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Appropriate Surgical Management of Small Hepatocellular Carcinomas in Patients Infected with Hepatitis C Virus

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Abstract. We investigated the incidence of recurrence after resection of small hepatocellular carcinomas (HCC) in patients infected with hepatitis C virus (HCV) to determine the appropriate surgical management of these patients. Sixty-one patients with anti-HCV antibody who underwent curative liver resection for small HCC (≦ 2.0 cm in greatest diameter) were categorized into two groups. Group 1 consisted of 27 patients with serum concentrations of type IV collagen 7S domain (7S collagen), a marker for hepatic fibrosis, < 8 ng/ml. Group 2 consisted of 34 patients with serum concentrations of 7S collagen ≧ 8 ng/ml. Serum concentration of 7S collagen correlated with the severity of active hepatitis and the degree of fibrosis in the noncancerous hepatic tissue, both of which are related to risk potential of hepatocarcinogenesis. Serum concentration of total bilirubin, aspartate aminotransferase activity, indocyanine green retention rate at 15 minutes, the proportion of patients who were Child-Pugh class B, and the proportion of patients with severe active hepatitis or cirrhosis (determined by histologic examination) were significantly higher in group 2 than in group 1. Platelet count was significantly lower in group 2. Tumor-free survival rates were not different between the groups. In group 1, nonanatomic resection was a risk factor for recurrence by univariate and multivariate analyses (odds ratio = 3.45, $p = 0.040$). In group 2, nonanatomic resection was not a risk factor for recurrence. In patients with small HCV-related HCC, anatomic resection is recommended when the serum concentration of 7S collagen is low (< 8 ng/ml) because the potential of hepatocarcinogenesis may be low even after the operation.

Through advances in medical imaging and screening for hepatocellular carcinoma (HCC) in patients infected with hepatitis B virus (HBV) and hepatitis C virus (HCV), the number of patients with small HCC has been increasing [1]. The outcome after liver resection for HCC is unsatisfactory because of a high rate of recurrence [1, 2]. Although liver resection is the best treatment for HCC, the determination of the optimal extent of resection is often difficult because most patients have chronic liver disease such as chronic hepatitis or liver cirrhosis. Some investigators have reported improved outcome after major hepatectomy [3, 4], and others have found that the operative method was not related to outcome [5–8]. For HCC in patients with cirrhosis, limited liver resection has been recommended [9, 10]. Makuuchi et al. [3, 11, 12] recommend anatomic resection along the portal system, if possible, because intrahepatic metastasis is thought to occur through the portal vein. The outcome in their patients was better in those who underwent anatomic resection than in those who underwent nonanatomic resection (partial or limited resection). Previous studies have investigated outcomes after surgical resection of HCC in patients with and without hepatitis virus [3, 7–10, 13]. These studies have included patients with HBV as well as HCV, and also have included patients with a wide range of tumor sizes. Because the prevalence of multicentric carcinogenesis is higher in patients infected with HCV than in patients infected with HBV [14–16], and because outcomes differ after surgical management of small and large HCC lesions [6, 13, 17], the optimal surgical management of patients with small HCC lesions associated with HCV infection remains unclear. In addition, it is difficult to examine the histologic findings of noncancerous hepatic tissue before surgery in all patients.

Recurrences after resection of a primary HCC are thought to result from intrahepatic spread through the portal vein and from newly developed HCC (multicentric carcinogenesis) after surgery in patients with chronic liver disease caused by hepatitis virus, especially HCV [2, 4, 17–20]. The incidence of HCC development and the prevalence of multicentric carcinogenesis in patients infected with HCV increases with progression of active hepatitis and hepatic fibrosis [15, 21, 22]. These findings suggest that the incidence of newly developed HCC after resection of primary HCC (multicentric recurrence) also increases with the progression of active hepatitis and hepatic fibrosis. To determine the appropriate operative method in patients with small HCV-related HCC, it is important to consider the potential of hepatic carcinogenesis that is related to active hepatitis and hepatic fibrosis.

Recently type IV collagen 7S domain (7S collagen), involved in connective tissue metabolism, has been reported as a biochemical marker for assessing the fibrogenesis and fibrosis that occur during

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the development of cirrhosis [23, 24]. Increased concentrations of 7S collagen reflect accelerated metabolism of the basement membrane [25].

In this study, we investigated the incidence of recurrence after resection of small HCC in patients infected with HCV, using this marker for liver fibrosis to determine the appropriate surgical management of these patients.

