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Prevalence of gastric cancer versus colorectal cancer in Asians with a positive fecal occult blood test

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Abstract

Aim Prior studies have reported conflicting results on the yield of esophagogastroduodenoscopy (EGD) in patients with a positive fecal occult blood test (FOBT). Our aim was to compare the yield between EGD and colonoscopy performed in a racially diverse population with a positive FOBT.

Methods A retrospective, cross-sectional study of FOBT positive patients who underwent EGD and colonoscopy from January 1, 1999 to November 1, 2008. Endoscopic lesions deemed responsible for GI bleeding were identified. Results Two hundred and eighty-seven patients met entry criteria, among which, 63% were Asian and 81% were immigrants to the U.S. Forty-four patients had EGD findings deemed responsible for a positive FOBT, the most common being esophagitis (25.0%) and gastric ulceration (15.9%). Forty-two patients had colonoscopic findings likely responsible for a positive FOBT with the most frequent lesion being colonic polyps ≥ 9 mm in diameter

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L. W. Day (🖂) San Francisco General Hospital (3D-5), 1001 Potrero Avenue, San Francisco, CA 94110, USA e-mail: lukejohn.day@ucsf.edu (76.2%). Prevalence of lower and upper GI tract lesions responsible for positive FOBT was similar (14.6% vs. 15.3%, p=0.2). There was no association between a patient reporting upper GI symptoms, or the presence of anemia and the detection of upper GI tract lesions on endoscopy. Gastric adenocarcinoma (n=3) was as prevalent as colorectal adenocarcinoma (n=4). All three patients with gastric adenocarcinomas were Asian (prevalence 1.6%).

Conclusions In our racially diverse population evaluated for a positive FOBT, gastric adenocarcinoma was as prevalent as colorectal adenocarcinoma; however, gastric adenocarcinoma was limited to Asian patients. EGD and colonoscopy should be considered in the evaluation of patient populations similar to ours, particularly Asian immigrants.

Keywords Colonoscopy · Colorectal cancer · Esophagogastroduodenoscopy · Fecal occult blood test · Gastric cancer · Pancreatobiliary neoplasms · Sensitivity · Specificity

Introduction

Few formal guidelines exist for performing an esophagogastroduodenoscopy (EGD) in patients with a positive fecal occult blood test (FOBT). Detection of clinically significant upper gastrointestinal (GI) tract lesions, including gastric cancer, in this clinical setting is variable. An equal frequency of significant upper and lower GI tract lesions in FOBT positive patients has led some to conclude and advocate performing bidirectional endoscopy [1, 2]. Others have argued that EGD under the same circumstances leads to the detection of clinically insignificant upper GI tract lesions and that such a strategy is not cost-effective nor a useful first step [3–5]. Rather this group [3–5] supports performing an EGD only after an initial colonoscopy is performed and is negative. Additionally, several studies have demonstrated a low incidence of gastric cancer in FOBT positive patients in the U.S., and Europe which supports not performing an initial EGD in these patients [6, 7].

In order to determine which FOBT positive patients should undergo EGD, multiple factors have been evaluated to stratify risk including the presence of upper GI symptoms, anemia, and absence of colonoscopic findings [1, 5, 8, 9]. One factor that has not been analyzed in previous research is race. Previous studies have mainly evaluated Caucasian, non-immigrant patients; this inherently makes it difficult to generalize these findings. In many health-related areas, immigrants comprise a vastly different population with varying environmental exposures. Primary among these differences are the prevalence of gastric cancer and Helicobacter pylori. Asians living within the U.S., and overseas have a much higher rate of gastric cancer when compared to other racial groups [10]. Additionally, rates of H. pylori infection are higher in immigrant populations [11, 12], which could lead to greater rates of GI ulceration or mucosal inflammation. Both these factors may be responsible for a positive FOBT and necessitate EGD for further diagnosis. To date, few studies have addressed this question; U. S. studies, that have included Asian patients, are limited by small sample sizes [1, 2, 4, 5, 8, 13] and methodological constraints, such as relying on database or claims information [14].

Our study aim was to compare the yield between EGD and colonoscopy performed for a positive FOBT in a racially diverse public hospital over a nearly 10-year time period.

