Mistakes in colorectal cancer and how to avoid them

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Colorectal cancer (CRC) is one of the most common malignancies and the second leading cause of cancer death in both sexes in developed countries. Over the past 30 years, a great advance in the understanding of this disease has occurred, from colorectal carcinogenesis to diagnosis, prevention and treatment. Although the majority of CRCs are related to environmental factors, up to 25% of cases have a familial component and potential genetic basis, and highly penetrant monogenic germline mutations account for up to 5% of all CRC cases. Identification and characterization of these hereditary disorders have allowed modification of their natural history, with a substantial decrease in morbidity and mortality among high-risk patients. Nonetheless, the majority of patients who are at high risk of CRC remain undiagnosed due to lack of suspicion. On the other hand, studies from the past two decades have suggested that besides adenomas, serrated polyps are also precursors of CRC, responsible for up to 15–30% of all malignancies. Several studies have demonstrated that serrated polyps are common precursors of colonoscopy interval cancers (cancers diagnosed within the surveillance interval after a complete colonoscopy), mainly due to their challenging clinical management. Finally, strategies for CRC prevention have shown efficacy in reducing CRC incidence and mortality, and colonoscopy is an integral part of CRC screening strategies. The main objective of screening colonoscopy is the detection and removal of premalignant lesions or early CRC. However, colonoscopy is not perfect, and some lesions may be missed. Colonoscopy quality is an emerging concept, and some quality indicators have been demonstrated to be directly related to the development of interval CRC. Here we discuss the major mistakes that are made when gastroenterologists deal with CRC diagnosis, prevention and treatment, and how to avoid them. The list of mistakes and the discussion that follows is evidence based and integrated with our longstanding clinical experience.

Mistake 1 Failing to test for hereditary CRC syndromes in CRC patients who have no family history of the disease

Lynch syndrome, an autosomal dominant disorder caused by germline mutations in DNA mismatch repair (MMR) genes (i.e. MSH2, MLH1, MSH6 and PMS2), is the most common form of hereditary CRC, accounting for 1–3% of all tumours. Familial adenomatous polyposis (FAP), another autosomal dominant disease caused by germline mutations in the APC gene, is the most frequent polyposis syndrome. Although a positive family history of Lynch syndrome or FAP must prompt them to be ruled them out in any at-risk relative, it is important to be aware that de novo cases occur in a significant proportion of patients, especially cases of FAP. Therefore, it is highly recommended that universal tumour MMR testing—by immunohistochemistry and/or microsatellite instability testing—be performed in any patient diagnosed with CRC to exclude Lynch syndrome, regardless of family history. Testing for germline mutations in the APC or MUTYH genes should be considered in those diagnosed with multiple (i.e. >10) cumulative adenomatous polyps. In 2002, another polyposis gene was identified, the MUTYH gene, in which biallelic mutations cause an autosomal recessive pattern of inheritance, usually referred to as MUTYH-associated polyposis (MAP). Classic FAP is characterized by the presence of hundreds to thousands adenomatous polyps throughout the colon and rectum and an almost 100% risk of CRC. Attenuated FAP (AFAP) is a variant of FAP with a milder disease course, characterized by a reduced number of polyps (10–100), later age at onset, frequently right-sided distribution of polyps and a lower CRC risk (up to 70%). In a large cross-sectional study, APC mutations were found in 80% (95% CI, 71–87%) of individuals who had more than 1,000 adenomas, 56% (95% CI, 54–59%) of those with 100–999 adenomas, 10% (95% CI, 9–11%) of those with 20–99 adenomas, and 5% (95% CI, 4–7%) of those with 10–19 adenomas. Biallelic MUTYH mutations were found in 2% (95% CI, 0.2–6%) of patients who had more than 1,000 adenomas, 7% (95% CI, 6–8%) of those with 100–999 adenomas, 7% (95% CI, 6–8%) of those with 20–99 adenomas, and 4% (95% CI, 3–5%) of those with 10–19 adenomas. Accordingly, a significant number of patients with FAP, especially those with AFAP, carry neither MUTYH nor APC germline mutations. Of note, Palles et al. identified heterozygous germline variants in the POLE and POLD1 genes in individuals with a family history of multiple adenomas and CRC, but no detectable mutations in APC or MUTYH.

Mistake 2 Excluding a diagnosis of familial adenomatous polyposis in patients who do not have germline mutations in the APC and MUTYH genes

FAP is characterized by the development of multiple adenomas in the colorectum, a high risk of CRC, and the existence of extracolonic manifestations. Germline APC mutations causing FAP with an autosomal dominant pattern of inheritance were first described in 1991. Since then, a great body of evidence on FAP has been generated, including pathophysiology, genetics, clinical phenotype and prevention. However, in the past two decades, studies have suggested that serrated lesions are also associated with an increased risk of developing CRC. Historically, adenomas were considered as the only type of polyp with malignant potential. However, serrated polyps are common precursors of colonoscopy interval cancers (cancers diagnosed within the surveillance interval after a complete colonoscopy), mainly due to their challenging clinical management. Finally, strategies for CRC prevention have shown efficacy in reducing CRC incidence and mortality, and colonoscopy is an integral part of CRC screening strategies.
precursors of CRC, being responsible for up to 15–30% of all malignancies.  

