recurrence of HCC was strongly suspected on the basis of tumor markers or imaging, selective hepatic angiography, ultrasound-guided biopsy, or both was conducted to establish a definitive diagnosis.

Histology

The system of the Liver Cancer Study Group of Japan [21] was used to categorize histologic findings. The histologic grade of differentiation (well, moderate, or poor) of HCC was determined according to a modification of Edmondson and Steiner [22]. The grade score (severity of active hepatitis) and stage score (degree of hepatic fibrosis) in noncancerous hepatic tissues were determined by the score of the histologic activity index [23], which was determined by four events, i.e., periportal necrosis with or without bridging necrosis, intralobular degeneration with focal necrosis, portal inflammation, and fibrosis.

Statistics

The survival rates were calculated by the Kaplan-Meier method and were compared with those from the log-rank test. The tumor-free survival time was measured from the date of resection until the detection of a recurrent tumor or the endpoint of this study (31 July 2006) in patients without recurrence. Cox's proportional hazard model with stepwise variable selection was used for multivariate analysis. A p value of less than 0.05 was considered significant. Variables were selected on the basis of previous studies or our own clinical experience. The variables chosen were age ($\geq$65 or <65), gender, history of alcohol abuse (intake of at least 86 g of ethanol daily for at least 10 years) [24], history and response to IFN therapy (SVR, BR vs. NR, and no treatment), total bilirubin ($\geq$1 or <1 mg/dl), albumin concentration ($\geq$3.5 or <3.5 g/dl), indocyanine green retention rate at 15 min (ICGR15, $\geq$20 or <20%), platelet count ($\geq 10 \times 10^4$ or $< 10 \times 10^4/\mu l$), aspartate aminotransferase (AST) activity (>40 or $\leq$40 IU/L), ALT activity (>45 or $\leq$45 IU/L), serum α-fetoprotein concentration (AFP, >20 or $\leq$20 ng/ml), the largest diameter of the main tumor (>4 or $\leq$4 cm), the degree of differentiation of the main tumor (well-, moderate vs. poorly differentiated HCC), the number of tumors (single or multiple, including intrahepatic metastasis), microscopic portal invasion, the grading score (0, 1, or 2-4), the staging score (0-3 or 4), and operative method.

Results

There was no operative mortality. Intractable pleural effusion that called for use of diuretics and treatment by thoracocentesis developed postoperatively in three patients, intra-abdominal infection in two patients, bile leakage in two patients, and gastric ulcer in two patients. The tumor-free and cumulative survival rates after SHR in the 51 patients are shown in Figure 1.

By univariate analysis, NR and lack of interferon therapy ($p = 0.0089$), high ICGR15 ($p = 0.0068$), high AST ($p = 0.0607$), high ALT ($p = 0.0930$), large tumor (>4 cm, $p < 0.0001$), and multiple tumors ($p = 0.0105$) were risk factors for HCC recurrence after SHR (Table 2). Multivariate analysis showed that NR and lack of IFN therapy, high ICGR15, large tumor, and multiple tumors were independent risk factors for HCC recurrence after SHR (Table 3). The tumor-free survival rate was higher in SVR and BR patients than in other patients, including NR patients and patients who did not undergo IFN therapy ($p = 0.0089$, Fig. 2). The tumor-free survival rate was higher in patients with small tumor ($\leq$4 cm) than in patients with large tumor (>4 cm, $p < 0.0001$, Fig. 3). The clinicopathologic findings in patients who were sustained viral responders or biochemical responders and in other patients are shown in Table 4. The mean age and gender distribution were similar in the different groups. Although serum concentrations of total bilirubin, albumin, and ICGR15 were not significantly different between the groups, platelet count was significantly higher in patients who were sustained viral responders or biochemical

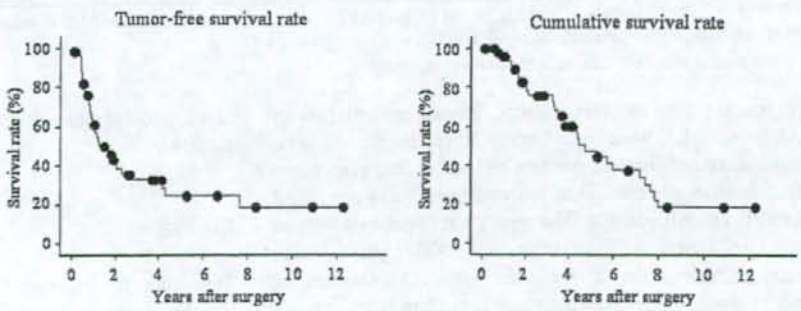

Fig. 1 Tumor-free and cumulative survival rates after second hepatic resection in all patients

Table 2 Tumor-free survival rates after second hepatic resection for recurrent hepatocellular carcinoma by univariate analysis

Factors (numbers of patients)		Survival rates (%)			
		4 years	8 years	12 years	*p* value
Age (years)	≥65 (28)	36	27	27	0.914
	<65 (23)	31	22	–	
Gender	male (47)	36	26	26	0.514
	female (4)	–	–	–	
Alcohol abuse	+ (12)	45	33	33	0.678
	− (39)	31	23	23	
Interferon therapy	SVR + BR (9)	74	74	74	0.0089
	NR + no therapy	42	24	15	15
Total bilirubin (mg/dl)	≥1.0 (20)	–	–	–	0.286
	<1.0 (31)	38	28	28	
Albumin (g/dl)	≥3.5 (39)	36	27	27	0.156
	<3.5 (12)	19	–	–	
ICGR15 (%)[a]	≥20 (16)	15	–	–	0.0068
	<20 (34)	42	34	34	
Platelet count ($\times 10^4/mm^3$)	≥10 (35)	32	27	27	0.156
	<10 (16)	37	18	–	
AST (IU/L)	>40 (37)	23	16	16	0.0607
	≤40 (14)	56	44	44	
ALT (IU/L)	>45 (33)	23	16	–	0.0930
	≤45 (18)	52	41	41	
α-Fetoprotein (ng/ml)	>20 (17)	32	32	–	0.866
	≤20 (34)	34	21	21	
Tumor size (cm)	>4.0 (4)	0	0	0	<0.0001
	≤4.0 (47)	36	27	27	
Differentiation of main tumor	Well, moderate (39)	27	21	21	0.469
	Poor (12)	58	39	–	
Tumor number	Single (36)	41	28	28	0.0105
	Multiple (15)	15	–	–	
Portal invasion	+ (15)	47	36	36	0.690
	− (36)	26	18	18	
Grade	0, 1 (16)	42	42	42	0.264
	2–3 (35)	28	19	–	
Stage	0–3 (28)	36	36	36	0.334
	4 (23)	27	13	–	
Operative methods	anatomic (4)	25	–	–	0.649
	nonanatomic (47)	34	26	26	

ICGR15 = indocyanine green retention rate at 15 min; AST = aspartate aminotransferase; ALT = alanine aminotransferase; SVR = sustained viral response; BR = biochemical remission; NR = no response

[a] One patient who was intolerant of ICG was excluded

responders than in other patients. The serum activities of AST and ALT were significantly lower in patients who were sustained viral responders or biochemical responders than in other patients. Thus, active hepatitis was controlled in SVR and BR patients. The proportion of patients with an elevated serum AFP concentration (>20 ng/ml), tumor size, differentiation of the main tumor, prevalences of portal invasion and multiple tumors, grading score, staging score, and operative methods were similar in the different groups.

