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Gastrointestinal Endoscopy for Patients with High Levels of Serum CEA and CA19-9

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Abstract: Serum levels of tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), are often measured to detect potential malignancy. When these levels are high, the presence or absence of malignancy is confirmed via a more detailed examination using gastrointestinal (GI) endoscopy and computed tomography. The rate of confirmation of malignancy upon such a follow-up is unknown. This study aimed to investigate the malignancy detection rate via GI endoscopy for patients with high levels of serum CEA and CA19-9. All patients who underwent such GI endoscopy between January 2018 and February 2019 at Showa University Hospital were included in this study. The patients were divided into a follow-up group and a screening group, depending on the purpose of measuring their serum CEA/CA19-9 levels. There were 156 patients who underwent GI endoscopy because of high CEA/CA19-9 levels within the study period. Advanced malignant lesions were detected in 10 patients (6.4%), including seven cases of colorectal cancer and three cases of upper GI malignancies. In the screening group, six cases (5.7%) of GI malignancies were detected, none of which were found in asymptomatic patients without anemia. In the follow-up group, four cases (7.8%) of GI malignancies were detected; three patients were asymptomatic, and one patient had anemia. Our findings suggest that high serum CEA/CA19-9 levels in asymptomatic patients without anemia and without a history of malignancy do not indicate the presence of malignancy. However, high serum CEA/CA19-9 levels may indicate the potential presence of GI malignancies for patients with a history of malignant tumors, even if they are asymptomatic and do not have anemia.

Key words: CEA, CA19-9, endoscopy, malignancy, cancer

Introduction

Gastrointestinal (GI) cancer is one of the leading causes of morbidity and mortality from malignant disease in Western and Asian countries. Globally, colorectal cancer is the fourth and

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gastric cancer the sixth most common malignancy[1]. In Japan, population-based cancer screening is conducted for gastric, colorectal, lung, breast, and uterine cancer. Because of the high incidence of gastric cancer, population-based screening is recommended for individuals older than 50 years, either annually, by performing conventional double-contrast barium radiography, or biennially, by performing upper GI endoscopy[2, 3]. In Japan, a fecal immunochemical test is performed for population-based colorectal cancer screening.

The most effective modality to detect both gastric and colorectal cancer is an endoscopic examination, and the gold standard for cancer diagnosis is a pathological examination, usually by endoscopic biopsy. Therefore, upper GI endoscopy and colonoscopy are recommended if abnormalities are found during primary screening. Private medical facilities in Japan offer various kinds of individual screening at the patient's own cost. These tests often entail measuring serum levels of tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), as only a blood sample is required[4-8]. CEA levels are useful for surgical treatment planning, posttreatment follow-up, and determining the prognosis of patients diagnosed with colorectal cancer[9]. Additionally, a meta-analysis reported by Deng *et al.* suggested that preoperative elevation of CEA levels is an independent indicator of adverse prognosis[10]. However, low rates of sensitivity, particularly in the early stages of the disease, prevent the use of any of these serologic markers to diagnose colorectal and gastric cancer[9, 11-13]. Moreover, elevated levels of CEA may also be caused by benign diseases, such as gastritis, peptic gastroduodenal ulceration, diverticulitis, liver disease, chronic obstructive pulmonary disease, diabetes, and any acute or chronic inflammation[14]. From the viewpoint of lifestyle factors, CEA levels are significantly higher in smokers than in non-smokers[15, 16].

When tumor marker levels are high, a more detailed examination is performed with the help of GI endoscopy or computed tomography to confirm the presence or absence of malignancy. However, the rate of confirmation of malignancy upon such a follow-up is unknown. In this study, we investigated the rate of malignancy, as determined by endoscopic examination, for patients with high tumor marker levels.

Patients and methods

The present study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee on Human Studies of Showa University, Tokyo, Japan. This was a retrospective, single-center study of consecutive patients who underwent GI endoscopy between January 2018 and February 2019 at Showa University Hospital.