Methods

We conducted a retrospective, cross-sectional study of electronic medical records and endoscopy reports of patients who underwent EGD and colonoscopy at the San Francisco General Hospital (SFGH) from January 1, 1999 to November 1, 2008. SFGH is a level-one trauma public hospital providing gastroenterology inpatient and outpatient services to over 5,000 patients annually.

A systematic search of the Provation[®] (Wolters Kluwer Health, Minneapolis, MN, USA) endoscopy software was performed for colonoscopies performed between January 1, 1999 and November 1, 2008 at SFGH for one of the following procedural indications: (1) positive FOBT, (2) occult blood loss, (3) hemepositive stool, or (4) occult GI blood loss. Patients were included in our study if they had an outpatient EGD performed within 90 days of the colonoscopy, an outpatient GI clinic visit for evaluation of a positive FOBT one year prior to both endoscopic procedures, documented positive FOBT prior to colonoscopy, and age over 40 years. Patients had to have three positive consecutive Hemoccult II[®] (Beckman Coulter, Brea, CA, USA) guaiac cards recorded within their electronic medical record prior to their clinic visit.

Patients were excluded if they had an incomplete EGD and/or colonoscopy, poor/fair bowel preparation on colonoscopy, or underwent endoscopy as an inpatient. Patients who had a positive FOBT obtained by digital rectal examination from a healthcare provider were not included.

All demographic data were obtained by reviewing the patient's initial outpatient GI clinic note. Demographic data included the age of the patient at the time of colonoscopy, sex, race, immigrant status, country of birth, active/previous tobacco usage, active/previous alcohol usage, non-steroidal anti-inflammatory drug (NSAID) usage within 6 months prior to colonoscopy, and history of overt GI bleeding within the previous 2 years prior to colonoscopy.

Laboratory data collected included hematocrit, hemoglobin, platelets, international normalized ratio (INR), creatinine, ferritin, and percentage iron saturation. Laboratory data had to be performed within 1 year prior to colonoscopy. If multiple laboratory values had existed, then the closest value to the date before their colonoscopy was recorded. The definition of anemia was hematocrit \leq 40% for males, \leq 34.9% for females, and iron deficiency anemia was ferritin \leq 10 ng/mL or percentage iron saturation \leq 15%. Patients did not have to have all of the above laboratory tests performed to be included in the study.

Gastrointestinal symptoms were divided into upper and lower symptoms. Upper GI symptoms were defined as dysphagia, odynophagia, reflux symptoms, dyspepsia/midepigastric abdominal pain, early satiety, nausea/emesis, anorexia, or weight loss. Lower GI symptoms were hematochezia, melena, diarrhea, constipation, left lower quadrant abdominal pain, or change in stool caliber. All symptoms had to have been present for at least 3 months prior to the outpatient GI clinic appointment and documented in the patient's initial GI outpatient clinic note.

Endoscopic findings were recorded using the patient's colonoscopy and EGD reports as documented by the attending gastroenterologist who performed the procedure. If biopsies were obtained during endoscopy, the histological diagnosis as documented in the patient's electronic medical record was recorded. Endoscopic lesions retrospectively deemed likely to be responsible for a patient's positive FOBT were divided into two categories: upper and lower GI tract lesions. Upper GI tract lesions included esophageal, gastric, or duodenal ulcers (defined as one ulceration ≥ 1 cm in diameter or more than three documented ulcerations ≤ 1 cm in diameter), erosive esophagitis (Los Angeles grade C or D or Grade III or IV), erosive gastritis, vascular ectasia (\geq 3 vascular ectasias, or one vascular ectasia \geq 8 mm in diameter), esophageal or gastric cancer, portal hypertensive (HTN) gastropathy, or esophagogastric varices. Lower GI tract lesions included vascular ectasia (≥ 3 vascular ectasias or one vascular ectasia ≥ 8 mm in diameter), active colitis with ulceration(s), polyps greater than 9 mm in diameter, or colorectal cancer [1–3, 8].

The frequency of endoscopic findings for patients undergoing EGD and colonoscopy were determined. Categorical variables were compared using the Pearson's chi-square test. A *p*-value of less than 0.05 was considered statistically significant. Statistical software used was Stata (version 9.2, StataCorp[®], College Station, Texas, USA).

The study protocol was approved by the University of California, San Francisco Committee on Human Research.