Discussion

Treatment for recurrent HCCs includes SHR, ablation therapy such as microwave coagulation therapy and

Table 3 Risk factors for recurrence after second hepatic resection for recurrent hepatocellular carcinoma by multivariate analysis

Factors	Risk ratio	95% confidence interval	*p* value
NR + lack of interferon therapy	17.660	2.252–138.496	0.0063
ICGR15 (≥20%)[a]	0.396	0.179–0.878	0.0227
Tumor size (>4 cm)	0.140	0.030–0.643	0.0115
Multiple tumors	0.330	0.143–0.766	0.0098

ICGR15 = indocyanine green retention rate at 15 min

[a] One patient who was intolerant of ICG was excluded

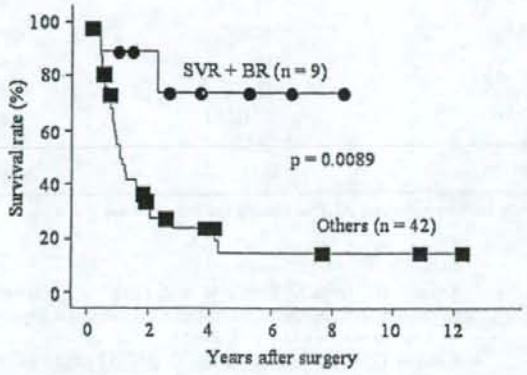

Fig. 2 Comparison of tumor-free survival rates in patients who were sustained viral responders or biochemical responders with other patients. Circle, 9 patients who were sustained viral responders or biochemical responders; square, other 42 patients

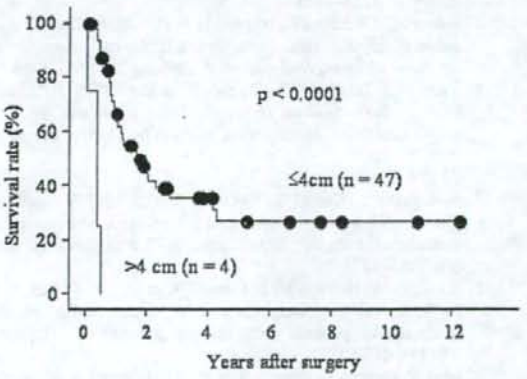

Fig. 3 Comparison of tumor-free survival rates in patients with large tumor and small tumor. Circle, 47 patients with small tumor (≤4.0 cm); another line, 4 patients with large tumor (>4.0 cm)

radiofrequency ablation therapy, and transarterial therapy such as transcatheter arterial embolization. Liver transplantation is another option in selected patients with impaired liver function. Although the value of SHR for recurrence has been demonstrated, indications for SHR are unclear. The tumor-free survival rate in patients with chronic hepatitis is unsatisfactory because multicentric carcinogenesis persists as long as hepatitis remains active. Recurrence is not uncommon following SHR, even when the resection is considered curative.

Although prognostic factors after first resection for HCC have been evaluated by many investigators, there are a few studies about prognostic factors after SHR. In addition, viral status in patients has not been evaluated in the previous study. In this study univariate analysis showed that NR and lack of IFN therapy, high ICGR15, high AST, high ALT, large tumor, and multiple tumors are risk factors for recurrence. In addition, the tumor-free survival rate was higher in SVR and BR patients than in other patients, nonresponders, and patients who did not undergo IFN therapy. Multivariate analysis showed NR and lack of IFN therapy, high ICGR15, large tumor, and multiple tumors are independent risk factors for HCC recurrence after SHR. Previous studies have indicated that active hepatitis with a sustained increase in the serum aminotransferase activity is a risk factor for recurrence [1, 2, 6, 25]. Other recent studies found that HCC is less likely to develop in patients in whom IFN normalized serum ALT activity, even when HCV RNA remained detectable [11, 12]. IFN therapy also suppresses carcinogenesis after surgery [13, 14, 16, 26, 27]. In this study, active hepatitis had been suppressed in SVR and BR patients, and the tumor-free survival rate after SHR was significantly higher in these patients than in others. Thus, the induction of remission of active hepatitis by IFN therapy suppressed carcinogenesis after SHR. The study of IFN therapy after tumor ablation by Shiratori et al. [16] showed that the rate of second or third recurrence was lower in the IFN group than in the control group, although the incidence of first recurrence of a new foci of HCC was similar in the two groups. It is possible that what is called the first recurrent tumor had already developed by the time of the first operation, and the remission of active hepatitis by IFN therapy suppressed subsequent carcinogenesis. Thus, SHR is likely to be associated with a low incidence of recurrence when IFN therapy has controlled chronic hepatitis C. IFNα was the first therapy for chronic hepatitis C. The combination of IFN and ribavirin increases SVR rates compared with IFN alone. The combination of a

Table 4 Clinicopathologic findings in patients who were sustained viral responders or biochemical responders and other patients

	SVR + BR ($n = 9$)	Others ($n = 42$)	p value
Age (mean ± SD)	67.2 ± 6.7	65.9 ± 6.3	0.561
Gender (male:female)	8:1	39:3	>0.999
Total bilirubin (mg/dl)	0.8 (0.7, 1.0)	0.8 (0.5, 1.3)	0.822
Albumin (g/dl)	3.7 (3.6, 4.2)	3.8 (3.3, 4.1)	0.388
ICGR15 (%)[a]	16.4 (10.5, 21.5)	17.1 (6.3, 26.7)	0.695
Platelets ($\times 10^4/mm^3$)	17.7 (15.2, 23.4)	11.1 (6.8, 20.5)	0.0016
AST (IU/L)	34 (25, 53)	56 (29, 104)	0.0091
ALT (IU/L)	25 (18, 64)	67 (23, 119)	0.0165
Tumor size (cm, mean ± SD)	2.4 ± 1.1	2.6 ± 1.5	0.615
Differentiation of main tumor (well:moderate:poor)	0:6:3	4:29:9	0.520
Multiple tumors	4	11	0.421
Portal invasion	3	12	>0.999
Grade (0:1:2:3)	1:3:5:0	1:11:29:1	0.574
Stage (0–1:4)	6:3	22:20	0.488
Operative methods (anatomic:nonanatomic)	0:9	4:38	>0.999

ICGR15 = indocyanine green retention test at 15 min; AST = aspartate aminotransferase; ALT = alanine aminotransferase

[a] One patient who was intolerant of ICG was excluded

pegylated IFN and ribavirin significantly increases SVR rates and is now recognized as the standard therapy [28]. Such IFN therapy is recommended in patients with chronic hepatitis C, even after resection of primary HCC.

The independent risk factors for recurrence after SHR include large tumors and multiple tumors. Thus, a close follow-up after the first operation is important for detecting HCC recurrence at an early stage. When a small recurrent tumor is detected, liver resection or ablation therapy is indicated. We reported that anatomic resection is a favorable prognostic factor in patients in whom IFN was effective [29]. Thus, anatomic resection may be more useful than ablation therapy in such patients. On the other hand, SHR or transarterial therapy is usually used in patients with advanced recurrent tumors such as large tumors and multiple tumors because intrahepatic recurrence was strongly suspected to represent metastasis, in which case IFN therapy is unlikely to be effective. Such lesions require additional treatment such as anticancer chemotherapy.

In conclusion, patients in whom active hepatitis has been controlled by IFN therapy are the best candidates for SHR. IFN therapy should be recommended in patients undergoing resection of an HCV-related HCC because SHR prolongs life if there is a recurrence after liver resection.

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Original Paper

Convenience of a Tape-Guiding Technique in Different Types of Hepatectomy

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KEY WORDS:
Tape-guiding; Hanging maneuver; Hepatectomy

ABBREVIATIONS:
Tape-Guiding Technique (TGT); Hepatocellular Carcinoma (HCC); Intrahepatic Cholangiocarcinoma (ICC); Inferior Vena Cava (IVC); Right Hepatic Vein (RHV); Middle Hepatic Vein (MHV); Left Hepatic Vein (LHV); Short Hepatic Vein (SHV)

ABSTRACT

Background/Aims: The liver hanging maneuver is widely used in right lobectomy to resect huge tumors and harvest living donors. The convenience of tape assistance in other types of hepatectomy is not well known.

Methodology: Tape-guiding technique (TGT) was applied in 30 hepatectomies of different type between April 2003 and April 2006. The indications were liver carcinoma in 22 and living-donor in 8. Hepatectomies included right lobectomy, 14; left lobectomy with caudate lobectomy, 8; left lobectomy without caudate lobectomy, 2; lateral segmentectomy, 3; central bisegmentectomy, posterior segmentectomy, and superior dorsal partial resection, 1 each. A tape was placed in front of the inferior vena cava for right hepatectomy and left hepatectomy with caudate lobectomy. In other hepatectomies, the tape was positioned to be the target of parenchymal dissection.

Results: TGT was successfully performed in all 30 cases. Tape facilitated dissection by helping the surgeon maintain orientation, and traction on the tape flattened the parenchyma, making it easier to identify and manage vessels and ducts. With an assistant holding the tape, the surgeon's left hand was free, and ligation and suturing was easier and more secure.

Conclusions: The TGT is a convenient technique that is applicable to different types of liver resection.

