Clinicopathological Features of “Intraductal Papillary Neoplasm of the Bile Duct” and Patient Outcome after Surgical Resection

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Short title: Characteristics of IPNB

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ABSTRACT

Background/Aims: Intraductal papillary neoplasm of the bile duct (IPNB) represent biliary papillary tumor mainly growing in the bile duct lumen resembling intraductal papillary mucin-producing neoplasm of the pancreas. However, its clinical spectrum and characteristics have not been fully evaluated.

Methodology: To define the clinicopathologic characteristics and prognosis of IPNB patients, we present 6 cases of IPNB who underwent surgical resection.

Results: Patients were 3 males and 3 females, aged between 47 and 79 years. Five patients had history of hepato-biliary disease. Image showed cystic or diffuse dilatation of bile ducts. Tumor markers were not valuable for diagnosis. All patients underwent hemihepatectomy with or without resection of the caudate lobe or extrahepatic bile duct. Examination showed polypoid tumors in 5 cases though one had no evident tumor(s). Mucin was observed in 3 cases. Five cases were well-differentiated adenocarcinoma and one had poorly differentiated adenocarcinoma. Vascular invasion was rare and lymph node metastasis was not observed. In-situ spread of carcinoma was seen along biliary mucosa in 3 cases. Five cases survived without tumor relapse for long periods but one died of tumor recurrence at 31 months.

Conclusions: Complete resection of IPNB based on accurate preoperative assessment of tumor extension provides good prognosis.

KEY WORDS: intraductal papillary neoplasm, liver, dilated bile duct, hepatectomy, good prognosis

ABBREVIATIONS: intraductal papillary neoplasm (IPNB), intraductal papillary mucin-producing neoplasia (IPMN), intrahepatic cholangiocarcinoma (ICC)
INTRODUCTION

Intraluminal papillary tumors of extra- or intra-hepatic bile ducts generally show high or low grade dysplasia or are well-differentiated adenocarcinoma (1-3). These types of tumors are not infrequently associated with superficial spread of carcinoma cells along the biliary mucosa without invasiveness (4). In Japan, these tumors are classified at present by different classification systems as either papillary type extrahepatic bile duct carcinoma or intraductal growth type intrahepatic cholangiocarcinoma (ICC) (5, 6). Approximately 10% of hilar bile duct carcinomas are of the papillary type while approximately 15% of ICC are intraductal growth type (7). Biliary papillomatosis or papilloma are also sometimes included in this category of biliary tumors (8, 9).

This type of biliary papillary tumors shows less invasiveness and more favorable outcome compared with other types of ICC and not infrequently presents as multifocal papillary epithelial lesions in the bile duct with or without mucin production (10-12). Interestingly, the clinicopathological features of intraductal papillary neoplasm of the bile duct (IPNB) resemble those of intraductal papillary mucin-producing neoplasia (IPMN) of the pancreas. Chen et al (10) and Nakanuma et al. (11) surveyed such cases in Japan and also in Taiwan, and they proposed the collective term of IPNB for such biliary papillary tumors after suspecting that IPNB could be a counterpart of IPMN of the pancreas (11, 13-17). Recent pathologic studies showed that mucin-producing ICC or extraheaptic bile duct carcinoma, oncocytic biliary cystadenoma, cystoadenoma/cystadenocarcinoma with luminal communication with the bile duct, in addition to biliary papilloma/papillomatsois, could be included as IPNB (18-20). That
is, IPNB is proposed to include collectively these biliary tumors that have so far been
diagnosed under different terms. IPNB is considered to be of relatively low-grade
malignancy (6, 17, 21). However, the clinical spectrum and characteristics of IPNB
itself including postsurgical prognosis had not been fully evaluated and this category
has not been classified within the category of epithelial liver tumors by the WHO
classification (22).

We recently reported two cases of IPNB with special emphasis on imaging and
macroscopic findings (23, 24). Our experience with these two cases prompted us to
survey retrospectively all cases of intrahepatic cholangiocarcinoma and bile duct
carcinoma of the hepatic hilum. Six cases of IPNB including 2 cases reported
previously were found to be IPNB by pathological analysis. In the present study, we
examined the clinical characteristics of these 6 cases of IPNB to consider treatment
policy for this disease.
METHODOLOGY

Definition of pathology

IPNB is characterized by intraluminal papillary growth of biliary lining epithelia of intra- and extrahepatic bile ducts. Frond-like papillary infoldings consisting of columnar epithelial cells with slender fibrovascular stalks are frequently found (11, 17). The lining biliary epithelium of the papillary tumor is dysplastic of low-grade or high-grade, or well-differentiated carcinoma. All resected specimen were fixed in 10% formalin and embedded in paraffin. From each specimen, more than 10 thin sections were cut and some of them were processed routinely including hematoxylin eosin staining while the remaining sections were used for the immunohistochemical study.

