Pathology of colorectal polyps and cancer

Adrian C Bateman

Abstract

Colorectal cancer (CRC) is one of the most common cancers worldwide. However, early detection and treatment can lead to very good clinical outcomes. This article highlights the pathology-related aspects of CRC that are most relevant to colorectal surgeons. This includes sections on epidemiology, aetiology, presentation, macroscopic and microscopic features, pathological staging, prognosis, precursor lesions and molecular pathways, follow-up and bowel cancer screening. The main section on CRC is preceded by a description of the types of colorectal polyp that are most commonly encountered in clinical practice, many of which are associated with the development of CRC.

Keywords Adenoma; bowel cancer screening; colorectal cancer; colorectal polyp; serrated lesion

Colorectal polyps

Adenomas

Colorectal adenomas are benign epithelial lesions that show dysplasia (which in this context are the microscopic features of neoplastic change within epithelial cells that are not malignant (i.e. carcinoma) in themselves but which may be associated with transformation to malignancy). A spectrum of endoscopic appearances exists and these can help to predict the lesion type.[1] On histopathological examination, the degree of dysplasia is now assessed as either 'low' (Figure 1) or 'high' (Figure 2). Approximately 5% of adenomas identified within bowel cancer screening programmes show high-grade dysplasia. The growth pattern may be tubular (which are often the smallest polyps), tubulovillous or villous ('finger-like') (which are often the largest polyps and commonly occur within the rectum) – with the distinction between tubular and tubulovillous adenomas often being subjective. This distinction is less important now that 'villousness' is no longer used as a defining feature for an advanced/high risk adenoma. Within the latest *British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection follow-up guidelines* (*BSG/ACPGBI/PHE guidelines*) (discussed in more detail later in this article), adenoma size 10 mm or greater and the presence of high-grade dysplasia are 'advanced' features.[2]

Unless a well-orientated polyp stalk or series of transverse sections from an endoscopic mucosal resection are present, it is usually not possible to comment on the proximity of the adenoma to the surgical margin. However, this is often not important as the endoscopic assessment of 'completeness of excision' is very useful and a diathermy burn can extend several millimetres into the adjacent mucosa anyway.

Adenomas can progress to colorectal cancer (CRC) along the 'adenoma-carcinoma' pathway and the risk of progression is increased in lesions 10 mm or greater in size and/or showing high-grade dysplasia (discussed later in this article).

Familial adenomatous polyposis (FAP) is inherited in an autosomal dominant manner and is associated with a range of mutations in the *APC* gene. Affected individuals develop multiple (hundreds or thousands) of adenomas within the large intestine – usually during their teenage years – and are at very high risk of development of CRC at a young age. These patients may also develop adenomas and carcinomas within the small intestine, fibromatoses (e.g. within the abdominal wall), gastric fundic polyps and congenital hypertrophy of the retinal pigment epithelium (CHRPE). The precise clinical manifestations depend on the position and nature of the *APC* gene mutation, e.g. some mutations result in 'attenuated' FAP, characterized by a reduced number of colorectal adenomas.

MUTYH-associated polyposis (MAP) is inherited in an autosomal recessive manner and is associated with bi-allelic mutations in the *MUTYH* gene – with either homozygosity (i.e. the presence of identical mutations within each allele) or compound heterozygosity (i.e. the presence of a different mutation within each allele) encountered. Affected individuals show large intestinal manifestations that are similar to attenuated FAP, i.e. multiple adenomas but at lower numbers than typically seen in FAP (e.g. 10–100 adenomas) and are also at increased risk of development of CRC. Extra-colonic manifestations include duodenal adenomas and gastric fundic polyps. In a similar way to *APC* mutations in FAP, the nature of the *MUTYH* mutations can alter the clinical manifestations of the condition.

Serrated polyps

The most well-known lesion in this group is the *hyperplastic polyp* (HP) and until around 30 years ago, this was the only type of serrated polyp recognized. Within the last 30 years, the *sessile serrated lesion* (SSL) (previously termed the sessile serrated adenoma/polyp) and the *traditional serrated adenoma* (TSA) have become characterized as additional important types of serrated polyp.

Hyperplastic polyp: the HP is still the most common type of serrated polyp, accounting for around 20–30% of all colorectal polyps. They can occur anywhere in the large intestine but commonly exist as multiple lesions, each <5 mm, within the rectum. They are believed to possess no significant risk of transformation to CRC. HPs may contain *BRAF* mutations – but not as commonly as is found in sessile serrated lesions (see below).

