Synchronous Double Primary Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma: A Case Report and Review of the Literature

Meng-Meng Qu
Lanzhou Medical College: Lanzhou University
Yuan-Hui Zhu
Lanzhou Medical College: Lanzhou University
Yi-Xiang Li
Lanzhou Medical College: Lanzhou University
Zhi-fan Li
Lanzhou Medical College: Lanzhou University
Jin-Kui Li
Lanzhou Medical College: Lanzhou University
Jun-Qiang Lei (leijq2011@126.com)
Lanzhou University First Affiliated Hospital https://orcid.org/0000-0003-3091-4308

Case report

Keywords: Double primary hepatic cancer, Hepatocellular carcinoma, Intrahepatic cholangiocarcinoma, Chronic liver infection, imaging

Posted Date: July 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-650018/v1

Version of Record: A version of this preprint was published at Medicine on November 19th, 2021. See the published version at https://doi.org/10.1097/MD.0000000000027349.

Abstract

Background: Synchronous double primary hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) (sdpHCC-ICC) located separately within a single liver is extremely rare. The purpose of this study is to investigate the clinical, imaging, pathological characteristics and prognosis of patients with sdpHCC-ICC, in order to enhance our understanding of the disease and improve diagnostic and therapeutic effect.

Case presentation: A 49-year-old female patient with obvious liver cirrhosis, who carried hepatitis B virus, was admitted to our hospital for physical examination. The level of α-fetoprotein (AFP) and carbohydrate antigen 19-9 (CA19-9) was found to be elevated. Abdominal ultrasonography and enhanced computed tomography revealed two solid masses located in segments (S) 4 and 6 of the liver, with malignant behaviors. The preoperation diagnosis was multiple primary hepatocellular carcinomas. We performed hepatic resection of both segments. The resected specimens revealed that the tumors in segments 4 and 6 were well-defined lesions of 5.0 cm and 2.5cm, respectively. Histopathological examination confirmed that the tumor of the 4th segment to be moderately and poorly differentiated ICC, and that the tumor of the 6th segment to be poorly differentiated HCC. Immunohistochemically, the ICC in S4 was positive for CK19 and negative for Heppar-1, while the HCC in S6 was positive for Heppar-1 and negative for CK19. Unfortunately，metastasis and recurrence of multiple organs and lymph nodes were observed only 3 months later.

Conclusions: The clinical characteristics of sdpHCC-ICC are usually atypical. It is of difficulty to make an accurate preoperative diagnosis. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection were both the independent risk factor to the development of sdpHCC-ICC. In patients with chronic liver disease, careful observation with imaging examination should be necessary. Tumor markers may be valuable to the diagnosis of it. The definite diagnosis depends on pathological examination. Hepatic resection may be the preferred and most effective treatment. The prognosis of synchronous occurrence of double hepatic cancers was poorer than for either HCC or ICC, and the origin of it needs further study.

Background

Primary liver carcinoma (PLC) can histologically be divided into 3 types according to World Health Organization [1]: hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CCA). Although HCC and ICC are the two main forms of primary liver cancer, the incidence of synchronous double primary hepatic cancers comprising both of them is very low [2–4]. The two types of tumors can be recognized concurrently in the same tumor or separately at different sites in the same liver. Allen [5] classified the tumors of concurrent HCC and ICC into three categories, which included type A (separate double nodules of HCC and ICC), type B (contiguous masses of HCC and ICC) and type C (the mixed tumor intermingling with components of both HCC and ICC). The two latter types of tumors are a form of cHCC-CCA according to the present consensus [6]; however, the former is separately regarded as synchronous double primary hepatocellular

carcinoma and intrahepatic cholangiocarcinoma (sdpHCC-ICC). The incidence of sdpHCC-ICC is extremely low in clinical practice. Therefore, only a few studies were performed to report [2–4, 7–9]. It is difficult to diagnose before operation, since the clinical characteristics remain poorly understood. We herein report a patient who underwent hepatic resection for sdpHCC-ICC with a background of hepatitis B virus (HBV) infection obvious liver cirrhosis. We also review the current literature of related clinicopathological and imaging features and analyzed the clinical diagnosis and treatment characteristics, in order to improve the clinical understanding of sdpHCC-ICC.

