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COLORECTAL CANCER AND ITS DETECTION, DIAGNOSIS, TREATMENT AND FOLLOW-UP: DISEASE AND TREATMENT PATHWAYS.

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COLORECTAL CANCER AND ITS DETECTION, DIAGNOSIS, TREATMENT AND FOLLOW-UP: DISEASE AND TREATMENT PATHWAYS

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Abbreviations

5-FU	5-fluorouracil
A&E	Accident and Emergency
APER	Abdominoperineal resection
AR	Anterior resection
BE	Barium enema
BSG	British Society of Gastroenterology
CEA	Carcinoembryonic antigen
COL	Colonoscopy
CRM	Circumferential resection margin
CT	Computerised tomography
CXR	Chest X-ray
DALM	Dysplasia associated lesion or mass
DVT	Deep vein thrombosis
EMR	Endoscopic mucosal resection
EUA	Examination under anaesthetic
FA	Folinic acid
FAP	Familial Adenomatous Polyposis
FBC	Full blood count
FOBT	Faecal occult blood test
FOLFIRI	5-fluorouracil plus irinotecan
FOLFOX	5-fluorouracil plus oxaliplatin
FSIG	Flexible sigmoidoscopy
GP	General Practitioner
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
HRQoL	Health-related quality of life
IAP	Ileoanal pouch
IBS	Irritable bowel syndrome
IRA	Ileorectal anastomosis
LR	Local relapse
MDT	Multidisciplinary team
MMR	Mismatch repair
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Clinical Excellence
OGD	Oesophagogastroduodenoscopy
PR	Per rectal
TME	Total mesorectal excision
TNM	Tumour Node Metastases
UC	Ulcerative colitis

1.1 Introduction

This paper sets out a series of descriptive conceptual models of colorectal cancer and its detection, diagnosis, treatment and follow-up. The paper is based on an update of the work reported in Trueman et al[1] and is intended to be useful for health economic modellers and other researchers working in the area of colorectal cancer evaluation. In particular, it is intended that this paper should provide a consistent conceptual basis for the development of health economic models of colorectal cancer services and technologies in the future. The paper is set out as follows. Section 1.2 details the methods used in the development of these conceptual models. Sections 1.3 presents the key disease-specific factors associated with colorectal cancer. Section 1.4 presents a series of problem-oriented conceptual models of colorectal cancer service pathways.

1.2 Methods for conceptual model development

The conceptual models presented within this chapter have been informed by guidelines for the management of colorectal cancer,[2-6] NICE Technology Appraisal Guidance documents and associated technology assessment reports,[7-17] other relevant literature (particularly Phillips et al[18]) together with considerable clinical input and scrutiny (see Acknowledgements). Whilst the conceptual models focus on colorectal cancer, the boundary around the disease and service pathways models is broader, including individuals who interact with the colorectal cancer service do not yet have and may never develop colorectal cancer (e.g. screen-eligible general population, individuals under surveillance for colitis). In line with the methods detailed by Tappenden et al,[19] two conceptual model views are presented here:

(1) A problem-oriented disease logic model which sets out key disease-related events and processes associated with colorectal cancer (Section 1.3).

(2) A problem-oriented service pathways model which represents the structure of the colorectal cancer system in terms of screening, surveillance, diagnosis, treatment and follow-up, as well as the management of other non-malignant pathologies which impinge upon the colorectal cancer service (Section 1.4).

1.3 A conceptual disease logic model of preclinical natural history and post-diagnosis risk

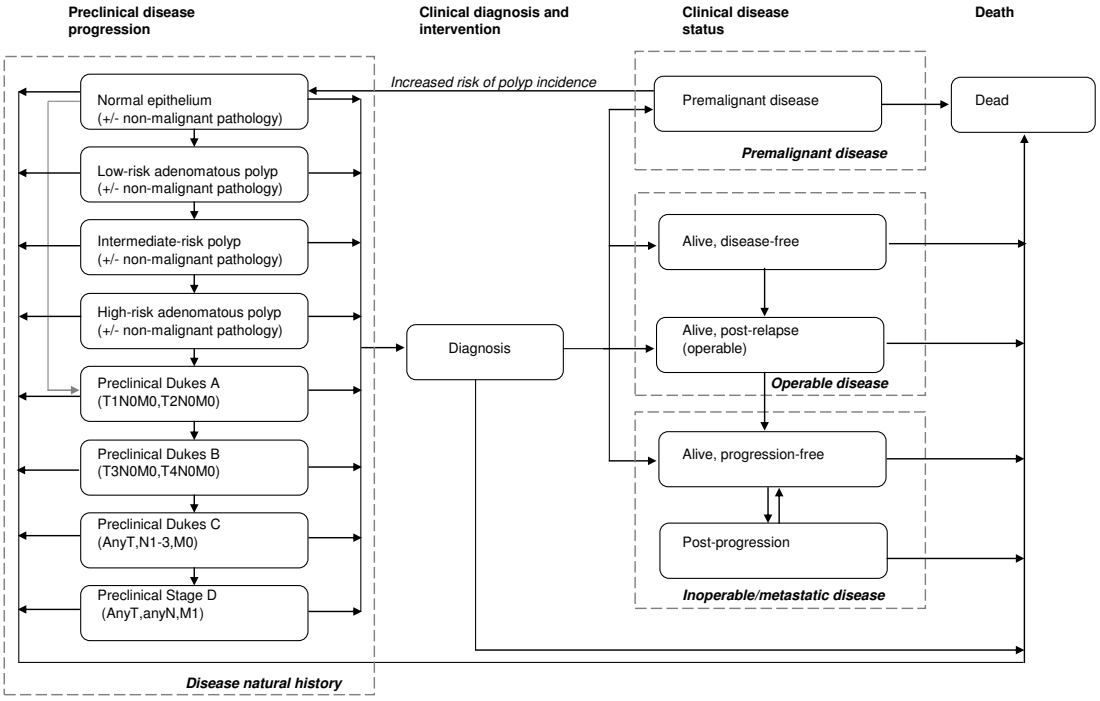
Figure 1 presents a disease logic model outlining key disease-specific characteristics associated with colorectal cancer, both sporadic and inherited, described in terms of preclinical disease progression, diagnosis, clinical disease and death. This conceptual model should be interpreted in terms of the individual's true underlying histology, rather than what is clinically known about the subject at a given point in time. The logic model includes the development of colorectal cancer as well as other non-malignant pathologies. Whilst

preclinical and post-diagnosis disease events relate to continuous processes, the model discretises these into mutually exclusive states using endpoints commonly described within the clinical and epidemiological literature. For the sake of simplicity, histology is described in terms of the "index lesion", that is, the most advanced adenoma or cancer present. Beyond lumping or splitting these states, other metrics could be used to describe disease progression, for example TNM tumour staging,[20] or the separate representation of synchronous neoplasia (adenomas, tumours or both). Whilst a common process is used to describe preclinical disease progression and clinical prognosis, event risk and sojourn time in each state may differ markedly between particular patient subgroups.

1.3.1 Disease-specific factors - Preclinical disease progression

Disease progression prior to detection and diagnosis cannot be directly observed, however numerous preclinical/subclinical features of colorectal cancer have been elucidated through epidemiological studies and analyses of indirect evidence. These are briefly discussed below.

Figure 1 Disease logic model for colorectal cancer



Tumour sites

Colorectal cancer includes carcinoma of the colon, rectum and rectosigmoid junction (ICD10 C18-C20).

Relationship between age and colorectal cancer incidence

Approximately 32,000 newly diagnosed cases of colorectal cancer are registered in England and Wales each year.[21;22] The disease is registered as the underlying cause of around 14,000 deaths annually.[23] The risk of developing colorectal cancer increases dramatically with

increasing age: between the ages of 45 and 49, the crude incidence rate is around 20 per 100,000 for men and women; above age 75, the incidence rate increases to around 400 per 100,000 in men, and 250 per 100,000 in women.[21]

Malignant transformation – the adenoma-carcinoma sequence and de novo cancers

It is widely accepted that most colorectal cancers arise from pre-existing adenomas through the adenoma-carcinoma sequence.[24] Indirect evidence suggests that a small proportion of cancers arise de novo, although this theory remains subject to some controversy.[25]

Relationship between adenoma formation and malignancy

Although colorectal adenomas are common by the fifth and sixth decades of life, the majority do not become malignant. Intermediate- and high-risk adenomas (advanced pathology i.e. ≥1cm, villous elements, severe dysplasia, or multiple presence)[5] have an increased predisposition to malignant transformation. Hyperplastic polyps pose a minimal risk of malignancy.

Sporadic and inherited colorectal cancer

Sporadic CRC accounts for between 90-95% of all cases, whilst the remainder are related to two inherited CRC syndromes: Familial Adenomatous Polyposis (FAP) and Hereditary Non-Polyposis Colorectal Cancer (HNPCC). HNPCC is caused by germline mutations in tumour suppressor mismatch repair (MMR) genes; this may be inherited or arise as a de novo genetic mutation in individuals without a family history of colorectal cancer. HNPCC is associated with earlier onset than sporadic colorectal cancer, typically around the age of 45. FAP is caused by mutation in the tumour-suppressor adenomatous polyposis coli (APC) gene. FAP is less common than HNPCC, and is characterised by hundreds of colorectal adenomatous polyps, duodenal adenomatous polyps and multiple extraintestinal manifestations. Adenoma development begins early in life; if the bowel is not removed, cancer usually develops around age 20-30 years. The lifetime risk of colorectal cancer for FAP patients is close to 100%.[18]

Other increased-risk groups for developing colorectal cancer

Dysplasia is recognised as a histopathological marker for malignancy.[18] Patients with long-standing ulcerative colitis and Crohn's colitis have an increased risk of developing colorectal cancer. Individuals with a positive family history despite the absence of genetic mutation also have an increased risk of developing the disease.

