

## CASE REPORT

# Aggressive resection of metachronous triple biliary cancer

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**Abstract :** Radical resection of recurrent cholangiocellular carcinoma (CCC) is rare. To date, only two patients have been reported to undergo major hepatectomy twice after pancreatoduodenectomy (PD) for metachronous CCC. This report describes a patient who underwent three metachronous radical resections of CCC with curative intent, consisting of PD followed by two hepatectomies, for cancer of the middle bile duct. A 60 year old male, who had undergone a distal gastrectomy for duodenal ulcer perforation in 23 years ago, underwent PD (Honjo method) for middle bile duct cancer (papillary adenocarcinoma) in 20 years ago at another hospital. In 12 years ago, he was referred to our hospital for further examinations of hepatic tumors and was diagnosed with CCC (S6, solitary, 4 cm). He underwent S6 subsegmentectomy of the liver. Pathological examination revealed a poorly differentiated CCC, considered a second primary cancer. In 6 years ago, subsequent follow up as an outpatient revealed repeated cholangitis, with CT showing a hilar mass caused by obstructive jaundice. He was diagnosed with a hilar cholangioma, and underwent hepatectomy and hepaticojejunostomy, which were safe despite surgical difficulties caused by severe adhesions and re-anastomosis. Pathological examination showed a well-differentiated CCC, considered the third primary cancer. The lung metastasis was revealed in 28 months after the last operation, however he has survived after partial lung resection without further metastasis. *J. Med. Invest.* 64 : 299-304, August, 2017

**Keywords :** *metachronous triple biliary cancer, hepatectomy, pancreatoduodenectomy*

## BACKGROUND

Radical resection for recurrent cholangiocellular carcinoma (CCC) is rare, with three metachronous radical resections reported to date in only two patients. Both patients underwent major hepatectomy twice after pancreatoduodenectomy (PD) for metachronous CCC (1). The recurrence rate after radical resection (R0) of intrahepatic cholangiocellular carcinoma (IHCC) is 50%-80%, with the rate of second resection being only 11% (2). Liver metastasis after initial resection of lower bile duct cancer has been reported in 9%-45% of patients, with the rate of second resection, including hepatectomy, being only 10% (3). Furthermore, only 2.1% of patients undergo complete radical hepatectomy for liver metastasis after PD (4). This report describes a patient who underwent repeated resections with curative intent of CCC after PD for cancer of the middle bile duct.

## CASE PRESENTATION

A 60 year old male underwent a distal gastrectomy for a duodenal ulcer perforation in 23 years ago. After 3 years, he underwent PD (Honjo method, Fig. 1) for middle bile duct cancer, pathologically diagnosed as a papillary adenocarcinoma, at another hospital, and was regularly followed-up at a local clinic.

After 8 years from primary resection, abdominal ultrasonography and abdominal computed tomography showed a hepatic tumor, and he was referred to our hospital for further examination.

Laboratory data at our institute are shown in Table 1. Multi-detector CT showed a solitary tumor in S6 ; its edge was enhanced from early phase, whereas its internal portion was gradually enhanced (Fig. 2). Enhanced-MRI showed a low intensity lesion on T1- and SPIO (superparamagnetic iron oxide) T1-weighted images, and a high intensity lesion on T2- and diffusion-weighted images (Fig. 3).

The patient was diagnosed with IHCC and underwent subsegmentectomy (S6, Fig. 1) in 12 years ago. Because the patient had undergone two previous abdominal operations, the operation time was relatively long (6 hours and 7 minutes) due to strong adhesions. Total bleeding during surgery was 140 ml.

The resected tumor was 4.0 × 2.5 cm in size. The edges of the tumor were clear, with its center showing extensive necrosis. Histopathologically, the tumor was diagnosed as a poorly differentiated CCC (mass forming type, 4.0 × 2.5 cm, s0, vp0, vv0, va0, b0, sm (-), pT2 N0 M0 fStage II ; Fig. 1, 4). It was considered a secondary primary cancer. Despite our strong recommendations, the patient refused adjuvant chemotherapy.

During follow-up as an outpatient, repeated cholangitis was observed, and CT revealed the extension of the right intrahepatic bile duct caused by hilar mass formation. Vessel invasions were suspected in the right hepatic artery and right portal vein (Fig. 5). Laboratory data at the second admission are shown in Table 1.

