Clinical Significance of Total Colonoscopy for Screening of Colon Lesions in Patients with Esophageal Cancer

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Abstract. *Aim: The objective of the present study was to evaluate the significance of pre-treatment screening for patients with esophageal cancer. Patients and Methods: A retrospective evaluation of the clinical significance of total colonoscopy in 136 patients with primary esophageal cancer was performed. Results: Twenty-three patients (16.9%) had diverticula, and five (3.7%) had colon cancer. Benign polyps were present in 57 patients (41.9%); 37 of these patients underwent endoscopic treatment, one underwent surgery (esophagectomy). Twenty-seven out of 32 patients (84.4%) who underwent histopathological studies had tubular adenoma. Significant associations were found between presence of colorectal lesions and body weight, body-mass index ($p<0.001$), Brinkman index ($p<0.001$), and the Sake index ($p<0.05$). Conclusion: Screening for colorectal lesions using total colonoscopy is important in patients with esophageal cancer, especially for those with a high body-mass index, and those who smoke or drink heavily.*

It is very important to ensure correct diagnosis and treatment of multi-organ cancer in patients with esophageal cancer. The Japan Esophageal Society reported that the incidence of double primary cancer in patients with esophageal cancer was 8.3% for synchronous lesions and 12.4% for metachronous lesions (1). Gastric cancer and head and neck cancer are relatively common cancer types associated with esophageal cancer (2, 3). Several risk factors, including smoking and alcohol consumption, have been shown to be strongly associated with esophageal cancer (4-6). These risk factors lead to upper aerodigestive tract cancer, such as oral cavity, oropharyngeal, and laryngeal cancer (7). The concept that common carcinogenic agents can lead to multiple types of cancer in adjacent regions is well-known as 'field cancerization' (8). Preoperative screening of the stomach and head and neck regions is, therefore, essential before treatment of esophageal carcinoma.

The incidence of colon and rectal cancer is reportedly 15.9% of all synchronous neoplasms in Japanese patients with esophageal cancer (1). About 1.5% of patients with esophageal cancer prior to treatment also have colon or rectal cancer. If a colonic lesion is missed, it has the potential to cause harm during re-treatment or reoperation or may even result in cancer-associated death. In addition, a gastric tube is usually used for reconstruction during total esophagectomy, but in patients with coexisting esophageal and gastric cancer, the colon or jejunum must be used for esophageal reconstruction after total gastrectomy. Screening of the entire colon and rectum is therefore essential in these patients.

Total colonoscopy is a safe and popular examination for screening of the colon and rectum. This procedure is useful as an endoscopic treatment (*e.g.* polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection) for early adenocarcinomas and pre-malignant adenomas in the colon and rectum. Early detection and removal of colorectal adenomas has been shown to be the most effective method of colorectal cancer prevention. In our Department, we routinely evaluate the colon and rectum during total colonoscopy as part of our screening protocol in patients with esophageal cancer. Few reports have investigated the usefulness of colonoscopy for such patients. We investigated whether total colonoscopy is useful for screening in patients with esophageal cancer.

Patients and Methods

Patients. We evaluated 136 patients with esophageal cancer who had undergone treatment in the Department of General Surgical Science of the Graduate School of Medicine of Gunma University between January 2007 and April 2012. None of the patients had received prior

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Key Words: Body-mass index, smoking, alcohol, neoplasms, multiple primary tumors, esophageal cancer, colonoscopy.

Table I. *Characteristics of patients with esophageal cancer with or without coexisting colorectal lesions.*

Characteristics		Esophageal cancer without colorectal lesion	Esophageal cancer with colorectal lesion	*p*-Value
		n=59	n=77	
Age (years)		66.2±8.6	66.0±6.9	0.62
Gender	Male	49	70	0.18
	Female	10	7	
Family history	Present	28	42	0.17
	Absent	25	33	
	Unknown	6	2	
Height (cm)		163.2±7.5	163.8±6.1	0.65
Body weight (kg)		55.0±7.7	60.3±8.7	<0.001
BMI		20.6±2.6	22.5±2.8	<0.001
Tumor location	Upper	7	11	0.37
	Mid	32	32	
	Lower	20	34	
Histological subtype	Squamous cell carcinoma	52	72	0.64
	Adenocarcinoma	5	3	
	Other	2	2	
Clinical stage*	I	18	19	0.41
	II	18	20	
	III	11	24	
	IV	12	14	
Brinkman index		698.8±483.2	1010.2±561.1	<0.001
Sake index		65.4±49.5	100.6±118.7	<0.05
Treatment of esophageal cancer	Surgery	35	48	0.52
	Radiation/chemoradiation	16	22	
	Endoscopic treatment	8	7	

