

Received: 2026.06.16
Accepted: 2026.09.09
Available online: 2026.09.21
Published: 2026.XX.XX

e-ISSN 1941-5923
© Am J Case Rep, 2026; 27: e954506
DOI: 10.12659/AJCR.954506

Duodenal Adenocarcinoma Recurrence Limited to the Choledochojejunostomy After Pancreaticoduodenectomy: A Case Suggesting Intraluminal Implantation With a Distinct Mucin Phenotypic Shift

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Yukihiro Shiota** 
BCDE 2 **Yoshimichi Ueda**
DE 1 **Azusa Kawasaki**
DE 1 **Akihiko Kida**
DE 1 **Yuji Hodo** 
DE 1 **Tokio Wakabayashi**

1 Department of Gastroenterology, Saiseikai Kanazawa Hospital, Kanazawa, Ishikawa, Japan
2 Department of Pathology, Keiju Medical Center, Nanao, Ishikawa, Japan

Corresponding Author: Yukihiro Shiota, Department of Gastroenterology, Saiseikai Kanazawa Hospital, Ni-13-6 Akatsuchimachi, Kanazawa, Ishikawa 920-0353, Japan, Phone: 81-76-266-1060; Fax: 81-76-266-1070, e-mail: shiota@r4.dion.ne.jp
Financial support: None declared
Conflict of interest: None declared

Patient: Male, 59-year-old
Final Diagnosis: Intraluminal implantation of duodenal adenocarcinoma at the choledochojejunostomy site
Symptoms: Fever
Clinical Procedure: Biliary stent placement • endoscopic and radiologic procedures • lithotripsy
Specialty: Gastroenterology and Hepatology
Objective: Unusual clinical course
Background: Intraluminal implantation of adenocarcinoma is well recognized, traditionally explained by the presence of exfoliated carcinoma cells (ECCs) and surgically created raw mucosal surfaces. However, whether phenotypic alterations of ECCs contribute to intraluminal implantation has not been systematically investigated.
Case Report: A 59-year-old man with duodenal adenocarcinoma developed recurrence at the choledochojejunostomy site 27 months after pancreaticoduodenectomy, despite the presence of 5 surgically created raw surfaces. Tumor cells in the recurrent lesion showed an intestinal immunophenotype (CK7-/CK20+) identical to that of the primary tumor, but a distinct phenotypic shift was observed. The recurrent tumor showed MUC5AC and MUC2, which were absent in the primary tumor. In contrast, MUC6 and CA19-9, both present in the primary lesion, were not detected in the recurrent lesion. Experimental studies in several epithelial malignancies suggest bile acids may modulate mucin expression, including MUC5AC, and activate tumor-associated signaling pathways. The findings in this case are compatible with intraluminal implantation and raise the possibility that bile acid-associated phenotypic modulation of ECCs, most notably reflected by the difference in MUC5AC expression between the primary and recurrent lesions, may have contributed to this unusual recurrence pattern. Radiotherapy resulted in temporary local control; however, the patient subsequently developed peritoneal carcinomatosis and died 54 months after pancreaticoduodenectomy.
Conclusions: Intraluminal implantation may proceed through sequential steps including attachment, engraftment, niche formation, and outgrowth. Although the extent of raw surfaces and the burden of ECCs are central to the attachment phase, we propose a novel hypothesis that phenotypic modulation of ECCs may also be an important determinant of engraftment and the later stages of intraluminal implantation.
Keywords: Anastomosis, Surgical • Bile Acids and Salts • Duodenal Neoplasms • Neoplasm Seeding • Pancreaticoduodenectomy
Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/954506>

 3426  1  7  24

Publisher's note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher



Introduction

In 1951, Morgan described implantation of rectal carcinoma into a suture line or fistulous mucosal defect as one form of local tumor spread [1]. A few years later, Beahrs and colleagues, based on 4 cases of colorectal carcinoma, proposed a model in which exfoliated carcinoma cells (ECCs) adhere to a raw mucosal surface and subsequently persist as recurrent tumors [2]. Subsequent cytological investigations confirmed that viable ECCs are frequently present in the bowel lumen during rectal or sigmoid cancer surgery, and that intraluminal washout can effectively reduce their burden [3,4]. In addition to ECC load and raw surface availability, it has been proposed that stapling-related mechanical factors contribute to implantation and anastomotic recurrence [5-7]. More recently, the potential role of the local microbiome in anastomotic recurrence has been discussed [8]. Although implantation has traditionally been explained primarily by mechanical and anatomical factors, little is currently known regarding whether dynamic phenotypic alterations of ECCs influence their capacity to survive and engraft at surgically injured sites. Bresalier and colleagues reported that mucin phenotypes can differ between primary colorectal carcinomas and their metastatic or recurrent lesions based on lectin histochemistry, an approach used at the time to characterize tumor-associated mucins [9]. Notably, among the cases examined, only a single anastomotic recurrence was included, in which the recurrent tumor exhibited a mucin phenotype distinct from that of the primary lesion. More recently, genetic analyses have provided evidence supporting clonal relatedness between primary tumors and anastomotic recurrences, indicating a shared origin, but the mechanisms of implantation remain unresolved [10,11].

This report describes a patient with duodenal adenocarcinoma who developed recurrence limited to the choledochojejunostomy after pancreaticoduodenectomy, despite the presence of 5 surgically created raw surfaces. The recurrent tumor exhibited an intestinal immunophenotype (CK7-/CK20+) consistent with that of the primary tumor but showed distinct mucin-related phenotypic differences. Given experimental evidence that bile acids can modulate epithelial phenotypes of carcinoma cells, including mucin expression [12], this unusual recurrence pattern raises the hypothesis that, in addition to raw surface availability and ECC burden, bile exposure and associated phenotypic modulation of ECCs may influence intraluminal implantation.

Case Report

An overview of the patient's clinical course is provided in **Table 1**. A 59-year-old man had been followed intermittently at another hospital for a duodenal ulcer. Repeat biopsy had been

recommended because of persistent endoscopic abnormalities, but follow-up was interrupted and subsequent biopsy was declined until he returned with progressive symptoms. An esophagogastroduodenoscopy performed approximately 2 months before surgery showed an ulcerative lesion in the bulb of the duodenum (**Figure 1A**), and biopsy confirmed adenocarcinoma.

Serological studies showed a normal carcinoembryonic antigen (CEA; 1.6 ng/mL, range < 5.0 ng/mL), and normal carbohydrate antigen 19-9 (CA19-9; 9.7 U/mL, range < 37 U/mL). Contrast-enhanced, cross-sectional computed tomography (CT) demonstrated wall thickening of the duodenal bulb (**Figure 1B**), but it showed no findings suggestive of metastatic disease. He subsequently underwent pancreaticoduodenectomy with modified Child reconstruction. An additional side-to-side Braun anastomosis was also performed (**Figure 1C**). The resected specimen showed a type 2 circumferential tumor measuring 40 × 35 mm, histologically classified as moderately differentiated adenocarcinoma (tub2 > muc > tub1), invading the pancreas (pT4 according to the UICC TNM Classification, 8th edition), with no lymphatic invasion (ly0), minimal venous invasion (v1), no perineural invasion (pn0), and no nodal involvement (pN0, 0/18). The proximal, distal, and radial resection margins were negative (**Figure 1D-1G**). The patient did not receive postoperative adjuvant systemic therapy.

The patient's postoperative course remained uneventful for almost 2 years. Approximately 27 months after surgery, the patient developed the first episode of cholangitis, prompting repeated endoscopic retrograde cholangiography (ERC)-related interventions thereafter. At the time of the first cholangitis episode, magnetic resonance cholangiopancreatography (MRCP) demonstrated intrahepatic bile duct dilatation consistent with a choledochojejunal anastomotic stricture, along with findings compatible with choledocholithiasis (**Figure 2A, 2B**). Laboratory test results showed a total bilirubin level of 1.37 mg/dL, aspartate aminotransferase of 133 U/L, alanine aminotransferase of 123 U/L, alkaline phosphatase of 1785 U/L (JSCC method; reference range, 115-359 U/L), and gamma-glutamyl transferase of 880 U/L, while CEA (0.6 ng/mL) and CA19-9 (12.1 U/mL) were within the normal ranges. ERC was therefore performed for therapeutic decompression and stone extraction. During this procedure, a subtle papillary mucosal irregularity was observed at the anastomosis (**Figure 2C, 2D**). The same site was subsequently histologically confirmed to harbor adenocarcinoma 10 months later, as described below, and the mucosal irregularity observed at the initial ERC was retrospectively considered an early manifestation of recurrence. However, at that time, this finding was interpreted as a reactive change associated with anastomotic stenosis, cholangitis, and obstructive cholestasis, and endoscopic treatment was therefore selected without biopsy. Interventions during this period consisted of balloon dilation, lithotripsy, stone extraction, and placement/

Table 1. Clinical timeline and corresponding figures.