Percutaneous transhepatic biliary drainage (PTBD) was performed, showing that the right hepatic bile duct was interrupted and stenotic (Fig. 6). He was diagnosed with hilar cholangioma and underwent right lobectomy of the liver and a repeat hepaticojejunostomy (8 hours and 16 minutes) in 6 years ago. Intraoperative findings were shown in Fig. 7. The caudate lobectomy was not undergone considering operative invasiveness and liver functional volume after safety margins of the bile duct were guaranteed by the diagnosis of frozen sections. Surgery was performed safely (total bleeding, 380 ml), despite difficulties caused by severe adhesions and re-anastomosis.

Received for publication January 26, 2017 ; accepted March 27, 2017.

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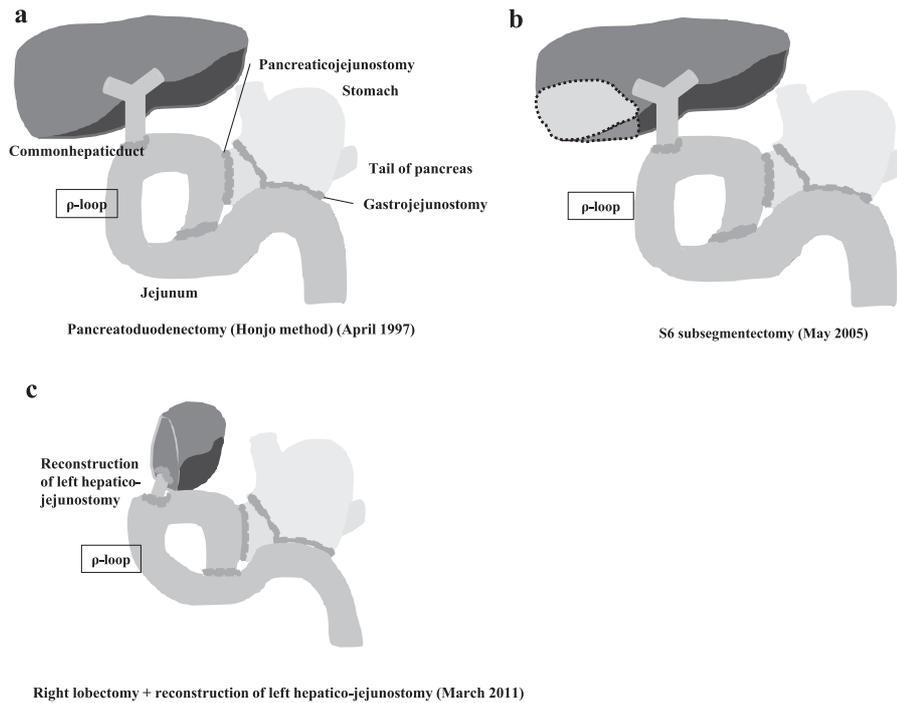


Fig. 1 Illustrations of the past surgical resections for metachronous triple biliary tract cancer. (a) Pancreatoduodenectomy (Honjo method) (b) S6 subsegmentectomy (c) Right lobectomy + reconstruction of left hepatico-jejunostomy.

Table 1. Laboratory data in our hospital.

	First admission	Second admission
AST (IU/l)	23	53
ALT (IU/l)	19	36
T-Bil (mg/dl)	0.7	0.8
ALP (IU/l)	391	405
$\gamma$ -GTP (IU/l)	66	126
AMY (IU/l)	65	65
CEA (ng/ml)	1.3	1.5
CA19-9 (U/ml)	5	11
AFP (ng/ml)	5	12
DACP(mAU/ml)	17	34
Span-1 (U/ml)	30	30
DUPAN-2 (U/ml)	25	25

Pathological examination of the resected specimen revealed a well-differentiated CCC, considered the third primary tumor (intraductal growth type, s0, vp0, vv0, va0, im(-) sm(-), T2 N0 M0 fStage II ; Fig. 8). Despite our strong recommendation, the patient refused adjuvant therapy. He survived without metastasis or recurrence after the operation, however, 28 months after surgery, lung metastases were found and partial lung resection was performed. Histological examination of the specimen showed the same features, indicating a further metastasis of the previous hilar bile duct cancer.

## DISCUSSION

Duplicated cancers has been defined as malignant tumors occupying sites distant from each other, with one not derived from the other tumor (5). In addition, duplicated cancers generally occur within one year (3). In our patient, the histological types of the three tumors differed, they occurred in different locations, and the times between occurrence were longer than one year each. Thus, these tumors can be diagnosed as metachronous triple biliary cancer.

