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The clinical presentation of colorectal cancer

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Introduction

Colorectal cancer is the second commonest cancer arising in the United Kingdom. In this chapter, we will discuss the etiology involving genetic and environmental factors, the presenting features of the disease, the clinical findings and the referral process.

Incidence and mortality

In 1996, colorectal cancer (CRC) accounted for over 15 000 deaths (68% colon, 32% rectal) and, by the turn of the millennium, there had been 33 173 new cases of CRC diagnosed in the UK in the previous 12 months. Stratified by sex, the incidence per 100 000 of the population (all ages) is 53.5–57.1 cases for men and 36.7–37.5 cases for women. The average age of diagnosis is in the 60–65 year group. The incidence by age stratification is 4 cases/100 000 for people under the age of 50; 100 cases/100 000 for those aged 50–69; and 300 cases/100 000 for those over the age of 70 [1,2]. In Australia, the UK, and the United States, it is the commonest cancer in women after breast (age standardization 22–33 cases/100 000) and in men after prostate and lung cancer (age standardized incidence 31–47 cases/100 000) [3]. Overall, it accounts for approximately 10% of all cancer deaths (Table 1.1) [1].

Survival rates for colorectal cancer have improved in recent years. Between the 1970s and 1990s, 5-year survival for colon cancer in men improved from 22% to 42% and rectal cancer rates improved from 25% to 39%. For colon cancer in women, 5-year survival increased from 23% to 40% and rectal cancer from 27% to 43%. Indeed, we are now seeing series reported with a higher survival rate for

Table 1.1 The incidence and deaths from colorectal cancer worldwide

	Incidence	Incidence ASR	Deaths	Deaths ASR
World				
Men	498 754	19.11	254 816	9.78
Women	445 963		237 595	7.58
UK				
Men	17 249	35.37	9 341	18.73
Women	15 924	25.28	9 047	13.76

Incidence and age-standardized ratio (ASR) expressed per 100 000 people [1].

rectal than colon cancer [4]. This probably relates to earlier detection of the disease and to the introduction of multidisciplinary team management of the disease. But, with an increasing elderly population in the UK, the incidence of CRC will rise and this will add to the burden on NHS cancer services.

Risk factors

A number of environmental and genetic risk factors have been identified for CRC. These include

- Age
- Nutrition
- Low physical activity
- Inflammatory bowel disease
- Genetic factors

It is estimated that about 80% of all cases of CRC are caused by diet alone [5]. Colorectal cancer is more common in Westernized countries than in Asia or Africa – the increased consumption of dietary fiber in the form of fruit, vegetables and cereals has been proposed as a protective factor. A high-fiber diet increases fecal bulk and decreases transit time. The issue of dietary fiber intake and the relationship to the risk of CRC were highlighted by the observations of Dennis Burkitt in the 1970s and 1980s, but these observations have recently been disputed [6]. There is evidence that a diet rich in red or processed meat may increase the risk [7]. The EPIC (European Prospective Investigation into Cancer and Nutrition) Study identified an increased risk with total consumption of meat [8]. The evidence for the effect of dietary fat is not consistent [9]. Folate has been shown to have a protective effect in a number of prospective cohort studies, and a number of randomized

control trials have demonstrated a decreased risk of recurrent adenomas with calcium supplements. Selenium may also have an anti-carcinogenic effect. Whilst alcohol increases the risk for CRC, the evidence for tobacco is inconclusive.

Epidemiological studies have highlighted that men who are physically active are at decreased risk of developing CRC [10]. There is no consistent link between CRC and obesity but there is an association between obesity and the development of adenomas.

Patients with inflammatory bowel disease, both ulcerative colitis and Crohn's colitis, have a higher risk of developing CRC than the general population. In ulcerative colitis, the cumulative risk is reported as 2% at 10 years, 8% at 20 years and 18% by 30 years [11]. The incidence for Crohn's colitis is reported to be higher. Individuals who develop adenomatous polyps are also at increased risk of developing CRC.

There are a number of protective factors, including a lower incidence in patients taking aspirin. Hormone replacement therapy is also associated with a relative risk reduction. Cyclo-oxygenase-2 (COX-2) inhibitors and the statins have also been shown in population-based studies to provide some protection.

