Clinical characteristics of small bowel tumors diagnosed by double-balloon endoscopy: Experience from a Chinese tertiary hospital

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ABSTRACT

Background/Aims: *To determine the characteristics of small bowel tumors (SBTs) in patients underwent double balloon endoscopy (DBE) and to compare the clinical value of DBE with other diagnostic tools.*

Materials and Methods: *A retrospective study was conducted in patients underwent DBE procedures from March 2008 to April 2017.The demographic, clinical and pathological characteristics of patients with SBTs were recorded, while the diagnosis of SBTs was achieved either by DBE biopsy or surgical specimens.*

Results: *One thousand one hundred and two patients (761 males, range 3-85 years) were enrolled in this study, with 1140 procedures completed in total. 99/1102 patients (9.0%) had SBTs, including benign polyps (20, 20.2%), gastrointestinal stromal tumors (GISTs) (24, 24.2%), lymphomas (13, 13.1%), adenocarcinoma (39, 39.4%), and neuroendocrine tumors (3, 3.0%). The most common clinical symptom for benign polyps was obscure gastrointestinal bleeding (OGIB) (75.0%). But among patients with malignant SBTs, the main indication for DBE was chronic abdominal pain (43.8%), followed by OGIB (36.3%), vomit (10.0%), abnormal images (6.3%) and diarrhea (3.8%) (P<0.001). Moreover, SBTs were primarily located in the jejunum alone (40/99, 40.4%). DBE had better sensitivity (89.2%), specificity (95.2%), positive predictive value (PPV) (90.0%), and negative predictive value (NPV) (94.8%) than other tools for suspected SBTs.*

Conclusion: *Small bowel tumor is mainly located in jejunum and with OGIB and abdominal pain as major complaints. DBE is a reliable method for the diagnosis of SBTs compared with other diagnostic tools.*

Keywords: *Double-balloon endoscopy, small bowel tumors, location, diagnosis*

INTRODUCTION

The morbidity of small bowel tumors (SBTs) is not very high throughout the world, with annual incidence of 0.5-1.5/100,000 in males and 0.2-1.0/100,000 in females (1), which account for approximately 2-5% of all digestive neoplasms (2). However, most of the SBTs are malignant or have malignant potential, including gastrointestinal stromal tumors (GISTs), lymphomas, primary adenocarcinomas, neuroendocrine tumors (NETs), etc. (3,4). Moreover, they lack clinical symptoms in their early stage and are hard to reach through conventional endoscopy because of their deep location (5). Thus, early identification, diagnosis, and intervention of SBTs become extremely important in clinical practice.

In this regard, capsule endoscopy (CE) and double-balloon endoscopy (DBE) represent a milestone in detecting small bowel diseases (8,9). DBE, in particular, has advantages over conventional endoscopy and CE, for it not only allows us to access the entire small bowel, but also facilitates further diagnosis and treatment including biopsy, endoscopic polypectomy, balloon-assisted dilatation, etc. (10).

In this study, we retrospectively reviewed clinical records of patients who underwent DBE in our hospital. We aimed to investigate the characteristics of SBTs in patients who underwent DBE and compare the diagnostic values of DBE with other examinations.

METHODS

Patients

This study was retrospectively conducted with 1140 patients who were suspected of small bowel diseases and received DBE either antegrade or retrograde between March 2008 and April 2017 in Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China. The diagnosis of SBTs was achieved either by DBE biopsy

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or by using surgical specimens. Exclusion criteria were as follows: suspected SBTs without later histological confirmation and patients with incomplete information. This study was approved by the institutional ethics board of Ruijin Hospital.

Data collected

Demographic, clinical, and pathological characteristics of patients were recorded. Demographic parameters included patients' age, gender, and smoking and alcohol history. Clinical parameters included indication for DBE, tumor markers like carcinoembryonic antigen (CEA) and carbohydrate antigens (CA19-9 and CA125), and location of lesions. Pathological findings were recorded according to biopsy or histology of surgical specimens.