Patients

Between 1990 and December 2005, consecutive 40 patients with ICC and 58 patients with extrahepatic bile duct carcinoma underwent surgical resection at the Division of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences. Among these patients, four were diagnosed as intraductal growth type of ICC, three as cystadenocarcinoma of the liver, two as papillary type with an expanding growth pattern of bile duct carcinoma, and three were diagnosed as papillary type with infiltrating growth pattern of bile duct carcinoma. The above diagnosis was based on the *General Rules for the Clinical and Pathological Study of Primary Liver Cancer by Liver Cancer Study Group of Japan* (6) and *Classification of Biliary Tract Carcinoma by Japanese Society of Biliary Surgery* (5). In these 12 cases, we retrospectively re-examined the histopathological findings at our institute and found 6 cases to be included in IPNB. The study design was approved by the Ethics
Review Board of our institution and a signed consent for treatment was obtained from each patient at the time of operation.

Radical hepatectomy was performed to remove the hepatic or biliary tumor without leaving any residual tumor or distant metastases. Patients were followed at the outpatient clinic of our hospital every 3 months after surgery.

We analyzed the patient demographics, clinicopathological parameters, laboratory data, image findings by computed tomography (CT) or magnetic resonance image (MRI), surgical data and patient outcomes. Tumor markers examined in these patients were carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9).
RESULTS

Table 1 shows the demographics and preoperative findings of 6 patients with IPNB. Age ranged from 47 to 79 years. Three patients were males and 3 were females. Four patients had clinical symptoms while 2 were asymptomatic but liver dysfunction was detected by regular health checkup. Three patients had history of biliary stones and 3 had history of chronic viral hepatitis B. Two patients showed obstructive jaundice at hospital admission. Image findings showed the diffuse dilatation of bile ducts without tumor occlusion. With regard to laboratory tests, Case 2 had high level ALP but normal serum level of tumor markers. Case 3 had high serum levels of CA19-9, bilirubin and ALP. Case 4 had elevated levels of both CEA and CA19-9, as well as bilirubin and ALP. The other three patients had no abnormal laboratory data.

All patients underwent hemihepatectomy with or without resection of the caudate lobe or extrahepatic bile duct (Table 2). In Case 4, the cancer was positive at the cut edge of the bile duct although an additional resection was performed. Polypoid tumors were observed in 5 cases but Case 2 had no tumor macroscopically. Three cases showed mucin retention in the bile duct.

Table 3 summarizes the histopathological findings. Histopathological diagnosis was well-differentiated adenocarcinoma in 5 patients and moderately-to-poorly differentiated adenocarcinoma in one. Five cases showed an expanding growth pattern with distinct border from the surrounding tissue and one showed an intermediate growth pattern between expanding growth and infiltrating growth pattern. Case 4 showed lymph vessel invasion and Case 6 showed venous invasion but no vessel invasion was observed in the remaining four patients. There were no lymph node
metastases in our series. Cases 3 and 4 exhibited low curability of the solitary liver metastasis and remnant cancer cells at the resected edge of the bile duct. Intraepithelial extension of cancer cells along the biliary epithelium was observed in 3 patients. Immunohistochemical staining of mucin was performed in four cases (Cases 1-4). MUC1 was positive in 3 of 4 cases, MUC2 was positive in one of four, and MUC5A was not detected in 2.

One patient developed postoperative hepatic failure but recovered at 3 months after surgery (Table 4). Only Case 4 had tumor recurrence and received chemotherapy but died of cancer at 31 months. Other cases survived without tumor relapse for a long period.

Case presentations

Cases 2 and 3 have been presented in the previous reports (23, 24). In brief, Case 2 was a 79-year-old female who showed slight dilatation of the right intrahepatic bile duct on imaging and the bile duct progressively became dilated during a 2-year follow-up period but no solid mass or elevated tumor markers were noted. Hepatic resection was scheduled based on suspicion of mucin-producing bile duct carcinoma of the liver. Histopathological findings revealed carcinoma in situ with adenoma. Case 3 was a 47-year old man with a 3-cm protruding tumor in the right and common hepatic ducts. The disease was histopathologically diagnosed as well-differentiated adenocarcinoma with stromal invasion with liver metastasis.