Synchronous and metachronous neoplasia

Neoplasia may occur as a single event. However, synchronous tumours can occur, whereby two primary tumours are identified at the time of diagnosis within different parts of the

bowel, or where a primary colorectal tumour is accompanied by secondary metastases. Further, colorectal tumours may be accompanied by synchronous premalignant adenomas.[26] In a small number of cases, metachronous primary tumours may develop following the detection and removal of the index tumour (this is particularly common in HNPCC carriers).

1.3.2 Disease-specific factors - Diagnosis

Symptoms associated with malignant and benign colorectal pathology

The symptomatology of colorectal cancer is similar to several non-malignant pathologies including haemorrhoids, diverticular disease, constipation, coeliac disease, and irritable bowel syndrome (IBS). Common symptoms upon presentation include rectal bleeding, change in bowel habit, urgency, incomplete emptying, increased frequency, mucus, abdominal pain and peri-anal symptoms (for example pain on defecation, weight loss, and appetite loss).[27] Acute symptoms include obstipation, abdominal pain and vomiting which may indicate the presence of bowel obstruction. Left without intervention, obstruction may result in faecal peritonitis and imminent death.

1.3.3 Disease-specific factors - Clinical disease

Relationship between cancer stage and subsequent prognosis

Cancer stage at diagnosis is a strong predictor of subsequent prognosis.[2;28] Several staging classifications exist including the standard numerical staging system (I-IV), the Turnbull and Astler-Coller modifications[29;30] of the Dukes' staging system,[31] and the TNM staging system.[20] Table 1.1 presents the relationship between these staging systems together with approximate 5-year survival estimates.[28]

Table 1.1 Colorectal cancer staging classifications (from Van Cutsem[28])

TNM	Stage	Dukes' stage (including Turnbull modification)	5-year overall survival (likely range)
T in situ N0 M0	0	-	Likely to be normal
T1 N0 M0	I	A	>90%
T2 N0 M0	I	B	85%
T3 N0 M0	IIa		70-80%
T4 N0 M0	IIb		
T1-2 N1 M0 / T2 N2 M0	III	C	25-60%
T3 N1 M0 / T3 N2 M0	III		
T4 N1 M0	III		
Any T any N M1	IV	D	5-30%

Colorectal cancer recurrence

Following resection of the primary tumour, some patients will develop recurrence (relapse). Recurrence may be anastomotic (at the area of anastomosis), locoregional (at the site in the

abdomen of previous disease, and/or in the lymph nodes, but not necessarily in the bowel) or distant (spread to other organs, most commonly the liver and the lungs). Local relapse is a common problem for rectal cancer. Whilst local relapse rates tend to be low for colon cancer, this may be due to under-reporting (Personal communication: Dr Rob Glynne-Jones, Consultant Oncologist, Mount Vernon Cancer Centre). Broadly speaking, the risk of distant relapse increases with Dukes' stage. With the exception of a small proportion of patients in whom further resection is possible, the prognosis for patients with metastatic disease is poor, hence a key goal of adjuvant treatment is the avoidance of relapse. The risk of relapse is believed to be very low five years after surgical resection of the primary tumour.[32]

Potentially curative treatment for distant metastases

Resection of liver metastases may enable long-term cure in a small number of patients with distant metastases, although this depends on the number, location and extent of metastases and the volume of remaining liver following resection. In a lesser number of patients, similar benefits may be seen following the resection of pulmonary metastases.

1.3.4 Disease-specific factors - Death

Generally speaking, death due to colorectal cancer is a result of two specific causes: death due to metastatic disease and tumour burden, and in a lesser number of cases, faecal peritonitis resulting from bowel obstruction.

1.4 Conceptual service pathways models for colorectal cancer (Stage 2a)

A basic service breadth model describing the main components of the colorectal cancer service was previously outlined in Figure 3.1 and is therefore not reproduced here. This section draws out the complexity of the main colorectal cancer service pathways in England and Wales by presenting a series of diagrammatic service depth models together with supporting textual description. Owing to the size and complexity of the cancer system, the service pathways model is divided into nine related modular components:

Pathway A – Colorectal cancer presentation, referral and diagnosis

Pathway B – Treatment of colon cancer

Pathway C – Treatment of rectal cancer

Pathway D – Colorectal cancer follow-up after surgery with curative intent

Pathway E – Treatment of metastatic colorectal cancer

Pathway F – Surveillance of individuals with adenomatous polyps

Pathway G – Surveillance, diagnosis and treatment of FAP

Pathway H – Surveillance and management of HNPCC

Pathway I – Surveillance of long-standing ulcerative colitis/Crohn's disease

1.4.1 Pathway A – Colorectal cancer presentation, referral and diagnosis

Patients with significant colon or rectal pathology may present in a variety of ways. The most common entry routes for a diagnosis of colorectal cancer and other colorectal pathologies are:

1. Early detection via colorectal cancer screening.
2. Symptomatic clinical presentation to a GP;
3. Presentation at an A&E department;
4. Referral from elsewhere in secondary care;

The four main colorectal cancer diagnostic pathways (GP, A&E, secondary care referral and screening) are discussed in this section. A diagrammatic representation of current diagnostic pathways is presented in Figure 1.2.

As noted above, certain groups of patients are known to have an increased risk of developing colorectal cancer, these include:

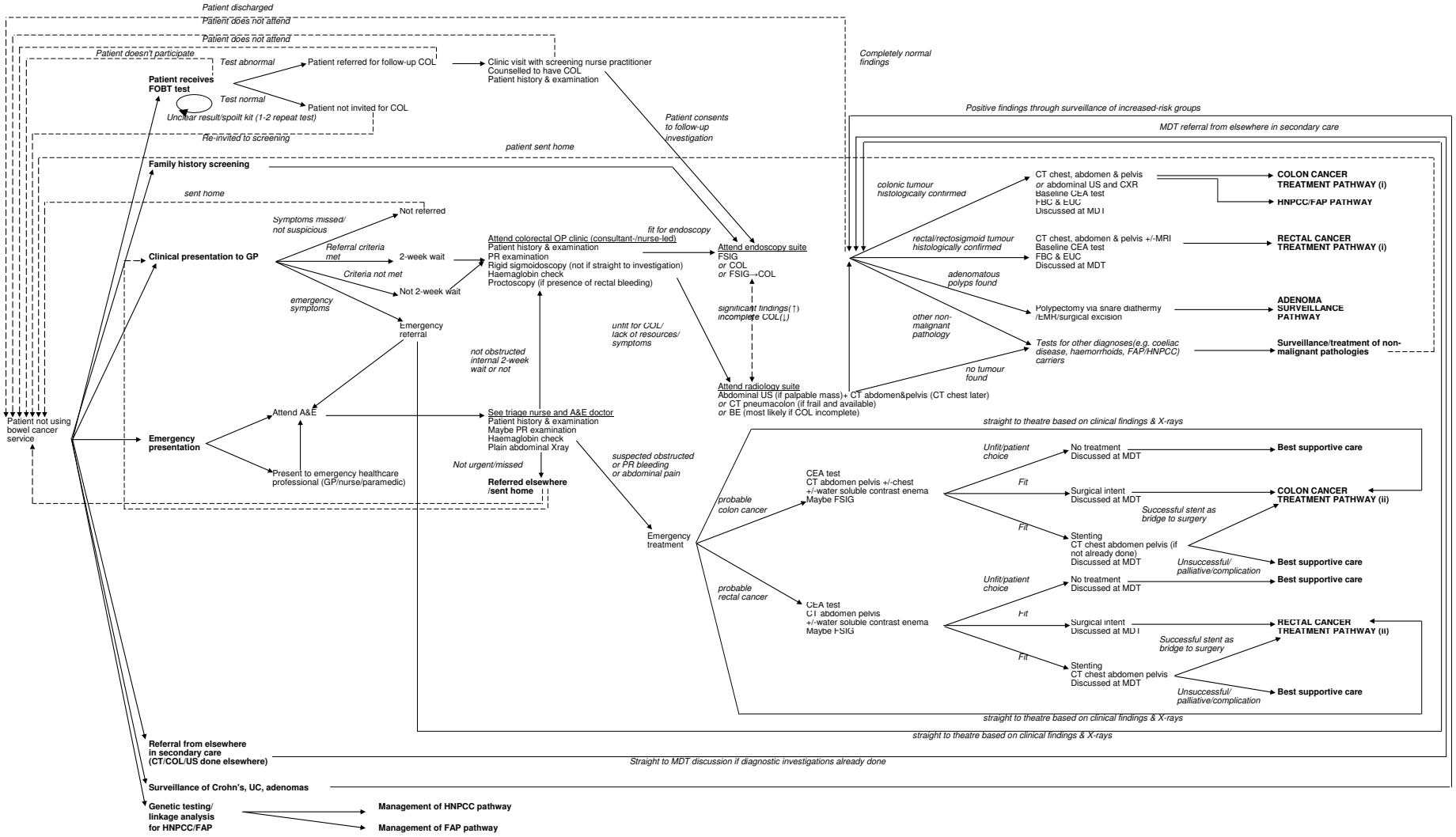
- Individuals who are identified with FAP;
- Individuals who are identified with HNPCC;
- Individuals who are identified as having adenomatous polyps;
- Individuals with long-standing Crohn's disease or ulcerative colitis (UC);
- Individuals with a positive family history with or without a known genetic mutation.

Whilst many individuals with FAP and HNPCC will have been identified through linkage (family history) analysis or through a clinical genetics department, some will present symptomatically through the main diagnostic pathways described in Figure 1.2. In particular, some cases of FAP and HNPCC will arise due to a de novo genetic mutation, hence they will not have a family history, but will instead be picked up as they develop symptoms. Asymptomatic individuals with a positive family history may also be invited to attend COL screening between the ages of 35 and 55. Patients may also enter the system through the surveillance of non-malignant conditions such as ulcerative colitis, Crohn's disease or through surveillance of individuals with a history of adenomas; these entry routes are detailed in Pathways I and F.