DBE procedure

Examinations of the small intestine used a double-balloon endoscope (EN-450 P5/20, Fujifilm, China). No special preparation was required for the antegrade approach besides an 8-12 h fasting. For the retrograde approach, bowel preparation was performed as in colonoscopy. The approach was eventually determined by the endoscopist based on the clinical symptoms or the suspected location of lesions detected by other diagnostic tools. In some circumstances, small bowel lesions were tattooed with India ink to serve as a reference for docking of antegrade or retrograde DBE, consequent endoscopic therapy, or future surgery.

Other diagnostic tools

Patients underwent other intestinal examinations; for example, barium enema, magnetic resonance imaging (MRI), computed tomography enterography (CTE), and CE were also recorded. Their diagnostic concordance with DBE was checked to compare the diagnostic efficacy of these tools.

Statistical analysis

The Statistical Package for Social Sciences Version 23.0 (IBM Corp.; Armonk, NY, USA) software package for Windows was used for statistical analysis. Continuous data were presented as means, mean±standard deviation, or range, and categorical variables were expressed as percentages. The ANOVA test was used to compare differences in continuous variables. Categorical variables were analyzed with Pearson's chi-squared test. A p value of <0.05 was considered statistically significant.

RESULTS

Morbidity of SBTs

A total of 1140 DBE examinations (antegrade 228 and retrograde 906) were performed in 1102 patients (761 males and 341 females, range 3-85 years) with no complications. Of them, 99 (9.0%) were diagnosed with SBTs, including 20 with benign polyps (adenomatous polyps 9, lipomas 2, lymphangiomas 5, and angiomas 4), 24 with GISTs, 13 with lymphomas, 39 with adenocarcinomas, and 3 with NETs. Endoscopic findings of SBTs are displayed in Figure 1.

Demographic and clinical data

The demographic and clinical data are shown in Table 1. The mean age of patients with SBTs was 53.35±12.70

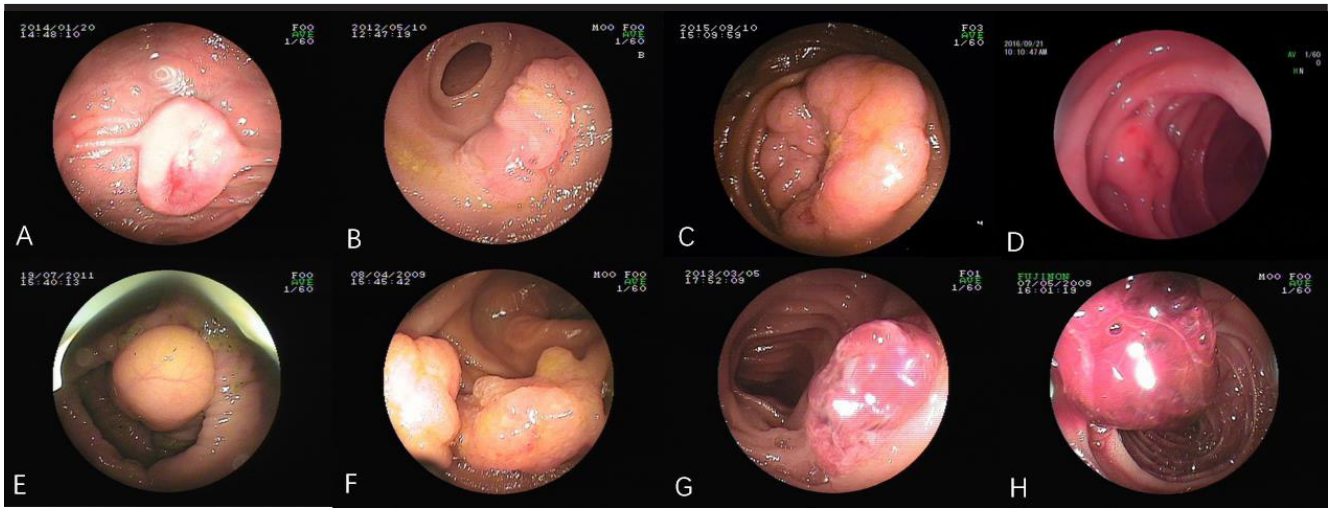

Figure X. Small bowel tumors diagnosed by double-balloon endoscopy. a) GIST b) lymphoma c) adenocarcinoma d) neuroendocrine tumor e) lipoma f) adenoma g) lymphangioma h) angioma.