Time after PD	Clinical event	Key findings	Intervention / outcome	Figure
0 months	Pancreaticoduodenectomy	Duodenal adenocarcinoma with pancreatic invasion; R0 resection; pN0 (0/18)	Pancreaticoduodenectomy with modified Child reconstruction with Braun anastomosis	Figure 1
27 months	First episode of cholangitis; first ERC	Choledochojejunostomy stricture with choledocholithiasis; edematous mucosa and irregular vascular patterns retrospectively suggestive of early tumor involvement; CEA and CA19-9 within normal ranges	Balloon dilation, lithotripsy, stone extraction, and ENBD	Figure 2A-2K
27 months + 6 days	Second ERC	Ulceration at the choledochojejunostomy after ENBD removal	Plastic stent placement because of persistent severe anastomotic stenosis	Figure 2L-2O
30 months	Third ERC	Persistent anastomotic stenosis and residual choledocholithiasis	Repeat balloon dilation, stone extraction, and FCSEMS placement	Figure 3
35 months	Fourth ERC	Irregular, granulation-like mucosal elevations at the choledochojejunostomy; stones within and proximal to the FCSEMS	FCSEMS removal and stone extraction	Figure 4
37 months	Radiological evaluation	Soft-tissue-density mass in the hepatic hilum with FDG uptake in both the hilar lesion and the choledochojejunostomy	Recurrence suspected radiologically	Figure 5
37 months	Fifth ERC with biopsy	Papillary protruding lesion at the choledochojejunostomy; biopsy confirmed adenocarcinoma	FCSEMS placement followed by radiotherapy (50 Gy/25 fractions)	Figure 6A, 6B
44 months	Sixth ERC for cholangitis after radiotherapy	Marked reduction in tumor size after radiotherapy; extensive biliary stones	FCSEMS replacement after biliary lavage and stone extraction	Figure 6C, 6D
54 months	Disease progression	Peritoneal carcinomatosis after temporary local control	Best supportive care; patient died	

Abbreviations: CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CT, computed tomography; ENBD, endoscopic nasobiliary drainage; ERC, endoscopic retrograde cholangiography; FCSEMS, fully covered self-expandable metallic stent; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PD, pancreaticoduodenectomy.

removal of plastic and self-expandable metallic stents, which temporarily improved biliary obstruction (Figures 2-4). In total, 6 ERC-related sessions were performed during the postoperative course; histological confirmation of adenocarcinoma was obtained for the first time at the fifth session.

At 37 months after the surgery, CT and MRCP showed a soft tissue density around the common hepatic artery (Figure 5A-5E). A subsequent ERC showed progression of the papillary lesion (Figure 6A, 6B), and targeted biopsy finally confirmed adenocarcinoma (Figure 7E, 7I, 7K). Positron emission tomography/computed tomography demonstrated fluorodeoxyglucose uptake at the choledochojejunostomy and in the soft tissue mass

around the hepatic artery (Figure 5F, 5G). Radiotherapy (50 Gy in 25 fractions) provided temporary disease stabilization, and the tumor decreased in size (Figure 6D); however, peritoneal carcinomatosis became evident several months later. The patient ultimately transitioned to best supportive care and died 54 months after his initial pancreaticoduodenectomy.

At the time of diagnosis of the recurrent lesion, a metachronous second primary tumor was also considered in the pathological differential diagnosis. The primary and recurrent lesions showed overlapping histological features. Immunohistochemical analyses performed at that time showed that the recurrent tumor exhibited the same intestinal immunophenotype (CK7-/CK20+)

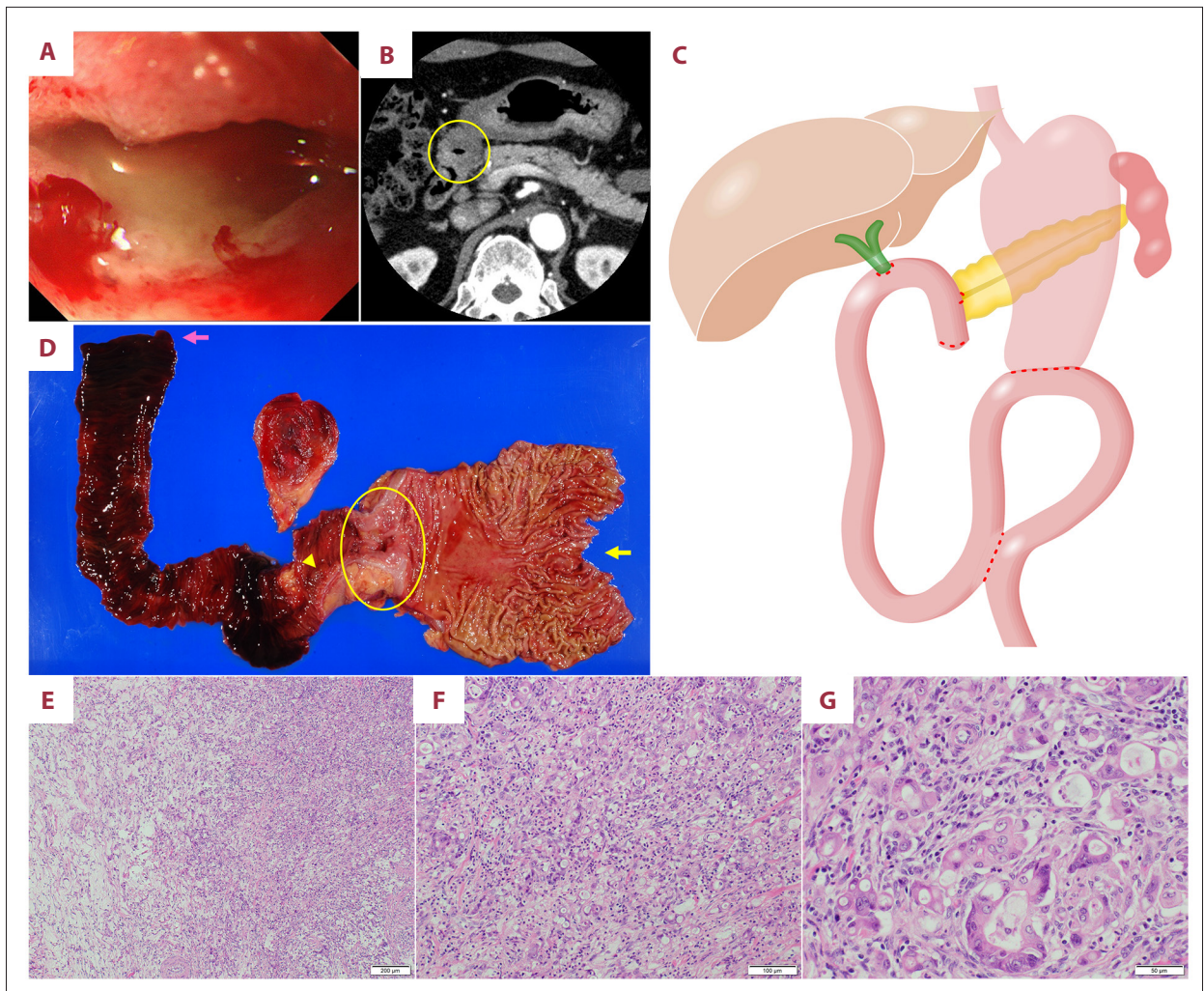


Figure 1. Diagnostic imaging, surgical findings, reconstruction schema, and histopathological features of the primary duodenal adenocarcinoma. (A) Endoscopic image of the duodenal bulb at diagnosis showing irregular mucosa with ulceration and slight bleeding, consistent with mucosal friability. (B) Contrast-enhanced computed tomography (arterial phase) demonstrating focal wall thickening of the duodenal bulb corresponding to the tumor (yellow circle). (C) Schematic illustration of modified Child reconstruction with an additional Braun anastomosis following pancreaticoduodenectomy. Five raw surfaces are indicated by red dotted lines: the jejunal stump, end-to-side pancreaticojejunostomy, end-to-side choledochojejunostomy, side-to-side Braun anastomosis, and end-to-side gastrojejunostomy. (D) Gross photograph of the surgical specimen obtained at pancreaticoduodenectomy. The primary duodenal adenocarcinoma is indicated by the yellow circle. The yellow arrow denotes the distal gastric transection margin, and the pink arrow indicates the distal jejunal transection margin. The opposite ends of these transected segments were subsequently used for reconstruction, forming the gastrojejunostomy and the blind end of the jejunal limb in Child reconstruction. The yellow arrowhead marks the major duodenal papilla. (E-G) Histopathological findings of the resected specimen. Low-power view showing invasive tumor growth (E), intermediate magnification demonstrating architectural atypia of glandular structures (F), and high-power view showing marked cellular atypia with mucin production (G). The tumor was diagnosed as predominantly moderately differentiated tubular adenocarcinoma with mucinous and well-differentiated components (tub2 > muc > tub1). White scale bars are shown in the lower right corner of panels E-G: 200 µm in E, 100 µm in F, and 50 µm in G.

