Int Surg 2012;**97**:17–22

Case Report

Primary Hepatic Cancers With Multiple Pathologic Features in a Patient With Hepatitis C: Report of a Case

Go Oshima[1], Masahiro Shinoda[1], Minoru Tanabe[1], Yohei Masugi[2], Akihisa Ueno[3], Kiminori Takano[1], Minoru Kitago[1], Osamu Itano[1], Shigeyuki Kawachi[1], Kentaro Ohara[2], Masaya Oda[4], Akihiro Tanimoto[3], Michiie Sakamaoto[2], Yuko Kitagawa[1]

[1]*Department of Surgery,* [2]*Department of Pathology, and* [3]*Department of Diagnostic Radiology, Keio University, School of Medicine, Tokyo, Japan*

[4]*Internal Medicine, Sanno Hospital, Tokyo, Japan*

We report a case of multiple primary hepatic cancers exhibiting different pathologic features coexisting in a patient with chronic hepatitis C. Computed tomography showed 2 tumors in segment 8, 20 mm (S8-A) and 5 mm (S8-B) in diameter, and a 10-mm tumor in segment 6 (S6). Based on the images, the S8-A lesion was diagnosed as cholangiocellular carcinoma or combined hepatocellular carcinoma and cholangiocarcinoma (combined HCC-CC). The other 2 tumors were diagnosed as HCC. The patient underwent partial resections of segments 6 and 8. We found 2 more tumors (S8-C was 6 mm in diameter and S8-D was 4 mm) in the resected segment 8 specimen. Histopathologic examination revealed that the S8-A and S8-C tumors were combined HCC-CC, the S8-B and S6 lesions were scirrhous HCC, and the S8-D tumor was an early HCC. This is a very rare case in which different hepatic cancers with multiple pathologic features coexisted.

Key words: Multicentric hepatocellular carcinoma – Combined hepatocellular carcinoma and cholangiocarcinoma – Scirrhous type of hepatocellular carcinoma – Early hepatocellular carcinoma – Multiple pathologic features – Hepatitis C virus – Chronic hepatitis

In patients with chronic hepatitis or liver cirrhosis caused by hepatitis C (HCV) or hepatitis B virus infection, hepatocellular carcinoma (HCC) can be multicentric.[1] When liver cirrhosis is caused by HCV, the rates of occurrence and multicentricity of HCC are particularly high.[2–4] We present a very rare case in which 5 hepatic cancers composed of 4 primary cancers with 3 different types of pathologic

Reprint requests: Masahiro Shinoda, MD, Department of Surgery, Keio University, School of Medicine, 35 Shinanomachi, Shinjuku, Tokyo 160-8582, Japan.
Tel.: +81 3 3353 1211; Fax: +81 3 3355 4707; E-mail: masa02114@yahoo.co.jp

features coexisted and occurred after 10 years of sustained virologic response to HCV.

Case Report

A 67-year-old Japanese man was referred to our hospital with liver tumors in segments 6 (S6) and 8 (S8), which had been detected during a routine check-up ultrasound for hepatitis C. This patient had been treated for hepatitis C using interferon therapy 10 years earlier, which resulted in a sustained virologic response. On referral to our hospital, he had no symptoms, and physical examinations showed no abnormal findings. Laboratory data on admission were as follows: white blood cell count, 5300/mm^3; red blood cell count, 442 $\times$ 10^4/mm^3; platelet count, 16.7 $\times$ 10^4/mm^3; prothrombin time, 100%; albumin, 4.8 g/dL; total bilirubin, 0.6 mg/dL; aspartate aminotransferase, 29 IU/L; alanine aminotransferase, 28 IU/L; alkaline phosphatase, 308 IU/L; γ-glutamyl transpeptidase, 45 IU/L; cholinesterase, 406 IU/L; and indocyanine green retention rate at 15 minutes, 21.3%. Serologic analyses for viruses were as follows: hepatitis B virus surface antigen, negative; hepatitis B virus core antibody, negative; HCV antibody, positive; and HCV RNA (polymerase chain reaction), not detected. The tumor markers prothrombin induced by vitamin K absence or antagonist II (34 mAU/mL), alpha-fetoprotein (AFP, 5 ng/mL), carcinoembryonic antigen (CEA, 1.6 ng/mL), and carbohydrate antigen 19-9 (CA19-9, 10 U/mL) were all within normal limits.