Brinkman index: Number of cigarettes consumed per day multiplied by years of smoking. Sake index: weight (g)/22 of ethanol consumed per day multiplied by years of drinking. *According to the sixth edition of the TNM classification of the International Union Against Cancer (UICC).

treatment for esophageal cancer. All patients underwent total colonoscopy for screening before esophageal cancer treatment. The median age of the patients was 66 years (range=43-82 years). A family history of cancer was defined as the presence of cancer in first- to third-degree relatives of the patients. The pre-treatment clinical tumor stage was classified according to the sixth edition of the TNM classification of the International Union Against Cancer (UICC)(9). We determined the tumor stage using computed tomographic scans of the neck, chest, and abdomen; bone scans; endoscopic ultrasound; endoscopy; fluorodeoxyglucose positron- emission tomography; and esophagography. All patients underwent bowel preparation in the form of laxatives (10 mg sodium picosulfate) and low-residue diets that began two days before their examination. The patients received 24 mg of a sennoside for bowel preparation the night before the examination and drank 200 ml of polyethylene glycol solution (Niflec; Ajinomoto Pharmaceuticals Co., Ltd., Tokyo, Japan) every 10 min on the examination day for a total intake of 2000 mL of polyethylene glycol solution. Polypectomy and endoscopic mucosal resection were performed as usual (10, 11).

Evaluation of alcohol consumption and smoking. The cumulative cigarette consumption was expressed as the Brinkman index (BI; number of cigarettes consumed per day multiplied by years of smoking) (12). We also assessed the drinking frequency and volume of alcohol intake according to beverage types. The volume was converted to grams of ethanol, and values for each beverage type were added. The ethanolic contents for the calculation were as follows: 5% for beer, 15% for Japanese sake (rice wine), 35% for shochu (a distilled alcoholic beverage made in Japan), 12% for wine, and 43% for whisky. The cumulative amount of alcohol consumption was then expressed as the Sake index [SI; weight (g)/22 of ethanol consumed per day multiplied by years of drinking]. The traditional Japanese drinking unit, the *gou*, corresponds to 22 g of ethanol; thus, the SI indicates the total *gou* consumed per day multiplied by years of drinking.

Statistical analysis. All values are expressed as the mean±standard deviation of the mean. Statistical analysis was performed with the chi-square test, Mann–Whitney *U*-test, and logistic regression analysis. We analyzed the associations between the risk of colorectal lesion development and the body-mass index (BMI), BI, and SI by calculating the relative risks as incident rate ratios using logistic regression analysis. The level of statistical significance was set at $p<0.05$.

Results

There were no abnormal findings in the colon or rectum in 59 out of the 136 patients (43.4%) (Table I). Twenty-three patients (16.9%) had diverticula, and five (3.7%) had colonic cancer (Table II). Three patients had carcinoma of the

Table II. *Treatment of colorectal lesions.*

	Type of lesion		
	Diverticula (n=23)	Benign polyp (n=57)	Carcinoma (n=5)
Surgery	0	1	4
Endoscopic resection	0	37	1
Observation	23	19	0

Table III. *Pathological findings of colorectal polyps.*

Pathology	Differentiation	Number of cases
Adenoma	High grade	5
	Moderate	3
	Low grade	4
	Unknown	15
	Sessile serrated	1
Hyperplastic polyp		4
Unknown		6
Total		38

Table IV. *Coexistence of colorectal lesions in 77 out of 136 patients with esophageal cancer.*

	Type of lesion		
	Diverticula	Benign polyp	Carcinoma
Location of tumor	(n=23)	(n=57)	(n=5)
Cecum and ascending colon	7	14	1
Transverse colon	3	5	
Descending colon	3	5	
Sigmoid colon	6	14	3
Rectum	0	10	1
Multiple	4	8	
Unknown	0	1	

Table V. *Multivariative analysis of risk factors for colorectal lesion.*

	p-Value	Odds ratio	(95% confidence interval)
BMI	<0.001	45.3	(5.65-463)
BI	0.09	5.38	(0.77-41.4)
SI	0.29	32.9	(0.13-27794)

BMI: Body-mass index; BI: Brinkman index; SI: Sake index.

sigmoid colon, and one each had carcinoma of the cecum and rectum. Colorectal cancer was resected with esophagectomy in four patients. One patient with an adenoma was treated by endoscopic mucosal resection. Benign polyps were present in 57 patients (41.9%); 37 of these patients underwent endoscopic treatment, one underwent surgery (esophagectomy), and 19 underwent no treatment (follow-up only). Histopathological examinations were performed in 32 patients with benign polyps. Twenty-seven out of these 32 patients had tubular adenoma (Table III), one had a sessile adenoma, and four had hyperplastic polyps. In three patients, polyps were lost to examination. The polyps were located in either the cecum or ascending colon in 14 patients, transverse colon in five, descending colon in five, sigmoid colon in 14, rectum in 10, and multiple sites in eight; one patient had an unknown lesion (Table IV). Diverticulae were located in either the cecum or ascending colon in seven patients, transverse colon in three, descending colon in three, sigmoid colon in six, and several sites in four.