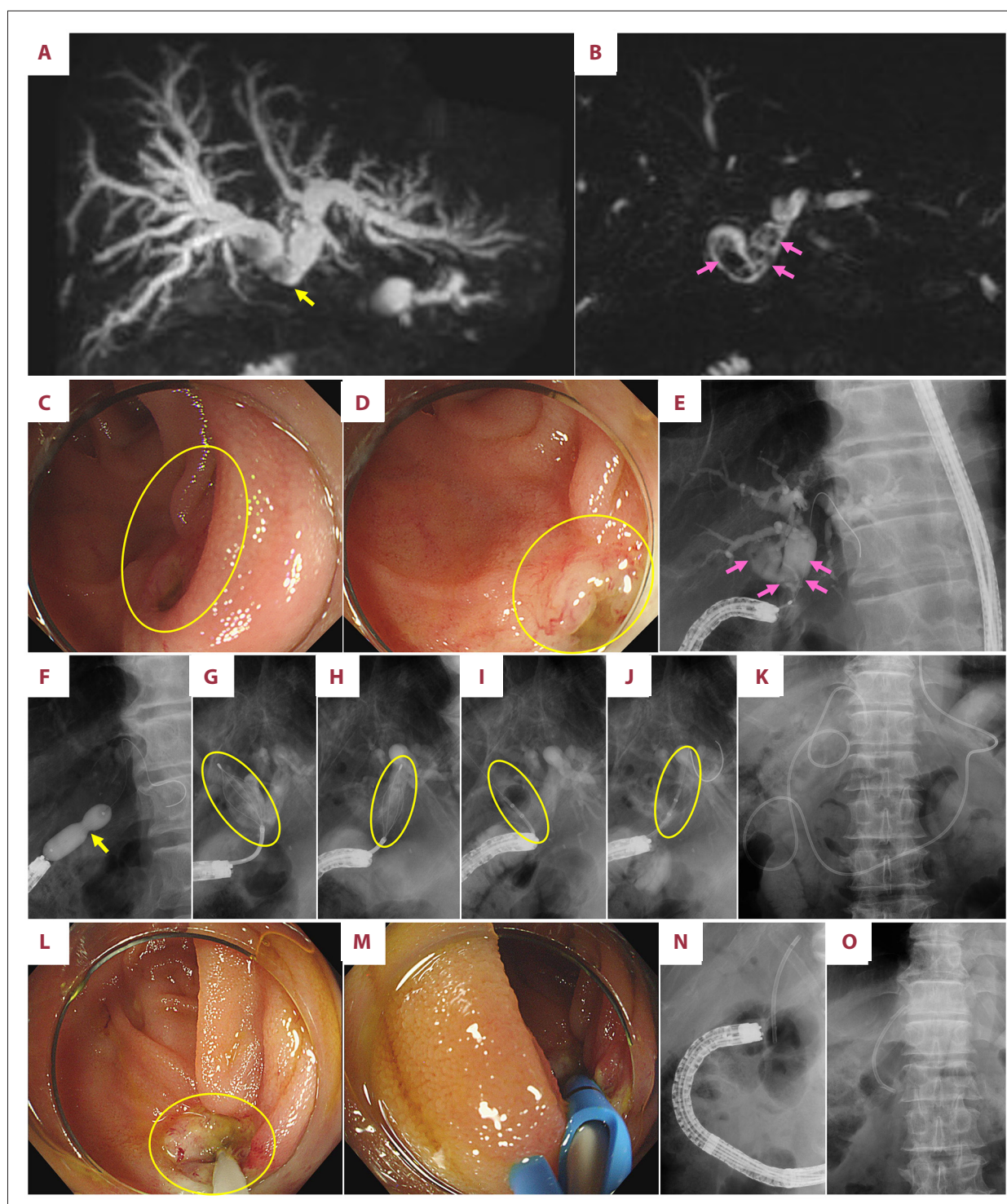


Figure 2. Imaging findings at the onset and management of the first episode of cholangitis 27 months after surgery. (A) Three-dimensional magnetic resonance cholangiography (MRC) demonstrating upstream bile duct dilatation consistent with stenosis at the choledochojejunal anastomotic site (yellow arrow). (B) Cross-sectional MRC image showing extensive filling of calculi from the hepatic duct immediately proximal to the anastomosis extending into the bilateral intrahepatic bile ducts (pink arrows). (C, D) Endoscopic images obtained at the first identification of the choledochojejunal anastomotic site. Panel C shows a distant view and panel D a close-up view. Although a distal attachment cap was used, frontal visualization of the entire anastomosis is difficult because of the reconstructed intestinal anatomy. The anastomotic margin is slightly elevated

(yellow circle in **C**) and appears smooth on distant view. On close inspection, edematous mucosa with irregular vascular patterns is observed (yellow circle in **D**). (**E**) Endoscopic retrograde cholangiography (ERC) demonstrating radiolucent filling defects within the dilated bilateral hepatic ducts (pink arrows). (**F-K**) ERC-related therapeutic procedures. Balloon dilatation of the choledochojejunal anastomotic site is shown in panel **F** (yellow arrow). Initial dilatation is attempted using a 13-15-mm balloon (KANEKA Biliary Balloon Dilatation Catheter) up to 4 atm (14 mm); however, expansion of the anastomotic stenosis is insufficient, while marked dilatation of the bile duct occurs. This raises concern about bile duct injury due to stone entrapment between the balloon and the bile duct wall. Therefore, stepwise and gradual dilatation is performed using a 10-12-mm balloon, with 3 dilatations up to a maximum pressure of 7 atm (12 mm). A residual notch remains, with a diameter of approximately 6 mm (yellow arrow). Subsequent stone extraction procedures include mechanical lithotripsy using a basket catheter in the right hepatic duct (**G**) and left hepatic duct (**H**), followed by balloon extraction from the right (**I**) and left (**J**) hepatic ducts (yellow circles). An endoscopic nasobiliary drainage (ENBD) tube is then placed (**K**), and daily biliary lavage performed to facilitate elimination of biliary sludge. (**L-O**) Findings at the second ERC session performed 6 days later for placement of a plastic stent (PS), since severe anastomotic stenosis without bile leakage on ENBD cholangiography suggests a high risk of recurrent cholangitis after simple ENBD removal. Panel **L** shows the endoscopic appearance after ENBD removal, with ulceration at the anastomotic site (yellow circle). Panel **M** shows the endoscopic view during PS placement. Panels **N** and **O** show fluoroscopic images during PS deployment and after endoscope withdrawal, respectively.

