

Small bowel tumors detected and missed during capsule endoscopy: Single center experience

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Abstract

AIM: To characterize small bowel (SB) tumors detected by capsule endoscopy (CE), and identify missed tumors.

METHODS: The study included 145 consecutive patients in whom 150 CEs were performed. Following CE, the medical records of the study population were reviewed. Results of double- or single-balloon enteroscopy performed after CE and the results of surgery in all

patients operated on were retrieved. The patients were contacted through telephone interviews or postal mail. In addition, the national cancer registry and the polish clinical gastrointestinal stromal tumor (GIST) Registry were searched to identify missed neoplasms.

RESULTS: Indications for CE included overt and occult obscure gastrointestinal bleeding ($n = 81$, 53.7%), anemia ($n = 19$, 12.7%), malabsorption ($n = 18$, 12%), abnormal CB follow through ($n = 9$, 6%), abdominal pain ($n = 7$, 5%), celiac disease ($n = 5$, 3%), neuroendocrine tumor ($n = 3$, 2%), Crohn's disease ($n = 2$, < 2%), Peutz-Jeghers syndrome ($n = 2$, < 2%), other polyposes ($n = 2$, < 2%), and diarrhea ($n = 2$, < 2%). The capsule reached the colon in 115 (76.6%) examinations. In 150 investigations, CE identified 15 SB tumors (10%), 14 of which were operated on or treated endoscopically. Malignancies included metastatic melanoma ($n = 1$), adenocarcinoma ($n = 2$), and GIST ($n = 3$). Benign neoplasms included dysplastic Peutz-Jeghers polyps ($n = 4$). Non-neoplastic masses included venous malformation ($n = 1$), inflammatory tumors ($n = 2$), and a mass of unknown histology ($n = 1$). During the follow-up period, three additional SB tumors were found (2 GISTs and one mesenteric tumor of undefined nature). The National Cancer Registry and Polish Clinical GIST Registry revealed no additional SB neoplasms in the post-examination period (follow-up: range 4.2-102.5 mo, median 39 mo). The sensitivity of CE for tumor detection was 83.3%, and the negative predictive value was 97.6%. The specificity and positive predictive value were both 100%.

CONCLUSION: Neoplasms may be missed by CE, especially in the proximal SB. In overt obscure gastrointestinal bleeding, complementary endoscopic and/or radiologic diagnostic tests are indicated.

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Key words: Capsule endoscopy; Small bowel tumor; Tumor miss rate; Gastrointestinal bleeding; Gastrointestinal stromal tumor

Core tip: The aims of this study were to characterize small bowel (SB) tumors detected by capsule endoscopy (CE) and identify SB tumors missed by CE. The study included 150 consecutive CE investigations. Following CE, the medical records of the study population were reviewed and the patients contacted by telephone or postal mail. National cancer registries were searched to identify missed neoplasms. CE detected 15 SB tumors (10%). During the follow-up period, three additional SB tumors were found. The sensitivity of CE for tumor detection was 83.3% and the negative predictive value 97.6%. The specificity and positive predictive value were both 100%.

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INTRODUCTION

Capsule endoscopy (CE) has become a first-line diagnostic tool in obscure gastrointestinal bleeding (OGIB) when the small bowel (SB) is a suspected source. Compared with push enteroscopy (PE), which is performed to establish the source of bleeding, CE detects more than twice as many clinically-significant abnormalities (56% *vs* 26%), whereas any abnormalities are detected in 63% with CE *vs* 28% with PE^[1]. Balloon-assisted enteroscopy (BAE), most often double-balloon enteroscopy (DBE), is performed following both a negative CE or as a complementary procedure guided by the CE findings. Initial studies suggested that CE and DBE have a comparable diagnostic yield in patients with suspected SB disease, including OGIB, when the whole SB is visualized^[2]. Now evidence is growing that CE misses a significant number of lesions detected on enteroscopy^[3,4]. In a recent meta-analysis, the yield of DBE after previously-negative CE was 27.5%^[5]. Nevertheless, CE remains the preferred initial diagnostic test because of its noninvasiveness, better tolerance, and ability to view the entire SB.