INTRODUCTION

The liver hanging maneuver in right lobectomy was introduced by Belghiti (1) in 2001. Since then, it has become widely accepted as a safe and easy technique for managing huge tumors invading the diaphragm. Kokudo and co-workers (2) modified the maneuver into the sling suspension technique and have used it in donor right lobectomy, posterior segmentectomy with right hepatic vein (RHV), and left lobectomy with caudate lobectomy and middle hepatic vein (MHV). Although Belghiti's "hanging" maneuver means the technique using a tape positioned in front of the IVC, further modifications of the maneuver using a tape in different space, such as donor left lobectomy without caudate lobectomy with or without MHV (3,4) had been reported. We also felt that the tape-guiding technique has advantages and can be applied in various situations of hepatic parenchymal dissection. This report describes the use of the tape-guiding technique (TGT) in different types of liver resection.

METHODOLOGY

Between April 2003 and April 2006: 30 patients underwent hepatectomy using the TGT. The group consisted of 19 men and 11 women, with median age of 64 (20 to 80) years old. The surgical indications were hepatocellular carcinoma (HCC) in 12, intrahepatic cholangiocarcinoma (ICC) in 9, metastatic tumor in 1, and living-donor for transplantation in 8. Among the 22 patients with liver tumor, the diameter of the main tumor ranged from 2.0 to 18.0 (median: 5.7) cm. In 7 patients, the tumor had invaded to the main portal veins, roots of the hepatic veins, main hepatic duct, or diaphragm. Types of hepatectomy included right lobectomy in 14, left lobectomy with caudate lobectomy in 8, left lobectomy without caudate lobectomy in 2, lateral segmentectomy in 3, central bi-segmentectomy, posterior segmentectomy, and partial resection of the superior dorsal region between the anterior segment and caudate lobe in 1. Hepatic anatomy and type of hepatectomy were classified based on Healey's segments (5).

This study was conducted in accordance with the Helsinki Declaration and the Guidelines of the Ethics Committee of our institution. Written informed consent for participation was obtained from each patient.

Surgical Approach

Tape-positioning: For right lobectomy, left lobectomy with caudate lobectomy, posterior segmentectomy with the right hepatic vein (RHV), and partial resection of superior dorsal region between the

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TABLE 1 Operative Blood Loss, Transfusion, and Complications

Type of hepatectomy	No. of patients	blood loss (g) Range (median)	Blood transfusion	Bile leakage	Ascites
Right lobectomy	14	50-5100 (1170)	4	2	0
Left lobectomy	10	700-3500 (1480)	2	1	0
Others	6	240-1500 (1110)	1	1	1
Total	30	50-5100 (1700)	7	4	1

anterior segment and caudate lobe, a tape was placed between the dorsal surface of the liver and the IVC **(Figure 1A)**. In 17 of these 24 cases, mobilization of the resection side of the liver and division of the short hepatic veins (SHV) were performed so that the tape could be positioned under direct vision. In the other 7 cases, the tumor was too large, hard, or had invaded the diaphragm or the root of the hepatic vein, so that mobilization of the liver was difficult. In these cases, the tape was passed prior to hepatic mobilization. In such cases, we began the dissection by ligating and dividing several short hepatic veins from the caudate process and then proceeded to develop the anterior plane of the IVC with long forceps, according to Belghiti's (1) method. When the forceps were not long enough to pass through the space between the dorsal liver surface and the IVC because of a huge tumor, after additional dissection from both the caudal and cranial sides, a probe with a thick tip was passed caudal-to-cranial through the plane anterior to the IVC, the tip was tied with a ligature stitched to a tape, and the probe was withdrawn, pulling the tape into place **(Figure 2)**.

For left lobectomy without caudate lobectomy or lateral segmentectomy, mobilization of the lateral segment, exposure of the anterior surface of the MHV and left hepatic vein (LHV), and division of the cranial side of the ligamentum venosum was performed, and the root of the LHV encircled. The left end of the tape was pulled inferiorly along the ligamentum venosum. When the middle and left hepatic veins joined deep in the hepatic parenchyma or when harvesting a living donor, the LHV was not encircled to avoid injury to the vein, and the cranial end of the tape was placed just to the left of the root of the LHV **(Figure 1B)**.

Parenchymal dissection: Hepatic parenchyma was dissected with a Cavitron Ultrasonic Surgical Aspirator (CUSA Excel TM; Valley lab, Boulder, CO) and bipolar electrocautery (CMC TM III, Valley Forge Scientific Co. Oaks, PA), starting from the anterior surface of the liver and moving toward the tape. During dissection, the hepatoduodenal ligament usually was clamped for 15 minutes with 5-minute intervals of restored flow to minimize blood loss. Vascular obstruction was not performed when harvesting donor livers.

In right lobectomy without MHV and left lobectomy with caudate lobectomy and MHV, parenchymal dissection was started from the anterior surface along the right side of the MHV, and was directed to the middle of the tape lying on the anterior surface of

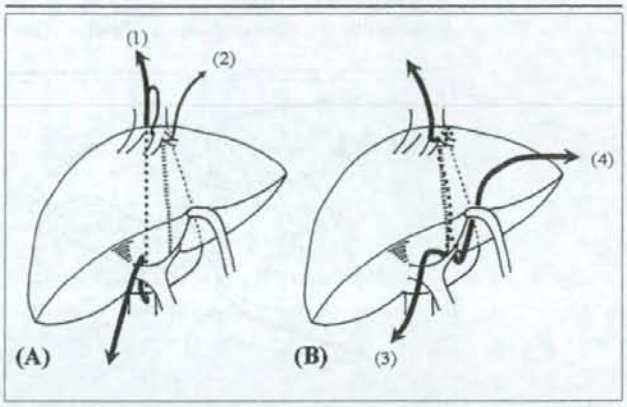

FIGURE 1 (A) Use of the tape-guiding technique in right lobectomy, left lobectomy with caudate lobectomy, posterior segmentectomy with the right hepatic vein, and partial resection of the dorsal liver. The tape is placed between the dorsal surface of the liver and anterior surface of the inferior vena cava (1). In right lobectomy with middle hepatic vein (MHV) and left lobectomy with caudate lobe without MHV, when possible, the root of the MHV is encircled prior to mobilization, and the cranial end of the tape is led to the left side of the MHV (2). **(B)** The course of the tape in left lobectomy without caudate lobectomy (3) and lateral segmentectomy (4).

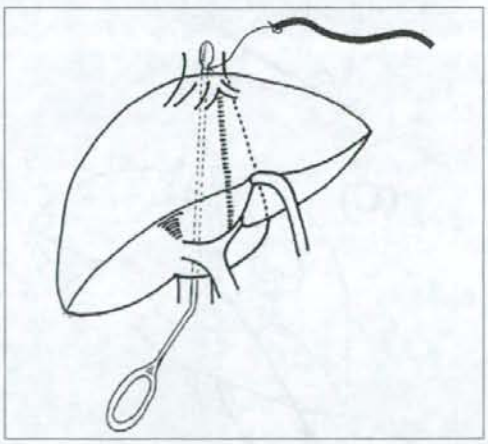

FIGURE 2 The tape-passing procedure between the dorsal surface of the liver and anterior surface of the inferior vena cava (IVC) in the patient with a large, hard tumor. A probe with a thick tip is passed caudal to cranial through the plane anterior to the IVC. The tip is tied with a ligature sutured to the tape, and the probe is withdrawn, leaving the tape in place.

the IVC. During deeper parenchymal dissection, the tape was gently elevated to help to control bleeding. In right lobectomy with MHV and left lobectomy with caudate lobectomy without MHV, the dissection was carried out along the left side of the MHV and directed towards the tape. When possible, the root of the MHV was encircled first, and the cranial end of the tape was pulled to the left side of the MHV **(Figure 1A(2))**.

In left lobectomy without caudate lobectomy and MHV, dissection began on the anterior surface between the two lobes along the left side of the MHV, and was slightly curved to the left as the plane developed. The tape placed along the ligamentum venosum was lifted gently to serve as a guide. In lateral segmentectomy, after ligation and division of hepatic pedicles to the left lateral inferior and superior areas, parenchyma was dissected toward the root of the LHV while lifting the tape. Posterior segmentectomy including the RHV also was carried out from the anterior border of the anterior and posterior segments along the left side of the RHV and directed towards the tape placed on the IVC **(Figure 3A)**.

For central bisegmentectomy, dissection between the left lateral and medial segments and division of the MHV and right anterior hepatic pedicle were the initial maneuvers. Then, a tape was placed at the bottom of the dissected plane, and remnant parenchyma between the anterior and posterior segments was dissected using the tape as a guide **(Figure 3B)**.