Patients and Methods

Patients

Since 1991, 67 patients with anti-HCV antibodies have undergone curative liver resection for small HCCs (≦ 2.0 cm in greatest diameter) at our institution. The concentration of 7S collagen was measured before surgery in all patients. Six patients were excluded from the study because they developed lethal postoperative complications or received interferon after operation. Hence there were 61 evaluable patients. Curative surgery was defined as complete resection of all macroscopic tumor. Absence of tumor cells along the parenchymal transection line was confirmed histologically. No tumors were present in the remnant liver, as seen by computed tomography (CT) 3 to 4 weeks after operation. Of the 61 patients, 45 patients were men and 16 were women. Age ranged from 46 to 72 yr (mean ± SD, 63 ± 6 yr). Patients were examined preoperatively by ultrasonography, plain and enhanced CT, lipiodol CT, and angiography. Since May 1993, CT during arteriography and CT during arterioportography have been performed if possible. Intraoperative ultrasonography was performed in all patients. Anatomic resection (subsegmentectomy, segmentectomy, or bisegmentectomy) was performed in 43 patients, and nonanatomic resection (partial resection) was performed in 18 patients. The 61 patients were divided into two groups. Group 1 consisted of 27 patients with serum concentrations of 7S collagen < 8 ng/ml. Group 2 consisted of 34 patients with serum concentrations of 7S collagen ≧ 8 ng/ml.

The study was conducted in accordance with the Helsinki Declaration and the guidelines of the ethics committee of our institution.

Viral Markers and 7S Collagen

Serum samples obtained before operation from all patients were assayed for HBV and HCV. Serum was examined for hepatitis B surface antigen with an enzyme immunoassay (International Reagents, Kobe, Japan). Samples were examined for anti-HCV antibody by second-generation or third-generation enzyme-linked immunosorbent assay (Ortho Diagnostic Systems, Tokyo, Japan). Serum 7S collagen concentration was measured with a type IV collagen 7S domain RIA kit (Diaiatron Co., Tokyo, Japan), which uses a polyclonal antibody against the 7S domain of type IV collagen isolated from human placenta.

Detection of Recurrence

After operation, serum concentrations of alpha-fetoprotein were measured every 3 months. Ultrasonography, CT, or magnetic resonance imaging with or without chest radiography was performed every 3 months. When tumor recurrence in the remnant liver was suspected on the basis of tumor markers or imaging, angiography or a biopsy under ultrasonographic guidance (or both) was performed for definitive diagnosis.

Pathologic Examination

Resected specimens were cut into serial slices 5-mm-thick, fixed in 10% formalin, and stained with hematoxylin and eosin. The histologic grade of tumor differentiation was assigned using a modification [26] of the classification by Edmondson-Steiner [27]. Noncancerous hepatic tissues were examined pathologically. A histologic activity index (HAI) [28] with some modifications [29] was used to evaluate the severity of active hepatitis (histologic activity score) and the degree of fibrosis (histologic fibrosis score). HAI scores (components 1 to 3) of 0 indicated no activity (histologic activity score, 0); scores of 1 to 3 indicated minimal activity (histologic activity score, 1); scores of 4 to 8 indicated mild activity (histologic activity score, 2); scores of 9 to 12 indicated moderate activity (histologic activity score, 3); and scores of 13 or greater indicated severe activity (histologic activity score, 4). Component 1 indicated the degree of periportal necrosis with or without bridging necrosis and piecemeal necrosis; component 2 indicated the degree of intralobular degeneration and focal necrosis; and component 3 indicated the degree of portal inflammation. The degree of fibrosis (histologic fibrosis score) was determined by component 4 of the HAI score. A histologic fibrosis score of 1 indicated portal fibrous expansion, a score of 2 indicated portal-portal septa without architectural distortion, a score of 3 indicated portocentral septa with architectural distortion, and a score of 4 indicated cirrhosis. At least two pathologists without any knowledge of the clinical and laboratory data examined all materials.