Ultrasonography disclosed two hypoechoic tumors, one 10 mm in size in S6, and the other 20 mm in diameter in S8. Contrast-enhanced computed tomography (CT) revealed three tumors: one in S6 measuring 10 mm, and two in S8, measuring 5 mm and 20 mm in diameter. The 5-mm tumor in S8 showed an enhancement in the arterial phase and isodensity in the late phase (Fig. 1a and 1b). The 20-mm tumor in S8 showed a heterogeneous and peripheral enhancement in the arterial phase and no washout in the late phase (Fig. 1c and 1d). The 10-mm tumor in S6 showed an enhancement in the early phase and a washout in the late phase (Fig. 1e and 1f). Contrast-enhanced magnetic resonance imaging (MRI) with gadoxetic acid disodium (Primovist; Bayer Schering Pharma, Berlin, Germany) showed defects in the hepatobiliary phase in all tumors. Based on these imaging findings, the 5-mm tumor in S8 and the 10-mm tumor in S6 were diagnosed as typical HCC. However, the 20-mm tumor in S8 was more difficult to diagnose, and its differential diagnosis included HCC with necrotic component, metastatic tumor, cholangiocellular carcinoma (CCC), as well as combined hepatocellular carcinoma and cholangiocarcinoma (combined HCC-CC). Because upper gastrointestinal endoscopy and total colonoscopy showed no possible primary lesions, and there was also a retraction around the 20-mm tumor in S8, we narrowed down the possibilities to CCC or combined HCC-CC.

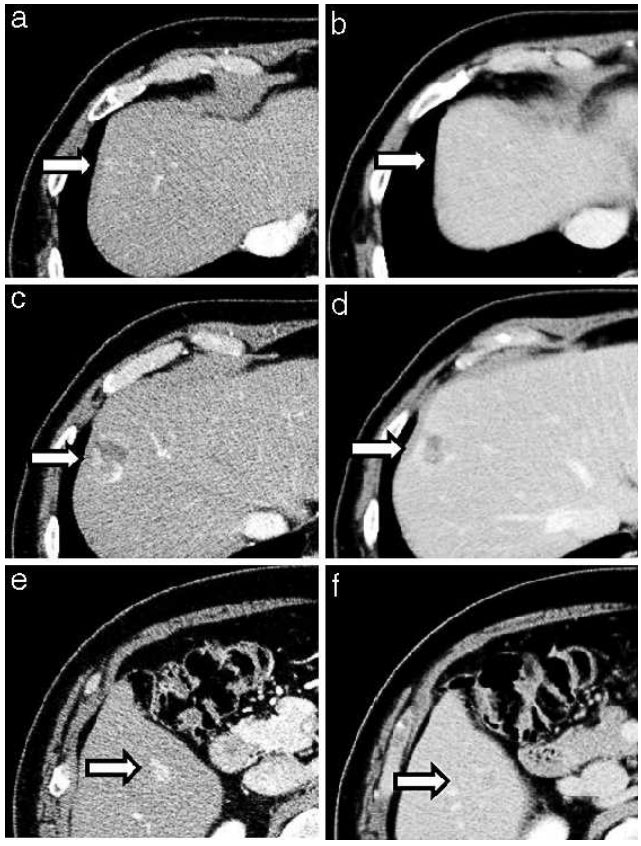

Fig. 1 Contrast-enhanced computed tomography. Three tumors were detected, measuring 5 mm (a, b) and 20 mm (c, d) in diameter in S8, and 10 mm (e, f) in S6. Early phase (a, c, and e) and late phase (b, d, and f) findings are shown. Arrows indicate tumors.

In light of these findings, we carried out partial hepatic resections of S6 and S8. The resected S6 and S8 specimens weighed 30 and 70 g, respectively. On gross examination, there were in total 5 hepatic tumors. The resected specimen of segment 6 contained a tumor, 12 mm in diameter, which showed a white lobular-shaped firm mass without capsule formation (Fig. 2a). The segment 8 specimen contained 4 tumors: 22 mm (S8-A), 10 mm (S8-B), 6 mm (S8-C), and 4 mm (S8-D) in size, all of which presented as a white firm mass without

