Cholangiolocarcinoma With Multiple Recurrences Successfully Treated With Repeated Liver Resection and Radiofrequency Ablation

NOBUTAKA SATO[1], KENSUKE YAMAMURA[1], ERI ODA[1], SHINICHI AKAHOSHI[1],
HIDEAKI YUKI[2], TOSHIHIKO MOTOHARA[3], HIDEAKI MIYAMOTO[4],
DAIKI YOSHII[5], YOSHIHIKO KOMOHARA[5] and TORU BEPPU[1]

[1]Department of Surgery, Yamaga City Medical Center, Kumamoto, Japan;
[2]Department of Radiology, Yamaga City Medical Center, Kumamoto, Japan;
[3]Department of Gastroenterology, Yamaga City Medical Center, Kumamoto, Japan;
[4]Department of Medical Oncology, Yamaga City Medical Center, Kumamoto, Japan;
[5]Department of Cell Pathology, Graduate School of Medicine, Kumamoto University, Kumamoto, Japan

Abstract. *Background/Aim: The prognosis of cholangio-locarcinoma, a rare malignant liver tumor derived from hepatic progenitor or stem cells, is considered relatively good; however, it frequently recurs. We herein present the diagnosis, histological findings, and treatment of cholangiolocarcinoma. Case Report: A 65-year-old woman with a large liver tumor (70 mm in diameter) was referred. Hepatocellular carcinoma was suspected based on strong early enhancement and delayed washout by enhanced computed tomography. The patient underwent curative left tri-sectionectomy. Histologically, she was diagnosed with pure cholangiolocarcinoma in a slightly fibrous liver. Three metachronous recurrent lesions (all ≤10 mm in diameter) were found between fifteen and twenty months after the initial hepatectomy. One lesion and the remaining two lesions were treated with hepatectomy and radiofrequency ablation, respectively. Two years after the initial diagnosis, she was doing well without recurrence. Conclusion: Repeated hepatectomy and radiofrequency ablation might be useful for small intrahepatic recurrences of cholangiolocarcinoma.*

Cholangiolocarcinoma (CLC), previously named as cholangiolocellular carcinoma, is a rare malignant liver tumor arising from hepatic progenitor or stem cells; CLC is also

Correspondence to: Toru Beppu, Department of Surgery, Yamaga City Medical Center, 511, Yamaga, Kumamoto, 861-0593, Japan. Tel: +81 968442185, Fax: +81 968442420, e-mail: tbeppu@yamaga-mc.jp

defined as a variant of combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) by the 2018 World Health Organization classification (1, 2). cHCC-CCAs comprising CLC in more than 90% of the entire tumor are defined as CLC. (3). Due to its low incidence of 0.56% in patients with resected primary liver cancer, the clinicopathological features of CLC are not well defined (4). Macroscopically, CLC mimics mass-forming type intrahepatic cholangiocarcinoma (ICC); however, its malignant features are less extensive compared to ICC (5). Long-term survival after liver resection is significantly higher in patients with CLC compared to those with mass-forming type ICC.

Liver cirrhosis (27%) and chronic hepatitis with varying degrees of fibrosis (73%) were defined as the background liver conditions in a study of 30 patients with CLC (3). In another study, 76% of the 29 patients had chronic liver disease, which was significantly greater than 48% in those with mass-forming type ICC (6).

In diagnostic imaging studies, CLC mimics mass-forming type ICC in the liver periphery and often shows clinical and imaging findings similar to those of hepatocellular carcinoma (HCC) (7-10). On arterial phase images, CLC appears as a mass with early and complete enhancement or with predominantly peripheral enhancement. Contrast medium retention in the lesion is observed in half of the patients (7-10).

Standard treatment for ICC and cHCC-CCA, including CLC, is liver resection and systemic chemotherapy (11, 12). In contrast, radiofrequency ablation (RFA) has not been recommended for ICC because of insufficient local control (13). Because of the lower malignant feature compared with ICC, RFA for CLC is considered to provide good local control and long-term survival (14).

Herein, we report a patient with CLC and multiple recurrences who was successfully treated with repeated liver resections and RFA treatments.

