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ORIGINAL ARTICLE

Clinicopathologic Characteristics and Long-Term Prognosis of Scirrhous Hepatocellular Carcinoma

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Abstract
Background Clinicopathologic features and long-term outcomes in patients with scirrhous hepatocellular carcinoma (S-HCC) are not fully defined.
Methods We compared data of 37 patients with S-HCC and 604 with usual HCC (U-HCC) undergoing surgery.
Results The S-HCC group showed less HBV infection (78.4 vs. 92.0%, $P = 0.02$), low serum AFP level (2320 ± 6356 vs. 3297 ± 18690 ng/ml, $P < 0.0001$), less delayed washout during CT (72.7 vs. 90.7%, $P = 0.004$), and low usefulness of clinical diagnostic criteria (32.4 vs. 57.5%, $P = 0.003$), compared to the U-HCC group. More portal vein invasion (18.9 vs. 4.1%, $P = 0.03$) and less liver cirrhosis (35.1 vs. 65.1%, $P = 0.001$) and fibrous capsule (40.5 vs. 81.6%, $P < 0.001$) were noted in the S-HCC group than the U-HCC group. Long-term survival rates were similar between the S-HCC and U-HCC groups, even with subgroup analysis according to Child-Pugh score and modified UICC stage.
Conclusion The S-HCC group showed distinct patient and tumor characteristics but similar long-term outcome.

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Keywords Scirrhous hepatocellular carcinoma · Hepatectomy · Prognosis · Survival · Recurrence

Introduction

According to the World Health Organization classification, scirrhous hepatocellular carcinoma (HCC) is a subtype of HCC characterized by diffuse fibrosis along the sinusoid-like blood spaces and varying degrees of atrophy of tumor trabeculae [1]. Abundant fibrotic changes are noted in almost the entire area of the largest cross-section of this tumor [2]. The rate of scirrhous HCC varies between 0.2 and 4.2%, depending on pathological definition adopted [3–5].

Several previous studies revealed the radiologic and pathologic features of scirrhous HCC. Radiological findings included a homogenous architecture, hypervascularity in the tumor periphery, prolonged enhancement, absence of tumor capsule, and a retraction of the liver surface [6–9]. Scirrhous HCC is often misdiagnosed as cholangiocellular carcinoma, metastatic carcinoma of liver, and mixed hepatocellular carcinoma and cholangiocarcinoma (CCC) because of heterogenous enhancement in the arterial phase and prolonged enhancement in the late phase attributed to abundant fibrous stroma [10]. Although a few reports compared the characteristics of scirrhous HCC with those of usual HCC, they also focused on radiological or pathological findings [2, 11, 12]. Clinical characteristics and long-term prognosis of patients with scirrhous HCC were not established. Better prognosis in patients with scirrhous HCC was suggested in a few studies, although a relatively small number of patients were observed for only a limited time [2, 12].

Clinical diagnostic criteria are widely used for the diagnosis of HCC. Most guidelines suggest a diagnosis of HCC based on elevated serum alpha-fetoprotein (AFP)

level and typical image findings, which is arterial hypervascularization on a dynamic CT or MRI, in a high risk group [13, 14]. However, little is known about the usefulness of these clinical diagnostic criteria in patients with scirrhous HCC.

The purpose of this study was to evaluate patient and tumor characteristics, usefulness of clinical diagnostic criteria, and long-term prognosis after curative resection in patients with scirrhous HCC, compared to those with usual HCC.

Methods

Patient Selection

A total of 1,658 patients underwent partial hepatectomy for HCC at our institute between October 1999 and August 2009. Among them, 37 patients (5.7%) with pathologically proven scirrhous HCC (scirrhous HCC group) and 604 patients with usual HCC (usual HCC group) were included in this study. Scirrhous HCC was defined as HCC in which the scirrhous area comprised more than 50% of the tumor [11]. Patients with previous therapy for HCC (i.e., surgical resection, radiofrequency ablation, transarterical chemoembolization), multiple tumors (three or more nodules), histologic subtype of fibrolamellar or sarcomatous HCCs, tumors with cholangiocarcinoma component, palliative resection of the liver, and follow-up periods <6 months after hepatectomy were excluded. Their medical records, radiologic findings, and pathologic data were reviewed.

Comparison of Baseline Characteristics of Patients and Tumors

Age, sex, presence of viral markers, Child-Pugh class, and serum AFP levels of the scirrhous HCC group were compared with those of the usual HCC group. Findings of triphase helical computed tomography (CT) and dynamic magnetic resonance imaging (MRI) were reviewed by our expert radiologists. Size, numbers, location, and presence of typical imaging patterns were compared between the scirrhous HCC group and the usual HCC group. Typical imaging pattern for HCC was defined as enhancement on arterial phase and washout on portal or delayed phase on dynamic imaging. In addition, it was evaluated whether clinical and imaging findings of the patients in the two groups fulfilled the clinical diagnostic criteria of the American Association for the Study of Liver Diseases (ASSLD) guideline [14]. Diagnosis of HCC can be made without biopsy based on typical dynamic imaging and/or elevated serum AFP level in patients with liver cirrhosis (LC) according to this guideline [14]. Modified International Union against Cancer (UICC) stage [15] of the scirrhous HCC group was compared with those of the usual HCC group. Histologic findings of resected specimens were reviewed by an expert liver pathologist. Edmondson–Steiner tumor grading, microvascular invasion, intrahepatic metastasis, fibrous capsule formation, and portal vein invasion of tumors, and the presence of liver cirrhosis in background liver were compared between the two groups.

Comparison of Outcomes After Surgical Resection

After curative resection, patients were regularly monitored by blood chemistry, serum AFP, and contrast-enhanced triple-phase CT at 3 month intervals for 2 years and every 6 months thereafter. In case of recurrence, appropriate treatment modalities were applied, including transcatheter arterial chemoembolization, radiofrequency ablation, repeated surgery, liver transplantation, sorafenib, and/or supportive care based on extent of recurrent tumors and liver function of the patients. The cumulative overall survival rates and recurrence rates were evaluated in patients with scirrhous HCC and those with usual HCC. In addition, subgroup analysis for those outcomes was performed according to Child-Pugh score [16] and modified UICC staging [15].