In one patient with small HCC located between the right anterior superior area and the caudate lobe, the cranial half of the hepatic parenchyma between the right and left lobes was divided along the right side of the MHV using the tape described previously. Then, the vessels from the right hepatic pedicle to the area surrounding the tumor were divided, and the ischemic area was removed with the tumor **(Figure 3C)**.

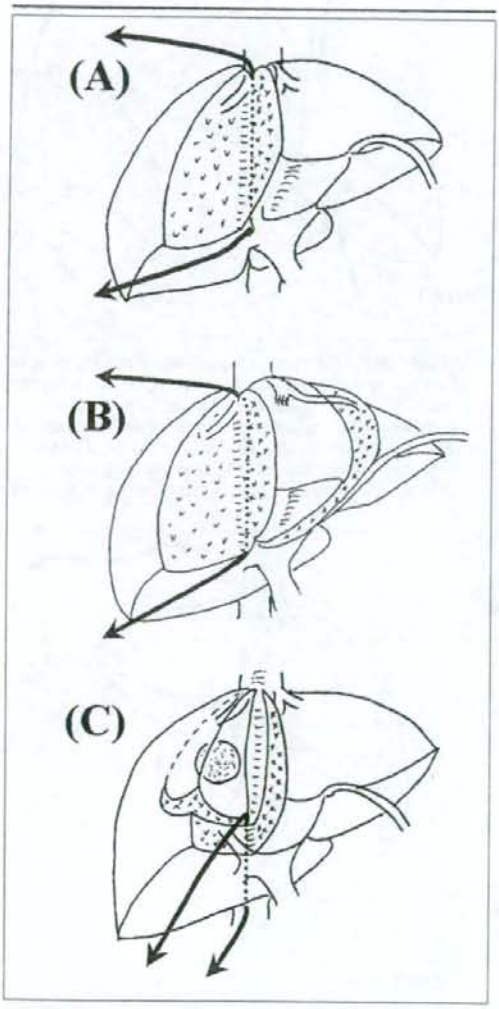

FIGURE 3 Parenchymal dissection in posterior segmentectomy with the right hepatic vein **(A)**, central bisegmentectomy **(B)**, and partial resection of the dorsal liver **(C)**.

RESULTS

The TGT was safely and easily performed in all 30 cases. Blind dissection along the anterior surface of the IVC prior to hepatic mobilization was performed without complication whenever it was attempted (4 of 14 right lobectomies and 3 of 8 left lobectomies).

During the parenchymal dissection, the tape placed behind the liver clearly indicated the direction of the dissection. Traction flattened the section and protected any large vessels near the plane by making them easier to see and control. Free use of the left hand helped to perform maneuvers such as ligation and suturing vessels more securely. Estimated blood loss, transfusion, and complications are shown in **Table 1**. The patient with the greatest blood loss, 5100g, underwent right lobectomy without mobilization before parenchymal dissection for 13cm ICC. In this patient, clamping of the hepatoduodenal ligament was incomplete, since the patient had dense adhesion around the hepatic hilum due to previous total gastrectomy. When the destination of the dissection slid from the middle of the tape, bleeding from the injured short hepatic veins was troublesome.

Although all patients were discharged from hospital without major complications, 4 patients developed a biliary fistula, but all fistulas healed spontaneously. The sources of the leaks were the roots of the caudate branches of the caudate lobe in 2 patients. In the other 2 patients, the leaks were more peripheral branches. Intractable ascites developed in one patient who underwent partial resection of the dorsal area of the liver. This resolved in 2 months with conservative treatment.

DISCUSSION

This study demonstrated the many advantages of

the TGT in different types of hepatectomy. Compared with the usual left-hand-guiding technique (6), the target of the dissection was much less ambiguous. And since the surgeon's left hand was free, operative maneuvers such as ligation and suturing were performed easily and securely. The advantage is particularly clear when performing left-sided hepatectomy because it is laborious for the surgeon to keep his left hand behind the left lobe when standing on the right side of the patient.

Although bleeding from the deeper parenchyma near the IVC was controlled more easily by gentle lifting of the tape, every effort should be made to orient the dissection directly toward the middle of the tape to avoid injury of the short hepatic veins. Since the tape itself has no effect on hemostasis during superficial and middle-depth parenchymal dissection, use of standard techniques remains essential to minimize the bleeding.

A few comments regarding the blind dissection along the anterior plane of the IVC, the incidence of bleeding from an injured SHV has been reported to be 1.4 to 4% (1,2). Kokudo and co-workers (7) have proposed adjunctive intraoperative ultrasound to make the procedure safer and easier. Nevertheless, it is clear that tape-positioning is easier and safer after completion of routine hemi-liver mobilization and division of SHVs. Ultimately, the surgeon must decide the best approach in each individual patient. According to our personal experience, division of all SHVs following only left-sided hepatic mobilization is more laborious than that following right-sided mobilization. Hence, we recommended tape passage as the initial maneuver when performing left hepatectomy with caudate lobectomy.

There were no deaths and only 4 biliary fistulas (13%). These results are consistent with our previous report of patients who had at least 2 liver segments resected (11/78, 14%) (8). Most biliary leaks were from caudate branches. These may have been difficult to identify because they were compressed by surrounding parenchyma when lifted by the tape. Therefore, it is essential to look for biliary branches from the caudate lobe by occasionally loosening tension on the tape during the dissection near the hilar plate.

TGT is a convenient tool for the hepatic surgeon, which facilitates exposure, reduces the risk of surgical misadventure, and creates a more comfortable environment for the surgeon to operate. It is useful in a wide variety of procedures, and other applications are likely to be forthcoming.

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Response to Interferon Therapy Affects Risk Factors for Postoperative Recurrence of Hepatitis C Virus-Related Hepatocellular Carcinoma

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Background: Interferon therapy might reduce recurrence after resection of hepatitis C virus-related hepatocellular carcinoma, especially among sustained virologic or biochemical responders.
Methods: Of 209 patients who underwent curative resection for early-stage hepatitis C virus related hepatocellular carcinoma, 70 patients underwent interferon therapy. A sustained virologic or biochemical response was achieved in 40 patients (SVR/BR group). Thirty no responders and 139 patients who had not received interferon therapy were classified as the NR/non-IFN group. Risk factors for postoperative recurrence in each group were analyzed.
Results: The tumor-free survival rates in the SVR/BR group were significantly higher than those in the NR/non-IFN group. By multivariate analysis, the presence of multiple tumors was independently associated with recurrence after resection in both groups, while histologic evidence of cirrhosis was another independent risk factor for postoperative recurrence in the NR/non-IFN group.
Conclusions: Newly multicentric carcinogenesis after resection could be suppressed when active hepatitis is controlled by interferon therapy. Patients with single hepatitis C virus related hepatocellular carcinoma detected after successful interferon therapy are good candidates for surgical resection. Adjuvant interferon therapy might be indicated for patients who undergo curative resection for single hepatocellular carcinoma associated with hepatitis C.
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KEY WORDS: **hepatocellular carcinoma; hepatitis C virus; interferon; postoperative outcome**

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers in Asia and Africa, and its incidence is increasing in the Western world [1,2]. Since chronic infection with hepatitis C virus (HCV) is closely associated with development of HCC [3], surveillance of patients with HCV infection has made possible the detection of HCC at an early stage [4]. Patients with early-stage HCC should be considered for any of the available treatment options, including local ablation therapy, liver transplantation, and surgical resection. Recently, radiofrequency ablation (RFA) has been accepted as new technique for the treatment of HCC. Although several reports have shown that RFA for small HCC can provide effective local control of tumors and favorable survival rates, RFA cannot achieve complete necrosis of tumors in all cases [5,6]. Although the long-term outcomes after liver transplantation are satisfactory in patients with early-stage HCC [7,8], liver transplantation for HCC is limited because of the shortage of donors and the high associated costs [9]. Hepatic resection therefore has been the first-line therapeutic option for early-stage HCC [10]. However, the outcome after hepatic resection for HCC is still unsatisfactory because of the high incidence of tumor recurrence, especially in the liver remnant [11,12].