Risk Factors for Recurrence after Operation

We evaluated the risk factors for recurrence in each group. Variables were selected for their potential relation to recurrence based on previous studies or our clinical experience [2–4, 7, 8, 16, 17, 19, 30–36]. The variables chosen were, age (≦ 65 or > 65 years), gender, history of intake of at least 86 g of ethanol daily for at least 10 years, history of blood transfusion [37], Child-Pugh class (A or B) [38], total bilirubin (≦ 1.0 or > 1.0 mg/dl), albumin (< 3.5 or ≧ 3.5 g/dl), platelet count (< 10 or ≧ 10 x $10^4/\mu$l), aspartate aminotransferase (≦ 40 or > 40 IU/l), alanine aminotransferase (ALT, ≦ 45 or > 45 IU/l), alpha-fetoprotein (≦ 20 or > 20 ng/ml), the number of tumors (single or multiple), differentiation of the main tumor (well-differentiated HCC or moderately or poorly differentiated HCC), portal invasion, histologic activity score (0 to 2 or 3 to 4), histologic fibrosis score (0 to 3 or 4), operative method (anatomic resection or nonanatomic resection), and tumor-free margin. When the surgical margin by pathologic examination was less than 5 mm, it was defined as tumor-positive.

Statistics

Student's *t*-test was used to analyze differences in age, and the Mann-Whitney test was used to analyze differences in laboratory values and tumor size. Correlations between 7S collagen concentrations and histologic findings in the noncancerous hepatic tissue were analyzed using Spearman's rank correlation. Clinicopatho-

Table 1. Clinicopathologic features in patients with small hepatocellular carcinomas and chronic hepatitis C.

	Type IV collagen 7S domain		
	< 8.0 ng/ml	8.0 ng/ml	
Parameter	Group 1 (n = 27)	Group 2 (n = 34)	p value
Age (years, mean ± SD)	62.9 ± 5.4	62.6 ± 6.0	0.87
Gender (M/F)	21:6	24:10	0.57
Alcohol abuse	11	10	0.42
History of blood transfusion	11	6	0.083
Total bilirubin (mg/dl)[a]	0.7 (0.5, 1.2)	0.9 (0.6, 1.4)	0.032
Albumin (g/dl)[a]	3.8 (3.3, 4.2)	3.5 (3.1, 4.0)	0.32
Platelet count ($\times 10^4/\mu$l)[a]	13.9 (7.6, 24.0)	9.4 (6.0, 17.5)	0.084
AST (IU/L)[a]	50 (24, 105)	67 (37, 110)	0.019
ALT (IU/L)[a]	57 (22, 114)	71 (41, 127)	0.087
$ICGR_{15}$ (%)[a]	15.3 (10.2, 25.3)	19.1 (11.7, 35.2)	0.026
Alpha-fetoprotein (> 20 ng/ml)	10	18	0.30
Child-Pugh class A	23	20	0.046
Differentiation of main tumor			
Well	6	16	0.13
Moderate	13	11	
Poor	8	7	
Single/multiple	20/7	29/5	0.34
Portal invasion	3	1	0.31
Histologic activity score			
0–2	24	13	< .0001
3, 4	3	21	
Histologic fibrosis score			
0–3	15	9	0.034
4; cirrhosis	12	25	
Anatomic resection	14	5	0.0025
Positive surgical margin	15	16	0.61

AST: aspartate aminotransferase; ALT: alanine aminotransferase; $ICGR_{15}$: indocyanine green retention rate at 15 minutes.
[a]Results are given as medians, with 10th and 90th percentiles.