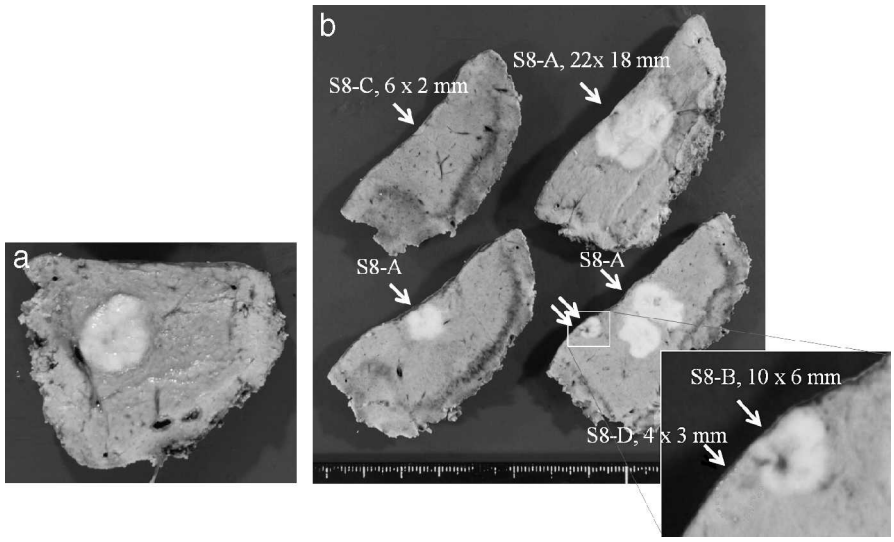

Fig. 2 Macroscopic findings of the resected specimens. The specimens of segment 6 (a) and segment 8 (b) are shown.

capsule formation (Fig. 2b). Histopathologic examination of the two tumors in S6 and S8-B revealed carcinoma cells that were arranged in an irregular moderate trabecular pattern with scirrhous growth features as characterized by fibrosis along the sinusoid-like blood spaces. This indicates that these tumors were of the scirrhous type, moderately differentiated hepatocellular carcinomas (Fig. 3a and 3b). These two scirrhous HCCs had no vascular and biliary invasions. On the other hand, the tumors in S8-A and S8-C showed two different histologic patterns and cell types that were intermixed—a hepatocellular carcinoma component composed of trabecular structures and a cholangiocellular carcinoma component made up of glandular structures with intraluminal mucin—indicating that these tumors were combined HCC-CC (Fig. 3c and 3d). The tumor in S8-A was accompanied by biliary and portal invasions. In addition, S8-D showed a vaguely nodular lesion with microscopically increased cell density. There were portal tracts within the lesion, but the tumor cells with increased nuclear cytoplasmic ratio were arranged in an irregular thin trabecular pattern and had focally invaded into the stromal tissue. Because of these findings, S8-D was considered an early hepatocellular carcinoma (eHCC) (Fig. 3e and 3f). The background liver showed mild periportal fibrosis and lymphatic infiltration, which were compatible with chronic hepatitis associated with HCV. In addition, mild pericellular and perivenular fibrosis with mild centrolobular fatty changes were observed. The locations and pathologic features of these 5 hepatic tumors are described in a schematic diagram (Fig. 4). Preoperative CT and MRI findings were retrospectively examined by 2 radiologists after pathologic examination was completed. The S8-A and S8-B tumors in the resected specimen were considered to correspond to the S8 lesions that were preoperatively detected by CT and MRI, but the S8-C and S8-D tumors in the resected specimen could not be found even by retrospective assessment of the preoperative CT and MRI images. Recurrence has not been observed at a follow-up at 15 months after the operation.

Discussion

In Japan, patients with chronic hepatitis or liver cirrhosis caused by HCV infection develop most HCCs.[1] When liver cirrhosis is caused by HCV infection, synchronous or asynchronous multiple tumors can affect the entire liver. These multiple lesions are caused by two mechanisms: intrahepatic hematogeneous tumor cell spread (intrahepatic metastasis) and *de novo* tumor development (multicentric occurrence). Although determining the carcinogenic mechanism for each tumor is difficult, in our patient, S8-C was thought to be an intrahepatic metastasis of S8-A, as the latter was microscopically accompanied by portal vein invasion, and both tumors existed closely in the same segment of the liver. On the other hand, the tumors in S6 and S8-B, both of which were scirrhous HCC, were thought to be multicentric because they showed no portal vein invasion and existed in distant segments of the liver.