Mistake 4 Assuming that serrated lesions are rare in Western countries

Serrated lesions—hyperplastic polyps, SSA/Ps and traditional serrated adenomas—are often flat and covered with mucus. These lesions are, therefore, difficult to visualize during colonoscopy and their prevalence underestimated, especially in the proximal colon. Indeed, the detection of proximal serrated lesions is highly variable and endoscopist dependent. To minimize the risk of missing such lesions, high-quality colonoscopy is required.

In a new study, the prevalence of the different serrated lesion subtypes among seven colonoscopy cohorts from five European countries was investigated. The prevalence of any serrated lesions was 14.1–27.2% (median 19.5%), of SSA/Ps without dysplasia was 2.2–8.2% (median 4.1%), and of SSA/Ps with dysplasia was 0.2–1.5% (median 0.5%). It has been suggested that in addition to the adenoma detection rate (ADR), which is one of the main quality indicators for colonoscopy, the serrated detection rate could also be used as a quality measurement.

Mistake 5 Believing there is strong evidence that surveillance colonoscopy reduces CRC incidence and mortality in patients who have colorectal polyps

Current guidelines recommend frequent surveillance colonoscopies for patients after colorectal polyp removal. However, there is uncertainty regarding the effectiveness and cost-effectiveness of these recommendations because of the lack of large-scale clinical trials. Indeed, although some studies suggest there is a protective effect of colonoscopy for patients with adenomas, no study has convincingly demonstrated that post-polypectomy surveillance reduces CRC incidence or mortality. In that sense, a recent large, nationwide study showed no excess risk of CRC after removal of low-risk adenomas, but a small excess risk after removal of high-risk adenomas. Therefore, although surveillance colonoscopy should be recommended, there is a need to generate new and robust evidence for its utility after polyp resection, with appropriate surveillance intervals.

Mistake 6 Believing that screening colonoscopy every 10 years is superior to annual or biannual faecal immunochemical testing in terms of CRC-specific mortality reduction for average-risk patients

CRC screening strategies for the average-risk population (i.e. asymptomatic individuals aged ≥50 years with no family history of CRC) fall into two broad categories: stool tests, which include detection of occult blood or exfoliated DNA, and structural exams, which include flexible sigmoidoscopy, colonoscopy and CT-colonography. Among these techniques, the search for occult blood in stool using the guaiac test and, more recently, the faecal immunochemical test (FIT) are predominantly implemented in Europe and Australia, where CRC screening is mainly programmatic. By contrast, colonoscopy is the dominant screening modality in the United States and Germany, where CRC screening is mostly opportunistic. Although randomized studies evaluating the effect of colonoscopy on CRC mortality are lacking, it is recommended as a first-line screening modality on the basis of observational studies. In the past 10 years, it has been suggested that screening with FIT is more effective and less costly than other strategies, and better accepted than colonoscopy. These data provide the rationale to compare colonoscopy with FIT in terms of CRC-specific mortality reduction, and such an investigation is ongoing.

Mistake 7 Assuming that the quality of colonoscopy depends exclusively on the experience of the endoscopist

CRC screening is effective in reducing the mortality and incidence of this disease. Colonoscopy allows the identification of polyps, and endoscopic polypectomy can effectively prevent the development of CRC. Nonetheless, colonoscopy has some limitations, and lesions can be missed at variable rates. The ADR has become the most important indicator of the quality of colonoscopy because it is directly related to key outcome indicators, such as interval cancer. The ADR is a marker that indirectly reflects other surrogate quality markers, such as preparation quality, the rate of complete colonoscopy, withdrawal time, and the dedication and experience of the endoscopist. However, besides the endoscopist’s performance, there are many other quality indicators that can be divided into three categories: pre-procedure (i.e. the appropriateness of the indication, informed consent fully documented, management of anti-thrombotic therapy), intra-procedure (i.e. quality preparation, visualization of the caecum, ADR, withdrawal time, adequate biopsy sampling in the study of chronic diarrhoea), and post-procedure (i.e. completed procedure report, management of adverse events).