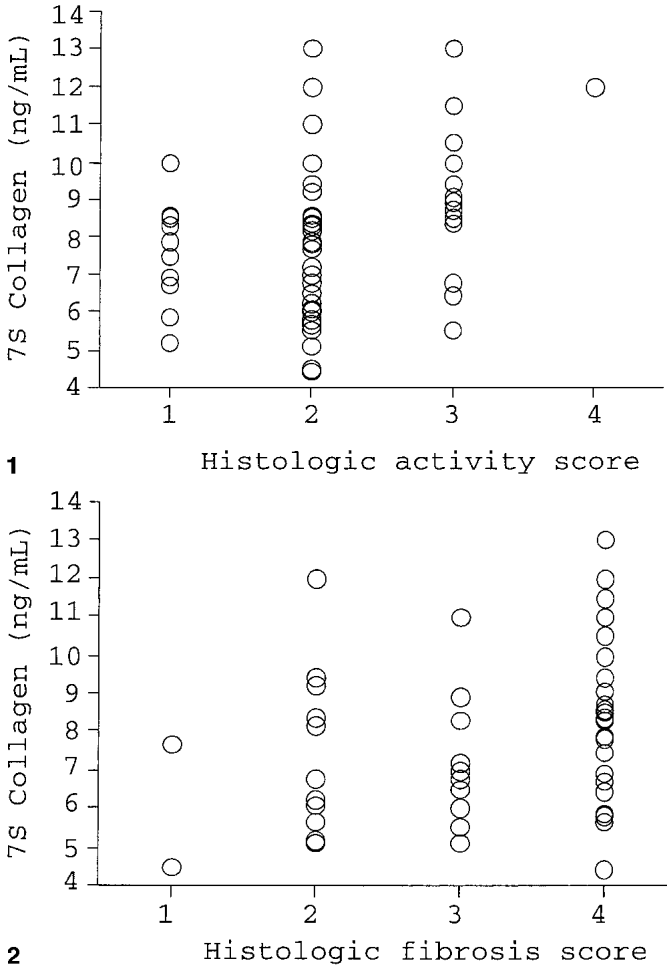

Fig. 1. Relationship between serum concentration of type IV collagen 7S domain (7S collagen) and severity of active hepatitis. Severity of active hepatitis was evaluated using the histologic activity score in the histologic activity index [29]. The serum concentration of 7S collagen correlated with the histologic activity score (Spearman's rank correlation; $\rho = 0.311$, $p = 0.016$).

Fig. 2. Relationship between serum concentration of 7S collagen and degree of hepatic fibrosis. Degree of hepatic fibrosis was evaluated with the histologic fibrosis score in the histologic activity index [29]. The serum concentration of 7S collagen is correlated with the histologic fibrosis score (Spearman's rank correlation; $\rho = 0.389$, $p = 0.0026$).

logic variables were analyzed for their possible role as risk factors after operation. Tumor-free survival rates were determined by the Kaplan-Meier method and compared by the log-rank test. Covariates with p values < 0.1 in the log-rank test were entered into a Cox regression model with forward stepwise selection. The significance level was set at $p = 0.1$ for entry into and removal from the model.

Results

Serum concentration of total bilirubin, aspartate aminotransferase activity, and indocyanine green retention rate at 15 minutes were significantly higher in group 2 than in group 1 (Table 1). Platelet count was significantly lower in group 2 than in group 1. The proportion of patients classified as Child-Pugh class B was significantly higher in group 2 than in group 1. The proportion of patients with high histologic activity scores (3 or 4) and high fibrosis scores (4, liver cirrhosis) was significantly higher in group 2 than in group 1. Twenty-five patients (74%) in group 2 and 12 patients (44%) in group 1 had histologic fibrosis scores of 4 (liver cirrhosis). The proportion of patients who underwent anatomic resection was significantly higher in group 1 than in group 2.

Serum concentrations of 7S collagen correlated with the histologic activity score ($\rho = 0.311$, $p = 0.016$; Fig. 1) and the histologic fibrosis score ($\rho = 0.389$, $p = 0.0026$; Fig. 2).

Tumor-free survival rates were not different between the two groups ($p = 0.16$). In group 1, age ($p = 0.043$), ALT activity ($p = 0.078$), and nonanatomic resection ($p = 0.009$; Fig. 3) were possible risk factors for recurrence according to the log-rank test. By multivariate Cox regression analysis (Table 2), age [odds ratio (OR) = 2.56, $p = 0.090$], ALT activity (OR = 2.88, $p = 0.071$), and nonanatomic resection (OR = 3.45, $p = 0.040$) were possible independent risk factors for recurrence.

In group 2, male gender ($p = 0.04$), moderately or poorly differentiated HCC ($p = 0.027$), and multiple tumors ($p < 0.0001$) were possible risk factors for recurrence according to the log-rank test. By multivariate analysis (Table 2), the presence of multiple tumors (OR = 8.33, $p = 0.0005$) was an independent risk factor. Again, nonanatomic resection was an independent risk factor for recurrence in group 1. However, nonanatomic resection was not a sig-

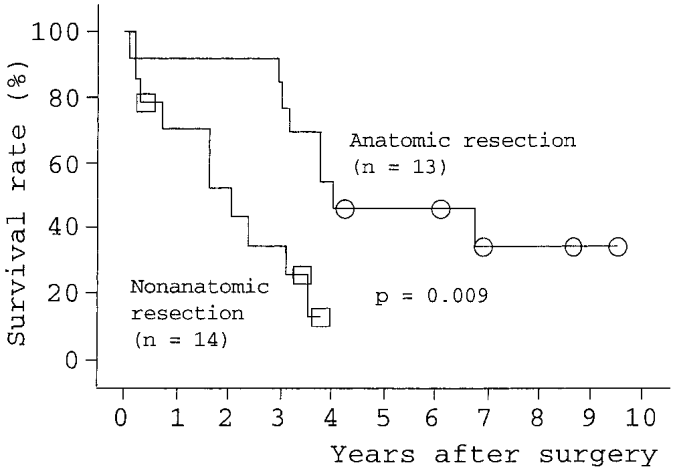

Fig. 3. Tumor-free survival rates in patients with low serum concentrations of 7S collagen (< 8 ng/ml). Tumor-free survival rate was significantly higher in patients who underwent anatomic resection than in patients who underwent nonanatomic resection (log-rank test; $p = 0.009$).