Data (age, sex, symptoms at first hospital visit, family history of malignant disease, endoscopic findings, pathological findings of endoscopic biopsy, blood count, and serum CEA and CA19-9 levels) of patients who underwent endoscopy because of high serum CEA and CA19-9 levels were obtained from their electronic medical records. The patients were classified into two groups according to the purpose of measuring their serum CEA/CA19-9 levels: a follow-up group, with previously identified malignant tumors, or a screening group, for whom regular cancer screening was undertaken. The cut-off values of serum CEA and CA19-9 levels in this study were set at

5 and 34 ng/ml, respectively. Patients with a blood hemoglobin concentration < 14 g/dl for males and < 12 g/dl for females were declared to have anemia, according to the standard reference ranges used at our hospital.

Statistical analysis

Data are presented as frequencies and percentages. The imputed data were statistically analyzed using JMP Pro 14 for Windows (SAS Institute Inc., Cary, NC, USA). A descriptive analysis was performed, and differences between the groups were tested using the Chi-square test and the Mann–Whitney U test. A p-value ≤ 0.05 was considered statistically significant.

Results

Patient characteristics

There were 156 patients who underwent GI endoscopy (upper GI endoscopy and/or colonoscopy) because of high CEA/CA19-9 levels within the study period. Table 1 describes the patients' baseline characteristics. There were 121 patients with elevated CEA levels (77.6%) and 50 patients with elevated CA19-9 levels (32.1%). The average hemoglobin concentration was

Table 1. Patient characteristics

N = 156		
Age	year, mean±S.D (range)	65.6±13.6 (30-90)
Sex	Male (%)	76 (48.7)
	Felmale (%)	80 (51.3)
Symptom	Syptomatic (%)	46 (29.5)
	Asymptomatic (%)	110 (70.5)
History of MD	Present (%)	51 (32.7)
	Absent (%)	105 (67.3)
Anemia	Present (%)	63 (40.4)
	Absent (%)	92 (59.0)
	Not performed (%)	1 (0.6)
CEA	≧ 5 ng/ml	121 (77.6)
	< 5 ng/ml	28 (17.9)
	n,m	7 (4.5)
CA19-9	≧ 37 ng/ml	50 (32.0)
	< 37 ng/ml	70 (44.9)
	n,m	36 (23.1)
UGE	Performed	156 (100.0)
	Not performed	0 (0)
CS	Performed	140 (89.7)
	Not performed	16 (10.3)

S.D; standard deviation, MD; malignant disease, n,m; not measured, UGE; upper GI endoscopy, CS; colonoscopy

13.6 and 12.5 g/dl for male and female patients, respectively, and 40 male (52.6%) and 23 female (28.8%) patients were anemic. There were 51 patients (32.7%) in the follow-up group and 105 (67.3%) in the screening group. In total, 139 patients (89.1%) underwent a colonoscopy at Showa University Hospital, one patient (0.64%) underwent colonoscopy at another medical facility, and 16 patients (10.3%) did not undergo colonoscopy, either due to age or because no request was made.

Detected malignant disease

Malignant lesions were detected in 10 patients (6.4%). Three of them (1.9%) were diagnosed with malignancy during upper GI endoscopy, and seven (4.5%) were diagnosed with colorectal cancer during colonoscopy. The details of these malignant lesions are presented in Table 2.

Table 3 summarizes the statistical significance of the cancer detection rate in terms of the

Table 2. Cases with newly detected gastrointestinal malignancies

Case	Sex	Age	Tumor maker	Diagnosis	Symptom	History of MD	Anemia	CEA	CA19-9	Pathology
1	Male	71	CEA	Advanced colon cancer	+	gastric cancer	−	9.1	14	adenocarcinoma
2	Male	68	CEA/CA19-9	Advanced colon cancer	+	−	−	5.8	491.1	adenocarcinoma (tub2 ～ por)
3	Male	74	CEA	Advanced colon cancer	+	−	−	40.8	156.6	adenocarcinoma (tub1)
4	Male	68	CEA	Early colon cancer	−	lung cancer	−	7.1	4.4	adenocarcinoma in adenoma
5	Male	85	CEA/CA19-9	gastric malignant lymphoma	+	−	−	9.5	3931.8	atypical lymphoid cells
6	Male	69	CEA	Advanced EGJ cancer	−	esophageal cancer	−	33.2	41.8	EGJ carcinoma.sig + tub1
7	Male	77	CEA/CA19-9	Advanced duodenal cancer	−	bile duct cancer	+	11.2	1729.7	adenocarcinoma
8	Female	76	CEA	Advanced colon cancer	−	−	+	25.7	n,m	adenocarcinoma (tub2)
9	Male	74	CEA	Advanced colon cancer	+	−	+	5.3	34	adenocarcinoma (tub2)
10	Male	46	CEA	Early colon cancer	+	−	+	6.8	18.2	Early colonic adenocarcinoma (tub1) in adenoma