Genetics

Whilst environmental factors probably act as a catalyst in genetically susceptible individuals, there are a number of hereditary factors that increase the likelihood of the development of CRC. When assessing a patient, the question of family history of CRC is often raised, and indeed many patients will have an affected relative, either first-degree (parent or direct sibling) or second-degree (grandparent, aunts, and uncles). However, for a patient presenting to the surgical outpatient clinic, those with a single relative diagnosed over the age of 60 have the same risk as the general population. Indeed, about 25% of patients with CRC have a positive family history. However, heritable factors account for 35% of the risk of developing CRC [12]. These heritable factors can be considered in two groups:

1. High-penetration autosomal dominant syndromes – familial adenomatous polyposis (FAP and variants) and hereditary non-polyposis colorectal cancer (HNPCC), which represent 2%–5% of all colorectal cancers and is associated with an 80% lifetime risk. In FAP families, direct mutation analysis will give positive results in 80% of families. In FAP, the mutation involves a tumor-suppressor gene (APC gene) on loci 5q that is inherited in an autosomal

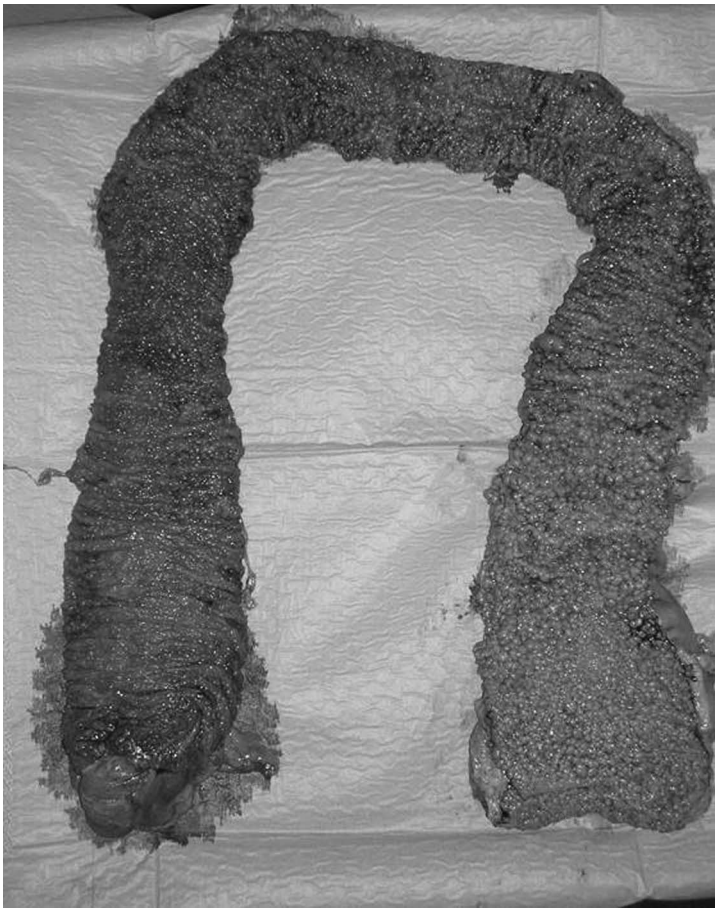

Figure 1.1 A proctocolectomy specimen removed from a patient with polyposis and no previous family history of the condition. The images show the 'carpet' of polyps extending around the entire colon from the anorectal junction to the ileocecal valve. The enlarged view of the rectum reveals the typical appearance of the multiple adenomata.

dominant pattern. The disease is characterized by the development of hundreds to thousands of adenomatous polyps. Depending upon the penetrance, patients may have a few polyps or an entire carpet involving the colon and rectum (Figure 1.1). Variants of the condition include Gardener's syndrome and Turcot's syndrome. In HNPCC, five different genes have been associated with the condition, making direct mutation analysis a more difficult problem. The majority of people have a germ-line mutation in a DNA mis-match repair gene. This microsatellite instability, which may be found at multiple

loci, including the 2p and 2q regions, is associated with increased genetic instability. Microsatellites are 50 000–100 000 di-nucleotide (e.g., CACACACA, etc.), tri-nucleotide (GTGCTGCTG, etc.), and tetra-nucleotide repeats that code for DNA repair proteins. Those genes that contain mutations cannot perform this repair function, DNA instability results and a malignancy may develop.

2. Familial clustering is likely to have a multifactorial mode of inheritance. Several genes are likely to be involved, some may predispose to adenomatous polyp formation [13,14]. The mode of inheritance is autosomal dominant but with a low penetrance [15]. The key determinants of risk are the youngest age of onset of CRC and the number of first-degree relatives involved.

