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Clinical impact of colonoscopy for patients with early gastric cancer treated by endoscopic submucosal dissection: A matched case–control study

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ABSTRACT

Background: Gastric cancer frequently occurs synchronously with colorectal cancer (CRC).
Aims: The aim of the present study was to assess the value of colonoscopy in patients with primariy early gastric cancer (EGC) indicated for endoscopic submucosal dissection (ESD) and to identify predictors for the risk of high-risk adenomas.
Methods: A total of 130 patients with EGC, who underwent both colonoscopy and gastric ESD, and 260 controls matched for age and sex, who underwent a colonoscopy as part of our institutional health check-up program.

The prevalence of high-risk adenomas in EGC patients vs. controls was evaluated.
Results: High-risk adenomas were found in 43 (33%) EGC patients and 37 (14%) controls ($P < 0.01$). Multivariate analysis showed the presence of EGC was significantly associated with high-risk adenoma [odds ratio (OR) 2.8, 95% confidence interval (CI): 1.7–4.9]. Among EGC patients, high serum CEA level (OR 2.4, 95% CI: 1.2–5.0) was an independent predictor for high-risk adenoma.
Conclusions: Patients with EGC had a significant risk for colorectal cancer. When endoscopists detected an early gastric cancer indicated for ESD, colonoscopy should be considered for EGC patients with high serum CEA levels.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, accounting for 1,360,000 new cases in 2012, and it is the second leading cause of cancer-related deaths (694,000 deaths) [1]. Long-standing evidence indicates that the detection and removal of precancerous lesions through colonoscopies reduces the incidence of CRC and associated mortality [2]. However, participation to the colonoscopy is still unsatisfactory [3]. Physician's recommendation is the key to improve participation to screening program [4].

Endoscopic submucosal dissection (ESD) has been widely accepted as a curative treatment for early gastric cancer (EGC) and favorable long-term outcomes have been reported [5–7]. During surveillance after ESD, occurrence of secondary neoplasms in the other parts of the gastrointestinal (GI) tract concerns. An adequate screening strategy for early detection of secondary neoplasms in the GI tract is essential for long-term survival. Some clinical and epidemiological studies have revealed close correlations between the incidence rates of gastric and colorectal neoplasms [8–10]. Furthermore, previous studies have suggested that the most common second primary site of synchronous and metachronous cancer in patients with gastric cancer is the colorectum [11–13]. Given 15-year preventive effects on CRC mortality in screening colonoscopy [2], patients with EGC indicated for ESD would enjoy protection from CRC death because of their expected long-term survival [14,15]. However, the risk for subsequent CRC in patients treated by gastric ESD has not been accurately clarified.

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The aim of the present study was to assess the value of colonoscopy in patients with primarily diagnosed EGC treated by ESD and to identify predictors for the risk. Understanding the value of colonoscopy and these predictors would help to improve the participation and contribute to developing a colonoscopy strategy for EGC patients.

2. Methods

2.1. Study population

This was a retrospective, matched case–control study. We identified cases from the institutional endoscopy database of the Shizuoka Cancer Center in Japan from January 2010 to December 2012. Eligible patients were newly diagnosed with EGC and underwent ESD; in addition, they had a colonoscopy for CRC within 1 year of the ESD. The control group consisted of healthy subjects who underwent esophagogastroduodenoscopy (EGD) and colonoscopy as part of our institutional health check-up program during the same period. For every enrolled case, two control patients, matched for age and sex, were selected by a biostatistician (M.K.) blinded to clinical information and the study concept. Patients were excluded if they had a history of colectomy, gastrectomy, or gastric ESD, major abdominal surgery, inflammatory bowel diseases, or familial polyposis (FAP). The study protocol was approved by the institutional review board at our center. Written, informed consent was obtained from all patients.

2.2. Endoscopic procedures

Patients were given a low-fiber diet and took preparatory medication the day before colonoscopy: 160 mg of sennoside or 7.5 mg sodium picosulfate at night. The morning of the colonoscopy, 68 g of magnesium citrate dissolved in 1.8 L of water or 137.155 g of polyethylene glycol dissolved in 2 L of water was used to clean the bowel. Scopolamine butylbromide or glucagon was administered just before the colonoscopy. Pethidine was used as an analgesic. Midazolam was used for patients who requested sedation.