MD; malignant disease, EGJ; esophagogastric junction

Table 3. Significance of cancer detection rate by patient background

			GI malignancy + N = 10	GI malignancy− N = 146	p value
Age	year, mean±S.D		70.8±10.1	65.3±13.7	0.22
Sex	M	(%)	9 (11.8)	67 (88.2)	< 0.01*
	F	(%)	1 (1.3)	79 (98.8)	
Group	Follow-up	(%)	4 (7.8)	47 (92.2)	0.61
	Screening	(%)	6 (5.7)	99 (94.3)	
Symptom	Syptomatic	(%)	6 (13.0)	40 (87.0)	0.03*
	Asymptomatic	(%)	4 (3.6)	106 (96.4)	
Anemia	Present	(%)	7 (11.1)	56 (88.9)	0.05
	Absent	(%)	3 (3.3)	89 (96.7)	

S.D; standard deviation, *; significantly different, M/F; male/female

patient's background. There were statistically significant differences in cancer detection rates between male and female patients ($p < 0.01$) as well as between symptomatic and asymptomatic patients ($p = 0.03$). There was no statistically significant difference in the detection rate of GI malignant tumors between patients with and without anemia ($p > 0.05$).

As summarized in Table 4, there was no correlation between serum CEA levels and the presence of GI malignancy ($p = 0.61$). Similar results were observed for serum CA19-9 levels ($p = 0.16$).

Screening group

In the screening group, six cases (5.7%) of GI malignancies were detected, of which five were colorectal cancer (four advanced cancer and one mucosal cancer), and one was gastric malignant lymphoma (see Tables 2 and 3). Of these six patients, five were symptomatic at the first visit to our hospital, and all patients were found to be anemic via blood tests. In the screening group, there was a statistically significant difference in the detection rate of GI malignancies in patients with or without symptoms and anemia ($p = 0.04$ and $p < 0.01$, respectively). Furthermore, no GI malignancies were detected in asymptomatic patients without anemia in the screening group (Fig. 1). Only 27 patients (25.7%) underwent cancer screening before undergoing endoscopy, whereas 78 patients (74.3%) had not previously undergone any cancer screening.

Table 4. Relationship between CEA/CA19-9 and the presence of gastrointestinal malignancy

	unit	Total	GI malignancy +	GI malignancy−	p value
CEA level (n = 121)	ng/mL, median	7.3	7.2	7.3	0.61
CA19-9 level (n = 50)	ng/mL, median	101.0	156.6	34.0	0.16

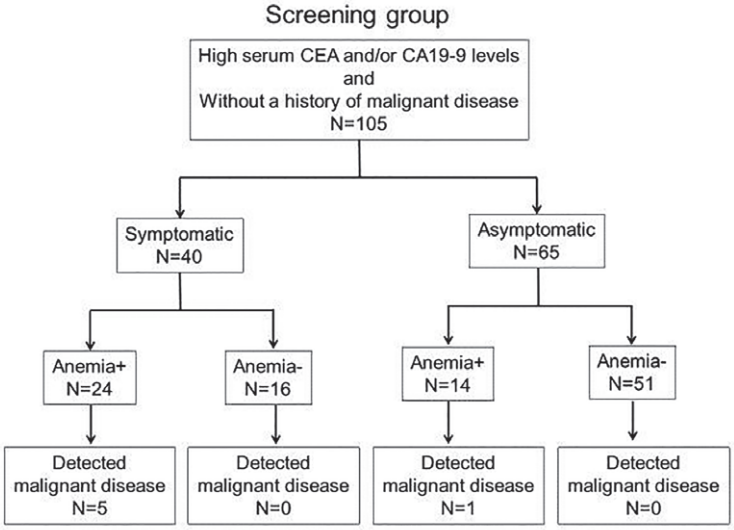

Fig. 1. Flow chart of the screening group based on their symptoms and the presence of anemia. There was no patient with GI malignancy without symptoms and anemia.