SB tumors are source of bleeding in some patients with OGIB, particularly younger patients. In a large series of patients undergoing CE, SB tumors were found in 2.4% (Rondonotti *et al*^[6]), 8.9% (Cobrin *et al*^[7]), 6.3% (Bailey *et al*^[8]), and 4.3% (Cheung *et al*^[9]) of cases. Malignant tumors were found in 4.2%, 4%, and 2.7% of patients, respectively. In a multicenter Belgian study, the percentage of malignant tumors was 2.5%^[10]. The percentage of DBE procedures detecting SB tumors is higher than with

CE, increasing up to 12% (27 of 225 patients in Choi *et al*^[11]) and up to 13.9% in the largest series described, comprising 1035 Japanese patients of whom 42.4% were examined because a SB tumor was suspected^[4].

A retrospective review of 183 cases in which DBE was performed at 7 North American centers found that DBE identified SB tumors in 15 patients who had prior CE, whereas lesions were found by CE in only 5 patients, and all 4 cases of primary adenocarcinoma were missed by CE^[3].

We performed a retrospective study to characterize SB tumors detected in consecutive patients who underwent CE at our center. The second aim of this study was to identify any SB tumors missed by CE in these patients.

MATERIALS AND METHODS

The results of all consecutive CE examinations (PillCam SB1, Given Imaging, Israel), which were assessed by two readers between March 2003 and July 2009 at a single center, were reviewed and categorized. In a standard evaluation, CE findings were further classified as negative or positive. Positive findings were also classified as clinically significant or insignificant lesions. Clinically significant lesions included angioectasias, tumors or polyps \geq 10 mm, active bleeding, blood clots, diverticula, mucosal breaks, and features consistent with celiac disease. Clinically insignificant lesions included red spots, white spots, erythema, focal atresia of villi, or small polyps.

As CE allows for only an approximate estimation of polyp size, a cut-off polyp diameter of 10 mm was used; this size is an accepted indication for polyp resection in patients with polyposis syndromes.

The preparation for CE included fasting from lunch-time and ingesting 3 L of glycol polyethylene the day before the examination. The patients ingested the capsule in the morning with 50 mL of water and 0.5 mL of simethicone (Espumisan, Berlin Chemie, Poland). The patients were allowed to drink more water no earlier than 2 h after capsule ingestion and eat no earlier than 4 h after capsule ingestion.

Follow-up data were obtained by reviewing hospital case notes. Results of push, double-balloon, single-balloon, and intraoperative enteroscopy performed following CE, and the results of any surgery performed were retrieved. Following the analysis of records, an attempt to contact the patients by phone or mail was made using a standardized interview. The questions referred to any serious diseases diagnosed following CE, including cancer, and operations performed.

Finally, the National Cancer Registry and the Polish clinical gastrointestinal stromal tumor (GIST) Registry were searched to identify any neoplasms possibly missed in the study population.

The study was approved by the institutional review board in accordance with the guidelines of the Declaration of Helsinki revised in 1989.

Table 1 Characteristics of the study population *n* (%)

Gender, males	71/145 (49)
Age	
(min, max)	(8, 85)
mean (SD)	50.1 (19.2)
Main indication for CE ¹	<i>n</i> = 150 ²
Overt obscure bleeding	58 (38.7)
Occult obscure bleeding	23 (15.3)
Anemia	19 (12.7)
Malabsorption	18 (12.0)
Abnormal SB follow through	9 (6.0)
Abdominal pain	7 (4.7)
Celiac disease	5 (3.3)
Neuroendocrine tumor	3 (2.0)
Peutz-Jeghers syndrome	2 (1.3)
Diarrhea	2 (1.3)
Crohn's disease	2 (1.3)
Polyposis syndrome	2 (1.3)

¹Primary indication was given; ²Capsule endoscopy (CE) was performed twice in 5 patients for the following reasons: incomplete examination (2 patients); recurring overt obscure gastrointestinal bleeding (OGIB) in a patient with normal first examination (1 patient) and recurring overt gastrointestinal bleeding in patients with abnormal first CE result and treatment instituted (mucosal breaks, angioectasias, 2 patients).

RESULTS

Over the study period, 145 patients underwent 150 CEs. The characteristics of the patients, including the indications for CE, are presented in Table 1. The most frequent indication for performing the procedure was OGIB (81 patients; 53.7%), which was occult in 23 patients (15.3%) and overt in 58 (38.4%).

