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Case Report

Recurrent Cholangiocarcinoma: Case Report and Literature Review

Adham Alkadri[1], Souad Ghattas[1], Kamal Abi Mousleh[2], Ribal Abi Hadeer[1], Youssef Mahfouz[1], Georges Sakhat[1], Marwan Haddad[3], Raja Wakim[4*]

[1]General Surgery Department, Resident - Mount Lebanon Hospital University Medical Center, University of Balamand , Beirut, Lebanon

[2]Faculty of Medicine - University of Balamand, Lebanon

[3]Head of Radiology Department - Mount Lebanon Hospital University Medical Center, University of Balamand , Beirut, Lebanon

[4]Head of General Surgery Department - Mount Lebanon Hospital University Medical Center, University of Balamand , Beirut , Lebanon

[*]**Corresponding author:** Raja Wakim, Head of General Surgery Department - Mount Lebanon Hospital University Medical Center, University of Balamand , Beirut , Lebanon

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Abstract

Conventionally, patients with recurrent cholangiocarcinoma have been treated palliatively, most often with supportive care only. Since intrahepatic cholangiocarcinoma (I-CCA) is an uncommon malignancy, treatment guidelines for I-CCA therapy have a low level of support, and guidelines for the treatment of recurrence are particularly challenging to establish. While a surgical approach is not clearly recommended for recurrent I-CCA in current guidelines, this approach has been reported as reasonable in a particular patient demographic and should be considered [1-3]. Herein we present to you a case of 56-year-old female patient presented with local recurrence 1.5 years post resection treated surgically.

Keywords: Cholangiocarcinoma; Recurrent cholangiocarcinoma; CA 19-9; CEA; Papillary intraductal cholangiocarcinoma

Abbreviations: ALP: Alkaline Phosphatase; CBD: Common Bile Duct; CCA: Cholangiocarcinoma; CT: Computed Tomography; FDG: Fluorodeoxyglucose; I-CCA: Intrahepatic Cholangiocarcinoma; IPNB: Intraductal Papillary Neoplasm of the Bile Duct; LFT: Liver Function Test; MRCP: Magnetic Resonance Cholangiopancreatography; PET: Positron Emission Tomography; PSC: Primary Sclerosing Cholangitis

Case

A 56-year-old woman was referred to our hospital on the 7th of August 2020, with post-prandial right upper quadrant pain radiating to the back of one-month duration, unrelieved by any pain medication or positional changes. The patient denied any fever, chills, anorexia, weight loss, nausea, or vomiting. She did not report a history of smoking or alcohol consumption. Past medical history was negative and past surgical history was notable for total hysterectomy for symptomatic uterine leiomyoma six years ago. On physical examination there were no pertinent findings except for right upper quadrant tenderness to palpation. Routine blood analysis and liver function tests were normal. Her α-fetoprotein level was 2.32 ng/mL (range: 0-8.1 ng/mL), carcinoembryonic antigen was 4.61 ng/mL (range: 1.00–5.00 ng/mL), and carbohydrate antigen 19-9 was 274.87 U/mL (normal range: 0-30.90 U/mL).

On further investigation and imaging, Computed tomography (CT) scan of the abdomen revealed a 33 mm hypodense left liver mass extending over the left portal vein branch and exerting a mass effect over the neighboring dilated biliary ducts and the laminated left portal branch. MRCP showed focal dilatation of the intrahepatic biliary ducts of the liver, notably in segment IV,

with a hypo signal T1, hyper signal T2 mass of 30 mm, enhancing after gadolinium, exerting a mass effect on the left portal trunk. CT guided biopsy of the liver mass was performed and showed a moderately differentiated adenocarcinoma.

