

Repeat bidirectional double-balloon enteroscopy 1 year later may be proper in Peutz-Jeghers patients with difficult-to-reach polyps



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ABSTRACT

Background and study aims Small-bowel polyps in patients with Peutz–Jeghers syndrome (PJS) are sometimes difficult to reach using double-balloon enteroscopy (DBE). However, they can induce intussusception, especially when ≥ 15 mm. This study aimed to review the outcomes of patients with such polyps.

Patients and methods All patients with PJS with small-bowel polyps that bidirectional DBE failed to reach and were ≥ 5 mm as shown by DBE enterography at our institution from May 2006 to April 2022 were retrospectively evaluated. The endpoint was the earliest occurrence of symptomatic intussusception induced by the polyp, endoscopic removal by repeat DBE or intraoperative endoscopy, or the last medical record describing the patient's condition.

Results This study included 27 polyps in 13 patients. All patients had extraluminal adhesions. None developed symptomatic intussusception, eight patients underwent endoscopic removal at repeat DBE without surgery, two patients underwent removal with intraoperative endoscopy, two patients were observed without polyp removal, and one patient had a polyp removed at repeat DBE and three unreachable polyps remained. Repeat DBE without surgery was able to remove 14 polyps (52%). Polyps ≥ 15 mm included 11 lesions in eight patients and were observed for a median of 14 months without symptomatic intussusception.

Conclusions The difficult-to-reach polyps may have a low risk of immediate symptomatic intussusception, possibly due to limited bowel mobility by extraluminal adhesions, and the likelihood of reaching them at repeat DBE was substantial. Hence, repeat DBE 1 year later may be proper in such patients with PJS.

Introduction

Peutz-Jeghers syndrome (PJS) is a hereditary polyposis syndrome characterized by gastrointestinal hamartomatous polyps and mucocutaneous pigmentations [1, 2, 3]. Small-bowel intussusception can be induced especially by polyps ≥ 15 mm

and 92.5% of intussusception events are treated surgically [4]. Endoscopic removal of small-bowel polyps ≥ 15 mm and eventually all polyps > 5 mm have been sought to avoid intussusception. Our previous studies [5, 6] suggest that repeated endoscopic removal of hamartomatous polyps can prevent intussusception in patients with PJS by applying such policies. However,

some small-bowel polyps are difficult to reach even using double-balloon enteroscopy (DBE) in the presence of extraluminal adhesions from previous abdominal surgery, which most patients with PJS have had. When DBE fails total enteroscopy, DBE enterography is performed to detect polyps in the unreachable area of the gastrointestinal tract. The long-term outcomes associated with these difficult-to-reach polyps are still unknown. The aim of this study is to retrospectively review the outcomes of patients with PJS with small-bowel polyps that could not be reached using bidirectional DBE.