Persistent active hepatitis and extensive fibrosis play important roles in the development of HCV-related HCC [13–15]. In treating HCC, it is therefore necessary to control recurrences that originate from intrahepatic metastases and also to control newly multicentric carcinogenesis after surgery [16–24]. Previous studies have indicated that HCC is less likely to develop in those in whom interferon (IFN) therapy was effective at normalizing the serum alanine aminotransferase (ALT) activity, even when the HCV RNA did not disappear [25–32]. Similarly, the control of active hepatitis is important in patients who have had a curative resection for HCV-related HCC, since continuous active hepatitis is strongly associated with recurrence after curative resection [33–36]. We have reported that patients in whom HCC is detected after IFN therapy are good candidates for hepatic resection because of the low incidence of postoperative recurrences [33], especially among virologic or biochemical responders [34,35]. Moreover, postoperative long-term IFN-α therapy appears to decrease the incidence of recurrences after a curative resection of HCV-related HCC [36]. We therefore hypothesized that IFN therapy might prevent recurrence due to new carcinogenesis after hepatic resection in the same way that IFN therapy decreases the incidence of HCV-related HCC.

Intrahepatic metastases and multicentric carcinogenesis after resection of HCC might be associated with different risk factors [16–21]. Tumor factors, such as venous invasion and the presence of multiple tumors, whose major mechanism is intrahepatic metastases, have been found to be risk factors for early recurrence [11,17,18]. On the other hand, several investigators have reported that newly multicentric carcinogenesis was closely linked to the status of the underlying liver [16–21]. In this retrospective study, we investigated whether different risk factors are associated with the postoperative recurrence of HCV-related HCC among each group based upon their response to IFN therapy.

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PATIENTS AND METHODS

Patients

Between January 1993 and March 2007, 279 patients with anti-HCV antibody, but not hepatitis B surface antigen, underwent a curative hepatic resection for HCC in the Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Hospital. Curative surgery was defined as the complete removal of all macroscopic tumors. The absence of tumor cells along the parenchymal transection line was confirmed histologically. Four perioperative deaths occurred from postoperative liver failure. Of the 279 patients, exclusive of operative deaths, 209 patients had early-stage HCC who met the Milan criteria [7] (single tumor ≤5 cm, maximum of three total tumors with none >3 cm, no major vessel invasion, and no extrahepatic involvement) were included in this study. Forty-three patients underwent a hepatic resection for HCC that had been detected after IFN therapy, and 27 patients received IFN therapy after curative resection. The type, dosage, and duration of IFN varied. The response to IFN therapy was determined virologically and biochemically. Of the 70 patients who received IFN therapy, 32 patients obtained a sustained viral response (SVR) that was defined as return of ALT activity to within the reference range and no detectable serum HCV RNA for at least 6 months after IFN therapy. A biochemical response (BR), which was defined as normalized ALT activity for at least 6 months after IFN therapy with or without the transient disappearance of serum HCV RNA, was obtained in eight patients. These 40 patients were defined as the responsive (SVR/BR) group, while the other 30 patients had no decrease in their ALT activity and had persistent serum HCV RNA. The NR/non-IFN group included these 30 no responders and 142 patients who had not received IFN therapy.

All patients were followed from resection until death or the end point of this study (December 31, 2007). The follow-up period ranged from 65 to 4,894 days (median, 1,491 days).

Detection of Recurrence

Serum alpha-fetoprotein was measured 1 month after surgery and every 3 months thereafter. Hepatic ultrasound scanning or CT was performed 1 month after surgery and every 3 months thereafter. When a recurrence of HCC was strongly suspected on the basis of tumor markers or imaging, selective hepatic angiography, ultrasound-guided biopsy, or both were performed to establish a definitive diagnosis.

Surgical Procedure and Pathology

The type of operative procedure was described using the Brisbane 2000 system [37]. A hemihepatectomy, bi-segmentectomy, and segmentectomy were all assumed to be anatomic resections. The classification system of the Liver Cancer Study Group of Japan [38] was used to categorize the histological findings. The grade (grade of active hepatitis) and stage (degree of hepatic fibrosis) in the non-cancerous portions were determined by the score of the histologic activity index [39,40], which was determined by four events, that is, periportal necrosis with or without bridging necrosis, intralobular degeneration with focal necrosis, portal inflammation, and fibrosis. Two pathologists without any knowledge of the clinical and laboratory data examined all materials.

Statistics

Differences in clinicopathologic findings were analyzed by the Mann–Whitney *U*-test or Chi-squared test. The tumor-free survival rates were calculated by the Kaplan–Meier method, and were compared with 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 variables chosen were age (≥65 or <65 years), gender, aspartate aminotransferase (AST) activity (≤40 or >40 IU/L), ALT activity (≤45 or >45 IU/L), total bilirubin (≤1.0 or >1.0 mg/dl), albumin concentration (<3.5 or ≥3.5 g/dl), platelet count (≥10 or <10 $\times 10^4/\mu l$), serum alpha-fetoprotein concentration (≤20 or >20 ng/ml), the largest diameter of the main tumor (<3.0 or ≥3.0 cm), the degree of differentiation of the main tumor (well, moderate or poor), the number of tumors (single or multiple), the presence of portal invasion, the grading score (0–1 or 2–4), the staging score (0–3 or 4), and type of hepatic resection (anatomic resection or nonanatomic resection).

TABLE I. Clinicalpathologic Findings in Patients With Hepatocellular Carcinoma

	SVR/BR (n = 40)	NR/non-IFN (n = 169)	*P*-value
Age (year)	65 (54, 71)	67 (56, 75)	0.010
Gender (M/F)	35:5	140:29	0.473
AST activity (IU/L)	43 (27, 91)	66 (36, 102)	<0.001
ALT activity (IU/L)	43 (26, 139)	74 (32, 117)	0.022
Albumin (g/dl)	4.1 (3.6, 4.4)	3.6 (3.3, 4.1)	<0.001
Total bilirubin (mg/dl)	0.8 (0.5, 1.3)	0.8 (0.5, 1.3)	0.436
Platelet count ($10^4/mm^3$)	14 (9, 21)	13 (8, 21)	0.100
Child-Pugh score (A/B)	39:1	156:13	0.238
High AFP (>20 ng/ml)	15	88	0.096
Anatomic resection	13	57	0.882
Tumor size (cm)	2.0 (1.5, 3.8)	2.5 (1.5, 4.0)	0.082
Number of tumors			
Single/multiple	27:13	132:37	0.157
Portal invasion	8	33	0.946
TMN stage			
I/II/III	7:21:12	27:101:41	0.684
Tumor differentiation			
Well/moderate or poor	4:36	18:151	0.904
Histologic activity index score			
Grade 0–1/2–4	9:31	34:135	0.738
Stage 0–3/4 (cirrhosis)	28:12	82:87	0.014

Data are presented as the median with the 10th and 90th percentiles indicated in parentheses. AST, aspartate aminotransferase activity; ALT, alanine aminotransferase; AFP, alpha fetoprotein.

RESULTS

The clinical features, laboratory test results, and pathologic findings of the surgical specimens are summarized in Table I. The mean age in the SVR/BR group was significantly younger than those in the NR/non-IFN group. Although the serum concentration of albumin just before surgery was significantly higher in the SVR/BR group than in the NR/non-IFN group, there were no differences in the serum concentrations of total bilirubin, the platelet counts, and the proportion of Child-Pugh A cirrhosis between two groups. The serum activities of aspartate aminotransferase and ALT just before surgery were significantly lower in the SVR/BR group than in the NR/non-IFN group. Although there were no differences in tumor-related factors, the proportion of stage 4 fibrosis (cirrhosis) in the SVR/BR group was lower than that in the NR/non-IFN group.

The tumor-free survival rates for the patients in the SVR/BR group and the NR/non-IFN group were 71% and 46% at 3 years; and 54% and 23% at 5 years, respectively (Fig. 1). The recurrence rates in the NR/non-INF group steadily increased over time. Conversely, only one patient in the SVR/BR group had a recurrence of HCC more than 4 years after resection. The tumor-free survival rate was higher in the SVR/BR group than in the NR/non-INF group ($P < 0.001$).

Table II shows the univariate analysis of risk factors for postoperative recurrence in each group according to the response to IFN therapy. In the SVR/BR group, the low platelet count, the presence of multiple tumors and a nonanatomic resection were possible risk factors for recurrence after resection. In the NR/non-INF group, low albumin concentration, the presence of multiple tumors, and histologic evidence of cirrhosis (stage 4 fibrosis) were associated with lower tumor-free survival rates. By multivariate analysis, the presence of multiple tumors was an independent risk factor associated with postoperative recurrence in both groups (Table III). In addition, histologic evidence of cirrhosis was another independent predictor of postoperative recurrence in the NR/non-INF group.