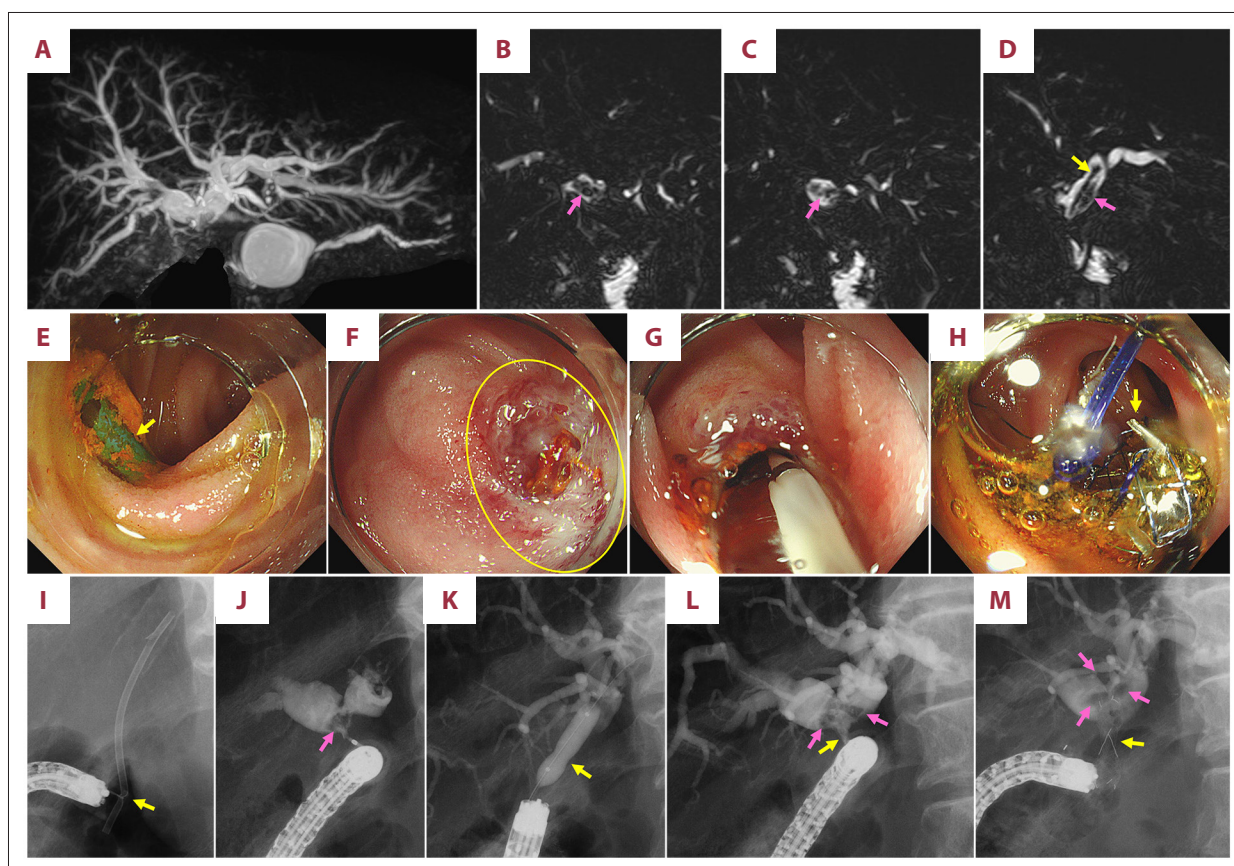


Figure 3. Imaging findings of planned endoscopic management with repeat balloon dilatation and covered self-expandable metallic stent placement for anastomotic stenosis. (**A**) Three-dimensional magnetic resonance cholangiography (MRC) performed immediately before the planned endoscopic retrograde cholangiography (ERC) at 30 months after surgery, demonstrating persistent dilatation of the bile ducts. (**B-D**) Cross-sectional MRC images showing shadow defects compatible with calculi in the right hepatic duct (**B**) and in the hepatic duct immediately proximal to the anastomosis extending into the right hepatic duct (**C**) (pink arrows). In the left hepatic duct (**D**), pink arrows indicate calculi, whereas a yellow arrow indicates the shadow of the indwelling plastic stent (PS). (**E-H**) Endoscopic images obtained during ERC-related procedures. The indwelling PS is identified (**E**, yellow arrow) and subsequently removed. After stent removal, ulcer formation is observed at the choledochojejunal anastomotic site (**F**, yellow circle). Balloon dilatation of the anastomotic stenosis is then performed using a REN EPBD balloon catheter (8 mm, up to 7 atm) with gradual pressure escalation, maintaining dilatation at 8 mm and 7 atm for 2 minutes (**G**). A fully-covered, self-expandable, metallic stent (FCSEMS) is subsequently placed across the anastomotic site to achieve sustained dilatation (**H**, yellow arrow). (**I-M**) Fluoroscopic images during ERC-related procedures. Panel **I**

shows the PS being grasped with a snare for removal (yellow arrow). After complete removal of the PS, cholangiography is performed (J), showing radiolucent filling defects consistent with residual calculi (pink arrow). Following repeat balloon dilatation (K), a slight residual notch remains at the anastomotic stenosis (yellow arrow). On repeat cholangiography (L), a yellow arrow indicates persistent narrowing at the anastomotic site, whereas pink arrows indicate residual calculi. A FCSEMS is then deployed across the stenotic segment (M), where the yellow arrow indicates the deployed stent, and pink arrows show residual calculi.

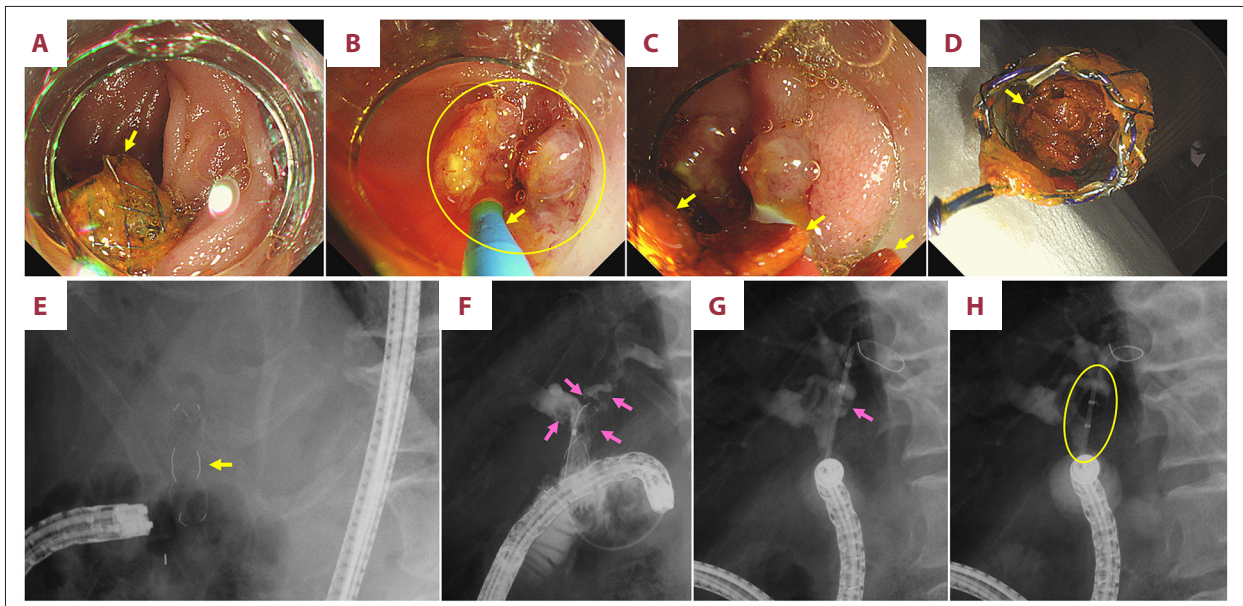


Figure 4. Endoscopic and fluoroscopic findings during the fourth endoscopic retrograde cholangiography (ERC) performed for planned removal of a fully-covered, self-expandable, metallic stent (FCSEMS). Considering the potential risks associated with long-term indwelling of a FCSEMS, a planned fourth ERC was performed 5 months after FCSEMS placement (35 months after surgery) with the intention of stent removal. (A-D) Endoscopic images. The previously placed FCSEMS is identified visually (A, yellow arrow) and subsequently removed. After FCSEMS removal, the choledochojejunal anastomotic site shows irregular, granulation-like mucosal elevations (B, yellow circle). These findings were not interpreted as local tumor recurrence at the time of examination. A contrast cannula inserted into the anastomosis is indicated by a yellow arrow. During balloon stone extraction, calculi of approximately a few millimeters in size, as estimated visually, are observed to be expelled from the anastomosis (C, yellow arrows). The retrieved FCSEMS is found to be filled with biliary calculi, indicating near-occlusion of the stent lumen (D, yellow arrows). (E-H) Fluoroscopic images. The FCSEMS is visualized fluoroscopically (E, yellow arrow), and contrast injection through a cannula positioned within the stent demonstrates radiolucent filling defects consistent with calculi in the bilateral hepatic ducts (F, pink arrows). During balloon stone extraction, small radiolucent filling defects are noted in the left hepatic duct (G, pink arrow). Follow-up cholangiography after completion of balloon extraction confirms the absence of residual calculi (H).

as the primary lesion (Figure 7B, 7C, 7F, 7G). Both lesions also showed absence of TP53 overexpression, increased CEA expression with focal loss of polarity, and comparable diffuse Ki-67 labeling. Based on these overlapping histological and immunohistochemical findings, the recurrent lesion was interpreted as recurrence of the primary duodenal adenocarcinoma rather than as a metachronous second primary tumor.

Subsequent immunohistochemical comparison of mucin-related protein expression showed a distinct phenotypic shift between the primary and recurrent lesions: MUC5AC expression, which was absent in the primary tumor, was detected in the recurrent carcinoma cells (Figure 7D, 7H-7L), and MUC2 expression was detected only in the recurrent tumor

(Figure 7M, 7S), whereas MUC6 and CA19-9, which had been present in the primary tumor, were not detected in the recurrent lesion (Figure 7N-7P, 7T, 7U). In contrast, MUC4 and MUC1 were consistently negative in both the primary and recurrent tumors (Figure 7Q, 7R, 7V, 7W). Immunohistochemical analyses were performed on 4-µm formalin-fixed, paraffin-embedded tissue sections using antibodies against CK7 (clone OV-TL, 1: 400; Dako), CK20 (clone Ks20.8, 1: 200; Dako), p53 (clone DO-7, prediluted; Roche), CEA (clone COL-1, 1: 2; Nichirei Biosciences), Ki-67 (clone MIB-1, 1: 50; Dako), MUC5AC (clone CLH2, prediluted; Leica), MUC2 (clone CCP58, prediluted; Leica), MUC6 (clone CLH5, prediluted; Leica), CA19-9 (clone C241:5:1:4, 1: 200; Leica), MUC4 (clone 8G7, 1: 200; Santa Cruz Biotechnology), and MUC1 (clone Ma695, 1: 200; Novocastra). Antigen retrieval