Moreover, of the six patients with malignant tumors in this group, only one had previously undergone cancer screening (colorectal), and the remaining five with GI malignancy had never undergone cancer screening.

Follow-up group

Four cases (7.8%) of GI malignancies were detected in the follow-up group (see Tables 2 and 3). Of them, one had esophageal gastric junction cancer, one had duodenal cancer, and two had colon cancer (one early and one advanced). In the follow-up group, six patients (11.8%) were symptomatic when the tumor markers were measured, and only one patient was found to have GI malignant disease, specifically advanced colon cancer. There were 25 (49.0%) patients in the follow-up group who were anemic, and of them, only one was found to have GI malignant disease (advanced duodenal cancer) (Fig. 2). In the follow-up group, 24 patients (47.1%) had undergone upper GI endoscopy, and 27 patients (52.9%) had undergone colonoscopy. Of the four patients with newly detected GI malignancy in this group, two patients had not undergone GI endoscopy in the previous three years.

Discussion

In this study, we investigated the incidence of GI malignant disease and its characteristics in patients who had undergone endoscopy due to high serum CEA and CA19-9 levels. Conventionally, tumor markers for GI cancer are used as ancillary indicators of therapeutic efficacy and as signs of recurrence of malignant tumors but are less useful as detection tools[9–13]. However, tumor markers are sometimes used as screening tools for cancer detection because they can be measured with simple blood tests. If the tumor marker level is high, further examination is required to confirm the presence or absence of cancer. In particular, serum CEA and CA19-9

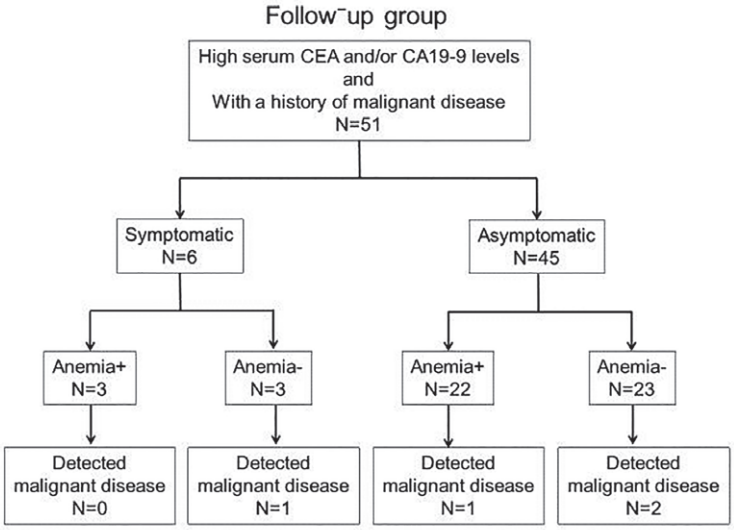

Fig. 2. Flow chart of the follow-up group based on their symptoms and the presence of anemia.

levels are sometimes high in patients with GI cancer. For such patients, it is necessary to perform highly invasive examinations, such as upper GI endoscopy and colonoscopy. Furthermore, for patients who have had malignant tumors in other organs, the effectiveness of GI endoscopy when high serum CEA and CA19-9 levels are detected during a follow-up hospital visit has not been clarified.

In the present study, most of the patients had high serum CEA levels. Because of the small number of patients that were negative for CEA, it was difficult to compare these results with those of previous studies regarding the efficacy of using serum CEA levels to detect GI malignancies. However, as shown in Table 4, CEA levels were not significantly correlated with the presence of GI malignancies.

In this study, patients were divided into a follow-up group and a screening group, due to differences in the reason for measuring CEA and CA19-9 levels and in potential cancer risks. The GI malignancy detection rate was not significantly different between the two groups, suggesting that the serum CEA and CA19-9 levels were not correlated with GI malignancy detection via endoscopy for patients as a whole.