After outpatient follow up in the clinic, the patient was scheduled for a left hepatectomy and was therefore re-admitted on the 20th of August 2020. Post-operative histopathological specimen examination showed papillary intraductal carcinoma with invasive tubular like component of the intrahepatic ducts extending to the liver parenchyma, liver limits are negative with microinvasion of bile duct limit. Absence of vascular embolus, presence of perineural sheaths. The pathological stage of the I-CCA was pT4.

After the operation, a multidisciplinary meeting was held to discuss the case and plan for further intervention, where a decision was taken for reoperation with total bile duct dissection and Roux-en-Y hepaticojejunostomy (Figure 1). She was then subsequently re-admitted on the 10th of September 2020 for implementation of the planned procedure. The patient underwent a successful and uncomplicated surgical course and was therefore discharged later with a plan to follow-up with an oncologist for adjuvant chemotherapy. She then received six sessions of chemotherapy and immunotherapy (with Pembrolizumab) and was considered to be in remission after completion.

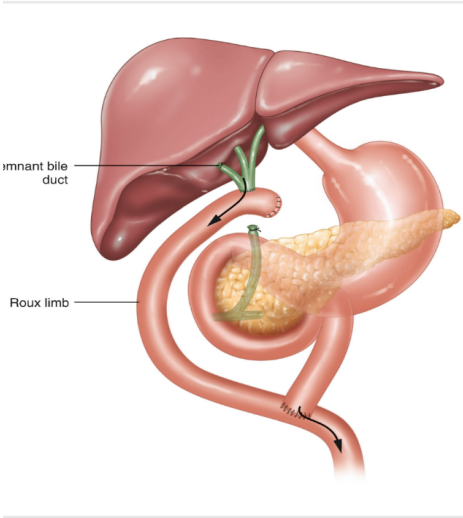

Figure 1: Roux-en-Y hepaticojejunostomy

On the 4th of February 2022, eighteen months after her surgeries, the patient presented to the ER for painless jaundice, pruritis and urinary symptoms. On further investigation, liver function tests (LFTs) were perturbated (total bilirubin 4.14 mg/dl, direct bilirubin 2.94 mg/dl, SGOT 137, SGPT 198, alkaline phosphatase ALP 418, GGT 720).

MRCP was performed that showed mild intrahepatic biliary duct dilatation and a new appearing 30x22 mm structure at the level of the choledochojejunostomy, isointense to the liver parenchyma, showing restriction on diffusion and mild enhancement after gadolinium administration. Such finding could represent either a collapsed bowel loop or a possible local recurrence. CT scan with oral contrast was then suggested (Figure 2A).

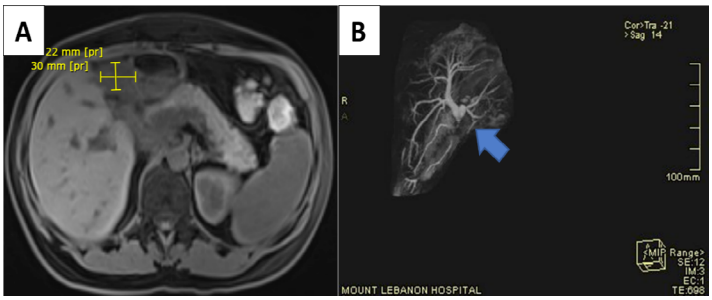

Figure 2: A: MRCP showing 30 x 22 mm structure at the surgical bed, at the level of the choledochojejunostomy isointense to liver parenchyma, showing restriction on diffusion and mild enhancement after gadolinium administration. It may represent either a collapsed bowel loop or local recurrence. **B**: MRCP abrupt cut-off at the choledocho-jejunostomy.

Afterwards, CT scan with contrast again showed the intrahepatic biliary ductal dilatation seen on MRCP, with the suspicious focal structure described at the surgical bed more likely suggestive of the small bowel anastomosis adherent to the common bile duct (CBD) and to the anterior abdominal wall showing minimal subcutaneous fat stranding. A follow up with positron emission tomography (PET) scan was then suggested for further assessment and evaluation (Figure 3).