Sessile serrated lesion: the SSL bears microscopic resemblance to the HP, but shows important microscopic differences which allow the distinction from HPs, e.g. prominent serration within the crypts and 'horizontal spreading' of crypts (Figure 3). They

Adrian C Bateman ***BSc MD FRCPath*** *is a Consultant Histopathologist at Southampton General Hospital, UK and an Honorary Professor at the University of Southampton. Conflicts of interest: none declared.*

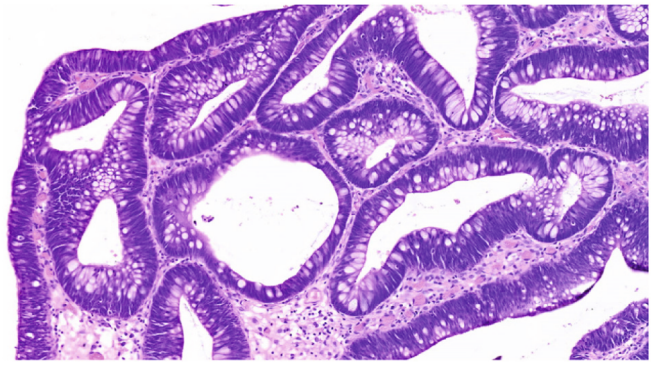

Figure 1 A tubular adenoma showing low-grade dysplasia. The epithelium lining the glands shows greater hyperchromasia (dark blue staining) than is seen in uncomplicated sessile serrated lesions. This is characteristic of (low-grade) dysplasia. The neoplastic glands are separated by lamina propria — a normal constituent of mucosa. *Haematoxylin and eosin stain*. Magnification ×200.

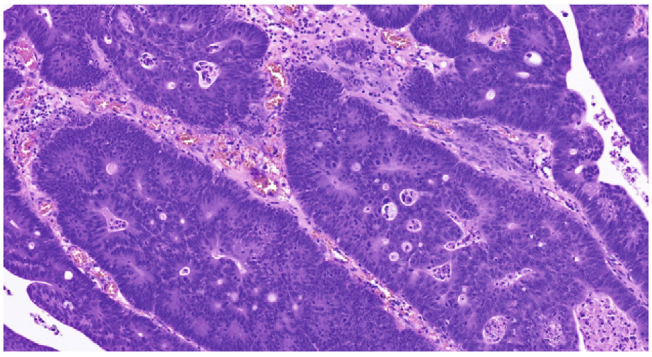

Figure 2 A tubular adenoma showing high-grade dysplasia. The epithelium lining the glands shows a more solid or cribriform (sieve-like) growth pattern and the degree of hyperchromasia is greater than seen in Figure 1. This is characteristic of high-grade dysplasia. *Haematoxylin and eosin stain*. Magnification ×200.

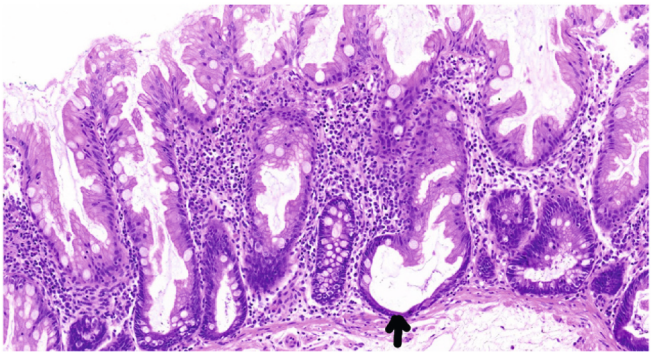

Figure 3 A sessile serrated lesion. The epithelium lining the glands shows sharp serrations and mucus is present within apical vacuoles and goblet cells. One distorted 'L-shaped' crypt is present (arrow) — this type of growth pattern is characteristic of sessile serrated lesions. *Haematoxylin and eosin stain*. Magnification ×200.

account for 10–15% of all colorectal polyps and can also occur anywhere in the large intestine, but are most commonly found in the right colon. SSLs <5 mm in size can occur but lesions >10 mm are not uncommon. At endoscopy, SSLs can be difficult to identify as they are often situated on mucosal folds and may have a 'mucin cap'. Education programmes in recent years have helped both endoscopists and histopathologists to recognize these lesions more reliably. Distinction between HPs and SSLs is important as SSLs may harbour areas of dysplasia (similar to that found in adenomas) and may progress to CRC along the relatively recently characterized 'serrated pathway'. SSLs commonly harbour mutations in the *BRAF* gene.