Statistical Analyses

For comparison of baseline characteristics of the two groups, independent-samples t test for continuous data and Fisher's exact test for categorical data was used. Cumulative overall survival rates and recurrence free survival rates were compared between the scirrhous HCC group and the usual HCC group using the Kaplan–Meier and time-dependent Cox regression analysis. Data were analyzed using SPSS version 18.0 (SPSS, Chicago, IL, USA). Unless otherwise indicated, data represents mean ± standard deviation. P values <0.05 were considered significant.

Results

Baseline Characteristics of Patients

The age of patients in the scirrhous HCC group was 53.2 ± 10.7 years and the male to female ratio was 2.7:1, which were similar to those of patients in the usual HCC group. All patients in the scirrhous HCC group and 97.6% of those in the usual HCC group displayed liver function compatible with Child-Pugh class A ($P = 1.00$). However, the proportion of patients with positive hepatitis B surface antigen (HBsAg) in the scirrhous HCC group was smaller than in the usual HCC group (78.4 vs. 92.0%, respectively;

$P = 0.02$). In addition, the serum AFP level in the scirrhous HCC group was 2320.1 ± 6356.6 ng/ml, which was significantly lower than the 3297.0 ± 18689.6 ng/ml in the usual HCC group ($P < 0.0001$; Table 1).

Image Findings, Usefulness of Clinical Diagnostic Criteria, and Stage

Size of tumors in the scirrhous HCC group was 4.6 ± 2.7 cm, which was similar to that in the usual HCC group ($P = 0.57$). The number and location of tumors were not significantly different between the two groups. Typical arterial enhancement was noted in 94.8% of patients with scirrhous HCC during CT and in 96.9% during MRI, which was similar to those with usual HCC (92.3% during CT, $P = 0.18$; 95.5% during MRI, $P = 1.00$). However, venous or delayed washout was less frequently noted in the scirrhous HCC group than in the usual HCC group (72.7 vs. 90.7% during CT, $P = 0.004$; 78.1 vs. 93.0% during MRI, $P = 0.008$). The proportion of patients fulfilling the AASLD clinical diagnostic criteria was lower in the scirrhous HCC group than in the usual HCC group (32.4 vs. 57.5%, respectively; $P = 0.003$). Before surgery, six patients (16.2%) among the scirrhous HCC group were misdiagnosed as cholangiocellular carcinoma or metastatic adenocarcinoma with imaging studies. Dynamic image findings of a representative case are shown in Fig. 1. Distribution of modified UICC stage was not significantly different between the two groups (Table 2).

Pathologic Findings

Portal vein invasion was more frequently observed in the scirrhous HCC group than in the usual HCC group (18.9 vs. 4.1%, respectively; $P = 0.03$). In contrast, the proportions of background LC and fibrous capsule formation in the scirrhous HCC group were lower than those in the usual HCC group (35.1 vs. 65.1%, respectively, for LC, $P = 0.001$; 40.5 vs. 81.6%, respectively, for capsule formation, $P < 0.001$). Edmonson-Steiner grade, intrahepatic metastasis, and microvascular invasion was similarly found between the two groups (Table 3). Gross findings and histology of the tumor of the case are shown in Fig. 2.

Long-Term Outcomes

Median follow-up duration was 36 months (range 10–125) for the scirrhous HCC group and 40 months (range 1–139) for the usual HCC group ($P = 0.87$). Nine patients (24.3%) in the scirrhous HCC group and 35 patients (12.0%) in the usual HCC group died during follow-up. The 1-, 3-, and 5-years cumulative overall survival rates in the scirrhous HCC group were 97.0, 78.2, and 73.3%, respectively, which were similar to the respective rates of 91.0, 83.5, and 77.3% in the usual HCC group ($P = 0.47$; Fig. 3a). HCC recurred in 16 patients (43.2%) in the scirrhous HCC group and 128 patients (43.0%) in the usual HCC group during follow-up. The 1-, 3-, and 5-years recurrence-free survival rate in the scirrhous HCC group were 70.2, 50.6, and 50.6%, respectively, which were not different from the respective rates of 71.5, 54.7, and 45.7% in the usual HCC group ($P = 0.61$; Fig. 3b). Subgroup analysis showed that cumulative overall survival rates and recurrence rates were not significantly different between the corresponding subgroups with scirrhous and usual HCC according to Child-Pugh score (Fig. 4) and modified UICC stage (Fig. 5).

Table 1 Baseline characteristics of patients in scirrhous hepatocellular carcinoma (HCC) group and usual HCC group

Characteristics	Scirrhous HCC group ($n = 37$)	Usual HCC group ($n = 604$)	P value
Age (years, mean ± SD)	53.2 ± 10.7	51.8 ± 9.9	0.41
Sex (male:female)	27:10	484:120	0.40
Viral marker (%)			0.02
HBs Ag (+)	29 (78.4)	549 (91.5)	
HCV Ab (+)	1 (2.7)	17 (2.8)	
HBs Ag (+) and HCV Ab (+)	0 (0.0)	3 (0.5)	
Negative	7 (18.9)[a]	31 (5.2)	
Child-Pugh score (%)			1.00
5	33 (89.2)	527 (87.3)	
6	4 (10.8)	62 (10.3)	
Serum AFP (ng/ml, mean ± SD)	2,320.1 ± 6,356.6	3,297.0 ± 18,689.6	<0.0001

HBsAg hepatitis B surface antigen, *HCV Ab* hepatitis C virus antibody, *AFP* alpha fetoprotein, *SD* standard deviation

[a] Non-alcoholic fatty liver disease ($n = 1$), *Clonorchis sinensis* infection ($n = 1$), and unknown ($n = 5$)