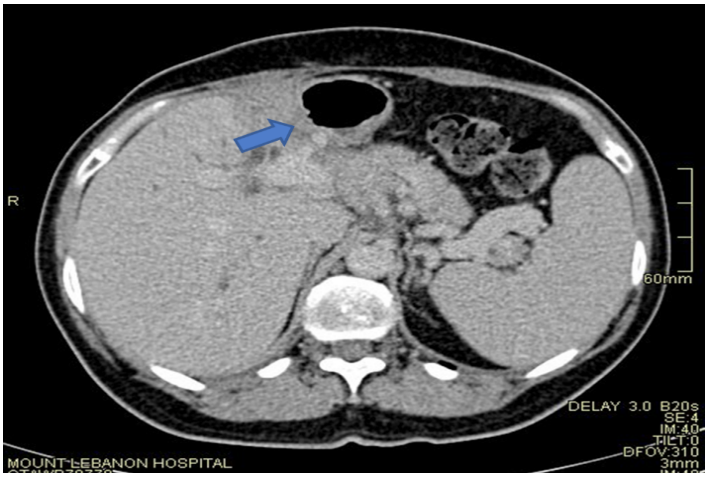

Figure 3: The suspicious focal structure described on the MRCP at surgical bed (blue arrow) is more likely suggestive of the small bowel anastomosis adherent to the CBD and to the anterior abdominal wall showing minimal subcutaneous fat stranding.

Fluorodeoxyglucose PET/CT (FDG-PET/CT) was later performed and confirmed a local recurrence of the cholangiocarcinoma (Figure 4). CA 19-9 levels were at 2202.56 U/mL, compared to 28.99 U/mL one year earlier after follow-up post-resection. Bilirubin levels were continuously increasing reaching a total bilirubin level of 16.09 mg/dl and a direct bilirubin level of 11.56 mg/dl.

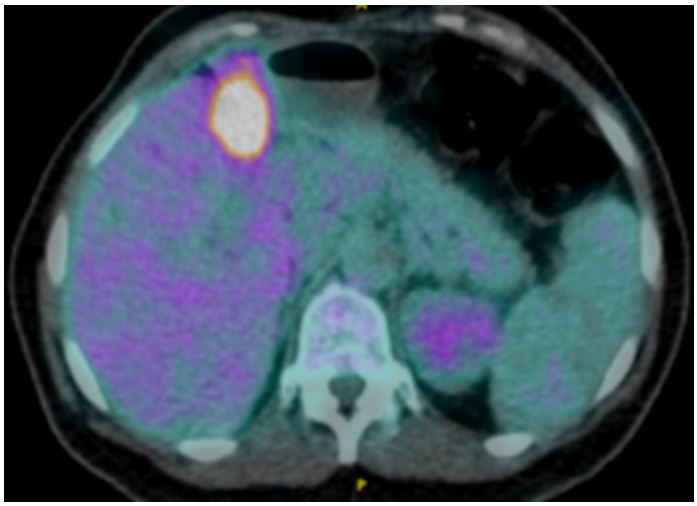

Figure 4: Focal intense FDG uptake anterior to the right hepatic lobe corresponding to an ill-defined soft tissue thickening inseparable from the hepatojejunal anastomosis with SUVmax 12.6, suspicious for locally recurrent disease.

Subsequently, a new multidisciplinary meeting was held with oncology, interventional radiology and the surgery team. After thorough discussion and planning, a decision for surgical resection of recurrent intrahepatic cholangiocarcinoma was taken. The patient was then discharged home and scheduled to return the following week for surgery.

On the 21st of February 2020, only two days following her discharge from the hospital, the patient presented to the emergency with high-grade fever, hypotension, severe pruritis and jaundice (total bilirubin 25.49, direct bilirubin 17.28, SGPT 637, SGOT 236, ALP 862, GGT 1538). After thorough evaluation, she was diagnosed with septic shock secondary to cholangitis. Appropriate care and resuscitation with Norepinephrine, IV antibiotics and fluids were started. As a result, she was scheduled for urgent operation.

