendation grade C

Low-moderate risk
This group comprises those with one of:
- One affected relative diagnosed with colorectal cancer under 50 years
- Two affected first-degree relatives diagnosed at age 60 years or older

Low-moderate risk individuals should be offered a ‘one-off’ screening colonoscopy at the age of 55 years.

Recommendation grade C

High-moderate risk
This group comprises those with one of:
- Three or more relatives with colorectal cancer in a first degree kinship* (but none under 50 years; a factor which confers high risk)
- Two relatives diagnosed with colorectal cancer under 60 years (or with a mean age at diagnosis under 60 years) in a first degree kinship*
- Both parents diagnosed with colorectal cancer under 60 years

* A first-degree kinship is a family group in which each affected individual is a first degree relative of the others. The individual seeking screening should be a first degree relative of one of these affected relatives.

High-moderate risk individuals should be offered colonoscopy every 5 years from the age of 50 to 75 years.

Recommendation grade C
High risk
This category encompasses Lynch syndrome and the polyposis syndromes. Criteria for inclusion include:

- Member of a family with known familial adenomatous polyposis (FAP) or other polyposis syndrome
- Member of a family with known Lynch syndrome
- Pedigree suggestive of autosomal dominantly inherited colorectal (or other Lynch syndrome-associated) cancer (Amsterdam criteria Table 2)
- Pedigree indicative of autosomal recessive inheritance, suggestive of MYH associated polyposis (MAP)

2.3.2.2 Lynch syndrome
This dominantly inherited condition is due to germline mutation in one of the mismatch repair (MMR) genes, and carries a 50–70% lifetime risk of colorectal cancer (often developing at an early age), as well as increased incidence of other cancers. The cancers are characterized by microsatellite instability (MSI) and loss of mismatch repair (MMR) protein, detectable by immunohistochemical staining. There is a preponderance of mucinous and right sided cancers compared to sporadic colorectal cancer populations. Indications for MSI testing are increasing with recent evidence supporting its use in all patients with colorectal cancer (Vasen et al., 2013). Further analysis of methylation status and BRAF mutation can distinguish sporadic cases of MSI from those with a genetic predisposition.

Full guidelines for the management of individuals with Lynch syndrome are available (Vasen et al., 2013), and anyone suspected of having it should be referred to a clinical genetics unit. Important points for the clinician managing these patients are:

- Carcinogenesis is accelerated, mandating colonoscopic screening intervals of no more than 2 years.
- There is evidence that aspirin significantly reduces colorectal cancer risk.
- The risk of metachronous cancer is high, and extended colectomy should be considered instead of segmental colectomy for the treatment of colorectal cancer.
- Prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy should be offered to affected women who have reached the end of their reproductive life, especially if they are undergoing surgery for colorectal cancer.

Colonscopic surveillance for Lynch syndrome mutation carriers should commence at the age of 25 years and continue for every 12–24 months up to the age of 75 years or until co-morbidity makes it clinically inappropriate.

Recommendation grade B

In families manifesting gastric cancer as part of the phenotype, biennial upper gastrointestinal endoscopy should be considered from age of 50 years and continue to age 75 years.

Recommendation grade C

2.3.2.3 Familial adenomatous polyposis (FAP)
This dominantly inherited syndrome is characterized by the development of hundreds of colorectal adenomas from late childhood and results in a risk of colorectal cancer approaching 100% by the age of 50 years. In around 20% of patient with FAP the genetic trait arises from a new mutation. The most important extra-colonic manifestations are duodenal and peri-ampullary adenomas and carcinomas, and desmoid disease.

Full guidelines for the management of individuals with FAP are available (Vasen et al., 2008), and anyone suspected of having it should be referred to a clinical genetics unit or specialist polyposis registry. Important points for the clinician managing these patients are:

- Genetic testing (or endoscopic screening if no mutation has been identified) should begin at around 12 years of age, unless the child is symptomatic.
- Prophylactic surgery is the mainstay of management, the type and timing determined by genotype, phenotype and personal circumstances.
- Lifelong follow-up is required, with annual surveillance of the retained rectum or ileo-anal pouch.
- Endoscopic examination of the duodenum using a side-viewing scope should start at age 30 years and continue at intervals determined by disease severity.

Annual colonoscopy should be offered to mutation carriers from diagnosis until polyp load indicates a need for surgery.

Recommendation grade B

Individuals from families where no mutation can be identified and genetic linkage analysis is not possible, should have annual surveillance from the age of 13–15 until age 30 years, and every 3–5 years thereafter until age 60.

Recommendation grade B

For individuals who have undergone either total colectomy and ileorectal anastomosis or proctocolectomy and ileal pouch-anal anastomosis, lifelong endoscopic annual surveillance of the retained rectum or anorectal cuff is recommended.

Recommendation grade B

Upper gastrointestinal endoscopy (using a side-viewing endoscope) at intervals determined by
Spigelman stage for mutation carriers is recommended from age 30 years.

Recommendation grade C

2.3.2.4 MYH-associated polyposis
This recently recognized polyposis syndrome has considerable overlap with FAP, although the polyp burden is often considerably less, and extra-intestinal manifestations are less frequent (Cairns et al., 2010). Management of the colon and rectum is essentially the same as FAP, although some individuals with a light polyp burden can be managed endoscopically, without the need for prophylactic surgery.

Colonoscopic surveillance is recommended every year from age 25 years for individuals who are bi-allelic MYH carriers (or homozygous carriers of other BER gene defects).

Recommendation grade C

Upper gastrointestinal endoscopy at 3–5 year intervals is recommended from age 30 years.

Recommendation grade C

2.3.2.5 Serrated polyposis
This poorly understood condition is characterized by the development of multiple hyperplastic polyps, sessile serrated polyps and serrated adenomas (Edelstein et al., 2013). There appears to be an inherited element, but the gene(s) responsible have not yet been identified and genetic testing is not available.

Annual surveillance colonoscopy is recommended. First-degree relatives should have five yearly screening from the age of 30 years.

Recommendation grade C

2.3.2.6 Peutz-Jeghers syndrome
This dominantly inherited syndrome results in characteristic gastrointestinal polyps, particularly in the small bowel, and peri-oral pigmentation (Cairns et al., 2010). The risk of gastrointestinal, and other cancers, is substantial. These patients should be referred to a clinical genetics unit or polyposis registry.

A baseline colonoscopy and upper GI endoscopy (OGD) is recommended at age 8 years. If significant polyps are detected, endoscopy should be repeated every 3 years. If no significant polyps are present at baseline endoscopy, routine surveillance is repeated at age 18, or sooner should symptoms arise, and then every 3 years.

Recommendation grade C

Small bowel screening using video capsule endoscopy (VCE) should be performed every 3 years, from age 8 years, or earlier if the patient is symptomatic. Magnetic resonance enterography (MRE) or CT enterography are reasonable alternatives in adult patients but CT enterography is not favoured in children due to radiation exposure.

Recommendation grade C

2.3.2.7 Juvenile polyposis
This is a rare syndrome due to mutation in the SMAD4 or BMPR1A genes, which results in typical polyps, particularly in the large bowel (Cairns et al., 2010). The risk of colorectal cancer is in the range 10–40%, and that of gastric cancer around 25%. Management is usually by endoscopic polypectomy, with surveillance intervals of 1–3 years, depending on polyp burden. Surgery (colectomy, proctocolectomy or gastrectomy) is sometimes required.

Those with a SMAD4 mutation frequently also have hereditary haemorrhagic telangiectasia, so bleeding or anaemia may not be due to the juvenile polyps, and appropriate investigations to exclude associated arteriovenous malformations should be done before any general anesthetic. These patients should be referred to a clinical genetics unit or polyposis registry.

Colonoscopic surveillance for at risk individuals and mutation carriers is recommended every 1–2 years from age 15–18 years, or earlier if the individual is symptomatic up to age 70 years.

Recommendation grade C

Upper gastrointestinal surveillance is recommended every 1–2 years from age 25 years.

Recommendation grade C

Conflicts of interest

None of the authors have any conflicts of interest to declare.

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References


3 Surgical Management

3.1 Access

3.1.1 Waiting times

The Department of Health published national referral guidelines in 2000 for suspected cancers, based on high-risk symptoms and signs, the so-called ‘2 week rule’. The recommendation was that units should see in excess of 95% of referrals within 2 weeks. This recommendation has successfully improved service delivery and patient processing within the NHS, although evidence of improved outcomes is unproven (Hitchins et al., 2014; Patel et al., 2014; Schneider et al., 2013).

In 2005, the NHS National Cancer Plan produced treatment targets for colorectal cancer, consisting of 62 days from ‘2 week’ referral and 31 days from the ‘decision to treat date’ (Department of Health, 2006). However, the health service’s primary emphasis should be on quality and outcomes, rather than on time to treatment (Murchie et al., 2014).

Treatment should begin within 31 days of the decision to treat.

Recommendation grade D

3.1.2 The multidisciplinary team (MDT)

A colorectal cancer MDT serving a population of 200 000 is expected to manage around 120 new...
patients per year. Quality cancer treatment depends on coordination between multiple treatments and treatment providers, the exchange of technical information, and effective communication between clinical, nursing and other disciplines involved in the patients’ management. Multidisciplinary teams (MDTs) should improve coordination, communication, and decision making between health-care team members and patients, and produce better outcomes. This can be achieved by reflective practice, audit, patient surveys, MDT ‘away days’ to develop the service delivered. Feedback should be systematically evaluated and any changes made to the care for both the general patient population and for individual patients, should be subsequently reviewed and evaluated by the team to see if improvement has been achieved. Despite the standardization of delivery of cancer services via this method, research showing the effectiveness of MDT working is scarce (Fennell et al., 2014; Fleissig et al., 2006).

The ACPGBI ‘Resources for Coloproctology 2015’ document (Association of Coloproctology of Great Britain and Ireland, 2015) informs clinicians, managers, medical directors, chief executives and politicians, to address any existing inequalities in care for patients and achieve uniform standards nationally.

The core colorectal MDT should include;
- Specialist surgeons (at least 2)
- Clinical oncologist
- Medical oncologist
- Diagnostic radiologist with gastrointestinal expertise
- Histopathologist
- Colonoscopist (surgeon, physician or specialist nurse)
- Clinical nurse specialist (CNS)
- Clinical trials co-ordinator or research nurse
- Palliative care specialist (doctor or nurse)
- MDT co-ordinator
- Administrative support (including data manager)

The extended MDT members should include;
- Gastroenterologist
- Liver surgeon
- Thoracic surgeon
- Interventional radiologist
- Dietician
- Liaison psychiatrist/clinical psychologist
- Social worker
- Clinical geneticist
- Specialist screening practitioner (SSP)
- Clinician with expertise in colonic stenting

The management plans for all colorectal cancer patients should be reviewed by a Colorectal MDT.

**Recommendation grade C**

### 3.1.3 Surgical specialization

There have been a number of reports assessing effects of surgical specialization and patient throughput (both the number of cases treated per surgeon and per hospital) on outcomes in colorectal cancer (Etzioni et al., 2014). The NICE colorectal cancer guidance (2004) identified 6 systematic reviews and 28 other studies in this field. The evidence indicates that better surgical specialization and training is associated with improved outcomes, particularly in rectal cancer (Archampong et al., 2012; Etzioni et al., 2014).

These benefits of surgical specialization appear more pronounced for rectal cancer than for colon cancer. In rectal cancer, 11 of 13 studies reported that more specialized surgeons achieved better outcomes. Six out of eight good quality studies showed significant effects on one or more of the following measures; survival rates (up to 5 years), quality of surgery (assessed by complication rates or tumour-free excision margins) and local recurrence rates (Archampong et al., 2012). Greater specialization is also associated with shorter in-patient stay and less frequent use of stomas (National Institute for Health and Clinical Excellence, 2004).

It is advised that each surgeon in the MDT should ideally carry out a minimum of 20 radical colorectal cancer resections per annum (The Association of Coloproctology of Great Britain and Ireland, 2012).

**Surgery for colorectal cancer should be performed by surgeons with appropriate training and experience, working within an MDT.**

**Recommendation grade B**

### 3.1.4 Role of the colorectal clinical nurse specialist (CNS)

The 2000 NHS Cancer Plan (Department of Health, 2000) initially highlighted the important role of the CNS within the pathway for cancer patients. The initial paper stressed that CNSs were needed to provide psychological support but subsequent papers acknowledge the wider contribution to the overall quality and effectiveness of patients’ cancer management (Department of Health, 2011a). National cancer patient surveys demonstrate that by having access to a CNS, patients’ cancer experiences are much better co-ordinated, leading to better outcomes (Quality Health.).

The colorectal CNS works autonomously and uses their training and experience of colorectal cancer to assist patients with their concerns and problems, whilst they are undergoing assessment, diagnosis, treatment and follow up of their disease. The CNS is seen as the
key worker or patient advocate and is the person within the MDT who is most accessible to patients, working closely with them and their families/carers to provide information and constant support at each stage of their care (National Cancer Action Team, 2010). Their role is pivotal to coordinate access to different services and clinicians during individual patients’ clinical journey.

As well as being a clinical expert within colorectal cancer, the CNS should possess a first level degree and have completed or is working towards, post-registration learning, specific to their specialism and role, such as advanced communication skills, leadership, management, teaching and research (Macmillan, 2015). The CNS will have a role in transforming patients’ experiences of cancer care by CNS-led activities such as improving quality and experience of care, reinforcing safety, increasing efficiency and demonstrating management and leadership (National Cancer Action Team, 2010).

3.2 Perioperative Care

The intention of treatment, whether curative, potentially curative or palliative should be discussed in the MDT and communicated to the patient and primary care team.

However, surgery for colorectal cancer should be avoided if the risks are deemed to outweigh the potential benefits, such as when the patient has major co-morbidity or the tumour is deemed unresectable. In this situation, a further opinion from another surgeon, or surgeons, or other relevant professionals, is encouraged if there are ongoing concerns about this decision in the mind of the surgeon, the patient, relatives or carers.

3.2.1 Optimization of co-morbidities and risk stratification

There is increasing need to consider colorectal cancer surgery in older and high-risk patients, who often have multiple and significant co-morbidities. Good preoperative preparation will reduce postoperative morbidity and mortality. Preoperative optimization should be considered in non-urgent surgery and should be initiated in the community with correction of anaemia, control of hypertension and diabetes and reduction or cessation of smoking and alcohol. Further optimization should take place at anaesthetic pre-admission assessment. The routine use of scoring systems such as ASA and POSSUM to evaluate operative risk is encouraged (Richards et al., 2010; Tekkis et al., 2003; Tekkis et al., 2004). Cardiopulmonary exercise (CPEX) testing should be considered for stratification of high-risk cases (Moran et al., 2016; West et al., 2014a; West et al., 2014b). However these stratification systems, though useful for large cohorts of patients, may be difficult to apply to individual patient risk and need to be interpreted with caution and by experienced surgeons and anaesthetists.

3.2.2 Informed decision making

Informed consent is the process of reaching a joint decision between the patient and the clinician(s), having discussed the recommended treatment and the likelihood of a successful outcome, the alternatives which may be available, providing clear information on the benefits and risks of the proposed and alternative treatments, the actual process of treatment and the implications of not having any treatment. A written record of consent, signed by the patient and the clinician should be the final part of this process. The UK Department of Health reference guide to consent for examination or treatment (Department of Health, 2009) and Consent: Supported Decision-Making (The Royal College of Surgeons of England, 2016) form the legal framework that health professionals need to take account of, in obtaining valid consent to examination, treatment or care.

It is recommended that the core members of the colorectal MDT should have received appropriate communication skills training. Patients should be offered a copy of their correspondence. Information regarding immediate recovery after surgery and enhanced recovery pathway should be provided.

The recognized morbidities associated with treatment should be fully discussed and documented, particularly, bleeding, infection, venous thromboembolism, anastomotic leak, and requirement for an unplanned stoma. Functional outcomes (bowel, urinary, sexual) following colorectal surgery should form part of the general discussion about the results and expectations of treatment.

A CNS should be available to provide support, assistance, information and advice to every patient and function as the ‘key worker’ or ‘case manager’. The CNS should have specific expertise in colorectal cancer including knowledge about, and mechanisms to access, stoma care, and be trained in communication skills and counselling.

Patients with colorectal cancer should meet and have access to a CNS as ‘Key Worker’ for advice and support from the time of their initial diagnosis.

Recommendation grade C

Patients should be offered written information, internet resources and copies of relevant correspondence.

Recommendation grade C
All patients undergoing surgery should have informed consent. Written consent should be obtained by the operating surgeon.

**Recommendation grade C**

### 3.2.3 Enhanced recovery after surgery (ERAS)
Enhanced recovery after surgery (ERAS) protocols are multimodal perioperative care pathways designed to achieve early recovery after surgical procedures by maintaining preoperative organ function and reducing the profound stress response incurred by surgery. For example, early introduction of diet and fluids within 24 h postoperatively has been shown to be safe and there is evidence that this may be beneficial (Lassen et al., 2009; Rawlinson et al., 2011; Spanjersberg et al., 2011). ERAS programs have been shown to be safe and effective, and increased implementation is justified (Zhuang et al., 2013). The majority of the evidence for ERAS implementation is in patients undergoing open colonic resection. The difference in ERAS principles between colonic resections and pelvic surgery are well recognized. These need to be tailored to individual cases when implemented in practice.

The essential principles of ERAS are as follows (Nygren et al., 2013):

1. Preoperative counselling and education
2. Preoperative medical optimization
3. Avoidance of oral mechanical bowel preparation
4. Preoperative carbohydrate drink, no overnight fasting
5. Standard anaesthesia management (premedication, pain control, PONV)
6. Antimicrobial and thromboembolism prophylaxis
7. Perioperative fluid management
8. Avoiding nasogastric and abdominal drains, early removal of urinary catheter
9. Preventing intraoperative hypothermia
10. Immediate postoperative diet
11. Early mobilization
12. Audit of practice and data collection

**Peri-operative care in elective surgery should be based on ERAS principles.**

**Recommendation grade A**

### 3.2.4 Preoperative fasting and carbohydrate loading
Preoperative administration of oral carbohydrate leads to reduced hospital stay and a trend towards earlier return of gut function (Noblett et al., 2006). Patients should receive a clear carbohydrate-rich beverage (12.6%) at a dose of 800 ml before midnight and 400 ml, 2–3 h before surgery. This reduces postoperative insulin resistance and maintains whole-body protein balance (Can et al., 2009; Yagci et al., 2008).

Preoperative carbohydrate loading should be considered in all patients undergoing elective colorectal cancer resection.

**Recommendation grade B**

### 3.2.5 Mechanical bowel preparation
Mechanical bowel preparation is not recommended in elective colon surgery. However this may not apply to anterior resection for rectal cancer. In patients undergoing restorative rectal cancer surgery, a randomized controlled trial showed a reduction of anastomotic and other septic complications with the use of mechanical bowel preparation (Breitgagnol et al., 2010). However a subsequent Cochrane review reported that routine use of mechanical bowel preparation prior to elective colorectal resection does not benefit patients, in terms of reduction of anastomotic leaks or other complications and can be avoided (Guenaga et al., 2011).

Routine use of mechanical bowel preparation prior to elective colorectal cancer resection should be avoided.

**Recommendation grade B**

Mechanical bowel preparation may be beneficial in restorative procedures for rectal cancer.

**Recommendation grade B**

### 3.2.6 Stoma formation and training
The need for a permanent, or defunctioning, stoma should be discussed with the patient prior to surgery, especially in patients with advanced disease and/or left sided cancers. Information about the potential need for stoma formation and the practical, psycho-sexual and lifestyle implications of living with a stoma should be provided by a stoma specialist nurse in order to promote positive and realistic expectations in patients who may require stoma-forming surgery. Preoperative preparation includes providing patients with information and resources to help them to become familiar with equipment and procedures for stoma self-care. Gaining familiarity in stoma self-care preoperatively can reduce a patient’s length of stay through increased confidence and competence in the early postoperative period. (Danielsen et al., 2013).

Postoperative intensive inpatient support by ward nurses and the stoma specialist nurse to develop the skills, knowledge and confidence to become autonomous and independent in stoma self-care is also important, including understanding the potential
complications. The stoma specialist nurse should help patients to develop positive coping strategies to promote independence and confidence-building. Preoperative stoma site marking is crucial for improving patients’ postoperative quality of life, promoting their independence and reducing the rates of complications (Baykara et al., 2014; Person et al., 2012).

Patients who may require a stoma should be counselled preoperatively and marked by a stoma care specialist. In an emergency situation, the stoma site should be marked by an experienced surgeon.

Recommendation grade B

3.2.7 Blood transfusion
Blood products may be required in the peri-operative management of colorectal cancer. There were previous concerns about potential increased risk of recurrence following peri-operative blood transfusion (McAlister et al., 1998). However a meta-analysis of three randomized, and two cohort studies, where control groups received either leucodepleted or autologous blood transfusion found no significant difference in cancer recurrence (Dionigi et al., 2007). Consent for blood transfusion should be obtained and documented in the clinical records (Department of Health, 2011b; Howell & Forsythe, 2011).

Patients should be consented for possible perioperative blood transfusion. For elective colorectal resections, ‘group and save’ may be sufficient, but formal cross-matching is recommended for more extensive surgery.

Recommendation grade C

3.2.8 Thromboembolism prophylaxis
Patients undergoing surgery for colorectal cancer are at risk of venous thromboembolism (VTE) and prophylactic measures should be used. A combination of graduated compression stockings, intermittent pneumatic compression devices (Morris & Woodcock, 2010) and low molecular weight heparin (LMWH) should be used to reduce risk of VTE following surgery (National Institute for Health and Clinical Excellence, 2010b). Patients undergoing pelvic surgery for malignancy should be considered for extended pharmacological VTE prophylaxis (National Institute for Health and Clinical Excellence, 2010b). The evidence for extended prophylaxis is contentious (Akl et al., 2008). If reduction in proximal deep venous thrombosis (DVT) is the aim, extending prophylaxis to 28 days postoperatively further reduces risk of proximal deep vein thrombosis (DVT) compared with peri-operative prophylaxis (National Institute for Health and Clinical Excellence, 2010b; Rasmussen et al., 2009).

A combination of graduated compression stockings, intermittent compression devices and LMWH should be used for VTE prophylaxis in patients undergoing surgery. Extended prophylaxis for 28 days postoperatively should be considered.

Recommendation grade B

3.2.9 Surgical site infection (SSI) prevention
Surgical site infections (SSI) impact on length of stay and unplanned readmissions. Current peri-operative recommendations to minimize risk of SSI includes use of antibiotic prophylaxis. A single dose of an intravenous antibiotic determined by local hospital policy, at least 30 min before surgery is recommended (Cima et al., 2013; Li et al., 2013; National Institute for Health and Clinical Excellence, 2008; Scottish Intercollegiate Guidelines Network, 2008). The use of preoperative high-inspired oxygen fraction may further improve outcomes (Hovaguimian et al., 2013). With these measures wound infection rates after elective surgery should aim to be less than 10%.

Peri-operative measures to minimize SSI should be considered. A single dose of broad-spectrum antibiotics prior to commencement of surgery should be administered.

Recommendation grade A

3.2.10 Intra-operative monitoring
Intra-operative maintenance of normothermia with infusion of warmed fluids and body heating by an upper body forced-air heating cover, or operating table heating mats, reduces wound infections and other complications (Mehta & Barclay, 2013; Tillman et al., 2013).

There are conflicting reports on the impact of perioperative fluid replacement on complications (Pestana et al., 2014). Titrated fluid administration according to variations in the cardiac output, measured by non-invasive monitoring reduces complication rates (Pearse et al., 2014).

3.2.11 Postoperative measures
Nasogastric decompression tubes should not be used as a routine in the postoperative period. If a tube is placed during surgery, it should generally be removed before the patient wakes up from anaesthesia. The routine use of nasogastric decompression delays the return of gut function, leads to an increase in pulmonary complications and prolongs hospital stay (Rao et al., 2011).
There remains a wide variation in the use of abdominal drains after colonic resection (Karliczek et al., 2006). Meta-analyses have revealed that routine prophylactic drainage of the abdominal cavity following colonic resection does not confer any advantages (Karliczek et al., 2006). However, a meta-analysis concluded that the use of a pelvic drain reduces the incidence of extraperitoneal colorectal anastomotic leakage and the rate of re-intervention after anterior rectal resection (Rondelli et al., 2014).

To control postoperative pain, patients should be prescribed regular paracetamol and opiates as required. Emerging data suggest that postoperative NSAIDs may adversely affect anastomotic leak rates and should be used with caution (Bhangu et al., 2014; Klein et al., 2012).

3.2.12 Anastomotic complications
Anastomotic dehiscence is a major cause of morbidity and mortality after colorectal cancer resection. The ACPGBI and ASGBI have issued an extensive document about reduction, diagnosis and management of colorectal anastomotic leakage (McDermott et al., 2016). For patients and their families being counselled for surgery when an anastomosis is being considered, a balanced discussion of anastomotic leakage and its immediate and long-term consequences including risk of associated mortality is necessary. Appropriate preoperative discussion with a stoma specialist may allow informed choice in patients where a permanent stoma is an option instead of an anastomosis (in particular a higher risk anastomosis). Patients who have suffered from anastomotic leakage should be given prompt and appropriate medical attention, as well as a frank and open explanation about the complication as soon as their condition permits.

Anastomotic dehiscence is more frequent after anterior resection and the risk increases with proximity to the dentate line. A randomized controlled trial demonstrated the benefit of a defunctioning proximal stoma in reducing clinical leak rates and the need for re-operation after low anterior resection (Matthiessen et al., 2007). Trials comparing defunctioning ileostomy with colostomy have reported conflicting results, however the balance of evidence marginally favours an ileostomy (Chen et al., 2013; Guenaga et al., 2007; Law et al., 2002).

Whilst a defunctioning stoma reduces the risk of anastomotic dehiscence, potential complications of stoma reversal and non-reversal should be considered prior to a restorative procedure (David et al., 2010). Abdominoperineal excision should not be regarded as an inferior operation to low anterior resection in the management of low rectal cancer on the basis of quality of life alone (How et al., 2012).

Bowel function after a low anterior resection is often problematic and many patients have urgency and frequency, partly attributable to loss of the reservoir function of the rectum. A colonic J-pouch or an alternative neo-reservoir such as an end-to-side anastomosis can improve function (Heriot et al., 2006).

Viable tumour cells can be demonstrated in the lumen of the colon at the time of operation (Umpleby et al., 1984), the use of a cytocidal washout prior to anastomosis is recommended and may reduce anastomotic recurrence (Rondelli et al., 2012).

The risk factors for anastomotic dehiscence include male sex, increasing age, obesity and low (<5 cm from anorectal junction) anastomosis after anterior resection.

Patients having an anastomosis should be made aware of the risks of potential complications, such as dehiscence, sepsis and strictures.

Recommendation grade D

Cytocidal washout of the rectal stump should be used prior to anastomosis.

Recommendation grade B

Colorectal units should audit their leak rate for colorectal cancer surgery.

Recommendation grade D

Colorectal units should expect to achieve an operative mortality of less than 20% for emergency surgery and less than 5% for elective surgery for colorectal cancer.

Recommendation grade B

After low anterior resection, a temporary defunctioning stoma should be considered.

Recommendation grade B

3.2.13 Rates of permanent stoma formation
The rate of permanent stoma formation after rectal cancer surgery varies considerably, with APE rates ranging from 9% to 50% across England (Morris et al., 2008). Case-mix and an increasingly elderly population may explain some of this variation but surgical approach and technical aspects are also important. The lowest rates tend to be achieved by specialist high-volume surgeons (Morris et al., 2011). The LOREC programme has addressed some of these issues. In low rectal cancers, the feasibility of restorative anterior resection may be debatable. Even though anterior resection may be feasible, other factors such as body habitus, pre-existing incontinence, need for preoperative therapy or
co-morbidities may mean that a permanent stoma is a better option for some patients (How et al., 2012).

Although defunctioning stomas are intended to be temporary at the time of surgery, up to 25% will become permanent (Kuryba et al., 2016; Sier et al., 2015). The ACPGBI National Bowel Cancer Audit of 4879 patients who had an ileostomy during anterior resection between 2009 and 2012 reported a reversal rate of 72.5% within 18 months (Kuryba et al., 2016). Although most surgeons aim to reverse a stoma within 2–4 months of initial surgery, the median time to closure was 10 months, possibly due to postoperative complications, adjuvant chemotherapy or reversal having a lower organizational priority. Non-closure was more likely in patients who are older (>80 years), have a higher ASA grade, higher T stage and multiple co-morbidities. Patients undergoing an open procedure and those in the most deprived quintile of socioeconomic deprivation were also less likely to be reversed.

