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Endoscopic retrograde cholangiography versus peroral cholangioscopy to evaluate intraepithelial tumor spread in biliary cancer

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ABSTRACT

Background and study aims: Localized type bile duct carcinoma (LBDC) is often accompanied by extensive intraepithelial tumor spread (ITS) ≥2 cm which makes radical resection more difficult. This retrospective case review compared the diagnostic accuracy of endoscopic retrograde cholangiography (ERC) and peroral cholangioscopy (POCS) to detect ITS beyond the visible LBDCs.

Patients and methods: Forty-four consecutive LBDC patients diagnosed between April 2004 to October 2008 who underwent radical resection with histopathological analysis were included in this study. Extensive ITS was found histopathologically in one-third of the cases (32%). The outcome parameters were the presence or absence of extensive ITS and the extent of extensive ITS proximal and distal to the main tumor.

Results: It was not possible to pass the cholangioscopic through the tumor sites in 6 cases. ERC correctly identified the presence of extensive ITS in 11/14 cases and did not yield any false-positive results. The three ERC-negative cases were all correctly identified by POCS plus biopsy since the cholangioscope could be passed in all three cases. The extent of extensive ITS was correctly diagnosed by ERC alone, ERC with POCS, and ERC with POCS plus mapping biopsy in 22%, 77%, and 100% of cases, respectively.

Conclusions: The presence of extensive ITS could be correctly detected in 80% of cases by ERC alone. POCS with mapping biopsy provided perfect diagnostic accuracy of not only the presence/absence but also the extent of extensive ITS. However, POCS has the limitation that the cholangioscope cannot be passed through the tumor sites in approximately 15% of cases.

Introduction

The mode of spread of bile duct carcinomas greatly differs depending on the macroscopic type of the main tumor. We previously reported that the mode of spread of bile duct carcinomas could be classified into 2 types: localized type bile duct carcinoma (LBDC) and diffuse sclerosing bile duct carcinoma (DSBDC). LBDC grossly appears as an elevated lesion with a relatively clearly formed border. Although the extramural invasion is often mild, it is important to examine any intraepithelial tumor spread (ITS) that is continuous with the main tumor and extends ≥2 cm into the mucosal epithelium in LBDCs [1]. The incidence of extensive ITS is approximately 20-30% [1,2]. On the other hand, extramural invasion and submucosal intramural spread are common in DSBDC [1]. The incidence of extensive ITS with DSBDC is approximately 3-4% [1,2], and extensive ITS is more frequently found in LBDC than DSBDC (about 20-30% vs. 3-4%). Therefore, in order to perform a curative resection without leaving any remaining cancer cells, the extent of the ITS into the bile duct mucosal epithelia must be accurately identified in LBDC and the extent of submucosal intramural and extramural spread must be evaluated in DSBDC.

When diagnosing ITS in LBDC, fine irregularities (so-called "fuzzing") in the bile duct wall that are continuous with the locally raised main tumor should be further examined by cholangiography. However, these changes are minor and often difficult to detect by cholangiography, making it difficult to accurately diagnose the extent of the spread based only on a cholangiographic examination. Therefore, direct visualization of the bile duct lumen using endoscopic techniques should be helpful to assess fine mucosal changes. Percutaneous transhepatic cholangioscopy (PTCS) was reported to be a useful technique to diagnose extensive ITS [3-5]. However, there are several disadvantages with PTCS. (1) The preparation of a percutaneous transhepatic bile duct drainage route can damage the portal vein branches.

(2) Percutaneous transhepatic insertion of the catheter into the bile duct has the risk of implanting cancer cells in the thoracic or peritoneal cavity through bile spillage. (3) It generally takes a few weeks to complete the route for the endoscopic examination.

With the recent development of videoscopic technology, the resolution of peroral cholangioscopy (POCS) has markedly improved, and this modality has been used to visualize fine mucosal changes in the bile duct. The present study investigated both the clinical impact and the limitations of POCS for diagnosing extensive ITS in LBDC.

Patients and methods

We examined a total of 129 consecutive patients with surgically resected extrahepatic bile duct carcinomas at Hokkaido University Hospital from April 2004 to October 2008. Of the 129 patients, 44 (34.1%) had LBDC and 85 (65.9%) had DSBDC. All LBDC patients who underwent POCS to evaluate ITS followed by surgical resection were examined in the present study. Based on our previous study [1], the incidence of extensive ITS was closely related to the macroscopic type of the main tumor. No patients with primary sclerosing cholangitis were treated in this study.

Patients with marked jaundice (defined as a total serum bilirubin level no less than 3.0 mg/dL) or acute obstructive cholangitis were excluded.

In accordance with the Declaration of Helsinki, written informed consent was obtained from each patient or their family members before endoscopic retrograde cholangioscopy (ERC) or POCS.

In all cases, radical resection was performed and a histopathological analysis was conducted. All 44 patients were followed for more than 6 months, and the median follow-up period was 795 days. The follow-up examinations were performed using abdominal

ultrasonography, computed tomography, and measurements of the serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels every 3–6 months by the appropriate medical support institutions.

As this study comprised a retrospective review of cases, patient consent was required, and the institutional review board of our institution approved the study protocols.

ERC and POCS

ERC was performed using a therapeutic duodenoscope (TJF-240 or TJF-260V; Olympus Medical Systems, Tokyo, Japan). For bile duct cannulation, wire-guided cannulation (WGC) using a triple-lumen papillotome (CleverCut3V, Olympus) was performed. Briefly, a papillotome preloaded with a guidewire (0.035-inch, hard guidewire, stiff-type Jagwire; Boston Scientific Japan, Tokyo, Japan) was inserted into the working channel of the duodenoscope. After inserting the guidewire into the bile duct, the papillotome was inserted deep into the bile duct along the guidewire. Bile duct cannulation was checked by visually confirming bile or by performing cholangiography. With regard to the WGC techniques, contrast agents were banned until the bile duct was cannulated. After performing deep cannulation into the bile duct, ERC with a papillotome was obtained. The bile duct was filled with a contrast medium until the intrahepatic bile ducts were visualized. Balloon-occlusion cholangiography was performed only in 1 patient because of pneumobilia. When there was no filling of the intrahepatic bile ducts with ERC, a guidewire was advanced to the tip of the papillotome, through the stricture and into the dilated bile duct through the stricture. Then, a papillotome was introduced over the stricture using the guidewire, and ERC was obtained until the intrahepatic bile ducts were visualized.