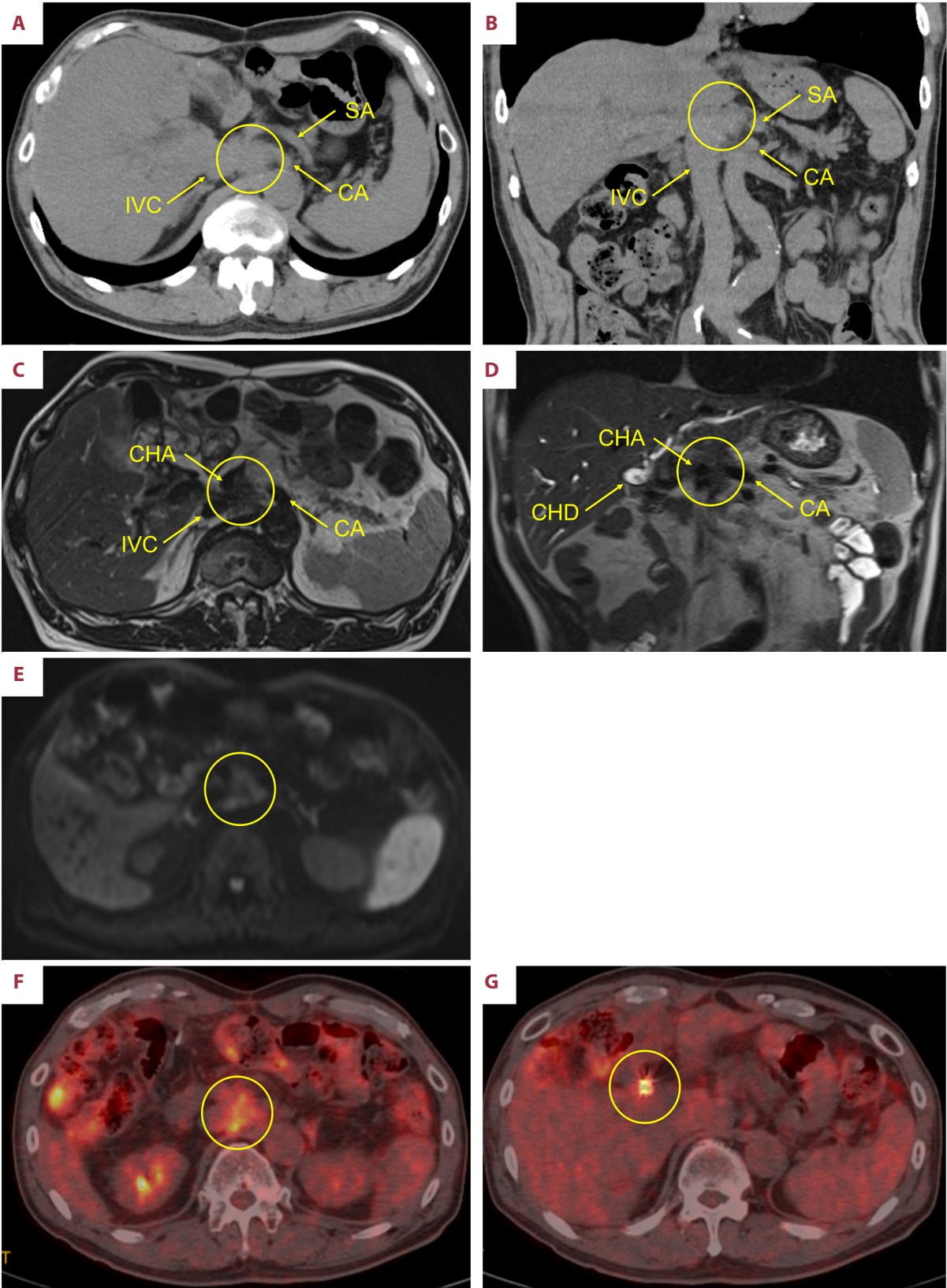


Figure 5. Imaging findings at the time a periarterial mass was identified 10 months after the diagnosis of anastomotic stenosis (37 months after surgery). (A, B) Non-contrast-enhanced computed tomography images in the axial (A) and coronal (B) planes demonstrating a soft-tissue-density mass in the hepatic hilum, adjacent to the celiac artery (CA), splenic artery (SA), and inferior vena cava (IVC). The lesion is indicated by a yellow circle. (C, D) Magnetic resonance imaging findings on T2-weighted images in the axial (C) and coronal (D) planes showing a mass lesion around the celiac artery and common hepatic artery (CHA), corresponding to the lesion identified on CT (yellow circles). Common hepatic duct (CHD) is also shown. (E) Diffusion-weighted magnetic resonance imaging demonstrating high signal intensity in the same hilar lesion (yellow circle). (F, G) Fluorodeoxyglucose positron emission tomography (FDG-PET) images obtained 1 month after histological confirmation of carcinoma by biopsy performed during the fifth ERC. Increased FDG uptake is observed in the hilar mass (F) and at the choledochojejunal anastomotic site (G), both indicated by yellow circles.

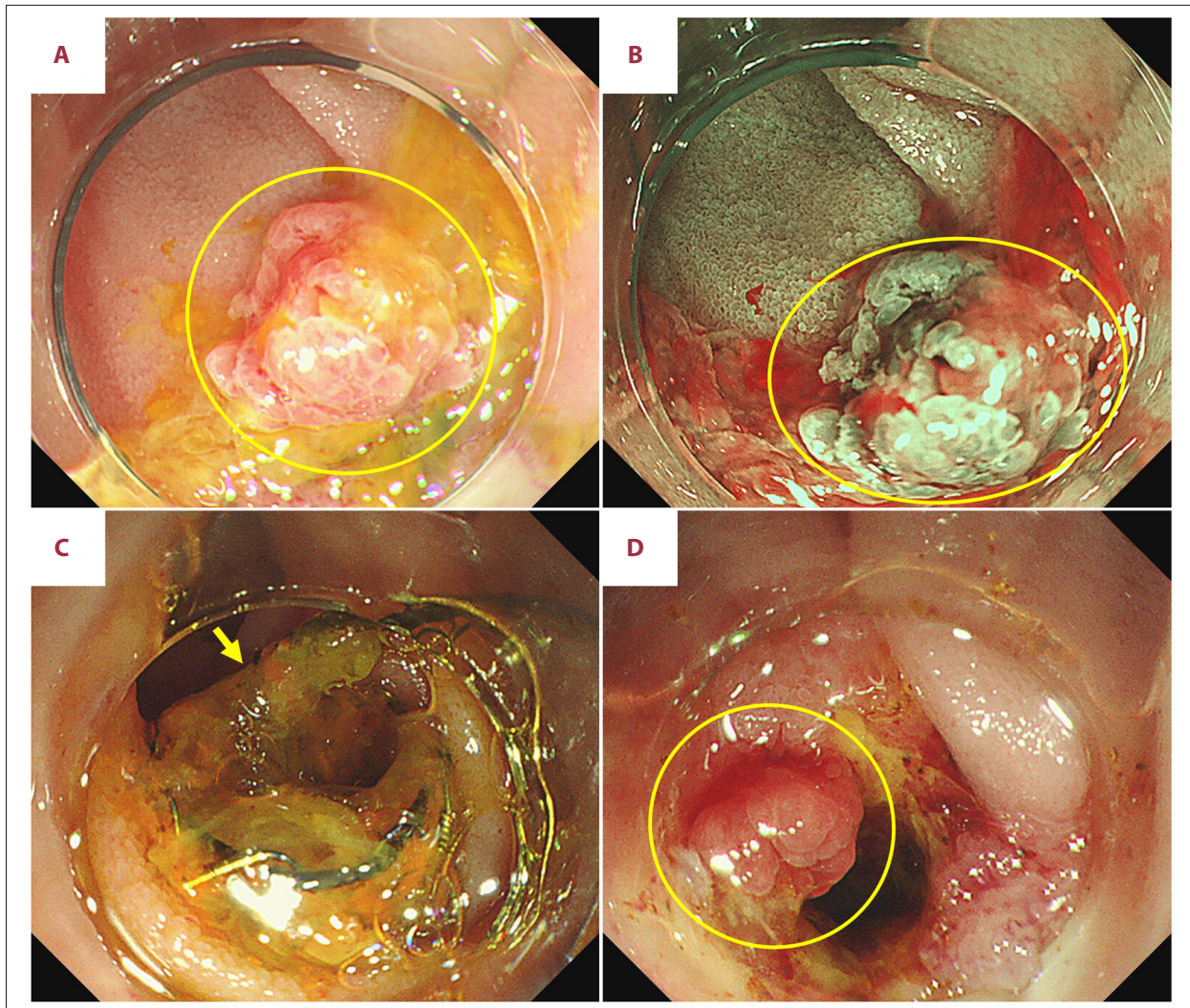


Figure 6. Endoscopic findings during the fifth and sixth endoscopic retrograde cholangiography (ERC) procedures performed for cholangitis after identification of the periarterial mass. (A, B) Endoscopic images obtained during the fifth ERC. White-light imaging (A) and narrow-band imaging (NBI) (B) show papillary protruding lesions at the choledochojejunal anastomotic site (yellow circles). At this time, recurrence of carcinoma at the anastomosis is recognized for the first time, and biopsy specimens are obtained. Subsequent balloon stone extraction is performed, followed by placement of a fully-covered, self-expandable, metallic stent (FCSEMS). (C, D) Endoscopic images obtained during the sixth ERC performed after radiotherapy. The indwelling FCSEMS is identified visually (C, yellow arrow), and the tumor at the anastomotic site is observed immediately after stent removal (D, yellow circle). The tumor shows a reduced size following radiotherapy. After FCSEMS removal, extensive biliary lavage results in the evacuation of a large amount of biliary stones. A FCSEMS is subsequently re-inserted to complete the procedure.

was performed using Protease 1 (Roche) for cytokeratin (CK)7 and CK20 and DISCOVERY CC1 (Roche) at 95 °C for the remaining antibodies. Immunostaining was performed on an automated staining platform (VENTANA BenchMark ULTRA; Roche), followed by hematoxylin counterstaining. Appropriate positive controls were included on separate slides in the same immunohistochemical staining runs and showed the expected immunoreactivity. Immunoreactivity for CK7, CK20, MUC5AC, MUC2, MUC6, CA19-9, MUC4, and MUC1 was evaluated according to the proportion of tumor cells showing distinct diaminobenzidine (DAB) staining and classified as positive (> 50% of tumor cells), partial (< 50% of tumor cells), or negative (no distinct DAB staining in tumor cells).

