Current State of and Problems Related to Cancer of the Intestinal Tract Associated with Crohn's Disease in Japan

DAIJIRO HIGASHI[1], HIDETOSHI KATSUNO[2], HIDEAKI KIMURA[3], KENICHI TAKAHASHI[4], HIROKI IKEUCHI[5], TORU KONO[6], RIICHIRO NEZU[7], KATSUYOSHI HATAKEYAMA[8], HITOSHI KAMEYAMA[8], IWAO SASAKI[9], KOUHEI FUKUSHIMA[9], KAZUHIRO WATANABE[9], MASATO KUSUNOKI[10], TOSHIMITSU ARAKI[10], KIYOSHI MAEDA[11], SHINGO KAMEOKA[12], MICHIO ITABASHI[12], SAYUMI NAKAO[12], KOUTARO MAEDA[2], HIROKI OHGE[13], YUSUKE WATADANI[13], TOSHIAKI WATANABE[14], EIJI SUNAMI[14], MASAYUKI HOTOKEZAKA[15], AKIRA SUGITA[16], YUJI FUNAYAMA[4,17] and KITARO FUTAMI[1]

[1]*Department of Surgery, Fukuoka University Chikushi Hospital, Chikusino, Japan;*
[2]*Department of Surgery, Fujita Health University, Toyoake, Japan;*
[3]*Inflammatory Bowel Disease Center, Yokohama City University Medical Center, Yokohama, Japan;*
[4]*Coloproctology Center, Tohoku Rosai Hospital, Sendai, Japan;*
[5]*Department of Inflammatory Bowel Disease Surgery, Hyogo College of Medicine, Nishonomiya, Japan;*
[6]*Advanced Surgery Center Sapporo Higashi Tokushukai Hospital, Sapporo, Japan;*
[7]*Department of Surgery, Nishinomiya Municipal Central Hospital, Nishinomiya, Japan;*
[8]*Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan;*
[9]*Department of Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan;*
[10]*Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, Tsu, Japan;*
[11]*Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka, Japan;*
[12]*Department of Surgery 2, Tokyo Women's Medical University, Tokyo, Japan;*
[13]*Department of Surgery, Hiroshima University, Hiroshima, Japan;*
[14]*Department of Surgical Oncology and Vascular Surgery, The University of Tokyo, Tokyo, Japan;*
[15]*Department of Surgery, Junwakai Memorial Hospital, Miyazaki, Japan;*
[16]*Inflammatory Bowel Disease Center, Yokohama Municipal Citizen's Hospital, Yokohama, Japan;*
[17]*Department of Surgery, Sendai Red Cross Hospital, Sendai, Japan*

Abstract. *Background/Aim: Cancer of the intestinal tract (small and large intestine) associated with Crohn's disease has a low incidence but can be fatal if it develops. Thus, the key question is how to deal with this type of cancer. The current study surveyed major medical facilities that treat inflammatory bowel disease (IBD) surgically in Japan in order to examine the clinical features of cancer of the intestinal tract associated with Crohn's disease and explore ways to deal with this cancer in the future. Patients and Methods: Sixteen major medical facilities that treat IBD surgically were surveyed regarding cancer of the intestinal tract associated with Crohn's disease. The medical facilities had treated 3,454 patients with Crohn's disease, 122 of whom had developed intestinal cancer. The medical facilities were surveyed regarding those 122 patients. Results: The incidence of intestinal cancer associated with Crohn's disease has increased yearly. Cancer most often developed in the left side of the colon and, particularly, in the rectum and anal canal. Seventy-six percent of cases were diagnosed preoperatively, 4% were diagnosed intraoperatively, while the remaining 20% were diagnosed pathologically after surgery. The most prevalent histological type of cancer was mucinous carcinoma (50%). Forty-two percent of cancers were differentiated, with 4% being poorly differentiated. The surgical procedure performed most often (67%) was abdominoperineal resection. The 5-year survival rate by stage was 88% for Stage I, 68% for Stage II, 71% for Stage IIIa, 25% for Stage IIIb and 0% for Stage IV. Overall, the 5-year survival rate was 52%. Conclusion: Gastrointestinal*

Correspondence to: Daijiro Higashi, Department of Surgery, Fukuoka University Chikushi Hospital, 1-1-1 Zokumyoin, Chikusino, Fukuoka 818-8502, Japan. Tel: +81 929211011, Fax: +81 929280856, e-mail: daijiro@fukuoka-u.ac.jp

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(GI) cancer associated with Crohn's disease had an incidence of 3.5%, but also involved a poor prognosis with a 5-year survival rate of 52%. Early detection through surveillance is crucial to improving the prognosis for patients. However, surveillance of the intestinal tract with endoscopy or contrast studies is technically and diagnostically hampered by Crohn's disease and intestinal strictures. A biopsy of the anal canal, a common site of cancer, can readily be performed and constitutes the first step in surveillance.