The capsule reached the colon in 115 (76.6%) examinations. CE revealed no abnormalities in 29 (19.3%) procedures, was abnormal and clinically significant in 82 (54.6%), and abnormal but insignificant in 37 (24.7%) procedures. No conclusions were drawn in 2 cases (1.3%). In the initial studies, the cleansing conditions were not routinely assessed by the reader, so this parameter could not be reported for the whole study population. The results of the 150 procedures are shown in Table 2.

Tumors ≥ 10 mm were identified in 15 patients (10%). Fourteen tumors were surgically or endoscopically resected. The characteristics of these patients are presented in Table 3. Of the 14 resected tumors, 6 were malignant (4%), 4 were benign (2.6%), and 3 were non-neoplastic (2%) and the precise histology of one non-malignant tumor was not retrieved. The most frequent indication for CE that resulted in tumor detection was overt OGIB (6 patients).

Longer follow-up was available for 139 patients (95.8%). Sixteen patients died (11%). In 6 patients (4.1%), the medical records were unavailable or the patient could not be contacted by phone or mail. However, they were included in the registries search. The median observation time of the living patients in whom the follow-up was performed was 39 mo (*n* = 124, range 4.2-102.5 mo).

It was established that CE missed 2 SB GISTs and

Table 2 Results of 150 capsule endoscopy examinations *n* (%)

Findings	<i>n</i> = 150
Significant findings	
Angioectasias	25 (16.7)
Mucosal breaks	20 (13.3)
Tumor or polyp(s) ≥ 10 mm	15 (10.0)
Diverticula	14 (9.3)
Celiac disease	5 (3.3)
Active bleeding with no visible origin	3 (2.0)
Insignificant findings	
Erythema or red spots	15 (10.0)
White spots	13 (8.7)
Other	7 (4.7)
Modeling of the bowel wall	2 (1.3)
Normal	29 (19.3)
Non-diagnostic	2 (1.3)

one SB mesenteric tumor. All three patients underwent CE due to overt OGIB.

In one patient, PE up to the ligament of Treitz was performed before CE and duodenal lymphangiectasis were seen. CE examination was complete and normal, but cleansing of the distal SB was poor. Following CE, CT angiography was performed and active SB bleeding was observed in the right mid-abdomen and a lesion within the ileocecal artery was suggested. Immediate surgery revealed bleeding in Meckel's diverticulum, and a non-bleeding jejunal 4-cm GIST that was 15 cm behind the ligament of Treitz. The mucosa covering the tumor was normal.

In the second patient CE was complete, but the SB cleansing was poor. On CE a diverticulum in the left mid-abdomen was seen. Subsequent laparoscopy revealed a 4-cm SB tumor that appeared to be a GIST. Unfortunately, the exact tumor location was not assessed. This patient did not undergo enteroscopy.

In the third patient, upper DBE was performed before CE and 150-170 cm of SB inspected. Upon withdrawal, a small clot firmly attached to the mucosa in the proximal jejunum was observed. A possible iatrogenic lesion was suspected and argon plasma coagulation performed. No other abnormalities were detected. Subsequent CE was complete and normal, however, contrast abdominal CT performed 11 mo later revealed a mass located between the pancreatic head and duodenum.

On laparotomy, a diagnosis of non-resectable mesenteric tumor was made, but intraoperative cytology and later histology did not confirm neoplastic disease. After 6 mo of observation without progression of the disease, the patient was lost to follow-up.

In addition, the National Cancer Registry and the Polish Clinical GIST Registry were searched for 144 patients (99.3%) whose national identity number was available, and this search did not identify any other (missed) SB neoplasms during the post-examination period. A plasmocytoma was diagnosed 14 mo after a normal CE in a female who underwent the procedure due to occult OGIB; this patient died 4 mo after the cancer diagnosis.

