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Original Article

Computed tomography enteroclysis combined with double-balloon endoscopy is beneficial to the diagnosis of small bowel submucosal tumors

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Abstract: Aim: To compare the effectiveness and diagnostic accuracy of computed tomography enteroclysis (CTE), double-balloon endoscopy (DBE), and CTE with DBE (CTE/DBE) for detecting submucosal tumors (SMTs) in the small intestine. Methods: The clinical data of 42 patients with pathologically confirmed small bowel SMTs seen at Renmin Hospital of Wuhan University between March 2012 and October 2020 were retrospectively analyzed. The value of CTE and DBE for detecting small bowel SMTs was then compared. Results: No remarkable difference was found with regard to the sensitivity, positive and negative predictive values, as well as diagnostic accuracy rate between DBE and CTE, but the specificity of CTE was significantly higher than that of DBE (50.0% versus 25.0%, $P = 0.001$). Additionally, CTE/DBE also presented a higher sensitivity than CTE (97.4% versus 84.2%, $P = 0.031$). However, CTE/DBE and CTE were not greatly different in the positive predictive values and diagnostic accuracy rates. Conclusion: These findings suggest that CTE was better at detecting small bowel SMTs than DBE. Additionally, the combination of CTE and DBE is more beneficial for detecting SMTs in the small intestine.

Keywords: Computed tomography enteroclysis, diagnosis, double-balloon endoscopy, small bowel tumor, submucosal tumors

Introduction

Small bowel tumors (SBTs) are considered rare, occupying 3-6% or so of all gastrointestinal neoplasms [1, 2]. The early diagnosis of SBTs is challenging for both clinicians and radiologists. Unfortunately, the clinical presentation of SBTs tends to be nonspecific [3-5]. In addition, the small bowel, located deep within the abdomen, poses significant challenges to effective endoscopic and radiographic evaluation, due to its length, mobility, and tortuosity. Recent advances in enteroscopy technologies, such as video capsule endoscopy (CE) as well as double-balloon endoscopy (DBE), have made it easier to detect SBTs [6-10]. Nevertheless, in patients with SBTs, the use of CE is limited by the risk of capsule retention, and CE can miss proximal small bowel lesions.

DBE is mainly advantageous for its ability to allow a detailed evaluation of the small bowel surface with tissue sampling and enable endoscopic treatment and placing of markers for more accurate identification of SBTs during surgery. Unfortunately, it is still invasive, with inherent adverse effects. Furthermore, total enteroscopy (TE) is not feasible for all patients. Sometimes tumors are also probably missed on DBE, usually due to their location in an area of the small bowel outside of the examination by DBE [11, 12]. In addition, its extensive application and availability have been limited by the technical challenges of conducting the procedure and the comparatively long time for procedure completion.

Computed tomography enteroclysis (CTE) combines the advantages of computed tomography (CT) and conventional enteroclysis into just one new technique and enables the determination of small bowel diseases regardless of their location (in intraluminal, intramural, or extramural areas) [13]. Thus, CTE has emerged as an

effective imaging tool for both the detection and characterization of SBTs because it allows exploration of the entire small bowel for disease detection and provides extra-intestinal information [14].

Submucosal tumors (SMTs) are defined as any intramural tumors growing underneath the small bowel mucosa, which are more frequently encountered than SBTs, but their diagnosis remains challenging. Although CTE and DBE are useful for investigating SBTs [8-10, 15], their value for detecting SMTs remains unclear. As far as we know, up to now, no related published study has attempted to evaluate the use of CTE and DBE in patients suspected to have small bowel SMTs. Accordingly, we compared the performance of CTE and DBE in identifying SMTs in the small intestine, and also explored the diagnostic value of the two in combination.