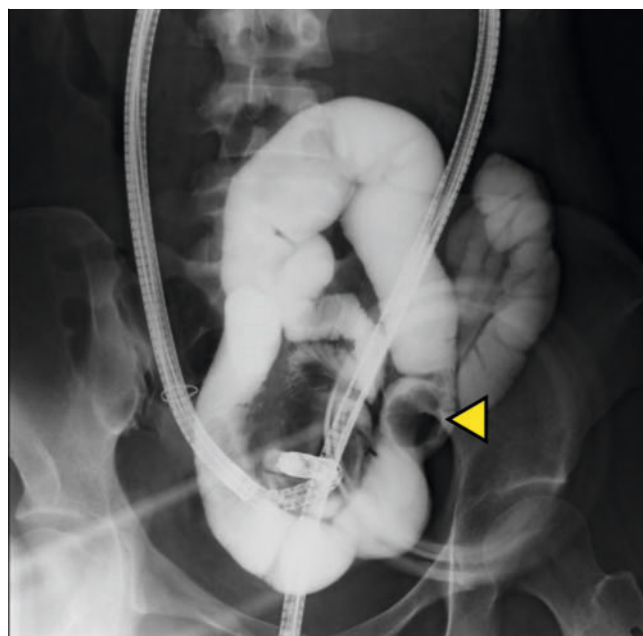
Patients and methods

Clinical data were retrospectively obtained from the medical records of patients with PJS who underwent DBE at Jichi Medical University Hospital, Tochigi, Japan from May 2006 to April 2022. This study included all patients with PJS who had small-bowel polyps that bidirectional DBE failed to reach and DBE enterography had demonstrated, as in ► **Fig. 1**. Bidirectional DBE was defined as an antegrade and a retrograde DBE performed within seven days. This retrospective, observational study was approved by the Institutional Review Board of Jichi Medical University and written informed consent was obtained from all patients.

DBE was usually performed under conscious sedation with pethidine and benzodiazepine (midazolam or flunitrazepam), and rarely with propofol or under general anesthesia. Polyethylene glycol electrolyte solution was normally administered the day before and on the morning of retrograde DBE for "split-dose" bowel preparation. A therapeutic-type double-balloon endoscope (EN-580T, EN-450T5/W, or EC-450BI5 with a dedicated over-tube; Fujifilm, Tokyo, Japan) was used with a transparent cap (D201-10704; Olympus, Tokyo, Japan) on the tip of the endoscope, with minimum carbon dioxide (CO₂) insufflation or the water exchange method. When single-time or repeated bidirectional DBEs using a therapeutic-type double-balloon endoscope failed total enteroscopy, a diagnostic-type double-balloon endoscope (EN-580XP or EN-450P5/20 with a dedicated over-tube; Fujifilm) was used because of an expectation of its better ability to be advanced in patients with extraluminal adhesions unless there was a special reason not to.

In DBE enterography, 200 mL of a 40% aqueous solution of amidotrizoate sodium meglumine was generally used as contrast medium. Contrast medium was infused through the scope with inflation of the balloon at the tip of the endoscope to suppress backflow. Then clear water was often injected, which pushed away the contrast medium to keep the proximal gastrointestinal tract clear and make the distal end visible, which facilitated finding polyps without overlap of the contrast-containing gastrointestinal tract.

Patients were observed from the time when a small-bowel polyp was detected by DBE enterography. Data regarding the polyps were analyzed, and the DBE insertion methods assessed. The endpoint was the earliest occurrence of one of the following: symptomatic intussusception induced by the polyp, endoscopic removal of the polyp by repeat DBE or intraoperative endoscopy, or the last medical record describing the patient's



► **Fig. 1** Retrograde DBE enterography showed a small-bowel polyp. The patient's abdomen was compressed with a plate to clearly demonstrate the polyp. The yellow arrow indicated the polyp.

condition between May 2006 and April 2022. The observation period per patient was determined cumulatively to avoid repeatedly counting the terms of polyps which overlapped in time because some patients with PJS had multiple heterochronic small-bowel polyps.

Endoscopic removal included not only conventional polypectomy but also endoscopic ischemic polypectomy (EIP) [6]; the strangulation of the base of the polyp by endoclips (TM090 or TM135; Kaneka, Tokyo, Japan, or HX-610-090L; Olympus) or a detachable snare (MAJ-254 or MAJ-340 or HX-400U-30; Olympus) to induce necrosis of the polyp. The detachable snare could not pass through the narrow channel of a diagnostic-type DBE. Therefore, the bare detachable snare with its shortened outer casing was used in such situations [7].

If the precise size of the polyp demonstrated by DBE enterography was not described in the medical record, its size was estimated from the DBE enterographic images. Unclear defective images shown by DBE enterography or defective images with an absence of polyps confirmed at the following DBE were excluded. Small-bowel polyps <5 mm were excluded because they were difficult to distinguish from air bubbles. When it was less than 10 days from detecting the small-bowel polyp to the last medical record without intussusception or endoscopic removal, the polyp was also excluded from review.