Serrated polyposis (SPP) (previously called hyperplastic polyposis) is characterized by the presence of multiple polyps within the large intestine — including sessile serrated lesions, hyperplastic polyps and adenomas. The current diagnostic criteria are:

(1) five or more serrated lesions proximal to rectum; all at least 5 mm in size and with at least two being 10 mm or more in size; or

(2) over 20 serrated lesions of any size throughout the large intestine, with five or more being proximal to the rectum. A minority of SPP is familial in nature, with both autosomal dominant and recessive forms described. Some inherited forms of SPP are associated with mutations in the *MUTYH* gene. Individuals with serrated polyposis are at increased risk of the development of CRC.

Traditional serrated adenoma (TSA) is the least common type of serrated polyp, accounting for around 1% of all colorectal polyps. They can occur anywhere in the large intestine but are most commonly found in the left colon. On microscopic examination, they often have a pronounced villiform architecture and possess characteristic features, e.g. eosinophilic cytoplasm, 'pencillate' nuclei and ectopic crypts that bud off the main crypts at 90 degrees. 'Pure' TSAs show subtle low-grade dysplasia, but sharply defined areas of more obvious dysplasia (low or high grade) are often seen. As with classical adenomas, progression to CRC can occur. TSAs commonly harbour *KRAS* mutations, although some contain *BRAF* mutations — this latter group are thought to be derived from *BRAF*-mutated SSLs.

Hamartomatous polyps

These polyps comprise a disorganized mixture of tissue components usually seen within the large intestinal mucosa, e.g. intestinal epithelium and splayed smooth muscle fibres. Examples include *juvenile/juvenile-type polyps* — characterized by a pedunculated architecture, dilated glands, stromal inflammation and surface ulceration; *Peutz–Jegher-type polyps* — characterized by a pedunculated architecture, with normal large intestinal mucosa mixed with prominent smooth muscle fibres; and *Cronkhite–Canada polyps* — with similar appearances to juvenile/juvenile-type polyps but usually sessile in nature. Juvenile polyposis syndrome is a familial condition inherited in an autosomal dominant manner. In about 50% of affected patients, mutations are found in the *SMAD4* or *BMPR1A* genes. The diagnostic criteria are: (1) five or more juvenile polyps within the large intestine; or (2) juvenile polyps throughout the gastrointestinal tract; or (3) any number of juvenile polyps in the presence of a family history of the condition. Affected patients are at

increased risk of CRC and other adenocarcinomas within the gastrointestinal tract.

Other polyps

Inflammatory polyps include *polypoid mucosal prolapse* — found for example in association with mucosal diverticulosis and in the rectum, and *'pseudopolyps'* that represent islands of possibly inflamed but surviving large intestinal mucosa within areas of ulceration, e.g. in active ulcerative colitis. *Polypoid granulation tissue* can sometimes be found at sites of intestinal anastomosis and not uncommonly undergoes biopsy, especially when the differential diagnosis includes recurrent malignancy.

A range of other benign polyps may also be found in the large intestine, e.g. *inflammatory fibroid polyp*, *perineurioma*, *Schwannoma*, *Schwann cell hamartoma*, *ganglioneuroma*, *granular cell tumour* and *leiomyoma*. However, a detailed discussion of these is beyond the scope of this article. Polyps can show mixed features and the term '*mixed polyp*' may be used in this situation. For example, polyps with a combination of SSL and TSA features may be encountered and are believed to represent a TSA evolving from an SSL. Most examples of combinations of SSL and 'tubular adenoma' are likely to represent SSLs in which adenomatous dysplasia has arisen, rather than a 'collision' of an SSL and an originally spatially separate tubular adenoma.

Colorectal cancer

Epidemiology

CRC is the third most common cancer worldwide, with just over 1.9 million new cases (men — 1.07 million, women — 865,000) and over 900,000 deaths recorded in 2020.[3] The highest incidence is in Australasia, high-income Asia-Pacific, high-income North America, and Europe.[4] Various associations with CRC incidence exist, e.g. a diet low in fibre and dairy products and high in red meat and processed meat, low physical activity and obesity.

Aetiology

Most CRC is believed to develop from precursor lesions within the colorectal mucosa. The most well-established pathway is the adenoma-carcinoma sequence, while the serrated pathway has become recognized more recently as an important mechanism that accounts for up to a third of cases. While familial clustering of CRC is not infrequently observed, inherited predisposition to CRC associated with a defect within a single gene (e.g. Lynch syndrome, familial adenomatous polyposis, MUTYH-associated polyposis) accounts for no more than 5% of cases. These pathways are discussed in more detail later in this article.