Case Presentation

A 49-year-old Chinese female patient was admitted to our hospital for evaluation of her two hepatic tumors which were observed in abdominal ultrasonography when he performed physical examination. She was diagnosed as hepatitis B viral infection positive and obvious liver cirrhosis 4 years ago. Then she had antiviral therapy with entecavir and anti-fibrosis therapy with compound soft-liver tablet of Trionyx nail. She also had a history of uterine leiomyomas for several years,and progesterone preparation was introduced for treatment. Medical check-ups included abdominal ultrasonography in outpatient department of our hospital. It revealed two solid hepatic tumors, and she was referred to our hospital in consideration of the progress of her condition. The laboratory findings included: platelet and white blood cell counts of 76.00×10^9/L and 2.91×10^9/L□respectively; hemoglobin, albumin, and total bilirubin levels of 120 g/L, 52.4 g/L and 17.3umol/L, respectively; and aspartate (AST) and alanine aminotransferase (ALT), alkaline phosphatase, and gamma-glutamyl transpeptidase concentrations of 34.6 U/L, 26.0 U/L, 129.4 U/L, and 48.4 U/L, respectively. She had a prothrombin time (percent) of 57.0%. Her indocyanine green retention rate at 15 minutes was 1.3%. Hepatitis B virus antigen was positive. Her serum alpha-fetoprotein was elevated (82.7 IU/ml□normal□5.8 IU/ml). The level of carbohydrate antigen 19 − 9 was also found to be elevated (270.6 U/ml ,normal□27 U/ml).

Abdominal contrast-enhanced ultrasonography (CEUS) identified two separate well-defined hypoechoic masses that were heterogeneous on the inside in the segment 4 (S4) and segment 6 (S6) of the liver (5.0×4.6 cm and 2.5×2.1 cm in size, respectively), and the enhanced characteristics suggested that both of them were hypervascular tumors (Fig. 1). Subsequently, preoperative abdominal contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) provided images of the two separate masses with different contrast features (Figs. 2 and 3). Based on these preoperative examinations, the liver tumors were diagnosed as atypical multiple primary hepatocellular carcinomas. The patient underwent partial liver resection and cholecystectomy. The resected specimen showed that the tumor in S4 was a well-defined off-white slightly hard elastic lesion, and that the tumor in S6 was a round yellowish-white soft elastic lesion. We carried out an intraoperative pathologic examination of a lymph node at the hepatic portal region and recognized tumor cells in the presented lymph node, so extensive lymphadenectomy was added to the hepatectomy. The pathological examination revealed that the S4 tumor was moderately and poorly differentiated ICC (Fig. 4A), while that of the S6 was poorly differentiated HCC (Fig. 4B). There were no cancerous emboli were found in vein and lymph vessel. The pathological findings of the hepatic tissue adjacent to the tumors included liver cirrhosis. The

immunohistochemical examination of the S4 tumor cells stained positive for CK19 and negative for Heppar-1, and the S6 tumor cells were positive for Heppar-1 and negative for CK19. According to the histological findings, the liver tumors in this patient were diagnosed as synchronous double primary liver cancers.

The postoperative course was uneventful and she was discharged on postoperative day 15. At the first follow-up after one month later, there were evidences of new recurrent lesions in the left lobe of the liver. So TACE was performed without any contraindications. Unfortunately, metastasis and recurrence of bilateral lung, left pubic bone and lymph nodes in the hepatoduodenal ligament and the paraaortic region were observed 3 months later. The patient died of liver failure 16 months after surgery.

