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Prophylactic total gastrectomy for hereditary diffuse gastric cancer: surgical and pathological results

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Summary: In this study, we examined the results of prophylactic total gastrectomy for patients with germline *CDH1* (E-cadherin) mutation. The 8 patients (3 male, 5 female) had a median age of 42 (range 38-51). All patients had an upper endoscopy or chromoendoscopy prior to surgery with only one patient identified as having a focus of diffuse gastric cancer. All patients underwent a total gastrectomy with Roux-en-Y esophagojejunostomy. For pathological analysis, the entire gastric mucosa was examined microscopically, which required up to 490 sections. Only one patient had unremarkable pathology. The other 7 patients had 1-77 foci of noninvasive cancer, and two of these patients had 4-12 foci of T1 invasive cancer. Thus, the majority of patients with germline CDH1 mutation have foci of noninvasive or invasive gastric cancer by middle age. Serial endoscopy provides inadequate screening, and total prophylactic gastrectomy is the procedure of choice for definitive treatment.

Introduction: In 1998, Guilford and colleagues carried out genetic linkage analysis with microsatellite markers and found significant linkage to markers flanking the gene for E-cadherin, *CDH1*, in three Maori families from New Zealand (1). Subsequently, *CDH1* mutations have been identified in families with hereditary diffuse gastric cancer in multiple different countries. Hereditary diffuse gastric cancer (HDGC) has been defined as any family that fits the following criteria: (1) two or more documented cases of diffuse gastric cancer in first or second degree relatives, with a least one diagnosed before age 50, or (2) three or more cases of diffuse gastric cancer in first or second degree relatives, independent of age of onset (2). *CDH1* germline mutations have now been demonstrated in about 30% of patients with the IGCLC clinical criteria. The lifetime risk of developing gastric cancer in patients who carry a *CDH1* mutation is estimated at 40% to 67% for men and 63% to 83% for women (2;3). Screening by upper endoscopy or chromoendoscopy is generally considered

inadequate in patient with germline *CDH1* mutation because most neoplastic foci lie within apparently normal-appearing epithelium (4). Prophylactic total gastrectomy for individuals with germline *CDH1* mutation was first described in 2001. Here we describe the presentation, treatment, and outcome of 8 patients who underwent total prophylactic gastrectomy at our institution.

Materials and Methods: Patients found to have a germline *CDH1* mutation and treated with a prophylactic total gastrectomy at our institution between April 2006 and February 2009 were included in this study. All patients were evaluated by a multidisciplinary team that included a geneticist, surgical oncologist, gastroenterologist, and nutritionist before surgery. In terms of the operative technique, all surgeries were performed via an upper midline incision. The distal division across the duodenum should be performed at least 1 cm beyond the pylorus, and the proximal division should be performed at least 1 cm above the squamocolumnar junction. The gastrectomy specimen was analyzed grossly by the surgeon to ensure the squamocolumnar junction was included in the specimen, and the specimen should be sent for frozen section analysis of proximal and distal margins to confirm that all gastric mucosa has been removed. Reconstruction was generally performed with a Roux-en-Y reconstruction with a 60 cm Roux limb to prevent bile reflux. Pathological mapping of the entire gastric mucosa was performed.

Results: Between April 2006 and February 2009, our institution performed prophylactic total gastrectomies on 8 patients from 5 HDGC families. There were 3 male patients and 5 female patients. The median age was 42 years old (range 38-51). All patients had a strong family history of diffuse gastric cancer and tested positive for germline *CDH1* mutation. Of the 5 families represented, there were 3 missense, 1 frameshift, and 1 splice site mutation. Median time from genetic testing to surgery was 3 months (range 1-7 months).

All patients in our series had an upper endoscopy or chromoendoscopy prior to surgery with only one patient identified as having a focus of diffuse gastric cancer. All patients underwent a total gastrectomy with Roux-en-Y esophagojejunostomy. Median operating time was 201 min (range 187-308), and length of stay was 7-8 days. Contrast study of the esophagojejunal anastamosis 5 days after surgery revealed no anastamotic leaks. One patient had an early postoperative complication (pulmonary embolism). Two patients had late complications (small bowel obstructions).

For pathological analysis in the 8 patients treated with total prophylactic gastrectomy at our institution, the entire gastric mucosa was examined microscopically, which required up to 490 sections. Only one patient had unremarkable pathology. The other 7 patients had 1-77 foci of noninvasive cancer, and two of these patients had multi-focal (4-12) foci of T1 invasive cancer.

For the 6 patients with at least 6 months follow up, the median weight loss was 19% of preoperative weight. The most weight loss (43% of preoperative

weight) was experienced by a 39 year old obese woman with a preoperative body mass index of 42.

Discussion: Early stage diffuse gastric cancer identified in patients with HDGC is characterized by the presence of multiple foci of signet-ring cell carcinoma confined to the superficial gastric mucosa (5). Some investigators have hypothesized that the natural history of HDGC involves the development of multiple foci of signet-ring cell carcinoma in most mutation carriers by 20 to 30 years of age. These foci may likely develop following the loss of the second CDH1 allele (6). Some of these foci can eventually invade the lamina propria and submucosa after acquisition of additional mutations or changes in the microenvironment of the surrounding carcinoma cells.

A significant challenge in managing patients with germline *CDH1* mutations is the inadequacy of current screening techniques. Diffuse gastric adenocarcinoma in HDGC patients is characterized initially by multiple infiltrates of signet-ring cell carcinoma that underlie normal mucosa (4). There is usually a wide distribution of small-sized lesions that make them difficult to identify with random endoscopic biopsies. Additionally, conventional white light endoscopy and even chromoendoscopy with vital dyes has poor sensitivity to detect these submucosal abnormalities (7).

There have been at least 6 separate series with patients with germline E-cadherin mutations who have undergone prophylactic total gastrectomy that have been reported (4;8-12). In these 6 studies, there were a total of 53 patients, and the majority of patients had normal upper endoscopies prior to their prophylactic total gastrectomies. Fifty patients (94%) had intramucosal or superficially invasive carcinomas identified in the gastrectomy specimen, and the majority of patients had multi-focal disease. The findings of our study confirm that the vast majority of patients with germline CDH1 mutation harbor foci of noninvasive or even invasive diffuse gastric adenocarcinoma despite usually normal screening endoscopies.

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