SD using this system. In case 2, a tumor marker DT of −29.5 days corresponded to a decrease in diameter to 64% of baseline but the RECIST-based evaluation was SD. Importantly, necrotic lesions were found in the target tumors in both cases, possibly leading to an underestimation of anticancer effect.

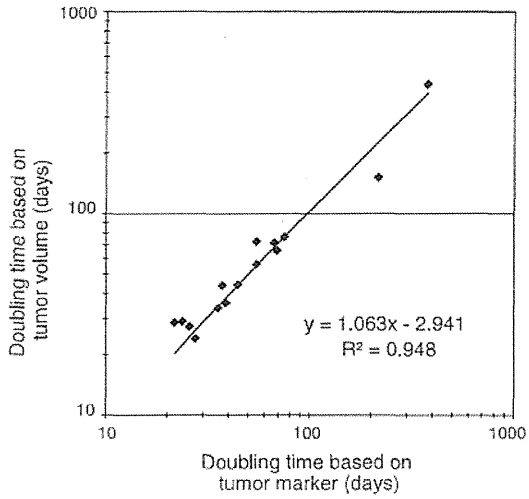

Fig. 2 Linear regression representation of the log tumor volume doubling time over the log tumor marker doubling time. *Each point* represents a data set from a single patient

Changes in tumor marker DT after the cessation of TSU-68 treatment

Changes in tumor marker DTs following the cessation of TSU-68 could be evaluated in four patients (Table 3). In each of these cases, the tumor marker DTs were elongated during TSU-68 administration compared with the baseline value and became shorter after the cessation of the treatment. Tumor marker DT after the cessation of TSU-68 was comparable with that before treatment in three patients and shorter in the remaining case.

Discussion

The production rate of a tumor marker per unit volume of the tumor mass can vary greatly among cancer patients who are positive for this marker. Hence, the serum levels of tumor marker are not directly proportional to the tumor volume. However, provided that the production rate per unit of tumor volume remains constant in each case, the changes in the serum tumor marker levels will directly correspond to the changes in tumor volume. Indeed, as we have shown in the present study, the DT of a tumor marker level and that of the corresponding tumor volume were almost identical in each patient in this study, at least during

Table 2 Tumor marker doubling time and treatment response evaluated by RECIST

Case no.	Marker	Tumor marker levels[a]		Doubling time (days)		Treatment response by RECIST
		At enrollment	At evaluation	During washout phase	During TSU-68 administration	
1	DCP	213	29	136.8	−21.1[b]	SD
2	AFP	60836	15312	38.6	−29.5[b]	SD
3	DCP	5993	5007	26.9	−231.6[b]	SD
4	AFP	144045	134030	75.3	−602.1[b]	SD
5	AFP	12004	12010	18.8	43004	SD
6	AFP	33859	33983	24.1	3010	SD[c]
7	AFP	61649	88056	71.7	115.8	SD
8	AFP	198	395	51.9	60.2	SD
9	AFP	45	92	28.0	60.2	PD
10	DCP	657	997	38.1	51.0	PD[c]
11	DCP	3188	8275	54.7	43.6	PD
12	AFP	3404	6430	24.7	32.4	PD[c]
13	AFP	53	203	88.5	15.5	PD[c]
14	AFP	19	544	376.3	12.4	PD
15	AFP	30	169	25.7	12.0	PD[c]

AFP alpha-fetoprotein, *DCP* des-gamma carboxyprothrombin, *SD* stable disease, *PD* progressive disease

[a] Unit of AFP is ng/ml and unit of DCP is mAu/ml

[b] Became negative when the tumor marker levels decreased following treatment; negative DT values correspond to the half-life

[c] Calculated using the values obtained at week 4 as treatment was discontinued at this time point. The treatment response evaluations using RECIST were also performed at week 4