Presentation

CRC classically presents with bleeding and/or mucus per rectum, a change in bowel habit, or tenesmus. These clinical features are usually associated with left-sided cancers. Right-sided cancers commonly present with non-specific features, especially anaemia. Cancers in any part of the large intestine can present with bowel obstruction or perforation. CRC may alternatively present as metastatic disease (e.g. within the liver) and this is most commonly associated with right-sided cancers due to the lower incidence of site-specific symptoms associated with these.

Macroscopic features

Early CRC developing within pedunculated polyps may not be appreciable to the naked eye and diagnosis requires microscopic examination. Sessile polyps harbouring early CRC often show subtle alterations in pit pattern at endoscopy, e.g. Kudo type 4 (branched or gyrus-like pits) or type 5 (non-structured) patterns.[5] More advanced CRC may be polypoid, ulcerated or structuring in nature. Ulcerated CRC commonly shows the classical features of a malignant ulcer, i.e. with raised everted edges. Increasing local tumour stage is characterized by infiltration through the muscularis propria and potentially by involvement of the peritoneal surface. The naked eye appearance of puckering of the peritoneal surface at the site of the tumour commonly means that involvement by tumour has occurred. Alternatively, the tumour may involve the mesorectal excision plane or extend into adjacent structures, e.g. the small bowel, bladder, prostate gland or vagina. The latter patterns of growth can be associated with the presence of a malignant fistula (a fistula is a granulation tissue-lined tract between two epithelial-lined surfaces).

CRC not uncommonly results in bowel obstruction, affecting the proximal colon or — especially with caecal cancers — the small bowel. The obstructed bowel becomes dilated and the mucosa may show a secondary colitis ('obstructive colitis'). Full-thickness bowel perforation may be seen, either through the tumour itself or within dilated bowel proximal to the tumour.

During macroscopic histopathological examination, CRC usually undergoes transverse sectioning at 4—5 mm intervals and this sometimes reveals narrow tongues of tumour traversing the bowel wall. This feature is commonly associated with the identification of venous invasion by tumour on microscopic examination.

Tumour-involved lymph nodes may be identified during preoperative radiological imaging or surgical resection and firm pale tumour-involved nodes can sometimes be identified during macroscopic histopathological examination. Any tumour-involved nodes within 1 mm of a non-peritonealized surgical margin (e.g. the mesorectal excision plane or the base of the mesentery) should be documented in the histopathology report, where they would usually prompt assessment as an R1 resection (i.e. microscopic involvement of a surgical margin).

Changes following neo-adjuvant therapy: CRC undergoing resection following chemoradiotherapy may show a spectrum of macroscopic features. A very good response to neo-adjuvant treatment commonly results in naked eye appearances that may be only subtly different to normal, e.g. a poorly defined area of mucosal flattening or slight thickening of the bowel wall that is apparent on transverse sectioning. In this situation, it is important for the pathologist to submit most or all of the presumed tumour bed for microscopic examination in order to look for evidence of residual adenocarcinoma. In contrast, a poor response to this treatment may result in a tumour that shows no obvious naked eye differences to one resected with no neo-adjuvant therapy.

Microscopic features

The vast majority of CRC are adenocarcinoma on microscopic examination and most are well-moderately differentiated in

nature. This most common pattern of CRC shows easily identifiable gland formation, with slightly columnar tumour cells and the presence of 'dirty' necrosis (i.e. necrosis associated with cellular and nuclear debris). These appearances are often sufficiently characteristic that microscopic examination can indicate a high likelihood of a colorectal primary origin on routine haematoxylin and eosin-stained slides alone when the tumour occurs at metastatic sites, e.g. the liver.

Some of the less common microscopic patterns of CRC are listed in Table 1.[6] Some patterns of adenocarcinoma, e.g. poorly differentiated, mucinous and lymphocyte-rich, are more commonly seen in Lynch syndrome and the presence of one of these tumour types should prompt the pathologist to consider this diagnosis.