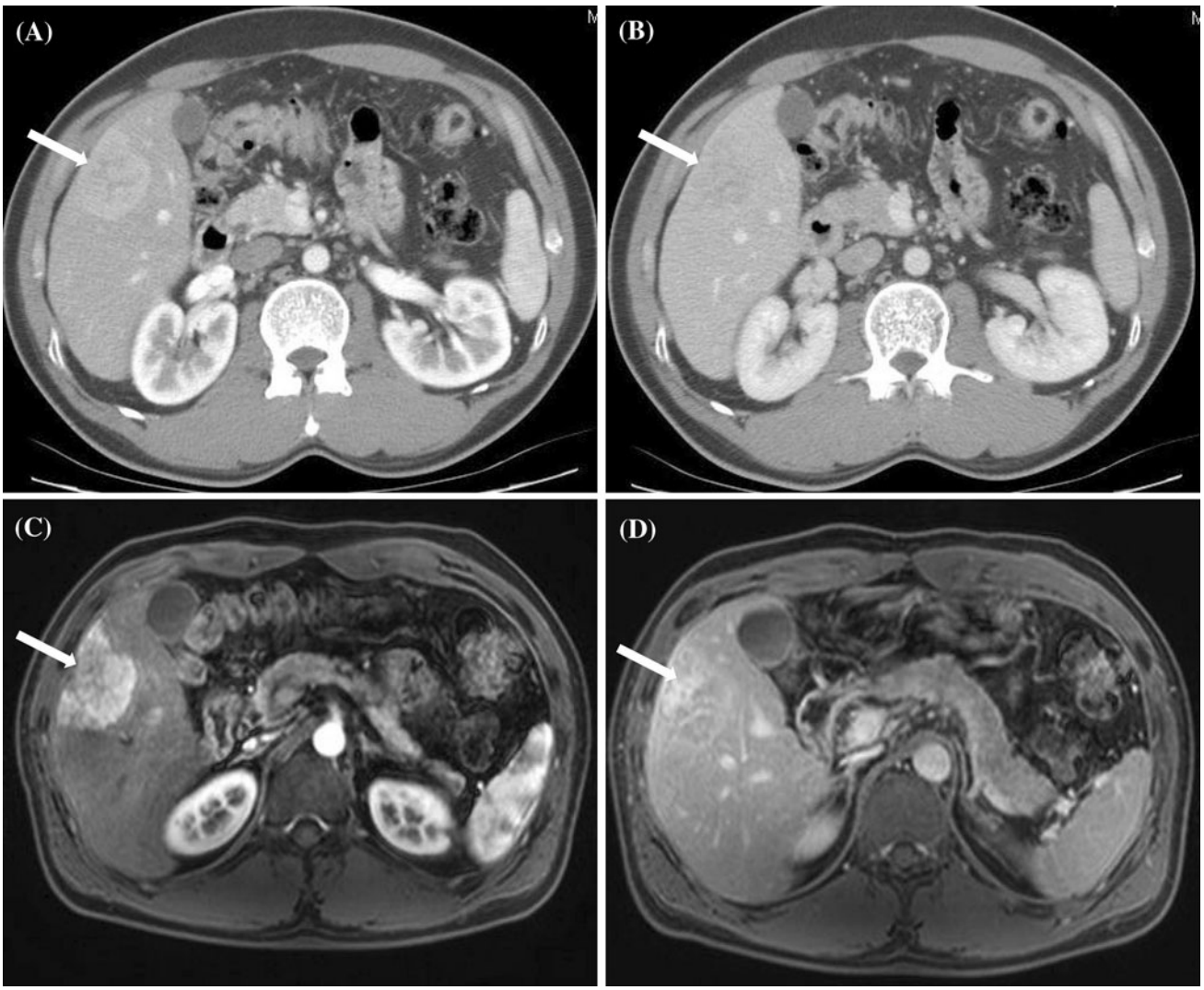

Fig. 1 Image findings of a 56-year-old male with a 5-cm scirrhous hepatocellular carcinoma (HCC) (*arrow*). CT images show a peripheral subtle enhancement of the tumor in the arterial phase (**a**) and a hypoattenuating lesion on the central portion in the delayed/portal phase (**b**). MRI findings also showed similar imaging patterns. In gadolinium-enhanced triphasic spoiled gradient images, mottled enhancement on hepatoma was noted in the arterial phase (**c**) and a tumor showed a peripheral area of hypointensity, leaving a central area of hyperintensity (**d**)

Discussion

Clinicopathologic features and long-term outcomes of patients with scirrhous HCC, a rare form of HCC with abundant fibrotic stroma, has not been clarified. Exploring the data of 37 patients with scirrhous HCC and 604 matched controls with usual HCC for up to 139 months, we revealed distinct clinical, imaging, and histologic characteristics of scirrhous HCC, e.g. less frequent association with HBV infection, lower level of serum AFP, atypical vascular pattern on dynamic imaging, less frequent fulfillment of clinical diagnostic criteria [13, 14], more frequent portal vein invasion, and less frequent background liver cirrhosis and fibrous capsule formation. In addition, we showed that long-term outcomes after curative resection of scirrhous HCC were similar with those having usual HCC, with subgroup analysis according to modified UICC staging [15] and Child-Pugh score [16].

To our knowledge, this is the first report including a large number of scirrhous HCC patients and matched controls with a long-term follow-up period to show the clinicopathologic characteristics and prognosis after surgery in patients with scirrhous HCC. There have been several reports about the radiological and histological features of scirrhous HCC [1, 2, 10–12, 17, 18]; however, little was revealed about the clinical characteristics and

Table 2 Image findings and stage of tumors in the scirrhous hepatocellular carcinoma (HCC) group and the usual HCC group

Characteristics	Scirrhous HCC ($n = 37$)	Usual HCC ($n = 604$)	P value
Size (cm, mean ± SD)	4.6 ± 2.7	4.4 ± 2.8	0.57
Number			0.37
One	37 (100.0)	574 (95.0)	
Two	0 (0.0)	30 (5.0)	
Location (%)			0.30
Right	24 (64.9)	452 (74.8)	
Left	12 (32.4)	128 (21.2)	
Both lobes	1 (2.7)	24 (4.0)	
Typical imaging pattern (%)			
Arterial enhancement in CT	28 (84.8)	518 (92.3)	0.18
Venous/delayed washout in CT	24 (72.7)	507 (90.7)	0.004
Arterial enhancement in MRI	31 (96.9)	506 (95.5)	1.00
Venous/delayed washout in MRI	45 (78.1)	493 (93.0)	0.008
Satisfaction of clinical diagnostic criteria	12 (32.4)	347 (57.5)	0.003
Modified UICC stage (%)			0.10
I	3 (8.1)	107 (17.7)	
II	29 (78.4)	445 (73.7)	
III	4 (10.8)	48 (7.9)	
IVa	1 (2.7)	1 (0.2)	
IVb	0 (0.0)	3 (0.5)	

SD standard deviation, *UICC* International Union Against Cancer

Table 3 Pathologic findings of scirrhous hepatocellular carcinoma (HCC) group and usual HCC group

Characteristics	Scirrhous HCC ($n = 37$)	Usual HCC ($n = 604$)	P value
Edmondson-Steiner grade (%)			0.04
I + II	32 (86.5)	542 (89.7)	
III + IV	5 (13.5)	62 (10.3)	
Liver cirrhosis in background liver (%)	13 (35.1)	381 (63.1)	0.001
Fibrous capsule formation (%)	15 (40.5)	493 (81.6)	<0.0001
Portal vein invasion (%)	7 (18.9)	25 (4.1)	0.003
Intrahepatic metastasis (%)	5 (13.5)	57 (9.1)	0.39
Microvascular invasion (%)	19 (51.4)	243 (40.2)	0.23

long-term prognosis of scirrhous HCC. Moreover, the size of the included patients was small and follow-up duration was relatively short in most previous studies [19, 20].