Discussion

sdpHCC-ICC is a rare special primary liver malignancy, which pathogenesis is still unclear. The possible pathogenesises for sdpHCC-ICC are presumed as follows: HCC and ICC arise independently and separately; HCC arises first and transforms to ICC or vice versa; malignant transformation of hepatic progenitor cells occurs, and they differentiate completely or incompletely into HCC and ICC [10].

In some previous reports, sdpHCC-ICC was generally included as cHCC-CCA [5, 11–12]. However, the World Health Organization (WHO) reclassified cHCC-CCA in 2004, and called independent HCC and ICC occurring simultaneously in the liver as double primary carcinoma, which were excluded from cHCC-CCA. The proportion of sdpHCC-ICC is usually much lower than that of cHCC-CCA. A previous retrospective study reported that sdpHCC-ICC occupied 0.23% of primary liver cancers [13]. According to the Surveillance, Epidemiology, and End Results (SEER) database, the actual incidence of sdpHCC-ICC was estimated to be far less than 0.8% [14]. Considering it is so rare, it is very difficult to diagnose before pathological confirmation of the surgical specimens. None of 10 patients was diagnosed accurately preoperatively in the above-mentioned retrospective study [13]. In fact, Inaba et al. [2] indicated that most cases of multiple liver tumors were diagnosed initially as HCCs, with only about 20% being accurately diagnosed as synchronous primary hepatic tumors. The case of our report was also misdiagnosed as multiple HCCs prior to pathological confirmation.

There have been reports noted a relationship between chronic liver inflammation and sdpHCC-ICC, as most cases involved chronic hepatitis or cirrhosis [2, 4]. It is well-recognized, however, that hepatitis or liver cirrhosis caused by HBV or HCV infection has been suggested to be potential risk factors for HCC and ICC [15–17]. Moreover, these relationships were supported by previous studies which showed that chronic liver inflammation played a significant role at the molecular level in coincidental double primary tumor of liver HCC and ICC [18, 19]. Of these, HCV infection may be considered to have one of the closest associations with development of sdpHCC-ICC, and to-date, most of cases have been detected in livers infected with HCV [2, 20, 21]. For example, the report of 33 synchronous double cancer cases by Watanabe et al [20] confirmed that 72.7% of patients were HCV infection, while only 9.3% of patients were

HBV infection. However, in our study, the 49-year-old female had a history of HBV infection with obvious cirrhosis of the liver.

The clinical manifestations of HCC and ICC are not specific, and only a few patients have discomfort such as fatigue in early time, which can not help to make accurate diagnosis. In practice, blood tumor markers and imaging findings are helpful to determine the diagnosis of primary liver cancers. Tumor markers are intrinsically linked to certain tumors. Heppar-1 and AFP are commonly used as the most significant tumor marker for HCC, while CK7 and CA19-9 are valuable markers for differentiating ICC from HCC [23, 24]. According the study of Cao[22],the frequency of simultaneously increased AFP and CA19-9 levels in sdpHCC-ICC (29%) was significantly higher than that in pure HCC (9%) or ICC(6%). This may be an important characteristic of sdpHCC-ICC, and might help to distinguish multiple HCCs or ICCs from sdpHCC-ICC before surgery. In our report, the simultaneously elevation for both AFP and CA19-9 levels may provide some information. Nevertheless, the tumor markers were not sensitive and specific enough to diagnose sdpHCC-ICC. cHCC-CCA also has HCC and ICC components, the elevation of two tumor markers can also be observed, which needs imaging examination to help further diagnosis.