Changes following neo-adjuvant therapy: the microscopic changes in CRC resected after chemoradiotherapy parallel those seen on naked eye examination. The typical features of response to neo-adjuvant treatment with a good tumour response are — in addition to a reduction in volume of neoplastic glandular tissue — fibrosis and chronic inflammation with foamy macrophages. Several systems have been developed to score the degree of tumour regression present and the current *Royal College of Pathologists* recommended system is given in Table 2.[7]

Biopsy diagnosis of CRC: establishing a firm diagnosis of CRC on endoscopic biopsy may be challenging. The most confident diagnosis of CRC requires the presence of neoplastic epithelium, e.g. glands, within the submucosa of the large intestine. While this can be seen, it is more common to receive superficial tissue fragments that contain neoplastic epithelium but in which it may be difficult or impossible to confirm — on histopathological grounds alone — whether the material is derived from an adenoma or a carcinoma. In this situation and even if definite submucosa is not present, the finding of irregularly shaped and placed neoplastic glands within a stroma showing desmoplasia (a cellular stroma that is characteristically found in invasive carcinoma) is often sufficient for a diagnosis of adenocarcinoma, but with the caveat that clinicopathological correlation is required in order to arrive at a firm diagnosis of cancer (Figure 4).

Microscopic types of colorectal carcinoma[6]

Tumour type	Tumour subtypes
Adenocarcinoma	Adenocarcinoma NOS
	Serrated adenocarcinoma
	Micropapillary carcinoma
	Poorly cohesive and signet ring adenocarcinoma
	Medullary carcinoma
	Adenosquamous carcinoma
	Undifferentiated carcinoma
	Carcinoma with sarcomatoid component
Neuroendocrine tumour	Neuroendocrine tumour — grades 1—3
	Hormone-producing neuroendocrine tumours
Neuroendocrine carcinoma	Small cell and large cell types
Mixed neuroendocrine—non-neuroendocrine neoplasm (MiNEN)	

NOS, not otherwise specified, i.e. with no special subtype-defining histopathological features.

Table 1

Diagnosis of CRC in adenomatous polyps: the diagnosis of early CRC arising within an adenomatous polyp may also be difficult. This is because the twisting of a pedunculated adenoma ('torsion') — as most commonly occurs within the sigmoid colon — commonly leads to entrapment of adenomatous glands ('epithelial misplacement') between splayed muscularis mucosa fibres in the polyp stalk and this can simulate adenocarcinoma. This situation is particularly encountered within bowel cancer screening programmes as polyp torsion commonly leads to haemorrhage and therefore to a positive faecal occult blood test. Guidance exists for pathologists in this situation and in the most difficult cases, referral to a pathology 'board' (i.e. a small group of experienced gastrointestinal pathologists) may be appropriate.[8]

Pathological staging

Dukes' staging was introduced for rectal cancer staging in 1932 and its use was subsequently extended to colonic cancer, but it has now been superseded by pathological tumour/node/metastasis (TNM) staging. Despite this, it is worth being familiar with Dukes' staging as historical histopathology reports for CRC will include this (Table 3). Pathological TNM staging is widely used and provides prognostic information as well as guiding management (Table 3).

Prognosis

The prognosis of CRC is closely linked to the tumour stage and early stage tumours generally have an excellent prognosis (e.g. pT1N0 — >90% 5-year survival). In contrast, the presence of distant metastases indicates a poor prognosis (e.g. 5—10% 5-year survival). Additional microscopic features that are most clearly associated with a worse prognosis include poor differentiation and the presence of extramural venous invasion by tumour. More recently, further microscopic features that are also associated with worse outcome have been identified, e.g. intramural venous invasion, intramural or extramural small vessel invasion (lymphatics, capillaries or post-capillary venules), perineural invasion, and tumour budding (which is the presence of separate groups of up to four carcinoma cells at the advancing edge of the tumour).[7]

DNA extracted from representative formalin-fixed and paraffin-embedded tumour blocks is nowadays commonly used to assess the mutation status of the *BRAF*, *KRAS* and *NRAS* genes. The presence of a mutation within one or more of these genes indicates that the tumour is not likely to respond to anti-epidermal growth factor receptor (EGFR) therapies such as cetuximab.

Histopathology dataset reporting: in the 1990s it became apparent that the quality of information contained within histopathology reports for major cancer resection specimens was very variable. The *Royal College of Pathologists* began the process of publishing recommended datasets for all major cancer resection types, starting with CRC — with the first edition being published in 1998. These

The current *Royal College of Pathologists* recommended system for the degree of tumour regression following neo-adjuvant therapy in colorectal cancer[7]

Microscopic appearance	Tumour regression score
No viable cancer cells	0
Single cancer cells or rare groups of cancer cells	1
Residual cancer with evident tumour regression, but more than single cancer cells or rare groups of cancer cells	2
Extensive residual cancer with no evident tumour regression	3

Table 2

datasets are regularly updated, with the CRC version now in its fourth edition. The datasets comprise text articles describing the optimal methods for dealing with 'wet' (formalin-fixed) specimens, e.g. macroscopic description, dissection and block selection (the choice of tissue for processing and the production of glass microscope slides). They also list the microscopic features that are important for multidisciplinary team management decisions and the determination of prognosis. The recommended data items can be included in histopathology reports in either proforma style or as free text, depending on the laboratory information management systems in use within different laboratories.