Results

Between January 1, 1999 and November 1, 2008, 1,186 colonoscopies were performed for an indication of a

Fig. 1 Flow diagram of FOBT positive patients evaluated with EGD and colonoscopy. Note: 9 patients had both EGD and colonoscopy findings to explain their positive FOBT positive FOBT at SFGH. We excluded 899 patients; 86.8% of whom did not have an EGD performed in addition to their colonoscopy. Interestingly, among these patients who did not undergo EGD, two-thirds did not have an explanation for their positive FOBT on colonoscopic findings. Two hundred and eighty-seven patients met our study inclusion criteria (Fig. 1). The mean age of patients was 58.9 (SD 8.1) years. The majority of patients were Asian (63.4%), female (65.2%), and immigrants to the U. S. (81.2%) (Table 1).

Endoscopic findings observed in patients who underwent both EGD and colonoscopy are depicted in Table 1 and Fig. 2. The most frequent lesion reported on colonoscopy was colonic polyps (51.6%) with a mean of 2.3 (SD 1.5) polyps detected per patient. Among polyps detected, 72.3% were adenomatous and 26.4% were hyperplastic polyps on histology. On the other hand, one-third of patients with a positive FOBT had a normal EGD. A majority of patients



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Table 1 Clinical characteristics of included and excluded patients

Clinical characteristics	
Age (y) (mean [SD])	58.9 (8.1)
Sex (<i>n</i> [%])	
Male	100 (34.8)
Female	187 (65.2)
Ethnicity (n [%])	
Asian	182 (63.4)
Hispanic	64 (22.3)
Caucasian	22 (7.7)
African-American	15 (5.2)
Unknown	4 (1.4)
Country of birth (<i>n</i> [%])	
China	83 (28.9)
United States	37 (12.9)
Vietnam	27 (9.4)
Philippines	19 (6.6)
El Salvador	14 (4.9)
Mexico	2 (0.7)
Other	29 (10.1)
Unknown	76 (26.5)
Laboratory Data (mean [SD])	
Hemoglobin (g/dL)	13.4 (1.6)
Hematocrit (%)	39.6 (4.0)
Platelets (1,000/µL)	265 (76)
INR	1.1 (0.3)
Creatinine (mg/dL)	0.98 (0.59)
Ferritin (ng/mL)	163 (199)
Iron percentage saturation (%)	22 (12)
Patient characteristics (n [%])	
Cigarette use	76 (26.5)
Alcohol consumption	91 (31.7)
NSAID usage	98 (34.2)
Iron deficiency anemia	25 (8.7)
GI bleeding within 2 years prior to colonoscopy	1 (0.3)
Upper GI symptoms (n [%])	
Epigastric pain/dyspepsia	102 (35.5)
Reflux	63 (22.0)
Weight loss	25 (8.7)
Dysphagia	11 (3.8)
Nausea/emesis	9 (3.1)
Anorexia	4 (1.4)
Early satiety	4 (1.4)
More than two upper GI symptoms present	51 (17.8)
No upper GI symptoms	129 (44.9)
Lower GI symptoms ($n [\%]$)	
Hematochezia	51 (17.8)
Constipation	33 (11.5)
Melena	18 (6.3)
Diarrhea	12 (4.2)
Left lower quadrant pain	4 (1.4)

Clinical characteristics	
Change in stool caliber	1 (0.3)
More than two lower GI symptoms present	39 (13.6)
No lower GI symptoms	207 (72.1)
EGD indications (n [%])	
Positive FOBT only	128 (44.6)
Midepigastric abdominal pain/dyspepsia	84 (29.3)
Anemia/iron deficiency anemia	26 (9.1)
Reflux	20 (7.0)
Bleeding	12 (4.2)
Dysphagia	7 (2.4)
Abnormal radiographic imaging	3 (1.0)
Weight loss	3 (1.0)
Other (nausea, early satiety, Barrett's esophagus evaluation)	4 (1.4)
Colonoscopic findings in patients who did not undergo EGD (n [%] of excluded group)	
Normal colonoscopy	145 (18.6)
Colonic polyp <9 mm	106 (13.6)
Colonic polyp ≥9 mm	228 (29.2)
Hemorrhoids	178 (22.8)
Diverticulosis	87 (11.2)
Abnormal mucosa	12 (1.5)
Vascular ectasia	11 (1.4)
Malignant tumor	8 (1.0)
Abnormal perianal region	4 (0.5)
Stricture	1 (0.1)

INR international normalized ratio

who underwent EGD were discovered to have GI mucosal inflammation: non-erosive gastritis (30.7%), duodenitis (9.8%), esophagitis (4.9%), and erosive gastritis (1.7%).