Discussion

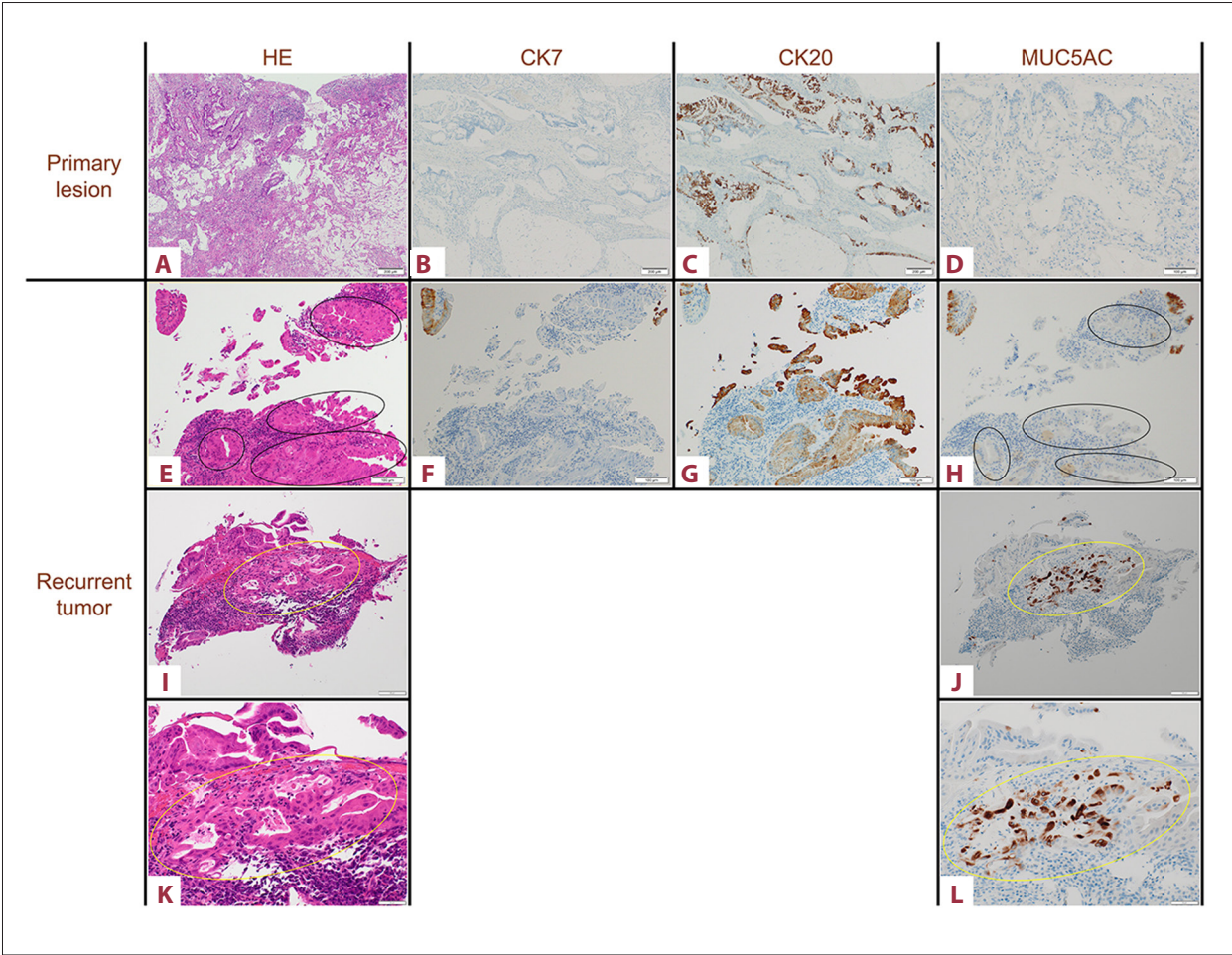
Duodenal adenocarcinoma is a rare malignancy, and recurrence after curative pancreaticoduodenectomy has been reported [13,14]. However, our PubMed literature search identified no previous reports describing a similar pattern of recurrence

limited to the choledochojejunostomy after pancreaticoduodenectomy for duodenal adenocarcinoma.

In the present case, although a metachronous second primary tumor was considered in the pathological differential diagnosis, the overlapping histological and immunohistochemical features of the primary and recurrent lesions supported recurrence of the primary duodenal adenocarcinoma rather than a metachronous second primary tumor.

Pathological evaluation of the pancreaticoduodenectomy specimen showed negative surgical margins. Taken together with the anatomy of the modified Child reconstruction, this finding renders residual disease at the choledochojejunostomy transection margin or along the surgical dissection plane unlikely. These findings prompted consideration of intraluminal implantation as a mechanism for the recurrence.

An alternative route of ECC exposure should also be considered. Microscopic intraoperative contamination of the bile duct stump cannot be completely excluded. However, this appears less likely given the operative sequence: the jejunum distal to