Mistake 8 Referring all malignant polyps for surgical treatment

Malignant polyps are defined by the invasion of adenocarcinoma through the muscularis mucosa but limited to the submucosa (pT1). These polyps account for up to 12% of polyps in polypectomy series and the incidence is increasing with more widespread screening programs. Approximately 80–90% of adenomas are <1 cm in diameter and, therefore, easily excised by conventional snare polypectomy. However, the treatment of larger lesions can be more challenging and require more advanced techniques, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), which are being used with increasing frequency in specialized centres. EMR and ESD afford the opportunity for complete excision rather than having to adopt a piecemeal approach to excision. This is a critical initial step in the overall management of malignant polyps because complete excision facilitates more comprehensive histological examination. Unfortunately, this is not the usual presentation in routine clinical practice. Typically, a patient presents for evaluation after a resected polyp, which was thought to have a...
benign appearance on endoscopy, is found to have an invasive focus of adenocarcinoma on final pathological review. Then the difficult task is to stratify the risk of residual or recurrent disease and the risk of lymph-node metastasis. Accordingly, the management of malignant polyps can be challenging and often requires a multidisciplinary approach. After successful polypectomy, regardless of technique, appropriate decision analysis must be applied to those polyps considered malignant. Patients with polyps that are concerning for malignancy during endoscopy or resected polyps that have any high-risk features (positive or indeterminate resection margins, margin <1 mm, lymphovascular invasion, poor differentiation, submucosal invasion [sm3], or tumour budding) should be referred for segmental colectomy, if medically appropriate, as the incidence of lymph-node metastasis is high (up to 20%). On the contrary, polyps that have no risk factors (margin >1 mm, no lymphovascular invasion, well or moderately differentiated, superficial submucosal invasion [sm1] and no tumour budding) can be managed endoscopically. Currently, there is no established standard for surveillance after endoscopic removal of malignant polyps in patients who are not undergoing surgery. Most authors suggest initial follow-up endoscopy after 3–6 months, but the duration of subsequent surveillance varies.37

Mistake 9 Thinking that interval cancers after a negative colonoscopy are mainly due to fast-growing lesions

Although colonoscopy is the gold standard for direct evaluation of the colon, as a tool it remains imperfect. The diagnosis of CRC within a short interval following a colonoscopy in which cancer had not been detected has been well described. Over the past decade, our knowledge of this problem has increased substantially. Terms such as ‘post-colonoscopy’, ‘missed’, and ‘interval’ CRC have all been used to describe these entities. A consensus panel has proposed that interval CRCs be generally defined as “CRC diagnosed after a screening or surveillance exam in which no cancer is detected and before the date of the next recommended exam.”44 Accordingly, interval post-colonoscopy colorectal cancer (PCCRC) is the preferred terminology. A meta-analysis of population-based studies has determined a pooled prevalence of interval PCCRC of 3.7% (95% confidence interval, 2.8–4.6%) among patients with newly diagnosed CRC.44

There are three predominant explanations for interval PCCRC: missed neoplasms (either cancer or significant polyps), incompletely resected lesions and new lesions.45 It is important to recognize that the relative impact of each of these putative explanations has largely been estimated through the use of algorithms.45 However, missed lesions are probably the most important contributor to the problem of interval PCCRC (52% of them).51,52 The problem of incomplete resection is increasingly recognized and may explain up to 20% of interval PCCRC.53 Finally, new lesions account for up to 25% of interval PCCRC and have been linked to more aggressive or rapidly growing lesions in the setting of the serrated pathway of carcinogenesis. Indeed, interval cancers have the CpG island methylator phenotype, somatic BRAF mutations and microsatellite instability (all of which are characteristic of the serrated neoplasia pathway) more often than non-interval cancers.53

Mistake 10 Assigning patients who have hyperplastic polyps <10 mm in diameter in the rectum or sigmoid colon for endoscopic surveillance

There is considerable evidence that individuals who have only rectal or sigmoid hyperplastic polyps represent a low-risk cohort.54 The coexistence of hyperplastic polyps with adenomas at index colonoscopy does not increase the risk of adenomas and advanced adenomas at surveillance compared with the presence of adenomas alone.55 Accordingly, current guidelines recommend that if the most advanced lesions at baseline colonoscopy are distal hyperplastic polyps <10 mm in size, the interval for follow-up colonoscopy should be 10 years.27,28

Conflicts of interest: The authors declare there are no conflicts of interest.

References


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### Your colorectal cancer briefing

**UEG Week sessions**

- **‘Management of advanced colorectal cancer’ at UEG Week 2015** [https://www.ueg.eu/education/session-files/?session=14028&conference=109].

- **‘Screening for colorectal cancer’ at UEG Week 2015** [https://www.ueg.eu/education/session-files/?session=14028&conference=109].

- **‘A tailored approach to advanced rectal cancer’ at UEG Week 2015** [https://www.ueg.eu/education/session-files/?session=14578&conference=109].


- **‘Colorectal cancer (CRC): Cure by early detection and local treatment’ at UEG Week 2014** [https://www.ueg.eu/education/session-files/?session=11223&conference=76].

- **‘Endoscopic management of early colorectal neoplasia’ at UEG Week 2014** [https://www.ueg.eu/education/session-files/?session=592&conference=48].

- **‘Endoscopy meets pathology: Interdisciplinary management of colorectal polyps’ at UEG Week 2013** [https://www.ueg.eu/education/session-files/?session=601&conference=48].

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**Society conferences**

- **ESGE/ESDO Quality In Endoscopy 2015—Colonoscopy & Colonic Neoplasms** [https://www.ueg.eu/education/conference-files/?conference=110].


- **‘Colon cancer’ session at ESGAR/ESPC Bowel Imaging Workshop 2013** [https://www.ueg.eu/education/session-files/?session=945&conference=50].

- **‘Rectal cancer’ session at ESGAR/ESPC Bowel Imaging Workshop 2013** [https://www.ueg.eu/education/session-files/?session=526&conference=50].

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**European guidelines**