Recently, some studies have examined the imaging findings in cases of ICC [25–27]. Ultrasound usually shows hypoechoic mass. However, characterization of a malignant mass on US is often limited because of its variability and nonspecificity [28]. CT and MRI reveal as well-defined solid tumor and various types of contrast enhancement[25, 27]. The main features of ICC are “delayed reinforcement” ,which appear enhancement feature with peripheral enhancement on the early phase and mild centripetal progression of enhancement over time in dynamic CT and MRI [29]. The preoperative CT or MRI findings always diagnose as “atypical liver cancer” and cannot give an accurate diagnosis in many cases. [20]. The primary mass features of enhanced CT or MRI image are “fast wash-in and fast wash-out,” which are the main features of HCC. But the secondary masses were always considered to be the satellite nodules or intrahepatic metastasis of primary tumor. So, clinicians can make a diagnosis of multiple liver malignant tumors for sdpHCC-ICC patients. In fact, the CT or MRI images of sdpHCC-ICC are mainly the combinations of the image features with HCC and ICC. Clinicians should consider the possibility of sdpHCC-ICC even if its incidence is very low when the same image is characterized by HCC and ICC. On review of the CT and MRI features of our patient, we admitted that the larger tumor had several features of ICC, but it was still difficult to confirm the diagnosis. In this case, the diagnosis might have been further confused by the knowledge of a higher prevalence of HCC than ICC in HBV patients. Therefore, for patients with simultaneous increase of AFP and CA19-9, sdpHCC-ICC should be strongly suspected especially in chronic hepatitis patients, even if the prevalence of it is very low. A variety of imaging methods and should be combined to improve the preoperative diagnosis of sdpHCC-ICC.

For treatment of these patients with sdpHCC-ICC, although several other methods have been tried, surgical resection is regarded as the treatment of choice because it can provide an accurate diagnosis as well as a chance of cure and is especially suitable for patients without cirrhosis of the liver [30, 31]. However, commonly combined liver cirrhosis has the risk of serious postoperative complications, such as seroperitoneum, hypoproteinemia, and pleural effusion. These complications may have been prevented

with protein complement and diuresis actively after the operation [32]. So strict choice of patients before surgery is important, and general physical condition should be considered, for example, any pre-existing cirrhosis and tumor extent [33, 34]. Recently, aggressive treatments including liver transplantation have been used on patients as a radical choice [35]; however, the long-term curative effect of liver transplantation need to be further researched. Transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) also can be considered according to the size and location of the tumors, which are widely used for unresectable masses and patients with recurrence after resection. However, sdpHCC-ICC contains more fibrous tissue and fewer vascular components than HCC, and therefore, the therapeutic effect of TACE or PEI is limited [36]. In our case, we performed hepatic resection on the patient for the first method, and the treatment of TACE was also used because of the intrahepatic recurrence after 45 days of the resection. The patient showed evidence of metastasis or new recurrent lesions.

The prognosis of double primary cancer varies among different studies. However, the prognosis of sdpHCC-ICC has commonly been recognized to be poorer than that of either HCC or ICC due to the ability of metastasis and recurrence of the double type[37]. Cao retrospectively studied the clinical characteristics of 35 cases of sdpHCC-ICC and revealed that tumor recurrence developed in 77.1 % of patients, and distant metastases were detected in 20 % of patients after partial hepatectomy. The median overall survival (OS) was 18 months, and the 1-year, 3-year, 5-year OS rates were 60.0%, 28.9%, and 23.1 %, respectively [22]. Multivariate analysis showed that the tumor size, histological

differentiation of the ICC component and presence of lymph mode metastasis were independent risk factors for OS. In addition, Li et al also noted in their study that the ICC tumor size can affect not only patient's disease-free survival (DFS), but also OS, while HCC tumor size can only effect OS [32]. We speculated that the

influence of ICC on DFS, OS, or even the overall situation of patients with sdpHCC-ICC was greater than that of HCC. Therefore, for patients with sdpHCC-ICC, the clinician may need to pay more attention to the development and management of the ICC.

Conclusions

In summary, we have reported an extremely rare case of simultaneous double primary liver cancer consisting of HCC and ICC at separate locations of the liver in patients who infected B-viral chronic hepatitis. Although sdpHCC-ICC is very rare, the occurrence of it should be considered in the differential diagnosis of multiple liver tumors. The combination of tumor markers analysis and imaging findings may be helpful to determine an accurate preoperative diagnosis, but the final diagnosis depends on pathological and immunohistochemical examination. Surgery remains the primary treatment option. The prognosis of patients with sdpHCC-ICC is poor, and the ICC component plays a more significant role than the HCC component in influencing prognosis. Since chronic liver inflammation may give rise to double

primary liver cancer, it is of much importance that more attention is paid to sdpHCC-ICC and more information about patients with such cases need to be collected for further research.