Case Presentation

A 65-year-old woman visited our hospital with epigastric pain. She had been undergoing treatment for rheumatoid arthritis at the referred clinic, but her condition was well controlled. Her body mass index was 18.0 kg/m^2. She had a history of alcohol use (20 g daily) and smoking (30 cigarettes daily) for about 45 years. She had good liver function and no history of viral hepatitis or metabolic diseases including diabetes mellitus, hypertension, and dyslipidemia. She had Child-Pugh grade A chronic liver disease (5 points). Among the several tumor markers that were evaluated, only alpha fetoprotein was slightly elevated at 10.2 ng/ml (normal, ≤10 ng/ml).

Contrast-enhanced computed tomography (CT) imaging revealed a solitary, hypodense tumor, with the largest diameter of 70 mm, in the medial to ventral anterior sector of the liver (Figure 1). The tumor showed strong early enhancement and delayed washout with peripheral enhancement. By retrospective investigation, penetration of the middle hepatic artery and middle hepatic vein into the tumor was evident from the arterial phase to the portal venous phase. Gadolinium d-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced (EOB) magnetic resonance imaging (MRI) (Figure 2) revealed that there was no fat content in the chemical-shift images. The tumor showed mildly high intensity on T2-weighted images and high intensity on diffusion-weighted images on b800 image. The calculated mean apparent diffusion coefficient was 1.4×10^{-3} mm^2/s. The tumor showed homogenous enhancement in the arterial phase, and the degree of tumor enhancement was decreased in the portal venous phase. The tumor exhibited a low signal in the hepatobiliary phase.

The preoperative diagnosis was stage II HCC (T2N0M0) based on the classification of the Liver Cancer Study Group of Japan (15). The tumor was adjacent to the right anterior and umbilical Glissonean pedicle but exhibited expansive growth. The indocyanine green retention rate at 15 min was 7.3%, and the volumetric liver resection rate was approximately 55%; therefore, left trisectionectomy was planned according to the institutional resection criteria (16, 17). Lymph node dissection was not performed due to the absence of lymphadenopathy. The operation was completed with curative intent, the operation time was 337 min, and total blood loss was 700 ml with no blood transfusion.

The macroscopic and microscopic images of the tumor specimens are shown in Figure 3. Macroscopically, the tumor was a well-circumscribed, whitish-colored nodule, 6.5 cm in diameter (Figure 3A). Histologically, the main tumor exhibited moderately differentiated adenocarcinoma components with eosinophilic cytoplasm and fibrous stroma in 90% of the tumor mass. Small duct components with hyalinized fibrous stroma were observed in the tumor center comprising approximately 10% of the entire tumor (Figure 3A). These tumor cells appeared to have proliferated by replacing the surrounding normal hepatocyte cords. Mucin production was not found in the tumor or the satellite nodule, which was 7 mm in size and composed mainly of small duct components with hyalinized fibrous stroma. Capsule formation or vascular invasion was not observed. By immunohistochemical staining, almost all cancer cells were positive for cytokeratin 7, cytokeratin 19, neural cell adhesion molecule (NCAM or CD56), epithelial membrane antigen, and SOX9 (Figure 3B) and negative for hepatocyte-specific antigen, insulinoma-associated 1, gross cystic disease fluid protein-15, glypican-3, hepatocyte nuclear factor 4 alpha, synaptophysin, and chromogranin A. Features suggesting HCC and ICC were not detected. These observations were consistent with stage III pure intrahepatic CLC (2). Slight portal fibrosis and mild inflammation were observed in non-cancerous areas.

Fifteen months after the first hepatectomy, a solitary recurrent lesion, 10 mm in diameter, was found in segment 6 of the residual liver (Figure 4A and D). The imaging findings were similar to those of the previously resected tumor. Most of the laboratory values and all tumor markers were within normal limits. Partial hepatectomy by thoracotomy was planned. To reduce intraoperative blood loss, precoagulation by RFA (18) was performed on the resection line. The operation time was 188 min, and total blood loss was 230 ml without blood transfusion. The recurrent lesion, a well-circumscribed, whitish-colored tumor nodule, was resected (Figure 3C). The histopathological characteristics of the recurrent tumor were similar to the primary tumor; however, the stromal components were less than those of the primary tumor (Figure 3C). The histopathological features of the non-cancerous area were identical to those of the primary resected specimen. The Ki67 labeling indices were 16% and 24% in the primary and recurrent lesions, respectively (Figure 3D).