Case 1. A 68-year-old female. CT showed dilatation of the left intrahepatic bile duct (Fig. 1). A left hepatectomy was performed. The resected specimen showed a papillary tumor in the dilated bile duct of segment 3 of the liver (Fig. 2). A diagnosis
of papillary growing well-differentiated adenocarcinoma without invasion was made (carcinoma in situ) (Fig. 3).

Case 4. A 69-year-old male. CT showed a filling tumor in the hilar bile duct (Fig. 4) with obstruction of the common hepatic duct. A left hepatectomy with caudate lobe resection was performed. The resected specimen showed a papillary tumor in the hilar bile duct, with superficial spread to intrahepatic bile duct in the right paramedian and lateral sectors (Fig. 5). Mucin production was not observed. Moderately-to-poorly differentiated adenocarcinoma with massive stromal invasion and vessel invasion was found.

Case 6. A 74-year-old male. Computed tomography (CT) scan demonstrated marked dilatation of the bile duct in the caudate lobe and common bile duct (Fig. 6). Since mucin-producing biliary carcinoma was suspected, a left hepatectomy including the caudate lobe and resection of the common bile duct were performed. The resected specimen showed the papillary growing tumor and massive mucin in the cystic bile duct of the caudate lobe (Fig. 7). Papillary growth of dysplastic epithelium with thin fibrous stroma was observed in the papillary tumor (Fig. 8). The pathological diagnosis was well-to-moderately differentiated adenocarcinoma including mixed type cells such as biliary or pancreatic epithelium-like cells, oncocytic cells and mucinous cells.
DISCUSSION

There has been an increase in the number of reported cases of biliary neoplasms of the hepatobiliary system characterized by marked dilatation of the bile ducts or cystic biliary lesions with or without mucin secretion, and mucinous lesions or tumors, possibly due to recent advances in radiological diagnosis (25-29). The number of patients who undergo surgical treatment for such lesions has also increased due to diagnostic and surgical improvements along with development of imaging modalities (17, 21, 30-33). To date, such tumors have been diagnosed and treated under different pathological diagnoses. Nakanuma et al. recently proposed that such tumors could be collectively termed IPNB with the concept that IPNB may evolve through a common pathologic process and shares clinicopathological features with pancreatic IPMN (11). There have been many clinical studies on these biliary tumors from the aspect of individual or each disease category, though there have been no clinical studies on these diseases under the concept of IPNB.

In our series of 6 patients, four presented with abdominal symptoms due to biliary obstruction by mucin or intra-luminal tumor growth. However, two patients did not have remarkable symptoms but the onset of liver dysfunction. Therefore, secondary check-up by image diagnosis is necessary in patients with such complaints. Chronic inflammation of the biliary system such as a hepatolithiasis is the background lesion of IPNB (10, 11). Five of our patients had histories of biliary stone or viral hepatitis B. Although hepatolithiasis was not found in our series, the association of chronic inflammation with occurrence of IPNB should be considered. Viral hepatitis might be a risk factor for intrahepatic, extrahepatic and hilar bile duct tumors (34).
Helical CT and MR imaging can identify dilation and cystic changes in the biliary and pancreatic ducts in asymptomatic patients (26-28), making the diagnosis of malignancy possible and providing reliable follow-up of the patients. Morphological classification of biliary neoplasm with cystic or dilated bile duct has been reported by Kawarada et al in 1991 (35). Recently, Yeh et al.(17) reported the reliable classification of cholangiographic types according to the histopathological types of IPNB, which were classified by various malignant cystic tumors. According to this imaging classification, type IC (disproportional biliary dilatation in the absence of discernible neoplasia) was found in 3 patients of the present series, type IIA (intrahepatic polypoid or cystic neoplasia) in 2 and type IIB (intrahepatic polypoid or cystic neoplasia extending to the extrahepatic bile duct) was detected in 1. Yeh et al. (17) reported 3 cases of type IC were histopathologically carcinoma in situ while the others of type IIA or B were carcinoma with stromal invasions. Therefore, their morphological classification using image diagnostic tool may be reliable to identify malignancy of IPNB. Mucobilia detected as a filling defect by cholangiography is characteristic for diagnosis of IPNB (17, 25, 28, 29, 36). In our series, 3 of 6 cases had evidence of mucin production by image diagnosis or resected specimens but this was not observed in the other 3 cases. It should be necessary to consider IPNB in patients showing dilated bile duct without mucin production as well. Although CEA or CA19-9 are usually elevated in biliary malignancies (37, 38), high levels of these tumor markers were detected in only 2 cases, which were invasive carcinoma, and therefore these markers may not be sensitive diagnostic tools for early-stage IPNB. Yeh et al.(36) reported that elevated serum CEA level was helpful in distinguishing
intraductal growth type of ICC and intraductal papillary neoplasm of the liver (IPNB) as a precursor lesion. ALP level was elevated in 2 cases in our series. In Case 2, only ALP level was high and this finding was the first clue to diagnose the present condition. Elevated levels of serum ALP might be associated with biliary carcinoma. Elevated diagnostic tools such as bile cytology or biopsy of bile duct via the route of percutaneous transhepatic biliary drainage, or positron emission tomography may be useful for the diagnosis of malignancy.