The prevalence of clinically significant upper and lower GI tract lesions was equivalent (15.3% vs. 14.6%, respectively, p = 0.2). Polyps greater than 9 mm in diameter constituted the majority of explanations for patient's positive FOBT, when a lower GI source was suspected. Four patients were diagnosed with colorectal adenocarcinoma (1.4%); 3 were found to have a colonic mass on endoscopy, and one patient had adenocarcinoma *in situ* within a polyp. Conversely, mucosal inflammation was determined to be responsible for over one-third of patient's positive FOBT when an upper GI source was believed to be the etiology; the most frequent reason being erosive esophagitis. Three patients were diagnosed with gastric adenocarcinoma, all of whom were Asian. Nine patients had dual findings on EGD and colonoscopy that likely contributed to their positive FOBT (Fig. 1).

Given that patients with a positive FOBT will undergo colonoscopy, we attempted to determine patient characteristics that would enable one to predict upper GI pathology



that would necessitate an EGD. First, over half of our patients reported upper GI symptoms with the most frequently reported symptom being dyspepsia/midepigastric abdominal pain (35.5%). There was no association between upper GI symptoms and detection of clinically relevant upper GI tract lesions; 54.5% of patients with upper GI symptoms had significant upper GI tract lesions discovered on EGD versus 45.5% of asymptomatic patients, p=0.9. Secondly, the presence of iron deficiency anemia was not associated with the detection of upper GI tract lesions. There was a trend of our study population with significant upper GI tract lesions having no iron deficiency anemia present prior to endoscopy (90.9% had no iron deficiency anemia vs. 2.3% with iron deficiency anemia in patients with significant upper GI tract lesions detected on EGD, p=0.2).

We performed a subgroup analysis on asymptomatic patients with a positive FOBT. Within this group of 89 patients, 15 patients (16.9%) had clinically significant upper GI tract lesions and 10 patients had lower GI tract lesions (11.2%) determined to be responsible for a patient's positive FOBT (p=0.5).

There was no difference in the detection of significant lower GI tract lesions as well as no difference in the detection of colorectal adenocarcinoma between Asian and non-Asian patients (Table 2). Non-Asian patients were more likely to have erosive esophagitis detected compared with Asian patients (9.5% vs. 0.5%, respectively, p < 0.001), whereas there was a trend toward Asian patients having a greater proportion of erosive gastritis detected. All three gastric adenocarcinomas were reported in Asians; when compared to non-Asians the difference was not significant.

The three patients diagnosed with gastric adenocarcinoma had a mean age of 63.3 (SD 10.7) years, two were male, and none had evidence of iron deficiency anemia. Two patients were Chinese immigrants, and one patient was from Vietnam. All patients had symptoms of vague abdominal pain, and one patient had symptoms of weight loss and early satiety. Two patients had tubular adenomas detected on colonoscopy, one of which was >9 mm. Among four patients with colorectal adenocarcinoma, the mean age was 61.3 (5.1) years, two patients were Asian, and three were female. At upper endoscopy, three patients with colorectal adenocarcinoma had nonerosive gastritis.

Discussion

Among our racially diverse patient population the prevalence of upper GI tract lesions deemed responsible for a patient's positive FOBT were as common as lower GI tract lesions. Moreover, near equal rates of colorectal adenocarcinoma and gastric adenocarcinoma were found. Asian patients with a positive FOBT who underwent dual endoscopy had a higher prevalence of gastric cancer (1.6%) compared with colorectal cancer (1.1%) illustrating that both EGD and colonoscopy may both be necessary in the evaluation of a positive FOBT in Asian patients.