Diagnosis route 1 – Participation in colorectal cancer screening

Colorectal cancer screening using biennial guaiac FOBT has recently been rolled out across England for individuals aged 60-69 years. A programme extension up to age 74 is currently in implementation. Individuals are sent an FOBT kit and are asked to collect 2 samples from each of 3 separate bowel motions.[33] Participants are required to return completed FOBT kits for analysis within 14 days of collecting the first sample. In the event that the test result is unclear, spoilt or subject to a technical failure, 1-2 repeat tests may be dispatched.

Figure 1.2 Main diagnostic pathways for colorectal cancer



Individuals who fail to return the completed test kit are sent a reminder letter. Subjects in whom a normal test result is obtained are re-invited to participate in the next screening round provided they still meet age eligibility criteria and provided they have not opted out of the programme. Subjects in whom an abnormal test result is found are invited to attend a clinic visit with a screening nurse practitioner to discuss whether they wish to undergo a follow-up COL, to answer any questions about the procedure and to assess the patient's fitness to undergo COL.[33] The subject may decline this invitation; these individuals would likely be re-invited to participate in the next screening round provided they are still eligible. If they test positive at the subsequent screening round and again decline the invitation to the nurse clinic, the patient's GP would be informed and they would no longer be invited to participate in the programme (Personal communication: Julietta Patnick, Director, NHS Cancer Screening Programmes, Sheffield). For subjects who attend the clinic, COL would be the investigation of choice, however complete COL to the caecum may not be possible in some patients. In such instances an alternative test, for example barium enema (BE) or CT colonography (CTC) may be used. Subsequent diagnostic pathways are identical to those for symptomatic patients.

Diagnosis route 2 – Patients who present symptomatically to their GP

Patients who present symptomatically to their GP and are either referred or not (appropriately or missed), based upon current guidelines for the referral of patients with suspected colorectal cancer.[3] The GP may undertake certain investigations themselves which trigger the decision to refer, for example screening blood tests, liver function tests and US examinations. Where referral is deemed appropriate, there are three broad options:

(1) Fast-track referral ("2-week wait") - where one or more of the following symptoms and signs occur:
    - Rectal bleeding with a change in bowel habit towards looser stools and/or increased frequency of defecation persistent for 6 weeks (≥40 years of age).
    - Rectal bleeding persisting for 6 weeks or more without a change in bowel habit and without anal symptoms (≥60 years of age).
    - Change in bowel habit towards looser stools and/or more frequent stools persisting for 6 weeks or more without rectal bleeding (≥60 years of age).
    - Right lower abdominal mass consistent with involvement of the large bowel (all ages).
    - Palpable rectal mass (intraluminal and not pelvic, all ages).
    - Unexplained iron deficiency anaemia and a haemoglobin of 11g/100ml or below (men, all ages).
    - Unexplained iron deficiency anaemia and a haemoglobin of 10g/100ml or below (non-menstruating women).[3]

(2) Emergency admission - if the patient has acute obstructive symptoms such as obstipation, abdominal pain (although this may be present without obstruction) and vomiting, or non-obstructive symptoms such as profound rectal bleeding, they may be referred directly to A&E.
(3) Standard referral - not "2-week wait" i.e. where the above criteria are not met.

Patients who are referred either as a "2 week wait" or as a standard referral are invited to attend a normal clinic which may be either nurse- or consultant-led. At the clinic:

- All patients would undergo a general consultation (patient history and general examination e.g. abdominal examination);
- All patients would have a per-rectal (PR) examination to determine whether the patient has a palpable mass in their rectum or anal canal;
- All patients would undergo either a rigid sigmoidoscopy or FSIG to look for the presence of rectal cancer. FSIG is currently less common at this stage although may sometimes be used as "straight to investigation" on the basis of symptoms described in the referral letter from the GP, perhaps via a specialist nurse-led one-stop clinic;
- Most patients would have a haemoglobin check undertaken by a phlebotomist;
- If there is evidence of rectal bleeding, the patient would also have a proctoscopy which allows for the visualisation of the anal canal (usually looking for haemorrhoids, visualising around 8 cm of the anal canal and rectum).

From the clinic, the patient would either attend an endoscopy suite or a radiology suite.

If the patient attends the endoscopy suite, investigative options include:

- FSIG - if this suggests the presence of cancer or adenomas, the patient would undergo COL to rule out synchronous disease;
- COL - this is the gold standard diagnostic investigation, however this carries the greatest risk of perforation and subsequent complications. If complete COL to the caecum is not possible, the patient may undergo a completion BE in the radiology suite. The use of diagnostic CTC is increasing and is likely to lead to the phasing out of BE, however this is not available in all centres.

If the patient attends the radiology suite following the clinic visit, they will undergo one of three investigations:

- If a palpable mass is found during the abdominal examination in the clinic, the patient may have a CT scan of their abdomen and pelvis (they would receive a chest CT later);
- A BE which is performed by a radiographer/supervising radiologist and reported by a radiologist or a radiographer. BE may be elected in place of endoscopy based on the

patient's symptoms, particularly abdominal pain and constipation, or where a diagnosis of diverticular disease is considered more likely than cancer. Alternatively BE, may be elected for patients who are unfit for COL.

- If the patient is frail, they may undergo CTC performed by a radiographer/supervising radiologist and reported by radiologist (subject to availability of this technology).

Each of the above investigations carries a small risk of complications such as colonic perforation either due to bowel preparation or the procedure itself. The majority of perforations manifest symptomatically shortly after the test. Many perforations can be managed conservatively, however some will require emergency surgery. Conservative management may be followed by repeated radiological investigation, most likely BE.

Patients with a completely normal diagnosis on the basis of the above tests may be discharged at this point. If a tumour is found at endoscopy, the patient will undergo staging of the chest, abdomen and pelvis via a CT scan or abdominal US and chest x-ray (CXR). If a tumour is found at radiology, the patient will attend the endoscopy suite for direct bowel visualisation/biopsy via COL to rule out synchronous disease. If the patient has not already undergone a CT scan of their chest, they will do so at this point. Right-sided or transverse colon tumours are not necessarily visualised and biopsied, although two criteria of malignancy should be fulfilled before resection such as a positive BE and anaemia, a positive CT scan, or presence of a palpable mass. Diagnosis can only be confirmed through histological confirmation via biopsy; where this is not possible, e.g. emergencies or patients who do not undergo endoscopy, diagnosis is confirmed later via resection histology.

If the neoplasia is rectal or rectosigmoid, most patients receive an MRI and CT scan, with the remainder undergoing CT alone. Patients with a positive diagnosis of colorectal cancer may have a baseline CEA test and appropriate treatment options or palliation would be discussed at a Multidisciplinary Team (MDT) meeting. A full blood count (FBC) and electrolytes, urea and creatinine (EUC) examination are also undertaken.

If the patient is diagnosed with other non-malignant pathology but is considered to be at an increased-risk of subsequently developing colorectal cancer due to the presence of adenomas, they will have their polyps removed through polypectomy with snare diathermy or endoscopic mucosal resection (EMR). This may require a second visit if the endoscopist is not proficient in EMR. These patients are subsequently offered endoscopic surveillance using COL, in line with BSG guidelines[5] (see Pathway F). In a small number of cases it will not be possible to remove adenomas via polypectomy and surgery may be required. Other non-

neoplastic diagnoses such as hyperplastic minimal risk polyps are either left in situ or removed by polypectomy with snare diathermy, usually without subsequent surveillance. Individuals with other non-malignant pathologies may be offered further tests to establish a diagnosis and possibly further treatment; these patients would be subsequently be managed by a medical team.

Diagnosis Route 3 – Presentation at A&E

Patients may present either at an A&E department directly, or may be referred to A&E as an emergency admission after seeing their GP, or following a visit from an emergency care practitioner (nurses or paramedics). The patient would see a triage nurse to establish how quickly they need to be seen. The patient would then see an A&E doctor who would take their history, undertake a general examination (with or without a PR examination) and arrange simple investigations as deemed appropriate i.e. blood tests and plain abdominal x-ray, based on a number of factors, such as abdominal pain, or concerns regarding obstruction. Patients believed to be suffering from obstruction would be referred directly to surgery on the basis of their history and general examination only (the need for admission depends on symptoms at presentation). Only rarely do patients present at A&E with haemorrhage sufficient to warrant emergency admission; whilst many patients present with PR bleeding, most will settle spontaneously and can be subsequently investigated in an outpatient setting. A proportion of individuals presenting at A&E would be referred elsewhere if their diagnosis is considered to be non-surgical. For example, patients presenting with symptoms of gastroenteritis such as abdominal pain and diarrhoea may be referred to a medical team, mainly based on their history, however an abdominal x-ray may be ordered to rule out obstruction, and blood tests will be done as part of their work-up. A more common route of referral is with iron deficiency anaemia, presenting to the physicians/A&E with cardiac failure, angina, myocardial infarction, or shortness of breath. Patients without urgent symptoms may be sent home or referred for diagnostic investigations either as an internal 2-week wait or standard referral. A proportion of individuals presenting at A&E directly will be sent home if diagnostic investigations do not suggest the presence of significant colorectal pathology, benign or otherwise.

If the patient is thought to be obstructed due to the presence of a colorectal tumour, they may receive a CEA test, however this is sometimes not done at baseline due to the emergency context of care. The patient may also receive a CT of their abdomen and pelvis prior to surgery (again this may not happen due to the emergency context). For these patients, CT is used to look for the cause of the patient's symptoms such as obstruction secondary to the tumour. As these patients would not have undergone COL, a biopsy specimen would not be

available for histological confirmation. A radiologist would report on any evidence of metastases and thus stage the patient. A water soluble contrast enema may also be used to assess whether the patient is suffering from complete obstruction or pseudo-obstruction.

In some cases, the patient will go straight to theatre without undergoing further imaging based on their clinical findings (i.e. the patient's history and examination) and erect chest and abdominal film x-rays. These patients would not undergo a CT of their abdomen and pelvis, contrast enema or MRI if the cancer is rectal. Imaging would instead be undertaken postoperatively if the patient recovers from their emergency surgery. It is also possible that a patient may not undergo any imaging whatsoever; for example if a patient is admitted unwell with peritonitis (secondary to a perforated tumour) they may go straight to theatre, with all imaging taking place postoperatively.