Table 3 Characteristics of patients with tumor or polyp(s) ≥ 10 mm detected on capsule endoscopy and the results of follow-up

No.	Age (yr)	Sex	Indication for CE	Bleeding on CE	CE reached the colon	DBE result	Surgery result	Neoplasm
1	21	F	PJS	-	√	NA	Dysplastic Peutz-Jeghers polyp	yes
2	25	M	Polyposis	-	-	NA	Dysplastic Peutz-Jeghers polyp	yes
3	30	M	Overt OGIB	-	-	NA	Meckel's diverticulum	no
4	36	F	Occult OGIB	√	-	NA	SB adenocarcinoma	yes
5	37	F	Occult OGIB	-	-	Dysplastic Peutz-Jeghers polyp in jejunum	Not operated on	yes
6	47	M	Malabsorption	√	√	NA	Unknown but benign	unknown
7	50	M	Abnormal SBFT	-	√	NA	Not operated on	unknown
8	53	M	Overt OGIB	√	-	NA	GIST	yes
9	53	M	PJS	-	√	NA	Dysplastic Peutz-Jeghers polyp	yes
10	56	M	Anemia, disseminated melanoma malignum	-	-	NA	Melanoma malignum metastasis	yes
11	59	F	Overt OGIB	√	√	Submucosal tumor	Venous malformation	no
12	60	F	Overt OGIB	-	√	NA	GIST	yes
13	64	F	Overt OGIB	-	√	NA	SB adenocarcinoma	yes
14	68	F	Occult OGIB	-	-	NA	Inflammatory tumor	no
15	68	F	Overt OGIB	-	√	NA	GIST	yes

CE: Capsule endoscopy; NA: Not applicable; DBE: Double-balloon enteroscopy; OGIB: Obscure gastrointestinal bleeding; SBFT: Small bowel follow through; PJS: Peutz-Jeghers syndrome; GIST: Gastro-intestinal stromal tumor; M: Male; F: Female.

Based on these data, in a per patient analysis the sensitivity of CE for tumor detection was 83.3% and the negative predictive value was 97.6%. The specificity and positive predictive value were both 100%.

DISCUSSION

We performed a retrospective study of consecutive patients who underwent CE at our center for various reasons. We then followed these patients and found three tumors missed by CE. To the best of our knowledge, this is the first study with such a specific, tumor-oriented follow-up. The percentage of tumors found in our study (10%) was higher than in other CE series, which may be explained by the strict selection of patients who undergo CE at our center^[6-10]. This may be the result of a lack of reimbursement for CE by the national health care system. OGIB, for which CE had the highest diagnostic yield, was the indication for CE in 81 (53.7%) examinations in our series and CE resulted in tumor detection in 9 OGIB patients (11.1%). The diagnostic algorithm included an upper and lower endoscopy and push enteroscopy. The latter was performed in 35 (24.1%) patients before CE and was negative, which eliminated proximal intestinal vascular abnormalities, making a tumor diagnosis more likely. In the studies which analyzed only OGIB patients, a SB mass was found in 10%^[12] and 7.18%^[13] of cases. In the CE results in the study by Cobrin *et al*^[7], SB tumors were detected in 9% of patients with OGIB and the number of OGIB patients in the other CE series cited was not given.

In our study, the median follow-up was slightly over 3.2 years (39 mo). This seems sufficient for a serious symptomatic diagnosis, which might have been missed by

CE, to be made during complementary investigations.

During follow-up, we found two cases of GIST in the SB not detected by CE. Both lesions were diagnosed intra-operatively. The first lesion was located in the proximity of Treitz's ligament; the mucosa covering the tumor was normal and the source of active bleeding was Meckel's diverticulum. Thus, one might suppose that this tumor would not be recognizable on CE. The exact location of the second GIST could not be given precisely. Notably, the bowel cleansing for CE in these two patients was poor.

The third missed lesion was first found on contrast CT, and was located in the proximal SB. This is in concordance with observations made by others. Postgate *et al*^[14] described 5 significant lesions missed by CE that were found using other imaging modalities [DBE in 3 patients, CT enterography (CTE), and magnetic resonance enterography (MRE) in the 2 remaining patients]; 4 of which were located in the proximal jejunum. Chong *et al*^[15] described 4 tumors in the proximal ileum that were missed by CE but found with DBE. This particular location, where many lesions were missed, may be partly explained by a rapid transit of the capsule through the duodenum and the proximal jejunum that enhances the risk of missing a lesion in the proximal SB.

The complementary role of DBE in CE-positive and CE-negative patients is widely accepted. Among our patients, the first with GIST underwent PE that did not reach the segment with the tumor. The second patient with GIST did not undergo enteroscopy. In the third patient, DBE included the involved segment but failed to provide a diagnosis.