The permanent stoma rate following rectal cancer resection of colorectal units should be audited.  
Recommendation grade D

Patients should be warned that there is potential significant delay in ileostomy closure following anterior resection and up to 25% may never get reversed.  
Recommendation grade B

3.3 Surgical Resection Technique

3.3.1 Rates of curative resection

Tumours that are completely excised are classified as R0, those with microscopic (but not macroscopic) margin involvement are classified as R1 and those with macroscopic margin involvement as R2. However, it is advisable to correlate macroscopic margin involvement with the intra-operative findings at an MDT meeting discussion prior to designation as R2 (Loughrey et al., 2014), given the significant prognostic impact of this interpretation.

A R0 resection should be achieved in >90% of colorectal cancers predicted to be resectable on appropriate staging.  
Recommendation grade B

3.3.2 Malignant colorectal polyp

The ACPGBI published a document on management of malignant colorectal polyps in 2013. Subsequent treatment of patients with malignant polyps depends on the risk of residual disease, age and co-morbidity. The risks of polyp surveillance vs the risks of surgical resection should be discussed with the patient (Williams et al., 2013). An ongoing SPECC (Significant Polyp Early Colorectal Cancer) Program is in progress to address these issues (Moran & Dattani, 2016).

3.3.3 Resection of colon cancers

The concept of complete mesocolic excision (CME), which parallels total mesorectal excision (TME) for rectal cancer, has sparked a renewed interest in optimizing the quality of colon cancer surgery (Hohenberger et al., 2009; West et al., 2010). The terminology surrounding complete mesocolic resection can be confusing. Complete mesocolic excision equates to precise anatomical excision of the colon and its mesentery, maintaining an intact mesocolic fascia, separating the visceral and parietal layers. This approach is intrinsic in a meticulous technique for cancer surgery. CME should be accompanied by appropriate central vascular ligation (CVL), however, the exact definition of CVL is more difficult to standardize and the potential oncological benefits may be compromised by increased morbidity with extensive mobilization of the duodenum and pancreas to access the mesenteric root (Bertelsen et al., 2016).

In conclusion, there is no controversy that careful surgical technique respecting embryological planes of CME is advocated. The exact contribution of extreme CVL should be tested further before wide adoption (Konvouinisios et al., 2015).

Resection of colon cancer focussing on quality of mesocolic excision improves oncological outcomes.  
Recommendation grade C

3.3.4 Resection of rectal cancers

The ‘concept of TME’ (total mesorectal excision) is accepted as optimal surgery for rectal cancer (Heald, 1988). A report on outcomes after a TME surgical educational programme in Stockholm suggests that TME training results in a reduction in local recurrence, a reduction in the abdominoperineal excision rate and improved survival (Martling et al., 2000). Tumours in the mid and lower rectum require a TME. However, refinements for upper rectal cancers mean that adequate lymph node clearance can be achieved by a mesorectal transection at 5 cm beyond the distal margin of the tumour. The principles of TME apply to all operative techniques for rectal cancer whether by open, laparoscopic or robotic surgery.

The recent focus is on the optimum management of low rectal cancer. An English National Development Programme (www.lorec.nhs.uk) for colorectal MDT’s was delivered between 2010 and 2013 and focused on preoperative clinical and radiological assessment,
selective preoperative radiotherapy and chemoradiotherapy, optimal surgical treatment and accurate pathological analysis of the resected specimen (Moran et al., 2014). The background to this initiative was the marked variation in APE rates across England (Morris et al., 2008; Morris et al., 2011) and the poor outcomes following APE due to a high CRM involvement rate and subsequent recurrence. A key element of this programme was optimal preoperative planning by clinical assessment and imaging. In the context of low rectal cancer, the operative strategy should be defined as four variants, namely TME with intersphincteric resection and colonoanastomosis, TME with ultra-low Hartmann’s, TME with an intersphincteric APE or an extralaparotomic APE (ELAPE). The concept of a ‘trial dissection’ prior to a decision of APE or anterior resection should be obsolete.

Accurate staging requires a combination of clinical assessment by an experienced surgeon and radiological imaging. This will influence the selection for neo-adjuvant therapy when appropriate and help determine the surgical strategy. If an APE is required this should be tailored to achieve a clear CRM. An ELAPE is the recommended approach for locally advanced low rectal cancers, which involve the external sphincter or the levator ani.

The concept of ELAPE is an anatomical one, involving perineal dissection ‘outside’ and on the caudal surface of the levator complex. Although generally accepted as best performed in the prone position involving turning the patient during the operation (Palmer et al., 2014), the principal of ELAPE may also be adequately completed in the supine Lloyd-Davis position (Moran & Moore, 2014; Moran et al., 2014). The prone position allows for improved access, haemostasis and facilitates training (Moran et al., 2014).

ELAPE results in a larger perineal defect if both levators are widely excised and either a surgical flap or a biological mesh may reduce morbidity. There appears to be little difference in morbidity between the two reconstructions (Foster et al., 2012). Ongoing prospective trials may provide the scientific evidence (Musters et al., 2014). The evolving approach of a ‘tailored’ ELAPE based on clinical examination and MRI imaging allows an individualized approach with unilateral or bilateral levator excision to achieve a clear CRM whilst reducing morbidity (Moran & Moore, 2014).

Care should be taken to preserve the pelvic autonomic nerves and plexuses. Perforation of the tumour or the rectum during the operation should be avoided.

Transanal total mesorectal excision (TaTME) has the potential to improve access for TME surgery in the lowest part of the rectum and possibly reduce morbidity (Lacy et al., 2015). Technological advances and international collaboration amongst surgeons aims to bring this technique into mainstream practice for selected cases and a multinational, multicentre registry is ongoing in the Pelican Centre, Basingstoke with over 1000 cases registered. The current COLOR III trial has been designed to evaluate involved CRM rates with TaTME, compared with laparoscopic TME (Deijen et al., 2016). Long-term follow-up data regarding functional results, local recurrence and survival are awaited (Bjorn & Perdawood, 2015). Surgical training in TaTME is likely to involve cadaveric courses, proctoring and mentorship with contribution from all stakeholders (Penna et al., 2016).

Choice of rectal resection should be tailored to the individual patient, focussing on achieving R0 resection, low morbidity and restorative procedures in appropriate cases.

Recommendation grade C

Patients requiring ELAPE should be identified based on clinical assessment and imaging. Appropriate multidisciplinary expertise should offer these patients the complete package of care.

Recommendation grade C

3.3.5 Laparoscopic and robotic surgery

Laparoscopic surgery offers potential benefits and is increasingly used in elective colorectal cancer resection. The principles of surgical technique are the same as open surgery but laparoscopy facilitates access by minimal incisions, albeit with a reduction in other aspects such as tactile sensation and, until recently, three-dimensional vision. Training and experience are crucial and have been optimized by the English LAPCO programme (Coleman et al., 2011).

Ongoing reports suggest that short and long-term results of laparoscopic colorectal cancer surgery are equivalent to open surgery, but it is acknowledged that conversion to open surgery may be required (Fleshman et al., 2007). Randomized trials (Fleshman et al., 2007; Guillou et al., 2005) have demonstrated that lymph node harvest is similar to open surgery.

Early reports on post-site recurrence in laparoscopic colorectal cancer surgery appear unfounded (Kuhry et al., 2008). Blood loss and blood transfusion requirements, short-term outcomes of wound infection and hospital stay are reduced with laparoscopic surgery, which generally involves longer operating time. Long-term follow up suggests less incisional herniation and possible reduction in small bowel obstruction (Guillou et al., 2005). The EnROL trial demonstrated similar physical fatigue and other patient reported outcomes in
patients treated by laparoscopic or open surgery within an ERAS, but laparoscopic surgery significantly reduced length of hospital stay (Kennedy et al., 2014).

Laparoscopic resection for colon cancer is well established. There is debate about role of laparoscopic rectal cancer surgery. The Color II trial reported that laparoscopic surgery in patients with rectal cancer resulted in similar 3-year locoregional recurrence, disease-free and overall survival to those having open surgery (Bonjer et al., 2015). A meta-analysis indicates the benefits for laparoscopic rectal resection being shorter hospital stay, earlier return of bowel function, reduced blood loss and number of blood transfusions, lower rates of abdominal postoperative bleeding and late intestinal adhesion obstruction (Trastulli et al., 2012). Conversion rate of laparoscopic to open resection has evolved from as high as 29% in the CLASSIC trial (Guillou et al., 2005) to 9% for rectal cancer surgery in the ALaCaRT trial (Stevenson et al., 2015).

ALaCaRT (Australasian Laparoscopic Cancer of the Rectum) was a randomized, non-inferiority trial based at 24 sites (26 accredited surgeons) in Australia and New Zealand. A total of 475 patients with T1–T3 rectal adenocarcinoma, less than 15 cm from the anal verge were recruited. Non-inferiority of laparoscopic surgery compared with open surgery for successful resection was not established. Although the overall quality of surgery was high, these findings do not provide sufficient evidence for the routine use of laparoscopic surgery for rectal cancer (Stevenson et al., 2015). Similarly, the ACOSOG Z6051 trial reported that in patients with stage II or III rectal cancer, the use of laparoscopic resection compared with open surgery for successful resection failed to meet the criterion for non-inferiority for pathologic outcomes (Fleshman et al., 2015). In both these trials a successful resection (clear circumferential and distal margin) was achieved more frequently with open compared with laparoscopic resection (statistically not significant), but operating time was longer in the laparoscopic group and blood loss, higher in the open group. In neither trial was there a significant difference in hospital stay.

Robotic surgery promises the next technological advance in the management of rectal cancer (Mirnezami et al., 2010a). Prospective trials like ROLARR (RObotic vs LAParoscopic Resection for Rectal Cancer) will report on its potential role (Collinson et al., 2012). Early indications suggested that robotic rectal cancer surgery is as safe and effective as laparoscopic surgery, with a possible benefit in males, the obese, and patients with low rectal cancers in terms of the need to convert to open surgery.

Laparoscopic resection should be considered in all patients with colon cancer. This should be performed by suitably trained, experienced surgeons who should audit outcomes and submit results to the NBOCA database.

**Recommendation grade A**

Open surgery results in similar outcomes compared with laparoscopic surgery for cancer of the rectum. Laparoscopic surgery may have some short term benefits.

**Recommendation grade B**

Patients undergoing laparoscopic surgery should be made aware of the possibility to convert to an open operation as a part of informed consent.

**Recommendation grade D**

### 3.3.6 Record keeping

Operation notes should be documented according to the guidelines issued by the Royal College of Surgeons (The Royal College of Surgeons of England, 2014).

A check-list should be used to construct an operation note for patients undergoing surgery for colorectal cancer.

**Recommendation grade D**

The Colorectal MDT should meet on a regular basis to allow timely decisions. Minutes should record clinical decisions and attendance.

**Recommendation grade D**

### 3.4 Other Management Issues

#### 3.4.1 Managing patients presenting as emergencies

Approximately 20% of colorectal cancers present as emergencies, mainly with bowel obstruction and less commonly bleeding and perforation. This is associated with high peri-operative mortality. A clinical diagnosis of obstruction should be confirmed by a contrast-enhanced CT scan to exclude pseudo-obstruction. A flexible sigmoidoscopy should be considered prior to surgery to assess the rectum and left side of colon.

Endoluminal stenting can be considered as a definitive palliative procedure, or as a bridge to surgery, in selected cases of large bowel obstruction (Cirocchi et al., 2013; Tan et al., 2012). There are some oncological concerns about its role as a bridge to surgery (Gorissen et al., 2013). Early results of the UK CReST trial, which randomized 246 patients to stenting as a bridge to surgery, vs immediate surgery demonstrated similar 30-day postoperative mortality (5.3% vs 4.4%) and length of stay (15.5 days vs 16 days). Overall stoma formation was reduced (45% vs 69%; \( P < 0.001 \)) in
patients randomized to the stent arm (Hill et al., 2016). However, data on longer term oncological outcomes are awaited.

Patients with obstruction must be carefully optimized for surgery, within the environment of high dependency or ITU if necessary, with particular focus on adequate fluid resuscitation (Association of Surgeons of Great Britain and Ireland, 2014).

All patients with suspected large bowel obstruction should have a contrast-enhanced CT.

**Recommendation grade C**

Selected patients with large bowel obstruction may be suitable for endoluminal stenting as a definitive palliative procedure.

**Recommendation grade B**

The use of a stent as a bridge to surgery can be considered.

**Recommendation grade B**

Patients with a predicted mortality of >10% should be managed in a Critical Care Unit.

**Recommendation grade D**

### 3.4.2 Managing colorectal cancer in older patients

The incidence of colorectal cancer rises with age and the majority of patients are over 70 years at presentation. With increasing longevity, many patients are diagnosed in their 80s and 90s. This population is often more complex to manage, with greater co-morbidity and are highly vulnerable to changes in physical performance and quality of life. This can make the challenges of major surgery unappealing for patients and clinicians. These issues are crucial when discussing optimum treatment for patients undergoing elective and emergency surgery for colorectal cancer (Neuman et al., 2013). There is an increasing awareness that performance status rather than biological age is central to decision making.

The surgical issues for patients with colorectal cancer are not exclusive to the older population. However, some aspects demand particular attention:

1. Patient fitness and personal choice are more important than age.
2. Location of tumour; for example major surgery for rectal cancer has a potentially greater impact on the older patient with increased risks of morbidity and mortality and alternative treatment options such as local excision and radiotherapy may be more appropriate.
3. Risks of harm and death from the proposed treatment.
4. Patient’s realistic life expectancy.

#### 3.4.2.1 Surgical options in older patients

Laparoscopic surgery appears to be safe, and may have advantages compared with open surgery, in older patients as suggested in a recent systematic review and pooled analysis of eleven studies (Grailey et al., 2013). Operative mortality and anastomotic leak rates were equivalent, but the length of stay was reduced. However, the series analysed were highly heterogeneous with a wide variation in the definition of ‘elderly’, ranging from 70–90 years (Grailey et al., 2013). Chaudhary et al. reported reduced morbidity, length of stay and a 30 day mortality of 1.7% from laparoscopic surgery in patients over 80 years (Chaudhary et al., 2012).

#### 3.4.2.2 Outcomes after surgery in older patients

Faiz et al. (2011) reported outcomes after elective colorectal surgery in over 28 000 patients over the period 1997–2007 (Faiz et al., 2011). For both proximal and distal cancers, the 30-day mortality doubled in the 85–89 years olds compared with younger patients; 8% vs 3.8% and 8.3% vs 3.7% respectively. Multivariate analysis confirmed advancing age to be an independent predictor of 30-day mortality. The use of laparoscopy was associated with reduced 30-day mortality, whereas male gender and Charlson co-morbidity score of >3 were associated with increased 30-day mortality.

This report also highlighted the large percentage of older patients dying within 1 year of surgery, up to 36% in the over 90s. This is an important consideration in assessing the use of surgical treatments where control of cancer may be more appropriate than attempts to cure at the cost of a higher morbidity and mortality.

#### 3.4.2.3 Emergency surgery in older patients

Mortality and morbidity from emergency surgery in colorectal cancer is high for all ages, though significantly greater for older patients (Neuman et al., 2013). It has been reported that over 40% of patients >70 years undergoing emergency surgery for benign and malignant conditions, are dead within 12 months, rising to >50% in those over 80 years (Mamidanna et al., 2012).

#### 3.4.2.4 Health-related quality of life and surgery in older patients

For many patients quality of life is often more important than quantity and this is particularly the case for many elderly patients. Mastracci et al. investigated this in a group of patients above 80 years compared to those under 70 years, using EORTC-C30, EORTC-CR38 and SF-36 to assess health-related quality of life after surgery for colorectal cancer. Patients over 80 years maintained quality of life in all domains.
except ‘vitality’ in SF-36, and presence of stoma-related problems had greatest impact (Mastracci et al., 2006). This suggests that with careful patient selection the impact of elective surgery can be minimized. Scarpa and colleagues compared the impact of laparoscopic and open surgery on outcome and specifically health-related quality of life in 116 patients, of whom 77 were over 70 years. There was no difference in HRQOL between laparoscopic and open surgery in the older population although fewer complications occurred in the laparoscopic group (Scarpa et al., 2013). The over 70’s recorded reduced global quality of life at 1 month compared with those less than 70 years old. The reduction in ‘Role Function’, ‘Cognitive Function’ and sleep disturbance persisted for 6 months.

3.4.2.5 Adjuvant chemotherapy and older patients
The role for adjuvant chemotherapy after potentially curative surgery for stage III colorectal cancer is established. However, trials of chemotherapy have generally excluded older patients and the impact of improved disease-free survival seen in adjuvant trials may not fully translate to an older population with competing risks of mortality and greater vulnerability to toxicity of chemotherapy. Nevertheless, fit older patients with high-risk stage III cancers will benefit from adjuvant therapy (Muss & Bynum, 2012).

3.4.2.6 Summary
Colorectal cancer is a devastating diagnosis for all patients. However, a frail or co-morbid older patient population is particularly vulnerable to the effects of this disease and its treatments. The fragile balance of physical, social and psychological wellbeing can be irreparably disturbed by surgery and its complications, meaning that many patients never return to their previous psychosocial status and many fail to survive 12 months after treatment. For these individuals careful consideration of treatment options is important, potentially including a compromise in achieving oncological excellence for better quality of life. However, older patients with colorectal cancer form a mixed group and those who are fit and free from major co-morbidity may wish to explore the full gamut of therapeutic options and can expect to enjoy outcomes not dissimilar to the general population.

Assessment of older patients for suitability of treatment should be based on co-morbidity and performance status, rather than age alone.

Recommendation grade C

Older patients being offered curative resection should be considered for laparoscopic surgery.

Recommendation grade C

Decision-making in older patients should consider co-morbidities, life expectancy and the natural history of the cancer.

Recommendation grade D

Older patients should be appropriately counselled about the risk of compromise of quality of life following surgery.

Recommendation grade D

Adjuvant chemotherapy should be considered in older patients with stage III colorectal cancer, with appropriate tailoring of treatment.

Recommendation grade B

3.4.3 Management of advanced and recurrent disease
3.4.3.1 Locally advanced and recurrent disease
Patients with locally advanced colorectal tumours may benefit from multi-visceral resection, beyond conventional excision planes. Likewise, multi-visceral resection may offer patients with local recurrence following rectal cancer surgery a second opportunity for cure. Recent advances have expanded the options for such patients, through improvements in reconstructive techniques and management of intra-operative challenges. Management decisions are highly complex and treatment requires a multidisciplinary, multimodality approach within a specialist unit. Therefore, patients should be managed within an appropriate MDT, based on the principles agreed by the Beyond TME Collaborative (Beyond TME Collaborative, 2013).

In order to achieve optimal results, appropriate selection of patients for radical surgery, which is often associated with significant morbidity is critical. CT chest, abdomen and pelvis should be performed to identify distant metastases. MRI pelvis can precisely locate the tumour, its relationship to significant structures such as the greater sciatic notch and major vessels and extent of sacral involvement in order to help plan the surgical approach. FDG PET/CT is useful for assessing uptake at the site of the mass and identifying occult distant metastases (Mirnezami et al., 2010b). If the patient is radiotherapy naïve, and biopsy-positive, long course CRT should be given before resection. Patients with a high suspicion of recurrence on MRI, which is FDG-PET positive but biopsy is not considered safe or feasible, can be managed with resection or watchful waiting.
Preoperative chemotherapy to downstage tumours has little value.

Resection should be sufficiently radical to achieve an R0 resection (Bhangu et al., 2013). Central disease with urogenital involvement will require en bloc resection (eg total pelvic exenteration if the trigone of the bladder is involved, anterior exenteration if uterus/vagina involved). Sacral involvement requires varying degrees of sacral resection. The S2/3 disc space is critical; below this level the sacrum can be resected without bony stabilization. Above the S2/3 disc some form of support is needed. Involvement of the pelvic side-wall requires attention to the layers of the sidewall with early control of the vessels and re-implantation of the ureter. Such techniques improve R0 margin status (Solomon et al., 2015). A multidisciplinary surgical team is key, which may include urology, vascular, orthopaedic, plastics and gynaecological surgeons in addition to colorectal surgeons (Beyond TME Collaborative, 2013).

Postoperative morbidity is significant and often relates to major problems with perineal wound healing. While perineal closure may be achieved primarily with, or without, the use of omentoplasty, biological or absorbable mesh, pedicled flaps are often required such as transpelvic rectus abdominus or gluteal rotational or advancement flaps. Postoperative chemotherapy offers limited benefit (Harris et al., 2016). Following surgery of this nature, quality of life is satisfactory and superior to non-surgical palliation (Harji et al., 2015).

Patients with locally advanced and locally recurrent rectal cancer should be referred to a specialist centre for consideration for resection.

Recommendation grade C

Preoperative imaging should include CT chest abdomen and pelvis to exclude metastases and MRI pelvis to accurately assess the recurrence.

Recommendation grade B

Surgery should aim to achieve an R0 resection.

Recommendation grade B

3.4.3.2 Liver metastases
Management of both synchronous and metachronous liver metastases needs careful evaluation for resectability with a potentially curative intent. A population-based study reported a significant variation in liver resection rates across cancer networks and with 5-year survival of 44% (Morris et al., 2010). There have been significant advances in the multimodality treatment of liver metastases, including neoadjuvant chemotherapy, non-anatomical resection and ablative therapies (Garden et al., 2006).

Colorectal MDTs should have a low threshold to refer cases to the hepatobiliary (HPB) MDT for potential intervention. The logistics and timing of surgery should be carefully coordinated between MDTs.

Recommendation grade B

3.4.3.3 Lung metastases
In selected patients undergoing lung metastectomy, 5-year survival up to 43% has been reported (Zampino et al., 2014). A systematic review of survival after lung metastectomy reported better outcomes with solitary metastases, absence of involved mediastinal lymph nodes, normal pre-thoracotomy CEA and longer interval between colorectal and lung resection (Gonzalez et al., 2013). The ongoing PulMICC trial aims to compare resection of lung metastases with active monitoring, initially as a feasibility study for a subsequent large randomized controlled trial.

Synchronous and metachronous liver or lung metastases should be considered for potentially curative treatments.

Recommendation grade B

3.4.3.4 Peritoneal metastases
Diffuse dissemination of colorectal cancer within the peritoneal cavity is an ominous finding in about 10% of patients at initial diagnosis and 25% at recurrence. In the 25–35% of patients with recurrent disease confined to the peritoneum, a proportion will be amenable to potentially curative local therapy, using a combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) (Elias et al., 2010; Klaver et al., 2010; Moran & Cecil, 2013). The 2013 NHS England commissioning document (NHS England, 2013) recommends the following suitability criteria:

- Disease amenable to complete tumour removal
- Absence of systemic metastatic disease
- Able to withstand major surgery
- Treatment at an experienced surgical centre with facilities for HIPEC

CRS/HIPEC was popularized by Sugarbaker, initially for Pseudomyxoma Peritonei (PMP) but its use was translated to colorectal peritoneal metastases. The rationale for this strategy is based on the ‘redistribution phenomenon’, which was initially described in perforated mucinous tumours of the appendix (Moran & Cecil, 2013; Sugarbaker, 1994). Free-floating intraperitoneal cells accumulate at predictable sites within the...
peritoneal cavity including sites of normal peritoneal fluid absorption such as the omentum (hence the omental 'cake') and the under-surface of the diaphragm (particularly the right), the effects of gravity resulting in disease in the pelvis and paracolic gutters, with relative sparing of motile organs, particularly small bowel unless there are adhesions from extensive prior surgery.

Whilst the biology of colorectal cancer in the peritoneal cavity is generally more invasive compared with PMP, the redistribution phenomenon may also apply to a subset with either limited disease, or ‘visceral sparing’ and thus amenable to CRS/HIPEC (Moran & Cecil, 2013). In this context the term resectable ‘colorectal peritoneal metastases’ (CPM or PMCR) is a useful concept helping to select appropriate candidates for intervention (Moran & Cecil, 2013).

The incidence of resectable CPM, without extra-abdominal spread, has been estimated at 3% of patients with colorectal cancer or approximately 1000 per year in England alone. However many will be unfit or unwilling, to undergo the complex strategy of CRS/HIPEC (Moran & Cecil, 2013). The current evidence-base for CRS/HIPEC in selected patients with CPM, which includes animal experiments (Verwaal et al., 2003), a single randomized controlled trial and a comprehensive review of a number of case series by the National Institute of Health and Care Excellence (NICE) (National Institute for Health and Clinical Excellence, 2010a). CRS/HIPEC results in a 5-year overall survival of 19% and is a recommended treatment option in carefully selected patients (National Institute for Health and Clinical Excellence, 2010a).

The crucial factor in CRS/HIPEC for CPM is that complete tumour removal is essential to optimize outcomes and to counterbalance the associated mortality and morbidity risks (National Institute for Health and Clinical Excellence, 2010a). In the largest multicentre review of 523 patients undergoing CRS and HIPEC, postoperative mortality was 3.3%, serious complications occurred in 31% and 57 patients (11%) required re-operation (Elias et al., 2010).

Scoring systems such as the Peritoneal Carcinomatosis Index (PCI range 0–39), the Simplified Peritoneal Cancer Index (SPCI range 0–21) and the 7 region count from the Netherlands Cancer Institute all describe the volume and spread of peritoneal disease within the abdomen and unsurprisingly ‘less is better’ (Elias et al., 2010; National Institute for Health and Clinical Excellence, 2010a).

Currently CT is the main mechanism for establishing extent of disease and estimating accurate preoperative PCI score (and thus likelihood of complete cytoreduction). Increasingly laparoscopy is recommended to aid selection and reduce ineffectual laparotomy (Iversen et al., 2013). The best results are in limited disease, usually confined to one or two quadrants of the abdomen, synchronous resection of the primary with peritoneal disease and with a minimum of 200 cm of uninvolved small bowel (Elias et al., 2010; Moran & Cecil, 2013).

A further emerging concept is ‘second look’ at 6–12 months for patients at high risk of CPM based on a perforated primary tumour, Krukenberg ovarian metastases or limited peritoneal disease at the primary operation (Elias et al., 2011; Moran & Cecil, 2013).

Patients with colorectal cancer and localized peritoneal disease at primary presentation or as localized recurrence may benefit from discussion with a peritoneal malignancy unit.

**Recommendation grade C**

**Optimal CT is currently the best imaging technique but is limited in low volume disease.**

**Recommendation grade C**

3.4.4 Other malignant conditions

3.4.4.1 Pseudomyxoma peritonei

Pseudomyxoma peritonei is a rare condition, characterized by accumulation of mucinous ascites, generally originating from a perforated mucinous tumour of the appendix. Patients may present unexpectedly at laparotomy or laparoscopy, as a perforated appendix or increasingly at cross-sectional imaging. The optimal treatment is macroscopic complete tumour removal by cytoreductive surgery (CRS) combined with hyperthermic intra-peritoneal chemotherapy (HIPEC). Assessment and treatment of pseudomyxoma peritonei has been commissioned by the English NHS at Basingstoke and Christie Hospital Manchester.

Patients with a perforated mucinous appendiceal tumour or pseudomyxoma peritonei should be discussed with a peritoneal malignancy unit.

**Recommendation grade C**

3.4.4.2 Neuroendocrine neoplasms

Although colorectal neuroendocrine neoplasms (NENs) are rare, the incidence of these tumours is rising. Diagnosis, classification and grading (G1-3) of these tumours should be based on morphology, confirmatory immunohistochemical markers, mitotic count and Ki 67 index. Consensus guidelines on management of colorectal NENs have been published by the European Neuroendocrine Tumour Society (ENETS) (Caplin et al., 2012; Ramage et al., 2016). There has been recent
renewed interest in the diagnosis and management of NENs, with new treatment advances including hormonal therapy, tyrosine kinase and mTOR inhibitors, chemotherapy, peptide receptor radionuclide therapy and hepatic artery embolization. Review of histology and staging investigations by a regional neuroendocrine tumour (NET) MDT should be arranged.

These tumours should be staged similar to that for bowel adenocarcinoma, for the site of origin, if known. In the absence of distant metastases, standard surgical resection of the primary tumour and locoregional lymph nodes should be performed. However, small incidental tumours may not require further treatment beyond complete endoscopic removal or local excision.