In our study, 37 cases (5.7%) were pathologically confirmed as scirrhous HCC among 1,658 patients who underwent partial hepatectomy for HCC at our institute during a recent 10-year period. The portion of scirrhous HCC among the whole HCC has been reported to range from 0.2 to 4.2% [2–5, 21], which is similar to ours.

Our results showed several unique clinical features of scirrhous HCC: less frequent HBV infection and lower serum AFP level. Our study, which was conducted in an area endemic for hepatitis B, indicated that HBV infection was less frequently associated with scirrhous HCC than usual HCC (78.4 vs. 91.5%, respectively; $P = 0.02$). Less frequent association with viral infection was also suggested by a previous report from Japan, a hepatitis C prevalent region. The authors showed that rate of HCV infection was 33% in the scirrhous type of HCC and 72% in the usual HCC [12]. Another study showed similar rates of HBV infection between the scirrhous HCC and the usual HCC groups [3]. Preoperative serum AFP in patients with scirrhous HCC were reported to be lower than those with usual HCC in this study (2320 ± 6356 ng/ml vs. 3297 ± 18689 ng/ml, respectively; $P < 0.001$). While the previous study also reported low serum AFP range in scirrhous HCC

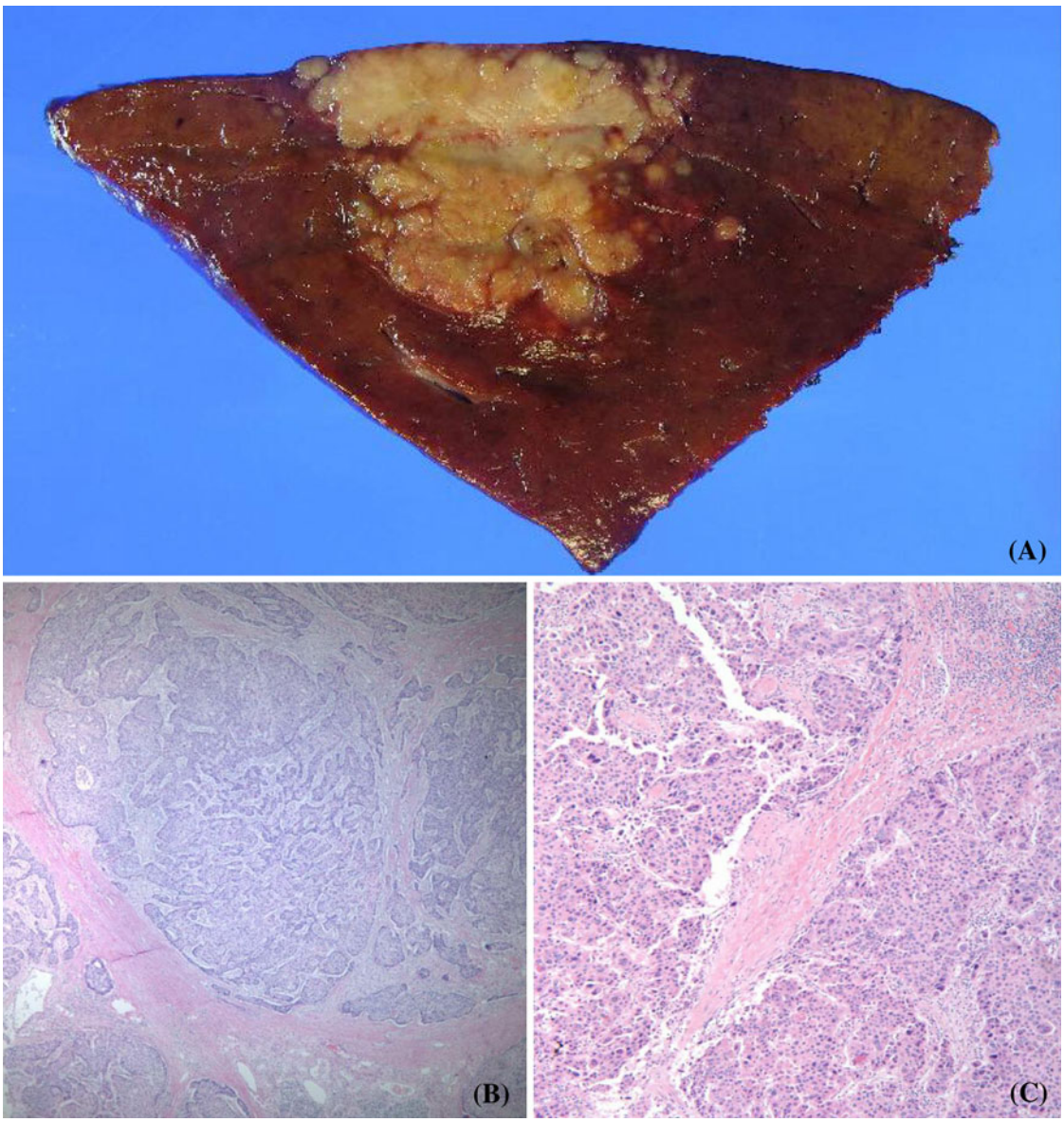

Fig. 2 Histologic finding of the case with scirrhous hepatocellular carcinoma (HCC). The tumor was located below the liver capsule and showed multinodular growth. **a** Microscopic examination showed dense fibrosis with tumor nests (hematoxylin and eosin, ×40). **b** The fibrosis was extended along the sinusoid-like blood spaces with atrophy of tumor trabeculae and showed hyalinization and lamellar pattern (hematoxylin and eosin, ×100) (**c**)

than usual HCC (2.0–4523 vs. 1.0–549,000 ng/ml) [2], two other studies revealed similar levels between the two groups [11, 12].