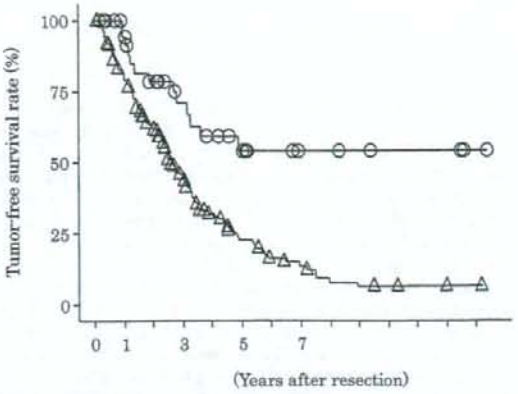

Fig. 1. Tumor-free survival rates after curative resection of hepatocellular carcinoma. Open circles: SVR/BR group (n = 40); open triangles: NR/non-IFN group (n = 169).

DISCUSSION

Because of recent progress in surgical techniques and perioperative management, the perioperative outcome of hepatic resection for HCC has markedly improved [10]. However, the high incidence of recurrence after resection remains a serious problem in patients with HCV-related HCC [11,12]. Postoperative recurrence of HCV-related HCC is thought to result from the growth of intrahepatic metastases in the residual liver and metachronous, multicentric carcinogenesis due to the underlying liver disease [16–24]. Accordingly, different strategies may be needed for the prevention and management of these two patterns of HCC recurrence.

Cirrhosis is a major risk factor for the development of HCV-related HCC [25,26]. In patients with chronic active hepatitis, fibrosis of the liver is established through repetitive necroinflammation and regeneration. It has been reported that the risk for the development of HCC increases with the degree of liver fibrosis, from 0.5% among patients with stage 0 or 1 fibrosis to 7.9% among patients with stage 4 fibrosis (cirrhosis) [25]. Several investigators have reported that histologic

TABLE II. Univariate Analysis for Factors Associated With Postoperative Recurrence

Factors	Number of patients	Tumor-free survival rate (95% CI) 3 years (%)	5 years (%)	*P*-value
SVR/BR group				
Type of resection				
Anatomic	13	90 (71–100)	90 (71–100)	0.032
Limited	27	62 (42–82)	39 (16–61)	
Number of tumors				
Single	27	81 (64–98)	68 (45–90)	0.001
Multiple	13	49 (16–81)	24 (0–53)	
Platelet count (10^4/mm^3)				
≥10.0	35	81 (66–96)	61 (40–81)	0.010
<10.0	5	20 (0–55)	20 (0–55)v	
NR/non-IFN group				
Albumin (g/dl)				
≥3.5	113	52 (42–62)	26 (16–35)	0.021
<3.5	56	33 (20–47)	17 (5–30)	
Number of tumors				
Single	132	49 (40–58)	26 (17–35)	0.007
Multiple	37	36 (20–52)	11 (0–25)	
Stage of fibrosis				
0–3	82	57 (45–68)	34 (22–46)	0.003
4 (cirrhosis)	87	35 (24–46)	13 (4–21)	

TABLE III. Multivariate Analysis of Factors Predicting Postoperative Recurrence

	Multivariate risk ratio[a]	*P*-value
SVR/BR group		
Presence of multiple tumors	3.9 (1.3–11.8)	0.018
NR/non-IFN group		
Presence of multiple tumors	1.7 (1.1–2.6)	0.014
Stage 4 fibrosis (Cirrhosis)	1.7 (1.2–2.4)	0.005

[a]Risk ratio with 95% confidence interval in parentheses.

status of the underlying liver disease, such as evidence of fibrosis and active hepatitis, is also associated with recurrence of HCC after resection, which suggests that newly multicentric carcinogenesis could play an important role in the development of recurrence after resection [16–23]. The incidence of newly multicentric carcinogenesis is considerably high, which was associated with approximately 50% of postoperative recurrences [24]. Several investigators have identified that IFN therapy suppresses the development of HCC by causing active hepatitis to go into remission and by improving hepatic fibrosis, which increases the survival rate in patients with HCV infection [25–32]. Moreover, SVR/BR to IFN therapy was identified as an independent factor for a lower incidence of postoperative recurrence [34,35]. In this study, the tumor-free survival rate was higher in the SVR/BR group than in the NR/non-INF group. The majority of HCC recurrence was detected in the SVR/BR group within 4 years after surgery, while recurrence of HCC occurred throughout the follow-up period in the NR/non-INF group. Histologic evidence of cirrhosis was a risk factor for postoperative recurrence in the NR/non-IFN group but not in the SVR/BR group. These findings support the hypothesis that controlling active hepatitis by IFN therapy can improve hepatic fibrosis and prevent the development of multicentric carcinogenesis after resection.

The growth of micrometastases via vascular invasion is considered another major form of HCC recurrence [24]. Because of the high likelihood of micrometastases of HCC spreading through the portal venous system, anatomic resection is theoretically effective for the eradication of micrometastases [41,42]. In this study, the tumor-free survival rate for patients who underwent an anatomic resection was much higher than that for patients who underwent nonanatomic resection in SVR/BR group. Although some studies have suggested that anatomic resection has a beneficial effect on recurrence-free survival after hepatic resection for single HCC [43,44], the superiority of an anatomic resection has been unclear. Previous studies identified that tumor-related factors such as tumor size, the presence of multiple tumors and portal invasion are significant factors associated with postoperative recurrence of HCC [11,16–18]. In this study, the presence of multiple tumors was an independent risk factor for postoperative recurrence, irrespective of the response to IFN therapy. Therefore, in patients with multiple tumors liver transplantation could be considered because the efficacy of adjuvant therapeutic approaches, such as postoperative hepatic arterial chemotherapy remains controversial. Conversely, curative resection provides the chance of cure for patients with single HCV-related HCC detected after successful IFN therapy. Patients who undergo curative resection for single tumor are good candidates for adjuvant IFN therapy.

CONCLUSIONS

Late recurrence of HCC after resection decreased and the histologic status of the underlying liver disease was not associated with postoperative recurrence in the SVR/BR group. These results suggest that newly multicentric carcinogenesis after resection could be suppressed when active hepatitis is controlled by IFN therapy. However, there was a high incidence of postoperative recurrence in patients with multiple tumors irrespective of their response to IFN therapy. Patients with single HCV-related HCC detected after successful IFN therapy are good candidates for surgical resection. Adjuvant IFN therapy might be indicated for patients who undergo curative resection for single HCV-related HCC.

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CASE REPORT

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Hepatocellular carcinoma (HCC) recurring 10 years after clearance of hepatitis B surface antigen and 20 years after resection of hepatitis B virus-related HCC

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Abstract A 62-year-old man had been followed up for chronic hepatitis B (HB) since 1973. Hepatocellular carcinoma (HCC) was detected in 1985, at the age of 42 years. Serum HB surface antigen and anti-HB envelope antibody were positive at that time. A right hepatic lobectomy was performed. In 1995, serum HB surface antigen had cleared spontaneously and liver function had normalized. In March 2005, at the age of 62 years, a 1.5-cm diameter hepatic mass was detected in the left lateral segment. At that time, he was seropositive only for anti-HB core antibody. A diagnosis of recurrent HCC was made, and partial hepatectomy was performed. Covalently closed circular HBV DNA was detected in both cancerous and noncancerous tissues by nested polymerase chain reaction (PCR). Cassette-ligation-mediated PCR showed that HBV DNA was integrated into the telomerase reverse transcriptase gene located on chromosome 5p15.

Key words Hepatocellular carcinoma · Hepatitis B virus · Human telomerase reverse transcriptase (hTERT) · Liver resection

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Introduction

It is well known that hepatitis B virus (HBV) can cause hepatocellular carcinoma (HCC). Persistent active hepatitis can result in progression to cirrhosis and the development of HCC. During the natural history of chronic hepatitis B (HB), seroconversion from HB surface antigen (HBsAg) to anti-HB surface antibody (anti-HBs) is associated with remission of active hepatitis and improvement of liver function and pathologic features.[1] Although it is thought that clearance of HBsAg from the serum indicates clinical cure and a decreased risk of carcinogenesis, HCC is sometimes detected after this seroconversion.[2–6] It has also been reported that occult HBV infection is important in the development of HCC.[4,7–10] In this report, we describe a case of HCC which recurred in 2005, 10 years after the clearance of HBsAg in 1995, and 20 years after resection of the first HCC while the patient was seropositive for HBsAg in 1985.

