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>
<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>

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

4.1.3 Early rectal cancer
t(t1-2 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 muscularis 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 (Barendse 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, local excision).**

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>
<td></td>
<td>≤1</td>
</tr>
<tr>
<td>pT1 sm1</td>
<td>–</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>5.2</td>
</tr>
<tr>
<td>pT1 sm2/3</td>
<td>–</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>17.8</td>
</tr>
<tr>
<td>pT2</td>
<td>–</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>16.7</td>
</tr>
</tbody>
</table>
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 side-wall.

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 increased 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 Brock 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 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...
futile treatment. In addition, there is no effect on risk of distant metastases or improvement of OS.

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 SCPRT 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 (Marijnens et al., 2002; Quirke et al., 2009; Taylor et al., 2011).

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**

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 downstaging 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).
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.rttqa.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*
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 radiosensitizer (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 SCPRT 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 SCPRT, then 6 weeks of FOLFOX neoadjuvant chemotherapy then surgery in 541 patients with fixed T3 or T4 tumours (MRI staging was not mandated) (Buijk 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 SCPRT 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 (Foxrot 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 FOLFIRI in 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 RECOURSE 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 ‘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 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, e.g. 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 organisations 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, dietetics, 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 Locating Bowel Cancer. Sam Ahmedzai has been employed by the National Institute of Health Research as National Specialty Lead for supportive and palliative care 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.

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