Precursor lesions and molecular pathways

The most common precursor lesions for CRC are adenomas and serrated polyps of the large intestine. The main pathological characteristics of these polyps have been described earlier in this article — including the polyposis syndromes SPP, FAP and MAP. The molecular pathways linking these precursors to CRC have become increasingly well characterized in recent years and are described below.

Adenoma-carcinoma sequence: this was the first molecular pathway to be described and is often referred to as the 'Vogelstein model'. This model links classical large intestinal adenomas to CRC through the accumulation of mutations paralleled by the development of low-grade and high-grade dysplasia and adenocarcinoma. Within this model, the sequence of genes in which mutations are acquired is typically: *APC*, *p53*, *KRAS*.

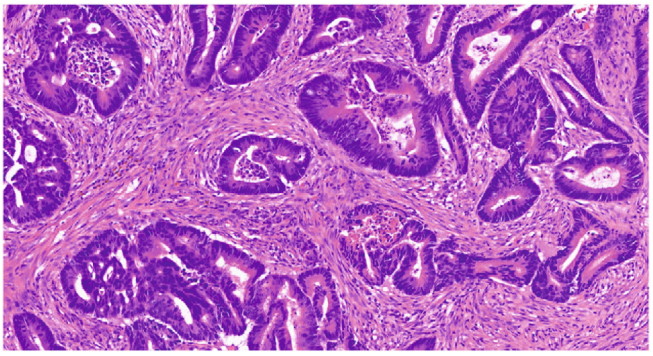

Figure 4 Adenocarcinoma within an endoscopic biopsy. The neoplastic glands are much more irregular in shape and placement than those within adenomas. The stroma is desmoplastic (interwoven spindle cells) in nature. This is characteristic of adenocarcinoma. *Haematoxylin and eosin stain*. Magnification ×200.

Serrated pathway: this has been much more recently described than the adenoma-carcinoma sequence and is thought to account for up to 30% of CRC. Two molecular routes exist within this pathway.[9] In the first route, SSLs containing *BRAF* mutations develop dysplasia in association with hypermethylation of their genome (the addition of CH_3 groups to DNA). Hypermethylation results in inactivation of genes and within SSLs, often affects the promoter region of *MLH-1* — the gene encoding the MLH-1 DNA mismatch repair enzyme protein. This leads to loss of MLH-1 expression and the accumulation of further mutations (explained in more detail in the next section). This route leads to the development of CRC that also shows loss of MLH-1 expression. Hypermethylation may alternatively result in the inactivation of other genes, e.g. *p16* and *MGMT*, leading to CRC that retains MLH-1 expression. In the second route, TSAs containing *KRAS* mutations lead to CRC that also contains *KRAS* mutations but that does not show loss of MLH-1 expression.

Lynch syndrome is an inherited cancer syndrome characterized by predisposition to several cancers, of which CRC is one of the most common associations (Table 4).[10] The syndrome is associated with the presence of a germline mutation in one of the genes encoding DNA mismatch repair (MMR) proteins — usually *MLH-1*, *MSH-2*, *MSH-6* and *PMS-2*, or in the *EPCAM* gene. MMR proteins identify and repair damaged DNA during DNA replication. Somatic mutation or loss of the second MMR gene copy (allele) (i.e. at the tumour site) results in imperfect DNA repair during DNA replication, leading to the accumulation of further genetic mutations and the development of neoplasia. Imperfect DNA replication also leads to length differences in non-coding DNA sequences termed 'microsatellites' and this situation is termed 'microsatellite instability' (MSI). The presence of 'high-level' MSI is a characteristic (although not specific) feature of Lynch syndrome-associated CRC.

The classical Lynch syndrome-associated CRC occurs within the right colon of a young patient (<50 years) and shows a poorly differentiated, mucinous or lymphocyte-rich appearance on histological examination. However, Lynch-associated CRC may occur in older individuals and within any part of the large intestine. Multiple CRC within a single individual (synchronous or metachronous) would also be a characteristic feature. Immunohistochemistry (IHC) performed on routinely available formalin-fixed and paraffin-embedded tumour tissue reveals loss of one — or a pair — of the DNA MMR proteins within the carcinoma cell nuclei in almost all cases of Lynch syndrome (Figure 5).[10] Depending on the pattern of MMR protein loss found, additional tests (*BRAF* mutation analysis and *MLH-1* promoter hypermethylation studies) may be required to exclude inactivation of the *MLH-1* gene as the cause (as may occur in the serrated pathway to CRC), rather than a germline mutation. In 2017, the *National Institute for Health and Care Excellence* (NICE) published guidance recommending screening for Lynch syndrome using either DNA MMR IHC or MSI testing in all