The patient developed second and third recurrences three and five months after the resection of the first recurrent lesion, respectively. The EOB-MRI showed that these were well-enhanced tumors, including one 4-mm tumor in segment 6 and one 9-mm tumor in segment 7, with hepatobiliary defect (Figure 4B-F). Percutaneous RFA under general anesthesia was performed for the 2nd recurrence. Contrast-enhanced ultrasonography with sonazoid™ and fusion imaging using ultrasonography and hepatobiliary EOB-MRI were performed. RFA was successfully completed, ensuring a sufficient safety margin. For the 3rd recurrence, the tumor was located deeper from the liver surface, near the inferior vena cava; therefore, open RFA was applied. At 2 years after the initial diagnosis, the patient was

Figure 1. *Preoperative abdominal computed tomography (CT) image of the tumor (arrow) in the liver. (A) Plain CT image shows the hypodense tumor, which exhibits early enhancement during the arterial (B) and portal venous (C) phases and delayed washout in the equilibrium phase (D). Vessel penetration into the tumor (arrow heads) was observed on axial CT images in the arterial phase (E) and coronal CT images in the portal venous phase (F).*
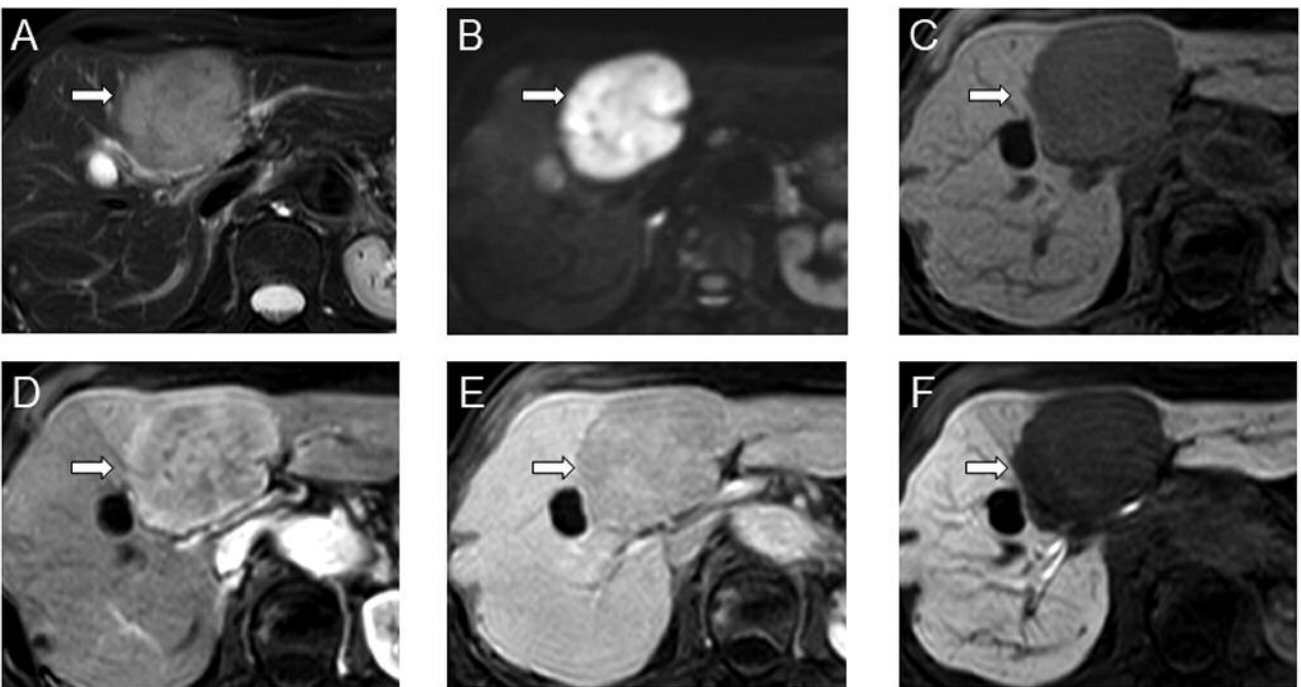