Materials and methods

Patients

The study retrospectively analyzed 42 DBE-tested patients who received CTE for the investigation of small bowel SMTs at Renmin Hospital of Wuhan University between March 2012 and October 2020. Inclusion criteria: (1) A definitive diagnosis of small bowel SMTs was confirmed by the histopathological findings of resected specimens collected during the surgery; (2) Both have been checked by CTE and DBE; (3) No history of allergy to contrast agents and anesthetics. Exclusion criteria: (1) There were contraindications to CTE or DBE; (2) Unable to swallow, have diarrhea, gastrointestinal obstruction, gastrointestinal fistula; (3) Patients with severe hypertension and irregular heart rate; (4) Pregnant or lactating woman. The bioptic examination under DBE was also evaluated because it seemed to have a great advantage in DBE over CTE. The criteria for no SMTs in the small intestine were as follows: First, when there is no tumor detected by CTE or DBE; and when there are negative histopathological findings from the resected surgical specimen. The study was conducted with approval from the Ethics Committee of Renmin Hospital of Wuhan University (NO. WDRY2012-K086).

CTE

Based on Liu et al.'s method [16], CTE was conducted. First, one transanal endoscope was inserted into the third part of the duodenum, and then one guiding wire was inserted through the forceps hole into the jejunum. After the nasal endoscope was removed, one nasoduodenal duodenum tube (16F) with one balloon at the tip was inserted into the duodenojejunal flexure along the guiding wire. Approximately 1,800 mL polyethylene glycol (PEG) solution that was warmed to approximately 37°C was infused into the small intestine at 150 mL/min via one pump after the balloon was inflated at the tip of the tube. After infusion of the PEG solution, the patient was immediately transferred to the CT unit, and a simple CT scan was conducted followed by one contrast-enhanced CT scan. The instrument was 64-slice spiral CT (GE, USA). After the contrast solution was injected, the images were obtained from the dome of the diaphragm to the pubic symphysis during the early arterial stage after 25 s, during the late arterial stage after 40 s, during the portal venous stage after 70 s, and during the equilibrium stage after 120 s-each during one single breath-hold. Multiplanar views were created using an attached workstation.

DBE

All DBEs were performed after appropriate written informed consent was obtained from the patient. Sedation with general anesthesia was performed under cardiorespiratory monitoring during the procedure by a certified anesthesiologist. Fujifilm EN-530T enteroscopy system (Japan) was used for all DBE procedures. In the light of the patient's clinical data and previous medical history, the expert endoscopist decided on the initial insertion route. Anterograde DBE required the patients to be nil by mouth for 6-8 hours, and retrograde DBE required preparation of the bowel with a mix of PGE solution and 2,000 mL of water 6 hours before the DBE. DBE was performed by two trained, experienced endoscopists under the principles and techniques stated by Yamamoto et al. [17]. The oral and anal procedures employed spot marking if necessary.

Indicators of observation

Main index: The detection rate of CTE, DBE and combined examination was compared. If abnormal lesions were found in either single examination of CTE or DBE, the combined examination result was considered positive. The gold standard of diagnosis was postoperative histopathological results.

Table 1. Characteristics of the patients participating in the study

Number of cases	42
Sex, male (%)	21 (50.0)
Age (years)	49.4±10.3
Time interval (median value) between CTE and DBE (d)	3±5.6
Cause for the tests (N, %)	
Gastrointestinal bleeding	33 (78.6%)
Abdominal pain	7 (16.7%)
Distention	1 (2.4%)
Weight loss	1 (2.4%)
Largest tumour diameter (cm)	3.3±1.9 (0.7-10)

CTE: computed tomography enteroclysis; DBE: double-balloon enteroscopy.

Secondary index: Complications were counted, and patients were followed up.

Statistical analysis

IBM SPSS 22.0 statistical analysis software was employed. Continuous variables were described by the mean ± SD. For comparisons of categorical variables, the chi-square test and/or Fisher's exact tests were used when suitable. $P < 0.05$ indicated a significant difference.

Results

General information

In this study, the male-female ratio was 1:1 (21:21), with mean age of 49.4±10.3 years old. The median duration between CTE and DBE was 3 days (1-8 days). The indications included gastrointestinal bleeding in 33 patients (78.6%), abdominal pain in 7 patients (16.7%), abdominal distention in 1 patient (2.4%), and weight loss in 1 patient (2.4%) (**Table 1**).