For statistical analysis between small-bowel polyps ≥ 15 mm and polyps <15 mm, a two-sided Mann-Whitney U test was used for median comparisons, a two-sided unpaired *t*-test for average comparisons, and Fisher's exact test for comparisons of outcome proportions, to report *P* values. These analyses were conducted with the EZR [8] software version 1.61 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

► **Table 1** Patient characteristics.

Gender	Male	6 (46%)
	Female	7 (54%)
Previous history of intussusception	Yes	9 (69%)
	No	1 (8%)
	Unknown	3 (23%)
Previous history of extraluminal adhesions	Yes	13 (100%)
	▪ Laparotomy	12 (92%)
	▪ Micro-perforation of ileum	1 (8%)
	No	0 (0%)
Patients with more than one polyp that bidirectional DBE failed to reach		7 (54%)
Age at which the first polyp was detected per patient (years)	Median	30
	Range	16–60
	Average	33.9
	Standard deviation	14.0
Age at which the polyp was detected per polyp (years)	Median	33
	Range	16–66
	Average	38.1
	Standard deviation	15.2
Polyp size (mm)	Median	10
	Range	5–30
	Average	13.9
	Standard deviation	6.53
Observation period (months) per patient	Range	3–91
	Median	14
	Average	28.8
	Standard deviation	27.2
Observational period (month) per polyp	Median	14
	Average	18.9
	Standard deviation	18.5

DBE, double-balloon enteroscopy.

► **Table 2** Patient outcomes.

Occurrence of symptomatic intussusception	0 (0%)
Only endoscopic removal at repeat DBE without surgery	8 (62%)
Only endoscopic removal with intraoperative endoscopy	2 (15%)
▪ Concurrent with laparotomic LOA	1 (8%)
▪ Laparoscopically assisted insertion with minimal LOA	1 (8%)
Observation without polyp removal	2 (15%)
Endoscopic removal of one polyp at repeat DBE without surgery and observation of three unreachable polyps	1 (8%)

DBE, double-balloon enteroscopy; LOA, lysis of adhesions.

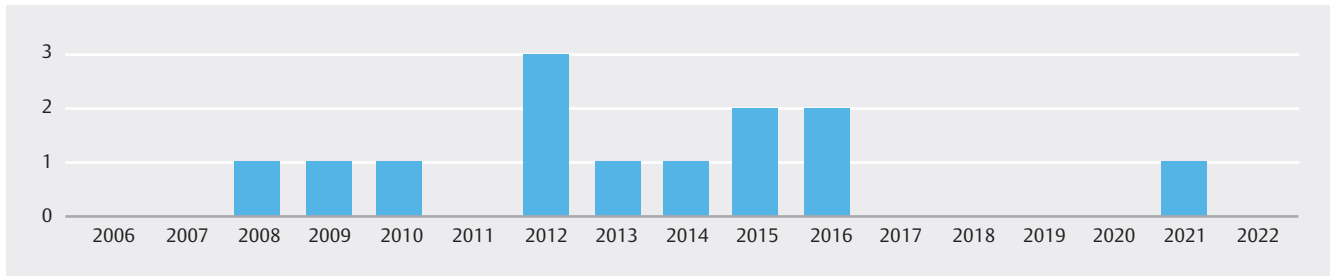
The median size of the included polyps was 10 mm. The median period of observation was 14 months both per patient and per polyp. Of the 13 patients included in this study, six patients have a family history of PJS, one patient has a father with suspected PJS, and six patients have no family history of PJS.