If complete obstruction is confirmed, the patient may:

1. Receive no active intervention if they are severely compromised by co-morbidity. These patients would subsequently receive supportive care, but may perforate and die of faecal peritonitis imminently or succumb to the effects of obstruction.
2. Go straight to surgery without CT. Once recovered, these patients would subsequently have a chest CT (plus a CT of their abdomen and pelvis if not previously done). The patient would then be discussed at an MDT meeting to determine further appropriate treatment and confirm histological diagnosis.
3. Undergo stenting. Stenting would be done by a consultant radiologist or consultant endoscopist with a subsequent CT scan of their chest (the patient would also undergo a CT scan of their abdomen and pelvis if not previously done). The patient would then be discussed at an MDT meeting to determine subsequent treatment. Stenting may be done for two reasons: either (a) to act as a bridge to elective surgery i.e. to make the patient nutritionally and medically fit for surgery with a view to reducing mortality, or (b) to relieve obstruction in a patient who is either unfit or has extensive metastatic disease so that they do not suffer subsequent perforation or undergo unnecessary emergency surgery when cure is impossible. In both instances, stenting allows the clinician to "buy time" to make a more informed decision about what is in the patient's best interests. If the intention is to buy time to optimise the patient for surgery, and the stenting is successful, the patient may later undergo surgery. If the stenting is unsuccessful or if the patient has a stent complication of perforation, the patient will go on to have emergency surgery at that point if they are deemed sufficiently fit. If the intention is to use stenting to relieve obstruction in an unfit patient or one with widespread incurable metastatic disease, and stenting is successful, the patient will subsequently receive palliative/supportive care. If

the stenting is unsuccessful and the patient is unfit for further treatment, they will die of faecal peritonitis imminently. These patients would not receive further imaging.

Diagnosis Route 4 – Referral from elsewhere in secondary care

Some patients enter the colorectal cancer system from elsewhere in secondary care, having previously undergone diagnostic investigations undertaken by another medical team (usually either CT or COL which suggest probable cancer), hence these patients are referred directly to the MDT. If the patient has symptoms but has not undergone diagnostic investigations, they may go to clinic first (see Diagnostic Route 2).

1.4.2 Pathway B – Treatment of colon cancer

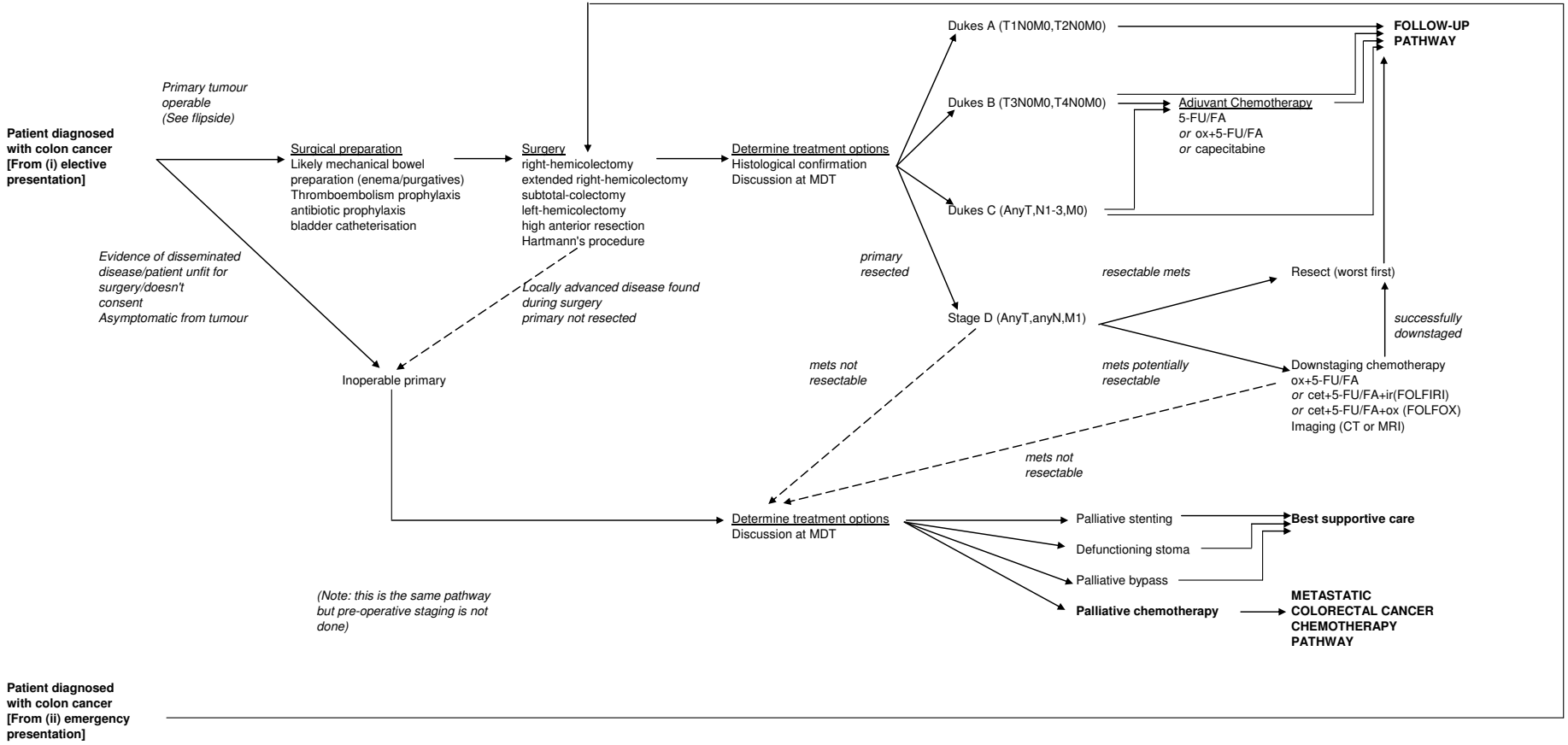
Figure 1.3 presents the main pathways for the treatment of patients who have a positive diagnosis of colon cancer.

Treatment of patients who are operable with preoperative curative intent

If the patient is operable, if there is no evidence of advanced disseminated disease, and if they consent, they would undergo surgical resection of the primary tumour (with or without prior stenting to optimise the patient - see Pathway A). Some patients who undergo stenting as a bridge to surgery may not subsequently undergo surgery. Some surgeons may require the patient to undergo mechanical bowel preparation i.e. enemas or purgatives such as Picolax, given the day before their surgery. In addition, patients may receive thromboembolism prophylaxis to avoid deep vein thrombosis (DVT) and pulmonary embolism, either using low-molecular weight heparin, graduated compression stockings, and intermittent pneumatic calf compression. All patients should receive antibiotic prophylaxis, usually at the induction of anaesthesia, to avoid postoperative sepsis. The patient would also undergo bladder catheterisation to monitor urine output during and after the operation, usually following anaesthetisation. Surgical excision is most likely to be a right-, extended right-, subtotal-, left-hemicolectomy, or high anterior resection (AR). Excision may be open or laparascopic.[17] If the tumour is not deemed fit for anastomosis (suturing or stapling of remaining colonic mucosa) due to technical impossibility or unacceptable patient risk, other techniques such as Hartmann's procedure may be used.

Some metastases may be missed by the diagnostic pathway (Pathway A) and later found at surgery; even in such instances, the primary tumour would still be resected unless unresectable locally advanced disease is identified during surgery.

Figure 1.3 Treatment pathways for colon cancer



Following surgery, patients typically remain in hospital for around 3-10 days. Longer may be required if the patient needs to learn how to manage their stoma, if they experience complications, or if their recovery is slow (Personal Communication: Dr Janine Yusuf, Surgical Registrar, Northern General Hospital, Sheffield). During recovery in hospital, nursing support is required to monitor blood pressure and pulse, drug administration and to provide general care. Physiotherapy support may also be required for mobilisation.

For elective cases, radiological staging and histological assessment of biopsy specimens would take place prior to surgery, and would be confirmed histologically post-surgery. For patients presenting as emergency cases, histological confirmation would be undertaken via examination of the resection specimen. Histology would typically be discussed with the patient around 6-weeks following surgery.

Following surgical resection and recovery, patients with Dukes' C colon cancer who are sufficiently fit will be offered adjuvant chemotherapy. Treatment usually commences 6 to 8 weeks following surgery if possible. NICE currently recommends 5-FU/FA, oxaliplatin plus 5-FU/FA and capecitabine as adjuvant chemotherapy options for Dukes' C colon cancer. In practice, oxaliplatin is sometimes used in combination with capecitabine. Adjuvant chemotherapy is given for a period of up to 6-months, although patients may discontinue treatment due to recurrence or unacceptable treatment-related toxicities.[14] Patients with Dukes' B colon cancer who are deemed to be at high-risk of relapse may also be offered adjuvant chemotherapy using 5-FU/FA based regimens, although the relationship between risk status and the clinical benefits of chemotherapy is unclear.[2] The decision to offer Dukes' B patients chemotherapy is likely to be influenced by the degree of extramural vascular invasion, poorly differentiated tumours (abnormal appearance of cells under a microscope), serosal involvement, the presence of perforation or obstruction, younger age, and patient choice. In some centres just one of these features may be enough to trigger the decision to offer adjuvant chemotherapy (Personal communication: Professor Matt Seymour, Professor of Gastrointestinal Medicine, University of Leeds). Following surgical resection, patients would be followed up according to local protocols (see Pathway D).