The problem of cancer associated with inflammatory bowel disease (IBD) is widely recognized in the treatment of ulcerative colitis and there is widespread awareness of that problem in surveillance colonoscopy as well. There was thought to be little incidence of associated cancer in Crohn's disease; however, reported cases of associated cancer of the intestinal tract (small and large intestine) have increased over the past few years. Cancer of the intestinal tract associated with Crohn's disease has features that differ from usual intestinal cancer. There are few reported cases of associated cancer of the intestinal tract, with characteristics and prognosis not yet being adequately studied. The current study surveyed major medical facilities in Japan in order to examine the current state of and problems related to cancer of the intestinal tract associated with Crohn's disease.

Patients and Methods

Major medical facilities in Japan that treat IBD surgically were surveyed regarding the number of patients with Crohn's disease they had treated over the past 20 years, type of Crohn's disease, sites of cancer when cancer was diagnosed, depth of invasion, histologic type, form of treatment and patients' prognosis. Medical facilities had treated 3,454 patients, 122 of whom were found to have cancer of the intestinal tract with an incidence of 3.5%. The postoperative prognosis was determined in 119 patients who were available for follow-up.

Results

Tallying in the number of patients who developed cancer by year revealed an apparent increase in the number of cases starting in 2001 (Figure 1). The ratio of male to female patients was 72:50, the mean age at which cancer developed was 45.9 years and the mean period from the onset of Crohn's disease to the development of cancer was 18.4 years. The type of Crohn's disease broke down into 9 patients with ileitis, 99 with ileocolitis and 14 with Crohn's colitis. In terms of the site of cancer, cancer developed in the left side of the colon in 86% of patients. Cancer was most prevalent in the anal canal (51%), followed by the rectum (29%) (Figure 2). In terms of the depth of invasion when cancer was detected, 91% of cancers were advanced with invasion reaching the muscularis propria (MP), whereas 9% of the detected cancers

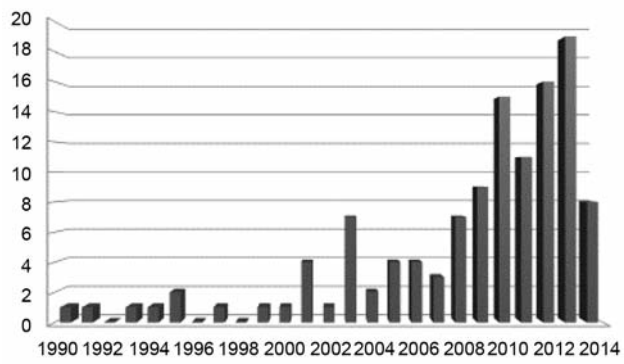

Figure 1. *Annual number of cases of cancer of the intestinal tract associated with Crohn's disease.*