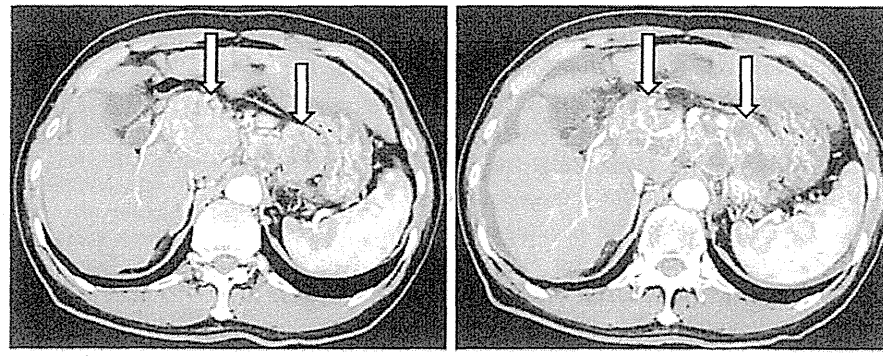

Fig. 3 A case in which a RECIST evaluation of PD was obtained even though the tumor marker levels had decreased. The lymph nodes around the hepatic arteries (target lesions, *arrows*) in this patient were enlarged and had become internally necrotic

Table 3 Tumor marker doubling time (days) before, during, and after TSU-68 treatment

Case no.	During washout phase	During the first 4 weeks of administration	During the last 4 weeks of administration	After cessation of administration
3	26.9	−97.1[b]	91.2	41.2
4	75.3	−79.2[b]	188.1	17.8
6[a]	24.1	3010	–	46.3
9	28.0	60.2	60.2	35.4

[a] Treatment was discontinued at week 4

[b] Became negative when the tumor marker levels decreased following treatment

washout phase prior to TSU-68 therapy. This indicates the possibility that tumor growth rates and any changes in them can be evaluated using tumor marker DT.

To validate the usefulness of tumor marker DTs for evaluating treatment responses, we compared this approach with the RECIST guidelines during TSU-68 administration. These two methods showed comparable results in most cases (12/15) and discrepancies were due to substantial tumor necrosis without volume shrinkage or to the appearance of new lesions in spite of the sustained effects of the drug on the target lesions. Tumor marker levels can be considered to represent viable tumor burden irrespective of the presence of necrosis or fibrosis. Evaluations based on tumor marker DTs may thus provide a better assessment of the efficacy of chemotherapeutic agents. Modified RECIST was proposed after the protocol of this study was completed. In modified RECIST, only areas with hyperattenuation were measured, excluding necrotic tissues. Modified RECIST was reported to be more useful than conventional RECIST in the evaluation of antiangiogenic agents. Although we did not directly compare tumor DT with modified RECIST in the present study, assessment based on tumor DT may be closer to modified RECIST than to conventional RECIST.

In several previous papers, early changes in AFP levels were used to assess responses to HCC treatments [30–32]. However, they evaluated only initial responses to therapy. In contrast, by evaluating tumor DT based on tumor marker levels, the effectiveness of a therapeutic agent can be monitored during its administration even when it changes over time.

In previous phase III trials of sorafenib, the response rate was not high but the overall survival was significantly improved [33, 34]. Slowing down the progression of a tumor, even if there is no reduction in the tumor volume, can therefore lead to prolonged survival. In the present study, the tumor marker DT was shortened after the cessation of TSU-68 treatment in four patients, i.e., tumor growth was accelerated, indicating that TSU-68 still inhibited tumor growth. Using RECIST evaluation, however, the treatment response in such cases will be judged as a PD, because this method does not consider time. Hence, in evaluating the response to cytostatic agents in particular, such as sorafenib and TSU-68, determination of the changes in the tumor growth rate may be substantially more adequate. Tumor marker levels can be easily measured repeatedly and, as shown in the current analysis, the corresponding DTs can thus be reliably calculated. Theoretically, the serum half-life of a tumor marker may affect the calculation of tumor DT. However, the half-life of AFP is 5 days and that of DCP is 40 h, which are much shorter than the tumor halving time even when TSU-68 is effective, and are negligible in calculations.