Case report

A 62-year-old man had been followed up for chronic HB since 1973. In 1985 (at age 42 years), a hepatic tumor was detected in the anterior superior segment (S8) by ultrasonography (US) and computed tomography (CT). Serum HBsAg was positive, serum anti-HBs was negative, HB envelope antigen (HBeAg) was negative, and anti-HB envelope antibody (anti-HBe) was positive (Table 1). Liver function tests indicated active hepatitis. Transcatheter arterial embolization and percutaneous transhepatic portal vein embolization were performed, followed by right lobectomy. He was transfused with 1500 ml whole blood and 880 ml fresh frozen plasma during the operation. The tumor measured 1.8 × 1.5 cm (Fig. 1A), and was classified as T1N0M0 according to the TNM system.[11] Pathologic examination revealed a moderately differentiated HCC and no microvascular invasion (Fig. 1B). Examination of the

Table 1. Results of laboratory tests at the times of the first and second operations

Test	First operation (Oct. 1985)	Second operation (March 2005)
Albumin (g/dl)	4.0	4.2
Total bilirubin (mg/dl)	0.6	0.6
Aspartate aminotransferase (IU/l)	50	24
Alanine aminotransferase (IU/l)	115	27
ICGR15 (%)	13.5	19.6
Prothrombin test (%)	105	113
HBeAg	–	–
Anti-HBe	+	+
HBsAg	+	–
Anti-HBs	–	–
Anti-HBc	+ (99% INH)	+ (99% INH)
HBV DNA	ND	–
Anti-HCV (titer)	ND	2.2
HCV RNA	ND	–
α-Fetoprotein (AFP; ng/ml)	57	4
AFP-L3 (%)	ND	0
PIVKA-II (AU/ml)	ND	21

ICGR15, indocyanine green retention rate at 15 min; HBeAg, hepatitis B envelope antigen; anti-HBe, anti-hepatitis B envelope antibody; HBsAg, hepatitis B surface antigen; anti-HBs, anti-hepatitis B surface antibody; anti-HBc, anti-hepatitis B core antibody; HBV DNA, hepatitis B virus DNA; anti-HCV, anti-hepatitis C virus antibody; HCV RNA, hepatitis C virus RNA; PIVKA II, protein induced by vitamin K absence or antagonist II; ND, not determined; INH, inhibition

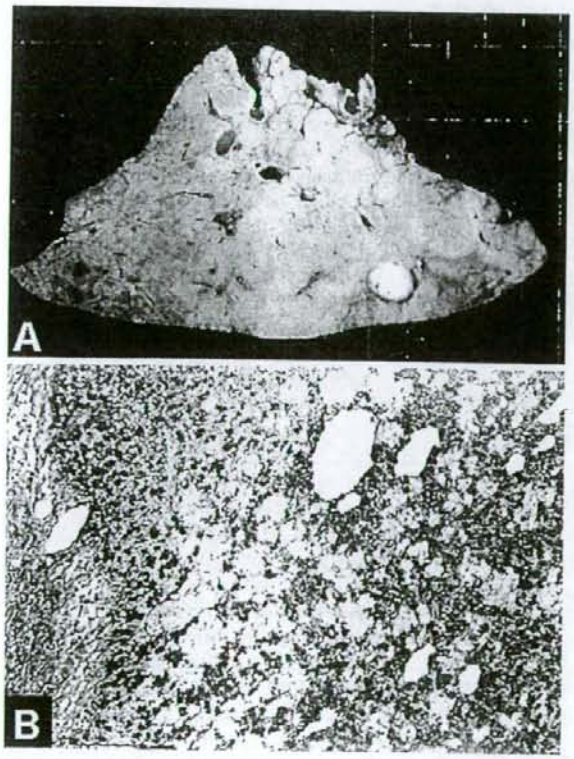

Fig. 1. A Resected specimen from the first operation. The tumor measured 1.8 cm × 1.5 cm and was mostly necrotic. **B** Pathologic examination showing that the tumor is a moderately differentiated hepatocellular carcinoma. H&E, ×20

nontumorous hepatic tissue showed minimal hepatitis activity (grade 1) and portal-portal septa without architectural distortion (stage 2) according to the histologic activity index score.[12] In 1995 (at age 52 years), serum HBsAg had cleared. In 1996, serum HBV DNA was negative by the polymerase chain reaction (PCR) method. Serum anti-hepatitis C virus antibody (anti-HCV; Ortho Diagnostic Systems, Tokyo, Japan) was positive, but serum hepatitis C virus RNA (Quantiplex HCV-RNA; Chiron, Emeryville, CA, USA) was negative. The anti-HCV titer was consistently low. The serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) had normalized in 1995. In March 2005 (at age 62 years), a hepatic mass measuring 1.5 cm in diameter was detected in the left lateral segment by CT and US. At that time, serum HBsAg, anti-HBs, and HBV DNA were all negative (Table 1). Anti-HB core antibody was positive. The anti-HCV titer was very low. Although the indocyanine green retention rate at 15 min was 19.6%, the results of other liver function tests were within the reference ranges. Renal function tests were abnormal because of renal failure following coronary artery bypass grafting and graft replacement of the ascending aorta at the age of 59 years. The levels of the tumor markers α-fetoprotein (AFP), AFP-L3 fraction, and protein induced by vitamin K absence or antagonist II were all within the reference ranges. In May 2005, partial hepatectomy was performed with a preoperative diagnosis of recurrent HCC. The tumor measured 2.5 × 2.0 cm (Fig. 2A), and was classified as T2N0M0. Pathologic examination showed a moderately differentiated HCC and no microvascular invasion (Fig. 2B), with nonactive hepatitis (grade 0) and portal fibrous expansion (stage 1) in the noncancerous tissue. The HB surface (*HBs*) gene and covalently closed circular (ccc)

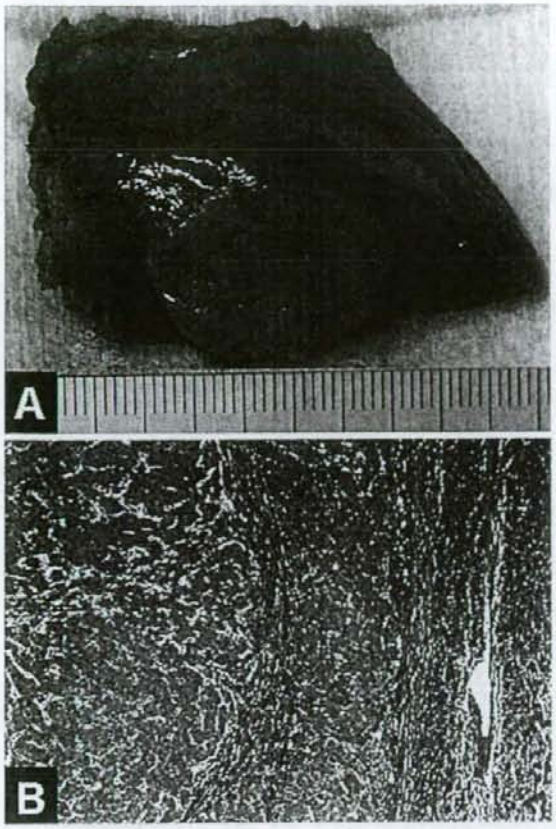

Fig. 2. A Resected specimen from the second operation. The tumor measured 2.5 cm × 2.0 cm. **B** Pathologic examination showing that the tumor is a moderately differentiated hepatocellular carcinoma. H&E, ×20

HBV DNA were detected in the tumor by PCR. The *HBs* gene, hepatitis B core (*HBc*) gene, and ccc HBV DNA were detected in the nontumorous tissue by PCR. The *HBx* gene was not detected in either tumor or nontumorous tissues by PCR (Fig. 3). Cassette-ligation-mediated PCR[10,13] showed that HBV DNA was integrated into the telomerase reverse transcriptase gene (*hTERT* gene) located on chromosome 5p15 in the tumor (Fig. 4). The patient is in good health without recurrent tumor 18 months after the second operation.