The location of the cholangioscope tip was precisely identified under

fluoroscopic images in accordance with the cholangiograms, and the POCS and ERC findings were precisely compared in the same session.

We classified bile duct carcinomas as LBDC or DSBDC based on the ERC findings. Localized type bile duct tumors are papillary type or nodular type bile duct carcinomas, but not diffuse sclerosing type bile duct carcinomas. Generally, the papillary type showed filling defects (cauliflower-like appearance) (Fig. 1), and the nodular type showed an abrupt obstruction, whereas the diffuse sclerosing type exhibited gradually tapering strictures (Fig. 2).

Of the 44 patients with LBDC, 28 patients showed a nodular type carcinoma and 16 patients had a papillary type carcinoma (Table 1). In this study, when ERC showed an LBDC, POCS was subsequently performed to detect extensive ITS in all patients. However, when ERC showed a DSBDC, POCS was not performed because extensive ITS rarely occurs with DSBDC [1]. We performed endoscopic nasobiliary drainage (ENBD) in 20 of 44 patients (45.4%) with marked jaundice (total serum bilirubin level ≥3.0 mg/dL) or acute obstructive cholangitis prior to POCS. We performed POCS after the ENBD when the reduced total serum bilirubin level was <2.0 mg/dL. No patients with a small caliber bile duct that did not allow POCS were included in this study.

Endoscopic sphincterotomy was performed before POCS. A videocholangioscope (CHF-B260, 3.1 mm diameter; Olympus) with an outer diameter of 3.4 mm and an accessory channeled diameter of 1.2 mm was advanced into the bile duct.

When POCS was performed to observe the bile duct lumen, the contrast medium and bile were aspirated, and then the lumen was repeatedly washed and perfused using sterile physiological saline. We also periodically aspirated fluid to maintain a low pressure in the bile duct during POCS.

Biopsy protocol

Following the cholangioscopic observation, biopsies were performed in the same session under a cholangioscopic image using 3-Fr ultrathin biopsy forceps (FB-44U-1; Olympus). The location of the tip of biopsy forceps through the cholanigioscope was precisely identified under fluoroscopic guidance in accordance with the cholangiograms.

In the series of hilar cholangiocarcinoma, a right hepatectomy and caudate lobectomy with extrahepatic bile duct resection should be indicated for Bismuth type I, II, IIIa, and IV tumors. This type of the surgical resection was allowed in order to resect the bile duct at the right border of the umbilical portion. Surgeons should need a preoperative assessment to determine that the cancer has not extended to the bile duct at the right border of the umbilical portion in order to indicate this type of surgical resection. Therefore, it is very important to take biopsy specimens from B4 confluence and/or B2 and B3 confluence. It is crucial to preoperatively assess the cancer extension into the bile duct proximal to the confluence of the anterior and posterior segmental ducts in Bismuth type IIIb or IV hilar cholangiocarcinomas. This preoperative information is useful to decide the type of liver resection, such as a left hemihepatectomy or left trisectionectomy. In the series of middle/lower bile duct cancers, a pancreaticoduodenectomy should be indicated. This type of surgical procedure enabled the bile duct to be divided at the confluence of the right and left hepatic bile ducts. Therefore, it is very important to take biopsy specimens from the confluence of the right and left hepatic bile ducts in middle/lower bile duct cancers.

The extent of bile duct resection generally depended on the type of surgical resection. An adequate preoperative assessment allowed us to select the proper surgical procedures for negative ductal margins. Subsequently, we biopsied the main tumor and lower

bile duct under direct vision with POCS. When biopsies under direct vision with POCS were insufficient, transpapillary biopsies using larger biopsy forceps (FB-45Q-1; Olympus) under fluoroscopic guidance were also conducted.

When the POCS could not be passed through the tumor site, a Howell Introducer (Wilson-Cook Medical, Winston-Salem, NC, USA) was advanced to the proximal side of the narrowed region along the guidewire, and exclusive forceps (HBIF-1.5-22; Wilson-Cook Medical) were inserted into the bile duct through the forceps channel in the same session. Under X-ray fluoroscopy, the forceps were pressed to the B4 confluence and the right anterior or posterior sectional duct, confluence of the right and left hepatic bile ducts as possible, and a sample was entrapped in the forceps cups.

All endoscopic procedures were performed by 2 endoscopists (H.K., M.K.) while the patient was under conscious sedation with intravenous pethidine hydrochloride and diazepam. A nasobiliary drainage tube was placed immediately after ERC and POCS to ensure continued drainage, and intravenous antibiotics were administered after ERC and POCS in all patients. The diagnostic accuracy, sensitivity, and specificity of ERC alone and ERC with POCS, with and without biopsy were calculated and compared with the final diagnosis for extensive ITS.

Definition of intraepithelial tumor spread of carcinoma cells

We defined ITS of carcinomas as intraepithelial atypical cells similar to the cells composing the surface of the main tumor. Because it is very difficult to distinguish between severe dysplasia and carcinoma in situ, these were included in the same category [6]. The length of the ITS was determined by measuring from the edge of the main tumor. In this study, extensive ITS was defined as spread ≥20 mm in length from the margin of the main lesion to

one side (proximal or distal).

Extensive ITS was histopathologically confirmed in 14 patients (31.8%).

Results

The subjects included 35 men and 9 women, with a median age of 68 years (range, 47-80 years). The site of biliary obstruction was hilar in 3 patients and extrahepatic in 41 patients (Table 1).

The main tumor was observed in all 44 patients and was either an elevated lesion in the bile duct lumen or a localized papillary polypoid lesion. Elevated lesions had the following characteristics: irregularly dilated and tortuous vessels (tumor vessels), oozing, and an irregular surface [7]. Using 3-Fr ultrathin biopsy forceps (FB-44U-1; Olympus), the main tumor could be diagnosed histopathologically in 42 patients (95.5%) with a median of 2 biopsies (range, 1-6 biopsies). For the remaining 2 patients, a sufficient sample could not be collected using this technique. However, for both of these cases, the main tumor was histopathologically diagnosed by a transpapillary biopsy using biopsy forceps (FB-45Q-1; Olympus) in the same session.

The scope could be positioned through the tumor site in 38 of the 44 patients (86.4%). In all of these cases, the main tumor and bifurcation of the hepatic bile duct could be observed. In 6 patients, the tumor blocked passage to the proximal side, but the margin of the main tumor and distal side could be seen.