Management of patients with operable or potentially operable metastatic disease

A proportion of patients present with distant metastases, some of which will be immediately resectable at presentation; this is most likely to be where the patient has metastases which are confined to the liver, or in a smaller proportion of cases, the lungs. If resectable, the primary tumour will usually be resected some weeks before the metastases (staged resection). In some cases, chemotherapy may render metastases resectable. NICE does not have a separate

recommendation concerning the use of irinotecan or oxaliplatin in this indication, although current guidance implies that either irinotecan or oxaliplatin could be used.[12] More recently, NICE has recommended the use of cetuximab plus 5-FU/FA and oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) as a downstaging treatment for patients with metastatic colorectal cancer when all of the following clinical criteria are met:

- The primary colorectal tumour has been resected or is potentially operable;
- The metastatic disease is confined to the liver and is unresectable;
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.[16]

The success of downstaging chemotherapy of liver metastases would be assessed using CT or MRI after a small number of treatment cycles. If downstaging is successful, the patient may undergo surgical resection. Patients who undergo hepatic resection would subsequently be followed up by liver surgeons, whilst those undergoing pulmonary resection would be followed-up by cardiothoracic surgeons. If downstaging is unsuccessful, patients would receive palliative interventions; this may involve continuing the same regimen of chemotherapy.

Treatment of patients who are inoperable

Patients with inoperable colon cancer may undergo palliative stenting, or receive a defunctioning stoma, a palliative bypass (without resection of the tumour), palliative chemotherapy, or supportive/palliative care (see Pathway E).

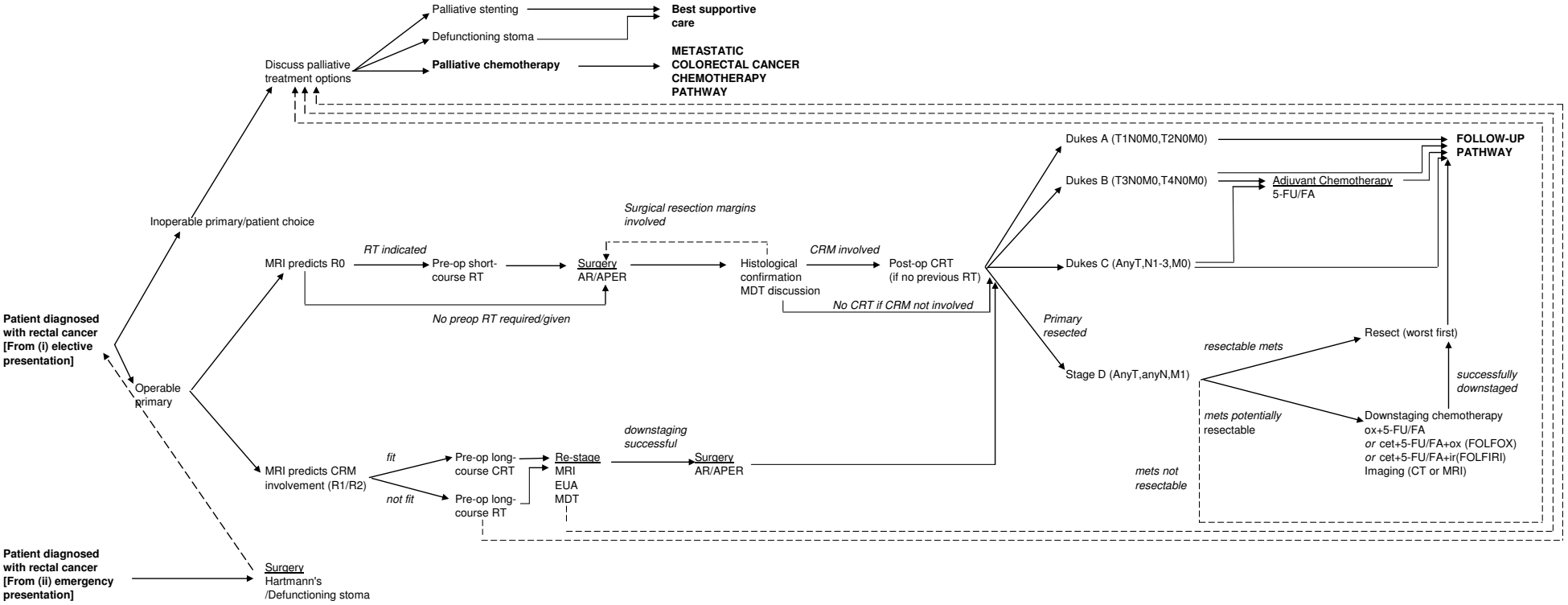
1.4.3 Pathway C – Treatment of rectal cancer

Figure 1.4 presents the main treatment pathways for patients who have a positive diagnosis of rectal cancer. The adjuvant treatment of rectal cancer differs from that for colon cancer, principally due to the benefits of chemoradiation (radiation plus concurrent chemotherapy) or radiation alone. Adjuvant chemotherapy may be used within similar indications to those for colon cancer (see Pathway B). Radiation therapy and/or chemotherapy may be used either pre-operatively or post-operatively in the adjuvant treatment of rectal cancer.

Management of patients who are operable with pre-operative curative intent

Unless presenting as an emergency, most rectal cancer patients undergo an MRI scan plus a CT scan, with the remainder undergoing a CT scan alone (see Pathway A). The results of the MRI scan are central in determining subsequent appropriate elective treatment.

Figure 1.4 Treatment pathways for rectal cancer



MRI predicts R0 resection (all margins histologically free of tumour)

Two main surgical procedures are used in the excision of rectal tumours: abdominoperineal resection (APER) and anterior resection (AR), although other techniques have been used.[18] Both APER and AR can be undertaken alongside total mesorectal excision (TME). The choice of resection technique is guided primarily by tumour location within the rectum. If the tumour is in the lower third of the rectum and the rectal MRI scan suggests that an R0 resection is possible, the surgeon will likely plan to undertake an APER. Conversely, if the tumour is in the upper two thirds of the rectum, it is likely that the surgeon will plan to undertake an AR. Some lower third rectal cancers are amenable to low AR, provided that 1cm distal clearance can be obtained and the MRI predicts an R0 resection. Decisions concerning the use of AR/APER will also depend on likely bowel function following surgery and patient preference.

Prior to surgical excision, some patients may undergo short-course pre-operative radiotherapy to reduce the risk of LR even if the tumour is fully mobile and easily resectable. Short-course pre-operative radiotherapy is given as five fractions of 25Gy over 5 days. A proportion of patients will undergo surgery without pre-operative radiotherapy. Resection histology would be confirmed following surgery and discussed at an MDT meeting. If CRM involvement is confirmed after surgery, patients who have not previously received radiotherapy may be offered post-operative chemoradiation, typically involving 5 weeks of radiation therapy plus concurrent chemotherapy using a 5-FU/FA based regimen or capecitabine. Patients in whom a successful R0 resection is achieved would not undergo further resection or post-operative chemoradiation. Patients may subsequently be offered adjuvant chemotherapy using 5-FU/FA based regimens according to local protocols, fitness and perceived risk of relapse. The decision to offer adjuvant chemotherapy is typically based on lymph node involvement, CRM involvement, extramural vascular invasion, pT4, acute presentation with obstruction, and tumour perforation.

MRI predicts R1/R2 resection (margins involved)

If the MRI predicts an R1/R2 resection, the patient would be offered long-course pre-operative radiotherapy (with or without 5-FU/FA based chemotherapy, dependent on whether the patient is able to tolerate treatment-related toxicities) to downsize the tumour. Long-course pre-operative radiotherapy (with or without concurrent chemotherapy), typically given as 25-28 fractions at 45Gy-50.4Gy, is used for macroscopic tumour shrinkage to facilitate successful resection, to reduce LR risk, and to increase the probability of sphincter preservation. Long-course chemoradiation is often used for MRI-predicted CRM involvement or for bulky, node-positive predicted T3 tumours. A pre-treatment loop ileostomy would

usually be fashioned. Patients who receive long-course radiation therapy undergo a laparoscopic or trephine defunctioning stoma to stop the bowel motion passing the irradiated field thereby avoiding complications and patient discomfort. The success of downsizing pre-operative therapy would be assessed by MRI. If the MRI results are equivocal for operability, the patient may have an examination under anaesthetic (EUA). Assessment for operability takes place around two months after completion of 5 weeks of chemoradiation. If the tumour remains inoperable, a further period of two months is advisable before reassessing for operability with or without EUA. Results would be discussed within an MDT setting. Surgical preparation (bowel preparation unless defunctioned by loop ileostomy prior to long-course chemoradiation, thromboembolism prophylaxis, and antibiotic prophylaxis) is required (see Pathway B). If the tumour is successfully downsized, the patient would undergo surgery (note that downsizing after chemoradiation may permit a restorative AR). The patient may be offered adjuvant chemotherapy using 5-FU/FA based regimens. If downsizing is unsuccessful, the patient would receive palliative/supportive care.

As with colon cancer, if the patient presents with synchronous metastases, it may be possible to resect part of the liver and/or the lungs (see Pathway B). If resectable, the primary tumour will be resected some weeks before the metastases. If the metastases are not initially resectable, it may be possible to downstage a proportion of tumours using chemotherapy. The success of downstaging would be assessed using CT or MRI. If downstaging is successful, patients would undergo surgical resection and would subsequently be followed up by surgeons. If downstaging is unsuccessful, remaining treatment options would be palliative (see Pathway E).

Management of patients who are inoperable

Patients who present as an emergency may undergo a Hartmann's procedure or receive a defunctioning stoma to relieve the obstruction. This may render the tumour operable, in which case the patient would be staged and subsequently follow the pathways for operable rectal cancer described above. If perforated, a subtotal colectomy with ileostomy is likely to be required. Palliative stenting is unlikely to be a viable option for the majority of rectal cancer patients due to the technical impossibility of stent insertion low in the rectum, the patient's awareness of the stent, and the likelihood of patient intolerance due to tenesmus (an ineffectual urge to evacuate the bowels). The remainder would be treated palliatively. Palliative treatment of rectal cancer is typically similar to that for colon cancer in terms of the chemotherapy options available (see Pathway E). If the patient has not previously received radiotherapy, they may also be offered dose-limited palliative radiotherapy for metastatic disease.