Overall, any individual with two affected first-degree relatives aged less than 75 years at diagnosis has over twice the lifetime risk of CRC as compared to the general population. There are no national guidelines for surveillance in this cohort although it is known that these family members develop polyps more frequently than the general population, as has been demonstrated in a population-based screening trial [16]. Polypectomy does lead to a substantial reduction in cancer incidence in this group [17]. Surveillance is usually offered on a 5-yearly basis [18,19,20].

Pathogenesis

The development from a single cellular event to a metastatic tumor occurs in a stepwise progression from normal mucosa to adenoma to invasive carcinoma. The development of a malignancy within the colon is well characterized through the adenoma–carcinoma sequence [21]. The majority of carcinomas develop from benign, pre-neoplastic lesions – adenomatous polyps, following the accumulation of changes that occur within the cells of the lining of the bowel. Although we know the genetic sequence of events within this process, the etiology is multifactorial, involving genetic susceptibility, environmental factors and somatic changes during the initiation and progression of this process [22].

The genetic model for the progression of development of the neoplasm can be represented in a stepwise series of genomic events involving alterations in several oncogenes (K-ras) and tumor-suppressor genes (APC, DCC/DPC4, P53), DNA repair genes (*h*MLH1 and *h*MSH2), cell adhesion molecules (epCam), angiogenic factors (VEGF), as well as epigenetic changes (DNA methylation) and microsatellite instability (Figure 1.2).

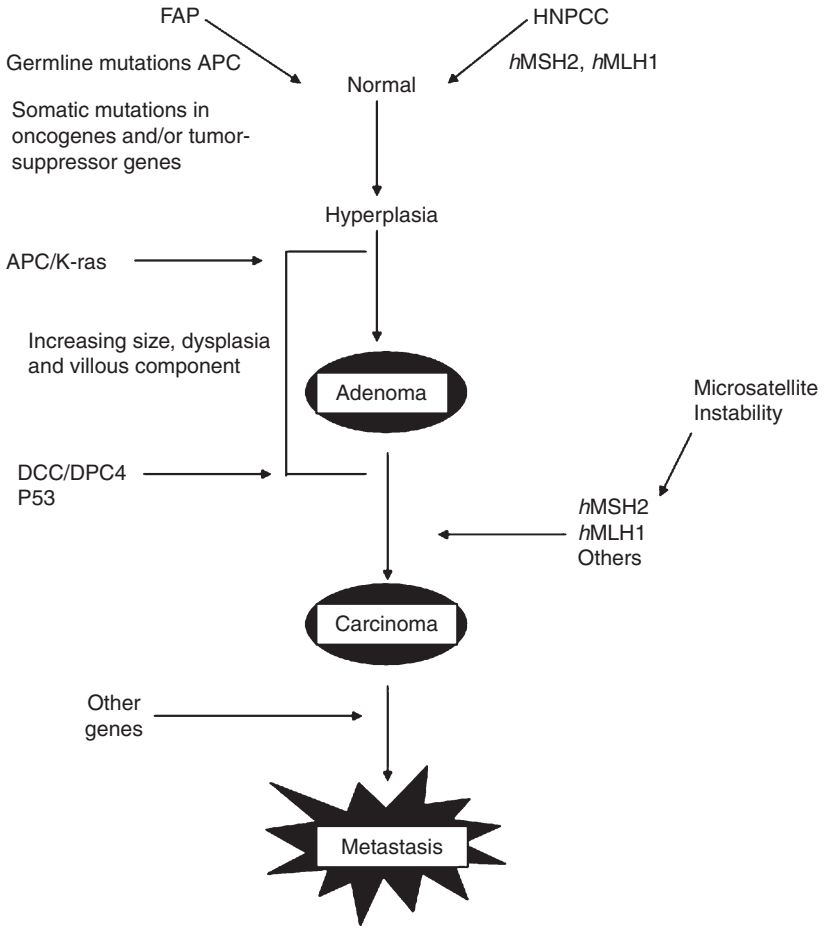

Figure 1.2 Alterations in several oncogenes and tumor-suppressor genes according to the two major mechanisms of genomic instability: microsatellite instability and chromosomal instability.