years. There was no significant difference in mean age among different diagnoses (between patients with benign and malignant diagnosis p=0.085). Among patients with malignant SBTs, the mean age of patients with adenocarcinomas, GISTs, lymphomas, and NETs was 55.4, 56.4, 51.4, and 52.3 years, respectively. A total of 59.6% of the patients with SBTs were male. No significant difference was observed in gender, smoking history, and alcohol history among the prevalence of different SBTs (*P*>0.05, respectively) (Table 2). Tumor markers like CEA, CA19-9, and CA125 significantly increased in patients with adenocarcinomas (58.4%), compared to the other malignant SBTs (GISTs 12.5%, lymphoma 7.7%, and NETs 0.0%) (*P*<0.001). However, in patients with benign polyps, no significant increase of tumor markers was observed. CEA, CA125, and CA19-9 had increased almost in the same proportion without significant difference. In patients with adenocarcinomas, CEA increased nearly 20 times than normal, while CA125 and CA19-9 were only twice as high as normal. The most common clinical symptom for SBTs was obscure gastrointestinal bleeding (OGIB) (44.4%). The indications for DBE among patients with malignant SBTs were OGIB (36.3%), chronic abdominal pain (43.8), diarrhea (3.8%), vomiting (10.0%), and abnormal images (6.3%) and there was a significant difference between benign and malignant diagnosis (p<0.001). Among those, the most frequent symptom for patients with GISTs is OGIB (79.2%), whereas in patients with lymphomas and adenocarcinomas, most of them presented with chronic abdominal pain (64.3% and 56.4%, respectively).

Table 1. Clinical characteristics of patients with SBTs who underwent double-balloon endoscopy.

	Diagnosis						
Characteristics	GIST	Lymphoma	Adenocarcinoma	Neuroendocrine	Benign polyps	Total	p
Age (mean±SD, years)	56.42±10.32	51.38±12.22	55.41±9.90	52.33±1.53	47.10±18.71	53.35±12.70	0.33
Sex							0.71
Male	13(54.2)	10(76.9)	22(57.9)	2(66.7)	12(60.0)	59(59.6)	
Female	11(45.8)	3(23.1)	17(42.1)	1(33.3)	8(40.0)	40(40.4)	
Smoking	2(8.3)	1(7.7)	9(23.1)	1(33.3)	3(14.3)	16(16.2)	0.43
Alcohol	3(12.5)	2(15.4)	4(10.3)	0(0.0)	2(9.5)	11(11.1)	0.95
Indication for DBE							<0.01
OGIB	19(79.2)	2(14.3)	6(15.4)	2(66.7)	15(75.0)	44(44.4)	
Pain	4(16.7)	9(64.3)	22(56.4)	0(0.0)	4(20.0)	39(39.4)	
Diarrhea	0(0.0)	1(7.1)	1(2.6)	1(33.3)	1(5.0)	4(4.0)	
Vomiting	0(0.0)	1(7.1)	7(17.9)	0(0.0)	0(0.0)	8(8.1)	
Abnormal image	1(4.2)	0(0.0)	3(7.7)	0(0.0)	0(0.0)	4(4.0)	
Tumor marker							<0.01
CEA/CA125/CA199	3(12.5)	1(7.7)	22(56.4)	0(0.0)	1(4.8)	27(27.3)	
CEA (N<5ng/mL)	0	0	7(124.33ng/mL)	0	1(6.5 ng/mL)	8	
CA125 (N<35IU/mL)	1(38 IU/mL)	1(57.3IU/mL)	8(76U/mL)	0	0	10	
CA199 (N< 27U/mL)	2(31U/mL)	0	7(40U/mL)	0	0	9	

Table 2. Locations of small bowel tumor.