Morphologically well-differentiated (G1-2) NETs, previously classified as carcinoid tumours arise more frequently in the rectum. These are often diagnosed on routine sigmoidoscopy and can be locally excised, with a low risk of recurrence if small (<2 cm). More advanced well-differentiated NETs frequently follow an indolent clinical behaviour, even in the presence of distant metastases or unresectable primary disease. Morphologically poorly differentiated (G3) neuroendocrine carcinomas (NECs) are very aggressive malignant tumours, with a Ki 67 >50% in most cases and may be sub-classified as large cell and small cell NECs. These tumours are associated with a very poor prognosis.

Patients diagnosed with neuroendocrine neoplasms may benefit from referral to a regional centre specializing in NETs, for confirmation of histological diagnosis and advice on subsequent management.

**Recommendation grade C**

**Conflicts of interest**

None of the authors have any conflicts of interest to declare.

**References**


Hitchens CR, Lawn A, Whitehouse G, McFall MR. The straight to endoscopy service for suspected colorectal cancer: meeting national targets but are we meeting our patients’ expectations? Colorectal Dis 2014; 16: 616–9.


Loughrey M, Quirke P, Shepherd N. Standards and datasets for reporting cancers. Dataset for colorectal cancer


Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: the ALaCaRT Randomized Clinical Trial. *JAMA* 2015; **314**: 1356–63.


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4.1 Multidisciplinary Management of Rectal Cancer

4.1.1 Definition of rectal cancer

A definition of rectal cancer is important for optimal planning of neoadjuvant therapy and surgical strategy. Anatomically the rectum is distal to the sigmoid colon and its upper limit is the termination of the sigmoid mesocolon. A commonly used definition is an adenocarcinoma with a distal margin at or below 15 cm from the anal verge, measured by rigid sigmoidoscopy. Standard anatomical texts put this at the level of the third sacral vertebra (Williams & Warwick, 1980) but it is generally agreed by surgeons that the rectum starts at the sacral promontory (UKCCCR, 1989).

Whilst there remains debate about the proximal limit of the rectum, there is increasing recognition of the complexity of management of low rectal cancers. The Low Rectal Cancer Development Program (LOREC) has defined a “low” rectal cancer as an MRI-based anatomical definition of an adenocarcinoma with its...
lower edge, at or below the origin of the levators at the pelvic side-wall. This usually corresponds to a measurement of within 6 cm of the anal verge (PELICAN Cancer Foundation; Salerno et al., 2006a,b).

A low rectal cancer should be defined as an MRI-based anatomical definition of an adenocarcinoma with its lower edge, at or below the origin of the levators at the pelvic side-wall. This usually corresponds to a measurement of within 6 cm of the anal verge.

**Recommendation grade D**

### 4.1.2 Introduction

The Clinical Guidelines published by NICE (CG 131) in November 2011 defined three broad categories of rectal cancer, relating to the risk of pelvic local recurrence (LR) following treatment (Table 1) and represent a useful starting point for considering treatment strategy (National Institute for Health and Clinical Excellence, 2011). The increasingly widespread use of total mesorectal excision (TME), involving meticulous dissection of the mesorectal fascia (MRF) (Heald et al., 1982) has had a major impact in reducing LR of rectal cancer. The ‘low’ and ‘moderate’ LR groups can be considered as ‘resectable’ or ‘operable’, because the surgical MRF resection margin is not threatened. The ‘high’ LR risk group is at significant risk of surgical MRF resection margin being involved, unless some form of tumour downstaging can be achieved preoperatively.

In addition, both the ‘moderate’ and the ‘high’ LR risk groups are at significant risk of developing distant metastatic disease, which is the main cause of death. These considerations drive the current treatment and clinical research strategies described below (Table 4.1).

An involved circumferential resection margin (CRM), defined as tumour ≤1 mm from the surgical resection margin is an important, independent predictor of LR (historically up to 85%) (Nagtegaal et al., 2002; Quirke et al., 1986), distant metastases (DM) (Mawdsley et al., 2005) and poorer overall survival (OS) (Wibe et al., 2002), even after TME (Marijnen et al., 2003). The CRM can be involved by direct or discontinuous tumour spread, lymph node spread, lymphovascular spread and perineural spread (Nagtegaal & Quirke, 2008). The risk of CRM involvement is also related to the quality of TME surgery (Nagtegaal et al., 2002; Quirke et al., 2009). Local recurrence can also occur despite a clear CRM, possibly from lymphatic spread to pelvic side-wall nodes (Ueno et al., 2007). In patients undergoing surgery, with or without preoperative radiotherapy (RT), the combination of CRM and lymph node status may be a more effective discriminator of prognosis than TNM staging (Nagtegaal et al., 2007).

Magnetic resonance imaging (MRI) is the current gold standard imaging modality for pre-treatment assessment of CRM involvement (MERCURY Study Group, 2006; The Royal College of Radiologists, 2014). High resolution MRI is essential for optimal staging and to guide management decisions (Al-Sukhni et al., 2012; Battersby et al., 2015). A well-performed MRI can identify the extent of extramural spread (T3a-d), which has a greater predictive value for nodal involvement than assessment of lymph node size per se. Lymph node status remains difficult to assess pre-treatment with poor sensitivity and specificity, although sensitivity may be increased by the addition of diffusion weighted MRI sequences (Heijnen et al., 2013). Assessment of extramural vascular invasion (EMVI) by MRI may define a subgroup at high risk of local and distant recurrence (Al-Sukhni et al., 2012; Battersby et al., 2015; Chand et al., 2015). This has been highlighted by the MERCURY study; independent MRI-defined risk factors were EMVI, tumours <4.0 cm from the anal verge and anterior tumours. A systematic review and meta-analysis (Al-Sukhni et al., 2012) concluded that MRI specificity was significantly higher for prediction of CRM involvement (94%, 95% CI 88–97) than for T (75%, 95% CI 68–80) and N stage (71%, 95% CI 59–

### Table 4.1 Risk assessment for local pelvic recurrence according to MRI findings (National Institute for Health and Care Excellence, 2011)

<table>
<thead>
<tr>
<th>Risk of pelvic local recurrence</th>
<th>Characteristics of rectal tumours predicted by MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (resectable)</td>
<td>cT1 or cT2 or cT3a and no lymph node involvement</td>
</tr>
<tr>
<td>Moderate (resectable)</td>
<td>any cT3b or greater, in which the potential surgical margin is not threatened or any suspicious lymph node not threatening the surgical resection margin or the presence of extramural vascular invasion</td>
</tr>
<tr>
<td>High (borderline resectable or unresectable i.e. threatened or involved CRM)</td>
<td>a threatened (&lt;1 mm) or breached resection margin or low tumours encroaching onto the inter-sphincteric plane or with levator involvement</td>
</tr>
</tbody>
</table>
Standardized proforma based reporting (Taylor et al., 2010) may improve staging consistency nationally and increase minimum dataset collection to 100% as shown in the Royal College of Radiologists/NCIN CASPAR project (Tait, 2015).

All patients with rectal cancer being considered for curative surgery should have locoregional staging by high resolution MRI pelvis, unless there are contraindications.

**Recommendation grade B**

MRI should be reported as per Royal College of Radiologists’ guidance [BFCR(14)2]. Proforma based reporting can standardize and improve completeness of minimum staging data.

**Recommendation grade C**

Staging investigations should be reviewed by the Colorectal MDT in the context of the patients’ clinical history and findings, histology and results of other investigations to decide on the subsequent management of the patient.

**Recommendation grade D**

Colorectal MDTs should correlate pre-treatment radiological staging with post-surgical pathological stage.

**Recommendation grade D**

Radiotherapy and chemotherapy for rectal cancer should only be given after discussion and agreement by the Colorectal MDT, within facilities conforming to national guidelines.

**Recommendation grade D**

4.1.3 Early rectal cancer (cT1-2 N0 M0, MRF –ve)

Introduction of population-based bowel screening, combined with improved access to diagnostic services has resulted in a downward shift in rectal cancer stage at presentation. The term early rectal cancer (ERC) encompasses a set of macroscopic and microscopic features that characterize tumours with an excellent prognosis following standard surgery. Such tumours may also be amenable to local techniques that aim to preserve the rectum and reduce treatment-related morbidity.

Optimal management of ERC is yet to be determined; in fact there is no consensus as to the definition of ERC. A recent EAES/ESCP consensus conference stated that ‘ERC is a rectal cancer with good prognostic features that might be safely removed preserving the rectum, and that will have a very limited risk of relapse after local excision’ (Morino et al., 2015). ‘Conservative’ definitions such as this limit the application of rectal sparing treatment, whereas broader definitions increase the likelihood of under-treating patients. New multimodal treatment strategies may allow safe expansion of the application of rectal preserving therapy, while stratification through molecular profiling may personalize care and reduce risk of under-treatment.

Rectal neoplasms present as a spectrum, ranging from benign to malignant. The ‘Significant Polyp Early Colorectal Cancer’ (SPECC) programme, supported by ACPGBI aims to improve outcomes by reducing over treatment of benign lesions and under treatment of cancer. A significant rectal neoplasm is defined as a sessile polyp >20 mm in diameter, which is morphologically aberrant, where polypectomy may be unsafe or result in incomplete excision (Moran & Dattani, 2016).

Explain to patients and their family members or carers (as appropriate) that due to insufficient good quality clinical evidence, the optimal treatment for early rectal cancer is uncertain.

**Recommendation grade D**

Offer patients with early rectal cancer the opportunity to participate in clinical trials (if eligible) that evaluate the treatment options for early rectal cancer.

**Recommendation grade D**

4.1.3.1 Clinical assessment of rectal SPECC lesions

There are particular pitfalls associated with the evaluation of rectal SPECC lesions and it is important that MDT’s demonstrate appropriate expertise in the clinical, radiological and histopathological assessment of these cases. Evaluation should optimally include:

1. Detailed visualization of the lesion using magnified endoscopy, washing the tumour to characterize its dimensions, morphology, margins and pit patterns. Biopsies should be targeted at the most suspicious part of the lesion for malignancy.

2. Documentation of the location of the rectal SPECC lesion in relation to the upper border of the anal canal (anorectal ring) and quadrant of the bowel wall (anterior, posterior left lateral, right lateral) using a combination of digital rectal examination and either flexible or rigid proctoscopy. Placement of a tattoo in the rectum is generally not recommended.

3. Imaging of the lesion including MRI pelvis, ±endorectal ultrasound (ERUS). MRI will locate the rectal lesion, in relation to the pelvic floor, anterior organs, peritoneum and MRF, and characterize any T3 extension, EMVI or lymph nodes seen within the mesorectum.
4 ERUS is the most accurate modality to discriminate between T1 and T2 rectal cancer, but is highly operator dependent and is not universally available (Ashraf et al., 2012).

5 It should be appreciated that obtaining definitive histological diagnosis through biopsy may be confounded by either sampling error (superficial biopsies or sampling of an adenomatous component) or inter-observer variation in histopathological interpretation. Where malignancy is clinically suspected or biopsies report diffuse high-grade dysplastic changes, then specialist evaluation should be considered.

An MRI performed prior to local excision of all rectal SPECC lesions is recommended. A significant proportion (20–40%) of SPECC lesions with ‘benign’ histology on initial biopsy are subsequently found to contain cancer within the lesion on complete lesion excision, and interpretation of MRI performed immediately after full thickness local excision is often hampered by surgical artefact and the presence of reactive lymph nodes. A pre-treatment MRI also serves as an important reference, for comparison with follow up imaging, to enable early detection of luminal or lymph node recurrence.

In summary, the assessment, decision-making and treatment of rectal SPECC lesions are complex and continue to evolve. Expertise in imaging, pathology and surgery are essential to deliver a safe and effective ERC service and concentration of specialist services will facilitate this. For these reasons, NICE (CG 131) recommended formation of early rectal cancer MDTs.

Patients with significant rectal neoplasms (SPECC lesions) should be adequately assessed prior to any definitive treatment.

**Recommendation grade C**

Patients with significant rectal neoplasms (SPECC lesions), which may be suitable for rectal preserving treatment, should have access to an early rectal cancer MDT for further assessment and management.

**Recommendation grade D**

**4.1.3.2 Excised pT1 rectal cancer polyps**

A pT1 malignant rectal polyp is an adenocarcinoma arising within a pre-existing adenoma in which tumour cells have breached the muscosal mucosa, extending into the submucosa but not the muscularis propria (Williams et al., 2013). This is often an unexpected finding following snare polypectomy or endoscopic mucosal resection on lesions presumed to be benign.

Almost all locally removed malignant rectal polyps are stage I cancers and generally associated with an excellent prognosis. With no further treatment, the risks are of luminal recurrence and progression of involved undetected mesorectal lymph nodes. Current guidelines consider carcinoma within 1 mm of the resection margin as being involved but recent evidence suggests that the risk of recurrence is highest only when tumour is present at the resection margin or within diathermized tissue (Brown et al., 2016). Risk factors for lymph node involvement include extent of submucosal invasion, intramural lymphovascular invasion (LVI) and poor differentiation. However, these features are often difficult to assess due to destruction of important anatomical landmarks by the tumour and surgical factors such as piecemeal resection and diathermy artefact. Evidence of complete macroscopic removal by endoscopic assessment is important as pathological assessment of piecemeal specimens may be equivocal.

Patients found to have pT1 rectal cancer polyps following local excision should be routinely staged with pelvic MRI, unless this was performed prior to the procedure. Staging for distant metastases by CT should be routinely performed as for all colorectal cancers.

Piecemeal resection of significant rectal neoplasms (SPECC lesions) should be avoided, as this can preclude comment on the completeness of excision and complicates assessment of prognostic features.

**Recommendation grade C**

**4.1.3.3 Standard TME for early rectal cancer**

Standard primary radical TME is an oncologically effective treatment for early stage rectal cancer; only 2% and 12% of patients experience local or distant failure respectively (Peeters et al., 2007). However, radical resection of a rectal tumour requires a permanent stoma in approximately 25% of cases while many more patients have a temporary stoma, many of which are not reversed (Healthcare Quality Improvement Partnership, 2015). Six-month mortality following radical curative surgery for rectal cancer is 4.6% for patients aged 65–74 years rising to 13.4% for patients aged 75–84 years (Kapiteijn et al., 2001; Rutten et al., 2008). Recognized long-term morbidities of radical TME include impaired anal sphincter function, pelvic nerve damage (male and female urinary and sexual dysfunction) and small bowel adhesion formation.

**4.1.3.4 Local excision of early rectal cancer**

Early rectal tumours may be locally excised through the anus with low morbidity and mortality using Transanal Endoscopic Microsurgery (TEM) (Bach et al., 2009; Cataldo et al., 2005) allowing for preservation of the rectum and its function. Full thickness excision offers
accurate pathological assessment and potential cure for many pT1 and pT2 cancers. Morbidity and mortality after local excision are lower than after radical resection, with a reported 30-day mortality of 0.5% compared with 2.4% in a study of 5305 patients (You et al., 2007).

However, several case series have reported LR rates ranging from 5% to 28% for pT1 cancers and 11% to 45% for pT2 cancers following transanal excision (Endreseth et al., 2005; Garcia-Aguilar et al., 2000). These series predate accurate pre-treatment MRI staging, which may identify and exclude a proportion of high-risk patients.

These series also predate widespread adoption of ‘optimized’ endoscopically-assisted TEM or transanal minimally invasive surgery (TAMIS) and include patients treated using per-anal excision. Per-anal excision is associated with higher recurrence rates, whilst endoscopically-assisted techniques are broadly similar in efficacy (Barendsen et al., 2012; Moore et al., 2008).

Presence of untreated involved mesorectal lymph nodes is another cause of local disease failure following local excision. The risk of lymph node involvement increases with depth of bowel wall penetration; for pT1 tumours the risk ranges from 1% to 3% for Kikuchi sm1, 8% for sm2 and 23% for sm3 (Tytherleigh et al., 2008). Overall incidence of lymph node metastasis ranges from 6% to 14% for pT1 tumours, 17% to 23% for pT2 tumours, and 49% to 66% for pT3 tumours (Ricciardi et al., 2006).

Tumour implantation is another potential source of luminal recurrence and may explain why LR rates are often higher following local excision, than implied by the risk of lymph node metastasis. Prospectively collected data from the UK ACPGBI TEM Collaboration (n = 424) (Bach et al., 2009) (Table 4.2) identified depth of invasion, maximum tumour diameter and the presence of LVI as independent predictors for LR. The lowest LR rate of <5% was seen in well or moderately differentiated pT1 sm1 lesions, without intramural LVI, measuring <3 cm. However, the majority of pT1-2N0 rectal cancers had one or more of the identified risk factors, with significantly higher LR rates of 15–30% following TEM alone.

The risk of LR following local excision has to be considered within the context of alternative treatment by radical surgery and its morbidity and mortality risks. For most patients, a risk of LR <10% is acceptable but many will accept a risk of 30% to avoid the consequences of radical surgery (Johnston et al., 2013). Patient co-morbidity and life expectancy are important considerations in decision-making and there is no clear answer, although data are emerging on the efficacy of multimodal treatment of frail patients with ERC (Smart et al., 2016). Decisions need to be tailored to individual patients, although clinicians should leave patients in no doubt what is the standard of care for this stage of disease, offering the optimum chance of cure.

The Association of Coloproctology of Great Britain and Ireland introduced guidance for the use of local excision for ERC (Williams et al., 2013). These include:

- T1 cancer
- Maximum diameter <3 cm
- No lymphatic or vascular invasion
- Well or moderately differentiated

When these criteria are adhered to, lymph-node involvement and LR rates of less that 10% can be expected in this population. For similar stage of cancer, radical surgery is associated with mortality in 3–5%, major morbidity in 20–40% and likelihood of stoma of 40% (Marijnen et al., 2005). The impact of radical surgery for early stage disease on long-term quality of life is well established (Doornebosch et al., 2007). This introduces the concept of trade-off in ERC where improved functional outcome and quality of life are traded off against potentially poorer oncological outcome. It can be a complex model for decision-making in ERC management, balancing optimal oncological treatment with patient wishes to minimize the adverse effects of treatment.

Local excision with curative intent should be offered through endoscopic means (TEM, TEO,

Table 4.2 Rates of LR 36 months following full thickness TEM of well or moderately differentiated tumours stratified according to depth of invasion, tumour diameter and the presence of LVI (Bach et al., 2009).

<table>
<thead>
<tr>
<th>Depth of invasion</th>
<th>LyV</th>
<th>Maximum Tumour Diameter (cm)</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>pT1 sm1</td>
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<td>3.0</td>
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<td>+</td>
<td>5.2</td>
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<tr>
<td>pT1 sm2/3</td>
<td>–</td>
<td>10.5</td>
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<td></td>
<td>+</td>
<td>17.8</td>
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<tr>
<td>pT2</td>
<td>–</td>
<td>9.8</td>
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<td></td>
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TAMIS) in preference to traditional per-anal excision.

Recommendation grade C

Local full thickness excision with negative margins of pT1 sm1 tumours (well or moderately differentiated) leads to very low local recurrence rates and may be considered standard of care.

Recommendation grade C

4.1.3.5 Subsequent management after local excision

Following local excision pathology review, patients deemed be at an unacceptably high risk of LR should be considered for completion radical surgery. This approach is believed to offer good oncological outcomes (Bach et al., 2009; Hahnloser et al., 2005) and is quite different to salvage surgery for recurrent disease, where more extensive multimodality treatment may be necessary. Surgical outcomes are similar to radical surgery performed as the first procedure in terms of morbidity, mortality and length of hospital stay (Hompes et al., 2013). Anecdotally it is often technically more difficult that primary TME and permanent stoma rates may be higher compared to use of TME as primary treatment (van Gijn et al., 2013). There is no consensus on timing of completion surgery after local excision, which can vary from a few weeks to several months. Complications of local excision, such as wound dehiscence cause inflammation of the mesorectum and adherence of the mesorectal fascia to the pelvic sidewall.

Postoperative radiotherapy may be considered for ‘high-risk’ patients who are unable or unwilling to undergo TME surgery. However, the benefit of adjuvant radiotherapy in reducing recurrence risk following local excision remains unproven (Greenberg et al., 2008; Rackley et al., 2016) and requires further high quality prospective research.

In view of the increased risk of LR following local excision alone, patients must be offered regular surveillance to facilitate detection of recurrent disease at the earliest opportunity, in order to maximize the success of radical salvage surgery. Early detection can mitigate the impact of LR (De Graaf et al., 2009). Although the optimal surveillance strategy remains undefined, endoscopic assessment at 3–6 monthly intervals coupled with MRI pelvis at 3–6 monthly intervals and CT to detect distant metastases at 12 monthly intervals for 3–5 years is generally used.

After local excision, patients with unfavourable pathology should be offered completion surgery with anterior resection or abdominoperineal resection. Every effort should be made to minimize the number of patients treated in this way, by placing emphasis on pre-treatment assessment by expert MDTs.

Recommendation grade C

After local excision alone, patients should be followed up under a defined surveillance protocol to detect recurrent disease at the earliest stage possible. Current recommendations are 3–6 monthly MRI, CEA and flexible sigmoidoscopy.

Recommendation grade C

4.1.3.6 Preoperative radiotherapy for early rectal cancer

Maas et al. (2010) reviewed 2323 patients treated with CRT demonstrating a clear correlation between the clinical T-stage and the pCR rate (cT1: 58%, cT2: 28%, cT3: 16% and cT4: 12%). The success rate of an organ preserving approach that incorporates radiotherapy will be dependent on the tumour stages treated. Combining radiotherapy with TEM surgery may: (a) remove minimal residual primary tumour, (b) effectively treat microscopic mesorectal lymph node metastases, (c) facilitate local excision with clear margins and (d) reduce the likelihood of tumour implantation at surgery. However, limited prospective evidence exists to guide the use of radiotherapy and local excision as curative treatment for ERC.

The ACOSOG Z6041 (Garcia-Aguilar et al., 2012) and CARTS (Verseveld et al., 2015) trials investigated the safety and effectiveness of CRT and transanal excision for treatment of ERC. In addition, Appelt et al., (Appelt et al., 2015) studied the effectiveness of CRT combined with brachytherapy. Each of these studies reported high rates of organ preservation combined with low rates of LR, but all observed marked treatment-related toxicities that negated any benefit. A retrospective analysis of a cohort of UK patients (n = 62) with ERC, who were predominantly unfit for TME, treated with short course radiotherapy (SCRT) 25 Gy in 5 fractions and TEM reported high pCR rates (32%), low recurrence rates and low toxicity (Smart et al., 2016). The TREC trial evaluated the feasibility of randomizing fit patients with ERC between standard TME and rectal preservation using SCRT followed by TEM, is due to report results shortly. The international STAR-TREC trial will randomize patients with ERC into one of three arms; (a) standard surgery, (b) rectal preservation with mesorectal CRT and selective transanal excision or (c) rectal preservation with mesorectal SCRT and selective transanal excision. This study aims to recruit over 400 patients in the UK, Netherlands and Denmark to determine if TME surgery results in demonstrably lower pelvic relapse rates than the rectal sparing techniques.
In summary, multimodal treatment of ERC using CRT combined with either TEMS or brachytherapy has resulted in unacceptable toxicities, defeating the concept of rectal sparing surgery. These treatments may be taken forward in clinical studies such as STAR-TREC, which will introduce new mesorectal irradiation techniques for ERC, designed to reduce treatment related toxicities. The application of radiotherapy in ERC remains the subject of clinical trials.

Local excision after SCRT or CRT may be considered in patients with early rectal cancer who are unfit or refuse standard resectional surgery and appear to have residual disease. The role of preoperative radiotherapy and local excision in patients with early rectal cancer, who are fit for TME remains the subject of clinical trials.

**Recommendation grade C**

### 4.1.3.7 Contact x-ray brachytherapy (Papillon) and high dose-rate brachytherapy

An alternative strategy for treating ERC is with 50 KV contact x-ray brachytherapy (CXB), also known as the Papillon technique, on small lesions (<3 cm), either alone (cT1 tumours) or combined with a course of pelvic external beam radiotherapy (EBRT) for cT2 tumours or cT1-2 tumours >3 cm (Hershman et al., 2003). Several studies have reported promisingly low LR rates (Sun Myint et al., 2007). Since introduction of CXB to the UK in 1993 (Sun Myint, 2007), although its use remains limited, several UK centres are being equipped with a new generation of CXB machines (Gerard et al., 2011). NICE (IPG 532) has recommended that in patients for whom surgery is not considered suitable, current evidence on the efficacy and safety of CXB for early-stage rectal cancer is adequate to support its use. However in patients who are considered suitable for surgery, but choose not to have an operation, although the evidence on the safety of CXB is adequate, the evidence on efficacy is inadequate (National Institute for Health and Clinical Excellence, 2015b). Patient selection to undergo CXB should be through a colorectal MDT, which includes a clinical oncologist and a colorectal surgeon with expertise in local excision techniques. Patients should be informed of all available different treatment options to enable shared decision making before proceeding with treatment. Data on patients undergoing CXB should be submitted to a NICE-supported audit database, based at Guildford.

There are few randomized trial data on the use of CXB alone in patients with ERC (Lindegaard et al., 2007). One randomized trial evaluating the role of CXB boost following EBRT reported a significant increase in sphincter preservation compared to the no boost group (76% vs 44%; P = 0.004), with no difference in morbidity, LR, and 2-year OS (Gerard et al., 2004). A randomized trial (OPERA) evaluating whether a CXB boost improves organ preservation when compared to an EBRT boost, has started to recruit in France and plans are in progress to open this trial in the UK (Gerard et al., 2011).

The role of preoperative high dose-rate (HDR) brachytherapy was evaluated by NICE (IPG 531), stating that current evidence on the safety of this treatment for rectal cancer and its efficacy in reducing tumour size appears adequate (National Institute for Health and Clinical Excellence, 2015c) but there is no evidence that it provides additional benefit when used as a boost to EBRT. However, rectal HDR brachytherapy can be offered for bulky residual rectal tumours following EBRT, in patients not suitable for surgery or CXB. Rectal HDR brachytherapy can also be offered for recurrent tumours following surgery or EBRT for symptom control (Hoskin et al., 2004).

Contact x-ray brachytherapy (CXB) is considered a treatment option for patients with early rectal cancer as an alternative to TEM, for patients considered not suitable for surgery or for patients considered suitable for surgery, but who decline operation. This should only be offered with the appropriate arrangements in place for clinical governance, consent, audit and research, as recommended by NICE IPG 532.

**Recommendation grade B**

### 4.1.4 Resectable rectal cancer not involving the mesorectal fascia

(cT2-4[peritoneum] N0-2 M0, MRF −ve)

#### 4.1.4.1 Introduction

Two meta-analyses (Camma et al., 2000; Colorectal Cancer Collaborative Group, 2001), a systematic review (Munro & Bentley, 2002) and a Cochrane review (Wong et al., 2007) of randomized trials comparing the addition of radiotherapy (RT) to standard surgery consistently demonstrate a reduction of LR risk, with both pre- and postoperative RT, reduction of rectal cancer deaths but not improvement of OS. Radiotherapy delivery techniques in the early trials were sub-optimal by today’s standards, including use of large parallel-opposed fields, which were associated with increased non-cancer deaths (Colorectal Cancer Collaborative Group, 2001).

Preoperative RT to the pelvis can either be delivered by conventional fractionation (long course RT) of 45–50.4 Gy in 25–28 fractions over 5 weeks or by a short course of preoperative RT (SCPRT) of 25 Gy in 5 fractions over 1 week.
Long course RT is often used to shrink or ‘downstage’ the tumour prior to surgical resection and can be made more effective by adding synchronous fluoropyrimidine-based chemotherapy, also known as chemoradiotherapy (CRT). Surgery is usually performed 6–10 weeks after completion of CRT, to allow time for maximal response to occur. In contrast, SCPRT delivers a lower dose of radiation using larger doses per fraction, over a short duration followed by immediate surgery, which is scheduled for the following week. The short interval between commencing radiotherapy and surgery (usually ≤10 days) does not allow for any significant tumour shrinkage or downstaging.

### 4.1.4.2 Efficacy of SCPRT and long course CRT

The Swedish Rectal Cancer trial (n = 1168) defined clinical practice in the 1990s (Folkesson et al., 2005; Swedish Rectal Cancer Trial, 1997). It compared the addition of SCPRT prior to surgery with surgery alone and reported fewer LRs and improved 5-year OS with SCPRT. Since then significant advances in the multidisciplinary management of rectal cancer have resulted in a marked reduction of LR after TME alone, with centres reporting LR rates as low as 3–6% (Heald & Ryall, 1986; Martling et al., 2000). This raised the question of whether there remained any benefits for SCPRT in addition to TME.