Symptoms of colorectal cancer

The classic symptoms of large bowel obstruction – abdominal colic, absolute constipation, abdominal distension and vomiting – are now rarely seen in modern colorectal practice. With the increasing influence of health awareness, the population has become more "bowel aware." However, the symptoms of colorectal cancer do not indicate a clear diagnosis as there is considerable similarity with more common colorectal complaints such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), diverticulosis and its complications, and proctological conditions such as hemorrhoids. Recent UK data reports a delay of 10 months

between onset of symptoms and treatment of CRC, with a median patient delay of 3 months, usually because the patient does not think the symptoms are serious [22]. Much of the work on symptom presentation and delay of treatment was assessed through the Wessex Cancer Audit and the Wales–Trent Audit performed in the 1980s and 1990s [22]. The audits identified that 65% of the delay in patients having elective surgery occurred before referral to hospital, 15% waiting for an outpatient appointment and 20% during the diagnostic process [22]. The figures for proximal bowel cancer (cecum to splenic flexure) were 35% before GP referral, 19% waiting for outpatient appointment and 46% owing to hospital delay in diagnosis.

There was a significant delay in the 15% of patients referred to the physicians, compared to the 85% of patients with suspected CRC referred to the surgical team. In the Wales–Trent Audit this was similar, even when those presenting with anemia were excluded. Therefore, the time to referral, diagnosis and treatment has not changed over the last 20 years [22,23].

Clinical history

Colorectal cancer proximal to the splenic flexure does not usually present with symptoms of bowel cancer. Proximal disease referrals are usually due to the identification of an iron deficiency anemia (microcytic, hypochromic), an abdominal mass, or as an emergency presentation with signs and symptoms of intestinal obstruction [24,25,26]. However, for left colon and rectal cancer, the presentation is usually with rectal bleeding and a change in bowel habit, which is usually an increased frequency of defecation and/or looser stools [27]. Rectal bleeding occurs without anal symptoms in over 60% of patients [27,28]. In very low rectal cancer, the symptom of tenesmus – the feeling of incomplete evacuation – may occur, and anal pain usually indicates that invasion of the anal sphincter has occurred.

Clinical examination

If you don't put your finger in it, you'll put your foot in it.

The old surgical adage, beloved by consultant surgeons and emphasized to junior doctors, does continue to have clinical value. A palpable rectal mass is present in 40%–80% of patients with rectal cancer, and 82% of palpable rectal cancers may be assessed by GPs [29,30,31]. Despite the advances in diagnostic technology, there is much that can be gained by the clinical examination of the patient. In the outpatient

setting, a general physical examination of the patient and a digital rectal examination, together with examination using a rigid sigmoidoscope and proctoscope, allow accurate clinical assessment. If a rectal cancer is identified, bi-manual examination of female patients gives the surgeon further information, although magnetic resonance imaging (MRI) assessment may be more accurate for treatment planning.

Having identified a CRC, particularly if it is detected by sigmoidoscopy, it is important that the entire colon is visualized to exclude synchronous lesions, which are reported to occur in 4%–5% [31,32]. The recognition of adenomatous polyps away from the area of resection may lead to a change in the operative strategy. Whilst a barium enema may act as a good investigation to assess proximal bowel, particularly in the presence of a tumor impassable to endoscopic examination, the ideal modality to assess the proximal colon is colonoscopy. However, one of the disadvantages of colonoscopy is the inability to accurately localize the position of the tumor within the colon when planning surgery. A particular area of difficulty is the "malignant polyp" – tattooing of the colon allows the surgeon to accurately identify the area for resection during the operation.

Prior to treatment planning, an accurate clinical and radiological assessment of the patient is performed to stage local disease and to exclude distant disease. The current best practice is local staging by endoscopic assessment of the tumor, with MRI assessment of a rectal cancer, together with a CT scan of the chest, abdomen and pelvis to exclude distant disease. Preoperative investigations including a full blood count and biochemical profile are also important. Serum CEA (carcino-embryonic antigen) is of value only if the level is raised. However, long-term follow-up with a serum CEA is probably of little value as a screening tool for the detection of recurrence in colorectal cancers.

Referral to the multidisciplinary team process

The Calman-Hine Policy Framework for Commissioning Cancer Services first highlighted the need to deliver improved and co-ordinated cancer services with the need for a cancer network infrastructure [33]. The report aimed: "to create a network of care in England and Wales, which will enable a patient, wherever he or she lives to be sure that the treatment and care received is of a uniformly high standard."

Reviewing the published medical literature in the late 1980s and early 1990s, supplemented by registry studies, revealed that there could be significant improvements in survival as a result of specialist care for a number of cancers including colorectal cancer [34,35]. With these developments in mind, the NHS

Cancer Plan was introduced in 2000 to improve the diagnosis and treatment for patients of the five most common cancers [36]. The evidence for this concluded that

1. Patients treated by specialists or specialist units have improved outcomes or process of care [37]
2. Patients treated by surgeons or units with higher patient volumes have improved outcomes or process of care [38]

The establishment of multidisciplinary team (MDT) working with regular meetings to discuss patients and co-ordinate care is seen as a central element for cancer care. The MDT is defined as "a group of different health care disciplines, which meets together at a given time (whether physically in one place or by video or teleconferencing) to discuss a given patient and who are able to contribute independently to the diagnosis and treatment decisions about the patients" [22].