During the surgery, the surgical team started with the identification of the hepaticojejunostomy after adhesiolysis, where it was resected and sent to pathology. Intra-operative pathology report confirmed the recurrence of cholangiocarcinoma at the site of the anastomosis. A hepatic resection was then performed till reaching anterior and posterior bile ducts with negative margins were confirmed with frozen pathology. A new end to side hepaticojejunostomy was created. Finally, a lamellated drain was inserted near the anastomosis site (Figure 5).

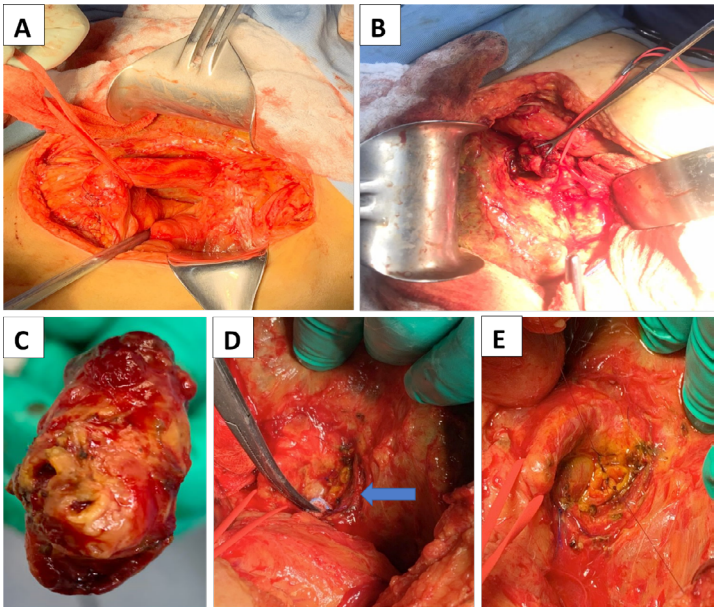

Figure 5: Pictures taken intra-operatively showing the (A) old hepaticojejunostomy, (B) dissection of the hepaticojejunostomy, (C) intrahepatic specimen removed until reaching negative margins, (D) posterior and anterior bile ducts (blue arrow), (E) end to side hepaticojejunostomy.

The post-operative hospital course was smooth, diet started 2 days post-op was well tolerated and escalated, subsequent LFTs were trending downwards (Total Bilirubin 5.73 mg/dl, direct bilirubin 3.82 mg/dl, SGOT 30, SGPT 163, Alkaline Phosphatase 434, GGT 584). The patient was finally discharged on day 4 post-op with the lamellated drain still in place, with a plan to follow-up in clinic. A new regimen of chemotherapy was started, consisting of Gemcitabine and Capecitabine.

Discussion

Intrahepatic cholangiocarcinoma (I-CCA) is an aggressive biliary tract cancer that develops from the biliary epithelium proximal to the second-degree bile ducts. The global incidence of I-CCA is increasing, and surgical resection is the only potentially curative remedy, even if the 5-year overall survival is minute, ranging between 15% and 45% due to various risk factors such as multifocal disease pattern, margin status, vascular infiltration, and lymph node involvement. Ample surgical resection is only achievable in 30–40% of I-CCA patients, often because of delayed diagnosis [4].

The incidence of I-CCA has increased significantly in the last few years, perhaps due to advances in differential diagnoses correlated to better imaging, molecular diagnostics, and pathology thoroughness [5]. Concurrently, mortality rates from I-CCA have shown a growing trend, predominantly justified by a better disease classification [6]. The prognosis of patients with I-CCA is unfavorable, with 5-year survival ranging from 15% to 45%, depending on tumor stage at diagnosis [7].