The outcomes of the 13 patients are presented in ► **Table 2**. No patient developed symptomatic intussusception induced by the polyp or required emergency surgery during the observation period. Only one patient had an asymptomatic intussusception confirmed by computed tomography (CT) scan, which did not require invasive treatment. Of 13 patients with PJS included in this study, eight patients (62%) underwent endoscopic removal of the polyps by repeat DBE without surgery, two patients (15%) underwent endoscopic removal of the polyps with intraoperative endoscopy, two patients (15%) were observed without polyp removal, and one patient (8%) had a polyp removed by repeat DBE and three unreachable polyps remained. The annual patients included in this study are shown in ► **Fig. 2**. The two patients, in the early period of this study, underwent endoscopic removal with intraoperative endoscopy with lysis of adhesions (LOA). Of the two patients, the patient in 2008 underwent bidirectional DBE with laparoscopically assisted insertion and laparoscopic minimal LOA. The other patient in 2009 underwent bidirectional DBE with laparotomic LOA, which was converted from laparoscopy due to dense adhesions. On the other hand, the 11 patients since 2010 underwent endoscopic removal without surgery or were observed without polyp removal. Of 27 small-bowel polyps included in this study, 14 polyps (52%) were removed by repeat DBE without surgery, seven polyps (26%) were observed without removal, and six polyps (22%) were removed with intraoperative endoscopy, as presented in ► **Table 3**. EIP was performed in the eight patients who underwent endoscopic removal without surgery, and conventional polypectomy was performed in the two patients that underwent endoscopic removal with intraoperative endoscopy.

There were 11 small-bowel polyps ≥ 15 mm in eight patients. Their median size was 20 mm and they were observed for a median of 14 months and an average of 20.2 months without

Results

Between May 2006 and April 2022, 74 patients with PJS underwent DBE at Jichi Medical University Hospital, and this study included 13 patients and 27 small-bowel polyps. Patient characteristics were presented in ► **Table 1**. There were nine patients with previous episodes of intussusception, and evidence of previous intussusception was not definitive in three patients based on their medical records. All patients had extraluminal adhesions before the polyps were detected: 12 patients at laparotomy and one with a history of micro-perforation of the ileum.



► **Fig. 2** The number of annual patients included in this study.

► **Table 3** Small-bowel polyp outcomes.

Occurrence of symptomatic intussusception	0 (0%)
Only endoscopic removal at repeat DBE without surgery	14 (52%)
Only endoscopic removal with intraoperative endoscopy	6 (22%)
▪ Concurrent with laparotomic LOA	3 (11%)
▪ Laparoscopically assisted insertion with minimal LOA	3 (11%)
Observation without removal	7 (26%)
DBE, double-balloon enteroscopy; LOA, lysis of adhesions.	

symptomatic intussusception until the endpoints, as presented in ► **Table 4**. There were three polyps ≥ 15 mm which were observed without endoscopic removal, and the average observation interval of these polyps was 35 months; A 25-mm polyp was observed for 91 months without intussusception. As shown in ► **Table 4**, small-bowel polyps < 15 mm were observed for a median of 12.5 and an average of 18 months without symptomatic intussusception. Their observation period and outcome proportions were similar to those of the polyps ≥ 15 mm.

The endoscopes and insertion methods of the 14 polyps removed by repeat DBE without surgery were shown in ► **Table 5**. Seven of them (50%) were reached using a therapeutic-type DBE, while others were reached using a diagnostic-type endoscope. Two of the seven polyps reached using repeat therapeutic-type DBE were reached by changing the insertion method from CO₂ insufflation to water exchange. Five other polyps were reached by the same method, three by water exchange and two by CO₂ insufflation.

Discussion

To the best of our knowledge, this is the first report to show the long-term outcomes of patients with PJS with small-bowel polyps that could not be reached by bidirectional DBE. This study shows that these polyps rarely induced symptomatic intussusception for a certain period and were likely to be reached and removed at repeat DBE.

Although small-bowel polyps especially ≥ 15 mm can cause intussusception in patients with PJS [4], such polyps in this

► **Table 4** Comparison of small-bowel polyps ≥ 15 mm and < 15 mm.