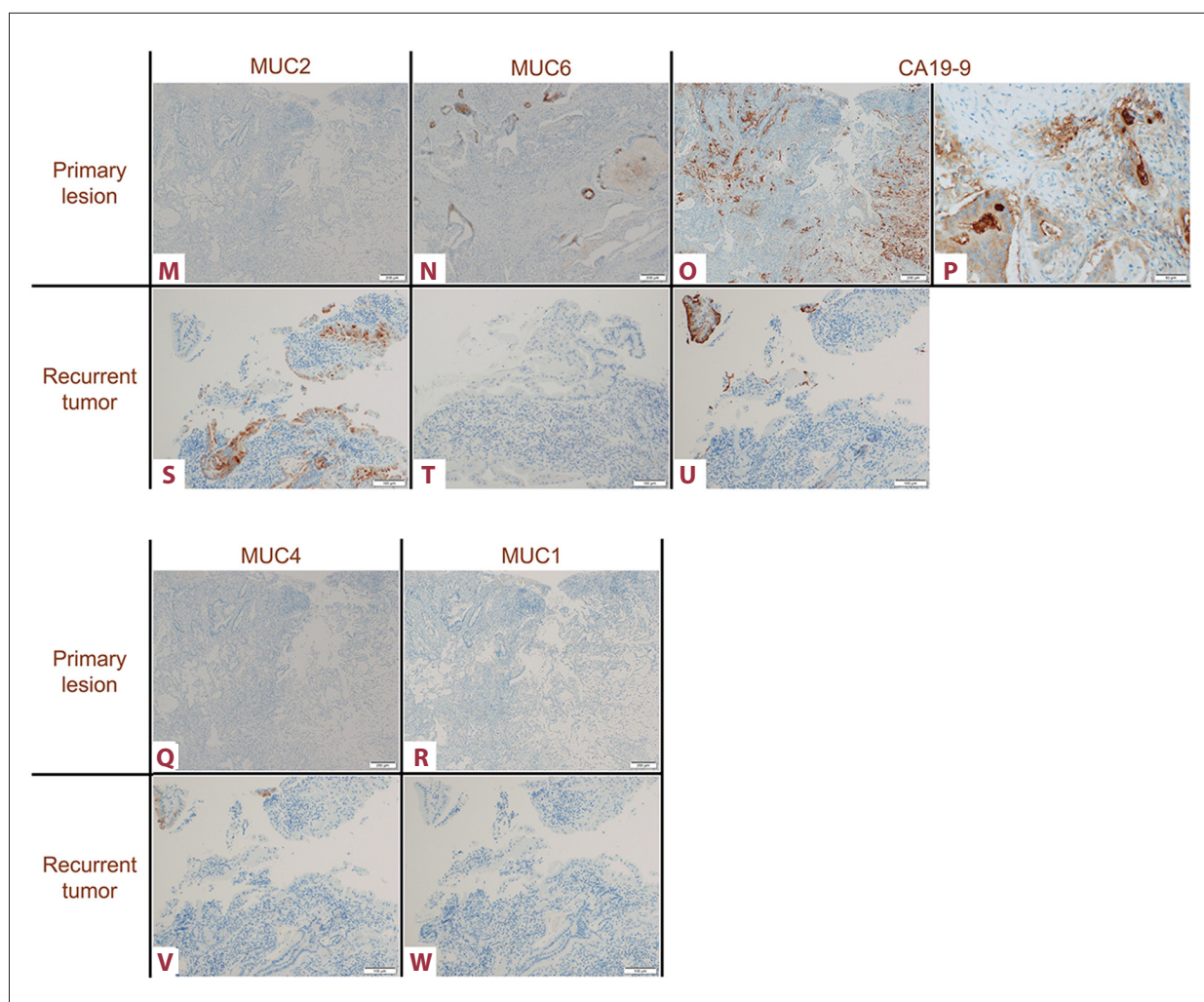


Figure 7. Histopathological and immunohistochemical comparisons between the primary tumor and the recurrent tumor at the choledochojejunostomy site. Hematoxylin and eosin (H&E) staining of the primary tumor (A) and the recurrent tumor (E, I, K) demonstrates comparable adenocarcinoma morphology. Immunohistochemical analyses show negative staining for CK7 (B, F) and positive staining for CK20 (C, G) in both the primary and recurrent tumors, demonstrating the same CK7-/CK20+ immunophenotype. In the primary tumor, MUC5AC and MUC2 are not detected (D, M). In contrast, MUC2 expression is observed in the recurrent tumor (S), whereas it is not detected in the primary tumor, and the recurrent tumor shows partial expression of MUC5AC. In the section corresponding to the H&E image of the recurrent tumor in panel E, the tumor areas are indicated by black circles; the corresponding areas in the MUC5AC-stained section (H) show inconspicuous staining that could not be clearly interpreted as positive. Because MUC5AC expression was not clearly demonstrable in this representative section, additional serial sections of the recurrent tumor biopsy were newly prepared for H&E and MUC5AC staining. Low-power H&E staining demonstrates morphologically identifiable carcinoma (I), and MUC5AC immunohistochemistry in the corresponding serial section demonstrates MUC5AC expression in the same tumor area (J). The corresponding tumor areas are indicated by yellow circles in panels I and J. Higher-magnification views of these areas are shown in panels K and L, respectively, with the corresponding tumor areas again indicated by yellow circles, confirming MUC5AC immunoreactivity in morphologically identifiable carcinoma. The primary tumor shows positive staining for MUC6 (N) and CA19-9 (O, P). Low-power examination of CA19-9 immunohistochemistry (O) demonstrates staining predominantly within extracellular mucin, whereas higher-power examination (P) confirms that CA19-9 staining is mainly associated with mucin pools with focal cytoplasmic positivity in a subset of tumor cells. In contrast, MUC6 and CA19-9 are not detected in the recurrent tumor (T, U). MUC4 and MUC1 are negative in both the primary and recurrent tumors (Q, R, V, W). White scale bars are shown in the lower right corner of each panel: 200 μ m in A-C, M-O, Q, and R; 100 μ m in D-J and S-W; and 50 μ m in K, L, and P.

the primary tumor and subsequently the stomach were transected and closed using linear staplers, thereby isolating the tumor-bearing gastrointestinal segment before transection of the common hepatic duct. Even if microscopic contamination occurred, it would represent an alternative route by which ECCs reached the choledochojejunostomy rather than an alternative to implantation itself. Such contamination could have increased local ECC exposure at this site; however, it would not by itself establish the biological processes underlying subsequent engraftment and tumor outgrowth.

Locoregional periductal recurrence with intraluminal extension was also considered as an alternative explanation. However, no radiological or endoscopic continuity was identified between the periarterial mass and the choledochojejunostomy lesion, and no intervening bile duct abnormality suggestive of continuous tumor extension was observed. Moreover, subtle endoscopic abnormalities retrospectively suggestive of tumor involvement were already present at the choledochojejunostomy at 27 months, before histological confirmation at 37 months, when the periarterial mass was also identified. The periarterial mass was clinically diagnosed and treated as a metastatic lymph node. Although its origin cannot be established histologically, the absence of lymphatic invasion (ly0), perineural invasion (pn0), and nodal metastasis (pN0, 0/18) in the original resection specimen, together with the earlier endoscopic abnormality at the choledochojejunostomy, raises the possibility that this mass represented nodal metastasis from the anastomotic recurrence rather than the source of direct periductal extension. Taken together, these findings support intraluminal implantation at the choledochojejunostomy as a mechanism for the recurrence in this case.

Most previous investigations of intraluminal implantation have focused on colorectal cancer. Since the introduction of the raw surface concept in the 1950s, implantation has been primarily framed as the interaction between raw surface availability and the burden of ECCs. Reconsidering the present case within this classical 2-factor model, however, shows an anatomical and biological discrepancy. In this postoperative configuration, the choledochojejunostomy represents a relatively distant raw surface from the original duodenal primary tumor compared with the gastric and jejunal transection lines and the pancreaticojejunostomy. The gastric transection line lies proximal to the primary tumor, requiring retrograde movement against peristalsis for exposure to shed ECCs; whereas, on the distal side, the jejunal transection line, pancreaticojejunostomy, and choledochojejunostomy are located progressively farther from the original tumor site. The Braun anastomosis lies even further downstream. If ECC viability and density decrease with distance from the primary lesion, the choledochojejunostomy would not be expected to constitute a favorable raw surface. A similar contradiction appears when considering the extent

of exposed surface area. The gastric transection line provides the largest raw surface, followed by the jejunal transection line and the Braun anastomosis, whereas the choledochojejunostomy offers only a limited raw surface in comparison. If implantation were governed solely by raw surface extent and ECC burden, recurrence would be anticipated at one of the more proximal and broader surfaces. The fact that the recurrence occurred exclusively at the choledochojejunostomy represents a marked deviation from this expectation and raises the possibility that an additional site-specific factor contributed to this unusual recurrence pattern. Although all 5 surgically created raw surfaces may be exposed to bile, the choledochojejunostomy is the site of direct and continuous bile inflow and therefore has a distinct pattern of bile exposure compared with the other raw surfaces. We considered this distinctive bile exposure as a potential site-specific factor.

Accumulating evidence in oncology suggests that bile acids contribute to angiogenesis, cancer cell proliferation and death, tumor invasion and metastasis, and inflammatory and immunological regulation [15]. Regarding bile acids and mucin phenotypes, experimental studies using pancreatic ductal adenocarcinoma cell lines have demonstrated that bile acid exposure induces overexpression of MUC4, which in turn accelerates carcinogenic processes through intracellular signaling pathways [16]. High MUC4 expression is also associated with a poor prognosis and increased invasiveness across multiple malignancies [17]. In the present case, however, MUC4 expression was absent in both the primary tumor and the recurrent lesion. Another mucin implicated in bile acid-related carcinogenesis is MUC5AC. Duodenal reflux of bile acids induces MUC5AC expression in Barrett esophagus via the PI3K/AKT/AP-1 pathway [12], and experimental colorectal cancer models have demonstrated that the secreted mucin MUC5AC can promote tumor behavior through interaction with the transmembrane protein CD44 [18]. In the present case, MUC5AC expression was absent in the primary tumor but was detected in the recurrent lesion at the choledochojejunostomy, which has a distinct pattern of bile exposure compared with the other raw surfaces and was the only raw surface where recurrence occurred. Importantly, *in vitro* studies have shown that MUC5AC expression can be induced rapidly after exposure to bile salts [19], a time window that is biologically compatible with the early stages of cellular attachment and engraftment during implantation. The experimental studies cited above involved malignancies or epithelial conditions other than duodenal adenocarcinoma, and comparable evidence for bile acid-associated mucin phenotypic modulation has not been established in duodenal adenocarcinoma. The present observation likewise does not directly establish that bile exposure induced MUC5AC expression or caused engraftment. Nevertheless, the site-specific recurrence pattern and the observed difference in MUC5AC expression between the primary and recurrent lesions raise the hypothesis that

bile acid–associated phenotypic modulation may have facilitated implantation of ECCs. In the present case, immunohistochemical analyses also demonstrated MUC2 expression in the recurrent lesion, whereas it was absent in the primary tumor. Previous experimental studies have shown that bile acid exposure can act as a chronic cellular stressor, leading to suppression of Notch signaling and induction of epigenetic alterations, thereby promoting CDX2-dependent intestinal differentiation with associated MUC2 expression in models of Barrett esophagus and intestinal metaplasia [20]. Thus, the detection of MUC2 expression in the recurrent lesion, but not in the primary tumor, may be compatible with activation of an intestinal differentiation program under sustained bile acid–associated cellular stress, although whether this mechanism contributed to the observed difference in MUC2 expression and its functional significance in the present case remain speculative.

Metastasis has been most extensively studied in the context of hematogenous dissemination, in which a multistep cascade, classically described as invasion, intravasation, survival in the circulation, extravasation, and colonization, has been proposed to explain systemic tumor spread [21]. In contrast, the implantation hypothesis in the present case involves a biologically distinct process: luminal implantation of ECCs onto a surgically created raw surface, occurring entirely outside the vascular compartment. To conceptualize this process more appropriately, we propose a 4-step descriptive framework consisting of attachment, engraftment, niche formation, and outgrowth, adapted from principles of engraftment biology rather than from classical metastatic biology. Within this framework, the quantity of ECCs, the extent of the raw surface, and possible stapler-related tissue entrapment may influence the attachment phase. In contrast, subsequent steps, namely engraftment and niche formation, may be influenced by the local wound-healing milieu of the raw surface and by site-specific environmental factors such as bile exposure. This conceptualization is consistent with prior observations that wound-healing programs can recreate a permissive stromal environment characterized by epithelial plasticity, inflammatory signaling, and extracellular matrix remodeling, which carcinoma cells are known to exploit during tumor progression [22,23]. Moreover, epithelial-mesenchymal transition programs, originally activated during wound repair, have been shown to be re-activated and co-opted by carcinoma cells to facilitate survival and adaptation in new microenvironments [24]. In this context, the surgically created raw surface may be interpreted not merely as a passive site of physical attachment, but as an active wound-healing niche characterized by epithelial plasticity and stromal remodeling, thereby potentially providing a permissive environment for tumor cell engraftment.

