Management of small-bowel polyps at double-balloon enteroscopy

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Abstract: Small bowel tumors (SBTs) are uncommon, insidious in presentation, and frequently represent a diagnostic challenge. The advent of video capsule endoscopy (VCE) and double-balloon endoscopy (DBE) is a significant breakthrough for visual diagnosis of SBTs throughout the small bowel. Contrast-enhanced computed tomography (CECT) and fluoroscopic enteroclysis had significantly lower diagnostic yields of tumors that were 10 mm or smaller in diameter, but VCE and DBE had high diagnostic yields regardless of tumor size. Regarding SBTs larger than 10 mm in diameter, CECT had a significantly lower diagnostic yield of epithelial tumors compared to subepithelial tumors, whereas fluoroscopic enteroclysis and DBE had high diagnostic yields regardless of the tumor type. VCE had a slightly lower diagnostic yield of subepithelial tumors (78%) compared to epithelial tumors. Therefore, a combined examination method by using CECT and VCE is useful for screening of SBTs. In case suspicious of stenosis, patency capsule should be performed to confirm passage before VCE. DBE is useful for further precise examination including biopsy and ultrasonography by using miniature probe, and enteroscopic treatment. After medical, enteroscopic, and surgical treatment, VCE is helpful for follow-up. DBE is safe and useful in resecting the SBTs deep within the small bowel without laparotomy. Indications of enteroscopic resection may be benign tumors regardless of epithelial or subepithelial type, localizing in the mucosal or submucosal layer, which are symptomatic at present or possibly symptomatic or transforming in the future. Malignant tumors localized in the mucosal layer may be indications although detecting at an early stage is challenging. In this review article, we describe management of SBTs/polyps by various modalities.

Keywords: Double-balloon enteroscopy (DBE); video capsule endoscopy (VCE); small bowel tumor (SBT); endoscopic resection

Deep enteroscopy and video capsule endoscopy (VCE)

The advent of VCE and double-balloon endoscopy (DBE) is a significant breakthrough for visual diagnosis of various diseases including vascular, inflammatory, tomorous, and diverticular lesions throughout the small bowel (1,2). VCE allows painless endoscopic imaging of the whole small bowel, but is contraindicated for patients with suspected or documented intestinal obstruction (3). The Agile patency system, however, allows physicians to perform VCE with greater confidence that the capsule will be safely excreted in patients at risk for capsule retention (4). DBE is more labor-intensive, but enables tissue sampling and interventional therapies including hemostasis, balloon dilation against benign stricture, and polypectomy (5). Since the invention of DBE, deep enteroscopy such as single-balloon enteroscopy (6) and spiral enteroscopy (7), also has been introduced. Single-balloon enteroscopy has an advantage of faster instrument preparation time, but a limitation that total enteroscopy rate is lower than DBE (8,9). Spiral

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enteroscopy has an advantage of shorter examination time, but limitations of an oral method only available and of inferior insertion depth to DBE at present (10). During enteroscopy, carbon dioxide insufflation is efficient to reduce abdominal distention and discomfort (11).

Diagnosis of small bowel tumors (SBTs)

SBTs are uncommon, insidious in presentation, and frequently represent a diagnostic challenge. The rarity of SBTs generally delays their recognition and treatment, which may lead to difficulty in clinical management. Malignant tumors arising from the small bowel have a poorer prognosis compared to tumors from other parts of the gastrointestinal tract (12).

Until recently, the small bowel was the only part of the alimentary tract not completely accessible by endoscopy. Only indirect evaluation was possible using small-bowel follow-through barium examination or enteroclysis, but patient discomfort, the high radiation dose, and labor intensiveness limit these barium studies (13). Computed tomography (CT) is often used as a frontline tool in the evaluation of abdominal symptoms. CT, CT enterography, and CT enteroclysis can identify masses, but these methods occasionally lack the sensitivity to diagnose small tumors and have a limited capacity to differentiate between tumor types (14). The advent of VCE and DBE is a significant breakthrough for the visual diagnosis of SBTs located deep in the small bowel. A multicenter European study indicated that VCE identified 124 SBTs (2.4%) in 5,129 patients undergoing VCE, and 80.6% of the tumors were identified solely based on the VCE findings (15). Among these patients, indications for VCE were: obscure gastrointestinal bleeding (108 patients), abdominal pain (9), search for primary neoplasm (6), diarrhea with malabsorption (1). The main primary SBT type was gastrointestinal stromal tumor (GIST) (32%) followed by adenocarcinoma (20%) and carcinoid (15%); 66% of secondary SBTs were melanomas. A Japanese multicenter study reported that DBE identified 144 SBTs (13.9%) in 1,035 patients undergoing DBE (16). In this study, the most common indication for DBE was the suspected presence of a SBT (42.4%). For subjects without SBT, the most common indication was obscure GI bleeding. Malignant lymphoma and GIST were the most frequent (21.5%) and the second-most frequent SBTs (18.8%), respectively, in this database. We have reported that 159 (20%) consecutive patients with SBTs (93 malignant and 66 benign) that located between the 3rd portion of

