Long-term Follow-up Reveals Low Incidence of Colorectal Cancer, but Frequent Need for Resection, Among Australian Patients With Inflammatory Bowel Disease

Christian P. Selinger,[*,‡] Jane M. Andrews,[§] Andrew Titman,[‖] Ian Norton,[¶] D. Brian Jones,[*] Charles McDonald,[*] Gavin Barr,[*] Warwick Selby,[#] and Rupert W. Leong,[*,**] on behalf of the Sydney IBD Cohort Study Group

*Gastroenterology and Liver Services, Concord Repatriation General Hospital, Sydney, Australia; ‡School of Translational Medicine, University of Manchester, Manchester, United Kingdom; §IBD Service, Department of Gastroenterology and Hepatology and School of Medicine, University of Adelaide at Royal Adelaide Hospital, Adelaide, Australia; ‖Department of Mathematics and Statistics, University of Lancaster, Lancaster, United Kingdom; ¶Department of Gastroenterology, Royal North Shore Hospital, Sydney, Australia; #A. W. Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Sydney, Australia; and **Faculty of Medicine, University of New South Wales, Sydney, Australia*

BACKGROUND & AIMS: **Inflammatory bowel disease can require surgical resection and also lead to colorectal cancer (CRC). We investigated the cumulative incidence of resection surgeries and CRC among patients with ulcerative colitis (UC) or Crohn's disease (CD).**

METHODS: **We analyzed data from a cohort of patients who participated in an inflammatory bowel disease study (504 with UC and 377 with CD) at 2 academic medical centers in Sydney, Australia from 1977 to 1992 (before the development of biologic therapies). We collected follow-up data on surgeries and development of CRC from hospital and community medical records or via direct contact with patients during a median time period of 14 years. Cumulative incidences of resection surgeries and CRC were calculated by competing risk survival analysis.**

RESULTS: **Among patients with UC, CRC developed in 24, for a cumulative incidence of 1% at 10 years (95% confidence interval [CI], 0%–2%), 3% at 20 years (95% CI, 1%–5%), and 7% at 30 years (95% CI, 4%–10%). Their cumulative incidence of colectomy was 15% at 10 years (95% CI, 11%–19%), 26% at 20 years (95% CI, 21%–30%), and 31% at 30 years (95% CI, 25%–36%). Among patients with CD, 5 of 327 with colon disease developed CRC, with a cumulative incidence of CRC of 1% at 10 years (95% CI, 0%–2%), 1% at 20 years (95% CI, 0%–2%), and 2% at 30 years (95% CI, 0%–4%). Among all patients with CD, the cumulative incidence of resection was 32% at 5 years (95% CI, 27%–37%), 43% at 10 years (95% CI, 37%–49%), and 53% at 15 years (95% CI, 46%–58%). Of these 168 subjects, 42% required a second resection within 15 years of the first surgery (95% CI, 33%–50%).**

CONCLUSIONS: **Patients with UC have a low incidence of CRC during a 30-year period (7% or less); the incidence among patients with CD is even lower. However, almost one-third of patients with UC and about 50% of those with CD will require surgery.**

Keywords: Colon Cancer Risk; Prognosis; Treatment; Therapy.

Inflammatory bowel diseases (IBDs) are chronic inflammatory gastrointestinal disorders comprising predominantly ulcerative colitis (UC) and Crohn's disease (CD).[1] IBDs are characterized by a variable level of inflammatory activity over time, but underlying intestinal damage is thought to accumulate except when early and prolonged mucosal healing is achieved. Increasing inflammatory burden and accumulated intestinal damage may ultimately necessitate resection surgery. The principal aim in the management of IBD is mucosal healing by using a variety of pharmacotherapies. Surgery in IBD is indicated for failed medical therapy or complicated IBD including strictures, toxic megacolon with potential

Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; IBD, inflammatory bowel disease; UC, ulcerative colitis.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2013.05.017

for perforation, fistulas, or development of malignant or premalignant mucosal change. IBD is associated with a significantly increased risk for colorectal cancer (CRC)[2] with a different pathogenesis than that for sporadic CRC.[3] Procarcinogenic mutations are believed to cause significant field damage, from which dysplasia and CRC may arise.[3] The risk for developing IBD-associated CRC is greatest in UC, with a cumulative incidence of 18% after 30 years on older meta-analysis, although newer studies have suggested lower cancer rates, especially in cohorts from community-based settings.[2,4,5] The risk of developing CRC is also increased in CD but probably less so than in UC, with a 10-year cumulative incidence of 3%.[6] These data stem largely from health care settings where patients are cared for by dedicated IBD specialists, in contrast to Australian patients with IBD, who largely receive care by general gastroenterologists, often in office-based community settings.