Tumors that recur after resection of biliary tract cancers are often unresectable ; these include multiple organ and distant lymph node metastases, as well as perivascular nerve plexus invasion. Recurrences are considered resectable when localized, but the effects of aggressive resection of CCC recurrence remain unclear. Repeated radical resections for metachronous biliary tract cancers after hepatectomy are extremely rare. To date, simultaneous occurrence of metachronial triple biliary cancer has been reported in only one patient (6), whereas metachronous occurrence has not been observed. Furthermore, to our knowledge, only two patients have undergone two or more liver resections after PD (1, 7). Liver resection for recurrent biliary tract cancer has been reported to significantly improve patient prognosis (14-16). One study described surgical resection for recurrent biliary tract cancer in 74 (12.2%) of 606 patients, including three patients who underwent PD for local recurrence, 24 who underwent hepatic resection for liver metastasis, and 23 who underwent resection for chest or abdominal wall metastasis (8). The three-year overall survival rate was significantly higher in patients who did than did not undergo surgical resection (32.0% vs 3.0% ;  $P < 0.001$ ). Furthermore, surgical resection for recurrent CCC was an independent prognostic factor for overall survival after recurrence (8). Although resection is the most effective treatment, if possible, chemotherapeutic agents,

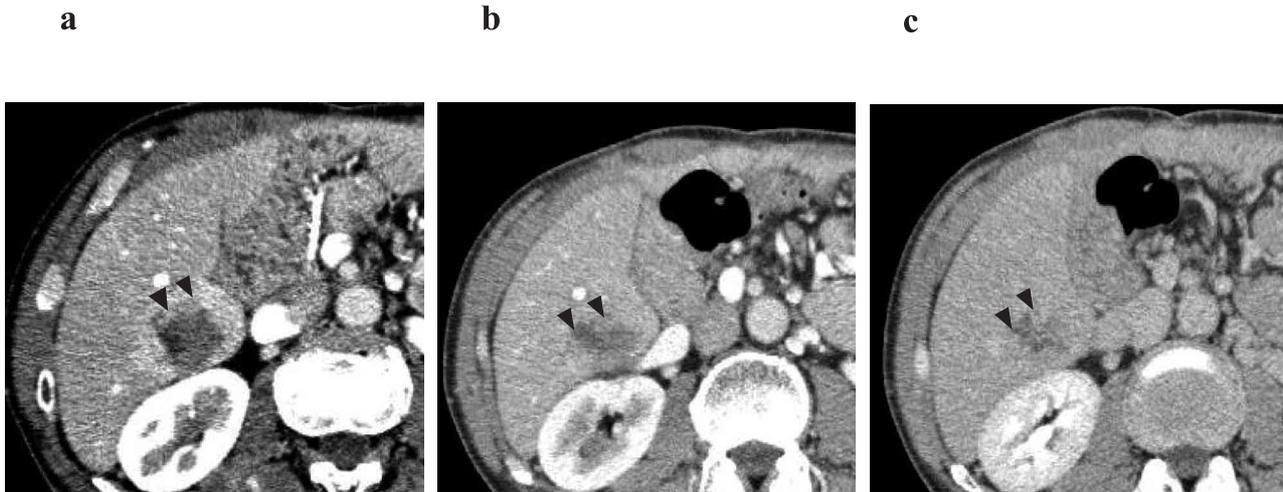


Fig. 2 Abdominal dynamic CT of our patient ; (a) early phase (b) portal phase (c) and late phase. The edges of the tumor were enhanced during early phase, whereas the internal area was slightly enhanced during portal and late phases.