A typical imaging pattern was defined as "hypervascular with washout in the portal/venous phase" [14]. In our study, contrast enhancement in the arterial phase during dynamic CT was noted in most cases in both the scirrhous and usual HCC groups. However, contrast washout during the portal/venous phase was less frequently noted in the scirrhous HCC group, compared to the control group (72.7 vs. 90.7%, respectively; $P = 0.004$). This is consistent with previous studies reporting that scirrhous HCC displays atypical features, prolonged enhancement in the late phase, and heterogenous enhancement in the arterial phase during dynamic CT [2, 11, 12]. To a certain degree, the enhancing and washout pattern of scirrhous HCC may mimic those of intrahepatic cholangiocarcinoma [22, 23]. The previously described Japanese study reported that these atypical patterns on images more frequently led to preoperative misdiagnosis in scirrhous HCC compared to usual HCC (36.0 vs. 2.1%) [2]. Slow wash-in and wash-out of the extravascular contrast material in the fibrous stroma of scirrhous HCC is believed to play a major role in this phenomenon [24]. In this study, the enhancing and washout pattern

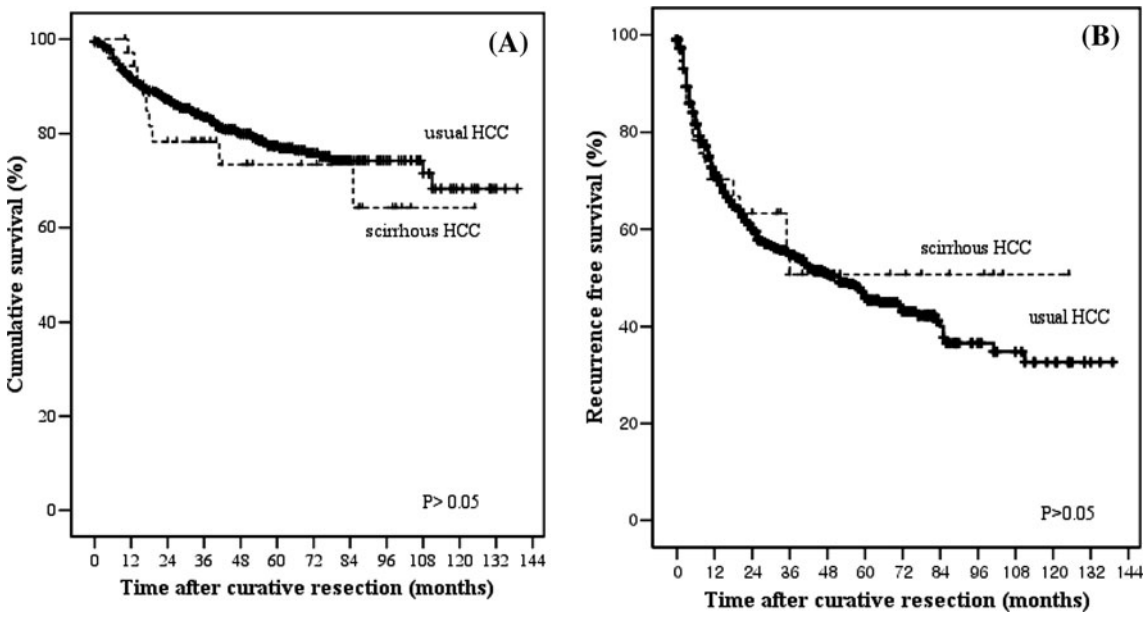

Fig. 3 Cumulative overall survival rates and recurrence free survival rates after hepatic resection in patients with scirrhous and usual HCCs. **a** The 1-, 3-, and 5-years cumulative overall survival rates were not significantly different between scirrhous and usual HCC groups (97.0, 78.2, and 73.3%, respectively, vs. 91.0, 83.5, and 77.3%, respectively; $P = 0.47$). **b** The 1-, 3-, and 5-years recurrence free survival rates in scirrhous and usual HCC groups were similar (70.2, 50.6, and 50.6%, respectively, vs. 71.5, 54.7, and 45.7%, respectively; $P = 0.61$)

during dynamic MRI of scirrhous HCC was similar with those evident during dynamic CT. While arterial enhancement was noted in 96.9% of scirrhous HCC, portal/venous washout was observed in only 78.1% in our study. These findings are also consistent with previous reports [7, 25, 26].

The present data reveal that clinical diagnostic criteria by the AASLD guideline [14] are less useful in scirrhous HCC. Only 32.4% of the scirrhous HCC group fulfilled the AASLD criteria, which is lower than the 57.5% of the usual HCC group ($P = 0.03$). Clinical diagnosis of HCC without biopsy can be made with typical image findings and/or elevated serum AFP level in a high-risk group with LC according to the above criteria. Therefore, clinical diagnostic criteria were less sensitive to detect scirrhous HCC, which showed a lower rate of LC, less typical imaging pattern, and low serum AFP level. To our knowledge, this is the first report about the usefulness of clinical diagnostic criteria on scirrhous type HCC.

Presently, the rate of LC was lower in scirrhous HCC than in usual HCC (35.1 vs. 63.1%, respectively; $P = 0.001$). Three previous studies indicated that background LC was less common in scirrhous HCC than usual HCC (38 vs. 53% [2]; 28.0 vs. 39.9% [11]; 33 vs. 57% [12], respectively), although the difference did not reach statistical significance due to small sample size. Moreover, scirrhous HCC showed less frequent capsule formation than controls in this study (40.5 vs. 81.6%, respectively; $P < 0.001$), consistent with previous reports comparing rate of capsule formation between scirrhous and usual HCC (29 vs. 81% [2]; 0.0 vs. 71.8% [11], respectively). In addition, our study revealed a more frequent portal vein invasion in the scirrhous HCC group than in controls (18.9 vs. 4.1%, respectively; $P = 0.003$). Similar findings were reported in a previous study reporting portal or hepatic vein invasion in 33% of scirrhous HCC and 9% of usual HCC ($P = 0.0019$) [11]. Scirrhous HCCs were usually located in the peripheral portion of liver, close to the liver capsule. Decreased portal perfusion in this area is reported to cause hypoxia of HCC which, in turn, leads to activation of hepatic stellate cells and release of hypoxia-induced mediators enhancing expression of genes important for angiogenesis [27, 28]. Consequently, scirrhous HCC could show a tendency to abundant fibrosis and more vascular invasion.