Regular colonoscopic surveillance has therefore been recommended for both UC and CD (if a significant proportion of the colon is affected) to aid early detection of precancerous and cancerous colorectal lesions, with a recommendation that IBD patients with endoscopically unresectable high-grade dysplasia with or without an associated mucosal mass lesion be considered for colectomy.[1]

Because UC is limited principally to the colon, total/subtotal colectomy offers the potential for "cure," albeit at the price of major surgery and the longer-term implications of ileostomy or pouch formation and their known complications. Surgical resection for CD may lead to periods of remission, but postoperative disease recurrence is extremely common, and further surgery is often required, even with ongoing preventative pharmacotherapy.[7] Multiple resections may be associated with ongoing symptoms (adhesion-related pain and diarrhea due to bile salt wasting) as well as causing short bowel syndrome,[8] which is associated with a significantly reduced quality and quantity of life.[9] Surgical resection also carries a small but important risk of perioperative morbidity and mortality, which is significantly higher in the elderly IBD patient.[10,11] The aim of medical management of IBD is therefore not only for the control of symptoms and induction and maintenance of remission but also to decrease the need for surgery.

The aim of this study was to determine the cumulative incidences for surgical resection and development of CRC in both UC and CD by examining the long-term follow-up of a previously well-described cohort of patients with IBD in Australia.

Methods

Patients

The study is based on a cohort of IBD patients first described by Andrews et al[12] in 1995. Patients were identified in the original study by a complete search of the medical case records of 2 Sydney teaching hospitals by using coding data for all admissions and discharges (Concord Repatriation General Hospital and Royal Prince Alfred Hospital) and a manual search of all case files of 17 affiliated community-based gastroenterologists and included whether they met diagnostic criteria for IBD according to accepted endoscopic, histologic, or radiologic criteria.[12] Two-thirds of 997 patients (533 with UC, 417 with CD, and 47 with indeterminate colitis/IBD-unclassified) in the original study cohort came from the community-based gastroenterologists' rooms. All cases were individually verified, ascertained, and classified by phenotype (transcribed to Montreal classification) at time of study entry. Follow-up clinical data on surgical resections and development of CRC were gathered from hospital and community medical records and by contacting the patients directly.

Statistical Analysis

Survival time analysis was used to study the incidence of surgery and CRC and to ascertain factors associated with an increased risk of experiencing surgery or CRC. Survival and causes of deaths were reported previously; 26% of patients had died during follow-up.[13] To avoid bias from many unrelated deaths, which occurred during the long follow-up, competing risk survival analysis was chosen over Kaplan–Meier analysis. Competing risk survival analysis, in contrast to Kaplan–Meier, can study several competing outcomes such as development of CRC, colectomy for other reasons, and unrelated death and can determine cumulative incidences for each discrete event. Competing risks analyses were performed by using the Fine–Gray model of proportional subdistribution hazards,[14] with corrected weights to account for left-truncation in addition to right-censoring[15] by using the *crhaz* and *survival* packages within the statistical software R. Death and colectomy for other reasons (for UC CRC incidence only) were treated as competing outcomes, whereas end of follow-up was treated as a censoring event.

For this follow-up study, patients were included if they were either diagnosed after 1977 or were yet to experience the studied events (surgery, CRC) in 1977. To avoid length-bias from prevalent cases, these patients were treated as being left-truncated from the time since diagnosis in 1977. Patients diagnosed before 1977 would be unrepresentative of the full patient population because their inclusion is dependent on survival (without surgery or CRC) between their date of diagnosis and 1977. As a consequence, these patients will have a longer time to event than the prospectively sampled set of patients. To account for this in the statistical analysis, the event times for the prevalent patients are taken to be left-truncated from their time since diagnosis in 1977. Left-truncated survival models account for the time of