Several risk factors are linked to I-CCA: Primary Sclerosing Cholangitis (PSC), inflammatory bowel diseases, infections of the biliary tract, hepatitis B and hepatitis C infections, liver cirrhosis, diabetes, obesity, alcohol, and tobacco. Nevertheless, for the most part I-CCA patients have no underlying liver disease, as in our patient [8,9].

The 5-year recurrence free survival varies, from 2% to 39% after curative resection for I-CCA [10]. The most frequent recurrence location is the liver (82.7%), particularly within 24 months from resection, whilst recurrence beyond 24 months is mainly unique to an extrahepatic location such as lymph nodes, lungs, or to a less common location like bone, skin, or chest wall [10].

I-CCA displays various development patterns and is categorized as mass-forming, periductal infiltrating, or mixed types, based on the Liver Cancer Study Group of Japan (LCSGJ) categorization [11]. The LCSGJ also outlines an intraductal growth pattern, which is rare and associated with an improved outcome. The mass-forming is the most widespread type, characterized by an intraparenchymal lesion with distinct margins, while the periductal-infiltrating type causes tumor infiltration along the bile ducts. Certain studies exhibit inferior survival after resection of the periductal infiltrating type contrasted with the mass-forming type, whereas other studies exhibit no disparity in survival [9,12]. Lately, histologic studies have classified I-CCA into large duct and small duct subtypes, based on macroscopic growth patterns [10].

Intraductal papillary neoplasm of the bile duct (IPNB) is a form of bile duct carcinoma that is described by intraductal growth. IPNBs are mainly observed in Far Eastern regions, where hepatolithiasis and clonorchiasis are indigenous. This variant exhibits a positive prognosis when contrasted with non-papillary cholangiocarcinoma [13]. A study by Jarnagin W. et al demonstrated the significance of the papillary cholangiocarcinoma histology as a prognostic factor after complete resection [14]. Cholangiocarcinoma with a primarily tubular growth pattern is a rare cancer of the bile duct with an intraductal exophytic growth pattern, representing around 7% of all resectable cases. In a study done by Tsukahara T. et al. contrasting cholangiocarcinoma with intraductal tubular growth formation versus intraductal papillary growth formation, no changes were found in the expression of immunohistochemical stains between the intraductal tubular type and the papillary type. The 5-year survival rate for patients in the tubular group was comparable to that in the papillary group (70% vs 68%, P=0.693), however, the rate of liver metastases in tubular cases was far greater than in papillary cases (P=0.012). This is possibly due to microscopic venous infiltration, the rate of which was considerably greater in the tubular group than in the papillary group (P=0.035) [15].

Patients with I-CCA typically present with non-specific symptoms such as ambiguous right upper quadrant pain, weight loss, and lethargy, though jaundice is less common contrasted to hilar CCA patients (15–16% of cases). I-CCA is most observed in asymptomatic patients undergoing imaging for disturbed liver enzymes or a reason irrelevant to I-CCA. Tumor markers like CA 19.9 and CEA are of limited diagnostic value attributed to their low sensitivity for early stage I-CCA. Consequently, I-CCA is often diagnosed at an advanced stage with substantial locoregional involvement and/or remote metastases and hence a complete surgical resection is only achievable in 30–40% of patients [4].

The role of serum markers such as carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) as diagnostic tools is controversial, yet they remain the mandatory markers for workup and follow up of recurrence [10]. For distal and intrahepatic cholangiocarcinoma (CCA), increased preoperative values of the tumor marker CA 19-9 are linked to an inferior prognosis [16].