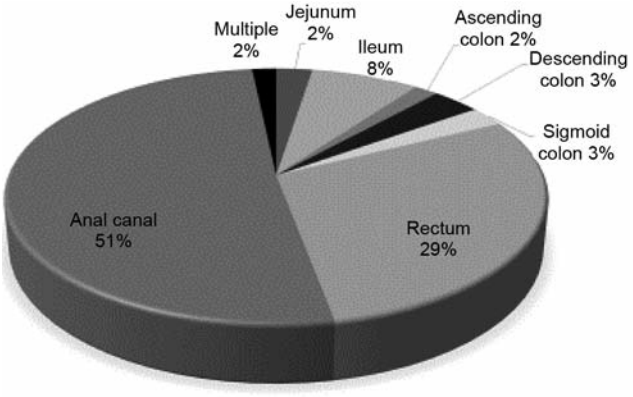

Figure 2. *Sites of cancer development.*

were cancers invading the mucosa (M) and submucosa (SM), *i.e.* early cancers (1). Metastasis to multiple organs was noted in 13% of cases (Figure 3). Seventy-six percent of associated cancers were definitively diagnosed preoperatively, 4% were diagnosed intraoperatively, while 20% were diagnosed pathologically after surgery. The most prevalent histologic type of cancer was mucinous carcinoma (50%). Well- and moderately-differentiated adenocarcinoma is often noted in typical colon cancer; however, only 42% of cancers of the intestinal tract are associated with Crohn's disease (Figure 4). In terms of the presence or lack of symptoms when cancer was detected, 61% of patients were symptomatic. The most frequent symptom was pain, followed by bowel obstruction and bleeding (Figure 5). Staging of this study was performed according to the classification of the Japanese Classification of Colorectal Carcinoma (1). Of the 122 identified patients, 199 were available for follow-up to determine their postoperative prognosis. The 5-year survival rate by stage was 88% for Stage I, 68% for Stage II, 71% for Stage IIIa, 25% for Stage IIIb and 0% for Stage IV (Figure 6). The

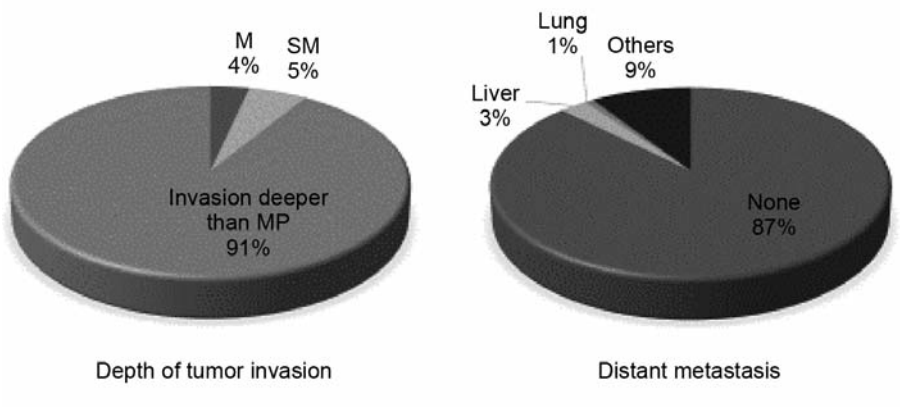

Figure 3. *Progression of cancer after detection.*

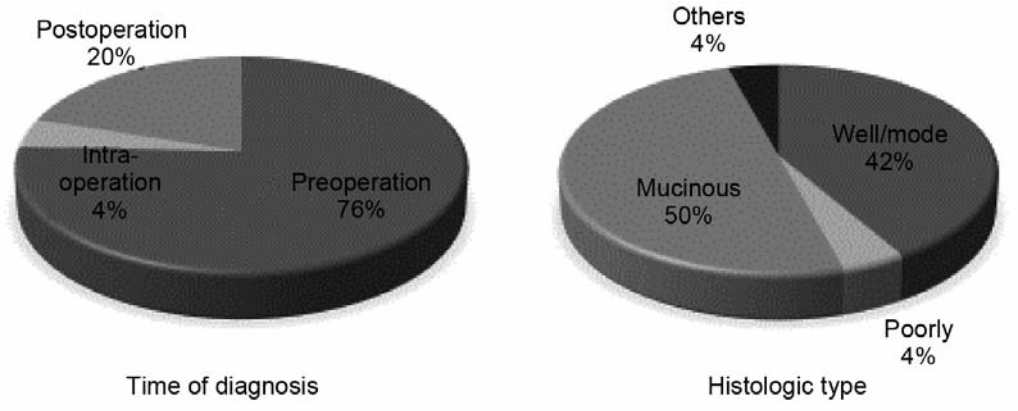

Figure 4. *Time of diagnosis and histologic type of cancer.*

overall 5-year survival rate for patients with associated cancer was 52% (Figure 7).

Discussion

The very first publications on cancer of the intestinal tract associated with Crohn's disease include a report by Warren *et al*. (2) who described cancer of the large intestine associated with Crohn's disease in 1948, as well as a report by Ginzburg *et al*. (3) who described cancer of the small intestine associated with Crohn's disease in 1956. Cancer associated with Crohn's disease usually develops at a younger age than cancer of the large intestine, in patients who have had Crohn's disease for 10 years or longer and in patients with extensive Crohn's disease (4-7). A meta-analysis in the UK and North America by Canavan *et al*. revealed a high risk of cancer of the small intestine and colon cancer developing in Crohn's disease (8). According to this work, the relative risk of cancer of the large intestine in Crohn's disease was 2.5, while the relative risk of cancer of the small intestine in Crohn's disease was 31.2. Chronic inflammation with strictures and fistulae, a prolonged duration of disease and ileitis have been reported as risk factors for associated cancer of the small intestine (9-12). According to Yano *et al*., the risk factors for cancer of the large intestine in Crohn's disease include sex (feminine prevalence), ileocolitis, Crohn's disease for 20 years or longer, age (under 25), anal lesions and history of intestinal surgery (13). In support, the current study demonstrated that cancer developed at an earlier age (45.9 years) than that at which cancer of the large intestine usually develops and also revealed that the period from the onset of Crohn's disease to the development of cancer was 18.4 years. Being younger and having Crohn's disease for a prolonged period may be risk factors for development of associated cancer. According to studies in Europe and the US, cancer of the large intestine associated with Crohn's disease develops more often in the right side of the large intestine (14) in