Pathological staging systems for colorectal cancer

Dukes' staging[a]	
A	Primary tumour does not extend beyond the outer limit of the muscularis propria (i.e. confined to the bowel wall); no regional lymph node metastases
B	Primary tumour extends beyond the outer limit of the muscularis propria; no regional lymph node metastases
C	Metastasis in one or more regional lymph nodes (may be subdivided into: C1 — highest lymph node uninvolved by tumour; C2 — highest lymph node contains metastatic tumour)
D (not included in original Dukes' system but added later)	Distant metastasis
Tumour/node/metastasis (TNM) (8th Edition)	
T1	Primary tumour invades submucosa
T2	Primary tumour invades muscularis propria
T3	Primary tumour invades subserosa or non-peritonealized pericolic or perirectal tissue
T4	T4a — primary tumour ulcerates visceral peritoneum T4b — primary tumour directly involves other organs or structures
N0	No regional lymph node metastases
N1	Metastasis in 1—3 regional lymph nodes (N1a — metastasis in 1 regional lymph node; N1b — metastasis in 2—3 regional lymph nodes; N1c — extramural tumour deposits without regional lymph node metastasis)
N2	Metastasis in 4 or more regional lymph nodes (N2a — metastasis in 4—6 regional lymph nodes; N2b — metastasis in 7 or more regional lymph nodes)
M1	M1a — distant metastasis within one organ without peritoneal metastases M1b — metastasis in more than one organ M1c — metastasis to the peritoneum with or without other organ involvement

[a] No longer in regular use but will be found in many historical colorectal cancer resection histopathology reports.

Table 3

patients with newly diagnosed CRC.[11] Currently, most regions of the UK use IHC for this purpose.

CRC exhibiting deficient DNA MMR, whether sporadic or arising in the setting of Lynch syndrome, possess a higher tumour mutation burden, resulting in the presence of a greater number of neo-antigens on the surface of the cancer cells. This renders the tumours sensitive to immunotherapy, e.g. with checkpoint inhibitors. Assessment of the DNA MMR status is therefore useful for directing oncological therapies as well as for Lynch syndrome screening. In contrast to tumours such as oesophago-gastric cancer, immunohistochemical determination

Neoplasms associated with Lynch syndrome[10]

Gastrointestinal

- Colorectal carcinoma[a]
- Gastric adenocarcinoma
- Small intestinal adenocarcinoma
- Pancreatic adenocarcinoma
- Cholangiocarcinoma

Gynaecological

- Endometrial carcinoma[a]
- Ovarian carcinoma

Other sites (examples)

- Urinary tract carcinoma (transitional cell)
- Prostatic carcinoma
- Cutaneous sebaceous tumours (Muir—Torre syndrome)
- Glioblastoma

[a] Colorectal carcinoma and endometrial carcinoma are the two neoplasms most commonly associated with Lynch syndrome.

Table 4

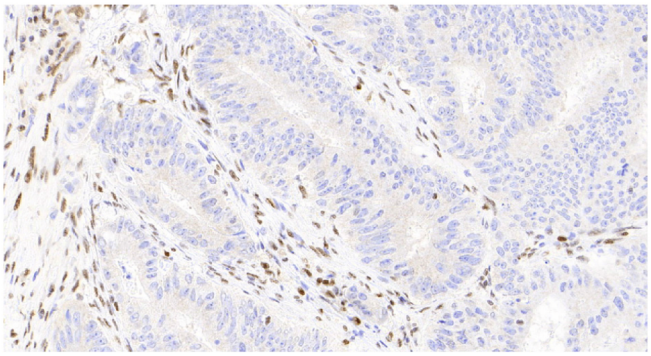

Figure 5 Adenocarcinoma showing loss of PMS-2 expression by the adenocarcinoma cells. The adenocarcinoma comprises glands with blue nuclei (i.e. stained with the haematoxylin counterstain only). Stromal and inflammatory cells still express PMS-2 and this positive staining (an 'internal positive control' — indicating that the stain is technically satisfactory) is evidenced by brown nuclei. This pattern of expression loss is very suggestive of Lynch syndrome associated with a germline mutation in the *PMS-2* gene. *PMS-2 immunohistochemistry*. Magnification ×400.