Two trials were designed to address this question: the Dutch Colorectal Cancer Group trial (n = 1861) (Kapiteijn et al., 2001; Peeters et al., 2007) and the UK MRC CR07/NCIC-CTG C016 trial (n = 1350) (Sebag-Montefiore et al., 2009). Patients were randomized between SCPRT followed by immediate surgery or initial surgery followed by selective postoperative RT (Dutch trial) or CRT (CR 07) in patients found to have a CRM ≤1 mm. Unlike the Dutch trial, TME was not a protocol requirement in CR 07 but was performed in 93%. The use of SCPRT halved the risk of LR from 10.9% to 5.6% (P < 0.001) and from 11.5% to 4.7% at 5-years (HR 0.39, P < 0.0001) respectively. There was no difference in OS in both trials, although neither was statistically powered to detect a difference. The commonest cause of death was distant metastatic disease.

Although patients found to have an involved CRM following SCPRT and TME remain at significant risk of LR (Marijnens et al., 2003), further radiotherapy given postoperatively is contraindicated. The risk of long-term radiation toxicity associated with this approach is considerable (over 84% at 5-years) (Svoboda et al., 1999).

The EORTC 22921 trial (n = 1011) (Bosset et al., 2005; Bosset et al., 2006) and the FFCD 9203 trial (n = 733) (Gerard et al., 2006) compared preoperative long course CRT with long course RT in resectable (cT3-4) mid and low rectal cancers. Patients in EORTC 22921 were randomized to receive adjuvant 5FU in a 2 × 2 trial design, whereas all patients in FFCD 9203 received adjuvant 5FU. TME was not a protocol requirement in either trial. Both trials demonstrated that synchronous 5FU with long course RT significantly reduced LR compared to RT alone (8–9% vs 17%). Compliance with adjuvant 5FU was poor (only 43% received the protocol dose in EORTC 22921). Despite an improvement in pCR rate and reduced LR the addition of chemotherapy in EORTC 22921 and FFCD 9203 did not translate into an improvement in either 5-year distant metastases or OS.

More recently, oral fluoropyrimidines (capecitabine and UFT) has replaced intravenous 5FU in various indications and tumour sites. Capecitabine has been demonstrated to be non-inferior to infusional 5FU in preoperative CRT regimens for rectal cancer (Hofheinz et al., 2012; O’Connell et al., 2014).

### 4.1.4.3 Efficacy of SCPRT vs long course CRT

Two randomized trials compared SCPRT with long course CRT in resectable rectal cancer. The Polish trial (n = 316) compared SCPRT followed by immediate TME with CRT followed by TME at 4–6 weeks in patients with low (palpable) rectal cancers (Bujko et al., 2004). Approximately one third of patients in each arm underwent APE with no difference in sphincter preservation rate, which was the primary end point. Although pathological complete response (pCR) was more common with long course CRT (15% vs 1% for SCPRT), this did not translate into improved LR (14% vs 9%), DFS or OS (Bujko et al., 2006).

The Trans-Tasman Radiation Oncology Group (TROG) 01.04 trial (n = 326) compared SCPRT, immediate TME and 6 cycles adjuvant 5FU with CRT, TME at 4–6 weeks and 4 cycles adjuvant 5FU in patients with ultrasound or MRI-staged T3N0-2M0 rectal cancer (Ngan et al., 2012a). There was no difference in 3-year LR (7.5% vs 4.4%, P = 0.24), 5-year distant metastases (27% vs 30%, P = 0.92) or OS (74% vs 70%, P = 0.62).

### 4.1.4.4 Preoperative vs postoperative CRT

Meta-analysis of radiotherapy trials in rectal cancer suggested that the benefit of postoperative RT is smaller than with preoperative RT in terms of local disease control, but with no significant effect on either cancer specific survival or OS (Colorectal Cancer Collaborative Group, 2001).

The German GAO/ARO/AIO-94 trial (n = 823) compared preoperative long course CRT, TME at 6 weeks and adjuvant 5FU with TME, postoperative CRT and adjuvant 5FU in patients with resectable uT3-4 rectal cancers. Preoperative CRT was more effective with
fewer LRs (6% vs 13%; \( P = 0.006 \)) and was associated with lower acute and late toxicity (12% vs 24%; \( P = 0.01 \)) (Sauer et al., 2004). However, there was no difference in distant metastases, DFS or OS (Sauer et al., 2012).

4.1.4.5 Early toxicity of SCPRT and long course CRT

Early trials of SCPRT using large parallel-opposed radiation fields reported postoperative mortality, especially in elderly patients (Cedermark et al., 1995). More recent trials of SCPRT using 3- or 4-fields followed by immediate surgery have not demonstrated any overall increased risk (Marijnen et al., 2002; Sebag-Montefiore et al., 2009; Swedish Rectal Cancer Trial, 1997). However, if surgery is performed beyond 11 days of commencing SCPRT, there is evidence that postoperative morbidity and mortality is increased particularly in older patients (Glimelius, 2014; van den Broek et al., 2013). With long course CRT, there does not appear to be increased postoperative mortality or complications (Sauer et al., 2004).

Use of SCPRT can impair perineal wound healing after APE (35% vs 22% in CR 07) but in patients undergoing anterior resection, anastomotic leak rate is not significantly increased (9% vs 7% in CR 07) (Sebag-Montefiore et al., 2009). Acute grade 3–4 toxicity of long course CRT is significantly higher than SCPRT (18.2% vs 3.2% in Polish trial) (Bujko et al., 2004).

SCPRT can occasionally cause acute lumbosacral plexopathy, which is associated with early onset pain or discomfort in the gluteal region and radiating down the legs (Frykholm et al., 1993; Marijnen et al., 2002).

4.1.4.6 Late toxicity and quality of life following SCPRT or long course CRT and surgery

There are currently more data published on late morbidity following SCPRT and surgery than following long course CRT (Glimelius, 2006). Recognized late adverse events include bowel obstruction, bowel dysfunction presenting as faecal incontinence to gas, loose or solid stool, evacuation problems or urgency, urinary and sexual dysfunction, pelvis and femoral neck fractures and increased second malignancies (Birgisson et al., 2007; Dahlberg et al., 1998; Gilbert et al., 2015). Fewer late adverse events were reported in more recent studies, which may be due to improved radiotherapy techniques and smaller volumes irradiated.

The Dutch trial reported that irradiated patients were more likely to experience faecal incontinence (62% vs 38%) and have less satisfaction with bowel function, which impacted on daily activities. However there were no differences in stoma function or urinary symptoms (Peeters et al., 2005). SCPRT had a negative effect on sexual function in males and females although no differences were seen in QOL between irradiated and non-radiated patients (Marijnen et al., 2005). The presence of a stoma did not significantly affect health-related QOL. The CR 07 trial showed that the main adverse effect in male patients was sexual dysfunction. The main cause for this was the surgery, but was made worse with the addition of SCPRT (Stephens et al., 2010). A recent report did not find any increase in second malignancy in clinical trials of pelvic radiotherapy (Wiltink et al., 2015).

The German GAO/ARO/AIO-94 trial reported fewer late grade 3–4 toxicities with CRT given preoperatively as compared to postoperatively (14% vs 24%, \( P = 0.01 \)), including chronic diarrhoea, small bowel obstruction and anastomotic strictures (Sauer et al., 2004).

When comparing SCPRT with long course CRT, the Polish trial did not identify any difference in patient reported anorectal or sexual function (Pietrzak et al., 2007) and the TROG 01.04 trial did not identify any difference in RTOG/EORTC late radiation toxicity (5.8% vs 8.2%, \( P = 0.53 \)) (Ngan et al., 2012a) or long-term QOL (Ngan et al., 2012b).

4.1.4.7 Selection of patients for preoperative radiotherapy

The routine use of MRI for locoregional staging has significantly improved the ability of the Colorectal MDT to predict the T and N stage and more importantly, identify patients at risk of an involved CRM (Beets-Tan et al., 2001; Brown et al., 2003). The MERCURY trial demonstrated that MRI accurately predicts a clear CRM (MERCURY Study Group, 2006). Reporting lymph nodes with heterogeneous signal intensity and irregular border as involved, rather than based on size alone increases accuracy (Smith & Brown, 2008). However, more than 50% of involved lymph nodes measure <5 mm in diameter and will not be visible on MRI (Wang et al., 2005). Newer diffusion weighted MRI sequences may detect more lymph nodes but does not reliably characterize their nature (Heijnen et al., 2013). MRI identifies EMVI (Smith et al., 2008) and predicts the depth of extramural invasion (MERCURY Study Group, 2007), both proven to correlate with prognosis. Significant data now exists to suggest that EMVI as identified on baseline MRI, on MRI after neoadjuvant therapy or pathologically acts as a poor prognostic factor for recurrence risk (Al-Sukhni et al., 2012; Battersby et al., 2015; Chand et al., 2015).

If disease does not involve or threaten the MRF, both SCPRT and long course CRT reduce the relative risk of LR by approximately 50% and appear equally effective. However, the absolute benefit remains small (5–6%) with the number needed to treat (NNT) ranging from 17 to 20, and the majority of patients receive
If a patient requires radiotherapy in addition to surgery, this should be given preoperatively. Patients who have undergone initial surgery and deemed to be at high risk of LR, such as involved CRM, although not ideal, should be considered for postoperative CRT. A dose of at least 45 Gy in 25 fractions with synchronous 5FU is recommended.

**Recommendation grade A**

### 4.1.5 Rectal cancer threatening, involving or beyond the mesorectal fascia (cT3-4 N0-2 M0, MRF +ve)

Prior to the widespread availability of MRI, the Second MRC Rectal Cancer trial (n = 279) randomized patients with clinically fixed or tethered cancers to long course RT followed by surgery 4 weeks later or surgery alone and demonstrated a reduction of LR with RT (Medical Research Council Rectal Cancer Working Party, 1996).

The ability of MRI to accurately assess the proximity of the primary rectal cancer, tumour deposits and EMVI to the MRF enables patients who are at risk of an involved CRM and consequent high-risk of local disease failure to be identified prior to surgery. Such patients can then be offered neoadjuvant treatment in an attempt to improve their outcomes. In this situation, the use of preoperative long course CRT with a concurrent single-agent fluoropyrimidine of either intravenous 5FU or oral capecitabine, followed by surgery 6–12 weeks later is recommended.

This strategy is based on data demonstrating significant tumour shrinkage and downsizing on imaging and histological assessment, when compared to that predicted on clinical staging. There are presently no randomized trial results on this specific group of patients, although the UK ARISTOTLE trial (ISRCTN09351447) is ongoing.

The significance of MRI-detected mesorectal lymph nodes lying close to the MRF and its impact on choice of neoadjuvant therapy and LR remains contentious. The presence of these findings in the absence of other high-risk features, is unlikely to result in an involved CRM (Shihab et al., 2010) providing a good quality TME is achieved.

An audited series of 88 such patients whose disease was ≤1 mm from the MRF on pre-treatment MRI demonstrated that overall only 76% were able to undergo surgery with achievement of a clear CRM and the overall pCR rate was 15% (Kulkarni et al., 2008). A retrospective pooled analysis of data from 7 UK centres of 680 patients with clinically fixed or MRI MRF involved rectal cancers reported 63% achieving a clear CRM following long course CRT (Sebag-Montefiore et al., 2005).

With optimal MRI staging, most patients with resectable rectal cancer not involving the mesorectal fascia (cT2-4[peritoneum] N0-2 M0, MRF –ve) should be amenable to surgery alone.

**Recommendation grade B**

Patients with resectable rectal cancer not involving the mesorectal fascia (cT2-4[peritoneum] N0-2 M0, MRF –ve) with MRI features suggesting a higher risk of LR (T3c disease, mesorectal lymph node involvement or EMVI) may be considered for preoperative RT to reduce local recurrence. In this situation both SCPRT followed by immediate surgery or long course CRT followed by delayed surgery are acceptable.

**Recommendation grade A**

In patients receiving SCPRT, surgery should be performed within 11 days from the first fraction of radiotherapy to minimize risk of complications. If surgery cannot be performed within this interval and the patient has already commenced radiotherapy, surgery should be delayed beyond 4 weeks.

**Recommendation grade B**

In patients receiving long course CRT, surgery should be scheduled 6–10 weeks after completion of CRT. A dose of at least 45 Gy in 25 fractions with synchronous 5FU or oral capecitabine is recommended.

**Recommendation grade B**

Presence of involved mesorectal lymph nodes and EMVI are associated with a higher risk of LR, despite achieving a clear CRM. Both Dutch TME and CR 07 trials reported significant LR reduction in stage III rectal cancers from 19% to 9% (P < 0.001) and 15.4% to 7.4% (HR 0.46; P < 0.001) with SCPR respectively (NNT 10–12). The Dutch TME trial also reported improved 10-year OS with SCPRT in stage III patients (50% vs 40%; P = 0.032).

Therefore, accurate initial staging of rectal cancers is key to selecting patients for the most appropriate preoperative treatment strategy and to avoid unnecessary use of radiation in as many as possible, as this increases late morbidity with no clinically meaningful benefit. The majority of patients with resectable rectal cancer not involving the mesorectal fascia (cT2-4[peritoneum] N0-2 MRF –ve), particularly if mrT2-3a-b N0, will be at a very low risk (<3%) of LR following surgery alone providing the surgeon achieves a good quality TME with a clear CRM (Marijnen et al., 2002; Quirke et al., 2009; Taylor et al., 2011).

If a patient requires radiotherapy in addition to surgery, this should be given preoperatively. Patients who have undergone initial surgery and deemed to be at high risk of LR, such as involved CRM, although not ideal, should be considered for postoperative CRT. A dose of at least 45 Gy in 25 fractions with synchronous 5FU is recommended.

**Recommendation grade A**

In patients receiving SCPRT, surgery should be performed within 11 days from the first fraction of radiotherapy to minimize risk of complications. If surgery cannot be performed within this interval and the patient has already commenced radiotherapy, surgery should be delayed beyond 4 weeks.

**Recommendation grade B**

In patients receiving long course CRT, surgery should be scheduled 6–10 weeks after completion of CRT. A dose of at least 45 Gy in 25 fractions with synchronous 5FU or oral capecitabine is recommended.

**Recommendation grade B**
The use of SCPRT followed by a 4–12 week delay to surgery can result in downstaging in rectal cancers of any initial stage, with pCR rates ranging from 9% in locally advanced disease (Radu et al., 2008) to 35% in early cancers (Bujko et al., 2009). In patients who require downstaging treatment but are not able to tolerate CRT, SCPRT with delayed surgery is an accepted option (Bujko & Kołodziejczyk, 2008; Pettersson et al., 2012).

Several phase II trials in this group of patients incorporated irinotecan or oxaliplatin with 5FU-based CRT have reported clear CRM resections in 70–80% and pCR in 15–20%. The current UK ARISTOTLE trial is comparing the combination of irinotecan with capecitabine CRT vs capecitabine CRT. In the UK the National Cancer Research Institute (NCRI) Radiotherapy Trials Quality Assurance Team (RTTQA) designs and implements quality assurance (QA) programmes for all NIHR CRN Clinical Research Portfolio trials that include a radiotherapy component which is aimed at improving quality and minimizing variations between participating centres (http://www.rttqasqa.org.uk). The radiotherapy planning protocol within the UK has been developed by consensus for the phase III ARISTOTLE trial and adopted as the standard of care by most centres. In the future, intensity modulated radiotherapy (IMRT) using volumetric modulated arc therapy (VMAT) is likely to be able to deliver treatment more efficiently, adopting similar volumes but with potentially more small bowel sparing.

Patients with rectal cancer threatening, involving or beyond the mesorectal fascia (cT3-4 N0-2 M0, MRF +ve) should be considered for preoperative RT to improve the likelihood of achieving a clear CRM. In this situation the most effective strategy is long course CRT, followed by surgery 8–12 weeks later. A dose of at least 45 Gy in 25 fractions with synchronous 5FU or oral capecitabine is recommended.  

**Recommendation grade B**

Patients with rectal cancer threatening, involving or beyond the mesorectal fascia (cT3-4 N0-2 M0, MRF +ve) and are not sufficiently fit to tolerate long course CRT, should be offered SCPRT followed by delayed surgery 8–12 weeks later, to allow time for maximal tumour shrinkage.  

**Recommendation grade C**

Patients should be restaged with MRI pelvis and CT chest, abdomen and pelvis towards the end of the 8–12 week interval between completion of RT and planned surgery.  

**Recommendation grade C**

Radiotherapy should be planned and delivered according to standardized protocols, such as the UK ARISTOTLE trial protocol.  

**Recommendation grade D**

### 4.1.6 Low rectal cancer

Approximately 40% of all rectal cancers originate in the lower rectum, commonly defined as a tumour with its lower edge at, or below, the origin of the levators at the pelvic sidewall, usually corresponding to within 6 cm of the anal verge (www.lorec.nhs.uk). There is general acknowledgement that low rectal cancers are amongst the most challenging for patients, and for colorectal MDTs, and for surgeons. They have worse oncological outcomes with a higher risk of CRM involvement and tumour perforation at surgery and consequently, a higher risk of LR and poorer survival compared with mid and upper rectal cancers (Nagtegaal et al., 2005). This is partly due to tapering of the mesorectum leading to ‘waisting’ of the specimen and compromise of resection margins. The anorectum is anatomically and functionally complex. The technical challenge is that there is a conflict between achieving oncological clearance and sphincter preservation to maintain function.

Curative management for a low rectal cancer often entails the need for a permanent stoma. Even if the sphincters do not require surgical excision, the combination of commonly-used neoadjuvant therapy, and a subsequent very low anastomosis often results in suboptimal anal function, and on occasion complete incontinence, with a major impact on quality of life (How et al., 2012). The external sphincter and puborectalis are contiguous with the levator complex with very little surrounding mesorectum at this level (none at the distal extremity) to act as a barrier to cancer spread. Thus an advanced rectal tumour may invade the external sphincter/levator complex and require complete excision of the sphincter complex and levator by an abdominoperineal excision (APE).

MRI can effectively visualize the lower rectum, and surrounding structures, enabling effective decision-making and personalized, precision surgery (Salerno et al., 2009; Shihab et al., 2009; Shihab et al., 2011) and facilitating appropriate selection for neoadjuvant therapy to improve curative resection rates (Burton et al., 2006).

Published reports suggest suboptimal surgery in patients undergoing APE (Marr et al., 2005; Nagtegaal et al., 2005) and a suggestion of overtreatment by neoadjuvant radiotherapy for some lower-risk patients (Moran et al., 2014). Simultaneously evidence has suggested that APE surgical technique can be improved by a focused approach, with wider resection margins, in what is now termed an extralevator APE (ELAPE) (West et al., 2010).
The Low Rectal Cancer Development Programme (LOREC; www.lorec.nhs.uk) was attended by 147 out of 164 (89.6%) MDT's from 151 English NHS Trusts (some Trusts have two Colorectal MDT’s) and key messages published (Moran et al., 2014).

There are no specific low rectal cancer trials, but subset analysis of phase III studies suggests an approximate halving of LR. There is no strong evidence to support the use of radiotherapy to increase sphincter salvage and additionally, adverse effects on sphincter function need to be considered. Based on the above considerations, the randomized phase II UK SAILOR trial (ISRCTN 02406823) is currently exploring the feasibility of taking patients with a low rectal cancer requiring an APE, with a predicted negative surgical resection margin, straight to surgery without preoperative CRT.

The key aim of surgical intervention is R0 resection, that is, a clear distal and circumferential margin in the resected specimen. Surgical resection of an advanced low rectal cancer generally requires an ELAPE but an understanding of the anatomy, and the terminology, translates into the fact that ELAPE may be performed with the patient in the supine or prone jack-knife position (Moore & Moran, 2012). In addition an inter-sphincteric APE is an excellent oncological procedure if the external sphincter is not involved and where reconstruction is deemed not feasible or safe. The entire hindgut is removed and the mesorectal plane can be used. A TME and coloanal anastomosis may be feasible. If this is not feasible, an APE (conventional or intersphincteric) should be performed.

Recommendation grade B

For a low rectal cancer lying above the level of the anal sphincter, which is not threatening (>1 mm) the levator muscle or MRF, the mesorectal plane can be used. A TME and coloanal anastomosis may be feasible. If this is not feasible, an APE (conventional or intersphincteric) should be performed.

Recommendation grade B

For a low rectal cancer lying above the level of the anal sphincter, which is ≤1 mm from the levator muscle or MRF or invading the levator, an ELAPE should be performed. ELAPE is an anatomical term implying surgical excision on the inferior aspect of the levator and the extent of levator excision is tailored to the patient and the tumour. This is generally preceded by long course CRT and an 8–12 week gap.

Recommendation grade B

For a low rectal cancer lying at the level of the sphincter, which is involving the submucosa only or the inner layer of the muscularis propria, the mesorectal plane can be used, continuing inferiorly into the intersphincteric plane as an APE (conventional or intersphincteric).

Recommendation grade B

For a low rectal cancer lying at the level of the sphincter, which involves the full thickness of the muscularis propria or extends into or beyond the intersphincteric plane to involve the external sphincter, an ELAPE should be performed. This is generally preceded by long course CRT and an 8–12 week gap.

Recommendation grade B

4.1.7 Future directions in the management of rectal cancer

Although the use of preoperative radiotherapy, with or without synchronous chemotherapy reduces local pelvic recurrence, this has not been shown to reduce distant metastatic relapse or improve OS. With increasing surgical quality through the use of TME and ELAPE, where appropriate, plus selective preoperative radiotherapy, local pelvic recurrence is now markedly reduced compared to historical reports, leaving distant metastatic relapse as the main cause of death. Strategies to improve outcomes include increasing the efficacy of CRT and introducing neoadjuvant chemotherapy before any other treatment, to address the issue of micrometastases as early as possible in the treatment pathway (Gollins & Sebag-Montefiore, 2016).
4.1.7.1 Improving the efficacy of CRT
A review of phase II and III studies identified an overall pCR rate of 13.5 per cent using a single agent fluoropyrimidine as a radiation sensitizer (Hartley et al., 2005). It was suggested that the pCR rate could be increased with increased doses of RT and the addition of a second cytotoxic drug. With regard to the latter strategy several promising phase II trials incorporating irinotecan have been reported (Gollins et al., 2011) but as yet no phase III trials although the ongoing UK phase III ARISTOTLE trial (ISRCTN09351447) is examining the addition of irinotecan to capecitabine in MRI-defined unresectable/borderline resectable rectal cancer.

However, five randomized phase III trials have been reported adding oxaliplatin to either 5FU or capecitabine during CRT: STAR-01 (Aschele et al., 2011), ACCORD 12/0405 PRODIGE 2 (Gerard et al., 2012), CAO/ARO/AIO-04 (Rodel et al., 2015), NSABP R04 (Allegra et al., 2014) and PETACC-6 (Schmoll et al., 2013). Only two have published long-term outcomes as full-length reports, the French ACCORD12 (Gerard et al., 2012) and German AIO-04 (Rodel et al., 2015). The ACCORD 12 trial (n = 598) compared 45 Gy with capecitabine against 50 Gy with oxaliplatin and capecitabine and reported no difference in pCR rate (the primary endpoint), 3-year DFS or OS (Gerard et al., 2012). The German CAO/ARO/AIO-04 trial (n = 1265) compared long course 5FU-containing CRT followed by 16 weeks of 5FU-based postoperative chemotherapy, with or without oxaliplatin. The addition of oxaliplatin increased DFS from 71.2% to 75.9% (HR 0.79, P = 0.03) (Rodel et al., 2015). However the benefit of intensified CRT is not known due to the addition of oxaliplatin to both the concurrent and adjuvant chemotherapy components and the use of different 5FU dose intensities between treatment arms.

The NSABP R-04 (Allegra et al., 2014) and PETACC 6 trials (Schmoll et al., 2013), reported in abstract form, do not describe any improvement in cancer outcomes for their primary end point (LR and DFS respectively) and data are awaited from the STAR 01 trial (Aschele et al., 2011).

At present, no reliable predictive biomarkers of response to long course CRT have been identified, which have subsequently been verified as usable in routine clinical practice (Glynne-Jones et al., 2013; Glynne-Jones & Harrison, 2011). However, this is currently an active area for research.

4.1.7.2 Neoadjuvant chemotherapy
A number of phase II trials have evaluated the addition of neoadjuvant chemotherapy to long course CRT, suggesting higher compliance and lower acute toxicity compared to conventional adjuvant chemotherapy, with a minimal risk of progression during treatment. The EXPERT and EXPERT-C trials used 12 weeks of oxaliplatin/capecitabine (OxCap), then CRT, then surgery. A radiological response rate was seen in 70%, with only two patients (1%) progressing (Chau et al., 2006; Chua et al., 2010; Dewdney et al., 2012). The GCR3 phase II trial (n = 108) of pre- vs postoperative OxCap demonstrated lower toxicity and better compliance when given preoperatively (Fernandez-Martos et al., 2010). The CRUK-funded phase II COPERNICUS pilot trial (n = 60) showed that 8 weeks oxaliplatin/fluorouracil (OxFU) prior to SCRT and surgery is feasible with a high response rate (Gollins et al., 2015).

A Polish phase III trial compared standard long course CRT followed by surgery, with SCRT, then 6 weeks of FOLFOX neoadjuvant chemotherapy then surgery in 541 patients with fixed T3 or T4 tumours (MRI staging was not mandated) (Bujko et al., 2016). Although there was no difference in R0 resection rate (the primary end point), local and distant failure or DFS, a marginally statistically significant improvement in overall survival was reported in the neoadjuvant chemotherapy arm (73% vs 65%; P = 0.046).

Two further phase III trials employed a similar design to the Polish study although with differing durations of chemotherapy following SCRT in the experimental arm, 18 weeks in the Dutch/Scandinavian RAPIDO trial (NCT01558921, recruitment completed in mid 2016) and 12 weeks in the Chinese STELLAR trial (NCT02533271, recruitment ongoing). The US PROSPECT (NCT01515787) is comparing 12 weeks of FOLFOX alone followed by surgery (although poorly responding patients also receive preoperative long course CRT) and a further 12 weeks of postoperative FOLFOX, against standard long course CRT, surgery and 16 weeks of adjuvant FOLFOX.

4.1.7.3 Watch and wait
It is well established that 10–20% of patients achieve pCR following preoperative CRT. If such patients can be accurately identified following CRT, it may be possible to avoid surgery (Maas et al., 2015). However, no randomized controlled trial data currently exist. Published retrospective series demonstrate considerable heterogeneity in patient selection, imaging modalities, CRT regimens, methods of defining clinical complete response (cCR) and follow-up protocols (Glynne-Jones & Hughes, 2012).

Habr-Gama’s group in Brazil have carefully followed patients presenting with digitally palpable low rectal cancers who have a cCR following 5FU-containing long course CRT. In a recent report of 70 patients with
tumours within 7 cm of the anal verge, 47 (68%) had a cCR and 50% of long-term responders avoided surgery (Habr-Gama et al., 2013). However, it is unclear how these single-institution results in predominantly smaller, low rectal cancers might be applicable to more advanced cancers of the mid or upper rectum with presumed greater incidence of nodal metastases in the larger tumours.

A recently reported propensity score-matched cohort analysis of 129 patients with rectal cancer achieving a cCR in North West UK (OnCoRe) who were watched within a more intensive follow up protocol, showed 44 (34%) had local re-growth, with 36 of 41 (88%) with non-metastatic re-growth being surgically salvaged. There was no difference in 3-year OS between the matched cohorts. By contrast, patients managed by watch and wait had a better 3-year colostomy-free survival (74% vs 47%, HR 0.445, P < 0.0001) (Renchan et al., 2015).

A Royal Marsden study (NCT01047969) examined the safety of deferred surgery in patients achieving a cCR and a Danish Colorectal Cancer Group prospective observational study in patient with low rectal cancer (NCT00952926) is assessing the frequency of LR after CRT in patients with low rectal cancer. In addition the European Network for Watchful Waiting has been started in Denmark (kfe.onk@slb.regionsyddanmark.dk).

A watch and wait policy in a patient achieving radiologically and endoscopically confirmed cCR is presently considered a trade off between oncological and functional outcomes. Patients need to be aware this approach remains a new management under evaluation and that this should not be offered as an intention to treat. There remains some confusion within the literature as some treatment series include ‘near’ cCR (which is not clearly defined), and managed by local surgery, rather than watch and wait only.

In selected patients with complete clinical response (cCR) after preoperative long course CRT, a watch and wait approach can be considered. A defined surveillance protocol, such as used in OnCoRe, is necessary to identify local disease re-growth at the earliest stage possible.