Several reports recommended hemi-hepatectomy or extended hemi-hepatectomy for all cases especially for those with extending tumors or diffusely dilated bile ducts. In 5 cases, complete resection was possible. However, one case with invasive carcinoma had tumor-positive at the cut edge of the bile duct in the present study. In this study, 2 of 3 cases who did not show polypoid lesions by preoperative image diagnosis, the resected specimens showed remarkable protruding tumor lesions. Mucin might interrupt the detection of these primary tumor lesions. Case 2 still showed no polypoid lesions in the dilated bile duct and, to our knowledge, such case has not been reported before our previous publication.

Our study identified 4 cases with histopathologically confirmed early-stage or non-invasive carcinoma and two cases showed invasive carcinoma with liver metastasis. Yeh et al. reported that 59 of 124 IPNB patients had invasive carcinoma. Therefore, one should consider the possibility of stromal or vessel infiltration, or distant metastasis in some population even in IPNB based on our present study and other reports. Superficial spreading of the tumor along the biliary epithelium is also a characteristic feature of IPNB, which was
observed in 3 cases in the present series. In one case, the carcinoma extended superficially to the extrahepatic bile duct, an unexpected finding during the operation given the normal gross appearance (23). Therefore, intraoperative histologic diagnosis is necessary. This is a serious problem in curative surgical resection of biliary carcinoma (32). It is important to decide on major hepatic resection in such cases because of diffuse dilatation of the bile duct extending in a segment or lobe and multi-focal carcinogenesis (11, 14, 25, 33).

When the cystic tumor without prior disease was inspected macroscopically, such disease is sometimes diagnosed or classified as bile duct cystadenoma or adenocarcinoma by the WHO criteria at this stage (22). In our series, Cases 2 and 6 were thought to be a cystadenocarcinoma based on image diagnosis (13). However, these cases showed the connection the large bile duct which was a characteristic feature of IPNB. Wheeler (44) reported a case of biliary cystadenoma or carcinoma with ovarian-like stroma. The latter was a diagnostic feature and all patients were females, similar to pancreatic mucinous cystic neoplasm. Devaney and colleagues (45) summarized the clinical features of hepatobiliary cystadenomas and cystadenocarcinomas. Ovarian-like mesenchymal stromata was detected in 85% of their patients. A tumor without ovarian-like stroma was also found in a male patient who showed better prognosis after surgical resection compared to tumors with ovarian-like stroma. Therefore, IPNB might be included their series. None of our six patients showed ovarian-like mesenchymal stroma in the sub-epithelial stroma. Zen and Nakanuma et al. and others (11, 19, 36, 46) examined mucinous expression. The expression of MUC1, MUC2, and CK20 correlated with aggressive from IPNB to
invasive or mucinous carcinoma of the bile duct. In our series, the expression of MUC2, MUC5A and CK20 was negative in Cases 1-3. Further studies of cellular characteristics such as protein expressions or genetic alterations will be necessary to clarify the pathogenesis of IPNB (14). IPNB remains only partially recognized at present and systematic criteria defined by many pathologists is expected in the near future. Understanding the histopathological findings of IPNB would be useful for intraoperative diagnosis, which may contribute to complete surgical resection and better patient prognosis.