The presence or absence of extensive ITS was diagnosed by ERC alone in 35 of the 44 patients (79.5%; Table 2), but the extent of extensive ITS could not be identified (Table 3). Excluding 6 patients in whom the scope could not be passed through the tumor site, extensive ITS could be diagnosed in 38 patients (Table 2). Endoscopic findings of extensive

ITS in the bile duct mucosa included an irregular fine granular pattern (Fig. 3), and a fish-egg-like pattern with small red nodules in the center (Fig. 4). Meanwhile, non-cancerous mucosa was observed as a white flat normal mucosa and hyperplastic or regenerative mucosa with a scale-like appearance. Of the 14 patients with extensive ITS, irregular fine granular patterns were seen in 8 patients, with fish-egg-like patterns in 6 patients. However, among these 14 patients, the scope could be passed through the tumor site to examine the proximal and distal sides in 13 patients. Furthermore, because the marginal zone of ITS was white and smooth like the normal mucosa in 3 patients, the extent of spread was underdiagnosed based on endoscopy alone (Table 4). However, in these 3 patients, the extent of extensive ITS was accurately determined by biopsy mapping using biopsy forceps (FB-44U-1, FB-45Q-1; Olympus).

Using ERC alone to diagnosis the presence or absence of extensive ITS correctly identified 11 of the 14 patients with extensive ITS among the 44 patients (accuracy, 79.5%; sensitivity, 78.6%; specificity, 100%; positive predictive value, 100%; negative predictive value, 94.3%; Table 2). ERC with POCS and ERC with POCS plus biopsy were used to correctly diagnose the presence or absence of extensive ITS in all 14 patients with extensive ITS among 38 patients, after excluding 6 patients in whom the scope could not be passed through the tumor site (accuracy, 100%; sensitivity, 100%; specificity, 100%; positive predictive value, 100%; negative predictive value, 100%; Table 2).

ERC alone was used to correctly identify the extent of extensive ITS in 3 of the 14 patients with extensive ITS among all 44 patients. ERC with POCS was successfully used to diagnosis the extent of extensive IS in 10 of the 13 patients with extensive ITS among 38 patients, after excluding 6 patients in whom the scope could not be passed through the tumor site. ERC with POCS plus biopsy correctly diagnosed the extent of extensive ITS in all 13

patients with extensive ITS among 38 patients, after excluding 6 patients in whom the scope could not be passed through the tumor site (Table 3).

Biopsies under direct vision with POCS using 3-Fr ultrathin biopsy forceps (FB-44U-1; Olympus) were used to correctly diagnose the presence or absence of extensive ITS proximal to the main tumor in all 44 patients with a median of 4 biopsies (range, 2-12 biopsies). The presence or absence of extensive ITS distal to the main tumor, except for lower bile duct carcinoma, was correctly identified in 34 of 36 patients (94.4%) with a median of 2 biopsies (range, 1-4 biopsies).

For the 6 patients in whom the scope could not be passed through the tumor site, the extent of extensive ITS was accurately determined by biopsy mapping using a Howell Introducer and forceps (HBIF-1.5-22; Wilson-Cook Medical). Percutaneous transhepatic biliary drainage, biopsy, and PTCS were not performed in all 6 cases.

Detailed examinations using serial longitudinal sections revealed no positive ductal margins in any of the 44 patients, including 12 cases in which the distance between the cancerous and surgical margins were within 5 mm. No cancer recurrence at the site of the choledochojejunostomy has been observed in our series of patients.

With regard to POCS-related complications, acute ascending cholangitis was seen in 4 patients (9.1%) despite biliary drainage at the time of the procedure, but was mild and alleviated by conservative therapy within 2 days after the POCS examination in all cases. Intrahepatic abscess and acute pancreatitis were not seen. In addition, other severe complications, such as retroperitoneal perforation, did not occur.

Discussion

In the present study, the incidence of extensive ITS was high and occurred in

31.8% of LBDC cases. Based on irregular fine granular and fish-egg-like patterns, the rate of correct diagnosis was 21.4% for ERC alone, 76.9% for ERC with POCS, and 100% for ERC with POCS plus biopsy. However, some disadvantages of the transpapillary approach were that the hepatic side of the tumor site could not be observed in some cases and observations near the papilla were difficult.

With LBDC, even when the cholangiography findings suggested that there may be difficulty passing the endoscope, the endoscope could be passed through the tumor site and the bile duct could be observed in many cases. However, in 13.6% of cases, passing the endoscope through the obstruction was difficult, and this is one of the technical barriers of POCS. In the present study, the distal side could be observed in all patients who underwent POCS. Regarding techniques that can be used to reach through the obstruction, it has been reported that using a 10-Fr plastic tube stent as part of the pretreatment enables the endoscope to be passed through the obstruction to observe the proximal side of the obstruction [8], thus compensating for the disadvantages of a transpapillary approach. The biliary drainage plastic tube stent, including the ENBD tube, may cause hyperplastic or regenerative changes in the mucosa, which has a scale-like appearance that is identifiable by POCS. Using POCS, it is possible to distinguish between cancerous mucosa, which has irregular fine granular patterns and fish-egg-like patterns, and non-cancerous mucosa, which has a scale-like appearance.

The extent of extensive ITS was underdiagnosed when assessed solely on endoscopic findings in 3 of the 14 patients, but biopsies were able to compensate for these underdiagnoses. By combining biopsy with endoscopy, extensive ITS could be accurately diagnosed. With videoscopy in POCS, fine mucosal changes that could not previously be examined can now be analyzed, but it is important to note that the marginal zone of extensive ITS may contain a single layer of histopathologically flat cancerous epithelium [1]. With flat,

extensive ITS, a combination of POCS and biopsy appears necessary. In the future, more patients need to be studied to establish diagnostic criteria for extensive ITS using videoscopy and a new endoscopic classification system.

In recent years, a new diagnostic method based on narrow band imaging (NBI) has been successfully used to diagnose gastrointestinal diseases [9]. In addition, the usefulness of combining NBI with bile duct observation has been documented [10]. Compared to conventional endoscopy, the light intensity with NBI is lower, but the characteristics of the tumor surfaces, tumor vessels, and small vessels around the tumor are enhanced, making the observations easier. As bile is seen as red, even a small amount of bile lowers the observation performance. Therefore, bile aspiration and sufficient washing with physiological saline are necessary, and compared to conventional endoscopy, caution must be exercised with complications of ascending cholangitis.