Radiological imaging is more readily available than BAE and remains the next diagnostic step at many cen-

ters. With respect to conventional radiological SB imaging, CE is superior in diagnosing mass lesions. A small study comparing CE to barium enterography in children with Peutz-Jeghers syndrome (PJS) showed that polyps with a diameter of 10 mm and more were detected with similar frequency with both modalities, but CE identified significantly more polyps < 10 mm^[16]. The performance of CE compared with newer radiological SB imaging is still a subject of debate. The first study comparing CE and magnetic resonance imaging (MRI) in patients with PJS (4 patients) or familial adenomatous polyposis syndrome (FAP, 16 patients) showed that smaller polyps were seen much more often with CE, whereas polyps larger than 15 mm were detected at similar rates with both CE and MRI^[17]. However, a subsequent study performed in 19 PJS patients showed that CE missed large polyps (> 15 mm) detected on MRE in three patients, suggesting that MRE may be less prone to miss large polyps and more reliable in their size assessment^[18]. With regard to CTE, both CE and CTE were performed in 32 patients with OGIB described in a retrospective study by Khalife *et al*^[19]. When CTE followed CE, it helped to identify tumors not detected by CE ($n = 2$) and excluded suspected tumors ($n = 3$). In another retrospective study of 17 patients with SB tumors who had both CE and CTE, CE detected SB tumors in 6 patients and CTE in 16, with a significant difference in the sensitivity of the two methods^[20]. In a prospective comparison of CTE and CE in 58 patients with OGIB, the sensitivity of CTE for detecting SB bleeding sources and SB masses was significantly greater than that of CE^[21]. In our study, (angio) CT followed CE and helped to establish the source of bleeding in two patients.

The risk of rebleeding in 42 patients with OGIB and negative CE was first evaluated by Macdonald *et al*^[22] who observed bleeding episodes in only 2 overt OGIB patients during 17.3 mo of follow-up. Subsequently, Park *et al*^[23] observed 57 OGIB patients, of whom 46 had overt OGIB, for a median time of 31.7 mo. They found a substantial cumulative rebleeding rate of 35.7% in CE-negative patients, recommending further investigation or close observation of such patients^[23]. The results of these studies suggest that following a negative CE, overt OGIB patients were the most likely to benefit from further investigation.

In summary, in patients with overt OGIB and normal or insignificant CE, the risk of missing a lesion in the SB cannot be underestimated. In our opinion, BAE should be the next diagnostic tool used when symptoms strongly suggest that the source of bleeding is located in the SB. In the remaining cases, or when BAE is not easily available, CT or MRI seem to be a rational choice in further evaluations. According to the most recent studies, CT or MRI enterography may be the best choice. Laparotomy remains a diagnostic option when these tests are normal or not available, with the advantage of therapeutic possibilities.

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COMMENTS

Background

Capsule endoscopy (CE) has become a first-line diagnostic tool for obscure gastrointestinal bleeding (OGIB) and small bowel (SB) polyp or tumor detection, but the reliability of negative CE for excluding gross SB pathology is unclear.

Research frontiers

SB tumors detected by CE were characterized in a retrospective cohort. At follow-up, three additional SB tumors missed by CE were identified. In patients with overt OGIB, negative CE does not exclude significant disease.

Innovations and breakthroughs

This is the first study of CE with a specific, tumor-oriented, long-term follow-up.

Applications

In patients with significant clinical symptoms, the risk of missing a lesion in the SB cannot be underestimated. In overt OGIB, supplementary diagnostic methods should be used to visualize SB, including balloon enteroscopy, computed tomography, and magnetic resonance enterography.

Terminology

CE is a method of visualizing the walls of the gut and used mainly to investigate the SB, which is difficult to access by conventional endoscopy, but is also used to visualize the esophagus and colon. A small, pill-like camera is ingested by the patient and moves naturally throughout the gastrointestinal tract, taking thousands of pictures. These pictures are sent to a detector connected to the patient's skin during the examination and assessed later by a reader on the computer. The camera pill is excreted with the stool.

Peer review

This study has the strengths of large enrollment and SB tumor-oriented follow-up. It is well written.

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