Recommendation grade C

4.2 Systemic Chemotherapy for Colorectal Cancer

Chemotherapy plays an increasing role in the management of colorectal cancer and has contributed to the continued improvement in outcomes over the last two decades. The use of chemotherapy should be agreed by the colorectal MDT and should be administered, within facilities conforming to national standards.

4.2.1 Adjuvant chemotherapy

4.2.1.1 General recommendations

The choice of adjuvant therapy should be made jointly by the patient and the supervising oncologist, taking into account the patient’s risk factors for recurrence, their co-morbidities and performance status, any specific contraindications, side-effect profile of the agent(s) and the patient’s preference for method of administration.

4.2.1.2 Lymph node positive (stage III) disease

It has been convincingly demonstrated that adjuvant fluoropyrimidine chemotherapy improves disease-free survival (DFS) and overall survival (OS) in stage III (Dukes’ C) colon cancers (National Institute for Health and Care Excellence, 2011). By extrapolation, current national guidelines (NICE, ESMO etc) also recommend the use of adjuvant chemotherapy in rectal cancer.

Oral forms of 5FU, namely uracil-tegafur (UFT) and capecitabine have been shown to be as effective as intravenous (i.v.) modulated 5FU and are licensed for adjuvant therapy (Lembersky et al., 2006; Twelves et al., 2012). Many patients prefer oral chemotherapy for its convenience. Although the toxicity profile is altered, the overall level of toxicity is similar to i.v. modulated 5FU. NICE (TA 100) has approved oral capecitabine for adjuvant use (National Institute for Health and Care Excellence, 2006).

The addition of oxaliplatin to fluoropyrimidine chemotherapy in stage III patients reduces recurrence risk further. Three randomized phase III trials (MOSAIC, NSABP C-07, XELOXA) comparing oxaliplatin/5FU (Andre et al., 2004; Yothers et al., 2011) and oxaliplatin/capecitabine (Haller et al., 2011) with modulated 5FU monotherapy have demonstrated consistent results (total 6624 patients). NICE (TA 100) has approved oxaliplatin for this indication (National Institute for Health and Care Excellence, 2006). Long-term follow up data from the MOSAIC trial has shown a 4.2% OS improvement in stage III but no difference in stage II patients (Andre et al., 2009). However, the benefits of adding oxaliplatin should be weighed against the side-effects and acceptability of the regimen. In general, a higher risk, otherwise fit patient should be offered an oxaliplatin-based combination as their risk of death from cancer significantly outweighs their risk of death from other causes.

The elderly population are identified to be under-represented in randomized controlled trials, as the median age of trial patients is often around 10 years younger than the median age of patients diagnosed with colorectal cancer. Meta-analyses have hinted at a lack of benefit from the addition of oxaliplatin to 5FU (McCleary et al., 2013), however data from the most recent XELOXA trial...
suggest that the elderly population gain similar benefits to their younger counterparts (Haller et al., 2011). However, this will be at the expense of increased toxicity. There are competing risks with age, particularly risk of dying from other causes and therefore careful assessment of the individual is warranted.

A number of trials have explored additional agents as adjuvant strategies in colon cancer, including irinotecan (Van Cutsem et al., 2009), cetuximab (Alberts et al., 2005) and bevacizumab (de Gramont et al., 2012). So far these trials have not demonstrated any improvements in DFS or OS. There are a number of trials (completed or ongoing, including the UK SCOT trial) investigating the use of a shorter duration of oxaliplatin-based chemotherapy, comparing 3 months with the standard 6 months of treatment.

An alternative strategy is to use neoadjuvant chemotherapy, which is a standard of care in oesophageal and gastric cancers. The UK FOXTROT trial is currently investigating the role of neoadjuvant oxaliplatin-based chemotherapy in radiologically defined higher-risk colon cancer (Foxtrot Collaborative Group, 2012).

4.2.1.3 Lymph node negative (stage I and II) disease
There is less evidence supporting the use of adjuvant chemotherapy in stage II (Dukes’ B) than in stage III. The UK QUASAR I trial was designed to determine the benefit of adjuvant chemotherapy in patients considered to be at lower risk of recurrence. The trial randomized 3239 patients (91% with stage II) to i.v. modulated 5FU or observation. Use of chemotherapy reduced relative risk of recurrence by 22% (HR 0.78) and improved OS by 3.6% (Gray et al., 2007). Sub-group analysis of stage II patients treated within the MOSAIC trial showed a smaller but statistically borderline significant incremental benefit by adding oxaliplatin (Tournigand et al., 2012).

Oxaliplatin is not routinely recommended or licensed in patients with stage II cancers (National Institute for Health and Care Excellence, 2011), although there may be rationale to consider its use in stage II patients with multiple high-risk factors, given their overlapping poor prognosis with stage III disease. Known high-risk features in stage II cancers include pT4 stage, obstructed tumours, poor or mucinous differentiation, EMVI and fewer than 12 lymph nodes assessed histologically.

Microsatellite instability (MSI) appears to confer a better DFS in stage II colon cancers (especially right sided) compared to microsatellite stable tumours (Popat et al., 2005), with no apparent benefit from adjuvant chemotherapy. Initial reports that MSI is also a predictive marker for the lack of efficacy from adjuvant 5FU (Des Guezt et al., 2009) have been largely refuted (Hutchins et al., 2011). The UK Royal College of Pathologists recommend the assessment of MSI either by genetic assessment or by immunocytochemistry for the four mismatch repair (MMR) proteins in stage II patients who are being considered for adjuvant therapy. Commercially available novel array-based platforms have been developed to fine tune stage II patients into high and low risk groups, in order to refine discussions with individual patients about the pros and cons of adjuvant therapy. To date these tests add significant cost and may add little over and above MSI assessment for the individual patient (Gray et al., 2011).

The recurrence risk of stage I (Dukes’ A) colon cancers is generally low, with a 5-year OS of over 90% (Cancer Research UK, 2016). Although no trials have formally evaluated the role of adjuvant chemotherapy in this group of patients, it is unlikely to be of any clinically useful benefit.

4.2.1.4 Adjuvant chemotherapy in rectal cancer
Current UK practice, supported by NICE guidance (GC 131) (National Institute for Health and Care Excellence, 2011), is to complete local treatment of the primary tumour with surgery, with or without pelvic radiotherapy, before considering adjuvant systemic chemotherapy. Although a systematic review of 9785 patients with rectal cancer in 21 randomized trials demonstrated modest DFS (HR 0.75) and OS (HR 0.83) improvements with postoperative chemotherapy (Maas et al., 2015), these trials pre-dated the widespread use of optimal TME surgery and preoperative radiotherapy. The one study which tested adjuvant chemotherapy following preoperative radiotherapy (EORTC 22921) failed to demonstrate a benefit (HR 0.91). Recent meta-analysis of four trials that incorporated preoperative radiotherapy suggested limited or no benefit from adjuvant chemotherapy (DFS HR 0.91, P = 0.230) (Breugom et al., 2015).

Several factors combine to reduce the effectiveness of adjuvant chemotherapy in rectal cancer, including treatment delay and poor compliance. Ongoing morbidity from surgery and radiotherapy reduces patients’ tolerance of adjuvant chemotherapy. Temporary ileostomies, which are expected to be performed in approximately 75% of patients having a low anterior resections, can cause dehydration and electrolyte imbalance from a high output and reduce compliance to chemotherapy, leading to reduced DFS and OS. In EORTC 22921 and CHRONICLE less than half of patients (43% and 48% respectively) completed all cycles of chemotherapy. In EORTC 22921 and the I-CNR-RT trial 27% and 28% of patients respectively were unable to start adjuvant chemotherapy.

Fluoropyrimidines with or without oxaliplatin should be considered as options for the adjuvant
treatment of patients with stage III colorectal cancer following potentially curative surgery.

Recommendation grade A

In general a higher risk, otherwise fit, patient should be offered an oxaliplatin-based regimen.

Recommendation grade A

Patients with high-risk stage II colorectal cancer should be considered for adjuvant chemotherapy.

Recommendation grade A

MSI or MMR protein assessment should be available to clinicians, allowing fully informed discussions with the patient diagnosed with stage II colorectal cancer and being considered for adjuvant chemotherapy.

Recommendation grade B

4.2.2 Systemic chemotherapy for advanced disease

4.2.2.1 Locoregional recurrence

Local recurrence of colorectal cancers should be considered for salvage resection, in selected cases seeking the opinion of a centre specializing in extended resectional surgery. If resection is not deemed possible, palliative treatment with chemotherapy (or chemoradiotherapy) may achieve significant tumour shrinkage and in discussion with the patient and MDT may offer the opportunity to reconsider salvage surgery.

4.2.2.2 Unresectable primary disease

Unresectable primary disease is most commonly seen in rectal cancers, but also occurs in colon cancers. The use of chemotherapy and/or radiotherapy may improve symptoms and survival. In some patients, a good response to treatment may enable reconsideration of surgical intervention.

4.2.2.3 Operable metastatic disease

Patients with technically operable liver or lung metastases may benefit from resection. Five-year survival following resection of colorectal metastases is around 40%, though no randomized controlled trial data exists (Garden et al., 2006; Kanas et al., 2012). Whether patients with lung only metastases, benefit from surgical resection remains debated. PulMICC is a randomized phase III trial for patients with resectable lung metastases, exploring the role of surgical resection vs palliative chemotherapy.

The EPOC (EORTC 40983) trial compared oxaliplatin/5FU given before and after surgery, to surgery alone in patients with liver limited metastatic disease (Nordlinger et al., 2008) reported a marginal improvement in 3-year PFS approaching statistical significance (HR 0.79; \( P = 0.058 \)). The New EPOC trial focused on a similar group of patients with potentially resectable liver only metastases, with KRAS exon 2 wild-type tumours, comparing the addition of cetuximab to oxaliplatin/5FU/folinic acid (FOLFOX). This trial closed early after it became evident that the addition of cetuximab resulted in a worse DFS despite an improved response rate (Primrose et al., 2014).

These results have been variably interpreted as either suggesting a benefit, or alternatively no benefit from peri-operative oxaliplatin/5FU chemotherapy in this setting. Many now offer adjuvant chemotherapy to patients as standard and those with high-risk synchronous disease are offered neoadjuvant chemotherapy but optimum practice remains undefined.

Where metastases are unresectable, currently patients fall into 2 groups:

- metastatic disease is inoperable at presentation, however, might become resectable with curative intent if a good response to therapy occurs.
- metastatic disease will not become suitable for potentially curative surgery, even if a good response to therapy occurs.

Sub-group analyses from randomized trials and non-randomized evidence exists to support the use of preoperative combination chemotherapy +/- biological therapy, prior to resection in patients with ‘potentially’ operable liver metastases (National Institute for Health and Clinical Excellence, 2009). Such patients should be discussed by the MDT, in the presence of a hepatic surgeon. If appropriate, following radiological and surgical review, preoperative combination chemotherapy should be delivered for at least 8 weeks prior to re-imaging.

4.2.2.4 Inoperable metastatic disease

Selection of patients for chemotherapy requires the opinion of an oncologist experienced in delivering colorectal cancer chemotherapy. A large number of factors including performance status, serum biochemistry and overall tumour burden influence the choice of chemotherapy and the patient’s ability to tolerate treatment. These can also independently predict for progression and survival. Performance status is a particularly potent indicator. In a meta-analysis of patients treated in trials of 5-FU based chemotherapy, median survival times were 4, 10 and 14 months for patients with ECOG performance status scores of 2, 1 and 0 respectively (Thirion et al., 1999).

A number of meta-analyses of palliative single-agent chemotherapy have shown improved survival in the region of 3–6 months with chemotherapy compared with best supportive care alone, in advanced colorectal cancer. When reported, chemotherapy either improved
or maintained quality of life (Simmonds, 2000). The oral 5FU prodrugs, UFT and capcitabine have shown equivalent survival and increased ease of administration compared to bolus 5FU and low dose folinic acid, and are approved by NICE (TA 61) as single agents for first-line treatment (National Institute for Health and Care Excellence, 2003).

Combination regimens with intravenous 5FU plus either, irinotecan or oxaliplatin have been shown to offer survival benefits in both first and second-line situations. Current NICE guidance supports the use of all three of the active drugs (a fluoropyrimidine, oxaliplatin and irinotecan) and as such has deemed them to be cost effective (National Institute for Health and Care Excellence, 2005). Improved results have been reported in studies in which all three of these agents are used in the majority of patients (Grothey & Sargent, 2005).

In patients with stable or responding disease after 3 months therapy, a rest from treatment with close observation until disease progression was not shown to be detrimental to survival and contributed to improved quality of life in the UK COIN trial (Adams et al., 2011). Within this trial it was suggested that a sub-group of patients with thrombocytosis benefited from a continuation of therapy beyond 12 weeks, although this awaits validation in other trial sets. The Dutch CAIRO 3 trial has demonstrated a survival advantage in patients receiving 4 months of oxaliplatin, capcitabine and bevacizumab and then being maintained on bevacizumab and capcitabine compared to bevacizumab alone (adjusted HR 0.8, $P = 0.035$) (Simkens et al., 2015).

Raltitrexed, a folate anti-metabolite is licensed for use as a substitute for 5FU/FA or capcitabine, when these are contraindicated. The common reasons are cardiotoxicity and DPD deficiency. NICE (GC 131) has recommended the use of raltitrexed under these circumstances (National Institute for Health and Care Excellence, 2011).

4.2.2.5 Addition of biological therapies

Targeted monoclonal antibodies have been used in conjunction with chemotherapy. Bevacizumab, an antibody to vascular endothelial growth factor (VEGF), has been shown to improve overall and progression-free survival when used in addition to first-line irinotecan (Hurwitz et al., 2004) and first and second-line oxaliplatin-based combinations (Giantonio et al., 2007; Saltz et al., 2008). In patients who received bevacizumab during first-line therapy, there is evidence of benefit in continuing this into second-line therapy (Bennouna et al., 2013). However bevacizumab is currently not approved by NICE (TA 212) (National Institute for Health and Care Excellence, 2010). Aflibercept (Zaltrap), a fusion protein binding VEGF and PlGF, has been shown to improve survival in combination with irinotecan and 5FU (FOLFIRI) in the second-line (Tabernero et al., 2014) but is not approved by NICE (TA 307) (National Institute for Health and Care Excellence, 2014).

Cetuximab and panitumumab, epidermal growth factor receptor (EGFR) inhibitors, are potentially active in patients with RAS wild-type tumours. Data on the addition of cetuximab to irinotecan and oxaliplatin combinations in the first-line setting are inconsistent; improvement of PFS and OS was demonstrated in some trials (Bokemeyer et al., 2009; Van Cutsem et al., 2009) but not in other trials (Maughan et al., 2011). Addition of cetuximab to irinotecan as second-line therapy (Sobrero et al., 2008) and as a single agent in the last line setting (Jonker et al., 2007; Karapetis et al., 2008) has also demonstrated improved PFS and OS.

Panitumumab, which is fully humanized and administered 2–3 weekly, has been used in addition to an oxaliplatin combination as first-line therapy (Douillard et al., 2010) in addition to an irinotecan combination as second-line therapy (Peeters et al., 2010) and as a single agent in the last line setting (Amado et al., 2008; Van Cutsem et al., 2007) and demonstrated improved PFS and OS. The UK PICCOLO trial combined panitumab and single agent irinotecan in the second-line and failed to demonstrate any benefit in patients (Seymour et al., 2013).

The European licensing of cetuximab and panitumumab has now been changed to include both NRAS and KRAS wild-type (RAS wt) tumours. In 2009, NICE (TA 176) gave approval for cetuximab to be used in combination with FOLFOX or FOLFIRI chemotherapy for patients with RAS wild-type tumours who have potentially resectable liver metastases (National Institute for Health and Care Excellence, 2007; National Institute for Health and Clinical Excellence, 2009), based on the high expected response rates in this cohort of patients. Panitumumab has not been formally appraised by NICE and is thus not approved. More recently, NICE (TA 439) approved cetuximab and panitumumab to be used in combination with FOLFOX or FOLFIRI in RAS wild-type metastatic colorectal cancer as a first-line regimen (National Institute for Health and Care Excellence, 2017).

The recent FIRE 3 trial is the first phase III study to directly compare the biological agents, bevacizumab and cetuximab in combination with FOLFIRI in the first-line setting. It showed a 3.7 month OS improvement (28.7 vs 25.0 months, HR 0.77, $P = 0.017$) in the RAS wild-type cohort of patients receiving cetuximab/FOLFIRI vs bevacizumab/FOLFIRI (Stintzing et al., 2013) despite there being no difference in response rate or PFS.

Regorafenib is a novel oral tyrosine kinase inhibitor, which has demonstrated a 1.4 month OS benefit vs best
Supportive care alone in the last line setting (6.4 vs 5.0 months, HR 0.77; $P = 0.0052$) (Grothey et al., 2013). Regorafenib has not been formally appraised by NICE (TA 334) and has not been approved.

The RECURSE phase III trial compared trifluridine-tipiracil, an oral combination of a thymidine analogue (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil hydrochloride) with a placebo in patients with chemorefractory metastatic colorectal cancer. It demonstrated a 1.8 months improvement in OS (7.1 vs 5.3 months, HR 0.68; $P < 0.001$) (Mayer et al., 2015). NICE (TA 405) has approved the use of trifluridine-tipiracil as a treatment option, within the licensed indication on an agreed patient access scheme (National Institute for Health and Care Excellence, 2016).

Fit patients with resectable or potentially resectable liver or lung metastases should be reviewed in the MDT with a hepatobiliary (or thoracic) surgeon and colorectal oncologist, to evaluate operability and to decide on a combined plan of management to optimize the chance of achieving complete resection of all metastatic disease.

**Recommendation grade B**

Patients with unresectable metastatic disease should be discussed by the MDT and if appropriate, should be referred to an oncologist for consideration of chemotherapy.

**Recommendation grade C**

Surgeons and oncologists who deal with colorectal cancer should make it a priority to build close links with palliative care specialists and units.

**Recommendation grade D**

All clinicians who deal with colorectal cancer should be trained in communication skills, in the control of pain and other cancer symptoms.

**Recommendation grade D**

It is important that patients with colorectal cancer are offered the opportunity to ask questions and to have important information repeated at each consultation. Information giving should be seen as an essential part of every consultation.

**Recommendation grade D**

4.3 Supportive and Palliative Care

4.3.1 Definitions

Palliative care is defined as the ‘active holistic care of patients with advanced, progressive illness. Management of pain and other symptoms and provision of psychological, social and spiritual support is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families. Many aspects of palliative care are also applicable earlier in the course of the illness in conjunction with other treatments’ (National Institute for Health and Clinical Excellence, 2004). Although palliative care is mainly focused on ‘advanced, progressive’ stages of colorectal cancer, particularly in the very last months of life, more can be achieved by introducing some aspects of this earlier in the course of the illness in conjunction with other treatments’, as in the NICE guidance, in terms of health-related and psychological benefits to patients and their carers (Smith et al., 2012; Temel et al., 2010).

Over the past two decades, ‘supportive care’ as a separate but overlapping concept has developed. Supportive care is defined as: ‘[helping] the patient and their family to cope with cancer and treatment of it – from pre-diagnosis, through the process of diagnosis and treatment, to cure, continuing illness or death and into bereavement. It helps the patient to maximize the benefits of treatment and to live as well as possible with the effects of the disease’ (National Institute for Health and Clinical Excellence, 2004). It is distinct from palliative care in three main respects: First, it should start at the beginning of the cancer illness, based on the individual needs of the patient and family rather than being determined by the notion of prognosis. Second, it is concerned with managing acute treatment-related toxicities such as nausea, vomiting and diarrhoea, as well as long-term effects such as neuropathy and fatigue. Third, supportive care continues into ‘survivorship’ and rehabilitation for return to normal life after cancer. For these reasons, it is claimed that ‘Supportive care makes excellent cancer care possible’ (http://www.mascc.org).

Supportive and palliative care services should be available to all colorectal cancer patients at any stage of disease.

**Recommendation grade D**

4.3.2 Supportive care in the oncology setting

The ‘Multinational Association for Supportive Care in Cancer’ (MASCC) has produced several guidelines (http://www.mascc.org/guidelines) for delivery of supportive care, enabling oncologists to deliver optimal doses of anti-cancer treatment. The MASCC also produces validated assessment tools, eg for chemotherapy induced emesis, EGFR inhibitor skin toxicity. Adherence to the latest 2016 MASCC anti-emetic guidelines could improve the experience of the large majority of patients receiving chemotherapy (Herrstedt et al., 2017).
In UK cancer centres, trained specialist nurses and allied health professionals, as well as the oncologists routinely deliver aspects of supportive care. As anti-cancer treatments become increasingly more complex and with newly emerging toxicities from biological, immunomodulating and other antibody-based treatments it becomes more important for services to adapt to changing MASCC and other supportive care guidelines.

There is evidence that initiating lifestyle changes and encouraging exercise regimes early on, even before initiation of adjuvant treatment and during it, may help patients make an earlier recovery and return to productive life (Li et al., 2013). At present ‘pre-habilitation’ and rehabilitation during treatment are not widely available. Patients may benefit from being referred to services outside the cancer centre, including some hospices, which are developing rehabilitation units.

Symptoms arising during anti-cancer treatment are managed by experienced members of the oncology team, especially by specialist nurses and nurse prescribers. For patients who fail to respond to locally initiated symptom management, or who develop intolerable side-effects, hospital or community-based specialist palliative care services can offer an extra layer of advice and supervision. Acute oncology services should also have access to specialist palliative care backup (Shankland et al., 2012).

Oncology teams should be familiar with guidance for supportive care, including MASCC guidelines and assessment tools.

Recommendation grade B

4.3.3 Supportive care after cancer treatment

Once patients have completed their primary cancer treatment, there is a drive to discharge patients earlier back to the care of their primary care services. Whilst this may work well for many patients, some remain burdened by late side-effects or may have problems in adjusting to daily life. Post-treatment rehabilitation may help. Patients may be referred or self-refer to organizations such as Maggie’s Centres (https://www.maggiecentres.org/), which offer programmes for exercise, managing stress, nutritional advice and social security benefits. Many larger cities have information and support centres attached to, or separate from, the cancer centres and these may offer similar programmes. Exercise-based rehabilitation programmes can improve fatigue and quality of life in cancer survivors but there is large variability in protocols and adherence to them (Mishra et al., 2012).

For patients who are living longer after the completion of treatment and are currently disease-free, the National Cancer Survivorship programme, which started in 2007, has led to a multiplicity of models of support and care for survivors. Each cancer centre should be able to provide patients with information about how to access such support.

Patients who have persisting late side-effects from anti-cancer treatments are often in a difficult position, because primary care services are not trained to monitor and manage these, whilst oncology centres are poorly equipped to offer long-term support. In the larger cities, some acute hospital-based palliative care teams may be able to manage specific issues such as late drug side-effects and for the monitoring and weaning of doses of analgesics and other symptom medications.

Colorectal cancer patients who have completed anti-cancer treatment should have access to supportive care including rehabilitation.

Recommendation grade D

Long-term survivors of colorectal cancer should be monitored for late side-effects of treatment and be offered specialist support as needed.

Recommendation grade C

4.3.4 Palliative care in advanced disease and end of life care

There is no clear demarcation of when the ‘end of life’ begins, but the accepted timeframe is from when it is thought by the clinical team that the patient has one year or less of expected survival. Prognostication towards the end of life remains difficult and inaccurate, even in palliative care settings and clinicians must be clear and honest with patients who want to know their prognosis, explaining the reasons for uncertainty.

Patients should be encouraged to make ‘advance care plans’ (ACPs) to cover a range of topics including: preferred place of care, preferred place of death, advance decisions of refusal of treatments, do not attempt resuscitation (DNAR) choices. Having an ACP in place can help patients and their families feel more comfortable that future events have been reflected on and can reduce hospital admissions for elderly patients at the end of life (Martin et al., 2016). Discussion about concepts of ACPs should be performed with sensitivity and in stages, reflecting the clinical course of cancer in each individual. There is no place for ‘enforced’ discussion of these topics, especially preferred place of death or DNAR decisions, particularly at the beginning of advance care planning. Oncology teams should at the same time, be considering the ceiling of care for each patient and communicate this with other acute and community services. This needs to be kept under frequent review, and wherever possible, based on discussion with the patient and their families.
The 2015 Royal College of Physicians national hospital end of life care audit found that on the final hospital admission of over 9000 patients, only 4% of patients had an ACP known to the caring team (Royal College of Physicians, 2016). The audit also showed that by the time it was recognized that a patient may die during the admission, the median survival was <36 h. Recognizing dying so late and not having an ACP can compromise patients’ and families’ wellbeing, particularly if inappropriate interventions are started or other treatments are unnecessarily withdrawn.

During the last months of life, patients are often referred to specialist palliative care services but being referred too early or in an abrupt way can lead to rejection by some services, or be distressing to patients. Ideally patients should have access to information about the availability and potential benefits of specialist palliative care ‘should they need it’ in a non-threatening way before referrals are made. As well as specialist medical and nursing support, patients in the last year of life may need access to other members of the multidisciplinary palliative care team, e.g. physiotherapy, occupational therapy, dietics, psychological and spiritual support and benefits advice.

Patients with advanced colorectal cancer entering the last months of life should be encouraged and supported to make advance care plans.

Recommendation grade C

Colorectal cancer patients at the end of life should be offered information and access to specialist palliative care services in a sensitive way as early as possible.

Recommendation grade D

Patients with advanced colorectal cancer should have access to members of the wider palliative care team in all settings.

Recommendation grade D

4.3.5 Provision of specialist palliative care services and hospices

The UK has a particularly developed network of specialist palliative care services, many of these operated and funded by national or local charitable institutions and are based at hospices, which are remote from cancer centres or hospitals (The Economist Intelligence Unit, 2015). They provide both inpatient and day-patient facilities. The disconnection from the acute hospital can be a problem in some circumstances, e.g. patients needing acute oncology support or interventions such as paracentesis or blood transfusion, which are not provided in all hospices. Efforts should be made to provide local solutions to circumvent these issues.

Availability of specialist palliative care support within UK acute hospital trusts, in terms of 24 h, 7 days a week advice and 7 days a week access to a palliative medicine doctor remains inconsistent and generally poor (Royal College of Physicians, 2016). Therefore some oncology services need to make arrangements with local hospices in order to gain out of hours advice and support.

Hospitals caring for patients with advanced colorectal cancer should work towards round the clock access to specialist palliative care support.

Recommendation grade D

4.3.6 Last days of life

The NICE guideline for ‘Care of the dying adult in the last days of life’ places emphasis on the need to be alert to signs and symptoms of impending death, but also being aware of changes that could indicate stabilization or even temporary recovery (National Institute for Health and Clinical Excellence, 2015a). It makes recommendations about communication and shared decision-making; the maintenance of hydration including clinically assisted hydration if indicated and desired by the patient; pharmacological management of key symptoms (pain, nausea and vomiting, breathlessness, anxiety, delirium, agitation) and noisy respiratory secretions in the final days and hours; and the role of anticipatory prescribing. The NICE guideline stresses that all care, including prescribing for current and anticipated symptoms and for hydration, should be individualized and not done in a ‘one-size-fits-all’ fashion, as was previously considered.

Although there has been much emphasis on enabling patients to die in their own homes according to their wishes, many circumstances make this ideal not possible or desirable. These include new or increasing symptoms, or the need for hospital-based interventions for comfort. The initiation of appropriate clinically assisted hydration should be done in any setting and not be seen as the reason for hospital admission. Patients with subacute and long-term bowel obstruction from colorectal cancer may also be managed at home for prolonged periods using central or peripheral lines for hydration, together with specialist palliative care input for managing vomiting and pain.

All care including prescribing of medications and clinically assisted hydration should be given on an individualized basis according to clinical need and regardless of the setting. Anticipatory prescribing for future symptoms is encouraged, especially if the
patient expected to die out of hours or in the community setting.

Recommendation grade C

Conflicts of interest

Simon Bach has been a consultant for Ethicon Inc., Cincinnati, USA. Arthur Sun Myint has been a specialty adviser for NICE IPG 532 guideline on low energy contact X-ray brachytherapy (Papillon) for early stage rectal cancer. Andrew Renehan has received Lecture honoraria from Merck Serona and Sanofi and been a member of the advisory board of Beating Bowel Cancer. Sam Ahmedzai has been employed by the National Institute of Health Research as National Specialty Lead for supportive and community-based cancer research and has been Chair of the National Cancer Research Institute clinical studies group for supportive and palliative care research. The other authors have no conflicts to declare.