Our patient presented with recurrence at the anastomosis site, which resembled the presentation of perihilar CCA, hence the key objective of our pre-operative imaging was to evaluate tumor location and extension through the biliary tree, assess vascular infiltration at the hepatic hilum remnant, and to exclude the existence of nodal or distant metastases, in order to permit a

proper operative planning and staging. CT scan with IV contrast offers 86% accuracy for assessment of tumor's ductal extension, 89 to 92% sensitivity and specificity for portal vein infiltration, 83% to 93% for hepatic artery infiltration, but only 16% to 88% for lymph node involvement. MRI with MRCP, has same accuracy as CT, but offers a superior visualization of the biliary tree [10]. (PET) CT has a restricted function due to its low sensitivity in identifying tumor extension but maintains a significant role for detection of lymph node or distant metastases. Nevertheless, all Imaging should preferably be executed prior to biliary drainage [10]. On CT scans, I-CCA shows the usual appearance of a hypodense hepatic mass in the unenhanced phase with irregular borders, peripheral rim enhancing lesion in the arterial phase, and gradual hyper attenuation on venous and delayed phases [10].

Surgical resection represents the only possibly therapeutic management for patients with resect-able disease, though the majority of patients are not surgical candidates at the time of diagnosis due to advanced disease stage. The overall survival and disease-free survival depend on tumor status at the time of diagnosis and several risk factors. The effect of margin status the prognosis of patients undergoing liver resection for I-CCA continues to be a controversial issue. Several studies stated R0 resection as an important interpreter of survival and recurrence, while others proposed that margin status is not an important predictor of prognosis [10]. The effect of margin limit on prognosis is still disputed; So far, available data encourages the sanction that hepatic resection with negative limits should be the objective of surgical treatment in possibly resect-able I-CCA [10].

Lymph Nodes negative status carries a positive prognostic value, yet extensive lymphadenectomy is not regularly performed if lymph nodes are not macroscopically suspicious. Present evidence states that the incidence of lymph nodes metastases varies between 30% to 40% between patients undergoing lymphadenectomy [4,10]. Though the lack of evidence for routine lymphadenectomy in I-CCA patients, present guidelines indorse lymphadenectomy of porta hepatis lymph nodes to achieve a comprehensive staging and for the vital prognostic role of nodal invasion [10].

Systemic chemotherapy is the usual treatment of disease recurrence of I-CCA. Spolverato et al. reported a limited advance in median survival for patients that had undergone repeated surgery over those who obtained percutaneous ablation or intraarterial therapy [1]. Zhang et al. recounted a significant survival gain of repeated resection for larger mass sizes (>3 cm), and such findings were substantiated by Bartsch et al. in a small series evaluating redo hepatectomy to locoregional therapies [3,17]. If a R0 resection is attainable, a repeated hepatectomy in selected patients with recurrent I-CCA is valid [10].

While adjuvant chemotherapy is not a standard practice for I-CCA patients, a recent meta-analysis demonstrated that adjuvant chemotherapy is linked to a better overall survival and should be considered in patients with I-CCA after curative resection, especially in patients with advanced disease [18].

Till the time of this report, no RCTs examining the role of neoadjuvant chemotherapy in unresectable I-CCA patients. Hence explaining the reason for neoadjuvant chemotherapy not being applied as a standard in clinical practice, attributed to poor tumor response to treatment, and surgery being considered the best therapy if R0 resection is achievable. The role of radiation therapy for resected I-CCA patients is not well defined. Current guidelines do not suggest systematic use of radiation therapy after surgery [10].

In conclusion, an aggressive surgical practice for recurrent I-CCA attained adequate overall survival. Nevertheless, the ideal conditions for patient assortment need to be identified. So far, surgical indication for recurrent I-CCA remains individualized and should be done after interdisciplinary consideration in specialized centers to ensure low morbidity. In guidelines, repeated surgery should be stated as treatment option [3].