Figure 2. *Preoperative magnetic resonance (MR) images. (A) Fat-suppressed T2-weighted MR image; (B) diffusion-weighted MR image; (C-F) axial gadolinium d-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced (EOB) MR images of the precontrast (C), arterial (D), portal venous (E), and hepatobiliary (F) phases, respectively. Tumor is indicated using arrows.*
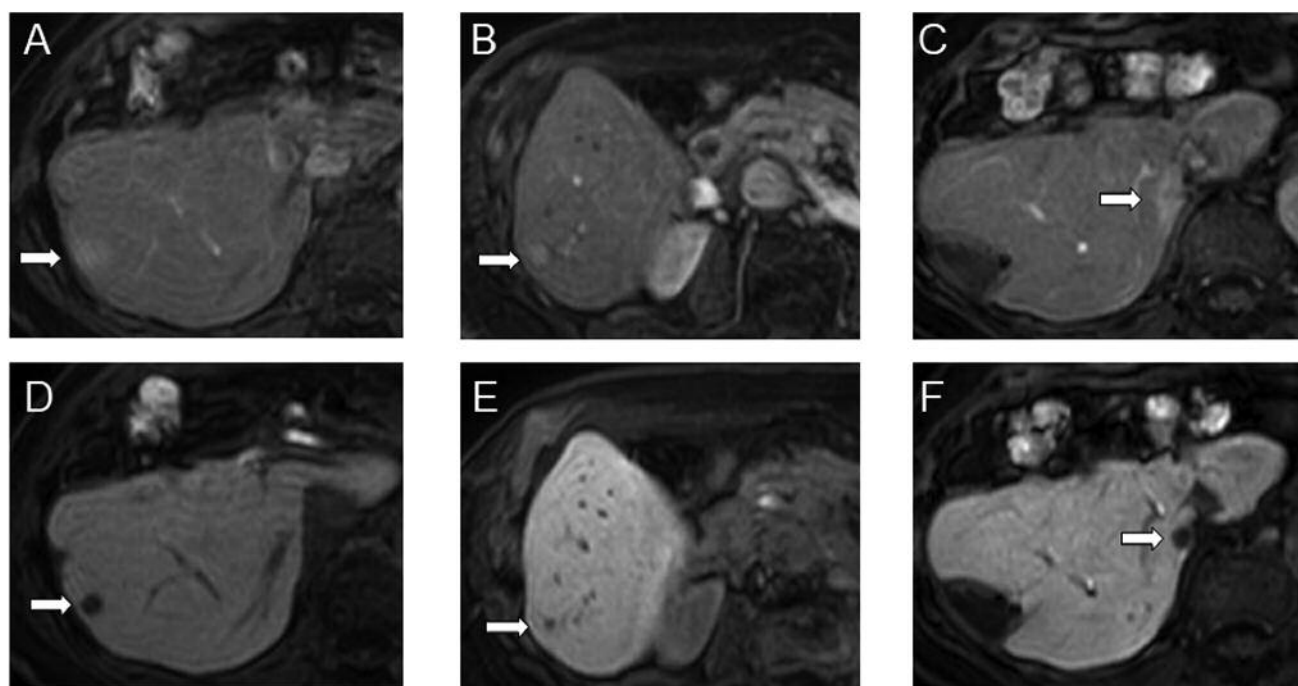
Figure 3. *Macroscopic and microscopic findings. (A) Macroscopic and microscopic findings of the primary tumor, which show a mass-forming growth pattern. Tumor cells are composed of antler-like and anastomosing patterns with abundant fibrous stroma. The arrowhead shows the satellite nodule. (B) Cancer cells are positive for cytokeratin 7 (#OVTL12/30; Nichirei, Tokyo, Japan), cytokeratin 19 (#M0888; DAKO, Glostrup, Denmark), neural cell adhesion molecule (#MRQ42; Nichirei), epithelial membrane antigen with luminal patter (#M0613; DAKO), and SOX9 with nuclear pattern (#AB5535; Merck Millipore, Burlington, MA, USA) and negative for hepatocyte (#M7158; DAKO). (C) Macroscopic and microscopic findings of the first recurrent tumor. (D) Staining for Ki67 (#7240; DAKO) in the primary and recurrent lesions.*

doing well with no CLC recurrence. The patient provided informed consent for all treatments.