Abbreviations

HCC, primary hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; sdpHCC-ICC, synchronous double primary hepatocellular carcinoma and intrahepatic cholangiocarcinoma; PLC, primary liver carcinoma; cHCC-CCA, combined hepatocellular carcinoma and cholangiocarcinoma; AFP, α-fetoprotein; CA19-9, carbohydrate antigen 19 − 9; HBV, Hepatitis B virus; HCV, hepatitis C virus; CEUS, contrast-enhanced ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; TACE, Transcatheter arterial chemoembolization; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; DFS, disease-free survival; OS, overall survival

Declarations

Consent

Consent was obtained from the patient for publication of this case report.

Ethics approval and consent to participate

Informed consent was obtained from the patient for publication of this case report and accompanying images. Its protocol was reviewed and approved by the ethics committee of the First Hospital of Lanzhou University.

Consent for publication

The patient signed informed consent and agreed the publication.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Science and Technology Plan Project of Chengguan District, Lanzhou City(2020RCCX0053)

Author contributions

QJL analyzed and interpreted the patient data regarding the disease of synchronous double primary liver tumors. MMQ performed the histological examination of the masses, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank all members of our group.

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Figures

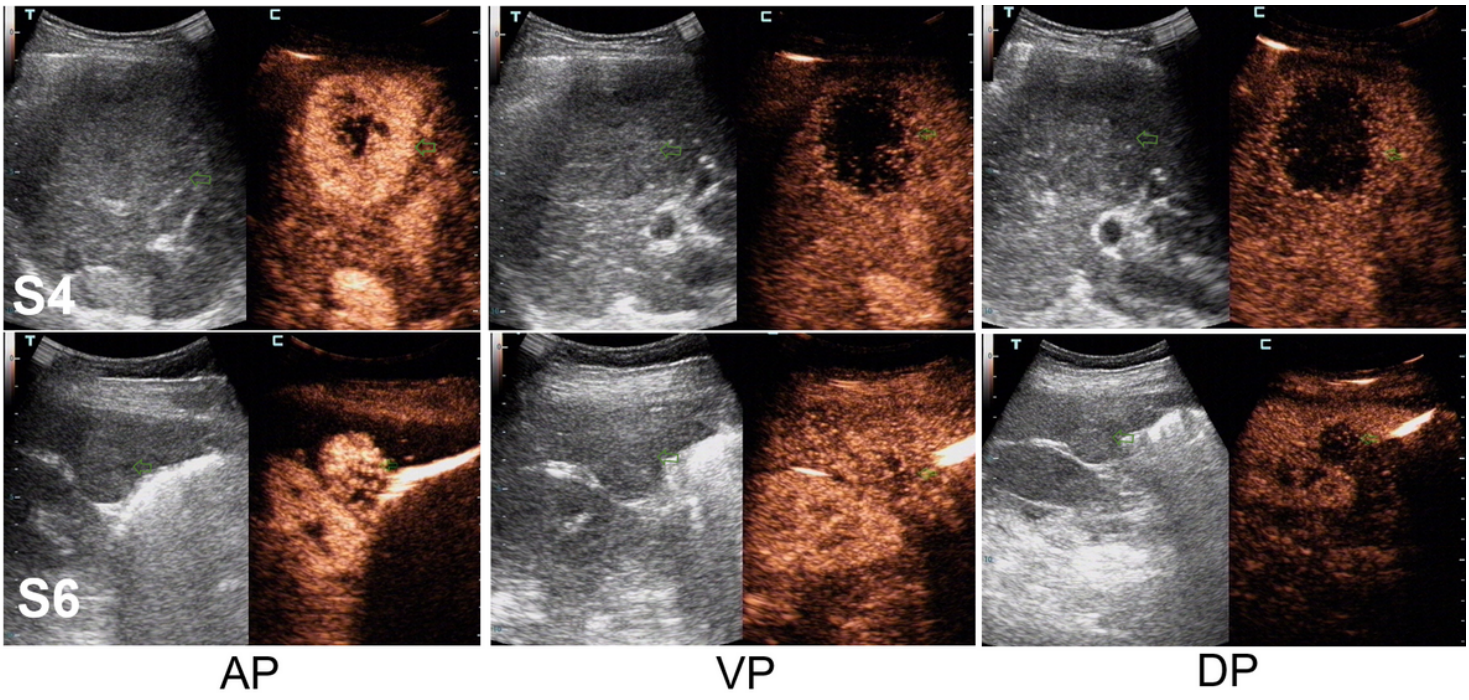

Figure 1

Abdominal contrast-enhanced ultrasonography(CEUS) identified two separate well-defined hypoechoic tumors that were heterogeneous on the inside in the segment 4 (S4) and segment 6 (S6) of the liver (green arrows; 5.0×4.6 cm and 2.5×2.1 cm in size, respectively). The S4 tumor presented high heterogeneous enhancement and the S6 tumor showed homogeneous enhancement in the arterial phase, The both tumors showed low enhancement in the portal venous phase and delayed phase. AP=arterial phase, VP= portal venous phase, DP= delayed phase