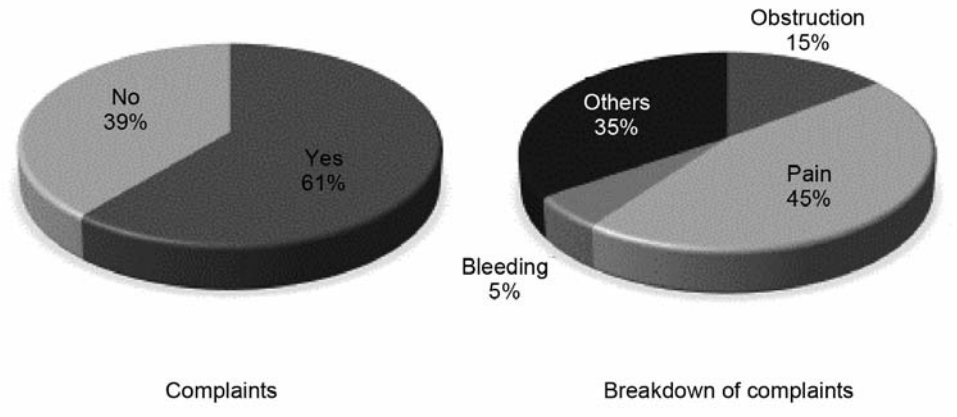

Figure 5. *Symptoms associated with cancer.*

contrast to Japanese studies showing that intestinal cancer associated with Crohn's disease develops more often in the left side of the large intestine (15). The current findings substantiate previous results since cancer developed more often in the left side of the large intestine, particularly in the rectum and anus. This may be a feature of cancer of the intestinal tract associated with Crohn's disease, particularly to the Japanese population. Compared to usual cancer of the large intestine, cancer of the large intestine associated with Crohn's disease consists of a larger proportion of mucinous carcinomas and signet ring cell carcinomas (3, 16-18). Similarly, the current survey indicated that most cancers (50%) were mucinous carcinomas. Mucinous carcinoma does not readily respond to anticancer agents or radiation therapy, which may account for its poor prognosis. In addition, intestinal cancer occurring in association with Crohn's disease is difficult to definitively be diagnosed preoperatively. The primary treatment for this type of cancer is surgery. In the cases surveyed here, cancer often developed in the rectum, with abdominoperineal resection being the procedure performed most often (Figure 8). Many cancers are diagnosed in an advanced stage, thus necessitating invasive surgery, *i.e.* resection of surrounding organs that have been invaded by cancer and intestinal adhesions due to Crohn's disease.

Medical treatment of Crohn's disease in patients with cancer is a topic to consider. A study has reported on the use of an agent for chemoprevention in IBD (19). Many drugs against Crohn's disease are not compatible with cancer treatment and, therefore, balanced diet and nutritive management currently constitute the primary approach for treating the disease. This important topic will be left for future consideration.

Choi *et al.* reported that Crohn's disease had a 5-year survival rate of 46% (20). Similarly, the current study noted