Discussion

The number of reports on CLC has been gradually increasing with its recent recognition of CLC in the 2018 World Health Organization classification (2). Although CLC is considered to originate from hepatic progenitor cells in the canals of Hering, a recent study has proposed that CLC arises from interlobular ducts based on morphometric and immunohistochemical analyses (19). Therefore, the origin of CLC remains controversial. The current patient was diagnosed with pure CLC based on the immunohistochemical staining showing that almost all cancer cells were positive for cytokeratin 7 and cytokeratin 19, NCAM, epithelial membrane antigen, and SOX9. SOX9 is the earliest marker of intrahepatic bile duct cells and controls the timing of their morphogenesis (20). In addition, SOX9 and NCAM are markers of hepatic progenitor cells (21). SOX9 is suggested to be a diagnostic marker for CLC, although few studies have reported SOX9 expression in CLC.

The clinical preoperative diagnosis was HCC in the current patient based on overt arterial enhancement with delayed washout and rim-like sign in the equilibrium phase. In almost all patients with CLC, the enhancement in arterial phase persists until the delayed phase (7-10). In the present case, the tumor exhibited a hypo-intense area in the hepatobiliary phase of EOB-MRI and had an apparent diffusion coefficient of 1.4×10^{-3} mm^2/s on diffusion-weighted MRI. However, by minute investigation, the tumor was diagnosed as CLC based on the tumor penetration of the middle hepatic artery and vein as well as the medial portal vein (22).

The present patient had large and multiple moderately differentiated CLCs, but the initial disease-free interval of 15 months was relatively long. Thereafter, three recurrences rapidly occurred within a five-month period. The Ki67 labeling indices were 16% and 24% in the primary and recurrent CLC lesions, respectively (Figure 3D). The reported Ki67 labeling index in ICC was approximately 23% (23), while few studies have observed a Ki67 labeling index of about 15% in CLC (24). Therefore, the recurrent lesions might have had a higher malignant potential.

Liver resection is the standard treatment approach for liver-limited ICC and cHCC-CCA including CLC, and better long-term survival is observed in CLC compared with mass-forming ICC after liver resection (5). One case study reported a patient
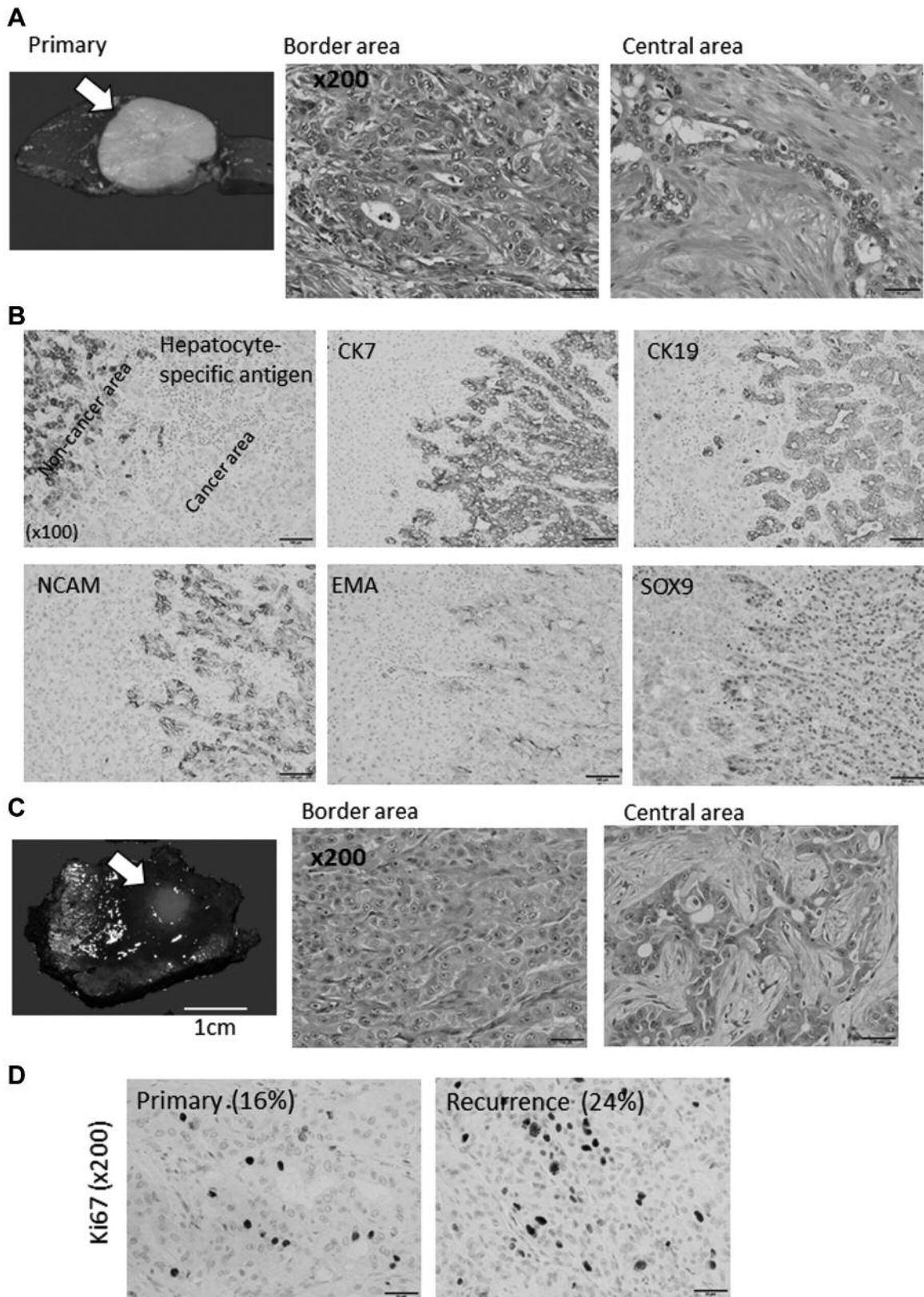
Figure 4. *Preoperative magnetic resonance images of the first, second, and third recurrences. EOB-MR images of the arterial and hepatobiliary phases of the first (A and D), second (B and E), and third (C and F) recurrences. Arrows indicate recurrent tumors.*