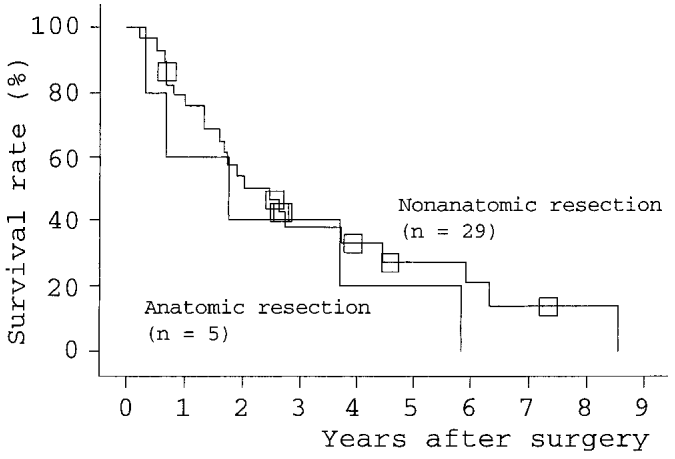

Fig. 4. Tumor-free survival rates in patients with high serum concentrations of 7S collagen (≧ 8 ng/ml). Tumor-free survival rates were not different between the two groups (log-rank test; $p = 0.34$).

Table 2. Risk factors for recurrence after resection of small hepatocellular carcinomas evaluated by multivariate Cox regression analysis.

	Risk ratio	95% CI	*p* value
Group 1 (7S collagen, < 8 ng/ml)			
Age (> 65 years)	2.56	0.865–7.63	0.090
ALT activity (> 45 IU/L)	2.88	0.910–9.09	0.071
Nonanatomic resection	3.45	1.06–11.1	0.040
Group 2 (7S collagen, ≧ 8 ng/ml)			
Multiple tumors	8.33	2.53–27.8	0.0005

CI: confidence interval.

nificant risk factor by univariate analysis (log-rank test; Fig. 4) and multivariate analyses in group 2.

Discussion

This study indicated that, in patients with small HCV-related HCCs, anatomic resection is recommended when the serum concentration of 7S collagen is low (< 8 ng/ml) because the possibility of multicentric recurrence may be low. In patients with a high concentration of 7S collagen (≧ 8 ng/ml), it is important to follow patients closely for recurrence after operation.

Recently, various treatments, including ethanol injection therapy, microwave coagulation therapy, and radiofrequency ablation, have been developed as ablative therapy for patients with small HCCs. These treatments are similar to resection of the tumor without the surrounding hepatic parenchyma (limited resection). The appropriate indications for these therapeutic modalities remain unclear. It is important to consider the potential of hepatic carcinogenesis to determine the appropriate treatment and operative method in patients with small HCV-related HCCs, because multicentric carcinogenesis after treatment often is found in such patients [15, 22].

In a previous study, 7S collagen correlated strongly with the histologic degree of periportal necrosis and hepatic fibrosis, and correlated weakly with the degree of intralobular degeneration and focal necrosis and the degree of portal inflammation [23]. In this study, we confirmed that 7S collagen correlated with the histologic activity score and the histologic fibrosis score. The incidence of HCC development and the prevalence of multicentric carcinogenesis in patients infected with HCV increase with progression of active hepatitis and hepatic fibrosis [15, 21, 22]. We also found that the prevalence of multicentric carcinogenesis increased with increases in serum concentrations of 7S collagen [22]. These findings indicate that 7S collagen reflects the severity of active hepatitis and the degree of hepatic fibrosis, and that 7S collagen is a possible marker for hepatic carcinogenesis.