POCS is less invasive than PTCS and carries no risk of damaging the portal branches or cancerous pleuritis and peritonitis due to bile spillage when constructing the percutaneous transhepatic bile duct drainage route. Preparation of a fistula is unnecessary, and POCS can be performed concurrently with ERCP. Therefore, POCS is a clinically significant tool for diagnosing extensive ITS in bile duct carcinomas.

In conclusion, POCS using a videoscope is extremely useful to identify extensive ITS. When determining the extent of spread, POCS has limited diagnostic capability, and a combination of POCS and biopsy is currently warranted.

Competing interests: None

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Abbreviations:

LBDC, localized type bile duct carcinoma; DSBDC, diffuse sclerosing bile duct carcinoma; ITS, intraepithelial tumor spread; PTCS, percutaneous transhepatic cholangioscopy; POCS, peroral cholangioscopy; ERC, endoscopic retrograde cholangiography; WGC, wire-guided cannulation; ENBD, endoscopic nasobiliary drainage; NBI, narrow-band imaging.

Figure legends

Figure 1

ERC image of localized type bile duct carcinoma.

ERC showing a filling defect in the superior extrahepatic bile duct.

Figure 2

ERC image of diffuse sclerosing type bile duct carcinoma.

ERC showing stricture in the hilar bile duct.

Figure 3

POCS image of an irregular fine granular appearance continuous with the main tumor.

A, B: Irregular fine granular lesions, whitish in color are seen.

C: Irregular fine granular lesions, uneven erosive mucosa, redness in color with the irregularly dilated vasculatures are seen.

Figure 4

POCS image of a fish-egg-like appearance continuous with the main tumor.

A, B: Numerous fish-egg-like lesions with a central red spot are seen.

C: Villous lesions with spotty red color markings are seen.

Table 1 Location and gross type of localized type bile duct carcinomas

Location of main tumor	Number (n = 44)	Gross type	
		Nodular (n = 28)	Papillary (n = 16)
Brl	3	3	0
Bs	10	5	5
Bm	23	16	7
Bi	8	4	4

Brl, right and left hepatic bile ducts; Bs, superior extrahepatic bile duct; Bm, middle extrahepatic bile duct; Bi, inferior extrahepatic bile duct.

Table 2 Diagnosis of the presence of extensive intraepithelial tumor spread by ERC alone or ERC with POCS with or without biopsy

All patients	Accuracy	Sensitivity	Specificity	PPV	NPV
ERC alone	35/44 (79.5%)	11/14 (78.6%)	35/35 (100%)	11/11 (100%)	33/35 (94.3%)
ERC with POCS*	38/38 (100%)	10/10 (100%)	28/28 (100%)	10/10 (100%)	28/28 (100%)
ERC with POCS + biopsy*	38/38 (100%)	10/10 (100%)	28/28 (100%)	10/10 (100%)	28/28 (100%)

ERC, Endoscopic retrograde cholangiography; POCS, Peroral cholangioscopy; PPV, positive predictive value; NPV, negative predictive value.

* Six patients were excluded because the scope could not be passed through the tumor site.

Table 3 Diagnosis of the extent of extensive intraepithelial tumor spread by ERC alone or ERC with POCS with and without biopsy