Many clinicians and studies advocate that EGD be performed in patients with a positive FOBT only if no significant lesions are diagnosed by colonoscopy [5, 8, 15]. However, our finding that both substantial upper and lower GI tract lesions are equally prevalent in FOBT positive patients, and that there was a trend of more significant upper GI pathology found in asymptomatic patients, suggests that using colonoscopy alone as an initial approach may not be optimal. Along the same lines, in our asymptomatic cohort, 10% of significant upper GI tract lesions would have been missed had the gastroenterologist stopped after finding a clinically significant lesion on colonoscopy. Previous research has suggested that EGD would reveal lesions that would result

	Asians $(n=182)$	Non-Asians (n=105)	<i>p</i> -value
Upper GI symptoms requiring EGD	94 (51.6)	64 (61.0)	0.1
Lower GI symptoms requiring colonoscopy	46 (25.3)	34 (32.4)	0.2
Selected colonoscopy findings responsible for + FOBT			
Colorectal adenocarcinoma	2 (1.1)	2 (1.9)	0.6
Polyps ≥9 mm	18 (9.9)	14 (13.3)	0.4
Acute colitis	2 (1.1)	1 (1.0)	0.9
Lower GI lesions responsible for + FOBT	25 (13.7)	17 (16.2)	0.6
Selected EGD findings responsible for + FOBT			
Erosive esophagitis	1 (0.5)	10 (9.5)	< 0.001
Erosive gastritis	5 (2.7)	0 (0)	0.09
Gastric ulceration	4 (2.2)	3 (2.9)	0.7
Gastric adenocarcinoma	3 (1.6)	0 (0)	0.2
Upper GI lesions responsible for + FOBT	25 (13.7)	19 (18.1)	0.3
Significant endoscopic lesions on EGD/colonoscopy responsible for + FOBT	45 (24.7)	32 (30.5)	0.3

Table 2 Comparison between Asian and non-Asian patients with positive FOBT evaluated by EGD and colonoscopy

Data are as n (%)

in little therapeutic intervention compared with colonoscopy [4, 5], a claim that is not supported by our study. In all instances where upper GI pathology was detected, this led to an intervention including initiation of medication (in most cases proton pump inhibitor), application of endoscopic therapy, or referral to surgery.

Some researchers have advocated that only FOBT positive patients with iron deficiency anemia [8, 16] and/ or upper GI symptoms [1, 5] should undergo EGD. For example, two GI societies contend that patients with occult blood loss and no anemia only require colonoscopy unless upper GI symptoms are present [17, 18]. However, we found that there was no association of upper GI pathology with symptoms or anemia; in particular the frequency of significant upper GI findings with and without upper GI symptoms was similar. Moreover, there was a trend toward asymptomatic FOBT positive patients having a greater prevalence of upper GI tract lesions discovered compared with lower GI tract lesions. Given that there were no predictors for detecting upper GI pathology and that asymptomatic patients may harbor more upper lesions leads one to consider performing an EGD in FOBT positive patients in addition to colonoscopy as part of their initial evaluation. While our study size of asymptomatic patients and patients with anemia may have been too small to detect a significant difference, our results add to this ongoing diagnostic debate.

The number of gastric cancers detected in our study is quite small which may explain why we were unable to detect a significant difference between Asian and non-Asian patients. However, a trend towards higher gastric cancer detection existed in Asian versus non-Asian patients with a positive FOBT (1.6% vs. 0%). At the same time, Asian patients with a positive FOBT who underwent dual endoscopy had a slightly higher gastric cancer detection rate (1.6%) compared with colorectal cancer (1.1%). Thus, in a test primarily used for colorectal cancer screening, the detection of gastric cancer in Asians was nearly equivalent to the detection of colorectal cancer. Both these points suggest that EGD and colonoscopy may both be necessary in the evaluation of a positive FOBT in Asian patients. While no formal recommendation can be given due to our small sample size, these data suggest that EGD coupled with colonoscopy should be considered in the evaluation of this patient population. These data highlight the need for larger prospective studies to further investigate the role of EGD in Asian patients with a positive FOBT.