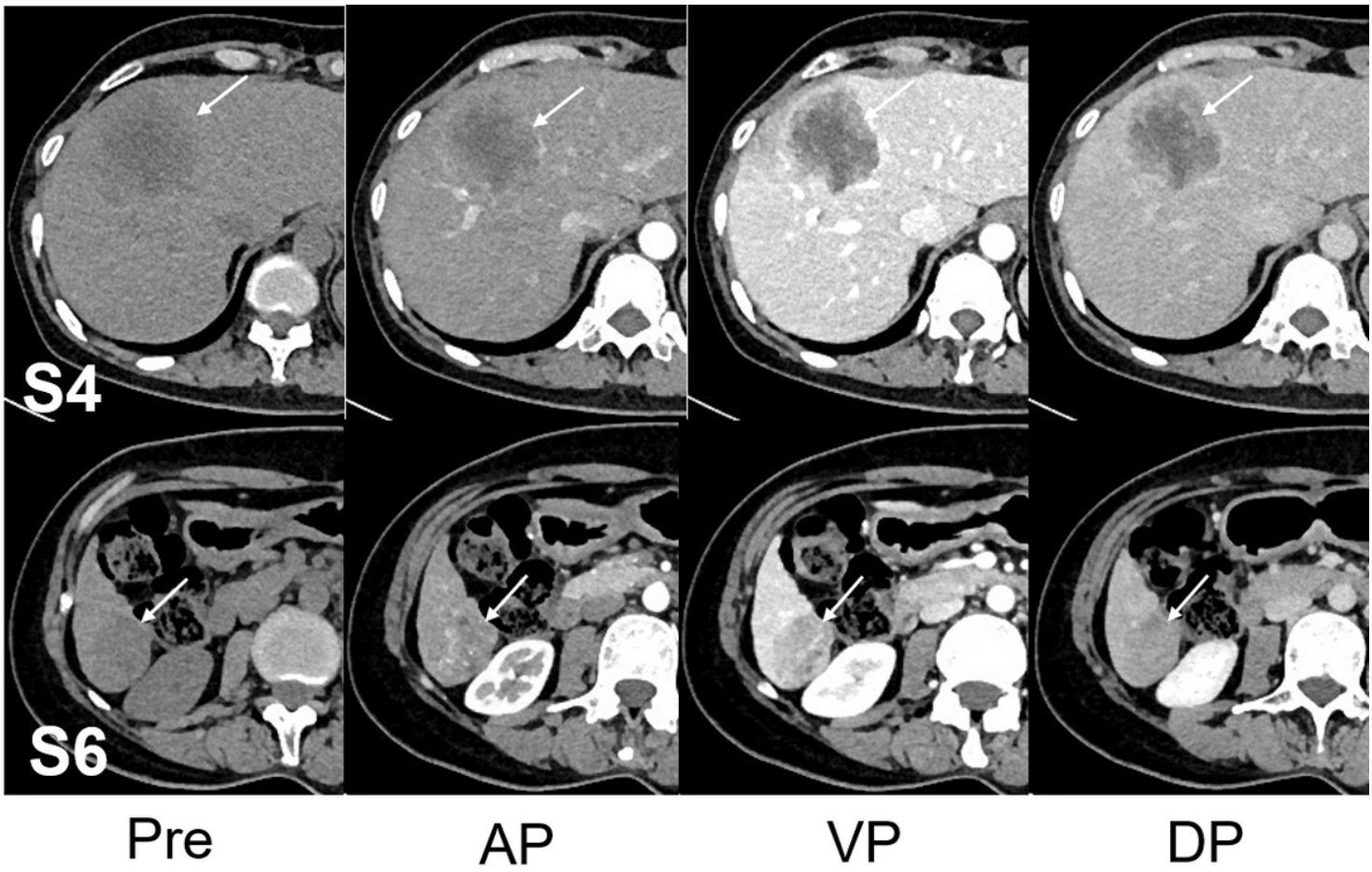

Figure 2

Abdominal computed tomography (CT) imaging of the two tumors (white arrows). Pre-contrast phase revealed two separate hypoattenuating hepatic masses in S4 and S6 (white arrows; 5.0×4.6 cm and 2.5×2.1 cm in size, respectively). On contrast-enhanced dynamic CT, the S4 tumor showed peripheral enhancement with central low density in the arterial phase and the peak enhancement appeared in the portal venous phase, and presented slightly centripetal enhancement in the delayed phase. The whole S6 tumor was heterogeneously enhanced in the arterial phase and followed by wash-out in the portal venous phase, and the delayed phase. Pre=pre-contrast, AP=arterial phase, VP= portal venous phase, DP= delayed phase