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References

1. Spolverato G, Kim Y, Alexandrescu S, Marques HP, Lamelas J, et al (2016) Management and outcomes of patients with recurrent intrahepatic cholangiocarcinoma following previous curative-intent surgical resection. Ann Surg Oncol 23: 235-43.
2. Souche R, Addeo P, Oussoultzoglou E, Herrero A, Rosso E, et al (2016) First and repeat liver resection for primary and recurrent intrahepatic cholangiocarcinoma. Am J Surg 212: 221-9.
3. Bartsch F, Paschold M, Baumgart J, Hoppe-Lotichius M, Heinrich S, et al (2019) Surgical Resection for Recurrent Intrahepatic Cholangiocarcinoma. World J Surg 43: 1105-1116.
4. Bridgewater J, Galle P, Khan S, Llovet J, Park J-W, et al (2014) Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 60: 1268-89.
5. Saha SK, Zhu AX, Fuchs CS, Brooks GA (2016) Forty-year trends in cholangiocarcinoma incidence in the U.S.: Intrahepatic disease on the rise. Oncologist 21: 594-9.

6. Khan SA, Genus T, Morement H, Murphy A, Rous B, et al (2019) Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. J Hepatol 71: 1261-1262.

7. Spolverato G, Bagante F, Weiss M, Alexandrescu S, Marques HP, et al (2017) Comparative performances of the 7th and the 8th editions of the American Joint Committee on Cancer Staging Systems for intrahepatic cholangiocarcinoma. J Surg Oncol 115: 696-703.

8. Raoof M, Singh G (2019) Rising trends in intrahepatic cholangiocarcinoma incidence and mortality: Getting at the root cause. HepatoBiliary Surg Nutr 8: 301-303.

9. Hwang S, Lee Y-J, Song G-W, Park K-M, Kim K-H, et al (2015) Prognostic impact of tumor growth type on 7th AJCC staging system for intrahepatic cholangiocarcinoma: A single-center experience of 659 cases. J Gastrointest Surg 19: 1291-304.

10. Lauterio A, De Carlis R, Centonze L, Buscemi V, Incarbone N, et al (2021) Current surgical management of peri-hilar and intra-hepatic cholangiocarcinoma. Cancers 13: 3657.

11. Yamasaki S (2003) Intrahepatic cholangiocarcinoma: Macroscopic type and stage classification. J Hepatobiliary Pancreat Surg 10: 288-91.

12. Shimada K, Sano T, Sakamoto Y, Esaki M, Kosuge T, et al (2007) Surgical outcomes of the mass-forming plus periductal infiltrating types of intrahepatic cholangiocarcinoma: A comparative study with the typical mass-forming type of intrahepatic cholangiocarcinoma. World J Surg 31: 2016-22.

13. Wan X-S, Xu Y-Y, Qian J-Y, Yang X-B, Wang A-Q, et al (2013) Intraductal papillary neoplasm of the bile duct. World J Gastroenterol 19: 8595-8604.

14. Tsukahara T, Shimoyama Y, Ebata T, Yokoyama Y, Igami T, et al (2016) Cholangiocarcinoma with intraductal tubular growth pattern versus intraductal papillary growth pattern. Modern Pathology 29: 293-301.

15. Jarnagin WR, Bowne W, Klimstra DS, Ben-Porat L, Roggin K, et al (2005) Papillary phenotype confers improved survival after resection of Hilar Cholangiocarcinoma. Ann Surg 241: 703-714.

16. Bergquist JR, Ivanics T, Storlie CB, Groeschl RT, Tee MC, et al (2016) Implications of CA19-9 elevation for survival, staging, and treatment sequencing in intrahepatic cholangiocarcinoma: A national cohort analysis. J Surg Oncol 114: 475-482.

17. Zhang S-J, Hu P, Wang N, Shen Q, Sun A-X, et al (2013) Thermal ablation versus repeated hepatic resection for recurrent intrahepatic cholangiocarcinoma. Ann Surg Oncol 20: 3596-602.

18. Ma KW, Cheung TT, Leung B, She BW, Chok KS, et al (2019) Adjuvant chemotherapy improves oncological outcomes of resectable intrahepatic cholangiocarcinoma. Medicine 98: e14013.