Diagnosis	Duodenum	Jejunum	Ileum	Jejunum and ileum	Duodenum and ileum
GIST	8(33.3)	12(50.0)	3(12.5)	0(0.0)	1(4.2)
Lymphoma	2(15.4)	2(15.4)	8(61.5)	0(0.0)	1(7.7)
Adenocarcinoma	9(23.1)	15(38.5)	9(23.1)	1(2.6)	5(12.8)
Neuroendocrine	2(66.7)	0(0.0)	1(33.3)	0(0.0)	0(0.0)
Benign polyps	5(25.0)	11(55.0)	4(20.0)	0(0.0)	0(0.0)
Total	26(26.3)	40(40.4)	25(25.3)	1(1.0)	7(7.1)

Locations of lesions

The locations of the SBTs are listed in Table 2. Generally, we determined the location of lesions by the inserted depth of the endoscope, the size of the enteric cavity, and the shape of the mucosal fold and villi. Among the 99 patients confirmed with SBTs, jejunum was detected as the primary location of lesions (40.4%, 40/99). The detection rate of tumors in the duodenum was 26.3%, which was similar to that of tumors located in the ileum (25.3%). Most of the tumors, such as adenocarcinomas, GISTs, and benign tumors, had a high incidence rate in the jejunum, whereas 61.5% lymphomas were located in the ileum.

Comparisons between DBE and other diagnostic tools

The diagnostic yields of different tools are listed in Table 3. We could see that DBE shows high sensitivity (89.2%), specificity(95.2%), positive predictive value (PPV) (90.0%), and negative predictive value (NPV) (94.8%) for suspected SBTs. Concerning the other diagnostic tools, CTE and PPV had high specificities (92.2% and 93.5%, respectively) whereas CE was a better choice as a screening method with 90.0% NPV. Meanwhile, 99 patients were diagnosed with SBTs in total. Of SBTs, 33 were not found by CTE while DBE had positive findings. Using CTE and MRI, nine malignant SBTs and three benign polyps were diagnosed, whereas DBE and CE had negative findings.

DISCUSSION

Small intestine represents almost 75% of the gastrointestinal (GI) tract extension, and its mucosa encompasses about 90% of the luminal surface area. However, the morbidity of SBTs is fairly low, which accounts for approximately 2-5% of all digestive neoplasms. In this study, we observed patients who underwent DBE procedures from March 2008 to April 2017. By analyzing the demographic, clinical, and pathological characteristics of patients with SBTs, we were able to determine the characteristics of SBTs and compare the clinical value of DBE with other diagnostic tools.

The fact that the frequency of patients with SBTs was higher than that of the general population in our database may be attributable to the reason that all our patients are selected for DBE because of abnormal CE findings or the presence of other concerning symptoms, such as OGIB, where incidence of SBTs may be expected to be higher. Of the 99 SBTs of our study, the detection rate for malignancy was 79.8%. In our study, adenocarcinoma had the highest incidence among the malignant neoplasms, whereas adenoma was the most common benign tumor. In the United States, the most common small bowel malignancies according to the National Cancer Database (NCDB, 1985-2005) and the Surveillance Epidemiology and End Results (SEER, 1973-2004) database are NETs (carcinoid) (37.4%), adenocarcinoma (36.9%), lymphoma (17.3%), and GISTs (8.4%) (12). Meanwhile, in the first Japanese multicenter study, SBTs were identified in 144 of 1035 subjects (13.9%) who underwent DBE between September 2000 and December 2005, of which malignant lymphoma and GIST were the most frequent (21.5%) and the second-most frequent SBTs (18.8%) (13). All showed the differences in SBT type prevalence among the countries Japan, the US, and Shanghai, China.

Alternatively, no specific sex and age difference suggesting SBTs were revealed in this study. The mean age

Table 3. Comparisons between double-balloon endoscopy and other diagnostic tools.