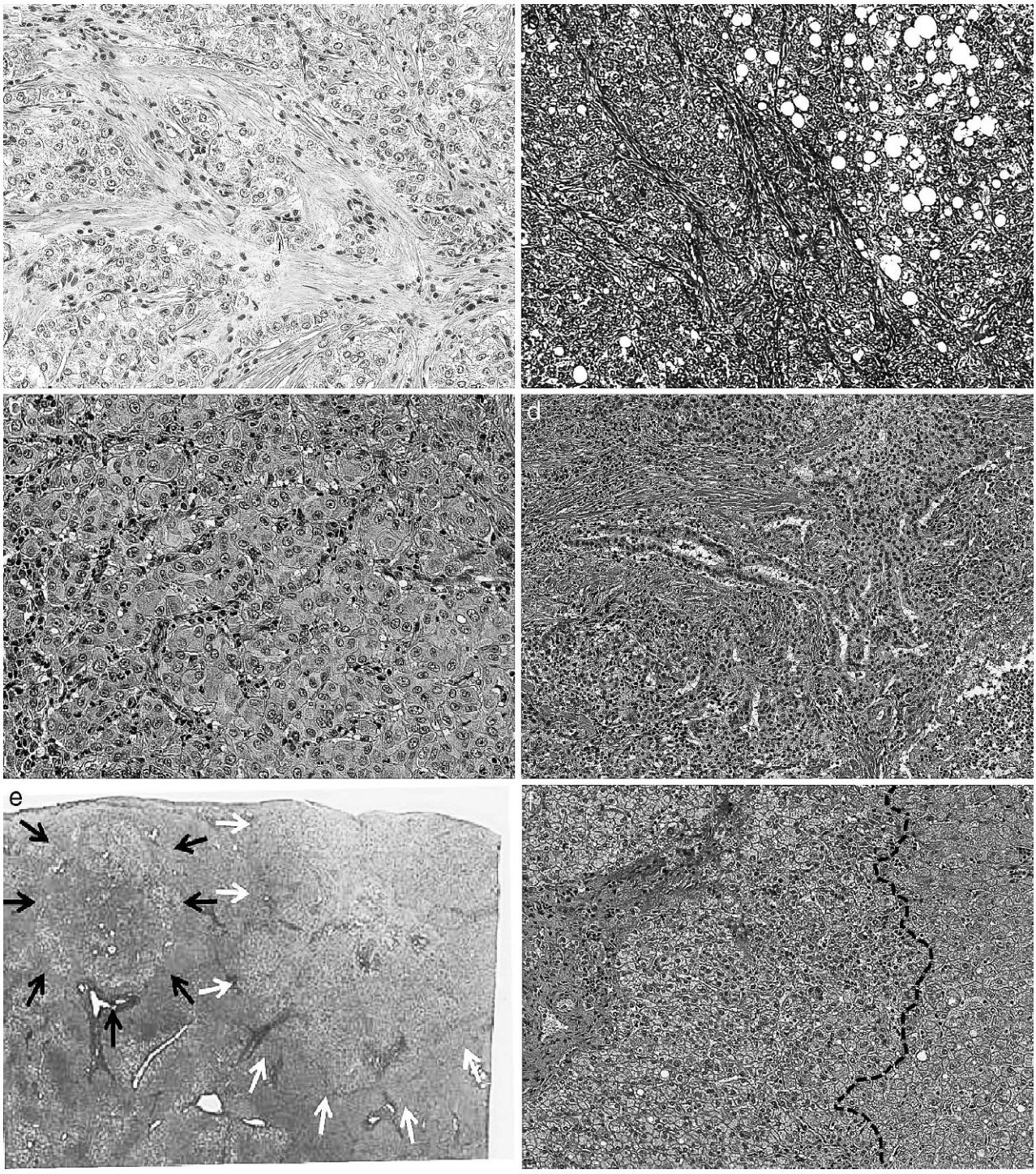

Fig. 3 Microscopic findings. The tumor in S6 was of the scirrhous type of moderately differentiated hepatocellular carcinoma (a) H&E stain (×20) (b) Azan-Mallory stain (×10). S8-A and S8-C lesions were combined HCC-CC. (c) Component of HCC (×20).
(d) Component of CCC (×10). S8-B was of the scirrhous type of moderately differentiated hepatocellular carcinoma (indicated by white arrows in loupe observation [e]). S8-D was an early hepatocellular carcinoma (indicated by white arrows in loupe observation [e]). The broken line indicates a borderline between carcinoma in S8-D (left side) and normal area (right side). (f) (×15).