1.4.4 Pathway D Colorectal cancer follow-up after surgery with curative intent

As noted in Chapter 5, a "gold standard" follow-up regimen does not exist; the timing and frequency at which each investigation is undertaken varies markedly between centres.[34] Figure 6.8 in the previous chapter presented the follow-up schedule recommended by the North Trent Cancer Network;[35] however this is not reflective of many cancer centres with respect to the types, quantities or timing of investigations used. Figure 1.5 presents the results of a recent ad hoc survey of the Royal College of Radiologists. This survey highlights considerable variation in the use of CEA, CT and US as part of routine colorectal cancer follow-up (provided through personal communication with Dr Rob Glynne-Jones, Consultant Oncologist, Mount Vernon Cancer Centre).

Figure 1.5a Variation in CT/US tests offered each year by centre within sample

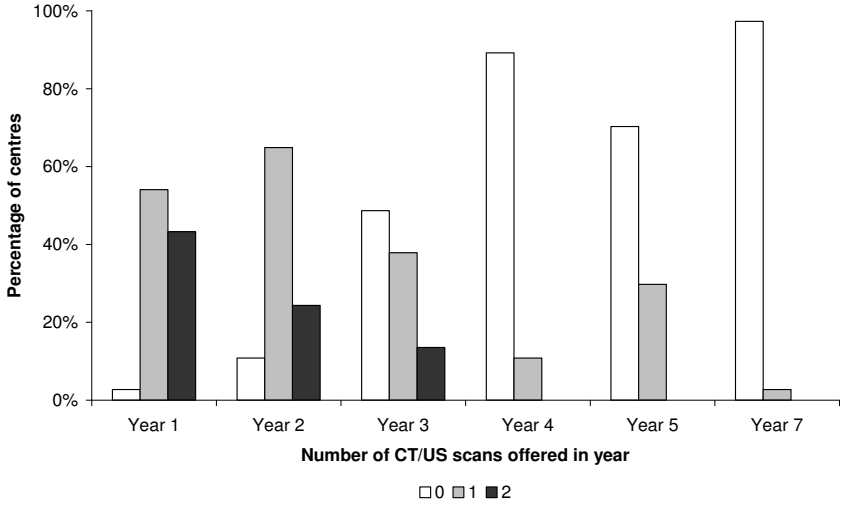


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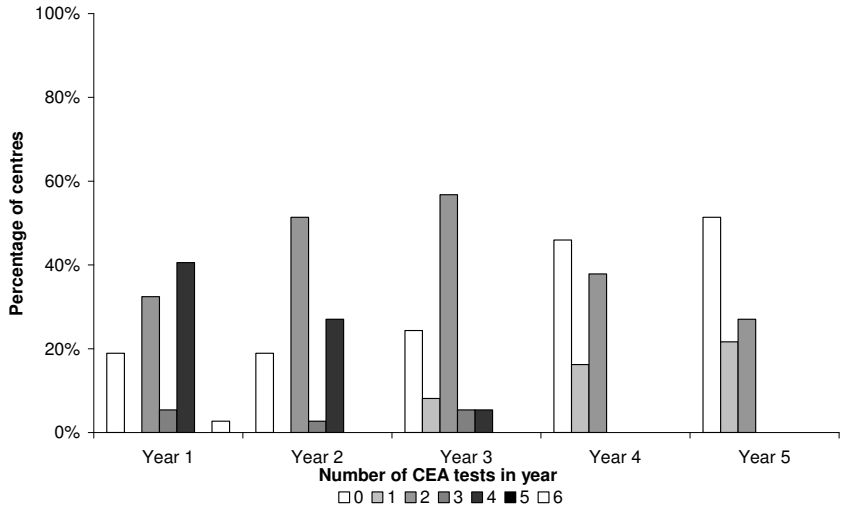
Figure 1.5b Variation in CEA tests offered each year by centre within sample



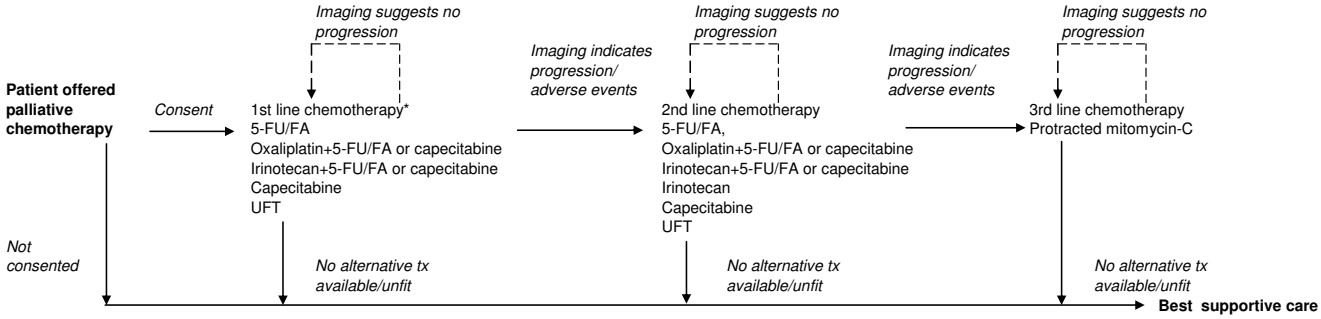
Irrespective of the follow-up schedule adopted, relapse in patients undergoing routine follow-up may be identified through abnormal rises in CEA, abnormal results identified through radiological imaging or COL, or symptomatic presentation during the interval between

scheduled follow-up visits. These patients may re-present via their GP or as emergency cases (see Pathway A), or alternatively they may present with symptoms at scheduled follow-up appointments. If CT or MRI of the liver/pelvis suggests recurrence, the patient may be offered further surgical resection, or downstaging/palliative chemotherapy as described in Pathways B, C and E.

1.4.5 Pathway E Treatment of metastatic colorectal cancer

For those patients who will not benefit from further surgery, treatment options are essentially palliative, and are intended to control symptoms and improve HRQoL. Survival benefits in this patient group are only possible through the use of active chemotherapy, although these are typically modest, even for newer agents.[7;8;36] If sufficiently fit, and they choose to receive further active treatment, patients may be offered chemotherapy using a variety of alternative regimens (see Figure 1.6).

Figure 1.6 Chemotherapy pathways for unresectable metastatic colorectal cancer



** a small number of patients may receive raltitrexed due to contraindications to 5-FU/FA or capecitabine*

NICE currently recommends infusional 5-FU/FA, alone or in combination with irinotecan or oxaliplatin as first-line and second-line treatment options for the management of advanced CRC.[12] Most commonly, 5-FU/FA-based regimens for advanced CRC are given according to the modified de Gramont regimen in the UK. This involves an initial bolus and subsequent infusional components which allow the majority of chemotherapy to be administered in an outpatient setting over 2-weekly cycles.[37] There is some evidence that giving all three cytotoxic drugs is better than two,[38] hence the optimal recommended treatment sequences are likely to be either 5-FU/FA plus irinotecan followed on progression by 5-FU/FA plus oxaliplatin or the reverse sequence, although treatment options are guided by patient preferences, tolerability of adverse events and patient fitness. Some patients will receive only a single line of therapy. Other treatment options include capecitabine and tegafur with uracil (UFT).[13] Following disease progression on second-line chemotherapy, a small proportion of patients may subsequently receive third-line salvage chemotherapy; this is likely to be mitomycin-C plus protracted 5-FU (Personal Communication: Dr David Radstone,

Oncologist Clinical Oncologist, Royal Devon and Exeter NHS Foundation Trust), although there is currently no firm guidance on which therapy should be used. Cetuximab is not currently recommended by NICE,[15] except in the downstaging of liver metastases which may subsequently become amenable to subsequent resection (maximum of 16 weeks treatment). Raltitrexed is not recommended in any indication,[12] but is used in some centres for a minority of patients who develop coronary artery spasm and therefore cannot receive 5-FU/FA based regimens. Bevacizumab is currently under appraisal by NICE as a first-line treatment.

1.4.6 Pathway F Surveillance of individuals with adenomatous polyps

Figure 1.7 presents the BSG guidelines for the surveillance of individuals in whom colorectal adenomatous polyps are found; this algorithm is described below.[5] Whilst patients are undergoing surveillance it is unlikely that they would be invited to attend screening. Adenoma surveillance is not usually recommended beyond the age of 75 years.

Management of low-risk individuals (1-2 small [< 1cm] adenomas)

Individuals in whom low-risk adenomas are identified would undergo polypectomy and subsequently receive either no follow-up or COL after 5-years. If the follow-up COL indicates no further polyps, the patient would be discharged. If surveillance COL at 5-years indicates intermediate- or high-risk adenomas, they would follow surveillance pathways below.

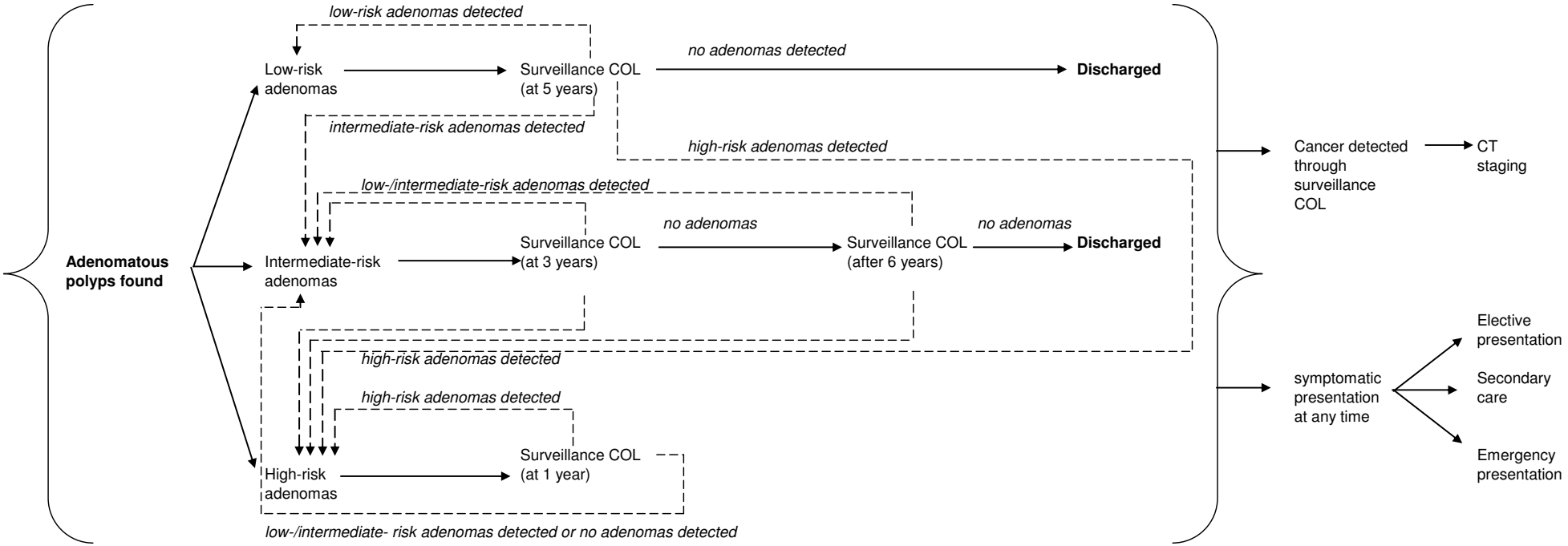
Management of intermediate-risk individuals (3-4 small adenomas, or at least one > 1cm)