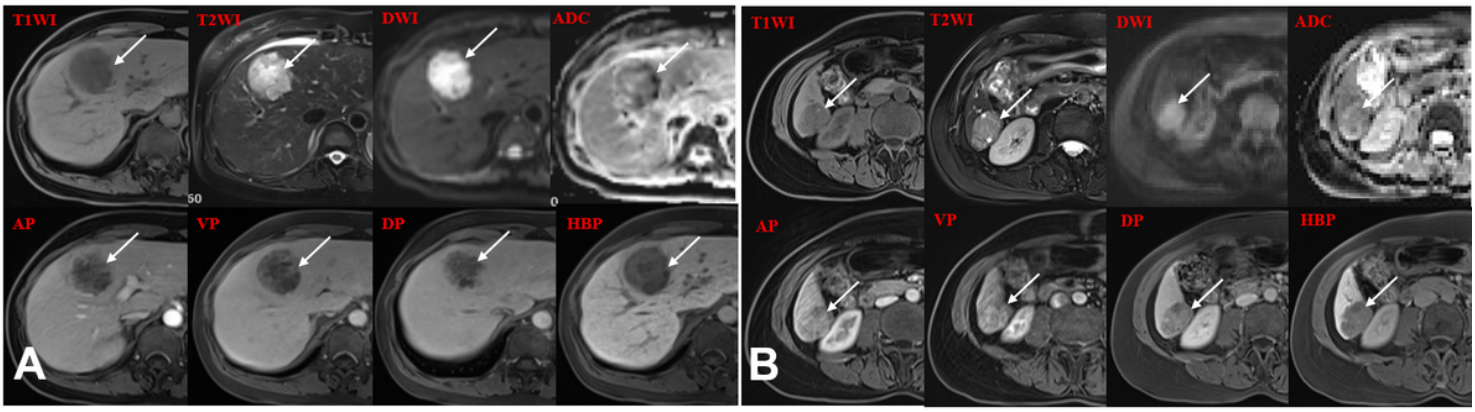

Figure 3

Abdominal magnetic resonance findings of the two tumors (white arrows). The tumors in S4(A) and S6 (B) indicated similar findings of low signal intensity on T1WI and high signal intensity on T2WI. The DWI(b=800mm²/s) showed high-intensity masses and ADC map from conventional DWI showed the massed with decreased signal intensity, suggesting both tumors diffusion restriction. The S4 tumor showed rim-enhancement throughout arterial, portal venous, and delayed phase. The S6 tumor showed