Serum CEA levels are known to be affected by other factors such as aging and smoking[14-16]. It is possible that patients in the current study were a mixture of smokers and non-smokers. Patients' smoking habits were not available for this study. However, it is difficult to determine whether elevated CEA levels are due to smoking or malignancy before scanning. Therefore, the presence of a smoking habit seems to be difficult to become the reason for not doing the endoscope.

This study showed that these patients' symptoms were significantly associated with the detection of GI malignant disease (see Table 3), anemia tended to be associated with the detection of GI malignancies, although this was not statistically significant. These tendencies were especially significant for patients with high CEA and CA19-9 levels without a history of malignant diseases (screening group). There was a statistically significant difference in the detection rate of GI malignancies with or without symptoms and anemia in the screening group. Of the six patients with newly detected GI malignancies in the screening group, only one was asymptomatic, and three patients had anemia. The asymptomatic patient who had advanced colorectal cancer had not received population-based cancer screening, and this case could have been detected without measuring tumor marker levels if a fecal immunochemical test would have been performed.

For asymptomatic patients in the study, GI malignancies were more frequently detected in the follow-up group (6.7%) than in the screening group (1.5%). In the follow-up group, 49.0% and 51.0% of patients had not previously undergone upper GI endoscopies and colonoscopies, respectively. This suggested that patients with a history of malignant tumors may need to be screened for GI cancer regularly, even if they are asymptomatic.

This study suggests that high serum CEA/CA19-9 levels may not be an accurate indication of GI malignancy for asymptomatic patients without anemia who have never been diagnosed with cancer. Thus, GI endoscopy for these patients might be unnecessary. By avoiding unnecessary examinations, medical resources and medical costs can be reduced, and the risk of complications associated with endoscopy may be avoided. Endoscopy is often considered a major risk for the

elderly; therefore, it is recommended that such invasive examinations only be performed after confirming the presence of symptoms and anemia.

Currently, the number of people undergoing population-based cancer screening in Japan is low[17]. This is reflected in the current study, where a low number of screening group patients had previously undergone population-based cancer screening (25.7%, data not shown). This may be due to the low tolerability of conventional double-contrast barium radiography, upper GI endoscopy, and the fecal immunochemical test. In recent years, new tumor markers, such as CA11-19[18, 19], have been identified, and blood-based gene biomarker panels have been developed[20]. It is essential to develop methods to improve the patient screening rate, thereby increasing the cancer detection rate. However, of the screening tools currently in use, the simpler methods are less effective than the more invasive ones. Therefore, new screening methods need to be developed, and the significance of tumor marker tests should be explained to the patient to improve the patient screening rate.

Second, among patients with high serum CEA/CA19-9 levels, only those who had undergone GI endoscopy were investigated. Therefore, the detection rate of malignant GI tumors for patients with high tumor marker levels in this study cannot be compared with the rates found in previous studies.

In conclusion, GI endoscopic examination is not recommended for patients with high serum CEA/CA19-9 levels who are asymptomatic, have no anemia, and have no history of malignancy. Furthermore, for patients with a history of malignant tumors and high serum CEA/CA19-9 levels, GI malignancies may be present, even if the patients are asymptomatic and without anemia.

There were some limitations to this study. First, this was a single-center, retrospective study with a limited population size. Second, among patients with high serum CEA/CA19-9 levels, only those who have undergone gastrointestinal endoscopy were investigated. Therefore, the detection rate of malignant GI tumors for patients with high tumor marker levels in this study cannot be compared with the rates found in previous studies.

In conclusion, GI endoscopic examination is not recommended for patients with high serum CEA/CA19-9 levels who are asymptomatic, have no anemia, and have no history of malignancy. Furthermore, for patients with a history of malignant tumors and high serum CEA/CA19-9 levels, GI malignancies may be present even if the patients are asymptomatic and without anemia.

Acknowledgments

The authors declare no conflicts of interest. We disclose that a version of this paper was presented at the Japanese Digestive Disease Week (JDDW2019) poster session in Japan on November 23, 2019. This paper has not been published elsewhere.

Conflict of interest

The authors have declared no conflict of interest.

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