In the present case, the observed mucin-related phenotypic shift, most notably the difference in MUC5AC expression

between the primary and recurrent lesions, together with the wound-healing raw surface at the choledochojejunostomy, raises the hypothesis that bile-associated phenotypic modulation may have contributed to engraftment and niche formation within the proposed 4-step framework. Although the present single-case observation does not directly establish that bile exposure caused engraftment or that implantation was the exclusive route of recurrence, the exclusive occurrence of recurrence at the choledochojejunostomy, a surgically created raw surface characterized by direct and continuous bile inflow, provides an anatomical and environmental context compatible with this hypothesis. Thus, rather than replacing the classical raw surface–based implantation theory, the present 4-step framework extends this concept by proposing local environmental modulation and tumor cell plasticity as potential factors influencing implantation beyond the initial attachment phase.

The observations in the present case may provide a basis for future mechanistic studies using molecular biological approaches to investigate the proposed relationship among bile exposure, phenotypic modulation, and intraluminal implantation.

Limitations

This study has several limitations. First, it is based on a single case, and the proposed mechanism should therefore be regarded as hypothesis-generating. Second, serial tissue sampling was not available, precluding determination of when the observed phenotypic changes, including the difference in MUC5AC expression between the primary and recurrent lesions, occurred during the course of recurrence. Consequently, the possibility that some of the observed phenotypic changes reflect natural clonal evolution during tumor progression cannot be completely excluded. Although the mucin-related phenotypic differences were observed between the primary and recurrent lesions, their relationship to bile exposure cannot be established from the present case. Third, no functional validation, such as *in vitro* bile acid exposure using patient-derived tumor cells, was performed. Fourth, repeated ERC-related mechanical interventions may also have modified the local wound-healing environment at the choledochojejunostomy. However, subtle endoscopic abnormalities retrospectively suggestive of early tumor involvement were already present at the initial ERC, indicating that tumor involvement at this site had likely already begun before these interventions were performed. Therefore, repeated instrumentation is unlikely to represent the primary mechanism underlying the recurrence, although its possible contribution to subsequent tumor expansion cannot be completely excluded. Finally, the proposed mechanism is supported primarily by experimental studies in the esophagus, pancreas, and colorectum rather than in duodenal adenocarcinoma or biliary epithelium.

Conclusions

The present case describes a recurrence of duodenal adenocarcinoma at the choledochojejunostomy after pancreaticoduodenectomy, a recurrence pattern consistent with intraluminal implantation. The recurrent lesion showed a distinct mucin-related phenotypic shift, raising the hypothesis that bile-associated phenotypic modulation of ECCs may represent a site-specific factor influencing intraluminal implantation. The proposed sequential framework of attachment, engraftment, niche formation, and outgrowth is an interpretive model in which raw surface availability and ECC burden may influence initial attachment, whereas bile-associated phenotypic modulation of ECCs is hypothesized to influence subsequent stages. This mechanistic interpretation remains hypothesis-generating, and alternative mechanisms of recurrence cannot be completely excluded. Further clinical observations and mechanistic studies are required to evaluate this hypothesis and the proposed framework.

Conflict of Interest

The authors declare that they have no conflict of interest.

Human/Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

References:

- Morgan CN. Cancer of the rectum: Lecture delivered at the Royal College of Surgeons of England. *Ann R Coll Surg Engl.* 1951;9:13-24
- Beahrs OH, Phillips JW, Dockerty MB. Implantation of tumor cells as a factor in recurrence of carcinoma of the rectosigmoid: Report of four cases with implantation at the dentate line. *Cancer.* 1955;8(4):831-38
- Sayfan J, Averbuch F, Koltun L, Benyamin N. Effect of rectal stump washout on the presence of free malignant cells in the rectum during anterior resection for rectal cancer. *Dis Colon Rectum.* 2000;43(12):1710-12
- Furuya S, Shiraishi K, Shimizu H, et al. Intraluminal washout in rectal and sigmoid colon cancer surgeries with double-stapling technique anastomosis: A single-institution prospective study. *Ann Gastroenterol Surg.* 2024;9(1):137-44
- Gertsch P, Baer HU, Kraft R, et al. Malignant cells are collected on circular staplers. *Dis Colon Rectum.* 1992;35(3):238-41
- Kluger Y, Galili Y, Yossipov J, et al. Model of implantation of tumor cells simulating recurrence in colonic anastomosis in mice. *Dis Colon Rectum.* 1998;41(12):1506-10
- Futami R, Shimanuki K, Sugiura A, et al. Recurrence of colonic cancer twice at the site of stapled colorectal anastomosis. *J Nippon Med Sch.* 2007;74(3):251-56
- Gaines S, Chao C, Hyman N, Alverdy JC. Gut microbiome influences on anastomotic leak and recurrence rates following colorectal cancer surgery. *Br J Surg.* 2018;105(2):e131-41
- Bresalier RS, Boland CR, Kim YS. Characteristics of colorectal carcinoma cells with high metastatic potential. *Gastroenterology.* 1984;87(1):115-22
- Costi R, Santi C, Bottarelli L, et al. Anastomotic recurrence of colon cancer: Genetic analysis challenges the widely held theories of cancerous cells' intraluminal implantation and metachronous carcinogenesis. *J Surg Oncol.* 2016;114(2):228-36
- Vakiani E, Shah RH, Berger MF, et al. Local recurrences at the anastomotic area are clonally related to the primary tumor in sporadic colorectal carcinoma. *Oncotarget.* 2017;8(26):42487-94
- Song S, Byrd JC, Guha S, et al. Induction of MUC5AC mucin by conjugated bile acids in the esophagus involves the PI3K/AKT/AP-1 pathway. *Cancer.* 2011;117(11):2386-97
- Nakagawa K, Sho M, Fujishiro M, et al. Clinical practice guidelines for duodenal cancer 2021. *J Gastroenterol.* 2022;57(11):927-41
- Onkendi EO, Boostrom SY, Sarr MG, et al. 15-Year Experience with surgical treatment of duodenal carcinoma: A comparison of peripapillary and extra-ampullary duodenal carcinomas. *J Gastrointest Surg.* 2012;16(4):682-91
- Fu J, Yu M, Xu W, Yu S. Research progress of bile acids in cancer. *Front Oncol.* 2022;11:778258
- Gál E, Veréb Z, Kemény L, et al. Bile accelerates carcinogenic processes in pancreatic ductal adenocarcinoma cells through the overexpression of MUC4. *Sci Rep.* 2020;10(1):22088
- Huang X, Wang X, Lu SM, et al. Clinicopathological and prognostic significance of MUC4 expression in cancers: Evidence from meta-analysis. *Int J Clin Exp Med.* 2015;8(7):10274-83
- Pothuraju R, Rachagani S, Krishn SR, et al. Molecular implications of MUC5AC-CD44 axis in colorectal cancer progression and chemoresistance. *Mol Cancer.* 2020;19(1):37

Informed Consent

Written informed consent for publication was obtained from the patient's family.

Acknowledgments

The authors would like to thank ALP Co., Ltd. (Kanazawa, Japan) for conducting the immunohistochemical studies. The authors received professional English-language editing support from a native English editor at FOLTE Co., Ltd. (Tokyo, Japan). All medical content, clinical interpretation, hypotheses, and conclusions were conceived and verified solely by the authors. The surgeons who performed the operative procedure were not involved in the study design, data acquisition, pathological analysis, interpretation of findings, or manuscript preparation. In accordance with the authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE), they were not included as co-authors. However, their clinical contribution to the patient's care is sincerely acknowledged.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

19. Ali MS, Parikh S, Pearson JP. MUC5AC upregulation by bile salts: An in vitro study. *Ann Otolaryngol Rhinol.* 2016;3(12):1154-56
20. Tamagawa Y, Ishimura N, Uno G, et al. Notch signaling pathway and Cdx2 expression in the development of Barrett's esophagus. *Lab Invest.* 2012;92(6):896-909
21. Lambert AW, Pattabiraman DR, Weinberg RA. Emerging biological principles of metastasis. *Cell.* 2017;168(4):670-91
22. Dvorak HF. Tumors: Wounds that do not heal. *N Engl J Med.* 1986;315(26):1650-59
23. Kalluri R, Weinberg RA. The basics of epithelial–mesenchymal transition. *J Clin Invest.* 2009;119(6):1420-28
24. Nieto MA, Huang RYJ, Jackson RA, Thiery JP. EMT: 2016. *Cell.* 2016;166(1):21-45