Small bowel submucosal tumor detection

With CTE, the rate of positive findings was 34/42 cases (80.9%). Whereas a false-positive result was found in 2 among 34 cases through a diagnosis of small bowel SMTs detected via CTE. The 32 confirmed cases of small bowel SMTs included 26 cases of gastrointestinal stromal tumor (GIST), 2 cases of hemangioma, 2 cases of leiomyomata, and 2 casas of lipoma (**Table 2**).

Totally 58 DBE procedures were conducted in 42 cases, including 17 antegrade DBE procedures, 9 retrograde DBE procedures, as well as 16 procedures covering combinations of the two means. TE was realized in 6 patients. Forceps biopsy was attempted in nine small bowel SMT cases, but the histological diagnosis was confirmed to be small bowel SMTs in only two cases. Positive findings were found in 35/42 cases (83.3%), and in 3 cases, a false-positive result was found through a diagnosis of small bowel SMTs detected via DBE. The 32 confirmed cases of small bowel SMTs included GIST (26 cases), leiomyomata (2 cases), lipoma (2 cases), haemangioma (1 case), and neuroendocrine tumor (NET) (1 case) (**Table 2**).

Figure 1 presents one case in which the SMT (GIST) was detected through both CTE and DBE and was given surgical therapy.

The sensitivity of CTE and DBE for detecting small bowel SMTs were 84.2% and 84.2%, respectively. CTE and DBE showed specificity values of 50.0% and 25.0%, respectively ($P = 0.001$), positive predictive values of 94.1% and 91.4%, respectively ($P = 0.570$), negative predictive values of 80.0% and 70.0%, respectively ($P = 0.121$), and rates of diagnostic accuracy of 80.9% and 78.6%, respectively ($P = 0.650$). The area under the curve of CTE, DBE and the combination of CTE/DBE diagnostic small bowel SMTs were 0.947 (95% CI: 0.880-1.000), 0.961 (95% CI: 0.903-1.000) and 0.625 (95% CI: 0.291-0.959), respectively (**Figure 2**). Although CTE was better than DBE for detecting small bowel SMTs, the only notable difference was in specificity. Additionally, the test results acquired through CTE combined with DBE (CTE/DBE) were compared to those acquired through DBE or CTE alone. According to the results, CTE/DBE had 97.4% sensitivity, while DBE or CTE had 84.2% sensitivity ($P = 0.031$). Whereas, a comparison of the results from CTE/DBE to those from DBE or CTE alone revealed no significant differences in diagnostic accuracy rates ($P = 0.094$) or positive predictive values ($P = 0.201$) (**Table 3**).

Small bowel submucosal tumors with different sizes

A total of 38 cases with a final diagnosis of small bowel SMTs with a mean largest diameter

Table 2. Final diagnosis of patients with small bowel submucosal tumours

Pathological diagnosis	CTE (positive/negative)	DBE (positive/negative)	CTE+DBE (positive/negative)	Duodenum/jejunum/ileum
GIST	29 (26/3)	29 (26/3)	29 (29/0)	2/15/12
Haemangioma	4 (2/2)	4 (1/3)	4 (3/1)	1/2/1
NET	1 (0/1)	1 (1/0)	1 (1/0)	0/0/1
Leiomyomata	2 (2/0)	2 (2/0)	2 (2/0)	0/2/0
Lipoma	2 (2/0)	2 (2/0)	2 (2/0)	1/1/0
Total	38 (32/6)	38 (32/6)	38 (37/1)	4/20/14

CTE: computed tomography enteroclysis; DBE: double-balloon enteroscopy; GIST: gastrointestinal stromal tumour; NET: neuroendocrine tumour.