References


Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schiller J, Colorectal Disease


Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schiller J, Colorectal Disease


Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schiller J, Colorectal Disease


Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schiller J, Colorectal Disease


Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schiller J, Colorectal Disease


Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schiller J, Colorectal Disease


Chua YJ, Barbachano Y, Cunningham D, Oates JR, Brown G, Wooterspoon A, Tait D, Massey A, Tebbutt NC, Chau I. Neoadjuvant capcitabine and oxaliplatin before...


Glimelius B. Optimal time intervals between pre-operative radiotherapy or chemoradiotherapy and surgery in rectal cancer? Front Oncol 2014; 4: 50.


National Institute for Health and Care Excellence (2005)

National Institute for Health and Care Excellence (2006)

National Institute for Health and Care Excellence (2005)


5 Follow Up, Lifestyle and Survivorship

5.1 Introduction
The role of follow up after curative treatment for colorectal cancer continues to evolve. The potential benefits of follow up for patients and Colorectal MDTs are
- Detection of potentially treatable recurrent disease.
- Detection of metachronous colorectal tumours and polyps.
- Provision of psychological support.
- Supporting audit, clinical governance and continuing professional development.

5.2 Detection of Potentially Treatable Recurrent Disease
Previous meta-analyses of randomized controlled trials of follow up after curative colorectal cancer resection have shown survival benefit in patients undergoing ‘intensive’ follow up, with odds ratio of 0.73 (95% CI 0.59–0.91) and 0.74 (95% CI: 0.59–0.93) respectively over ‘less intensive’ follow up (Jeffery et al., 2007; Tjandra & Chan, 2007). There was a reduction in the time to recurrence and more curative surgical procedures performed in the intensively followed up arm but there is no consensus as to what constitutes ‘intensive’ follow up. A more recent meta-analysis has found that although intensive monitoring resulted in earlier detection of recurrent disease by a median of 10 months, this did not confer any survival advantage over ‘less intensive’ monitoring protocols (Mokhles et al., 2016). Evidence suggests that serum carcinoembryonic antigen (CEA) and CT imaging are the two investigations that have significant potential to detect treatable metastatic recurrence in patients with colorectal cancer. Due to significant heterogeneity in these trials, this guideline is unable to recommend the optimal frequency and duration of follow up investigations.

The FACS trial reported that in patients who had undergone curative surgery for primary colorectal cancer, intensive CT imaging (CT of the chest, abdomen, and pelvis every 6 months for 2 years, then annually for 3 years) or CEA screening (serum CEA every 3 months for 2 years, then every 6 months for 3 years) each provided an improved rate of detected recurrence treatable with curative intent compared with minimal follow-up; there was no additional advantage in combining CEA and CT (Primrose et al., 2014).

5.3 Detection of Metachronous Colorectal Tumours and Polyps
Complete visualization of the colon is recommended prior to curative resection to detect synchronous cancers and adenomas. This can be achieved with optical colonoscopy or CT colonography in most patients. In patients who have undergone emergency resection, the remaining colon and rectum should be visualized within 6 months of surgery. Subsequent colonoscopic surveillance should be performed in accordance with British Society of Gastroenterology guidelines (Cairns et al., 2010).
The 2011 NICE guidelines recommend commencing follow-up 4–6 weeks after potentially curative surgery (National Institute for Health and Care Excellence, 2011). The follow-up should consist of:

1. A minimum of 2 CT scans of the chest, abdomen and pelvis in the first 3 years
2. Regular serum CEA (at least every 6 months in the first 3 years)
3. Surveillance colonoscopy 1 year after initial treatment. Further follow-up would be determined by local guidelines.

Re-investigation should be instituted if there are any clinical, radiological, or biochemical suspicion of recurrent disease. Regular follow-up should cease when the patient and healthcare professionals agree that likely benefits are outweighed by the risks of investigation or the patient cannot tolerate further treatment.

A minimum of two CT scans of the chest, abdomen and pelvis are recommended within the first 3 years of resection.

Recommendation grade B

Regular serum CEA (every 6 months in the first 3 years) could be used in addition to CT with local consensus.

Recommendation grade C

A ‘clean’ colon should be confirmed by colonoscopy or CTC at 1 year and subsequently at 5 yearly intervals.

Recommendation grade C

Follow up should cease in elderly or unfit patients by mutual agreement.

Recommendation grade D

5.4 Provision of Psychological Support

Follow up may be more important in those with social isolation as survival after cancer treatment is worse in those who are unmarried (Nilsen et al., 2008), or those with comorbidities. Thus, cancer-specific mortality is increased in patients with diabetes and colon cancer (Isomura et al., 2006). Patients’ preference is for follow up, but by whom, and where, may depend on local circumstances (Al Chalabi et al., 2014; McFarlane et al., 2012).

All patients should have access to appropriate support throughout the period of follow up.

Recommendation grade C

5.5 Supporting Audit, Clinical Governance and Continuing Professional Development

Audit of clinical outcomes underpins clinical governance. As hospital-specific and surgeon-specific outcome data on colorectal cancer in England and Wales become available in the public domain, accurate, relevant and timely acquisition of data has become a pre-requisite. Audit allows clinicians and MDTs to measure and compare their individual and unit outcomes. These audit data provide units and individuals with information to improve their practice.

Colorectal MDTs should be resourced to provide accurate and timely entry of data to NBOCAP.

Recommendation grade D

5.6 Lifestyle

5.6.1 Impact of physical activity on colorectal cancer recurrence and mortality

Population-based studies have demonstrated risk reduction in colorectal cancer through regular moderate physical activity (Howard et al., 2008; Isomura et al., 2006; Larsson et al., 2006; Nilsen et al., 2008). A meta-analysis reported that engaging in high levels of physical activity prior to the diagnosis of colorectal cancer was associated with a 25% lower cancer-specific mortality compared to those with low levels activities. In addition, survivors who were involved in high levels of physical activity during and after treatment for colorectal cancer lowers the risk of recurrence (Meyerhardt et al., 2006) and mortality (Schmid & Leitzmann, 2014) (Meyerhardt et al., 2006).

There is no consensus regarding the optimal level of physical activity required to achieve these benefits but the Chief Medical Officers from England, Scotland, Wales and Northern Ireland have published recommendations on the frequency and intensity of physical activity required to maintain a healthy lifestyle (Department of Health, 2011).

5.6.2 Impact of diet on colorectal cancer recurrence and mortality

Meyerhardt et al. (2007), reported that those on the highest quintile of a Western dietary pattern had an over 2-fold increased risk of colorectal cancer recurrence and mortality to those on the lowest quintile (Meyerhardt et al., 2007). McCullough et al. suggested that ongoing high consumption of red and processed meat before, and after, the diagnosis of colorectal cancer was associated with a 79% increased risk of cancer specific mortality (McCullough et al., 2013). High carbohydrate intake including sugar-sweetened beverages is
associated with an increased risk of disease recurrence and mortality (Meyerhardt et al., 2012) (Fuchs et al., 2014).

Patients should be encouraged to limit the consumption of red meat, processed meat and refined carbohydrates and observe a low carbohydrate diet.

Recommendation grade C

Advice on physical activity, weight management and diet should be available for cancer survivors during and after treatment.

Recommendation grade C

5.7 Improving Survivorship

The journey for cancer survivors begins at the point of diagnosis and continues beyond the completion of treatment. Survivors may develop a recurrence, a second cancer, metastases or suffer the long-term physical, emotional and psychological effects of cancer treatment. Provision of care for survivors should include cancer surveillance, intervention for consequences of treatment and health promotion.

The National Cancer Survivorship Initiative (NCSI) was set up in 2007 and is a partnership between NHS England and Macmillan Cancer Support. This alliance aims to provide cancer survivors with the necessary care and support to lead healthy and active lives. Further information about how NCSI aims to provide such care and support can be found in the ‘Living with and beyond cancer: Taking action to improve outcomes’ document drawn up in 2013 (Department of Health, 2013).

Key areas where interventions can make a significant difference in survivorship include:

• Structured Holistic Needs Assessment and Care Planning
• Treatment Summaries and Cancer Care reviews
• Patient education and support events (Health and Wellbeing Clinic)
• Advice about, and access to schemes that support people to undertake physical activity and healthy weight management.

A tailored follow-up plan to meet the needs of individuals and stratified according to oncological risk is desirable. This plan may need to be modified during the follow up process, depending on the presence of any ongoing symptoms or toxicities. The Treatment Summary should be generated by the cancer MDT to clarify the individualized follow up plan for the patient and primary care team. Patients who are unlikely to be fit for further invasive therapies could be discharged from secondary care with mutual agreement.

Cancer survivors should have access to information and support from the point of diagnosis.

Recommendation grade D

Individualized care planning, treatment and follow up plan should be developed for cancer survivors according to their needs, stage of their disease and co-morbidities. These should be communicated with patients and primary care.

Recommendation grade D

Conflicts of interest

None of the authors have any conflicts of interest to declare.

References


6 Audit and Outcome Reporting

6.1 Measuring Quality in Colorectal Surgery

Defining quality in colorectal cancer surgery is complex. Single metrics that describe safety or performance fail to adequately describe the complexity of colorectal care (Almoudaris et al., 2013). Meaningful performance measurement is dependent upon a) case-mix adjustment, b) an understanding of volume-outcome effects and c) reliable data sources.

a) Case-Mix Adjustment

Old age and patient co-morbidity significantly increase the likelihood of peri-operative events and mortality. To enable comparison of surgical performance, adjustment must be made for case-mix differences between providers. Scoring systems, such as Charlson (Charlson et al., 1987) and Elixhauser (Elixhauser et al., 1998) are used widely to case-mix adjust models derived from large clinical datasets.

Currently risk stratification models used for comparison of outcomes have limitations as they do not adjust for case mix, including BMI (body mass index) and socio-economic deprivation (Harris et al., 2009; Haydon et al., 2006).

b) Volume-Outcome Effects

Poor outcomes from low volume units/surgeons are difficult to identify due to statistical limitations. Hence funnel-plots are necessary to describe acceptable performance across varying volume ranges (Spiegelhalter, 2005).

c) Data Sources

The main data sources in the United Kingdom are:

6.1.1 Clinical Databases and the National Bowel Cancer Audit (NBOCA)

The National Bowel Cancer Audit (NBOCA) is commissioned by the Healthcare Quality Improvement Partnership (HQIP) delivered by the Health and Social Care Information Centre working in collaboration with the ACPGBI. The data are submitted from various NHS Trusts in the UK and the Republic of Ireland via the Open Exeter system. These data are used to examine variation in surgical practice, to describe outcome following colorectal resections for cancer and to derive predictive models of mortality (Tan et al., 2007; Tekkis et al., 2003; Tilney et al., 2009). Findings are disseminated in an annual report.

6.1.2 Routinely Collected Data

These datasets are primarily collected for administrative purposes but are increasingly used for clinical performance benchmarking. The Hospital Episode Statistics (HES) represents the dataset for NHS England [www.hesonline.nhs.uk] and Information Services Division Scotland (ISD) for Scotland [www.isdscotland.org]. Such databases comprise of clinical codes that relate to diagnoses, procedures and demographic information. These data can be used to examine procedure volumes and basic clinical outcomes, including inpatient mortality rates, readmission rates and length of hospital stay. HES data

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have been linked to other national datasets such as the Office of National Statistics and the Cancer Registry for additional clinical and outcome information, such as out-of-hospital survival and tumour staging. The latter National Cancer Data Repository (NCDR) has recently been used in research studies to compare institutional mortality rates following colorectal surgery in England (Morris et al., 2011). The NCDR can also be linked to the national Radiotherapy Dataset (RTDS) to investigate patterns of management of rectal cancer across the English NHS (Morris et al., 2016).

6.2 Surgeon Level Outcome Reporting

Surgeon level reporting of colorectal cancer surgery outcomes to the UK public was introduced in 2013. Capture of information on patients undergoing planned colorectal resection for cancer (excluding appendiceal neoplasms) are included in analyses. Surgeon level reporting has been spearheaded by Cardiac Surgeons but there are concerns amongst many surgeons that unit level reporting may be more appropriate. The ACPGBI agreed to participate in the process as the Department of Health stated that it would proceed with, or without the involvement of the ACPGBI. There are concerns regarding the quality of data and limitations of their interpretation. There are discrepancies in both information technology infrastructure and the availability of data capture personnel. As of 2013, NHS England (through the Healthcare Quality Improvement Partnership) has published 90-day risk-adjusted mortality figures for colorectal cancer patients undergoing planned surgery on a hospital and surgeon basis. This is based on data submitted to NBOCA.

6.3 Published Outcomes in Elective Colorectal Cancer Surgery

Monitoring of outcomes is required to define acceptable quality of care in elective colorectal cancer surgery. For the reasons already cited comparison can only be made when funnel plots are used to adjust for operative volumes, when data are reliable and when case-mix has been adjusted for. Outcomes for emergency surgery are generally less favourable.

The following figures represent some published outcomes following elective colorectal cancer surgery:

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Mean</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Day Mortality</td>
<td>2.90%</td>
<td>NBOCA</td>
</tr>
<tr>
<td>90 Day Mortality</td>
<td>4.50%</td>
<td>NBOCA</td>
</tr>
<tr>
<td>Length of Stay - Major Resection (days)</td>
<td>Median</td>
<td>NBOCA</td>
</tr>
<tr>
<td>Colon</td>
<td>7</td>
<td>NBOCA</td>
</tr>
<tr>
<td>Rectal</td>
<td>8</td>
<td>NBOCA</td>
</tr>
<tr>
<td>Return to theatre rates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-operation within 28-days of elective colorectal cancer resection</td>
<td>5.90%</td>
<td>Burns et al., 2011</td>
</tr>
</tbody>
</table>

Emergency Readmissions within 90 days:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>18.40%</td>
</tr>
<tr>
<td>Rectal</td>
<td>24.00%</td>
</tr>
<tr>
<td>Permanent Stoma rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>23.0%</td>
</tr>
</tbody>
</table>

5-year Survival:

| Dukes’ A | 93.2% | National Cancer Intelligence Network |
| Dukes’ B | 77.0% |                                    |
| Dukes’ C | 47.7% |                                    |
| Dukes’ D | 6.6%  |                                    |

Surgeons and trusts must make provisions for the prospective collection of accurate clinical data for submission to the National Bowel Cancer Audit (NBOCA).

Recommendation grade B

Conflicts of interest

Omar Faiz has no conflicts of interest to declare.

References


Association of Coloproctology of Great Britain & Ireland (ACPGBI): Guidelines for the Management of Cancer of the Colon, Rectum and Anus (2017) - Pathology Standards and Datasets

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7 Pathology Standards and Datasets

7.1 Background

Information gained from careful and accurate pathological examination of colorectal cancer resections informs prognosis for the patient and their subsequent treatment. It provides quality assurance for radiology, surgery and oncology and can be used for audit and research.

The Royal College of Pathologists (RCPath) dataset for colorectal cancer (3rd edition) (Loughrey et al., 2014) is a comprehensive evidence-based document embracing high quality pathology reporting. The purpose of this chapter is not to duplicate this document but to highlight the key messages to the colorectal MDT about specimen preparation and interpretation of the pathology report.

Many of the changes made in the 6th and 7th editions of TNM staging of colorectal cancer were not evidence-based and the present Royal College of Pathologists recommendation is to continue using TNM5. TNM8 was published in late 2016 and these changes will be adopted within the RCPath dataset from 1 January 2018.

All colorectal cancer resections including local excision specimens should be reported in accordance with the most up to date Royal College of Pathologists dataset.

Recommendation grade C

7.2 Clinical Information Required on the Specimen Request Form

Endoscopy and radiology reports, clinical letters and minutes of MDT discussion are available on the intranet at most NHS trusts. This information is invaluable to the reporting pathologist, especially in the setting of a favourable response to downstaging pre-operative chemoradiotherapy. Nevertheless it is good practice to include the following on the specimen request form.

- Nature of the resection and type of tumour
- In complex cases a diagram of the surgical findings and the procedure undertaken
- Whether the tumour was detected as part of a bowel cancer screening programme
- Histological type of the tumour on diagnostic biopsy
- Whether there is a history of chronic idiopathic inflammatory bowel disease or a relevant family history of colorectal cancer, or any other Lynch-syndrome associated cancers
- Preoperative clinical/radiological stage of the tumour
- If the patient received preoperative therapy
- If open, laparoscopic or robotic surgery has been performed
- The type and dissection plane of operation attempted e.g. type of abdominoperineal excision (APE) and type of local excision
- Whether the patient is receiving treatment within a clinical trial
Relevant clinical information needs to be included in the specimen request form.

**Recommendation grade D**

### 7.3 Preparation of Specimens before Dissection

Specimens should ideally be sent fresh and unopened, as soon as possible, after surgical resection. However, in practice this is often the exception. If not delivered fresh to the laboratory or a delay is anticipated, the specimen should be placed unopened in a large volume of formalin.

The specimen should not be opened in theatre as this compromises assessment of both the circumferential resection margin and serosal involvement.

**Recommendation grade C**

### 7.4 Specimen Handling

For anterior resection (AR) and APE specimens, the plane of the surgical dissection is evaluated (Appendix A) and photographs taken of the intact specimen to support this evaluation. The circumferential (non-peritonealized) surgical resection margin in the vicinity of the tumour is inked to enable subsequent identification of margin involvement. This is not limited to rectal cancers and should include colon cancers with associated circumferential colonic (non-peritonealized) resection margins, such as caecal and ascending colon tumours. The bowel is opened anteriorly above and below the tumour prior to further fixation. For small and polypoid tumours it is acceptable to open the bowel at the level of the tumour, as long as this does not compromise further assessment.

After fixation, macroscopic features are recorded and the tumour is sectioned at 3–4 mm transverse sections to produce slices that include the tumour, adjacent lymph nodes, serosa and circumferential resection margins (CRM). Photography of these slices is recommended to provide a permanent record and to complement the verbal pathology report at the MDT meeting.

The dataset recommends a minimum number of blocks to be taken in order to satisfactorily assess the microscopic pathological features. More diligent sampling is described for rectal tumours that have undergone preoperative therapy in which no residual tumour is identified macroscopically.

As many lymph nodes as can be found in a specimen should be examined histologically. The standard of lymph node retrieval is judged by a median of at least 12 per specimen. The highest lymph node is the first node identified by sectioning serially and distally from the vascular tie.

The number of lymph nodes retrieved should be a median of at least 12 per specimen.

**Recommendation grade B**

### 7.5 Core Data Items

#### 7.5.1 Macroscopic core data items

- Nature of specimen and type of operation
- Site of tumour
- Maximum tumour diameter
- Distance to the nearest longitudinal margin
- Tumour perforation
- Relation of tumour to the peritoneal reflection (rectal tumours only)
- Grade of the plane(s) of surgical excision (AR and APE specimens; Appendix A)
- Distance of the tumour from the dentate line (for APE specimens only)

Rectal cancer seldom spreads distally below the palpable edge of the tumour. It is only necessary to examine the longitudinal margins histologically if the tumour extends macroscopically to within 30 mm of one of these margins. An exception is a poorly differentiated tumour at biopsy, which can spread distally. The proximal doughnut is of no relevance and there is no need to send the distal doughnut, unless there is a question of distal involvement.

For AR and APE specimens, the quality of the resection is graded and continual feedback at the time of the MDT using the photographs taken of the intact specimen, is valuable in improving surgical quality and clinical outcomes (Bosch & Nagtegaal, 2012).

Tumour perforation is defined macroscopically as a visible defect through the tumour and is regarded as pT4b in the TNM5 staging system. Localized perforation through the tumour onto the circumferential resection margin is also staged as pT4b and not pT3.

Distance of tumour from the dentate line in abdominoperineal excision (APE) specimens should be documented for audit.

**Recommendation grade C**

The quality of TME in rectal cancer resections should be recorded with supporting photographic documentation.

**Recommendation grade B**

#### 7.5.2 Microscopic core data items

- Histological tumour type
- Histological differentiation
- Maximum extent of local invasion (pT stage) and maximum distance of extramural spread
Grade of tumour regression following preoperative (neoadjuvant) therapy

Resection margins (longitudinal and circumferential margins)

Lymph node status (number present, number involved, highest lymph node status)

Venous invasion

Histologically confirmed distant metastatic disease

Background abnormalities to include polyps, inflammatory bowel disease and polyposis syndromes

Tumour differentiation is based on architecture, specifically gland or tubule formation, and is assessed on the predominant pattern. Morphological assessment of differentiation applies only to adenocarcinoma of no specific type. Poorly differentiated adenocarcinomas are separated from well/moderately differentiated adenocarcinomas. Poorly differentiated tumours which are found to be mismatch repair deficient, and therefore have a better prognosis, are not graded.

The depth of tumour invasion beyond the outer border of the muscularis propria is an important prognostic factor, especially in rectal cancers. This distance, measured in millimeters, is reported when applicable.

The maximum degree of local invasion into or through the wall is based on the criteria for pT staging in the TNM5 staging system with pT4a sub-stage denoting invasion of adjacent organs and pT4b representing involvement of the serosal surface. Although the pT4 substages were reversed in TNM7, the RCPath guidelines continued to use TNM5 terminology in order to maintain consistency. It is accepted that some MDTs are using the TNM7 staging system for colorectal cancer and, if agreed locally, the pathology report should include both the TNM5 and TNM7 stages, clearly indicated as such. When TNM8 is adopted the pT4 sub classification will mirror TNM7.

A four tier system is recommended to assess the response to preoperative therapy:

- No viable tumour cells
- Single cells or scattered small groups of cancer cells
- Residual cancer outgrown by fibrosis
- Minimal or no regression

Following preoperative therapy, only the presence of tumour cells is used to determine the stage. Fibrosis, inflammation, necrosis or acellular mucin is ignored. Cases with complete pathological response are recorded as ypT0 ypN0 and Dukes’ staging is not applicable in this setting.

Involvement of the CRM, defined as ≤1 mm, is predictive of local recurrence and poor survival in rectal cancers. This should also be recorded in colonic tumours, particularly the cecum and ascending colon. Involvement is not restricted to direct continuity with the main tumour, but also includes tumour in veins, lymphatics, lymph nodes and discontinuous deposits.

Extramural deposits of tumour that have no lymph node structure and are not obviously within blood vessels are regarded as lymph node deposits that have completely effaced the original lymph node if they measure ≥3 mm in diameter, according to the TNM5. Smaller deposits are regarded as discontinuous extension of the main tumour and staged under the pT system. pN1 corresponds to involvement of 1–3 nodes and pN2 in involvement of four or more nodes. TNM6 and TNM7 recommended major changes to the definitions of lymph node involvement, particularly in relation to interpreting mesenteric discontinuous tumour deposits lacking identifiable lymph node or vascular structure. These changes are not evidence-based and are poorly reproducible, but more importantly can destabilize historical staging data and longitudinal analyses. For these reasons the RCPath continue to recommend TNM5 for colorectal cancer reporting.

There is now consistent evidence to show that the biology and outcome of tumour deposits is not equal to lymph node involvement or extramural venous invasion (EMVI) (Nagtegaal et al., 2016). Work on this is ongoing, therefore classifying patients with tumour deposits as pN1c has merits and this is reflected in TNM8.

It is well established that EMVI is an independent prognostic marker. There is conflicting evidence on the importance of intramural (intramuscular or submucosal) venous spread. Therefore all levels of venous invasion are included in the dataset. Frequency of venous invasion, including intramural and extramural should be at least 30%.

TNM5 is used for reporting of colorectal cancer. If TNM7 is used, it should be in addition to TNM5 and be clearly documented in the report.

Recommendation grade D

TNM8 will be implemented within the RCPath dataset from 1 January 2018 onwards.

Recommendation grade D

The circumferential resection margin (CRM) should be routinely recorded, as involvement of CRM is associated with a poor prognosis (≤1 mm).

Recommendation grade B

Detection rate of venous invasion should be regularly audited.

Recommendation grade C
7.6 Immunohistochemical and Molecular Investigations

Mismatch repair (MMR) deficient (or microsatellite instability-high, MSI-H) tumours account for approximately 14% of all colorectal cancers. The majority are due to sporadic mutations but 2–3% of tumours are due to a germline MMR gene mutation indicating patients with underlying Lynch syndrome. There is evidence to suggest that MMR deficient tumours have a better prognosis than MMR proficient tumours, particularly in Dukes’ B disease, and that MMR status may also have predictive significance with respect to benefit of adjuvant chemotherapy.

MMR status can be evaluated by immunohistochemistry and is considered a core dataset item in the following circumstances:

- Diagnosis of colorectal cancer at age less than 50 years
- Assessment of prognosis is important
- Poorly differentiated or mucinous tumours
- Presence of other morphological features suggesting possible MMR deficiency
- On request by oncologist or geneticist


Mutation status in exons 2, 3 and 4 of both KRAS and NRAS genes informs anti-epidermal growth factor receptor therapy and prognosis. BRAF V600E mutation predicts for a poor prognosis and also represents a potential target for double treatment with anti BRAF and EGFR therapies. Molecular analysis is listed under non-core data items.

Mismatch repair (MMR) status testing is recommended in all patients with colorectal cancer.

Recommendation grade C

7.7 Pathological Staging

Tumours are classified as R0 if completely excised at the longitudinal and circumferential resection margins and as R1 if there is microscopic involvement. R2 or macroscopic margin involvement should be correlated with the intra-operative findings at the multi-disciplinary team meeting. R2 status is not confined to the primary tumour resection but also for metastatic disease.

The TNM staging definitions are shown in Appendix B. The prefix ‘p’ is used to denote pathological staging. If preoperative chemotherapy and/or radiotherapy have been given the prefix ‘yp’ should be used. Pathological M staging can only be based on metastatic disease that has been submitted for histology. Involved lymph nodes distant from the main tumour or its main artery in the specimen are regarded as pM1.

The Dukes’ and Bussey modification of the original Dukes’ classification of resection specimens is recommended:

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dukes’ A</td>
</tr>
<tr>
<td>tumour limited to the bowel wall, lymph nodes not involved</td>
</tr>
<tr>
<td>Dukes’ B</td>
</tr>
<tr>
<td>tumour spread beyond the muscularis propria, lymph nodes not involved</td>
</tr>
<tr>
<td>Dukes’ C1</td>
</tr>
<tr>
<td>lymph node(s) involved but highest lymph node spared</td>
</tr>
<tr>
<td>Dukes’ C2</td>
</tr>
<tr>
<td>highest lymph node involved</td>
</tr>
</tbody>
</table>

Turnbull added Stage D to Dukes’ classification to denote the presence of distant metastatic disease.

The proforma for colorectal cancer resection specimens to include the macroscopic and microscopic data discussed above is shown in Appendix C.

7.8 Reporting of Local Excision Specimens

Local excision of colorectal cancer is undertaken either as a curative procedure for early (T1) colorectal cancer or as a palliative procedure in debilitated patients. The principles of pathological reporting are the same as in major resections. However in local excisions of early cancers with curative intent a number of features require special attention because they are used to determine the necessity for more radical surgery. This includes the assessment of completeness of excision and parameters that predict the presence of lymph node metastatic disease.

The best pathological information is derived when specimens are excised intact in their entirety. Polypoid lesions on a narrow stalk can be fixed intact while semipedunculated or sessile lesions are pinned out, mucosal surface upwards, on a small piece of cork or other suitable surface. Piecemeal removal of tumours is acceptable for palliative resections.

A template proforma for reporting local excision specimens is included (Appendix D). The core data items to be recorded are:

- Specimen type
- Site of tumour
- Overall specimen size (usually polyp size)
- Histological tumour type
• Histological differentiation
• Extent of local invasion (including depth and width of invasive component)
• Lymphatic invasion
• Venous invasion
• Presence of background adenoma
• Margin involvement by carcinoma (deep and peripheral)
• Minimum deep margin clearance of the invasive carcinoma
• pT stage

The Kikuchi system for sessile tumours and the Hag-gitt system for polypoid lesions provide prognostic information, particularly risk of lymph node involvement. However neither system is easy to apply in routine practice, especially if there is fragmentation or suboptimal orientation. Kikuchi level requires the presence of muscularis propria to accurately divide the submucosa into thirds. It has been proposed that depth of invasion beyond the muscularis mucosae and width of the invasive tumour provide more objective evidence of potential lymph node metastatic disease. On current evidence a firm recommendation cannot be made for one method of assessing the extent of local invasion and all four approaches are included in the proforma dataset.