arterial-enhancing and delayed wash-out. The hepatobiliary phase appeared as hypointense nodules. T1WI =T1-weighted images, T2WI=T2-weighted images, DWI=Diffusion weighted imagings, ADC=Apparent diffusion coefficient, HBP= hepatobiliary phase

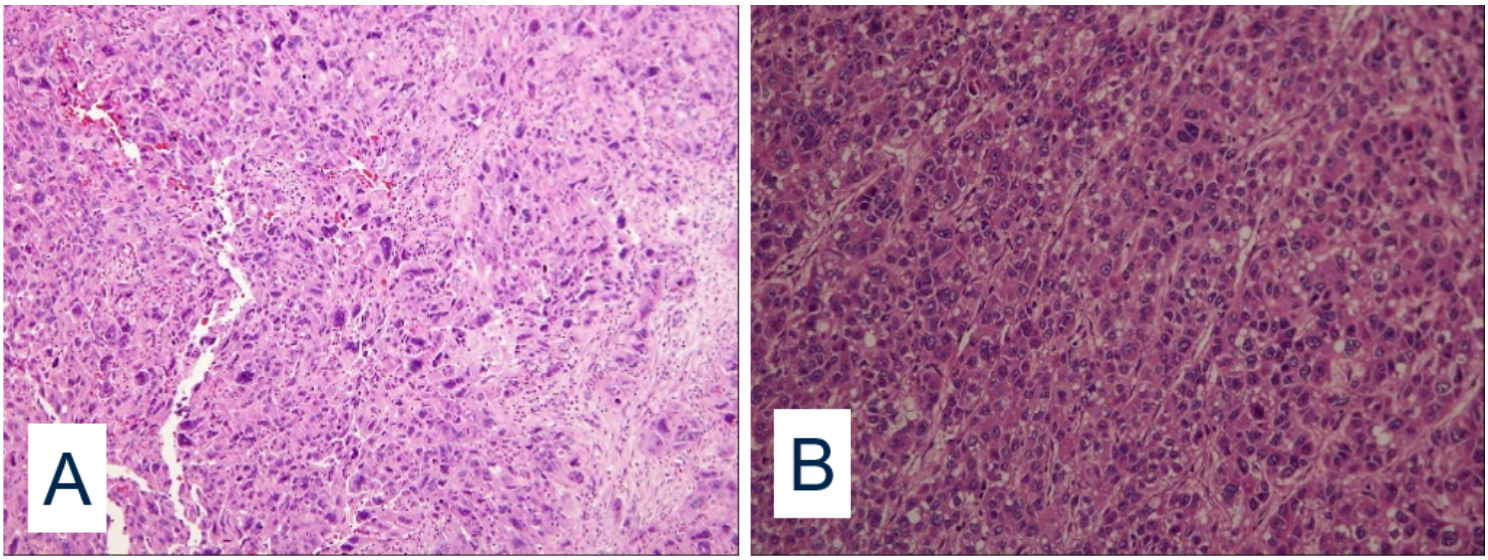

Figure 4

The histopathological findings of the two liver tumors (Hematoxylin and eosin staining,×100). The S4 tumor was moderately and poorly differentiated intrahepatic cholangiocarcinoma (A). The S6 was poorly differentiated hepatocellular carcinoma (B).