	≥ 15 mm	< 15 mm	P value
Number of small-bowel polyps	11	16	
Polyp size (mm)			
▪ Median	20	10	< 0.001
▪ Range	15–30	5–10	
▪ Average	20.9	9.06	< 0.001
▪ Standard deviation	4.17	1.71	
Observation period (months)			
▪ Median	14	12.5	> 0.99
▪ Range	6–91	3–60	
▪ Average	20.2	18.0	0.77
▪ Standard deviation	23.3	14.2	
Outcomes			
▪ Endoscopic removal	8 (73%)	12 (75%)	> 0.99
– at repeat DBE without surgery	5 (45%)	9 (56%)	0.70
– with intraoperative endoscopy	3 (27%)	3 (19%)	0.66
▪ Observation without removal	3 (27%)	4 (25%)	> 0.99
DBE, double-balloon enteroscopy.			

study did not induce symptomatic intussusception during the median 14-month and average 20.2-month observation period. While patients with PJS have often undergone abdominal surgery, and these operations make DBE insertion difficult [9] because postoperative extraluminal adhesions fix the gastrointestinal tract in place, it is considered that fixation due to adhesions mechanically prevents a polyp from being drawn into the distal side and inducing intussusception. All 13 patients in this study had extraluminal adhesions, which was recognized by fluoroscopy during DBE, 12 of which were attributed to previous laparotomy and one to a previous ileal micro-perforation.

It is recommended that small-bowel polyps > 10 to 20 mm in size in patients with PJS be removed to prevent intussusception and other complications [2, 3]. It is desirable to remove them

► **Table 5** Endoscopes and insertion methods of the 14 polyps removed by repeat DBE without surgery.

Failure to reach		
	Therapeutic-type endoscope	Diagnostic-type endoscope
▪ Water exchange	10	0
▪ CO ₂ insufflation	4	0
Successfully reached		
	Therapeutic-type endoscope	Diagnostic-type endoscope
▪ Water exchange	5	7
▪ CO ₂ insufflation	2	0

CO₂, carbon dioxide.

endoscopically whenever possible because surgical polypectomy can lead to further extraluminal adhesions, which makes subsequent DBE insertion more difficult. More than half of the small-bowel polyps that could not have been reached by bidirectional DBE were successfully reached, and removed by repeat DBE without surgery in this study. This suggests that the likelihood of reaching the polyps at repeat DBE is substantial. Therefore, if there are one or more small-bowel polyps that cannot be reached during a single DBE insertion in a patient with PJS, it is reasonable to perform repeat DBE with the intention of endoscopic removal to avoid the need for operative intervention. Repeat DBE could be performed 1 year later because these polyps did not induce symptomatic intussusception during the median 14-month and average 20.2-month observation period in this study.

It is reported that diagnostic-type double-balloon endoscopes can be inserted deeper than therapeutic-type endoscopes [9]. CO₂ insufflation is also effective to facilitate deeper insertion than with air insufflation [10], and the water exchange method in balloon-assisted enteroscopy may be able to increase the intubation depth compared to CO₂ insufflation [11]. These trends were confirmed in patients with PJS with extraluminal adhesions in this study as well. Currently, we have adopted the water exchange method in principle; however, this study includes some DBE insertion methods with CO₂ insufflation because some endoscopists who were not familiar with the water exchange method, adopted CO₂ insufflation in the past. In a single patient in this study, changing from the EC-450BI5 endoscope to the EN-580T may have helped to reach the small-bowel polyp since the EN-580T is about 50 cm longer than the EC-450BI5. Interestingly, some of the polyps that could not be reached with bidirectional therapeutic-type DBE insertion could be reached even with the same therapeutic-type endoscope and insertion method used in this study. This suggests that attempting DBE again with a focus on deeper insertion may improve the chance of reaching the polyps.

In this study, the two patients in the early period underwent intraoperative endoscopy with LOA, which allowed total en-

teroscopy and treatment of the small-bowel polyps. We initially expected LOA to enable total enteroscopy in the next treatment. It was true in the patient with laparoscopic minimal LOA. However, in the other patient, who underwent intraoperative endoscopy with laparotomic LOA, it did not enable total enteroscopy in the next bidirectional DBE. We considered that laparotomy exacerbates extraluminal adhesions to cause further difficulty for subsequent DBE insertion. Considering the risk of converting to laparotomy, we could not easily recommend intraoperative endoscopy to patients with PJS. Therefore, in the late period, we repeated DBE or observed the polyps. Nevertheless, laparoscopy-assisted endoscopy has the potential to be useful with the proviso that extraluminal adhesions that hinder the concentric circular insertion of the endoscope are detected first, and then minimal LOA is performed allowing insertion of the endoscope, because minimal LOA may not exacerbate extraluminal adhesions. Of course, if extraluminal adhesions are dense and the gastrointestinal tract is contracted together, such approaches will not be effective.