Submucosal lymphatic invasion and, to a lesser extent, venous invasion in pT1 colorectal cancer are strong predictors of lymph node involvement. Lymphatic and venous invasion should therefore be assessed separately and only recorded as positive if the features are considered definitive.

Involvement of the deep resection margin and mucosal resection margin by invasive tumour should be recorded. There is controversy over what degree of clearance is acceptable in tumours that extend close to the deep margin. Until there is further evidence, tumour less than 1 mm from the deep resection margin is considered involved. This should trigger consideration of further therapy, which may be endoscopic examination and possible re-excision of the polypectomy site.

The assessment of pT1 cancers can be difficult and it is recommended that all pT1 cancers are reported by two consultant pathologists.

Recommendation grade D

Conflicts of interest
Philip Quirke has been a consultant to Amgen, Roche diagnostics prognostic markers, HalioDx immunological markers,

Bowel Cancer Concern, NHSBCSP, Royal College of Pathologists. The other authors have no conflicts of interest to declare.

References

Appendix A:
Plane of Mesorectal Excision (AR and APE)

Plane Description

Mesorectal: The mesorectum should be smooth with no violation of the fascial covering. There should be a good bulk to the mesorectum both anteriorly and posteriorly, and the distal margin should appear adequate with no coning near the tumour. Any defect should not be more than 5 mm deep.

Intramesorectal: There should be a moderate bulk to the mesorectum with minor irregularity of the mesorectal surface. A moderate degree of coning of the specimen may be seen towards the distal margin. Importantly, the muscularis propria should not be visible, except at the area of insertion of levator muscles at the very distal aspect. There will be moderate irregularity of the CRM.

Muscularis propria: There will be substantial areas where mesorectal tissue is missing with deep cuts and tears down onto the muscularis propria. On
cross-sectional slicing, the CRM will be very irregular and formed by the muscularis propria in places.

**Plane of Excision of the Levators/Sphincters (APE only)**

**Plane Description**

*Extralevator:* The surgical plane lies external to the levator ani muscles, which are removed *en bloc* with the mesorectum and anal canal. This creates a more cylindrical-shaped specimen with the levators forming an extra protective layer above the sphincters. There should be no significant defects into the sphincter muscles or levators.

*Sphincteric:* Either there are no levator muscles attached to the specimen or only a very small cuff, and the CRM is formed by the surface of the sphincter muscles. There should be no deviations into the sphincter muscle themselves. The specimen shows coning at the level of the puborectalis muscle resulting in the classical surgical waist.

*Intra-sphincteric/submucosal/perforation:* The surgeon has inadvertently entered the sphincter muscle or even deeper into the submucosa. Perforations of the specimen at any point below the peritoneal reflection should also be classified into this group.

### Appendix B:

TNM classification of colorectal tumours

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT</td>
<td>Primary tumour</td>
</tr>
<tr>
<td>pT0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>pT1</td>
<td>Tumour invades submucosa</td>
</tr>
<tr>
<td>pT2</td>
<td>Tumour invades muscularis propria</td>
</tr>
<tr>
<td>pT3</td>
<td>Tumour invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissues</td>
</tr>
<tr>
<td>pT4</td>
<td>Tumour directly invades other organs or structures (pT4a) and/or perforates visceral peritoneum (pT4b)</td>
</tr>
<tr>
<td>pN</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>pN0</td>
<td>No regional lymph node metastatic disease</td>
</tr>
<tr>
<td>pN1</td>
<td>Metastatic disease in 1 to 3 regional lymph nodes</td>
</tr>
<tr>
<td>pN2</td>
<td>Metastatic disease in 4 or more regional lymph nodes</td>
</tr>
<tr>
<td>pM</td>
<td>Distant metastatic disease</td>
</tr>
<tr>
<td>pM0</td>
<td>No distant metastatic disease</td>
</tr>
<tr>
<td>pM1</td>
<td>Distant metastatic disease</td>
</tr>
</tbody>
</table>
## Appendix C  Reporting proforma for colorectal carcinoma resection specimens

<table>
<thead>
<tr>
<th>Specimen:</th>
<th>Tumour Involvement of margins:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total colectomy [ ]</td>
<td>N/A</td>
</tr>
<tr>
<td>Subtotal colectomy [ ]</td>
<td>N/S</td>
</tr>
<tr>
<td>Right hemicolectomy [ ]</td>
<td>Yes</td>
</tr>
<tr>
<td>Transverse colectomy [ ]</td>
<td>No</td>
</tr>
<tr>
<td>Left hemicolectomy [ ]</td>
<td>N/S</td>
</tr>
<tr>
<td>Anterior resection [AR] [ ]</td>
<td>Yes</td>
</tr>
<tr>
<td>Sigmoid colectomy [ ]</td>
<td>No</td>
</tr>
<tr>
<td>Hartmann’s procedure [ ]</td>
<td>Yes</td>
</tr>
<tr>
<td>Abdominopereineal excision [APE] [ ]</td>
<td>No</td>
</tr>
<tr>
<td>Other (state) [ ]</td>
<td>N/S</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of tumour:</th>
<th>Number of involved lymph nodes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caecum [ ]</td>
<td>(pN1: 1–3 nodes. pN2: 4+ nodes involved)</td>
</tr>
<tr>
<td>Right (ascending) colon [ ]</td>
<td></td>
</tr>
<tr>
<td>Hepatic flexure [ ]</td>
<td></td>
</tr>
<tr>
<td>Transverse colon [ ]</td>
<td></td>
</tr>
<tr>
<td>Splenic flexure [ ]</td>
<td></td>
</tr>
<tr>
<td>Left (descending) colon [ ]</td>
<td></td>
</tr>
<tr>
<td>Sigmoid colon [ ]</td>
<td></td>
</tr>
<tr>
<td>Rectum [ ]</td>
<td></td>
</tr>
<tr>
<td>Unknown [ ]</td>
<td></td>
</tr>
</tbody>
</table>

| Maximum tumour diameter:   |                                 |
|                           | mm                               |

<table>
<thead>
<tr>
<th>Distance of tumour to nearer longitudinal margin:</th>
<th>mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour perforation (pT4): Yes [ ] No [ ]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For rectal tumours:</th>
<th>Deepest level of venous invasion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relation of tumour to peritoneal reflection: (tick one):</td>
<td>None [ ] Submucosal [ ] Intramuscular [ ] Extramural [ ]</td>
</tr>
<tr>
<td>Above [ ] A stride [ ] Below [ ]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plane of mesorectal excision (AR and APE):</th>
<th>Histologically confirmed distant metastatic disease:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal [ ]</td>
<td>Yes (pM1) [ ] No (pM2) [ ]</td>
</tr>
<tr>
<td>Sigmoid [ ]</td>
<td>If yes, site(s):</td>
</tr>
<tr>
<td>Other (state) [ ]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plane of resection of the sphincters (APE only):</th>
<th>Separate abnormalities:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extralevator [ ] / Spincteric [ ] / Intrasphincteric [ ]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For APE specimens:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance of tumour from dentate line: mm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour type:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma [ ]</td>
<td>Yes [ ] No [ ]</td>
</tr>
<tr>
<td>If no, or variant (e.g. mucinous), specify</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Differentiation by predominant area:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Well/moderate [ ]</td>
<td></td>
</tr>
<tr>
<td>Poor [ ]</td>
<td></td>
</tr>
<tr>
<td>Not applicable [ ]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For pT4 tumours:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes [ ]</td>
<td>No [ ]</td>
</tr>
<tr>
<td>Tumour cells breach the serosa (pT4b) [ ]</td>
<td></td>
</tr>
<tr>
<td>Tumour invade adjacent organs (pT4a) [ ]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maximum distance beyond muscularis propria:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A (if intramural tumour) [ ]</td>
<td></td>
</tr>
<tr>
<td>Distance mm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre-operative therapy given:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes [ ]</td>
<td>No [ ]</td>
</tr>
<tr>
<td>Not known [ ]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response (if pre-operative therapy given):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No viable tumour cells [ ]</td>
<td></td>
</tr>
<tr>
<td>Single cells or scattered small groups of cancer cells [ ]</td>
<td></td>
</tr>
<tr>
<td>Residual cancer outgown by fibrosis [ ]</td>
<td></td>
</tr>
<tr>
<td>Minimal or no regression (extensive residual tumour) [ ]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complete resection (by &gt;1 mm) at all margins:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (R0) [ ]</td>
<td>No (R1) [ ]</td>
</tr>
<tr>
<td>No (R2) [ ]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TNM (5th edition): (y)pT (y)pN (y)pM</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Dukes stage:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dukes A (limited to m. propria, nodes negative) [ ]</td>
<td></td>
</tr>
<tr>
<td>Dukes B (beyond m. propria, nodes negative) [ ]</td>
<td></td>
</tr>
<tr>
<td>Dukes C1 (nodes positive; highest node negative) [ ]</td>
<td></td>
</tr>
<tr>
<td>Dukes C2 (highest node positive) [ ]</td>
<td></td>
</tr>
<tr>
<td>Stage D (histology proven distant metastasis) [ ]</td>
<td></td>
</tr>
<tr>
<td>N/A (no tumour OR no lymph nodes identified) [ ]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mismatch repair immunohistochemistry:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Performed: Yes [ ]</td>
<td>No [ ]</td>
</tr>
<tr>
<td>Result: Normal [ ]</td>
<td>Equivocal [ ]</td>
</tr>
<tr>
<td>Abnormal [ ]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If equivocal/abnormal, specify:</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Signature:</th>
<th>Date:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>/</td>
</tr>
<tr>
<td>SNOMED codes:</td>
<td>T</td>
</tr>
</tbody>
</table>

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### Appendix D  Reporting proforma for colorectal carcinoma local excision specimens

<table>
<thead>
<tr>
<th>Surname:</th>
<th>Forenames:</th>
<th>Date of birth:</th>
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<tr>
<td>Hospital:</td>
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<td>Date of surgery:</td>
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<td>Date of receipt:</td>
<td>Pathologist:</td>
<td>Surgeon:</td>
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**Specimen type:**
- Polyectomy
- Endoscopic mucosal resection (EMR)
- Endoscopic submucosal dissection (ESD)
- Transanal endoscopic microsurgical (TEMS) excision
- Other

**Site of tumour:**
- Caecum
- Right (ascending) colon
- Hepatic flexure
- Transverse colon
- Splenic flexure
- Left (descending) colon
- Sigmoid
- Rectosigmoid
- Rectum
- Unknown

**Size of specimen (maximum width):** mm  Not assessable

**Comments:**

---

**Tumour type:**
- Adenocarcinoma  Yes  No
- If no, or variant (e.g. mucinous), specify

**Differentiation by worst area:**
- Well/moderate
- Poor
- Not applicable

**Local invasion:**
- Submucosa (pT1)
- Muscularis propria (pT2)
- Beyond muscularis propria (pT3)

**For pT1 tumours:**
- Maximum depth of invasive tumour from muscularis mucosae mm
- Width of invasive tumour mm
- Haggitt level (polypoid tumours):
  - 1
  - 2
  - 3
  - 4
  - Not applicable

**Kikuchi level ( sessile tumours):**
- sm1
- sm2
- sm3
- Not applicable

**Lymphatic Invasion:**
- Not identified
- Present

**Deepest level of venous invasion:**
- None
- Submucosal
- Intramuscular
- Extramural

**Neoadjuvant therapy given:**
- Yes
- No
- Not known

**Response (if neoadjuvant therapy given):**
- No viable tumour cells
- Single cells or scattered small groups of cancer cells
- Residual cancer outgrown by fibrosis
- Minimal or no regression (extensive residual tumour)

**Background adenoma:**
- Yes
- No

**Involvement of margins by carcinoma:**
- Peripheral margin
- Deep margin
  - (*) Not assessable is appropriate if specimen received piecemeal

**Histological measurement from carcinoma to nearest deep excision margin mm**

**Pathological staging:**
- Complete resection (by >1 mm) of carcinoma at all margins:
  - Yes (R0)
  - No (R1)
  - No (R2)
  - Not assessable

**Mismatch repair immunohistochemistry**
- Performed:
  - Yes
  - No

**Result:**
- Normal
- Equivocal
- Abnormal

If equivocal/abnormal, specify

**Signature:**

Date  / /  
SNOED codes T / M
8.1 Background

In these guidelines, anal cancer refers specifically to squamous cell carcinoma (SCC) of the anus. The key recommendations from the ACPGBI position statement for the management of anal cancer (Lindsey, 2011) are referenced here.

Although anal cancer remains an uncommon tumour, its incidence has increased significantly in the past 20 years (Wilkinson et al., 2014) and is now ~1.2 per 100 000 population, with 1233 new cases diagnosed in the UK in 2013 (Cancer Research UK). There is a female preponderance, with a female to male ratio of 1.8:1. Human papillomavirus (HPV) infection is the main predisposing factor in 90% (Frisch et al., 1997), with subtype 16 and 18 found in 81% and 4% of tumours (Alemany et al., 2015). The presence of HIV or other causes of immunosuppression may accelerate anal cancer development.

Anal cancers are sub-divided into anal canal and anal margin tumours (within 5 cm radius of anal orifice). Anal canal SCCs have different patterns of locoregional spread to low rectal adenocarcinomas and are staged and treated differently. Anal margin SCCs arise from the hair-bearing skin, distal to the anal verge. However, the distinction between anal canal and anal margin may not be possible when a patient presents with a locally advanced tumour involving both sites.

8.2 Anal Cancer Multidisciplinary Team (MDT)

Anal cancer requires a specialist MDT approach to deliver appropriate treatment and optimize outcomes (Renehan & O’Dwyer, 2011a). In 2004 regional Anal Cancer MDTs were established within each cancer network (NICE, 2004). The underlying principles have been maintained for NHS Commissioning from 2013 onwards (NHS England, 2013). The agreed Anal Cancer MDT...
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8.3 Investigations

8.3.1 Presentation and diagnosis
Anal cancer may present with pain, bleeding, discharge, mass and occasionally tenesmus or sepsis. These symptoms may be mistaken for other benign conditions, resulting in delayed referral. Pelvic or perineal sepsis with, or without, fistula formation is sometimes seen with advanced tumours.

Among men who have sex with men (MSM), and who are HIV positive, the incidence is approximately 80 per 100 000 population in the modern highly active antiretroviral therapy (HAART) era. Amongst MSM who are HIV negative, risk remains increased compared with the general population (approximately 5 per 100 000 population) (Machalek et al., 2012). Despite these increased risks, HIV positive patients account for <10% of all anal cancer patients.

The role of routine testing of all patients with newly diagnosed anal cancer for HIV infection remains debated. In the practice of most Anal Cancer MDTs, HIV positive patients account for a small proportion of anal cancers and most will already have been diagnosed prior to developing cancer. However, identifying a patient to be HIV positive prior to commencing CRT may enable optimal management of both conditions. The NCRI PLATO trial mandates routine HIV testing of all potentially eligible patients.

Female patients should have up to date cervical cancer screening PAP smears prior to commencement of treatment if possible, due to the strong association with HPV infection.

A history of cigarette smoking is also relevant and patients should be encouraged to stop prior to commencement of treatment, as continued smoking is associated with poorer treatment outcomes (Linam et al., 2012; Ramamoorthy et al., 2008).

The median age of patients diagnosed with anal cancer is 60 years and 20% are 75 years or older. Therefore it is important to assess performance status and co-morbidities, particularly renal and cardiac conditions. Some patients will be unfit to tolerate the full standard treatment options and appropriate modification of treatment protocols will be required.

All patients with newly diagnosed anal cancer should have detailed assessment of co-morbidity and performance status to plan treatment.

Recommendation grade D

HIV testing should be routinely considered. For known HIV-positive patients, up to date assessment of immune status (viral load and CD4 count) should be obtained.

Recommendation grade C

Female patients should have up to date cervical cancer screening PAP smears.

Recommendation grade D

8.3.2 Pre-treatment assessment and staging
The current AJCC-UICC TNM 7th edition staging system should be used (Brierley et al., 2010). The T stage is based on size (T1: ≤2 cm, T2: >2 to 5.0 cm, T3 >5 cm) and in T4 tumours, invasion of adjacent organs such as vagina, urethra and bladder. Sphincter involvement does not constitute T4 disease. The N stage reflects the pattern of lymphatic spread (N1: mesorectal nodes, N2: unilateral internal iliac or/and inguinal nodes, N3: mesorectal and inguinal, or bilateral internal iliac or bilateral inguinal nodes). Less than 15% of patients have distant metastases at diagnosis. The TNM 8th edition was published in December 2016 (Brierley et al., 2016), but will only be implemented on 1st January 2018. The main change is that tumours of the anal margin and perianal skin, defined as within 5 cm of the anal margin will be classified with carcinomas of the anal canal.

Anal cancers should be routinely staged by detailed clinical assessment, magnetic resonance imaging (MRI) of the pelvis, computed tomography (CT) of the chest, abdomen and pelvis. The additional use of 18-
fluorodeoxyglucose positron emission tomography (18F-FDG PET/CT) can improve locoregional lymph node and metastatic staging, as well as aid radiotherapy planning (Jones et al., 2015). Endoscopic ultrasound (EUS) may provide better delineation of small T1 tumours (Otto et al., 2009) compared with MRI.

8.3.2.1 Detailed clinical assessment
A detailed clinical evaluation is mandatory to establish the size and exact location in relation to the anal verge and rectum, the degree of anal canal circumference involvement and its effect on sphincter and bowel function. Vaginal examination should be performed in females. Approximately 30% of patients will have palpable inguinal lymph nodes at presentation but up to half may be reactive to an inflammatory or infectious process. Patients who are unable to tolerate digital rectal examination should have examination under anaesthetic (EUA) for local disease assessment and biopsy.

8.3.2.2 Imaging
- **MRI pelvis:** For locoregional staging. Similar MRI sequences to those used for low rectal cancers should be utilized with pelvic phased array coils centred for the anal canal and including the anorectal junction/lower rectum. Recommendations for cross-sectional imaging in colon, rectum and anal cancer (second edition) have been published by the Royal College of Radiologists (The Royal College of Radiologists, 2014).
- **CT chest, abdomen and pelvis with intravenous iodinated contrast agent:** For detection of distant metastases. Both CT and MRI will detect enlarged pelvic side-wall and inguinal lymph nodes with similar accuracy, but MRI is better at characterizing mesorectal lymph nodes.
- **18F-FDG PET/CT:** For tumours at higher risk for lymph node and distant metastases (>T2). FDG PET/CT detects sites of lymph node involvement and distant metastases, which were not obvious on MRI or CT (Saboo et al., 2013) and can influence management in up to 29% of cases (Wells & Fox, 2012), particularly for defining gross tumour volume for radiotherapy planning. A recent systematic review and meta-analysis reported that whilst FDG PET/CT is highly specific (pooled estimate 90%) for detecting involved lymph nodes, the major concern is that it lacks sensitivity (pooled estimate 56%) (Caldarella et al., 2014). The NCCN Anal Carcinoma Guidelines 2016 (National Comprehensive Cancer Network, 2016) state that although routine use of 18F-FDG PET/CT has not yet been validated, it should be considered for all tumours in addition to diagnostic CT.
- **Endoscopic ultrasound (EUS):** EUS can assess the depth of invasion and relation to the anal sphincter muscles, particularly in small tumours. However this additional information is unlikely to aid the management of most anal cancers.
- **Inguinal lymph nodes:** Enlarged inguinal lymph nodes may be metastatic or reactive. Involved inguinal lymph nodes can be detected by clinical and radiological features, and in equivocal cases, fine needle aspiration (FNA) may be beneficial if it demonstrates SCC. These develop in 16–36% of patients (Gerard et al., 2001). Involved lymph nodes tend to be hard, irregular and can become fixed to underlying muscle or skin when extracapsular spread occurs. However, over 40% of involved lymph nodes measure <5 mm in diameter (Wade et al., 1989) and are clinically undetectable, even on 18F-FDG PET/CT. Conversely, enlarged (>1 cm short axis) lymph nodes may be reactive or metastatic.

Ultrasound assessment with or without fine needle aspiration (FNA) should be performed when management is dependent on knowing the nature of an enlarged lymph node (Esen, 2006). However, this may not be necessary if the lymph node is avid on 18-FDG PET/CT or there is high clinical suspicion of involvement, based on MRI characteristics. The staging and management of inguinal lymph nodes was reviewed in the ACPGBI Position Statement for Anal Cancer (Branagan, 2011). Sentinel node biopsy is not an established staging tool in patients with anal cancer.

Routine staging should consist of a detailed clinical assessment, MRI pelvis and CT chest, abdomen and pelvis. The use of 18F-FDG PET/CT in addition, should be considered, if available, for all patients with ≥T2 tumours and are suitable for radical chemoradiotherapy (CRT).

**Recommendation grade C**

The AJCC/UICC TNM staging system should be used. The current version is the 7th edition, but will this be replaced by the 8th edition on 1 January 2018.

**Recommendation grade D**

8.4 Treatment
The presentation of anal cancer can range from small, superficial tumours to large, extensively infiltrative tumours, involving multiple groups of pelvic lymph nodes. The aim of treatment is to achieve best oncological outcomes, in terms of locoregional disease control and overall survival at minimal cost, in terms of acute and late morbidity and treatment-related mortality.

Standard treatment for most patients with anal cancer is definitive chemoradiotherapy (CRT). The main purpose of using CRT in patients with smaller tumours, not
amenable to local excision, is to avoid major resection with stoma and to preserve anal sphincter function. At the opposite end of the spectrum, CRT offers potential cure to patients with surgically unresectable tumours, whilst retaining satisfactory sphincter function in most cases.

8.4.1 Surgery

8.4.1.1 Wide local excision

Local excision alone may adequately treat small (T1) tumours at the anal margin and can achieve good local control (Namiq et al., 2016; Wielfeldt & Thiele, 2009). The tumour should be excised with a margin of normal perianal skin and deeper tissue. On the deeper aspect a small portion of the distal internal anal sphincter may be removed to achieve an adequate margin. Where sphincter resection is considered necessary, patients should be warned of a risk of impaired continence. Small wounds may be left open whereas larger defects may require some form of advancement or rotational flap to cover. This should ideally be performed by an anal cancer MDT surgeon, following agreement within the MDT to attempt a complete excision.

In locally excised anal margin tumours, the minimum safe margin of excision is unknown, as there have been no published studies on this topic. To address this uncertainty, recruitment to ACT 3 (incorporated in the over-arching PLATO trial) is encouraged. This is a non-randomized phase II trial designed to determine if patients with ≤1 mm margins following local excision of anal margin tumours, who receive additional low-dose CRT, have acceptably low rates of locoregional failure.

On the other hand, anal canal SCCs are technically more difficult to excise due to their site, it is especially difficult to obtain adequate deep margin clearance without compromising continence (Namiq et al., 2016). Therefore, any attempt at local excision of an anal canal cancer should be regarded as more likely to represent a generous diagnostic biopsy rather than being a curative procedure. If the histology is reported as invasive SCC with a margin ≤1 mm, adjuvant CRT should be considered. Polypoid anal canal lesions can often be macroscopically locally excised for histological assessment, which may sometimes contain a focus of invasive SCC. Providing the excision margin appears adequate (>1 mm), careful surveillance may be performed.

There is an emerging entity known as SISCCA (superficially invasive squamous cell carcinoma of the anus) defined by an invasive lesion completely excised with ≤3 mm stromal invasion and ≤7 mm superficial spread (Arana et al., 2015). In carefully considered cases, with a clear surveillance plan, there may be a role for watch and wait in these patients.

8.4.1.2 Abdominoperineal excision

Abdominoperineal excision (APE) is no longer the primary treatment of choice for most anal cancers, not amenable to local excision (Northover, 1991). There are a small number of indications for APE as primary treatment: (i) when radiotherapy is contraindicated (for example, previous prostate or cervical radiotherapy), (ii) when the patient is unfit for CRT but deemed fit for a ‘once-only’ operation, or (iii) the patient declines CRT.

8.4.1.3 Formation of pre-treatment stomas

Patients with advanced tumours may need a defunctioning stoma prior to commencing treatment. Definite indications include bowel obstruction, significant incontinence, fistulation and peri-anal sepsis. Relative indications, such as vaginal invasion, severe tenesmus or severe defaecating pain are to improve the probability of the patient completing CRT with no unplanned treatment interruptions. Pre-treatment stomas are rarely required in patients with tumours ≤5 cm (Cooper et al., 2012) but above 5 cm, the necessity increases exponentially with size (Beaumont et al., 2012).

Despite achieving complete tumour response following completion of CRT the reversal rate of pre-treatment stomas is generally low (Cooper et al., 2012; Glynne-Jones et al., 2014a). These patients often have extensive destruction of the normal sphincter anatomy, as well as fibrosis and stenosis of the anal canal. Therefore, the type of stoma that is formed should be made with the knowledge that it is likely to be permanent and an end-colostomy is generally the most appropriate. Where stoma closure is contemplated, patients need to be counselled about the unpredictable and often poor functional outcomes in terms of evacuation and continence.

The presence of a perianal fistula should be managed by a long-term Seton prior to commencement of CRT. Interruption of CRT due to peri-anal sepsis is invariably associated with a poor outcome and is avoidable.

8.4.1.4 Inguinal lymph node dissection

Involved inguinal lymph node dissection is usually treated with the primary tumour using CRT. If radiotherapy to the pelvis is contraindicated, therapeutic block dissection of involved lymph nodes or prophylactic dissection of non-involved lymph nodes may be considered, as part of the APE (section 8.4.1.2).

T1 anal margin cancers (≤2 cm) may be locally excised, as long as this can be achieved without compromising sphincter function. This should ideally be performed by an anal cancer MDT surgeon,
following agreement within the MDT to attempt a complete excision.

**Recommendation grade C**

T1 anal canal cancers are unlikely to be adequately locally excised without compromising sphincter function. This should ideally be performed by an anal cancer MDT surgeon, following agreement within the MDT to attempt excision. However any attempt at local excision should be regarded as more likely to represent a generous diagnostic biopsy, unless it can be demonstrated that margins are clear.

**Recommendation grade D**

When a pre-treatment stoma is indicated, patients should be warned that such stomas are often permanent, even in the presence of local disease control.

**Recommendation grade C**

### 8.4.2 Chemoradiotherapy (CRT)

Chemoradiotherapy (CRT) using synchronous mitomycin and 5FU with low dose radiotherapy (30 Gy) was first trialed in the preoperative setting by Norman Nigro (Nigro et al., 1974). This resulted in high clinical and pathological complete response rates, enabling most patients to avoid surgery (Nigro, 1984). Subsequent non-randomized studies reported good outcomes with CRT alone (Cummings et al., 1980; Gerard et al., 1998).

#### 8.4.2.1 Randomized controlled trials

The UKCCCR ACT I (585 patients) and EORTC 22861 (110 patients) trials reported improved local control and fewer colostomies with CRT using mitomycin/5FU, compared with radiotherapy alone (Bartelink et al., 1997; Northover et al., 2010; UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research, 1996). The RTOG 87-04 trial (310 patients) reported improved disease-free survival (DFS) and fewer colostomies in patients receiving CRT with mitomycin/5FU, compared to 5FU alone (Flam et al., 1996).

The RTOG 98-11 trial (682 patients) compared 2 cycles of induction cisplatin/5FU followed by CRT using 2 further cycles of cisplatin/5FU vs standard CRT with mitomycin/5FU. Intensification of treatment resulted in significantly worse outcomes, in terms of toxicity, tumour control, colostomies and overall survival (Ajani et al., 2009; Gunderson et al., 2012). The UK ACT II trial (940 patients) was a 2 × 2 design comparing CRT using cisplatin/5FU vs mitomycin/5FU, with or without 2 cycles of adjuvant cisplatin/5FU. There was no difference in PFS between cisplatin and mitomycin, and no benefit from maintenance chemotherapy (James et al., 2013). The ACCORD-03 trial (307 patients) was also a 2 × 2 design, comparing 2 cycles of induction cisplatin/5FU vs no induction chemotherapy and a standard dose (15 Gy) vs a high dose boost (20–15 Gy). Colostomy-free survival was not improved by either induction chemotherapy or a higher dose of radiotherapy (Peiffert et al., 2012).

#### 8.4.2.2 Radiation dose, fractionation and delivery

Early trials (ACT I, EORTC 22861) using large parallel opposed phase I radiotherapy fields incorporated a 6 week gap before phase II, to allow improvement of the severe associated skin reaction. It is now recognized that prolongation of the overall treatment time by inclusion of a gap, or use of induction chemotherapy is detrimental to local control (Ben-Josef et al., 2010; Glynne-Jones et al., 2015; Glynne-Jones et al., 2011). The subsequent ACT II trial was designed to deliver 50.4 Gy in 28 fractions continuously over 5.5 weeks, with phase II commencing after 30.6 Gy instead of 45 Gy. Despite receiving a lower total dose in both phases compared to other trials, 90% of patients achieved complete clinical response.