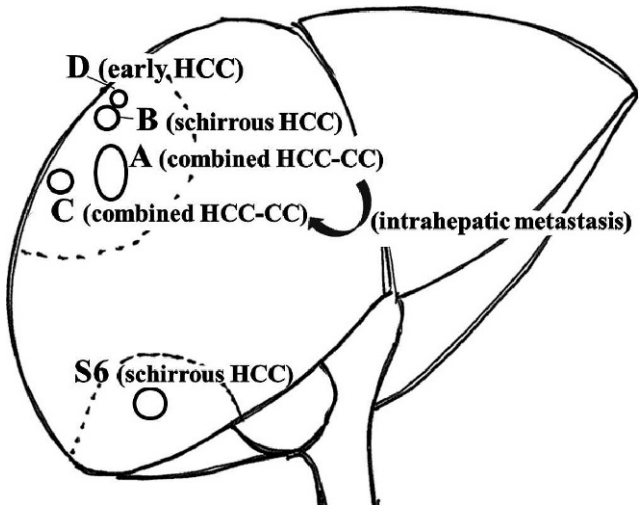

Fig. 4 Locations and pathologic features of 5 hepatic tumors.

In addition, S8-D was thought to be an eHCC. Therefore, we assume that our patient had 5 different coexisting hepatic cancers, of which 4 were primary cancers that arose multicentrically with multiple pathologic features and one was an intrahepatic metastasis.

Scirrhous HCC and combined HCC-CC are rare primary liver cancers, and in Japan, their frequencies have been reported to be approximately 4.6% and 0.54%, respectively, of primary liver cancers.[5,6] Most of the synchronous double primary hepatic cancers are a combination of HCC and CCC, and the frequency of the combination of scirrhous HCC and combined HCC-CC is extremely low. Our patient had 5 tumors, 1 combined HCC tumor with an intrahepatic metastasis, 2 scirrhous HCC-CC tumors, and 1 eHCC tumor. To our knowledge, this is the first published report of the coexistence of 5 hepatic cancers composed of 4 primary cancers with 3 different types of pathologic features in a single patient.

Accuracy and feasibility of preoperative diagnosis for primary hepatic cancers are of great interest. In our patient, 3 tumors (S6, S8-A, and S8-B) were preoperatively identified by CT and MRI, but 2 tumors (S8-C, 6 mm and S8-D, 4 mm) could not be identified, even by the retrospective assessment of the preoperative CT and MRI data. It is sometimes difficult to detect such tiny tumors using the currently available diagnostic devices. With regard to the 3 identified tumors, the preoperative diagnoses were not correct. The S6 and S8-B tumors were preoperatively diagnosed as classic HCC, but were in fact histologically a rare variant of HCC, scirrhous HCC. One of the characteristic features of scirrhous HCC is prolonged enhancement in the late phase in CT and MRI imaging,[7] but the feature varies depending on individual tumors. In addition, the finding of prolonged enhancement in the late phase is not specific to scirrhous HCC, and is frequently seen in CCC and metastatic tumors. Therefore, it is usually difficult to preoperatively diagnose scirrhous HCC. The preoperative CT findings of these 2 tumors showed early enhancement and washout (or isodensity) and were not consistent with the typical features or any features that are strongly associated with scirrhous HCC, suggesting that they were typical HCCs. We have to be aware that tumors with features that closely resemble the typical findings of HCC could also be differentially diagnosed as a rare variant of scirrhous HCC. The S8-A tumor was in fact histologically combined HCC-CC. The diagnosis of CCC or combined HCC-CC requires extra attention because additional operative procedures, such as lymph node dissection, may be necessary. However, definitive preoperative diagnosis of combined HCC-CC, in particular, seems to be challenging.[8] In our patient, although combined HCC-CC was included in the preoperative differential diagnosis of the S8-A tumor based on CT and MRI findings, we could not pinpoint the diagnosis to combined HCC-CC before surgery. Nakamura *et al*[9] hypothesized that a hypervascular tumor with high CEA and CA19-9 levels or a hypovascular tumor with a high level of AFP may indicate a preoperative diagnosis of combined HCC-CC, but these features did not correspond to our patient. Further advances in diagnostic devices or markers are needed to differentiate relatively rare hepatic cancers, such

as scirrhous HCC and combined HCC-CC, from typical HCCs.