the duodenum and the distal ileum of 806 patients who underwent DBE between June 2003 and May 2011 (17). In 93 malignant tumors, the most frequent was malignant lymphoma (51%) including follicular lymphoma, diffuse large B cell lymphoma, mucosa-associated tissue lymphoma, followed by GIST (16%), metastasis or invasion of cancers including lung, gastric, pancreatic, colon, and renal cell carcinoma (16%), adenocarcinoma (14%), and carcinoid (3%). Ethnic difference is evident between Caucasians and Asians in that carcinoids and metastasis from melanoma common in Caucasians are rare in Asians (18,19). In 66 benign tumors or polyps, the most frequent was hamartoma including Peutz-Jeghers polyp (PJP) in Peutz-Jeghers syndrome (PJS) and solitary hamartoma (42%), followed by adenoma including adenoma in familial adenomatous polyposis and solitary adenoma (21%), aberrant pancreas (12%), hemangioma (8%), lipoma (6%), symptomatic lymphangioma (5%), inflammatory fibroid polyp (3%), and leiomyoma (3%). The diagnostic yields of contrast-enhanced CT (CECT) stratified by size (> or ≤10 mm) and tumor types (epithelial or subepithelial origin) were as follows: smaller epithelial tumors, 0%; smaller subepithelial tumors, 24%; larger epithelial tumors, 58%; and larger subepithelial tumors, 92%. Those of fluoroscopic enteroclysis were as follows: smaller epithelial tumors, 0%; smaller subepithelial tumors, 50%; larger epithelial tumors, 97%; and larger subepithelial tumors, 95%. Those of VCE were as follows: smaller epithelial tumors, 75%; smaller subepithelial tumors, 83%; larger epithelial tumors, 91%; and larger subepithelial tumors, 78%. Those of DBE were as follows: smaller epithelial tumors, 100%; smaller subepithelial tumors, 97%; larger epithelial tumors, 98%; and larger subepithelial tumors, 94%. CECT and fluoroscopic enteroclysis had significantly lower diagnostic yields of tumors that were 10 mm or smaller in diameter (P<0.0001), but VCE and DBE had high diagnostic yields regardless of tumor size. Regarding SBTs larger than 10 mm in diameter, CECT had a significantly lower diagnostic yield of epithelial tumors (58%) compared to subepithelial tumors (92%, P=0.0003), whereas fluoroscopic enteroclysis and DBE had high diagnostic yields regardless of the tumor type. VCE had a slightly lower diagnostic yield of subepithelial tumors (78%) compared to epithelial tumors (91%) >10 mm in diameter, which was not significant. Comparisons among CECT, fluoroscopic enteroclysis, VCE, and DBE examinations showed that diagnostic yields of VCE and DBE were significantly higher than those of CECT, and the diagnostic yield of DBE was

significantly higher than that of VCE. When stratified by tumor site, the diagnostic yield of VCE for SBTs located only in the distal duodenum and/or the proximal jejunum (73%) was significantly lower than that for SBTs located in the other areas of the small bowel (90%). VCE had miss rate of 18.9% for SBTs. Of the SBTs that were overlooked by VCE, 14 (74%) were localized only in the duodenum or the proximal jejunum. This oversight may be caused by the shortcomings of the present version of VCE, including the impossibility of air insufflation and too rapid passage of VCE through the duodenum and proximal jejunum at a rate of a single 0.5-second image. The diagnostic yield of a combination examination using CECT and VCE (91%) was not significantly different from that of DBE (99%) (17). Endoscopic ultrasonography at DBE offers high-resolution cross-sections of SBTs and may contribute to diagnosis (20).

PJS features mucocutaneous pigmentation and gastrointestinal polyps, which occur most commonly in the jejunum and the ileum (at least 90% of cases) (21). Therefore, this syndrome is one of the most significant diseases that benefit from DBE and VCE (22,23). We have reported that total enteroscopy rate was higher at VCE (89%) than at DBE (52%; 27% in patients with two or more previous laparotomies and 90% in patients with only one or without). Fluoroscopic enteroclysis demonstrated fewer polyps than DBE, whereas VCE had detection rates similar to those of DBE. Considering patient discomfort and the accumulated radiation dose over a lifetime of surveillance and the resulting risk of cancer induction (24), VCE may replace barium examinations for surveillance (23,25).

Familial adenomatous polyposis develops small bowel polyps in 50% to 90% of patients. Small bowel cancers are a major cause of morbidity and mortality (26,27). The adenomas occurred predominantly in the jejunum. Patients with small bowel adenoma had more severe duodenal adenomatosis than those patients without small-intestinal adenoma. The prevalence of small-intestinal adenoma was higher in patients with a 3' mutation (100%) than in those with a 5' mutation (44%) and with a negative mutation. DBE detected significantly more small-intestinal adenomas than intraoperative enteroscopy (28). VCE underestimates the number of small bowel polyps (29) presumably because polyps are localized predominantly in the duodenum and the proximal jejunum.

Thus, first of all, we perform CECT and VCE for screening of SBTs. In case suspicious of stenosis, we perform patency capsule to confirm passage before VCE. Then, we perform DBE for further precise examination including biopsy and ultrasonography by using miniature probe, and enteroscopic treatment. After medical, enteroscopic, and surgical treatment, we use VCE for follow-up.