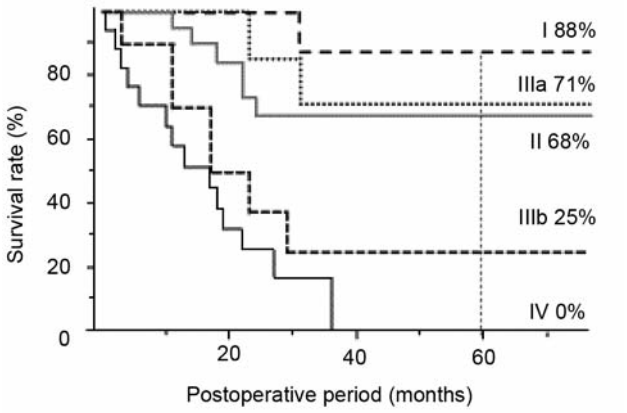

Figure 6. *Five-year survival rate (by stage).*

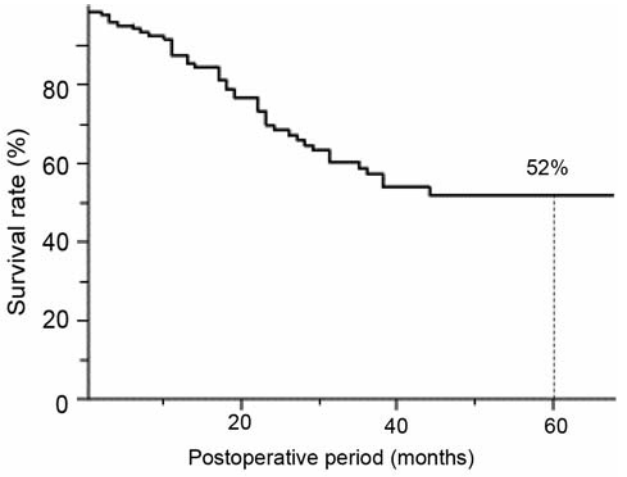

Figure 7. *Five-year survival rate (for all patients).*

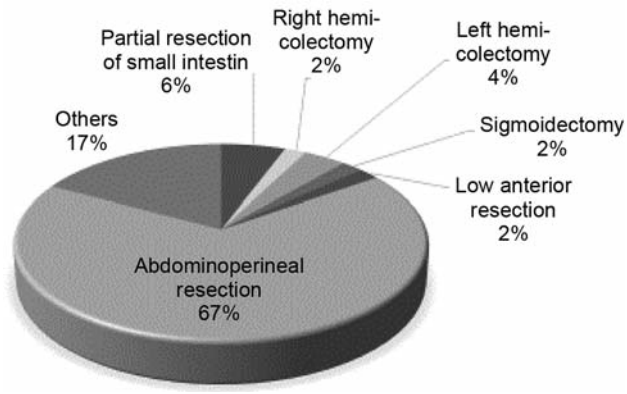

Figure 8. *Procedures performed to treat cancer of the intestinal tract associated with Crohn's disease.*

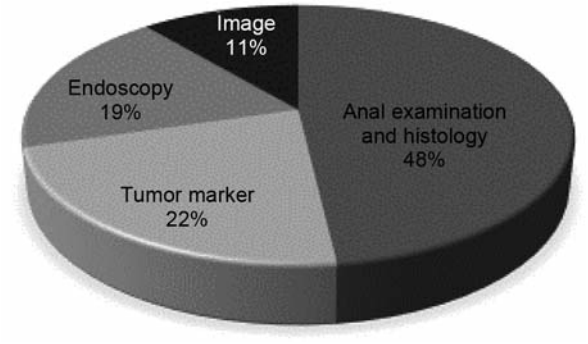

Figure 9. *Medical examinations for cancer surveillance in patients with Crohn's disease.*

a poor 5-year survival rate of 52%. Surveillance examinations for early detection are crucial to improving prognosis. There is widespread awareness of ulcerative colitis and other forms of IBD in surveillance colonoscopy (21) but endoscopy is hampered in Crohn's disease due to multiple strictures and adhesions caused by surgery. If severe anal lesions are present, an endoscope cannot be inserted because of pain and strictures. Imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) seldom lead to early diagnosis (22, 23); thus, the best approach at present is active histology. According to the current survey, surveillance efforts at different medical facilities most often involved an anal examination and histology (Figure 9). In Japan, common sites of colon cancer associated with Crohn's disease are the anal canal and rectum. Frequent and diligent biopsies of these sites should provide effective cancer surveillance. A multicenter study entitled "Establishment of a Program for Surveillance of Cancer of the Large Intestine Associated with Crohn's Disease" is currently in progress.

Conclusion

Major medical facilities that treat Crohn's disease surgically were surveyed regarding cancer of the intestinal tract associated with Crohn's disease, as well as the current state and problems related to this type cancer. The incidence of intestinal cancer associated with Crohn's disease is increasing yearly having a poor prognosis, with a 5-year survival rate of 52%. In Japan, cancer of the intestinal tract, associated with Crohn's disease, most often develops in the rectum and anal canal, with biopsies of those sites constituting the first step in surveillance.

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