Surgical intervention is another point of interest for primary hepatic cancers with multiple pathologic features, especially if CCC or combined HCC-CC is involved. The necessity of hilar lymph node dissection for combined HCC-CC is still under debate.[9,10] At our institute, hilar lymph node dissection is performed for preoperatively diagnosed combined HCC-CC in cases where the hilar lymph nodes appear metastatic from the preoperative imaging diagnosis or observation during surgery. In our patient, because the lymph nodes were not preoperatively and intraoperatively suspected to be metastatic, lymph node dissection was not performed. Postsurgical care, such as additional treatments including lymph node dissection or adjuvant chemotherapy, could be necessary in the future considering the possible recurrence in lymph nodes from the combined HCC-CC tumors in S8-A and S-8C. We have no immediate plans to do so because postoperative CT and serum tumor markers have not indicated any signs of recurrence at present, and we need to consider that the appearance of another tumor may not be lymph node metastasis but instead may be a multicentric occurrence of a new HCC. Considering the pathologic features of this patient, the possibility of a new HCC occurrence in the future is high. We will continue examining this patient by CT and tumor markers every 6 months so we can immediately plan the appropriate treatments for any recurrence such as lymph node metastasis or new HCC.

We reported a very rare case of 5 different coexisting hepatic cancers, whose pathologic features included scirrhous HCC and combined HCC-CC. Because of rarity and the diseases' natural characters, definite preoperative diagnoses were difficult in this patient. Special attention should always be given when encountering patients in whom unexpected tumors or whose tumor features are different from the preoperative diagnosis. The postoperative course of this patient is pathophysiologically interesting because the multiple pathologic features could have various patterns of recurrence. Considering the pathophysiologic characters of each tumor, long-term observation of the patient is necessary.

References

1. Liver Cancer Study Group of Japan. Survey and follow-up study of primary liver cancer in Japan. Report 13. *Acta Hepatol Jpn* 1999;**40**(5):288–300
2. Takano S, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. *Hepatology* 1995;**21**(3):650–655
3. Simonetti RG, Camma C, Fiorello F, Cottone M, Rapicetta M, Marino L *et al*. Hepatitis C virus infection as a risk factor for hepatocellular carcinoma in patients with cirrhosis. A case-control study. *Ann Intern Med* 1992;**116**(2):97–102
4. De Mitri MS, Poussin K, Baccarini P, Pontisso P, D'Errico A, Simon N *et al*. HCV-associated liver cancer without cirrhosis. *Lancet* 1995;**345**(8947):413–415
5. Kurogi M, Nakashima O, Miyaaki H, Fujimoto M, Kojiro M. Clinicopathological study of scirrhous hepatocellular carcinoma. *J Gastroenterol Hepatol* 2006;**21**(9):1470–1477
6. Ikai I, Itai Y, Okita K, Omata M, Kojiro M, Kobayashi K *et al*. Report of the 15th follow-up survey of primary liver cancer. *Hepatol Res* 2004;**28**(1):21–29
7. Kim SR, Imoto S, Nakajima T, Ando K, Mita K, Fukuda K *et al*. Scirrhous hepatocellular carcinoma displaying atypical findings on imaging studies. *World J Gastroenterol* 2009;**15**(18): 2296–2299
8. Taguchi J, Nakashima O, Tanaka M, Hisaka T, Takazawa T, Kojiro M A. Clinicopathological study on combined hepatocellular and cholangiocarcinoma. *J Gastroenterol Hepatol* 1996;**11**(8):758–764
9. Nakamura S, Suzuki S, Sakaguchi T, Serizawa A, Konno H, Baba S *et al*. Surgical treatment of patients with mixed hepatocellular carcinoma and cholangiocarcinoma. *Cancer* 1996;**78**(8):1671–1676
10. Sasaki A, Kawano K, Aramaki M, Ohno T, Tahara K, Takeuchi Y *et al*. Clinicopathologic study of mixed hepatocellular and cholangiocellular carcinoma: modes of spreading and choice of surgical treatment by reference to macroscopic type. *J Surg Oncol* 2001;**76**(1):37–46