IPNB or intraductal papillary growth type of ICC is a good indication for surgical resection, and complete resection is associated with better prognosis compared with other cholangiocarcinomas (30-33, 47). In our series, 5 of 6 cases had good prognosis without tumor recurrence after surgery. Only Case 4 developed multiple liver metastases at 7 months after resection, which had positive surgical margin. The recent report by Yeh et al.(17) revealed poor prognoses in patients with type III and IV (5 year survival rate was 17 and 14%, respectively) or with lymph node metastasis. Therefore, to accomplish good prognosis after treatment for IPNB, diagnosis at the earliest stage followed by curative resection is necessary.

In conclusion, we reviewed the clinicopathological features and patient outcome in 6 cases of IPNB after surgical resection. The latest image diagnostic tools were useful to find and diagnose IPNB. Since the malignant potential of IPNB is lower than other ICC or bile duct carcinoma, surgical resection is a better therapeutic choice for IPNB. It is necessary to make accurate assessment of tumor extension because of the
characteristic superficial spreading of tumor cells, since complete resection of IPNB provides good prognosis.
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Figure legends

**Fig. 1.** CT shows a dilated bile duct in the left liver.

**Fig. 2.** Macroscopic view of the resected right liver. Papillary carcinoma was found in the left lateral sector.

**Fig. 3.** Microscopic finding of IPNB. Hematoxylin-eosin staining, (X200). Note the papillary growing well differentiated adenocarcinoma *in situ* with mucinous cells.

**Fig. 4.** CT shows a papillary carcinoma (arrow) in the hilar bile duct.

**Fig. 5.** Macroscopic appearance of the resected liver. Note the papillary carcinoma (arrow) in the hilar bile duct. RHD: right hepatic duct.

**Fig. 6.** CT shows a papillary carcinoma in the bile duct of the caudate lobe.

**Fig. 7.** Macroscopic view of the resected liver. Note the presence of the papillary tumor in the cystic dilatation of the caudate lobe (arrow). LHD: left hepatic duct. CBD: common bile duct.

**Fig. 8.** Histopathological findings of IPNB (X100). Note the papillary growth of dysplastic epithelium in the papillary tumor.
Table 1. Patient demographics of IPNB

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Symptoms</th>
<th>History of hepatobiliary diseases</th>
<th>Image</th>
<th>Pancreatobiliary maljunction</th>
<th>CEA (ng/ml, n&lt;5)</th>
<th>CA19-9 (U/ml, n&lt;37)</th>
<th>Total bilirubin (mg/dl, n&lt;1.5)</th>
<th>ALT (IU/L, n&lt;42)</th>
<th>ALP (IU/L, n&lt;359)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 68/F</td>
<td>abdominal pain</td>
<td>choledocholithiasis</td>
<td>Diffuse dilatation of left IHBD</td>
<td>none</td>
<td>0.9</td>
<td>18.3</td>
<td>0.6</td>
<td>13</td>
<td>162</td>
</tr>
<tr>
<td>2 79/F</td>
<td>liver dysfunction</td>
<td>none</td>
<td>Diffuse dilatation of right IHBD</td>
<td>none</td>
<td>1.6</td>
<td>16</td>
<td>0.8</td>
<td>33</td>
<td>638</td>
</tr>
<tr>
<td>3 47/M</td>
<td>liver dysfunction</td>
<td>chronic hepatitis B</td>
<td>Diffuse dilatation of both IHBD with PL</td>
<td>none</td>
<td>2.2</td>
<td>217</td>
<td>9.2</td>
<td>135</td>
<td>2518</td>
</tr>
<tr>
<td>4 69/M</td>
<td>abdominal pain</td>
<td>none</td>
<td>Diffuse dilatation of left IHBD with PL</td>
<td>none</td>
<td>8.9</td>
<td>1282</td>
<td>5.7</td>
<td>45</td>
<td>306</td>
</tr>
<tr>
<td>5 68/M</td>
<td>abdominal pain</td>
<td>gall stone, chronic hepatitis B</td>
<td>Diffuse dilatation of left IHBD and CBD</td>
<td>none</td>
<td>2.0</td>
<td>33.2</td>
<td>0.3</td>
<td>22</td>
<td>253</td>
</tr>
<tr>
<td>6 74/M</td>
<td>itching</td>
<td>gall stone, chronic hepatitis B</td>
<td>Dilatation of IHBD in caudate lobe and CBD with PL</td>
<td>none</td>
<td>2.3</td>
<td>15.8</td>
<td>1.0</td>
<td>35</td>
<td>305</td>
</tr>
</tbody>
</table>