Locally advanced (T3-4) tumours have worse outcomes (Ajani et al., 2009; James et al., 2013; Sunesen et al., 2011) than less advanced (T1-2) tumours. Present trial data do not support radiation dose escalation above 54 Gy or use of induction chemotherapy, and further trials are needed to establish optimum treatment strategy, particularly for more advanced tumours (Glynne-Jones & Lim, 2011). On the other hand, many patients with anal cancer will not tolerate standard CRT due to co-morbidities or poor performance status. Using low dose CRT (30–40 Gy) can be a safer and yet effective compromise, especially for smaller tumours but longer follow-up data are needed (Charnley et al., 2005; Glynne-Jones et al., 2014b; Smith et al., 1994).

Capecitabine, which is an orally administered fluoropyrimidine, has been demonstrated to be as effective as infusional 5FU for adjuvant and palliative treatment in colorectal cancer (Twelves et al., 2005), as well as combined with radiotherapy in rectal cancer (O’Connell et al., 2014), but with a slightly differing toxicity profile. Although capecitabine has not been formally evaluated in a phase III anal cancer trial, its use instead of 5FU is supported by single centre series (Third et al., 2014) and within NCCN and ESMO guidelines (Glynne-Jones et al., 2014b; National Comprehensive Cancer Network, 2016).

Prophylactic low dose radiotherapy to clinically uninvolved inguinal lymph nodes is very effective in preventing recurrence and should be routinely given to all T2-4 tumours of the anal canal and margin. When omitted,
recurrence rates around 30% have been reported (Ortholan et al., 2012). The UK ACT II and RTOG 98-11 trials reduced the radiation dose to uninvolved pelvic lymph nodes to 30.6 and 36 Gy respectively, significantly reducing the severity of acute skin toxicity. Smaller tumours have a lower risk of inguinal lymph node recurrence without prophylactic inguinal radiotherapy, which may be safely omitted in most T1 tumours (Tomaszewski et al., 2012). However, as the acute and late toxicity associated with prophylactic inguinal radiotherapy when using modern radiotherapy techniques is low, along with studies indicating relative high rates of recurrence in non-irradiated patients (Matthews et al., 2011), the default position is to include the inguinal lymph nodes in the prophylactic low dose volume.

Recent modernization of radiotherapy facilities throughout the UK has enabled all units to routinely deliver highly conformal intensity-modulated radiotherapy (IMRT), using a range of delivery methods such as multiple fixed fields, volumetric modulated arc therapy (VMAT) and tomotherapy. The use of IMRT reduces the volume of normal tissue receiving high-dose radiation (Brooks et al., 2013), to reduce severity of acute and late toxicities. In addition, IMRT allows for variation of radiation dose to multiple planning target volumes (PTV) according to clinical requirement, including dose escalation given over the same number of radiotherapy fractions, known as simultaneous integrated boost (SIB). Although there have been multiple reported single centre series of IMRT for anal cancer, the only prospective trial completed was RTOG 0529 phase II (Kachnic et al., 2013). The early oncological outcomes appear comparable to conventionally treated patients but mature data on late toxicity are yet to be published.

The process for IMRT volume outlining, planning and delivery are highly complex and subject to very significant variations between oncologists and their centres. Therefore standardization of treatment is essential, particularly to avoid geographical miss of disease, which compromises cancer outcomes (Myerson et al., 2009; Ng et al., 2012). A UK consensus document for outlining, planning, dose objectives and constraints and dose delivery is available on-line at www.analimrtguidance.co.uk. This consensus has taken into account the excellent results achieved in the ACT II trial, together with a review of radiotherapy planning and dose delivered to patients in the trial and has resulted in an adaptation of the recommended dose prescription (Muirhead et al., 2014). These changes have been integrated into the UK PLATO phase III trial protocol, which will also oversee a quality assurance program for delivery of high quality radiotherapy for this population. A brief summary of the UK recommendations is as follows;

T1N0 tumours: planning target volume of the anal tumour (PTV_Anal) treated to 50.4 Gy in 28 fractions (1.8 Gy per fraction) over 5.5 weeks. The decision to use an additional elective (prophylactic) volume (PTV_Elec) to treat clinically uninvolved pelvic and inguinal lymph nodes is left to the oncologist.

T2N0 (and T3N0 at oncologist’s discretion) tumours: PTV_Anal treated to 50.4 Gy in 28 fractions over 5.5 weeks. In addition, all patients are to receive 40 Gy in 28 fractions (1.43 Gy per fraction) over 5.5 weeks to PTV_Elec.

T4N0 or any N+ (and T3N0 at oncologist’s discretion) tumours: PTV_Anal treated to 53.2 Gy in 28 fractions (1.9 Gy per fraction) over 5.5 weeks. The PTV to involved lymph nodes (PTV_Nodes) to 50.4 Gy in 28 fractions over 5.5 weeks. All other uninvolved lymph node regions (PTV_Elec) treated to 40 Gy in 28 fractions over 5.5 weeks.

Close adherence to the step-by-step directions within the UK guidance on how to outline and generate the various PTVs is recommended, ideally with mentoring by experienced departments for the first few cases. The AGITG guidelines and atlas for IMRT in anal cancer provides additional learning information (Ng et al., 2012).

8.4.2.3 Late toxicity of CRT
Pre-menopausal women should be counseled about premature radiation-induced menopause. Embryo cryopreservation prior to commencing CRT may enable female patients to have children, but will require a surrogate in addition and will delay commencement of treatment. Referral to the fertility team for discussion of options may be appropriate. Vaginal stenosis can occur and referral to a gynaecology CNS for advice and provision of vaginal dilators should be considered in all women after completion of treatment.

Male patients should be counseled about permanent azoospermia and offered the opportunity for sperm storage. Testosterone levels may be reduced with impaired physical, psychological and sexual function after treatment (Buchli et al., 2011). Erectile dysfunction may be due to low testosterone levels or nerve damage by radiation. Testosterone hormone replacement may be beneficial.

Patients treated for locally advanced tumours commonly experience incontinence from sphincter dysfunction or evacuatory problems secondary to fibrotic stenosis. Assessment and management by the pelvic floor specialists can be offered. In severe cases, a defunctioning stoma may be the only available option.

Radiation-induced small bowel strictures can present with obstructive symptoms and weight loss (Andreyev
et al., 2012) but are uncommon, due to the relatively low standard radiation doses used for anal cancer. Pelvic insufficiency fractures occur in up to 5% of patients, more commonly in women, causing lower back or pelvic pain (Herman et al., 2009). The radiological appearance may be misinterpreted for bone metastasis.

Definitive CRT (radiotherapy with synchronous mitomycin and either, infusional 5FU or oral capcitabine) is the standard treatment for all anal cancers that are not amenable to local excision, unless radiotherapy is contraindicated.

Recommendation grade A

Mitomycin is an important component of the CRT schedule but cisplatin can be used instead, if mitomycin is contraindicated. The routine use of induction or adjuvant chemotherapy is not recommended.

Recommendation grade A

Intensity modulated radiotherapy (IMRT) should be considered for all patients in whom definitive CRT is intended, in order to reduce acute toxicity and possibly late toxicity. Standardization of radiotherapy volume outlining, planning and delivery should be based on published consensus guidelines.

Recommendation grade B

The minimum radiation dose for microscopic disease should be 40 Gy in 28 fractions over 5.5 weeks using IMRT or 30.6 Gy in 17 fractions over 3.5 weeks using the original ACT II protocol. Uninvolved inguinal lymph nodes should be routinely treated in all T2-4 tumours, but may be selectively omitted in small T1 tumours.

Recommendation grade B

Treatment gaps (planned or unplanned) are detrimental to local control. Radiotherapy should be delivered continuously with no treatment gap. Formation of a pre-treatment stoma prior to commencement of CRT should be considered in patients with severe symptoms to enable better treatment compliance.

Recommendation grade B

8.4.3 Anal intraepithelial neoplasia (AIN)

Anal intraepithelial neoplasia (AIN) is often asymptomatic but may be associated with pruritus, bleeding, discharge and pain. AIN is caused by HPV infection and its clinical behaviour has strong parallels with cervical (CIN) and vulval/vaginal (VIN/VAIN) intraepithelial neoplasia. All three can occur together in the same individual. The clinical relevance of AIN is that it is a precursor lesion for anal SCC.

A recent overview of guidelines on the management of AIN have pointed to three key problems, which in turn are a source of much confusion. First, there are inconsistencies with terminology. AIN is traditionally graded as AIN I, II and III. To aid management algorithms, the terminology of LSIL and HSIL (low- and high-grade squamous cell intra-epithelial lesions) was introduced over a decade ago. LSIL corresponded to AIN I; HSIL to AIN II and III. More recently, the terms LGAIN and HGAIN, respectively low-grade and high-grade AIN, were introduced. Alam et al. (Alam et al., 2016) point out that some guidelines have confusingly restricted HGAIN to AIN III.

Second, of the three guidelines reviewed, Alam et al. (2016) showed that often the cited evidence is historic. Third, although HIV status (positive vs negative) and MSM status are hugely important in terms of transformation rates, this classification does not feature predominantly in clinical treatment and surveillance algorithms.

In a historic single institute series of 35 patients with AIN, the transformation to invasive SCC was estimated to be 50% in six immune-compromised patients (Scholfield et al., 2005). They estimated that AIN transformation rates to anal SCC in the general population were very low. More systematic evidence is now available through systematic review and advanced meta-analytic methods to estimate progression rates ‘from high-grade AIN to anal cancer of one in 633 patients (one in 377 in the HAART era) per year in HIV-positive MSM, and one in 4196 patients per year in HIV-negative MSM’ (Machalek et al., 2012). These categorizations should form the basis for stratification in management. Thus, a clinical algorithm based on the nomenclature of high-risk (HIV-positive MSM, and other immune-compromised such as transplant patients); high-moderate risk (HIV-negative MSM; HIV negative gay lesbian); and low-moderate (the ‘rest’) should be considered.

The central tenet of management of AIN (analogous to CIN) is that if one can induce regression or eradicate AIN, then malignant transformation can be prevented. However, to-date, there is no direct evidence to support this pathway to prevention of anal SCC (as there is for CIN to invasive cervical carcinoma). Targeted biopsies using high-resolution anoscopy and 3% acetic acid to the anal canal mucosa (similar to colposcopy) can help identify areas of AIN. Anoscopy is mandated in trials, but its role in clinical practice is not yet established.

The diagnosis of AIN can be suspected clinically or with the aid of magnification, but can only be confirmed and graded histologically. To avoid the risk of misdiagnosis of invasive disease and potential for over-
treatment, the diagnosis of AIN III should be confirmed by the specialist histopathologist within the Anal Cancer MDT.

There are several therapeutic options. Topical therapies include trichloroacetic acid, 5FU and immunomodulator creams (such as imiquimod). Ablative therapies including infrared coagulation, electrocautery, carbon dioxide laser and photodynamic therapy have also been used (Scholefield et al., 2011; Weis, 2013). Recent evidence from a Dutch randomized trial in 156 HIV positive MSM showed that electrocautery is better than imiquimod and fluorouracil in the treatment of AIN (where the endpoint was AIN regression/disappearance), but recognized that recurrence rates were substantial (Richel et al., 2013).

The surveillance of patients with AIN II and III is predominantly aimed at the identification of early invasive carcinoma that can be treated by local excision or localized CRT with reduced treatment-related morbidity. High-risk patients should be followed up at six monthly intervals for at least 5 years, ideally with periodic photographic documentation of the perianal region. There should be a low threshold to repeat biopsies of any changing or bleeding lesion. Small, discrete lesions should be excised.

During surveillance, historically multiple biopsies by mapping has been advocated, often repeatedly. This is increasingly less favoured because of risk of perianal scarring and pain, with little impact on management.

Through AIN surveillance, new histological entities are emerging. Superficially invasive squamous-cell carcinoma of the anus (SISCCA) is defined by three criteria: an invasive squamous carcinoma that (i) has an invasive depth of \( \leq 3 \) mm from the basement membrane of the point of origin, and (ii) has a horizontal spread of \( \leq 7 \) mm in maximal extent, and (iii) has been completely excised (Darragh et al., 2012). Currently, reported series are small but it may be that many of these can be managed by watchful waiting (Arana et al., 2015). This needs be considered through a specialist Anal Cancer MDT. Older terminology such as perianal Bowen’s disease have been abandoned.

All suspicious anal lesions should be excised or biopsied. Targeted biopsy of anal lesions suspicious for AIN is mandatory in high-risk groups to exclude invasive disease.

**Recommendation grade D**

All cases of AIN II and III should be reviewed and subsequently managed by the specialist Anal Cancer MDT.

**Recommendation grade D**
toxicities in patients with low CD4 cell counts, this is not a consistent finding. The use of cART seems to have reduced the toxicity of CRT (Alfa-Wali et al., 2012; Blazy et al., 2005; Fraunholz et al., 2011; Fraunholz et al., 2010; Hogg et al., 2009; Oehler-Janne et al., 2008; Wexler et al., 2008), but a significant and prolonged decline in CD4 cell count can still occur despite continued use of concomitant cART (Alfa-Wali et al., 2012; Wexler et al., 2008). Therefore patients with anal cancer should be considered for opportunistic infection prophylaxis prior to commencing CRT, in partnership with their HIV team. The British HIV Association has published guidelines for the treatment and prevention of opportunistic infections (Nelson et al., 2011). Combined ART should be started in patients newly diagnosed with HIV and continued during CRT in those known to be HIV positive.

Salvage surgery may be appropriate for PLWH with locoregional disease failure following CRT, although experience in this population is limited (Cunin et al., 2014). Patients with metastatic disease or further relapse following salvage surgery may be considered for palliative chemotherapy or best supportive care.

In summary, survival of PLWH has improved significantly since the advent of cART, including those with anal cancer. The overall principles of managing HIV patients with anal cancer, from referral to the regional Anal Cancer MDT, to staging, definitive treatment and follow up should be the same as in non-HIV patients, as outlined in these guidelines.

To avoid late presentation of anal cancer in people living with HIV (PLWH), there should be a low threshold for referring all suspected cases for EUA and biopsy of the anal canal and rectum.

**Recommendation grade D**

The overall principles of managing HIV patients with anal cancer, from referral to the regional Anal Cancer MDT, to staging, definitive treatment and follow up should be the same as in non-HIV patients, as outlined in these guidelines.

**Recommendation grade C**

PLWH who are to be treated with CRT should be started on combined anti-retroviral therapy (cART) and opportunistic infection prophylaxis should be considered prior to commencing CRT.

**Recommendation grade C**

### 8.5 Follow Up After CRT

The aims of follow up after completion of CRT for anal cancer are to (Renehan & O’Dwyer, 2011b):

1. Detect local disease failure amenable to successful salvage surgery.
2. Detect the development of distant metastases where early treatment may improve the prognosis or long-term survival.
3. Identify and manage late consequences of treatment. This may be due to the radiation alone or a combination of pre-existing tumour damage and radiation, which often occurs in locally advanced tumours.

Surveillance of patients should be performed within a protocol-driven program by the Anal Cancer MDT, for early detection of local disease failure following CRT.

**Recommendation grade D**

#### 8.5.1 Early assessment of response to CRT

Regression of anal cancers may be slow and can continue for up to 6 months following completion of CRT (Glynne-Jones et al., 2017). A decision to investigate for local disease failure should be deferred until such an interval, during which tumours should be carefully observed by clinical examination, ideally by the same clinician at 4–8 week intervals until complete clinical response. However, clinically non-responding or enlarging tumours should be biopsied earlier, in preparation for potential salvage surgery. Very early (6–8 week) assessment by MRI or other imaging modalities is generally unhelpful and is not recommended (Goh et al., 2010). However, recent data indicates that MRI assessment at 3 and 6 months may be able to identify those at risk of early relapse, who are amenable to R0 salvage (Kochhar et al., 2017).

Clinical assessment at 6–8 weeks following completion of CRT, then every 4–8 weeks until clinical and radiological complete response.

**Recommendation grade C**

Consider initial MRI between 3–6 months post CRT, particularly in more locally advanced disease, or if there is residual palpable abnormality.

**Recommendation grade C**

#### 8.5.2 Follow up after complete clinical response

Patients with local disease failure may be amenable to salvage surgery. Most failures (around 80%) occur within the first 2 years (Sebag-Montefiore et al., 2012). The follow up protocol from the ACT II trial is widely adopted in the UK, consisting of clinic visits every 2 months during the first year, every 3 months during the second year and every 6 months from years 3–5, which is in keeping with this pattern of failure. Clinical
assessment should consist of inspection of the perineum, anorectal digital examination and palpation for inguinal lymphadenopathy. In the case of suspicious findings, the patient should either be re-examined by the same clinician in 4–6 weeks or be referred to the Anal Cancer MDT surgeon for EUA and biopsy.

Follow up is recommended in all patients, the primary aim is to detect disease which is amenable to salvage surgical resection; secondary aim is to manage symptoms related to the cancer and its treatment.

**Recommendation grade C**

Once clinical and radiological complete response has been achieved, further clinical assessment at 3–4 month intervals until 24 months, then 6–9 month intervals until 60 months.

**Recommendation grade C**

8.5.3 Role of imaging

Following CRT, MRI pelvis is able to demonstrate tumour regression and document sustained response. The benefit of routine use of MRI in addition to clinical assessment alone remains unclear with no general consensus (Goh et al., 2010; Gourtsoyianni & Goh, 2014; Kochhar et al., 2012; Kochhar et al., 2017). NCCN and ESMO guidelines are also discordant on this issue, with MRI pelvis indicated as an option within the ESMO but not the NCCN guidelines (Glynne-Jones et al., 2014b; National Comprehensive Cancer Network, 2016). There may be merit in risk stratifying patients; with MRI being used for patients with T3/4 N+ disease at diagnosis and in those with residual changes after treatment completion. These patients are the most likely to develop locoregional failure and may be the hardest to detect clinically. In the PLATO (ACT 4 and ACT 5) trial, routine MRI pelvis has been scheduled at 3 and 6 months following CRT.

In patients with suspected or proven local disease failure, MRI pelvis together with other imaging modalities such as CT chest, abdomen, pelvis and 18F-FDG PET/CT should be performed to identify appropriate patients for salvage surgery and plan the optimal surgical approach.

The routine use of CT to diagnose distant metastases before symptoms arise may enable earlier treatment but the benefits in terms of improved quality of life and overall survival remain unproven. The NCCN guidelines indicate that this may be considered in patients at higher risk (T3-4 or N2-3) of developing pelvic lymph node recurrence or distant metastases, with annual CT over the first 3 years (National Comprehensive Cancer Network, 2016).

CT chest, abdomen and pelvis can be considered as per the colorectal cancer guidelines (first at 12–18 months, second at 24–36 months).

**Recommendation grade C**

Routine use of MRI pelvis beyond 12 months is not recommended, unless there is suspicion of, or proven local disease failure.

**Recommendation grade C**

8.5.4 Reversal of stoma

Patients who require formation of a stoma prior to CRT tend to have very advanced local disease. Such patients remain at higher risk of local disease failure following CRT and have a poorer prognosis (Cooper et al., 2012). Stoma reversal is not a realistic option in a high proportion of these patients (50–80%), usually due to disease failure or extensive permanent organ damage (Cooper et al., 2012; Glynne-Jones et al., 2012). If reversal is being considered, cross sectional imaging should be performed to exclude the presence of pelvic lymph node failure and distant metastases.

8.6 Management of Treatment Failure

Following completion of CRT, the most frequent site of treatment failure is the primary tumour. Less common sites of disease failure are inguinal or other pelvic lymph nodes and distant metastases, including liver, lung and retroperitoneal lymph nodes. Data from the ACT II trial indicate that 209 of 924 evaluable patients relapsed. Of these failures 54% occurred in the first year, 26% in year two and 13% in year 3. In 64% of the relapsed cases the disease was localized to the pelvis alone (Sebag-Montefiore et al., 2012). Local treatment failure can be divided into persistent local disease or local recurrence.

8.6.1 Local disease relapse

Up to 10% of patients will have persistent local disease, defined as biopsy proven cancer at up to 6 months following completion of CRT. Local recurrence is defined as biopsy proven local disease beyond 6 months in a patient who previously achieved complete clinical response (cCR). Most local relapses will be apparent within 24 months of completion of CRT.

Local relapses are usually palpable on digital examination, often before development of new symptoms. Obtaining histological confirmation is essential when there is suspicion of residual or recurrent disease. Post-treatment fibrotic tissue can look and feel like malignant
disease. Patients being considered for salvage surgery should be assessed and restaged with:

- Examination under anaesthesia and biopsies.
- MRI pelvis
- CT chest, abdomen and pelvis
- 18F-FDG PET/CT

Salvage surgery offers a second chance of cure and should be considered for all local relapses. Published data show that the proportion of patients with locally persistent/recurrent disease undergoing salvage surgery varies between 50% and 75%, but is highest in series from centralized centres working through one MDT (Renehan & O’Dwyer, 2011b). However, despite salvage surgery <50% of patients will survive beyond 5 years. The ACPGBI audit standard for the proportion of patients with local relapse (at primary site only) being offered salvage radical surgery is >60% (Renehan & O’Dwyer, 2011b).

On clinical and/or radiological suspicion of local relapse, re-staging investigations include MRI pelvis, CT chest, abdomen and pelvis, 18F-FDG PET/CT (as indicated). EUA/biopsy should be performed to confirm.

**Recommendation grade C**

All patients with treatment failure should be assessed by the Anal Cancer MDT. The percentage of patients with local relapse and undergoing subsequent salvage surgery should be audited.

**Recommendation grade D**

8.6.2 Salvage radical surgery

A detailed examination under anaesthesia and biopsy should be performed by the Anal Cancer MDT surgeon; particularly noting the size, location and fixity of the suspected disease. Salvage surgery for relapsed anal cancer is often associated with significant morbidity and a prolonged recovery period. In order to obtain maximal benefit, careful patient selection is essential. Preoperative clinical and radiological assessment of the patient should be focused on achieving clear margins (R0 resection) at salvage surgery. Presence of distant metastases is associated with a poor prognosis and usually excludes the patient from surgery.

For the majority of patients, salvage surgery involves the minimum of a radical APE. The need to extend this operation to encompass adjacent viscera and irradiated soft tissue of the perianal region, perineum and buttocks should be considered. A posterior or total pelvic exenteration is sometimes required to achieve clear margins. Wide removal of the ischiorectal fossa fat with extralevator resection is recommended when tumour has breached the puborectalis or external sphincter muscles. Delayed wound healing following salvage surgery is common (over 40%) and consideration should be given to perineal reconstruction (Renehan et al., 2005).

Radical APE for anal cancer is a specific operation distinct from APE for low rectal cancer. This should be performed by an experienced anal cancer surgeon, supported by an oncoplastic team.

**Recommendation grade C**

8.6.3 Regional disease failure

Inguinal lymph node recurrence is considered as regional failure. Suspected inguinal lymph node recurrence should be assessed by ultrasound ± FNA and restaged with CT chest, abdomen and pelvis MRI pelvis and possibly 18F-FDG PET/CT to exclude distant metastases.

Salvage surgery with pelvic lymph node dissection should be considered. This is associated with significant morbidity especially in patients who have previously received high-dose CRT to this region. In the occasional patient who did not receive prophylactic inguinal radiotherapy, salvage CRT may be considered but this requires careful planning to avoid significant radiotherapy overlap of critical organs.

8.6.4 Further radiotherapy

There is emerging evidence showing that following initial radiotherapy, tolerance to further radiation improves with time, due to limited long-term recovery of radiation DNA damage (Stewart & van der Kogel, 1994). Patients with local recurrence of anal cancer who are not suitable for salvage resection may benefit from further radiotherapy, with or without chemotherapy to the pelvis. Treatment to a small volume, using a dose and fractionation defined by the cumulative prior doses in the organs at risk and taking into account the degree of normal tissue recovery expected over time would be appropriate. Stereotactic radiotherapy may be possible in selected cases, with the intention of delivering a tumoricidal dose where feasible. A long interval from completion of initial CRT to recurrence (>2 years) predicts for a good response to further RT. Although this approach is unlikely to be curative, it can offer medium term control of local disease and palliation of symptoms.

8.6.5 Distant metastases

The development of distant metastases in the absence of local failure in anal cancer is infrequent, estimated at up to 10% (Northover et al., 2010). Distant metastases are
usually incurable and treatment with systemic chemotherapy to control disease and prolong survival should be considered. There are limited published data on the optimal systemic therapy regimen but a combination of cisplatin and a fluoropyrimidine (5FU or capecitabine) is often used. Treatment of eligible patients within clinical trials, such as InterAACT is encouraged. There is no systematically reviewed evidence to recommend resection or ablation of oligometastases. Early phase data indicate there may be a future role for immune checkpoint inhibitors in this group of patients (Morris & Eng, 2016).

8.7 Histopathology Reporting

This section should be read in conjunction with the Royal College of Pathologists (Loughrey et al., 2014) dataset for colorectal cancer (3rd edition).

Process

The Welsh audit of anal cancer demonstrated poor documentation overall (Karandikar et al., 2006). Use of structured proformas has been shown to improve histopathology reporting.

Local resections

The size of the lesion (usually anal margin) should be documented together with lateral and deep resection margins. All local excisions should be registered with the network anal cancer MDT. A prospective collection of local excision for anal SCC is the focus of the upcoming UK ACT3 trial within the PLATO umbrella trial. Positive margins have been defined as ≤1 mm and these patients will be offered chemoradiotherapy, with 3-year locoregional relapse as the primary endpoint.

The new terminology of Superficially Invasive Squamous Cell Carcinoma of the Anus (SISCCA) has been detailed under management of AIN.

Resection Specimen

This will usually be an anorectal excision for persistent disease following CRT, recurrence or complications. Cut up of the specimen should concentrate on size, depth of invasion (in relation to sphincters), involvement of adjacent organs and circumferential resection margins.

Histology Type

Usually squamous but other varieties can be recorded. Historically, variants such as basaloid and cloacogenic have been recorded, but these terms are no longer advocated in the WHO classification.

TNM Staging

Is different compared to rectal adenocarcinoma invading the anal canal. Pathological T staging essentially relates to size; and on clinical staging to invasion of adjacent organs and pattern of lymph node spread.

i pT1 to pT3 relates to size

ii pT4 is any size that invades adjacent organs. Note that the invasion of the sphincter muscle is not classified as pT4

iii Regional lymph nodes. N1 is a nodal involvement in the mesorectum; N2 is unilateral internal iliac/inguinal lymph node involvement; N3 is involvement of the mesorectal/inguinal, bilateral internal iliac and/or inguinal lymph nodes.

If the patient has had neoadjuvant treatment the staging should have the prefix ‘yp’.

The pathological findings should be reported using a proforma.

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Conflicts of interest

Andrew Renehan has received lecture honoraria from Merck Serona and Sanofi and been a member of the advisory board of Beating Bowel Cancer. Mark Bower is a British HIV Association and European AIDS Clinical Society guidelines writer. None of the other authors have any conflicts of interest to declare.

References


Fraunholz I, Weiss C, Eberlein K, Haberl A, Rodel C. Concurrent chemoradiotherapy with 5-fluorouracil and mitomycin C for invasive anal carcinoma in human immunodeficiency virus-positive patients receiving highly
active antiretroviral therapy. *Int J Radiat Oncol Biol Phys* 2010; 76: 1425–32.


Glynne-Jones R, Meadows H, Lopes A, Adams R, Sebag-Montefiore D. Compliance to chemoradiation (CRT) using mitomycin (MMC) or cisplatin (CisP), with or without maintenance 5FU/CisP chemotherapy (CT) in squamous cell carcinoma of the anus (SCCA) according to radiotherapy (RT) dose, overall treatment time (OTT) and chemoradiotherapy (CT) and their impact on long-term outcome: results of ACT II. *J Clin Oncol* 2015; 33: suppl; abstr 3518.


Palefsky JM, Holly EA, Ralston ML, Da Costa M, Greenblatt RM. Prevalence and risk factors for anal human


van Leeuwen MT, Vajdic CM, Middleton MG, McDonald AM, Law M, Kaldor JM, Grulich AE. Continuing declines in some but not all HIV-associated cancers in Australia after widespread use of antiretroviral therapy. AIDS 2009; 23: 2183–90.