Our study revealed that overall and recurrence free long-term survival after curative resection was not significantly different between scirrhous and usual HCC. The 1-, 3-, and 5-years cumulative overall survival rates were 97.0, 78.2, and 73.3%, respectively, in patients with scirrhous HCC and 91.0, 83.5, and 77.3%, respectively, in controls ($P = 0.47$). The 1-, 3-, and 5-years recurrence free survival rates in the scirrhous and usual HCC groups were similar (70.2, 50.6, and 50.6%, respectively, vs. 71.5, 54.7, and 45.7%, respectively; $P = 0.61$). While more portal vein invasion and less liver cirrhosis was noted in the scirrhous

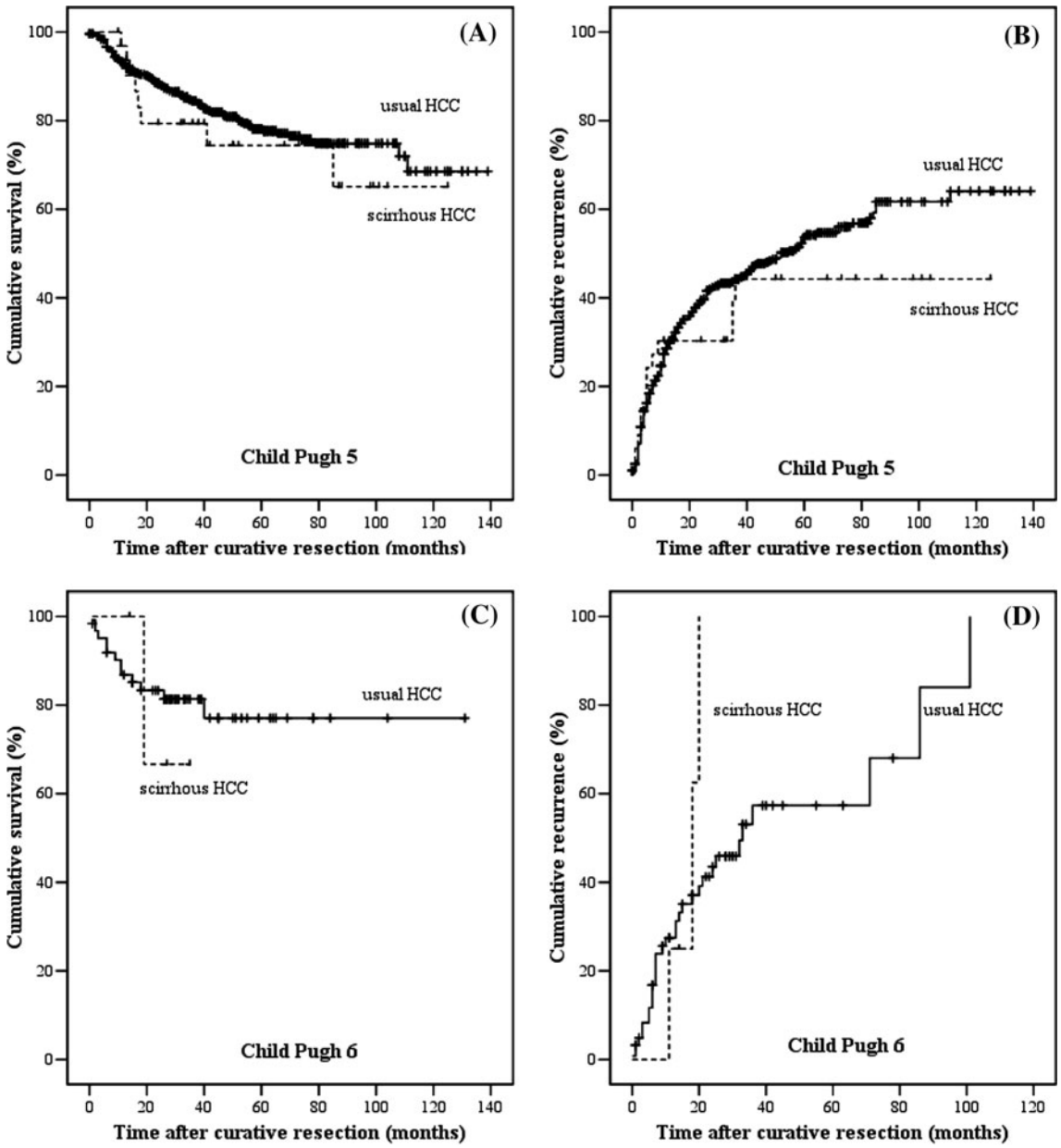

Fig. 4 Subgroup analysis according to Child-Pugh score. **a** The 1-, 3-, and 5-years cumulative overall survival rates of scirrhous HCC group and usual HCC group were not significantly different in patients with Child-Pugh score 5 (96.8, 79.3, and 74.4%, respectively, vs. 92.9, 84.4, and 78.1%, respectively; $P = 0.48$). **b** The 1-, 3-, and 5-years cumulative recurrence rates were similar between the two groups with Child-Pugh score 5 (30.3, 44.3, and 44.3%, respectively, vs. 27.3, 44.2, and 53.8%, respectively; $P = 0.45$). **c** The 1-, 3-, and 5-years cumulative overall survival rates of the scirrhous HCC group and the usual HCC group were not significantly different in patients with Child-Pugh score 6 (100, 66.6, and 66.6%, respectively, vs. 86.8, 81.3, and 77.0%, respectively; $P = 0.76$). **d** The 1-, 3-, and 5-years cumulative recurrence rates were similar between the two groups with Child-Pugh score 6 (25.0, 100.0, and 100.0%, respectively, vs. 27.5, 57.4, and 57.4%, respectively; $P = 0.30$)