IHBD, intrahepatic bile duct; CBD, common bile duct; PL, polypoid lesion; EHBD, extrahepatic bile duct; n, normal value; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase.
Table 2. Operative and macroscopic findings

<table>
<thead>
<tr>
<th>Operation</th>
<th>Surgical margin</th>
<th>Macroscopic appearance</th>
<th>Mucin in the bile duct</th>
<th>Tumor size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Left HH</td>
<td>negative</td>
<td>Papillary</td>
<td>Yes</td>
<td>16</td>
</tr>
<tr>
<td>2 Right HH+ Resection of CL and EHBD</td>
<td>negative</td>
<td>Unclear</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>3 Right HH+R of CL and EHBD</td>
<td>negative</td>
<td>Papillary</td>
<td>No</td>
<td>30</td>
</tr>
<tr>
<td>4 Left HH+R of CL and EHBD</td>
<td>positive</td>
<td>Papillary</td>
<td>No</td>
<td>40</td>
</tr>
<tr>
<td>5 Left HH+ Resection of CD and EHBD</td>
<td>negative</td>
<td>Papillary</td>
<td>Yes</td>
<td>15</td>
</tr>
<tr>
<td>6 Left HH+ Resection of CD and EHBD</td>
<td>negative</td>
<td>Papillary</td>
<td>Yes</td>
<td>14</td>
</tr>
</tbody>
</table>

HH, hemi-hepatectomy; CL, caudate lobe; EHBD, extrahepatic bile duct.

*Additional resection of extrahepatic bile duct during operation was necessary because of positive surgical margin.
Table 3. Histopathological findings.

<table>
<thead>
<tr>
<th>Pathological diagnosis</th>
<th>INF</th>
<th>ly</th>
<th>v</th>
<th>pn</th>
<th>lymph node metastasis</th>
<th>Tumor stage*</th>
<th>Curability*</th>
<th>SS</th>
<th>MUC1</th>
<th>MUC2</th>
<th>MUC5A</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Well-differentiated CC</td>
<td>α</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>none</td>
<td>1</td>
<td>A</td>
<td>no</td>
<td>p</td>
<td>n</td>
<td></td>
<td>CK20:n</td>
</tr>
<tr>
<td>2 Adenoma and carcinoma in situ</td>
<td>α</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>none</td>
<td>2</td>
<td>A</td>
<td>yes</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>p53:p</td>
</tr>
<tr>
<td>3 Well-differentiated CC</td>
<td>α</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>none</td>
<td>4†</td>
<td>C†</td>
<td>no</td>
<td>p</td>
<td>n</td>
<td>n</td>
<td>CK20:n</td>
</tr>
<tr>
<td>4 Moderately differentiated CC</td>
<td>β</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>none</td>
<td>1</td>
<td>C‡</td>
<td>yes</td>
<td>p</td>
<td>p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Well-differentiated CC</td>
<td>α</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>none</td>
<td>1</td>
<td>A</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Well-differentiated CC</td>
<td>α</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>none</td>
<td>3</td>
<td>B</td>
<td>yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CC, cholangiocellular carcinoma; INF, the predominant growth patterns infiltrating to the surrounding tissue; ly, lymphatic invasion; v, venous invasion; pn, perineural invasion. SS, superficial spreading of cancer along the epithelium of bile duct.

*The Classification of Biliary Tract Carcinoma and The General Rules for the Clinical and Pathological Study of Primary Liver Cancer.
†, presence of focal liver metastasis; ‡, presence of tumor positive at the surgical margin
p: positive, n: negative
### Table 4. Patient outcome

<table>
<thead>
<tr>
<th>Complications</th>
<th>Adjuvant treatment</th>
<th>Tumor recurrence</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>None</td>
<td>Alive without recurrence (16m)</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>None</td>
<td>Alive without recurrence (18m)</td>
</tr>
<tr>
<td>3</td>
<td>Liver failure</td>
<td>None</td>
<td>Alive without recurrence (6m)</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>5FU CAI</td>
<td>Died by cancer (31 m)</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>None</td>
<td>Alive without recurrence (108 m)</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>None</td>
<td>Alive without recurrence (39 m)</td>
</tr>
</tbody>
</table>

m, month, 5FU CI: continuous arterial infusion of 5-fluorouracil
Fig. 5
Fig. 6