Figure 1. GI stromal tumor in a 50-year-old man with gastrointestinal bleeding. A. Stained tumor lesions in the small intestine were detected by CTE. B. Submucosal tumor lesions were confirmed by DBE. C. GI stromal tumor highlighted by CD117 immunostaining confirmed by pathology (CD117 IH, Orig. mag. ×200). CTE: computed tomography enteroclysis; DBE: double-balloon enteroscopy.

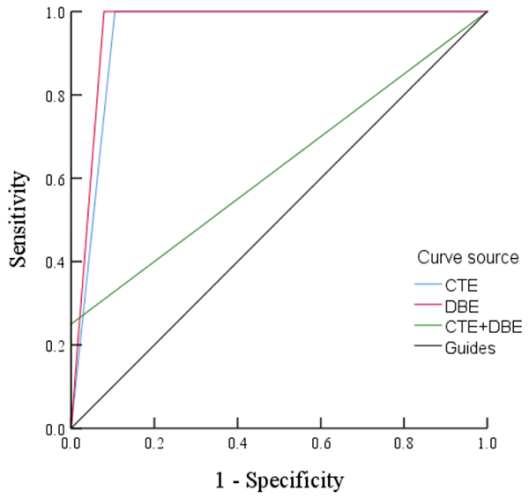

Figure 2. ROC curve of small bowel submucosal tumours diagnosed by CTE and DBE. CTE: computed tomography enteroclysis; DBE: double-balloon enteroscopy.

of 3.3±1.9 cm (range 0.7-10 cm) were divided into a large-size group (≥ 2 cm, n = 29) and a small-size group (< 2 cm, n = 9) according to the largest diameter lines of the tumors. In the large-size group, the sensitivity of CTE and DBE were 89.7% and 93.1%, respectively, which were not notably different (P = 0.640). The CTE/DBE combination strategy had 100% sensitivity, and there was no obvious difference between CTE/DBE and CTE for the large-size group (P = 0.075). In the small-size group, CTE

Table 3. Comparisons between computed tomography enteroclysis and double balloon endoscopy

	CTE	DBE	CTE+DBE
True positive	32	32	37
True negative	2	1	0
False positive	2	3	4
False negative	6	6	1
Sensitivity	84.2%	84.2%	97.4%
Specificity	50.0%	25.0%	
Accuracy	80.9%	78.6%	88.1%
PPV	94.1%	91.4%	90.2%
NPV	80.0%	70.0%	

CTE: computed tomography enteroclysis; DBE: double balloon enteroscopy; PPV: positive predictive value; NPV: negative predictive value.

Table 4. Small bowel submucosal tumors of different sizes

Tumour diameter	CTE (positive/negative)	DBE (positive/negative)	CTE+DBE (positive/negative)
≥ 2 cm	29 (26/3)	29 (27/2)	29 (29/0)
< 2 cm	9 (5/4)	9 (5/4)	9 (8/1)

CTE: computed tomography enteroclysis; DBE: double-balloon enteroscopy.

and DBE had the sensitivity of 55.6% and 55.6%, respectively. The CTE/DBE combination strategy had 88.9% sensitivity, and there was still an obvious difference in sensitivity between CTE/DBE and CTE for the small-size group (P = 0.013) (**Table 4**).

Location of small bowel submucosal tumors

The locations of the small bowel SMTs are summarized in **Table 2**. Among the 38 patients with histopathologically confirmed small bowel SMTs, the jejunum was detected as the most common primary location of the lesions (52.6%, 20/38). The detection rates of small bowel SMTs in the duodenum and ileum were 10.5% and 36.8%, respectively. Most of the tumors, such as GISTs and leiomyomata, had a high incidence rate in the jejunum.

Complications and follow-up

No complications were reported. After surgery, the clinical symptoms disappeared, and every patient showed alleviation in their conditions. The patients received a mean follow-up of 13.4 months, and meaningful improvements were obtained in the patients.

Discussion

Although CTE and DBE are useful for investigating SBTs, the one with a higher diagnostic value on SMTs in the small bowel is still under investigation. Thus, the CTE results in our research patients were compared with the findings of DBE in the same patients.