Individuals in whom intermediate-risk adenomas are detected would undergo polypectomy and 3-yearly surveillance COL. If the individual receives 2 consecutive negative COL examinations, they would be discharged. If low- or intermediate-risk adenomas are detected at follow-up, they would return to the beginning of this pathway. If high-risk adenomas are detected at follow-up, they would enter the high-risk pathway.

Management of high-risk *individuals (≥5 adenomas or ≥3 adenomas with at least one >1cm)*

Individuals in whom high-risk adenomas are detected would undergo polypectomy and a first surveillance COL after 1 year. If this COL identifies no adenomas, low- or intermediate-risk adenomas, the individual would enter the intermediate-risk pathway. If further high-risk adenomas are identified, the individual would then re-enter the high-risk surveillance pathway.

Figure 1.7 Surveillance pathways for colorectal adenomatous polyps (following baseline COL and polypectomy)

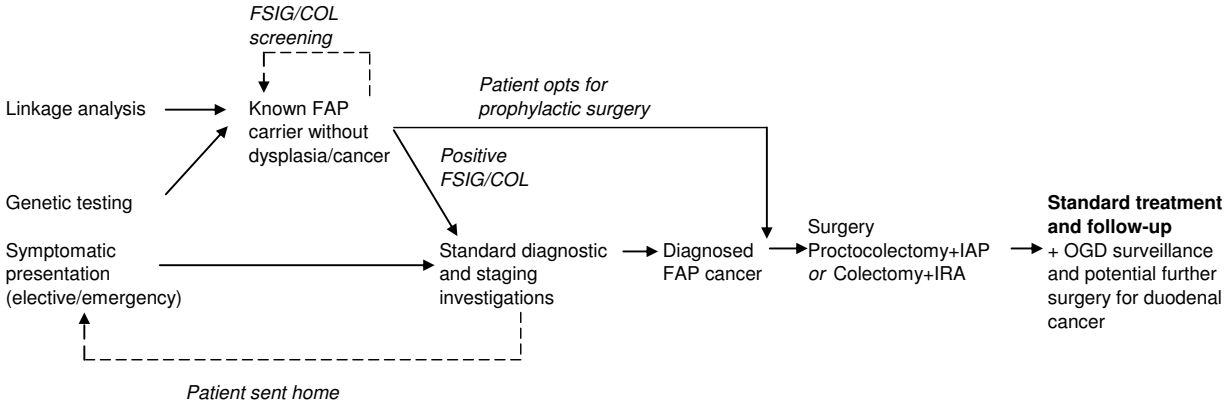


Note: Patient taken off the list if they do not attend after 3 invites

1.4.7 Pathway G Surveillance, diagnosis and treatment of Familial Adenomatous Polyposis

Typical pathways for the surveillance and management of FAP are presented in Figure 1.8.

Figure 1.8 Surveillance, diagnosis and treatment of FAP



FAP carriers are identified either through linkage analysis and/or genetic testing (direct mutation analysis) once they reach the age of around 12, or through COL investigations undertaken due to symptomatic presentation (see Pathway A). FAP patients in whom malignant colorectal tumours are not found are offered ongoing annual FSIG surveillance between the ages of 13-15 years. It is recommended that at the age of about 20 years, COL surveillance should be started, alternating between FSIG and COL thereafter. FAP carriers without a diagnosis of colorectal cancer may be offered prophylactic surgery at an early age. If cancer is found via surveillance endoscopy, the patient would undergo a CT scan of their chest, abdomen and pelvis or an abdominal US with a normal CXR. If the neoplasia is rectal, the patient will undergo an MRI scan. Upon a confirmed diagnosis of cancer, the patient will receive a haemoglobin test, a CEA test and treatment options will be discussed at an MDT meeting. Surgical options include:

(1). Surgical removal of the bowel and rectum via proctocolectomy plus ileoanal pouch (IAP) followed by duodenal surveillance via oesophagogastroduodenoscopy (OGD) (6-monthly to 3-yearly depending on the severity of duodenal polyposis);

(2). Surgical removal of the bowel via colectomy plus ileorectal anastomosis (IRA) followed by surveillance of the rectum using FSIG and duodenal surveillance via OGD (again 6-monthly to 3-yearly depending on severity of duodenal polyposis).

The choice of surgery is driven by:

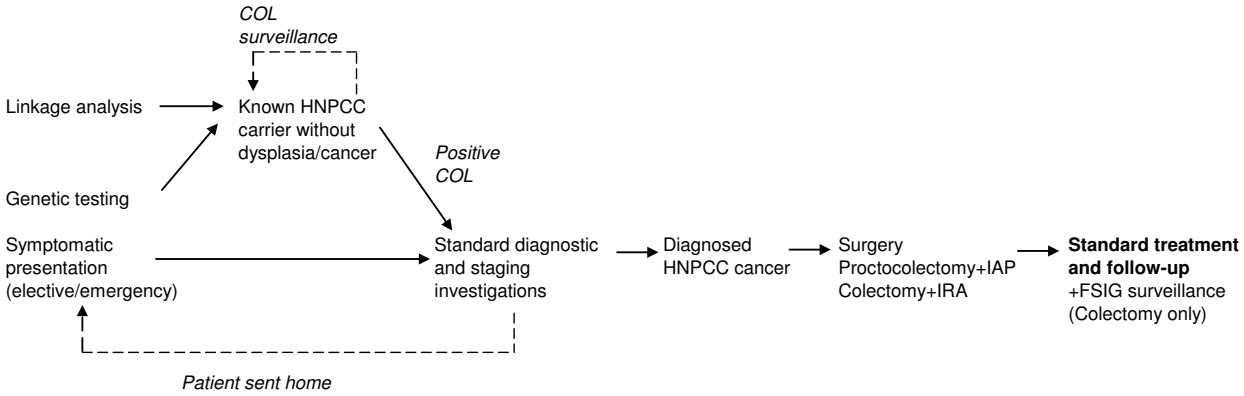
- Patient preference with respect to saving bowel and related functioning;
- The location of polyps - relative rectal sparing, lower risk of rectal cancer before 50 years but higher risk of infertility with rectal excision and pouch versus colectomy and IRA;
- The location of the cancer if present.

Following colectomy and IRA, polyp surveillance using rigid sigmoidoscopy or FSIG continues 6-12 monthly; identified polyps are controllable with argon plasma coagulation or snare polypectomy or fulguration (tissue destruction) by diathermy. The presence of a high polyp load which is not amenable to polypectomy, or the presence of rectal cancer, are indications for proctocolectomy and pouch or proctectomy and ileostomy. If further polyps or dysplasia are found after the primary surgery, the patient may have their rectum surgically removed and have an IAP as described above. Treatment of patients in whom cancer is identified is essentially the same as that for sporadic colorectal cancers in terms of resection, chemotherapy, and follow-up (see Pathways B and C). The patient would also subsequently undergo OGD surveillance as described above. If duodenal cancer is detected via OGD surveillance and the patient is sufficiently fit, the patient may be considered for Whipple's procedure (pancreaticoduodenectomy), which involves resecting the head of the pancreas, the duodenum and the bile duct (this is rare). If the patient is unfit for further surgery, they may be offered palliative/supportive care. Abdominal surgery may be prevented by the development of desmoid disease which usually presents as intestinal obstruction or a palpable abdominal mass; in such instances, palliative chemotherapy may be useful.

1.4.8 Pathway H Surveillance, diagnosis and treatment of Hereditary Non-Polyposis Colorectal Cancer

Typical pathways for the surveillance and management of HNPCC are presented in Figure 1.9.

Figure 1.9 Surveillance, diagnosis and treatment of HNPCC



As with FAP, HNPCC patients may be identified either through family history or through symptom-driven COL. Clinical genetics input is essential. Patients begin surveillance via COL every 2 years at the age of 25 or at 5 years younger than the youngest HNPCC affected relative (whichever is earlier). Surveillance continues until either: the patient reaches age 75, or until the causative mutation in that family has been excluded. Patients with probable cancer undergo a CT scan of their chest, abdomen and pelvis or an abdominal US with a normal

CXR. If the neoplasia is in the rectum the patient will undergo an MRI scan. Upon a confirmed diagnosis of cancer, the patient will also have a CEA test and treatment options will be discussed within an MDT setting. Following a confirmed diagnosis of CRC, or prophylactically, patients with HNPCC are offered:

(1) Surgical removal of their bowel and rectum via proctocolectomy plus IAP;
(2) Surgical removal of bowel via colectomy plus IRA followed by surveillance of the rectum using FSIG at 1-3 yearly intervals. This option is more usual than proctocolectomy.