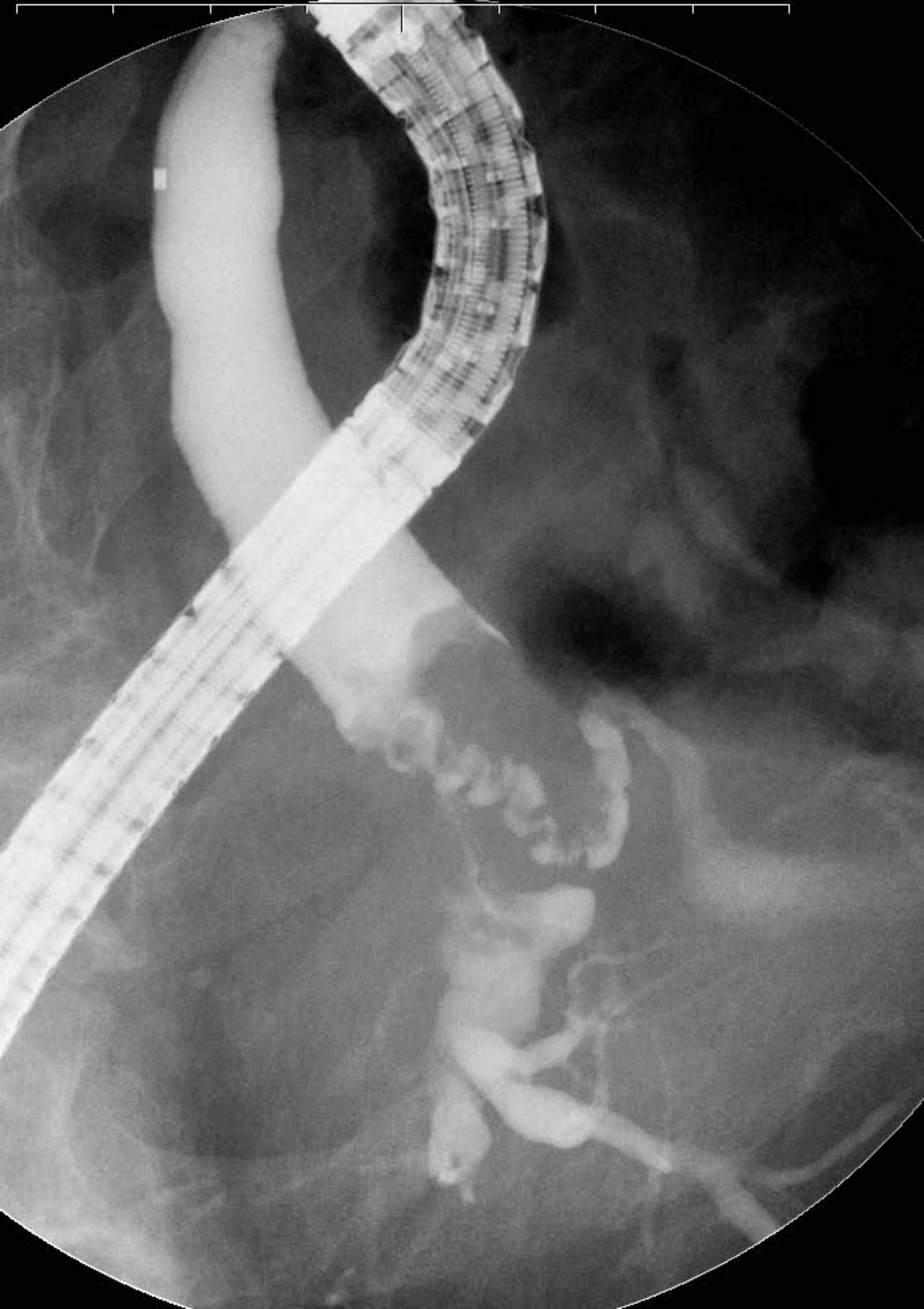
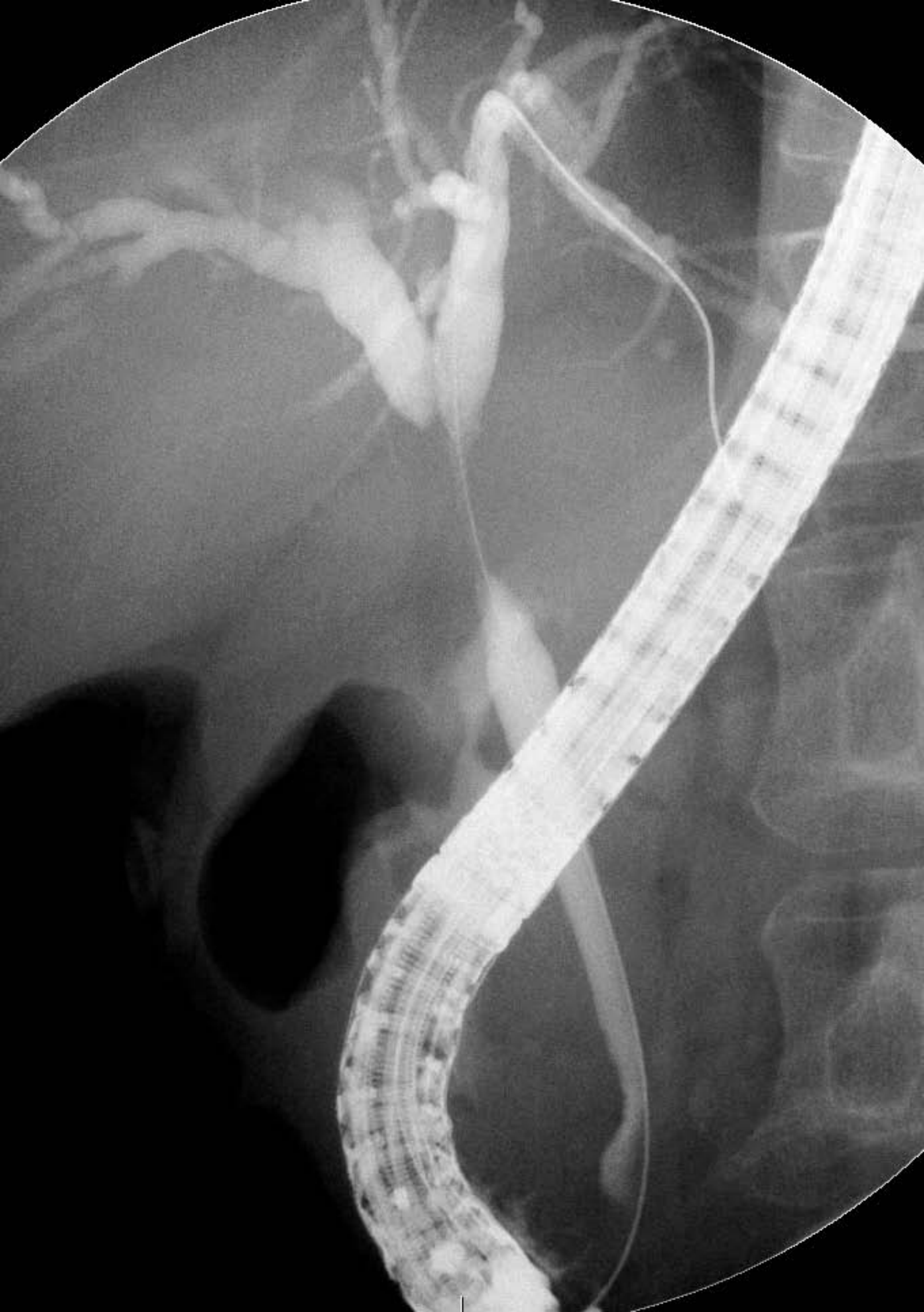
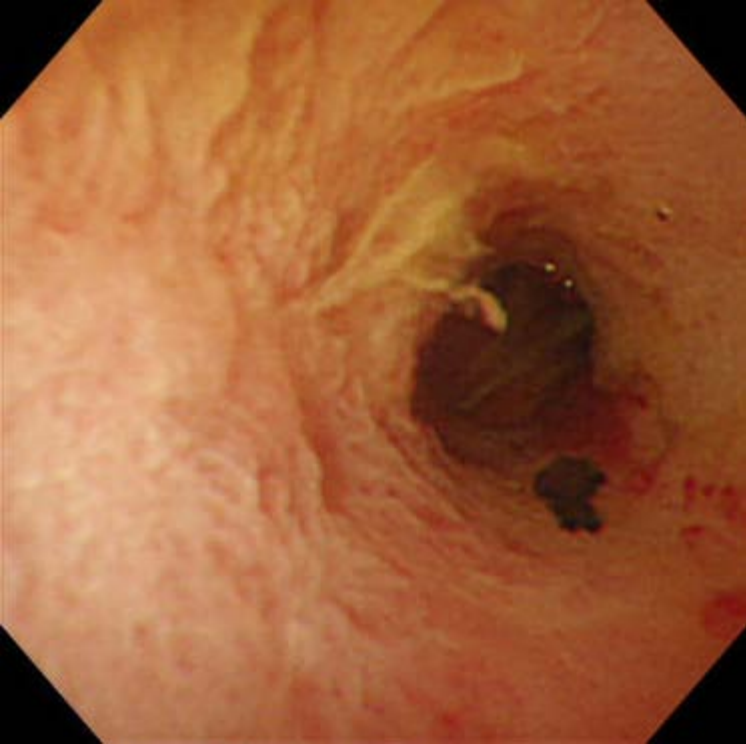
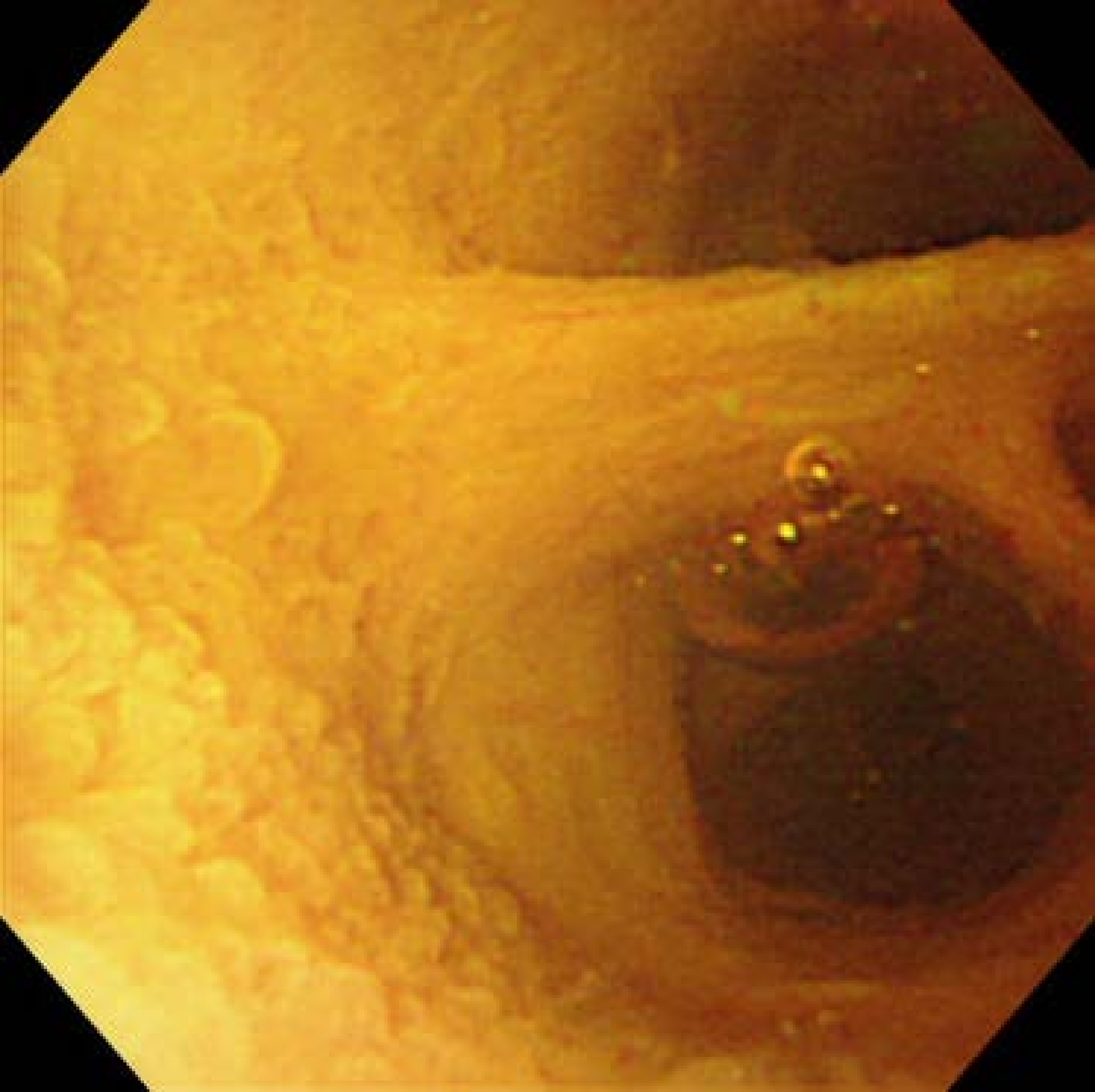