with a large CLC, 10 cm in diameter, who underwent liver resection seven times and postoperative adjuvant chemotherapy with gemcitabine and S-1 after the first operation (25). Surprisingly, the patient was still alive seven years after the initial liver resection. However, repeated liver resections in a short period are not always comfortable for patients with recurrent disease. Although systemic chemotherapy with cisplatin plus gemcitabine is an option in patients with recurrent biliary cancer, the response rate is only 26% and complete response is rarely achieved (26). Combination of gemcitabine with S-1 has recently become another treatment option (27). RFA has been developed mainly for small HCC and can provide excellent local control (13). A meta-analysis of 84 patients with ICC undergoing RFA (14) revealed that the 1-, 3-, and 5-year survival rates were 82%, 47%, and 24%, respectively. The local progression rate was relatively high (21%); however, the ablated tumor size varied from 0.8 to 10 cm. Tumor size <1.5 cm was reported as an important factor for good local control (28). A unique case report demonstrated that RFA could provide excellent local control in patients with small CLC (29). In that study, 10 CLC tumors, all ≤22 mm in size, were successfully treated with RFA seven times; none of the tumors exhibited local recurrence. The authors speculated that local control of CLC might be better than that of ICC as CLC usually presents as a hepatic parenchymal solid mass without periductal and vascular invasion, massive fibrosis, or cystic degeneration (5). Further, the authors emphasized the utility of intensive follow-up by EOB-MRI to detect recurrence of small-sized tumors. The patient was alive with no recurrence 9.2 years after the primary liver resection. In the present case, the second and third recurrent tumors were 4 and 9 mm in diameter, respectively, and both tumors were located in the peripheral liver; therefore, they were treated with curative RFA.

Conclusion

We herein presented the case of a patient with large and multiple CLCs who developed multiple postoperative recurrences. Primary and recurrent tumors were well controlled by liver resection in combination with RFA. Therefore, RFA should be considered as a therapeutic option for peripheral small hepatic recurrence of CLC.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

NS and TB conceived the study and wrote the draft of the paper; NS, KY, EO, SA, HY, SC, HM, and TB treated the patient and collected information; and YK and DY investigated the histological findings.

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