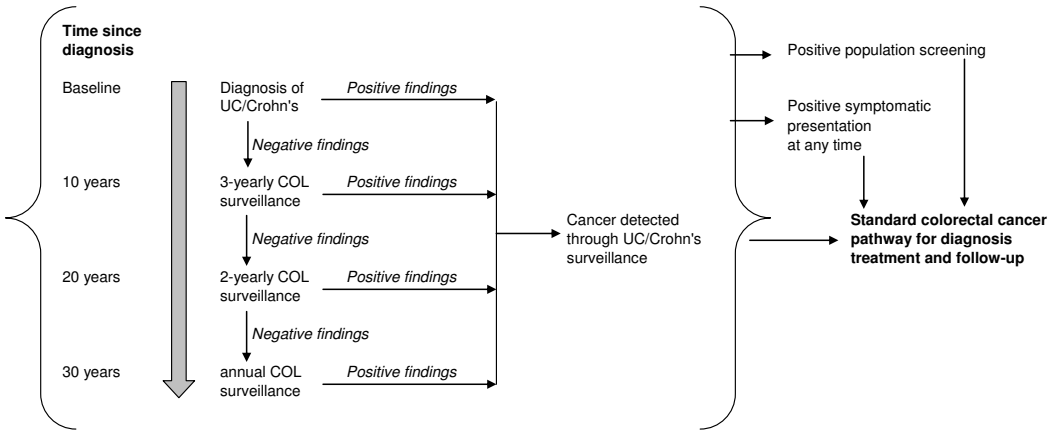
As with FAP, the choice of surgery is driven by patient preferences and tumour location. If further polyps or dysplasia are found in patients who have had a colectomy and ileorectal anastomosis, the patient will have their rectum excised and will have an IAP or permanent ileostomy as described above. As with FAP, HNPCC patients may also be offered OGD surveillance. The remaining treatment pathway is similar to that for sporadic cancer.

1.4.9 Pathway I Surveillance of long-standing ulcerative colitis*/Crohn's* surveillance groups

Figure 1.10 presents typical surveillance pathways for individuals diagnosed with UC/Crohn's disease. These patients are managed via their GP and gastroenterologists (seen for diagnosis of UC/Crohn's). Patients are offered regular COL surveillance at intervals of 1-3 years depending on time since initial diagnosis of UC/Crohn's:

- annual COL for patients who have had UC/Crohn's between 30/40 years;
- 2-yearly COL for patients who have had UC/Crohn's between 20/30 years;
- 3-yearly COL for patients who have had UC/Crohn's between 10/20 years.

Figure 1.10 Surveillance of long-standing ulcerative colitis/*Crohn's* disease



The finding of colorectal cancer, severe dysplasia or dysplasia associated lesion or mass (DALM) is an indication for proctocolectomy and IAP or permanent ileostomy. Pouch patients will need ongoing pouchoscopy and biopsy on a long-term annual basis.

Discussion

This paper has set out a series of descriptive conceptual models of colorectal cancer and its detection, diagnosis, management and follow-up. The conceptual models presented here have been drawn from a number of evidence sources including clinical guidelines and a substantial amount of expert opinion. It is important to recognise that clinical guidelines prescribe how certain aspects of a clinical system should be delivered nationally, whilst expert opinion is likely to reflect how the system is delivered locally. For certain aspects of the service, for example, diagnostics and follow-up following treatment with curative intent, the two evidence sources may conflict due to geographical variation. In particular this may be driven by local protocols, historical service provision, the current availability of resources, and local enthusiasms. Given this tension, the colorectal cancer service described in this paper inevitably reflects a mix of what should happen in principle and what does happen in practice. Further, the diffusion of ongoing research into day-to-day medicine means that the colorectal cancer service has evolved over time and will continue to do so in the future. These issues should be borne in mind when considering the content of this paper. Despite these concerns, it is anticipated that explicitly setting out our current understanding of the disease and its management may lead to greater consistency in health economic models of colorectal cancer, and ultimately the decisions arising from their use.

References

(1) Trueman P, Chilcott JB, Tappenden P, Lowson K, Pilgrim H, Bending M et al. Bowel cancer services: Costs and benefits. 2007. York, York Health Economics Consortium/School of Health and Related Research (University of Sheffield).

(2) National Cancer Guidance Steering Group. Improving outcomes in colorectal cancer: Manual update. 1-136. 2004. London, National Institute for Clinical Excellence.

(3) The National Collaborating Centre for Primary Care. Referral guidelines for suspected cancer in adults and children. Part 1, 1-421. 2005. London, National Institute for Health and Clinical Excellence.

(4) Department of Health. Referral guidelines for suspected cancer. 1-62. 2000. DH, available from http://www.dh.gov.uk (accessed 22/09/2009).

(5) Atkin WS, Saunders BP. Surveillance guidelines after colorectal adenomatous polyps. Gut 2002; 51(Suppl V):v6-v9.

(6) The Association of Coloproctologists in Great Britain and Ireland. Guidelines for the management of colorectal cancer. 2001. London, ACPGBI.

(7) Hind D, Tappenden P, Tumur I, Egginton S, Sutcliffe P, Ryan A. The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation. Health Technology Assessment 2008; 12(15):i-182.

(8) Ward S, Kaltenthaler E, Cowan J, Brewer N. Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation. Health Technology Assessment 2003; 7(32):i-93.

(9) Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P. The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation. Health Technology Assessment 2006; 10(41):i-204.

(10) Murray A, Lourenco T, de VR, Hernandez R, Fraser C, McKinley A et al. Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation. Health Technology Assessment 2006; 10(45):i-141.

(11) Tappenden P, Jones R, Paisley S, Carroll C. The cost-effectiveness of bevacizumab in the first-line treatment of metastatic colorectal cancer in England and Wales. European Journal of Cancer 2007; 43(17):2487-2494.

(12) National Institute for Health and Clinical Excellence. Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer (review of technology appraisal 33). Technology appraisal 93, 1-40. 2005. London, NICE.

(13) National Institute for Clinical Excellence. Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. Technology appraisal 61, 1-25. 2003. London, NICE.

(14) National Institute for Health and Clinical Excellence. Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer. Technology appraisal 100, 1-34. 2006. London, NICE.

(15) National Institute for Health and Clinical Excellence, Nat. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Technology appraisal 118, 1-34. 2007. London, NICE.

(16) National Institute for Health and Clinical Excellence. Cetuximab for the first-line treatment of metastatic colorectal cancer. Technology appraisal 176, 1-37. 2009. London, NICE.

(17) National Institute for Health and Clinical Excellence. Laparoscopic surgery for colorectal cancer. Technology appraisal 105, 1-25. 2006. London, NICE.

(18) Phillips PKS. Colorectal surgery: A companion to specialist surgical practice. 3rd ed. Philadelphia: Elsevier Saunders; 2005.

(19) Tappenden P. Conceptual modelling to inform health economic model development. Health Economics and Decision Science Discussion Paper 11/17 2011.

(20) Greene FL, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG et al. AJCC Cancer Staging Manual. 6th ed. New York: Springer; 2002.

(21) Office for National Statistics. Cancer statistics registrations: Registrations of cancer diagnosed in 2006, England. Series MB1 No. 37, 1-80. 2008. Surrey, Office of Public Sector Information.

(22) Welsh Cancer Intelligence and Surveillance Unit. Cancer Incidence in Wales 2003-2007. Report no. SA9/01, 1-11. 2009. Cardiff, WCISU.

(23) Office for National Statistics. Mortality statistics: Deaths registered in 2007. DR07, i-314. 2008. Surrey, Office of Public Sector Information.

(24) The evolution of cancer of the colon and rectum. Muto T, Bussey HJ, Morson BC. Cancer 1975; 36(6):2251-2270.

(25) Chen CD, Yen MF, Wang WM, Wong JM, Chen THH. A case-cohort study for the disease natural history of adenoma-carcinoma and de novo carcinoma and surveillance of colon and rectum after polypectomy: implication for efficacy of colonoscopy. British Journal of Cancer 2003; 88(12):1866-1873.

(26) Dinning JP, Hixson LJ, Clark LC. Prevalence of distal colonic neoplasia associated with proximal colon cancers. Annals of Internal Medicine 1994; 154(8):853-856.

(27) Selvachandran SN, Hodder RJ, Ballal MS, Jones P, Cade D. Prediction of colorectal cancer by a patient consultation questionnaire and scoring system: a prospective study. The Lancet 2002; 360(9329):278-283.

(28) Van Cutsem E, Kataja VV, on behalf of the ESMO Guidelines Task Force. ESMO minimum recommendations for diagnosis, adjuvant treatment and follow-up of colon cancer. Annals of Oncology 2005; 16(Suppl1):i16-i17.

(29) Turnbull RB, Kyle K, Watson FR, Spratt J. Cancer of the colon: the influence of the no touch isolation technique on survival rates. Annals of Surgery 1967; 166(3):420-427.

(30) Astler VB, Coller FA. The prognostic significance of direct extension of carcinoma of the colon and rectum. Annals of Surgery 1954; 139(6):846-851.

(31) Dukes CE. The classification of cancer of the rectum. Journal of Pathology 1932; 35:323-332.

(32) Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen CM et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: A final report. Annals of Internal Medicine 1995; 122(5):321-326.

(33) NHS Cancer Screening Programmes. The NHS Bowel Cancer Screening Programme: Information for Primary Care. 1-19. 2009. London, Department of Health Available from http://www.cancerscreening.nhs.uk/bowel/publications/kit-instructions.pdf [accessed 220909].

(34) Glynne-Jones R. Colorectal cancer follow-up - ad hoc survey of the Royal College of Radiologists in the UK. Data held on file . 2007.

(35) North Trent Cancer Network. Referral and management guidelines for colorectal cancers within North Trent. i-42. 2007.

(36) Tappenden P, Jones R, Paisley S, Carroll C. Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Health Technology Assessment 2007; 11(12):i-128.

(37) Cheeseman SL, SP Joel, Chester JD, Wilson G, Dent JT, Richards FJ et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. British Journal of Cancer 2002; 87(4):393-399.

(38) Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. Journal of Clinical Oncology 2004; 22(7):1209-1204.