Discussion

In this report, we describe a case of recurrent HCC 10 years after the clearance of HBsAg and 20 years after resection of the first HBV-related HCC. The duration between the first HCC and the recurrent HCC is the longest reported in the literature to date. The duration between the clearance of HBsAg and the detection of the recurrent tumor is the longest except for one case reported by Yoshino et al.[6]

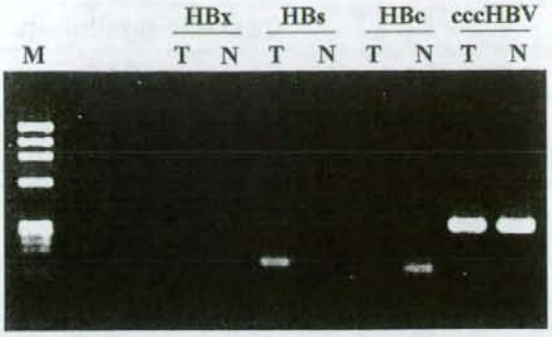

Fig. 3. Hepatitis B virus (HBV) DNA analysis of the resected sample. Detection of the *HBx* gene, *HBs* gene, *HBc* gene, and ccc HBV DNA was performed using specific primers in the tumor (*T*) and nontumorous (*N*) tissues. *M*, Marker (pBR322/AluI).

The mechanism of carcinogenesis in HCC associated with HBV includes mutagenesis and changes in proliferation and differentiation caused by the integration of HBV DNA.[14–17] HBx protein binds with p53 protein and inhibits p53-mediated prevention of neoplastic transformation,[18,19] and also activates cellular transcription factors.[20,21] Chronic inflammation and oxidative stress due to HBV infection induce DNA damage in hepatocytes.[22] Although we could not investigate the integration of HBV DNA at the time of the first operation in this patient, the first HCC is thought to have been caused by chronic HB, because he was seropositive for HBsAg and had active hepatitis at that time. At the time of the second operation, serum HBsAg and HBV DNA had cleared and liver histology had improved. Research on HBV DNA has shown that the *HBs* gene and ccc HBV DNA are detectable in HCC and nontumorous hepatic tissue, and that the *HBc* gene is detectable in noncancerous hepatic tissue; the *HBx* gene was not detected in either tumor or nontumorous tissues in our patient. Integration of HBV DNA into the *hTERT* gene has also been detected. Previous reports showed that HBV DNA was integrated into the *hTERT* gene, and that it also could play an important role in hepatic carcinogenesis.[23,24] These findings indicate that the patients have either occult HBV infection or integration of HBV DNA in their liver. Other possible mechanisms of hepatic carcinogenesis include inactivation of p53 by mutations and regional allelic deletions, although changes in the *p53* gene and p53 protein were not investigated in our patient.[25]

Hepatitis B antigens have been detected in the hepatic tissues of some patients after the clearance of serum HBsAg associated with the remission of active hepatitis, especially in those with a high anti-hepatitis B core antibody (anti-HBc) titer.[26,27] HBV DNA is often integrated into the host's chromosomes and plays an important role in hepatic carcinogenesis.[28] Thus, we speculate that, in our patient, the HCCs developed from multicentric origins, and that the integrated HBV DNA participated in the development of the recurrent HCC. In patients with chronic HB, screening for HCC is necessary even after clearance of serum HBsAg

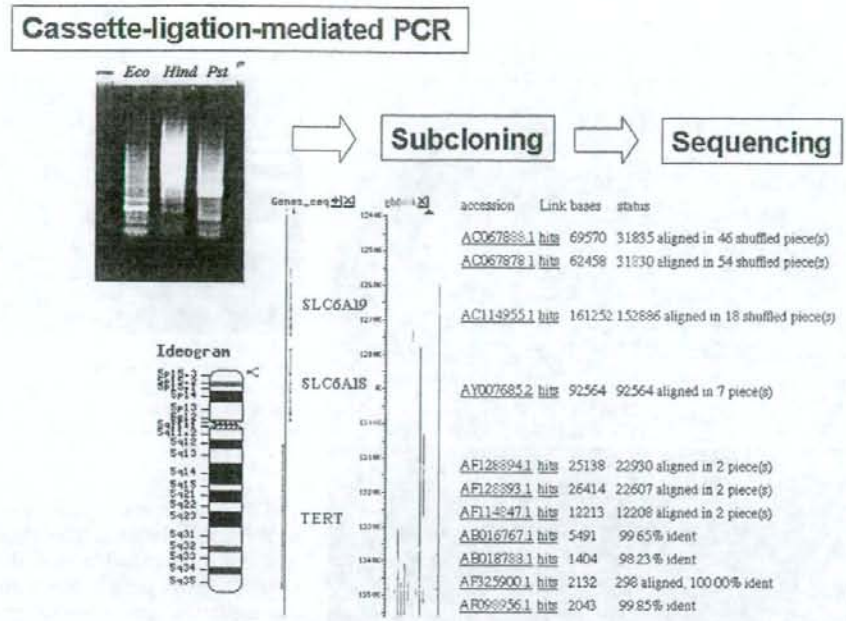

Fig. 4. Cassette-ligation-mediated polymerase chain reaction (PCR). HBV DNA is integrated into the telomerase reverse transcriptase (*hTERT*) gene located on chromosome 5p15. *Ident*, Identical

and HBV DNA and remission of hepatitis, because the oncogenic potential due to occult HBV infection or the integration of HBV DNA is considered to continue.[29]

Itsubo et al.[30] reported a case of recurrent HCC associated with HCV infection due to transfusion during the first liver resection. The first liver resection had been performed 18 years previously for HCC associated with HBV infection. In our patient, serum anti-HCV was positive and HCV RNA was negative in 1995. Although the HCV infection in the patient reported by Itsubo et al.[30] might have been caused by the transfusion during the first operation, it was transient because HCV RNA was negative and the levels of AST and ALT were within the reference ranges. Thus, the recurrent HCC was not directly caused by the HCV infection. However, an HCV superinfection might have played a role in the spontaneous HBsAg clearance in our patient.[31]

The rare case that we have reported indicates that long-term follow up is necessary for chronic HB, even after the clearance of serum HBsAg and HBV DNA and remission of hepatitis, because the oncogenic potential due to occult HBV infection or the integration of HBV DNA is considered to continue.

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ORIGINAL ARTICLE

A simple, noninvasively determined index predicting hepatic failure following liver resection for hepatocellular carcinoma

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Abstract
Background A novel index, the serum aspartate aminotransferase activity/platelet count ratio index (APRI), has been identified as a biochemical surrogate for histological fibrogenesis and fibrosis in cirrhosis. We evaluated the ability of preoperative APRI to predict hepatic failure following liver resection for hepatocellular carcinoma.
Methods Potential preoperative risk factors for postoperative hepatic failure (hepatic coma with hyperbilirubinemia, four patients; intractable pleural effusion or ascites, 30 patients; and variceal bleeding, one patient) as well as APRI were evaluated in 366 patients undergoing liver resection for hepatocellular carcinoma. Prognostic significance was determined by univariate and multivariate analyses.
Results Hepatic failure developed postoperatively in 30 patients, causing death in four. APRI correlated with histological intensity of hepatitis activity and degree of hepatic fibrosis, and was significantly higher in patients who developed postoperative hepatic failure than in others without failure. Risk of postoperative hepatic failure increased as the serum albumin concentration and platelet count decreased and as indocyanine green retention rate at 15 min, aspartate and alanine aminotransferase activities, and APRI increased. Only APRI was an independent preoperative factor on multivariate analysis. Of the four patients who died of postoperative hepatic failure, three had an APRI of at least 10.
Conclusions Preoperative APRI independently predicted hepatic failure following liver resection for hepatocellular carcinoma. Patients with an APRI of 10 or more have a high risk of postoperative hepatic failure.

Keywords Liver resection · Hepatocellular carcinoma · Liver failure · APRI · Platelet count

Abbreviations

HCC	Hepatocellular carcinoma
APRI	Aspartate aminotransferase/platelet count ratio index
Anti-HCV	Anti-hepatitis C virus antibody
HBsAg	Hepatitis B surface antigen
$ICGR_{15}$	Indocyanine green retention rate at 15 min
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
AFP	α-Fetoprotein
HAI	Histological activity index

Introduction

Liver resection in patients with hepatocellular carcinoma (HCC) may result in postoperative hepatic failure, since most patients with HCC also have chronic liver disease including cirrhosis [1–9]. To avoid resection likely to lead to postoperative hepatic failure, various methods have been developed for preoperative assessment of liver function [4,

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