In this study, nonanatomic resection was a significant independent risk factor for tumor recurrence in patients with low serum concentrations of 7S collagen (< 8 ng/ml). In contrast, nonanatomic resection was not a risk factor in patients with high serum concentrations of 7S collagen (≧ 8 ng/ml). In patients with low serum concentrations of 7S collagen, the posibility of multicentric recurrence may be low because the patients have mild active hepatitis and mild fibrosis, and the incidence of hepatic carcinogenesis is low. In such patients, anatomic resection along the portal system could remove occult intrahepatic metastases, which spread mainly through the portal vein, resulting in a high tumor-free survival rate. In patients with high serum concentrations of 7S collagen, the possibility of multicentric recurrence was high, and anatomic resection could not prevent such recurrence. For such patients, microwave coagulation therapy is an alternative therapy that is less invasive than partial resection [39]. In addition, treatment of HCV and prevention of multicentric carcinogenesis are necessary in patients with HCV-related HCC [40].

Résumé. Nous avons étudié l'incidence de récidive après résection d'un carcinome hépatocellulaire (CHC) de petite taille chez les patients porteurs du virus de l'hépatite C (HCV) afin de déterminer la prise en charge chirurgicale la plus adaptée de ces patients. Soixante et un patients ayant l'anticorps anti-HCV ayant eu une résection à visée curatrice de CHC de petite taille (≤ 2.0 cm dans son plus grand diamètre) ont été divisés en deux groupes. Groupe 1 était composé de 27 patients ayant une concentration sérique du collagène 7S de type IV «domaine» (7S collagène), un marqueur de fibrose hépatique, inférieure à 8 ng/ml. Le groupe 2 était composé de 34 patients ayant une concentration sérique de collagène 7S ≥ 8 ng/ml. Les concentrations sériques de collagène 7S corrélaient avec la sévérité de l'activité de l'hépatite et le degré de fibrose dans le tissu hépatique non cancéreux, potentiellement en rapport avec

l'hépatocarcinogénèse. Les concentrations sériques en bilirubine totale, de l'activité d'aminotransférase aspartate, le taux de rétention du vert d'indocyanine à 15 minutes, la proportion de patients Child-Pugh classe B et la proportion des patients atteints d'hépatite active sévère ou de cirrhose, déterminée par examen histologique, étaient significativement plus élevés dans le groupe 2 par rapport au groupe 1. Le taux de plaquettes était significativement plus bas dans le groupe 2. Le taux de survie sans tumeur n'était pas différent entre les groupes. Dans le groupe 1, la résection non-anatomique était un facteur de risque pour la récidive en analyse mono- et multidimensionnelle (rapport de côte = 3.45, $p = 0.040$). Dans le groupe 2, la résection non-anatomique n'était pas un facteur de risque de récidive. Chez les patients porteurs d'un CHC de petite taille en rapport avec le virus HCV, on recommande une résection anatomique quand la concentration de collagène 7S est basse (< 8 ng/ml) car dans ce cas, le potentiel d'hépatocarcinogénèse pourrait rester bas, même après opération.

Resumen. Con objeto de averiguar el tratamiento más adecuado para pacientes con carcinomas hepatocelulares (HCC), pequeños, infectados con virus de la hepatitis C (HCV) estudiamos la frecuencia de las recidivas tras resección hepática. 61 pacientes con anticuerpos anti-HCV que fueron hepatectomizados curativamente, por padecer HCC, pequeño (diámetro mayor < 2.0 cm) se dividieron en dos grupos. Grupo I, 27 pacientes que presentaron en el suero concentraciones < 8 ng/ml de 7S (colágena tipo IV), un buen marcador de fibrosis hepática y Grupo II 34 pacientes con concentraciones séricas de 7S colágeno > 8 ng/ml. La concentración sérica de 7S colágeno es proporcional a la gravedad de una hepatitis activa y al grado de fibrosis en tejido hepático no neoplásico, hecho que se relaciona con su potencial hepatocarcinogenético. La bilirrubina total, la actividad de la aspartato aminotransferasa, la tasa de retención a los 15 minutos de indocianina verde, el porcentaje de pacientes de clase B en la clasificación Child-Pug, así como el número de enfermos con hepatitis activa grave o cirrosis, determinados mediante estudio histológico, fue significativamente mayor en el grupo 2 que en el 1. El recuento plaquetario fue significativamente menor en el grupo 2. La tasa de supervivencia sin enfermedad fue igual en ambos grupos. En el grupo 1 los análisis uni y multivariables demostraron que las resecciones no anatómicas, aumentaban el peligro de recidiva (odds ratio = 3.54, $p = 0.040$). En el grupo 2 resecciones no anatómicas no incrementaron el riesgo de recidiva. En pacientes con HCV y pequeños HCC se recomiendan resecciones anatómicas cuando la concentración sérica de 7S colágena es menor de 8 ng/ml, ya que incluso tras la operación existe un riesgo potencial hepatocarcinogenético.

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