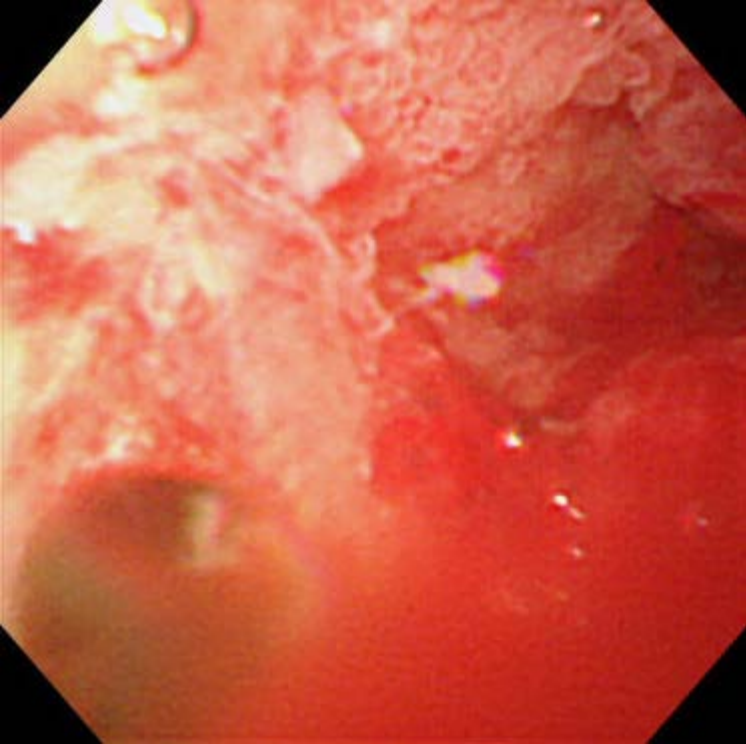
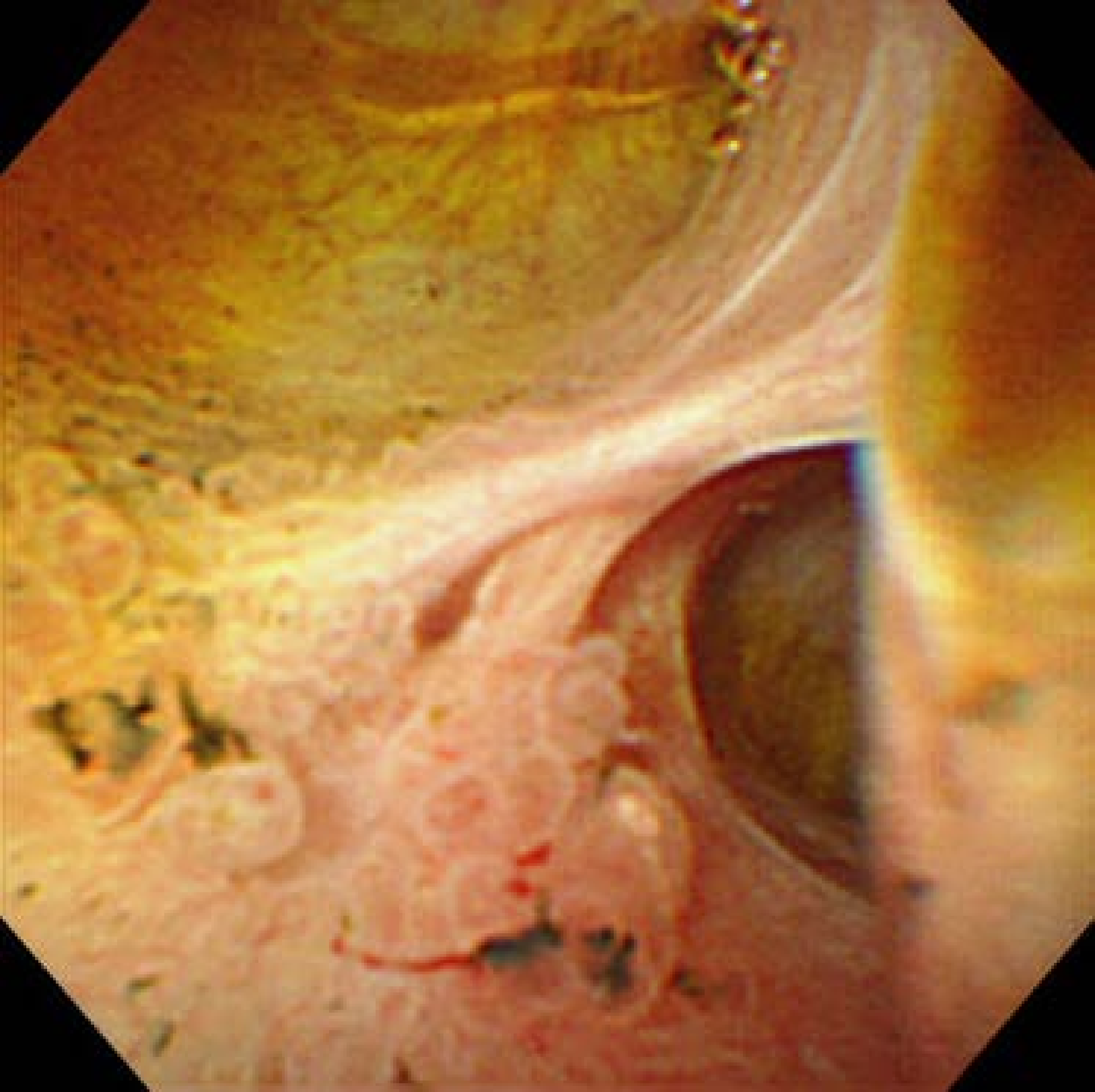
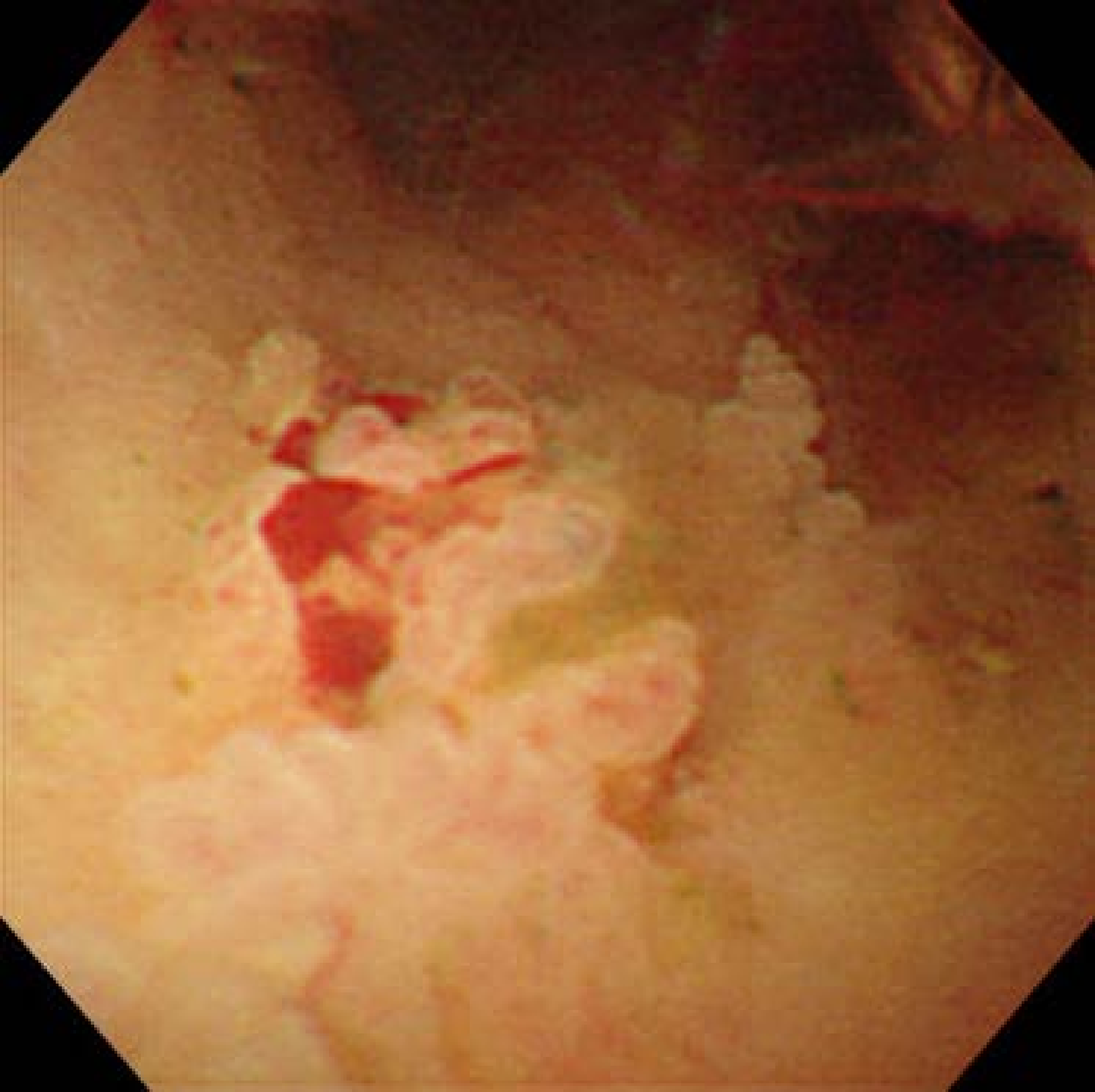
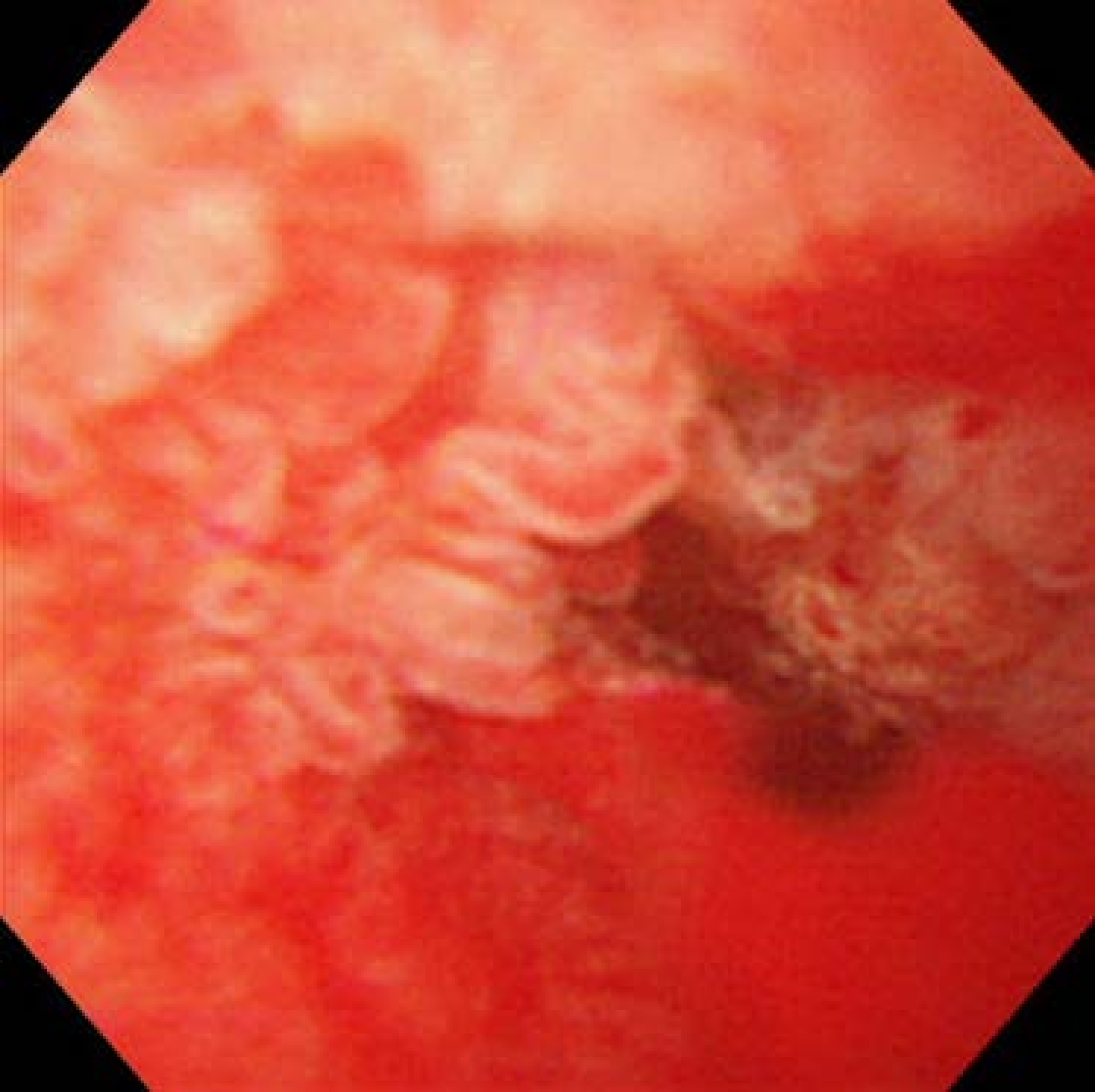
All patients	Accurate diagnosis	Overdiagnosis	Underdiagnosis
ERC alone	3/14 (21.4%)	0/14 (0%)	11/14 (78.6%)
ERC with POCS*	10/13 (76.9%)	0/13 (0%)	3/13 (23%)
ERC with POCS + biopsy*	13/13 (100%)	0/13 (0%)	0/13 (0%)