HCC group, less portal vein invasion and more liver cirrhosis was observed in usual HCC group. Similar survival rates between the scirrhous and usual HCC groups might come from an offsetting effect of these two major prognostic factors. A previous study involving 11 patients with scirrhous HCC and 230 with general HCC reported that overall and recurrence-free 5-year survival rates were 71 and 43% for scirrhous HCC and 20 and 2% for general HCC, respectively. The authors suggested that a better prognosis in scirrhous HCC could be attributable to the antitumor effects induced by cellular immunity [2]. In contrast, two other studies showed no difference in long-term prognosis between scirrhous and usual HCC groups [1, 11]. This discrepancy in prognosis among studies might

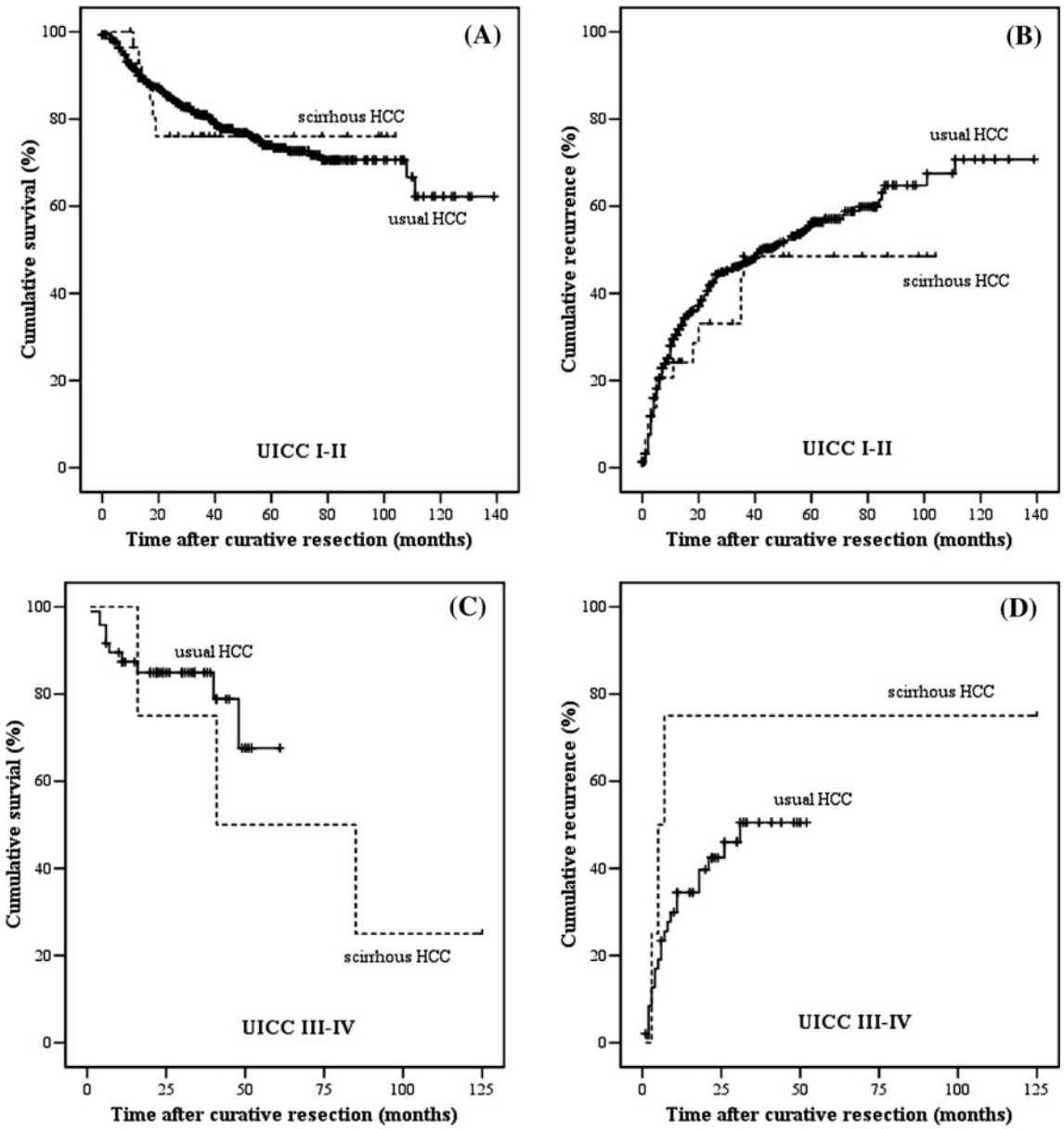

Fig. 5 Subgroup analysis according to modified UICC stage. **a** The 1-, 3-, and 5-years cumulative overall survival rates of scirrhous HCC group and usual HCC group were not significantly different in patients with modified UICC stage I-II (96.7, 78.1, and 78.1%, respectively, vs. 92.3, 83.6, and 77.9%, respectively; $P = 0.86$). **b** The 1-, 3-, and 5-years cumulative recurrence rates were similar between the two groups with modified UICC stage I-II (21.9, 45.1, and 45.1%, respectively, vs. 27.8, 44.7, and 53.8%, respectively; $P = 0.31$). **c** The 1-, 3-, and 5-years cumulative overall survival rates of the scirrhous HCC group and the usual HCC group were not significantly different in patients with modified UICC stage III-IV (100, 80, and 80%, respectively, vs. 88.3, 82.3, and 65.9%, respectively; $P = 0.78$). **d** The 1-, 3-, and 5-years cumulative recurrence rates were similar between the two groups with modified UICC stage III-IV (80, 80, and 80%, respectively, vs. 35.8, 52.8, and 52.8%, respectively; $P = 0.10$)

come from the small sample size and selection bias including mismatched liver function and stages between the scirrhous and usual HCC groups. Hence, we performed subgroup analyses about the long-term prognosis according to Child-Pugh score and modified UICC staging. To the best of our knowledge, our study is the first one revealing that scirrhous HCC and usual HCC presents a similar prognosis with subgroup analysis according to liver function and tumor extent.

Since we included only patients with pathologically confirmed scirrhous HCC after surgical resection, our study revealed the characteristics and prognosis of a specific group of patients with well-preserved liver function and early stage tumors. Data on patients with poor liver

function or unresectable scirrhous HCC were excluded. However, considering that diagnosis of scirrhous HCC is usually confirmed through pathologic examination of resected tumor, our study can be regarded as a reasonable and practical approach to elucidate any valuable data on scirrhous HCC.