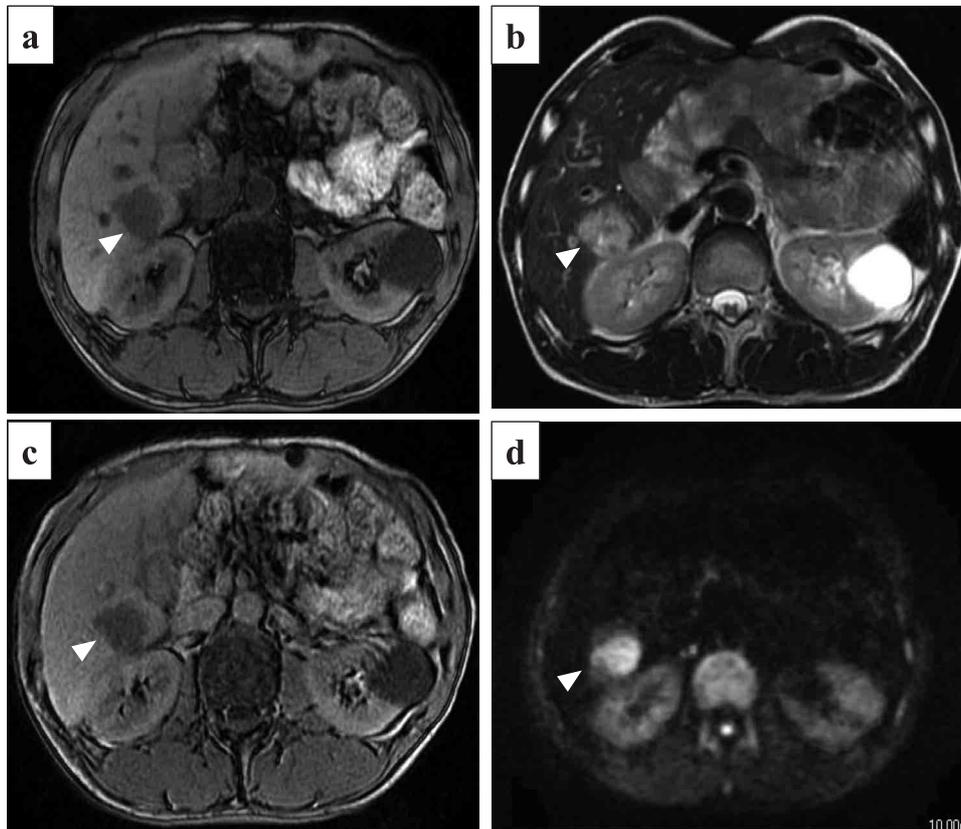


Fig. 3 Enhanced MRI, showed the tumor as a low intensity lesion on T1- (a) and SPIO T1-weighted (c : arrow) images, and as a high intensity lesion on T2- (b) and diffusion-weighted (d : arrowhead) images.

including gemcitabine, cisplatin, and tegafur-gimeracil-oteracil potassium (TS-1), have been shown successful results in patients with unresectable recurrent biliary tract cancers (9-12).

The combination of resection and chemotherapy may be a powerful option in the treatment of patients with recurrent tumors. For example, neoadjuvant or adjuvant GFP (gemcitabine, low dose cisplatin, and 5-fluorouracil) has been shown effective in patients

with bile duct cancer (13). Our treatment algorithm for patients with bile duct cancers therefore consists of R0 surgical resection after GFP treatment, whether the tumor is curable or not.

In this time, we did not undergo the caudate lobectomy. For perihilar cholangiocarcinoma, the major lobectomy with the caudate lobectomy is generally planned (19), however, there were some reports that caudate lobectomy was not related to the



Fig. 4 Specimen obtained following subsegmentectomy of the liver, showing a poorly differentiated tumor : 4 × 2.5 cm, s0, vp0, vv0, va0, im (-), sm (-).

prognosis considering the remnant liver volume, cancer margin of the bile duct and operative invasiveness (20, 21). In this case, we judged that caudate lobectomy was not suitable when we evaluated the patient's intraoperative findings and preoperative liver function volume.

Repeated radical resection for CCC is extremely rare. There are

some reasons that make the repeated surgery difficult, one of which would be the tumor factors such as location, the number of tumor and the size, especially the anatomical changes resulting from the intensive procedure performed at the previous resection.

In metachronous of biliary tract cancer, the clear evidence was not demonstrated so far. There are some reports which insisted the advantages of the resection by showing the long-term survival after repeated operation (17, 18). Aggressive resection is therefore an option for patients with repeated CCC.

## CONCLUSIONS

In conclusion, we have experienced the long-term survival case repeated radical resections for metachronous biliary tract cancers after hepatectomy. Aggressive resection is an option for patients with recurrent CCC.

## CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

## ABBREVIATIONS

AFP :  $\alpha$ -fetoprotein

AMY : amylase

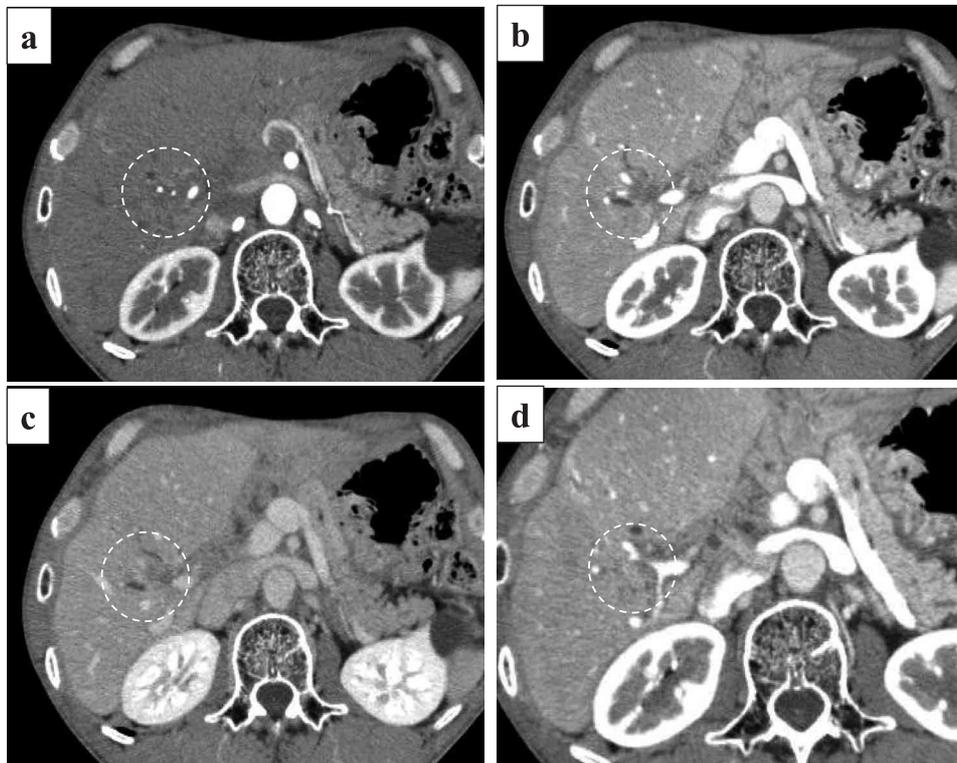


Fig. 5 Abdominal dynamic CT showing mass formations along the hilar bile duct. Marginally enhanced masses were observed during the arterial (a) and portal (b,d) phases, but were attenuated during the venous phase (c). Hilar lesions suggested invasion of the posterior segmental branch of the hepatic artery (a) and the right primary branch of the portal vein (b), but the hepatic vein was intact (c).

ALP : alkaline phosphatase  
 ALT : alanine aminotransferase  
 AST : aspartate aminotransferase  
 CA19-9 : carbohydrate antigen 19-9  
 CEA : carcinoembryonic antigen  
 DCP : des- $\gamma$ -carboxy prothrombin

DUPAN-2 : pancreas cancer-associated antigen-2  
 T-Bil : total bilirubin  
 $\gamma$ -GTP :  $\gamma$ -glutamyltranspeptidase

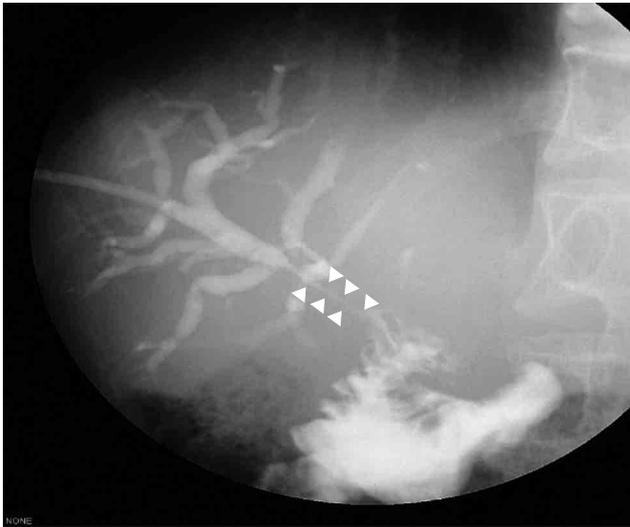


Fig. 6 Percutaneous transhepatic biliary drainage (PTBD), showing interruption and stenosis (arrowheads) of the right hepatic duct.