Colonoscopies were performed using a high-resolution video endoscope with a magnification function (PCF-Q240Z, CF-H260AZI, or PCF-Q260AZI; Olympus, Tokyo, Japan). All colonoscopies were performed by 14 endoscopists: 7 were experienced endoscopists who had performed more than 1000 colonoscopies and 7 were trainees who had done less than 1000 colonoscopies. All of the trainees performed colonoscopy under the supervision of experienced endoscopists. A magnified endoscopy with narrow-band imaging and indigo carmine spraying was used for evaluation of the histology of all detected lesions [16]. The quality of bowel preparation was graded as follows: (1) excellent, (2) good, (3) fair, (4) inadequate, or (5) poor according to the modified Aronchick scale [17]. The morphology, size, location, diagnosis, cecal intubation time, and procedure time were recorded. Polypectomy was performed on detected lesions when the size was judged as 5 mm or larger. Mean colonoscopy withdrawal times were calculated for each colonoscopist for only completely negative procedures (CN-withdraw time). Actual withdrawal times for individual procedures were substantially affected by the duration of magnified endoscopic observations or therapeutic procedures rather than the time spent examining the colonic mucosa during withdrawal [18]. The fixed specimens were examined histologically.

2.3. Data collection

All patients were interviewed by a nurse in the outpatient room about medical history, family history of CRC, and lifetime history of tobacco and alcohol use. Information including the indications for colonoscopy was extracted from medical records for each patient. The reference standard was histopathology using standard hematoxylin and eosin staining. When a specimen of the detected polyps was not obtained, optical diagnosis were recorded as a reference [16,19]. The cut off values for carcinoembryonic antigen (CEA) and Body Mass Index (BMI) were 5 ng/dL and 25, respectively. A positive family history for CRC was defined as one or more first-degree relatives had suffered from CRC. Cumulative alcohol use was calculated as follows. We defined a drink-equivalent as one 12-oz beer, one 6-oz glass of wine, one 3-oz mixed drink, or one 1.5-oz shot of liquor. The number of drink-equivalents per week was recorded.

2.4. Histological evaluation

Experienced pathologists blinded to clinical information evaluated all specimens. The histological type of the adenoma or carcinoma was determined using the World Health Organization classification [20]. Histological diagnosis for gastric and colorectal neoplasms was performed according to the Japanese Classification of Gastric Carcinoma [21] and the Japanese Society for Cancer of the Colon and Rectum guidelines 2010 for the treatment of colorectal cancer [22], respectively.

2.5. Study endpoints

The primary endpoint was the prevalence of high-risk adenomas in the EGC patients vs. controls. EGC was defined based on pathological diagnosis as gastric cancer that is confined to the mucosa or the submucosa, irrespective of the presence of lymph node metastasis. The total number, size, and histology of detected colorectal neoplasms, the odds ratio for high-risk adenomas, and distribution of detected colorectal neoplasms were evaluated as secondary endpoints. Advanced neoplasia was defined as a carcinoma, an adenoma $\geq$10 mm, or an adenoma with a villous component or severe dysplasia. High-risk adenoma was defined as a case with an advanced neoplasia or with 3 or more adenomas. For our analyses, we categorized the anatomic locations of lesions as right-side colon (cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure), left-side colon (descending colon), or rectosigmoid colon (sigmoid colon and rectum).

2.6. Statistical analysis

Assuming that 15% of patients in the control group had high-risk adenomas, a power calculation showed that the sample size of this study has a 90% power at a 5% significance level to detect a two-fold increase in the prevalence of high-risk adenomas in EGC patients. Conditional multivariate logistic-regression models were used to estimate the odds ratio (OR) as a measure of the association between various exposures and the risk of CRC, together with 95% confidence intervals (CI). P values less than 0.05 for associations were considered statistically significant. For multivariate analysis, we select variables that were statistically significant ($P < 0.05$) in the univariate analysis. JMP software ver. 8.0 (SAS Institute Inc., Cary, NC) was used for all analyses.

3. Results

During the study period, 2073 patients underwent both EGD and colonoscopy in our institution. Of these patients, 165 had EGC (189 lesions) treated by ESD. Of this group, 35 (21%) were not enrolled: 20 (12%) had a previous history of CRC, 14 (8%) had a previous history of gastric ESD; and 1 (0.6%) had diagnosis of FAP. The remaining 130 patients with 154 EGC lesions (102 males and 28 females; median age, 69 years) were included in our analysis (Fig. 1). The mean size of the EGC lesion was 20 mm, with a range of 4–83 mm.

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