In endoscopic removal of small-bowel polyps in patients with PJS, conventional polypectomy with a diagnostic-type DBE with a small accessory channel diameter may have an increased procedural risk because most hemostatic devices (e.g. HX-610-090L; Olympus) cannot be used, although a thin polypectomy snare can pass through the channel of the endoscope. Compared to conventional polypectomy, EIP of small-bowel polyps in PJS patients is assumed to be an easier and safer approach with both diagnostic-type [7] and therapeutic-type DBE [6, 12].

For polyps in patients with PJS that are impossible to reach by repeat DBE, one approach might be to carefully follow these polyps until another comorbidity requires laparotomy. Intraoperative endoscopic removal of the polyps during abdominal surgery can reduce the overall need for laparotomy. It must be kept in mind that the incidence of small-bowel cancer in patients with PJS is higher than in the general population, i.e., the cumulative risk of small-bowel cancer is 13% for those aged 15 to 64 years [13], and careful evaluation of morphological changes of polyps by capsule endoscopy, CT scan or magnetic resonance imaging (MRI) is essential.

CT scan and MRI, especially as enterography with enteral contrast medium, will be able to detect small-bowel polyps reasonably [14, 15]. Because small-bowel intussusception can be induced by polyps ≥ 15 mm according to the histological result [4], we guess 15 mm is a cut-off size of polyps associated with the risk of intussusception in patients with PJS, even on imaging studies. From the perspective of preventing intussusception, it is reasonable to perform follow-up DBE for small-bowel polyps once they reach 15 mm in size on the imaging study, especially in medical institutions in which DBE cannot be performed easily. When the polyp size increases rapidly, the polyp shape becomes irregular, or the polyp seems to invade the small-bowel wall, follow-up DBE should be performed due to the risk of malignancy, even in polyps < 15 mm. Because adenoma or adenocarcinoma can be shown in 30% of polyps > 20 mm in patients with PJS [16], these polyps require more attention when observed without removal.

This study shows the trend of the clinical course in patients with PJS who have small-bowel polyps that are difficult to reach by DBE due to extraluminal adhesions. These results are preliminary because this was a single-center, retrospective, observational study with a relatively small number of patients and small-bowel polyps. Further study is necessary to confirm the results.

Conclusions

In conclusion, the results of the present study show that small-bowel polyps in patients with PJS that could not be reached with bidirectional DBE, even polyps ≥ 15 mm, did not often lead to symptomatic intussusception. We consider that extraluminal adhesions, CO₂ insufflation, and use of therapeutic-type double-balloon endoscope can cause shorter DBE insertion, resulting in failure to reach small-bowel polyps in the deep small-bowel as first bidirectional DBE. The technical skill of the endoscopist may also be a factor. It would be desirable to study these possible risk factors with multivariate analysis in a large number of patients. The difficult-to-reach polyps in patients with PJS, possibly due to limited bowel mobility by extraluminal adhesions, may be associated with a low risk of immediate symptomatic intussusception. Of course, it is better to remove these polyps endoscopically to avoid complications, including intussusception, and the likelihood of reaching the polyps at repeat DBE is substantial. Repeat DBE could be performed 1 year later because there may be a certain quiescent period before intussusception occurs, according to these results.

Conflict of Interest

Dr. Yamamoto has patents for double-balloon enteroscopy produced by FUJIFILM Corporation, is a consultant for the corporation, and has received honoraria, grants, and royalties from the corporation. Drs. Sakamoto and Yano have received honoraria and grants from FUJIFILM Corporation. Other authors declare no conflicts of interest.

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