Best Practice & Research Clinical Gastroenterology 27 (2013) 257–267

Contents lists available at SciVerse ScienceDirect

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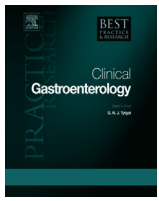

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Precancerous lesions in inflammatory bowel disease

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Keywords:
Dysplasia
Intraepithelial neoplasia
Colorectal cancer
Ulcerative colitis
Crohn's disease

A B S T R A C T

Reduction of mortality from colorectal cancer is a prime goal in the clinical management of patients with extensive, longstanding ulcerative colitis and colonic Crohn's disease. The cornerstone of current cancer prevention efforts is endoscopic surveillance for colorectal dysplasia, or intraepithelial neoplasia, the direct histological precursor of cancer. A diagnosis of dysplasia provides a reliable indicator of heightened cancer risk and an end-point for colonoscopic surveillance allowing most patients to undergo prophylactic colectomy before the development of incurable cancer. This article reviews the classification, pathological criteria and clinical implications of colorectal dysplasia, current recommendations for the performance of surveillance colonoscopy, recent technical advances in colonoscopic imaging to enhance the detection of dysplasia, and a summary of the molecular genetic events implicated in its development.

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1521-6918/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.bpg.2013.03.014

Introduction

The development of colorectal cancer (CRC) poses the most serious long-term health risk faced by patients with chronic inflammatory bowel disease (IBD), i.e., ulcerative colitis (UC) and colonic Crohn's disease (CD) [1–3]. Although CRC in the setting of IBD accounts for less than 0.5% of the total burden of CRC in the general population, its high relative incidence, especially among younger patients and those with longstanding extensive colitis, make its prevention one of the primary clinical goals in the long-term medical management of these patients.

The pathogenesis of CRC in IBD is a prototype of the 'inflammation-dysplasia-cancer sequence', a series of molecular alterations within the intestinal epithelium that is initiated and partially sustained by chronic inflammation, becomes expressed histopathologically as dysplasia, and culminates in invasive cancer [2,4]. As the immediate precursor of CRC in IBD, dysplasia plays a central role both in our clinical efforts to reduce mortality from cancer and in our scientific understanding of its pathogenesis. These two aspects of dysplasia provide the broad themes of this review.

CRC risk in IBD

The magnitude of the risks of CRC incurred by patients with IBD has not been firmly established because of methodological variations among published studies. As a rule, risk estimates based on population-based studies have been more conservative than those based on referral populations and other groups. For example, a widely cited meta-analysis based on data pooled from studies of diverse design estimated the cumulative risk among patient with UC to be 2%, 8% and 18% at 10, 20 and 30 years from disease onset, respectively [5]. In contrast, a recent meta-analysis of eight population-based cohort studies reported corresponding rates of $<$1%, 0.4–2% and 1.1–5.3% at 10, 15 and 20 years, respectively [6]. Despite these conservative data, however, the corresponding standardized incidence ratios were a substantial 2.4 or higher for the entire cohort, 4.8 for the subset with extensive colitis and 8.6 for patients with disease onset below ages 30–40 [6].

Importantly, patients with CD incur risks of intestinal cancer comparable to those with UC, a fact that has now been substantiated based on meta-analyses of pooled population-based [7] and non-population-based studies [8].

Despite variations among published studies with respect to the cumulative risks of developing CRC, there is sufficient consensus across the literature regarding *individual* risk factors for CRC in patients with IBD to help stratify patients by risk and to guide their management accordingly. The most firmly established factors are (a) the presence of dysplasia, discussed below; (b) increased disease duration beyond eight years; (c) increased disease extent, especially extensive or pancolitis, but also left-sided UC to an intermediate degree; (d) microscopic intensity of mucosal inflammation, and (e) concurrent primary sclerosing cholangitis. Other strongly suspected factors include early age of disease onset, a history of sporadic CRC in first-degree relatives and endoscopic disease severity [1].

Pathological features of dysplasia

Colorectal dysplasia, a term synonymous with intraepithelial neoplasia in the World Health Organization and Vienna nomenclature systems, is defined as an unequivocal neoplastic alteration of the intestinal epithelium that remains confined within the basement membrane in which it originated. As the earliest histologically recognizable precursor of CRC, a diagnosis of dysplasia serves both as the first clinical alert that neoplasia of the intestinal epithelium has been initiated and the most reliable harbinger of its progression to invasive cancer. It thereby provides the basic rationale for endoscopic surveillance, permitting the great majority of patients who remain dysplasia-free to avert colectomy while affording those diagnosed with dysplasia a window of opportunity for prophylactic colectomy prior to the development of CRC. Although this strategy is not ethically subject to formal validation in controlled trials, its effectiveness is supported by direct case-control-based evidence that it affords early cancer detection and by circumstantial evidence that it reduces cancer-related mortality [9]. Endoscopic surveillance has therefore been endorsed by professional societies in the U.S. and Europe according to guidelines discussed below.