A clinical study devoted to observing the effect of CTE on small intestinal bleeding showed that a total of 1087 patients suspected of small intestinal bleeding received CTE examination, and the overall diagnosis rate was 31.6%, and the diagnosis rate of CTE for the clinical manifestation of dominant small intestinal bleeding was higher than that of occult small intestinal bleeding [18]. Another meta-analysis showed that CTE had a sensitivity of 72% and specificity of 75% for the diagnosis of small intestinal bleeding [19]. In this study, the positive findings rate (80.9%) and sensitivity (84.2%) of CTE in small bowel SMTs were higher than in previous studies [18, 19], but the specificity (50.0%) was lower than in previous studies [19], which may be related to the different types of included diseases. Studies have reported that the detection rate of DBE in the diagnosis of small intestine diseases is 83.2% [20]. In this study, the positive findings rate of DBE in small bowel SMTs (83.3%) was similar to that in previous studies [20]. In addition, in this study, the sensitivity of CTE and DBE to detect small bowel SMTs with different sizes was similar, but the specificity of CTE to detect small bowel SMTs was higher than that of DBE. The possible reason is that DBE is easy to confuse extracellular small bowel SMTs with other similar diseases, and the misdiagnosis rate of small bowel SMTs detected by CTE is relatively low.

In our case series, 6/38 (15.8%) SMTs could not be detected by DBE. DBE failed to identify 3 ileal SMTs and 1 jejunal SMT because of the inability of the endoscope to reach the tumors, possibly for abdominal adhesion. Jejunal GISTs failed to be identified in two patients who underwent DBE, presumably because the GISTs were predominantly extraintestinal, with a minimal or absent intraluminal component. Likewise, Johanssen et al. also revealed that tumors may be missed on DBE [12, 13]. In addition, Hirano et al. reported that when they performed DBE in 9 patients with small bowel SMTs, the diagnosis of small bowel SMTs was neglected in 1/9 cases (11.1%); accordingly, they reported that to arouse attention [21]. In addition, the operation of DBE is very difficult. This method is an invasive examination, which requires two oral and anal examinations for a thorough examination of the small intestine, which is difficult for some patients to tolerate and costs a lot.

CTE may bypass this issue of detection to complement DBE. In our study, CTE has a sensitivity

of 85% to 95% for the diagnosis of SBTs and a specificity of 90% to 96% [22-29]. Our study suggested that CTE was able to detect 5 (83.3%) of the 6 small bowel SMTs that could not be detected with DBE. Additionally, DBE was able to detect 83.3% (5/6) small bowel SMTs that could not be detected with CTE, implying that the combined adoption of CTE and DBE will allow their ability to complement each other and that the rate of missed small bowel SMTs achieved via DBE or CTE will be notably lowered via their combination. Research report [30], the combined adoption of CTE and CE increased the detection rate of small bowel bleeding. The results of this study also found that the combined detection of CTE and DBE was more conducive to the detection of small bowel SMTs, which was similar to previous studies [30], indicating that not only CTE but also DBE should be performed for patients suspected of small bowel SMTs.

Bi-optic examination seems to have great advantages in DBE over CTE. However, in our study, forceps biopsy was attempted in 9 cases with small bowel SMTs, whereas bioptic examination confirmed the histological diagnosis to be small bowel SMTs in only two patients (22.2%). Therefore, considering that bi-optic examination provides limited information on SMTs, DBE is possibly unnecessary for the diagnosis of small bowel SMTs.

Conclusion

The study findings revealed that CTE was better at detecting small bowel SMTs than DBE. Additionally, the accuracy for detecting small bowel SMTs increased even higher in the cases which adopted combined CTE and DBE. However, the study has limitations: it was a single-center retrospective study, the sample size was comparatively small, elderly patients were not included in the analysis, and the follow-up was relatively short. The feasibility still needs to be verified by future multicenter prospective studies. In addition, elderly patients should be included, and follow-up time should be extended to further clarify the application value of the two detection methods.

Disclosure of conflict of interest

None.

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