In summary, our study reveals some unique clinicopathologic and imaging characteristics of scirrhous HCC, e.g. less frequent viral infection, low serum AFP level, atypical dynamic imaging, low usefulness of clinical diagnostic criteria, a tendency to portal vein invasion, and low rate of background LC and fibrous capsule formation. In addition, we show that long-term outcome after curative resection of scirrhous HCC is not significantly different from those of usual HCC, even between subgroups with corresponding Child-Pugh score and modified UICC staging.

Conflict of interest None.

References

1. Matsuura S, Aishima S, Taguchi K, et al. 'Scirrhous' type hepatocellular carcinomas: a special reference to expression of cytokeratin 7 and hepatocyte paraffin 1. *Histopathology*. 2005;47: 382–390.
2. Kurogi M, Nakashima O, Miyaaki H, Fujimoto M, Kojiro M. Clinicopathological study of scirrhous hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2006;21:1470–1477.
3. Ishak KG, Goodman Z, Stocker JT. Hepatocellular carcinoma. In: Rosai J, Sobin LH, eds. *Tumors of the Liver and Intrahepatic Bile Duct*. 3rd ed. Washington, DC: Armed Forces Institute of Pathology; 1999:199–230.
4. Iha H. Clinicopathological study on scirrhous hepatocellular carcinoma. A study of 12 resected cases. *Acta Hepatol Jpn*. 1994; 28:855–863.
5. Japan LCSGO. *Survey and Follow-Up Study of Primary Liver Cancer in Japan. Report 15*. Kyoto: Liver Cancer Study group of Japan; 2002.
6. Kim SH, Lee WJ, Lim HK, Park CK. Sclerosing hepatic carcinoma: helical CT features. *Abdom Imaging*. 2007;32:725–729.
7. Goshima S, Kanematsu M, Yamada T, et al. Small scirrhous hepatocellular carcinoma with central scar: MR imaging findings. *J Magn Reson Imaging*. 2002;16:741–745.
8. Yamashita Y, Fan ZM, Yamamoto H, et al. Sclerosing hepatocellular carcinoma: radiologic findings. *Abdom Imaging*. 1993;18: 347–351.
9. Yoshida J, Takayama T, Yamamoto H. Computed tomography of sclerosing hepatocellular carcinoma. *Comput Med Imaging Graph*. 1992;16:125–130.
10. Kim SR, Imoto S, Nakajima T, et al. Scirrhous hepatocellular carcinoma displaying atypical findings on imaging studies. *World J Gastroenterol*. 2009;15:2296–2299.
11. Kim SH, Lim HK, Lee WJ, Choi D, Park CK. Scirrhous hepatocellular carcinoma: comparison with usual hepatocellular carcinoma based on CT-pathologic features and long-term results after curative resection. *Eur J Radiol*. 2009;69:123–130.
12. Sugiki T, Yamamoto M, Taka K, Nakano M. Specific characteristics of scirrhous hepatocellular carcinoma. *Hepatogastroenterology*. 2009;56:1086–1089.
13. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol*. 2001;35:421–430.
14. Bruis J, Sherman M. AASLD practice guideline: management of hepatocellular carcinoma. *Hepatology*. 2005;42:1209–1235.
15. International Union Against Cancer (UICC). In: Sobin LH, Wittekind C, eds. *TNM Classification of Malignant Tumors*. 5th ed. New York. Wiley-Liss; 1997.
16. Christensen E. Prognostic models including the Child-Pugh, MELD and Mayo risk scores—where are we and where should we go? *J Hepatol*. 2004;41:344–350.
17. Okamura N, Yoshida M, Shibuya A, Sugiura H, Okayasu I, Ohbu M. Cellular and stromal characteristics in the scirrhous hepatocellular carcinoma: comparison with hepatocellular carcinomas and intrahepatic cholangiocarcinomas. *Pathol Int*. 2005;55: 724–731.
18. Chu PG, Ishizawa S, Wu E, Weiss LM. Hepatocyte antigen as a marker of hepatocellular carcinoma: an immunohistochemical comparison to carcinoembryonic antigen, CD10, and alpha-fetoprotein. *Am J Surg Pathol*. 2002;26:978–988.
19. Yeh CN, Hung CF, Lee KF, Chen MF. Sclerosing hepatocellular carcinoma: clinicopathologic features in seven patients from Taiwan and review of the literature. *Hepatogastroenterology*. 2005;52:1201–1205.
20. Kim BS, Lee SG, Hwang S, et al. Surgical treatment of sclerosing hepatocellular carcinoma. *Korean J Hepatol*. 2006;12:412–419.
21. Ikai I, Itai Y, Okita K, et al. Report of the 15th follow-up survey of primary liver cancer. *Hepatol Res*. 2004;28:21–29.
22. Asayama Y, Yoshimitsu K, Irie H, et al. Delayed-phase dynamic CT enhancement as a prognostic factor for mass-forming intrahepatic cholangiocarcinoma. *Radiology*. 2006;238:150–155.
23. Valls C, Guma A, Puig I, et al. Intrahepatic peripheral cholangiocarcinoma: CT evaluation. *Abdom Imaging*. 2000;25:490–496.
24. Yoshikawa J, Matsui O, Kadoya M, Gabata T, Arai K, Takashima T. Delayed enhancement of fibrotic areas in hepatic masses: CT-pathologic correlation. *J Comput Assist Tomogr*. 1992;16: 206–211.
25. Jeon TY, Kim SH, Lee WJ, Lim HK. The value of gadobenate dimeglumine-enhanced hepatobiliary-phase MR imaging for the differentiation of scirrhous hepatocellular carcinoma and cholangiocarcinoma with or without hepatocellular carcinoma. *Abdom Imaging*. 2010;35:337–345.
26. Yamashita Y, Fan ZM, Yamamoto H, et al. Spin-echo and dynamic gadolinium-enhanced FLASH MR imaging of hepatocellular carcinoma: correlation with histopathologic findings. *J Magn Reson Imaging*. 1994;4:83–90.
27. Troeger JS, Schwabe RF. Hypoxia and hypoxia-inducible factor 1alpha: potential links between angiogenesis and fibrogenesis in hepatic stellate cells. *Liver Int*. 2011;31:143–145.
28. Copple BL, Bai S, Burgoon LD, Moon JO. Hypoxia-inducible factor-1alpha regulates the expression of genes in hypoxic hepatic stellate cells important for collagen deposition and angiogenesis. *Liver Int*. 2011;31:230–244.