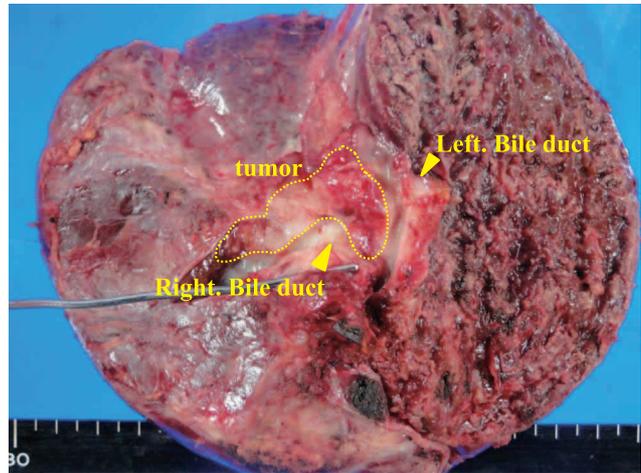


Fig. 8 Specimen obtained following right lobectomy of the liver (Ig, s0, vp0, vv0, va0, im (-), sm (-)). The pathological type was well-differentiated adenocarcinoma, differing from the pathological type of the previous tumor (Fig. 4).

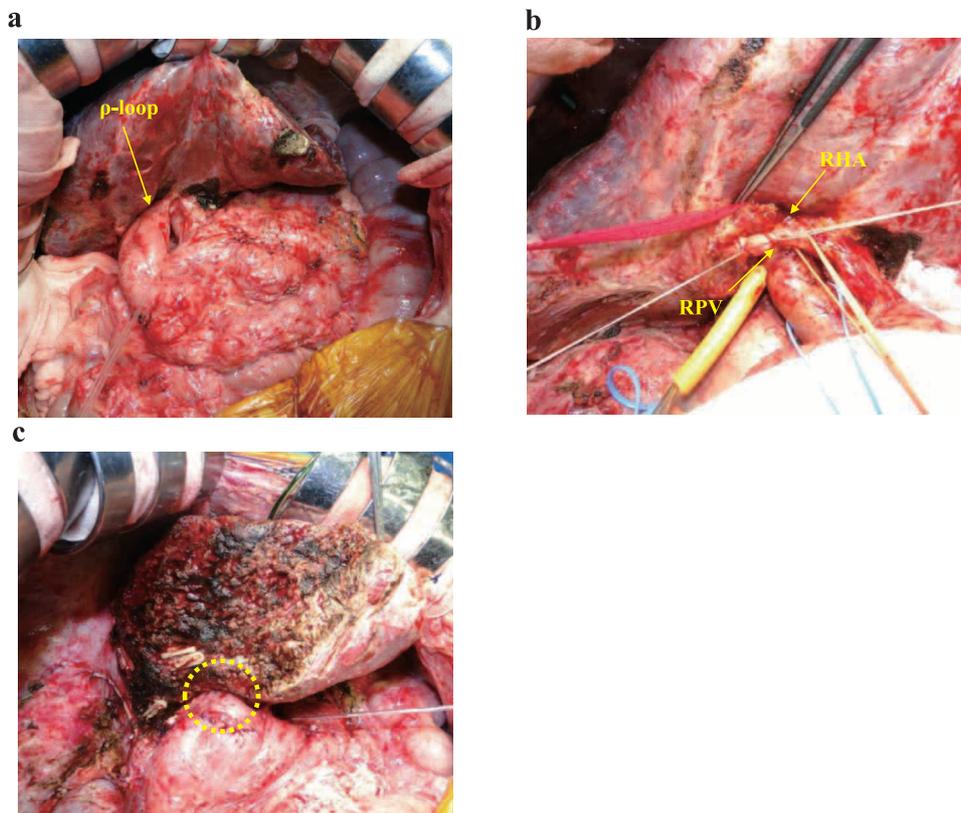


Fig. 7 Intraoperative findings in secondary reconstruction of the biliary tract. Severe adhesion around the p-loop (a). Detachment between right hepatic artery (RHA) / right portal vein (RPV) and tumor (b). Intrahepatic cholangiojejunostomy (plasty of B2 and B3+4) (c).

**COMPETING INTERESTS**

The authors declare that they have no competing interests.

**AUTHORS' CONTRIBUTIONS**

TI have been involved in drafting the manuscript and revising it critically for important intellectual content. MS, TI and YM and SI has operated this case. All authors read and approved the final manuscript.

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