Endoscopic treatment of SBTs

DBE is safe and useful in resecting the SBTs deep within the small bowel without laparotomy. Indications of enteroscopic resection may be benign tumors regardless of epithelial or subepithelial type, localizing in the mucosal or submucosal layer, which are symptomatic at present or possibly symptomatic or transforming in the future. Malignant tumors localized in the mucosal layer may be indications although detecting at an early stage is challenging. Indications and prognosis of enteroscopic resection for malignant submucosal tumors have not been reported.

During the procedure for not only sessile but pedunculated tumors, submucosal injection before resection is recommended to avoid postpolypectomy syndrome such as bleeding, perforation, and abdominal pain, because the small-intestinal wall is thin in the thickness.

One of the most frequent indications for enteroscopic resection is PJS (22,30,31). PJPs are mostly hamartomas, but in a few polyps, adenomatous change and foci of adenocarcinomas are present (32,33). The most frequent complications of PJS are intussusception and bleeding due to ulceration or infarction of the polyps, which often require multiple laparotomies (34). Enteroscopic polyp resection might preclude these complications, thereby obviating the need for multiple laparotomies (22). We have demonstrates that PJPs larger than 15 mm in diameter could harbor an adenomatous component and cause invagination. Therefore, as many polyps as possible, at least 10 mm in size (35), are proposed to be resected enteroscopically to lengthen the interval to the next polypectomy day in the future. PJPs that are bulky, locally concentrated in large numbers, invaginated, thick-stalked, and those with serosal retraction into the stalk are unsuitable for polypectomy because it can cause perforation. As described above, however, multiple laparotomy cause adhesion to interfere with enteroscopic accessibility deep in the small bowel. Although strangulated intussusception warrants emergent surgery, an invaginated polyp without strangulation can be enteroscopically removed after reduction of invagination by using air insufflation via retrograde approach or maneuvers at DBE (36). Ideally, double-balloon enteroscopic polypectomy should be performed when PJPs are relatively small, thereby avoiding the technically more difficult

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endoscopic resection of large polyps at a later stage (22). We hopefully perform enteroscopic resection of polyps throughout the small bowel at total enteroscopy, but in patients with two or more previous laparotomies total enteroscopy is significantly impossible even by P5 DBE scope (23). In these cases, laparoscopic-assisted double-balloon enteroscopy was reported to be an alternative technique (37). This technique, however, seems difficult and insignificant, compared with conventional laparoscopic surgery including single incision approach after tattooing which indicates inaccessible region at DBE (38). The surveillance guideline for small-bowel polyps in PJS recommended biannual small bowel follow-through starting at age ten before the advent of VCE (34,39), the surveillance guideline for small-bowel polyps in adult patients with PJS suggests that a barium study should be performed at first only to minimize radiation exposure, and then double-balloon enteroscopic polypectomy or surgical treatment, followed by VCE every 1-4 years, depending on the polyp growth rate in the small and large intestine. A negative barium study may be confirmed by VCE. For pediatric patients, the first episodes of intussusception occur at ages less than ten. Therefore, the barium study or magnetic resonance imaging study surveillance may start at around age six in patients with confirmed PJS. We feel that DBE in children aged around six is a possible procedure (40,41). After enteroscopic polypectomy or surgical treatment, VCE should be performed at the approved age of ten.

The other indications are adenoma with or without familial adenomatous polyposis, adenocarcinoma (42) or carcinoid localized in the mucosal layer, inflammatory fibroid polyp, and subepithelial tumors such as lipoma (43), hemangioma (44-46) aberrant pancreas, lymphangioma (47), and leiomyoma (17).

Complications of enteroscopy

In a systematic review involving 9,047 DBE procedures, a total of 61 major complications were reported, with a pooled major complication rate of 0.72% (95% CI, 0.56-0.90%). The major complications included perforation (n=20), pancreatitis (n=17), bleeding (n=6), aspiration pneumonia (n=8), and others (n=10). In the 20 patients with perforation, 5 had inflammatory bowel disease (3 of whom underwent related surgery), 4 had a history of surgery, and 3 had tumors where the perforation was located. In the 6,370 antegrade DBE procedures, the pooled pancreatitis rate was 0.49% (95% CI, 0.33-0.67%) (48). We have reported 2 perforation

episodes and 1 acute pancreatitis episode occurred of the 159 patients who underwent DBE, with complication rates of 1.3% and 0.6%, respectively. The perforation occurred at the contra-ampullary side of the 2nd portion of the duodenum in a patient with hemophilia and bleeding carcinoid, which required an emergent surgical omental patch. The other perforation occurred after polypectomy of a 50-mm polyp with 100-mm stalk invaginating from the terminal ileum to the ascending colon in a patient with PJS, which required emergent surgical wedge resection. Therefore, we should not resect an invaginated polyp before reduction of invagination. The complicating non-necrotising pancreatitis occurred in a patient with a medical history of multiple laparotomy due to invagination of PJPs, and the patient recovered on conservative therapy within two weeks (17).

Acknowledgements

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