Having set the standards for the management of patients in the hospital setting, the next task was to attempt to improve the referral pattern of patients to hospital and improve on the access to diagnostic services. This led to the "fast-track referral" or "two-week-wait" system (Figures 1.3 and 1.4).

Higher-risk criteria have been identified to allow primary care practitioners to direct patients through a fast-track or two-week-wait referral and these should

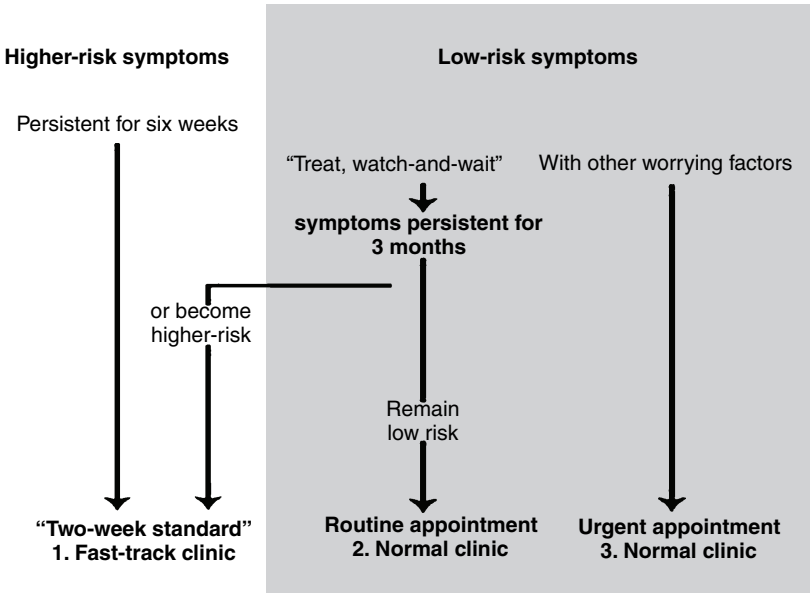

Figure 1.3 The guidelines for referral of patients with suspected colorectal cancer based upon clinical history and examination by the general practitioner.

REVIEW DATE: JUNE 2003

SUSPECTED CANCER REFERRAL PROFORMA COLORECTAL

☒ FAXBACK NUMBER: 0151 706 5655

The Royal Liverpool and Broadgreen University Hospitals
NHS Trust

PATIENT DETAILS		**GP DETAILS**
NAME:		NAME:
ADDRESS:		ADDRESS:
POSTCODE:	TEL:	FAX NO:
DOB: / /	NHS NO:	
INTERPRETER: YES / NO	LANGUAGE:	DATE OF REFERRAL:

CLINICAL INFORMATION

Please tick the relevant boxes.

OVER 60 YEARS ONLY:

Rectal bleeding persistently **WITHOUT** anal symptoms: ☐
(Anal symptoms include soreness, discomfort, itching, lumps, and prolapse as well as pain)

Change of bowel habit to looser stools and/or increased frequency of defecation, persistent for 6 weeks **WITHOUT** rectal bleeding ☐

ALL AGES:

Rectal bleeding **WITH** persistent change in bowel habit to looser stools and/or increased frequency of defecation persistent for 6 weeks ☐

A definite palpable right-sided abdominal mass with or without abdominal pain. ☐

A definite palpable rectal (not pelvic) mass ☐

Iron Deficiency anemia WITHOUT an obvious cause (Hb<11g/dl in men Or <10g/dl in post menopausal women). **Hb:** **MCV:** ☐

Tick if patient is fit for Phosphate enema at home prior to Flexible Sigmoidoscopy ☐

Recent Investigations **(please include all bowel investigations ordered):**

Patients past medical history:

Recent heart attack: Y / N Date: Angina: Y / N Stroke: Y / N

Current medication: Warfarin Y / N

Further comments:

If you are unsure whether this is the most appropriate method of referral for your patient please contact the colorectal nurse/TWR co-ordinator on 0151 706 3453 (or bleep 261)

Doctors Signature: Date:

Figure 1.4 An example of a referral proforma used.