The results of the analysis of the clinical features of the patients with esophageal cancer with or without colorectal lesions are shown in Table I. The body weight of patients with colorectal lesions was heavier than that of patients without lesions ($p<0.001$). The BMI of patients with colorectal lesions was also higher than that of patients without lesions ($p<0.001$). The BI and SI of patients with esophageal cancer with colorectal lesions were significantly higher than those of patients without colorectal lesions ($p<0.001$ and $p<0.05$, respectively). There were no differences in the age, gender, patient height, family history, tumor location, histological subtype, clinical stage, or treatment of esophageal cancer between patients with and those without colorectal lesions. In addition, among patients with a family history of cancer, there was no significant difference between the presence of colorectal lesions and first-degree relatives of patients with cancer, first- and second-degree relatives of patients with cancer, family history of colorectal cancer (data not shown). In the multivariate analysis of risk factors for colorectal lesion, BMI was an independent risk factor for colorectal lesions in patients with esophageal cancer (odds ratio=45.3) (Table V).

Discussion

The stomach is the most commonly used esophageal substitute (13). However, co-existence of gastric and esophageal cancer after gastrectomy is not rare. In such cases, a segment of the colon may be used to replace the resected esophagus (14). It is therefore important to examine the colon preoperatively. In this study, 62 out of 136 patients (45.6%) with esophageal cancer also had colon cancer and polyps before treatment. Most patients with colon polyps underwent endoscopic resection before esophageal cancer treatment.

Neoplastic lesions (mostly adenomatous polyps) are reportedly detected in 20-30% of screened patients (15, 16). Adenomatous polyps are the most frequent neoplasm found during colorectal screening. Removal of these lesions has been shown to reduce the risk of future colorectal cancer and advanced adenoma development (17). In our study, five adenocarcinomas and 57 colon polyps were found by total colonoscopy in patients with esophageal cancer. The precise prevalence of adenoma is unknown, but based on autopsy studies, it may be 30% or more among individuals aged >40 years in the United States and northwestern Europe (18-21). In Japan, a necropsy study showed that the incidence of adenomatous polyps was 18% in the Miyagi Prefecture and 30% in the Akita Prefecture (22). The incidence of colonic polyps in our study is higher than that in other studies that targeted the general population. Total colonoscopy is imperative for pre-treatment examination of patients with esophageal cancer. Kuwano et al. reported that the incidence of malignant colon lesions is 4% and that adenomatous lesions are more commonly found during barium examination (23). Total colonoscopy is superior to the use of barium enemas because polypectomy can be simultaneously performed.

We analyzed the clinicopathological characteristics of patients with and without various colorectal lesions to identify patients at high risk of developing malignant or neoplastic lesions on routine preoperative colorectal examination. First-degree relatives of patients with colorectal cancer have a 3- to 6-fold increased risk of developing colorectal cancer; screening colonoscopy has therefore been recommended in this cohort (24, 25). We also investigated the relationship between colorectal lesions in patients with esophageal cancer and a family history of cancer, however, no significant association was found. We have shown that patients with esophageal cancer with colorectal lesions have a higher BMI and body weight than those without colorectal lesions. BMI was an independent risk factor for colorectal lesions by multivariate analysis in our cohort. Most studies have shown a positive association between obesity and the risk of colorectal cancer (26-28). Patients with esophageal cancer are usually thinner because of low oral intake and cachexia. Obese patients with esophageal cancer should undergo screening of the colon and rectum. Patients with esophageal cancer with colorectal lesions were also shown to consume more cigarettes and alcohol than patients without colorectal lesions. This may indicate that smoking and alcohol use are risk factors for colorectal cancer (29) and adenomas (30). These results suggest that screening for colorectal lesions by total colonoscopy is important in patients with esophageal cancer, especially those with a high BMI, those who smoke heavily, and those who drink heavily.

In conclusion, co-existence of either a colorectal malignancy or adenoma with esophageal cancer is relatively common. Total colonoscopy for screening and treatment should be performed before esophageal cancer treatment if possible.

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