Definitions of premalignant and advanced colorectal polyps according to the 2019 BSG/SCP/PHE post-colorectal cancer and post-polypectomy guidelines[2]

Note that large (20 mm or greater) non-pedunculated polyps are included separately within these guidelines

Premalignant polyps

- Serrated polyps[a] (apart from hyperplastic polyps in the rectum <5 mm)
- Adenomatous polyps

Advanced polyps

- Serrated polyps 10 mm or greater in size
- Serrated polyps with dysplasia
- Adenomas 10 mm or greater in size
- Adenomas with high-grade dysplasia

ACPGBI, Association of Coloproctology of Great Britain and Ireland; BSG, British Society of Gastroenterology; PHE, Public Health England.

[a] Serrated polyps include hyperplastic polyps, sessile serrated lesions, traditional serrated adenomas and mixed polyps.

Table 5

of the tumour PD-L1 status is not a useful predictor of response to immunotherapy and therefore is not routinely performed.

Pathology and post-CRC resection/polypectomy follow-up

The *BSG/ACPGBI/PHE guidelines* were published in 2019 and focus endoscopic follow-up in patients thought to be at the greatest risk of development of CRC.[2] Under these guidelines, colorectal polyps are classified as 'premalignant' or 'advanced' according to their characteristics — which include the anatomical site, type and size of polyp and the presence/grade of dysplasia (Table 5). Microscopic examination is essential to determine the polyp type and presence/grade of dysplasia, while it is often also useful for confirming the polyp size. Patients with high-risk findings (two or more premalignant polyps plus one or more advanced polyps; or five or more premalignant polyps) are offered surveillance colonoscopy at 3 years, while those without these findings are no longer offered surveillance apart from within the NHS Bowel Cancer Screening Programme (discussed below) when they become eligible. Patients with large (>20 mm or greater) non-pedunculated polyps are given a site check if there is concern about completeness of excision and then also progress to surveillance colonoscopy at 3 years.

Bowel cancer screening

The NHS Bowel Cancer Screening Programme (BCSP) started in 2006 and is a good example of such a scheme.[12] Individuals within the screening age range (currently 54–74 years but with the aim of reducing the lower age limit to 50 years) are invited to undergo faecal occult blood (FOB) testing — via the faecal immunochemical test (FIT) — every 2 years and those with a positive result above the threshold (in England) of 120 µg Hb/g faeces are invited for colonoscopy. Colorectal adenomas are found in up to 40% of those undergoing colonoscopy in this context, with CRC found in just less than 1 in 1000 cases. The advent of the NHS BCSP has resulted in an increase in workload for histopathology laboratories, especially when the FIT FOB test replaced the guaiac FOB test. Most screening-detected polyps are adenomas <10 mm in size and serrated polyps — mainly hyperplastic polyps and sessile serrated lesions. While the majority of these lesions are straightforward to diagnose at microscopic examination, the reliable diagnosis of sessile serrated lesions and the differentiation between adenomas in which epithelial misplacement has occurred secondary to polyp torsion, and early (pT1) adenocarcinoma, are both potentially difficult and problematic areas for pathologists.

Summary

CRC is a common cancer with a wide geographical distribution. Early recognition and prompt treatment is however associated with clinical outcomes that are commonly much better than cancers occurring at other sites within the gastrointestinal tract. Bowel cancer screening programmes have resulted in improvements in the early diagnosis of CRC and potential precursor lesions. A better understanding of the molecular pathways leading to CRC — and in particular, the serrated pathway — has informed the creation of updated guidelines for endoscopic follow-up that are better focused on patients at the greatest risk of progressive disease. ◆

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Practice points

- Colorectal cancer (CRC) is one of the most common malignancies worldwide
- The prognosis of CRC is highly stage-dependent, with cancers identified and treated at an early stage usually associated with excellent clinical outcomes
- Precursor lesions to CRC include colorectal adenomas and sessile serrated lesions, which may exist as sporadic lesions or, less commonly, as polyposis syndromes
- The serrated pathway to CRC is relatively recently characterized and accounts for up to 30% of cases of this condition
- Lynch syndrome is an inherited condition characterized by the presence of a germline mutation within a DNA mismatch repair protein-encoding gene and with affected individuals at increased risk of development of a range of cancers, including CRC
- In the NHS, National Institute for Health and Care Excellence guidelines indicate that all patients with newly diagnosed CRC should undergo screening for Lynch syndrome and in the NHS this is most commonly undertaken using DNA mismatch repair enzyme immunohistochemistry on biopsy or resection tissue samples