ERC, endoscopic retrograde cholangiography; POCS, peroral cholangioscopy.

* One patient was excluded because the scope could not be passed through the tumor site.

Table 4 Characteristics of localized type bile duct carcinoma with extensive intraepithelial tumor spread

Case	Age/Sex	Location	Gross type	Passage of scope*	Extent of ITS	POCS findings of ITS	Existence of flat ITS**
1	67/M	Br	nod	possible	dis	FEL	(+)
2	71/F	Bs	pap	possible	pro & dis	IFG	(-)
3	72/M	Bs	pap	possible	pro	FEL	(-)
4	68/M	Bs	pap	possible	pro & dis	IFG	(-)
5	75/M	Bm	pap	possible	dis	FEL	(-)
6	66/M	Bm	nod	possible	pro & dis	IFG	(-)
7	74/M	Bm	nod	possible	pro & dis	FEL	(-)
8	66/F	Bm	nod	possible	pro	IFG	(+)
9	76/F	Bm	nod	impossible	pro & dis	IFG	(+)
10	73/M	Bm	pap	possible	pro & dis	IFG	(-)
11	60/M	Bm	nod	possible	pro & dis	IFG	(-)
12	80/M	Bi	pap	possible	pro	FEL	(-)
13	62/M	Bi	pap	possible	pro	IFG	(+)
14	65/M	Bi	pap	possible	pro & dis	FEL	(-)

ITS, intraepithelial tumor spread; M, male; F, female; Br, right hepatic bile duct; Bs, superior extrahepatic bile duct; Bm, middle extrahepatic bile duct; Bi, inferior extrahepatic bile duct; nod, nodular type; pap, papillary type; dis, distal portion of main tumor; pro, proximal portion of main tumor; FEL, fish-egg-like pattern; IFG, irregular fine granular.

* Passage of the scope through the tumor site. ** Existence of flat mucosa similar to normal mucosa at the margin.