		True positive	True negative	False positive	False negative
DBE		99	218	11	12
CTE		58	47	4	33
CE		16	54	5	6
MRE		12	18	12	5
Barium enema		2	4	2	5
	Sensibility	Specificity	Accuracy	PPV	NPV
DBE	89.2	95.2	93.2	90.0	94.8
CTE	63.7	92.2	73.9	93.5	58.8
CE	72.7	91.5	86.4	76.2	90.0
MRE	70.6	60.0	63.8	50.0	78.3
Barium enema	28.6	66.7	46.2	50.0	44.4

of patients with SBTs was 53.3 years, which was a little lessened by the patients with benign polyps such as lymphangioma and angioma. The mean age of those patients with SBTs was 52.7 years in a Japanese DBE study, which is comparable with our results (13). Males were predominant both in patients with malignant SBTs and in those with benign polyps, although there was no statistical difference.

There was no significant difference in smoking and alcohol history in patients with malignant and benign SBTs according to the results of the DBE. Tumor markers CEA, CA19-9, and CA125 are widely used in GI cancer patients, although reports have shown the value of tumor markers as prognostic factors; clinical studies evaluating the roles of tumor markers in monitoring of therapeutic efficacy are limited (14,15). However, in our study, we could see the levels of these three markers obviously increased in patients with malignant SBTs (adenocarcinomas 56.4% positive, GIST 12.5%, lymphoma 7.7%, and NETs 0.0%). Meanwhile, in patients with benign SBTs, tumor markers are nearly negative, which shows that tumor markers are helpful in the differential diagnosis of malignant and benign lesions.

Similar to many other studies, the most common indication for DBE has been shown to be OGIB (3,16). However, our study noted that the most common clinical manifestation of patients with adenocarcinomas was abdominal pain (43.8%). The high percentage may be explained by the stricture caused by the adenocarcinoma. Based on our data and the results of others, SBTs are most frequently located in jejunum. This may be the result of dietary influences or there may be several protective mechanisms of the distal small bowel, which are less prominent in the proximal small bowel (17).

In the past, the diagnosis of SBTs was made mainly through barium enema and abdominal CT/MRI. However, more accurate methods for diagnosis of SBTs became possible after the development of CE and DBE or CTE. Traditional examinations like abdominal CT/MRI are the initial screening methods for tumors. However, they are not sufficient for the diagnosis of mucosal or small lesions of the small bowel. Because of its risk of obstruction and numerous contraindications, barium enema is not being frequently used day by day.

Since the 21st century, CE and DBE as new endoscopic methods for small bowel exploration have become available, which make the GI tract being directly visualized. However, lower positive predictive values (76.2%) caused by the unique anatomical features of the small bowel are limitations of CE. Furthermore, according to a study by Imaoka et al., two-thirds of patients with SBTs were identified with stenosis or ulceration, which may cause capsule retention compared to DBE. CTE combines helical CT and enterography, which as a complementary examination to DBE could be helpful in determining the cause in patients with SBTs. As shown in Figure 4, CTE had a specificity of 92.2% for SBTs detection. However, optimal identification of SBTs with CTE depends on a homogeneously and well-distended small bowel, as reflected by the sensitivity of 63.6%. What is more, CTE facilitates choosing the antegrade or retrograde approach of DBE and assessing the extent of SBTs progression on one hand. On the other hand, DBE is more advantageous in helping diagnose SBTs with biopsy than CTE. Therefore, combining CTE and DBE may become a better option to choose (18).

Our study had several limitations. First, all data were collected retrospectively. Furthermore, not everyone who underwent the DBE had produced the other imaging examination. Moreover, the study cannot represent all patients with SBTs because the study did not take patients who did not receive DBE into consideration.

In conclusion, SBT is a disease with low morbidity, which is mainly located in jejunum and represents OGIB and abdominal pain. DBE is a relatively safe method for the diagnosis of SBTs, and it conveys high levels of sensitivity and specificity for the detection of SBTs. DBE is believed to be a reliable method for the diagnosis of SBTs compared with other procedures.

Ethics Committee Approval: Ethics committee approval for this study was received from the Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine.

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

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