One could argue that our results are possibly biased given that a significant portion of colonoscopies were excluded (780 patients) because they did not fulfill our inclusion criteria of having an EGD performed within 90 days of it thereby introducing some ascertainment bias into our study. Potentially, these patients did not undergo EGD because a lesion was discovered on colonoscopy that could explain their positive FOBT and thus clinicians felt inclined not to proceed with an EGD. However, further examination of this excluded group revealed that only onethird of these patients had lesions that could have potentially resulted in a positive FOBT (Table 1). Therefore, two-thirds of excluded patients did not have an identifiable cause of their positive FOBT from colonoscopic examination alone. This group of patients could have benefited from further examination with an EGD and possible upper GI tract lesions may have been detected to help explain patients positive FOBT. Additional upper GI tract lesions, such as ulcerations, vascular malformations,

and even cancer could have accounted for a positive FOBT in a large proportion of these excluded patients which could have altered our final conclusions. It is unclear why these patients did not undergo EGD, but highlights the heterogeneity of beliefs and practices among gastroenterologists in their approach to FOBT positive patients.

We detected a near equal proportion of gastric adenocarcinoma compared with colorectal adenocarcinoma. These results differ significantly from the previous U.S. studies in which gastric cancer was not detected and in all cases, the rates of colon cancer far exceeded those of gastric cancer [3, 5, 14, 16]. These previous studies mirror U.S. cancer registry data where colorectal cancer surpasses that of gastric cancer [10]. Such a higher detection rate of gastric cancer deserves further clarification. Our results are likely explained by our patient population. While gastric cancer is relatively uncommon in the U.S., it is one of the most prevalent cancers throughout Asia; nearly 40% of new cases are diagnosed in China with colorectal cancer having considerably lower incidence rates [19]. Given that our patient population consisted of over 60% of Asians, the majority of whom were from China, and 96% of whom were immigrants to the U.S., it is not surprising that our gastric cancer detection rate is higher. While FOBT has been shown not to be an effective screening test for gastric cancer in the Asian population [20-22], its positivity should raise suspicion. Additionally, the incidence of gastric cancer has been reported to be low in long term follow up studies in patients undergoing colorectal cancer screening using FOBT [6, 7]. However, these studies examined patients where the incidence of gastric cancer was low in their patient population and to date no long term studies have examined an Asian cohort.

Lastly, 73% of patients in our study had no explanation for their positive FOBT, even after examination with EGD and colonoscopy. This is higher in comparison to the previous literature with detection rates of 38% to 64% [3, 5, 8, 14-16]. Our low detection rate of clinically relevant lesions may be the result of several issues. There may have been a number of lesions within the small bowel, such as vascular ectasias, inflammation, or malignancy that were undetected. Other factors besides GI blood loss may help to explain our high rate of undetectable sources for a positive FOBT. Fecal occult blood tests are inexpensive but nonspecific and require specific dietary and medication restrictions when they are utilized. Diet [23] and particular medications [24, 25] may produce false positive results or impede guaiac reactivity [26-28]. We were unable to account for these factors in our patient population, both of which may have contributed to our lower detection rates for explaining a positive FOBT.

There were several limitations of our study. This was a retrospective study that abstracted demographic and clinical information. Information recorded in a patient's electronic medical record may be inaccurate, have missing data, or improperly entered information. Additionally, documentation of endoscopic findings on EGD or colonoscopy was dependent on the interpretation of the attending gastroenterologist performing the procedure and thus introduces observer bias. Moreover, the decision to perform an EGD in patients with a positive FOBT or if colonoscopy found no source for the positive FOBT, was left to the discretion of the attending gastroenterologist. We were unable to account for the reasons behind the decisions not to perform an EGD given that we performed a retrospective study. This highlights the heterogeneity of beliefs and practices among gastroenterologists in their approach to FOBT positive patients. As a result, two-thirds of excluded patients who underwent colonoscopy did not have an explanation for their positive FOBT and may have benefited from an upper endoscopy. Such decisions may have affected our results in that upper GI tract lesions, could have been responsible for occult blood loss in many of these unknown cases. Also, there were several potential confounders that may have affected our increased detection of gastric cancer for which we were unable to account. Known factors that can affect the development of gastric cancer include diet [29], family or personal history of gastric cancer, and socioeconomic status [30] were not identified in our database and thus we were unable to adjust for these factors in our analysis.

In conclusion, our study examined a large racially diverse population of FOBT positive patients and found an equal prevalence of upper and lower GI tract lesions as potential sources of GI blood loss. Contrary to other studies, we detected near equal numbers of gastric and colorectal adenocarcinoma, with a greater detection of gastric cancer noted in Asian patients, suggesting that EGD coupled with colonoscopy should be considered in the evaluation of this patient population.

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