Another application of tumor marker DTs is the estimation of tumor growth rates when the lesions are untreated. DTs may correlate with the malignant potential of the tumor. We have shown that tumor marker DTs remained similar before the administration and after the cessation of TSU-68, which may be a characteristic of cytostatic agents in contrast to cytotoxic agents [35–37]. The decision to continue cytotoxic agents that only slow down tumor growth could be partially based on the tumor marker DT prior to treatment.

There are several limitations to the use of tumor marker DTs in the evaluation of cancer drug treatment responses. First, DTs cannot be calculated when a tumor does not produce tumor markers. Second, a tumor marker profile may change during treatment, possibly as a result of somatic mutation and clonal selection in the tumor cell population. This may make interpretation of changes in DTs difficult. Lastly, whether an elongated but still positive DT is associated with improved prognosis has yet to be confirmed. In the natural course of HCC, the tumor volume DT has been reported to be associated with prognosis [38]. We thus speculate that a treatment associated with elongation of tumor marker DT can be continued if there are no alternative treatments and the side effects are tolerable.

In conclusion, we have shown that serum tumor marker levels can be used to evaluate viable tumor burden irrespective of the presence of tumor necrosis that can compromise radiographic evaluations. This may be particularly useful in the evaluation of cytostatic agents.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Cannistra SA. Phase II trials in *Journal of Clinical Oncology*. J Clin Oncol. 2009;27:3073–6.
2. Paesmans M, Sculier JP, Libert P, Bureau G, Dabouis G, Thiriaux J, et al. Response to chemotherapy has predictive value for further survival of patients with advanced non-small cell lung cancer: 10 years experience of the European Lung Cancer Working Party. Eur J Cancer. 1997;33:2326–32.
3. Buyse M, Thirion P, Carlson RW, Burzykowski T, Molenberghs G, Piedbois P. Relation between tumour response to first-line chemotherapy and survival in advanced colorectal cancer: a meta-analysis. Meta-Analysis Group in Cancer. Lancet. 2000;356:373–8.
4. Goffin J, Baral S, Tu D, Nomikos D, Seymour L. Objective responses in patients with malignant melanoma or renal cell cancer in early clinical studies do not predict regulatory approval. Clin Cancer Res. 2005;11:5928–34.
5. Keppke AL, Salem R, Reddy D, Huang J, Jin J, Larson AC, et al. Imaging of hepatocellular carcinoma after treatment with yttrium-90 microspheres. AJR Am J Roentgenol. 2007;188:768–75.
6. Miller FH, Keppke AL, Reddy D, Huang J, Jin J, Mulcahy MF, et al. Response of liver metastases after treatment with yttrium-90 microspheres: role of size, necrosis, and PET. AJR Am J Roentgenol. 2007;188:776–83.
7. Burton A. REGIST: right time to renovate? Eur J Cancer. 2007;43:1642.
8. Therasse P, Eisenhauer EA, Buyse M. Update in methodology and conduct of cancer clinical trials. Eur J Cancer. 2006;42:1322–30.
9. Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. Eur J Cancer. 2006;42:1031–9.
10. Stroobants S, Goeminne J, Seegers M, Dimitrijevic S, Dupont P, Nuyts J, et al. 18FDG-positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec). Eur J Cancer. 2003;39:2012–20.
11. Antoch G, Kanja J, Bauer S, Kuehl H, Renzing-Koehler K, Schuette J, et al. Comparison of PET, CT, and dual-modality PET/CT imaging for monitoring of imatinib (STI571) therapy in patients with gastrointestinal stromal tumors. J Nucl Med. 2004;45:357–65.
12. D'Amico AV, Desjardin A, Chen MH, Paik S, Schultz D, Renshaw AA, et al. Analyzing outcome-based staging for clinically localized adenocarcinoma of the prostate. Cancer. 1998;83:2172–80.
13. Sheu JC, Sung JL, Chen DS, Yang PM, Lai MY, Lee CS, et al. Growth rate of asymptomatic hepatocellular carcinoma and its clinical implications. Gastroenterology. 1985;89:259–66.
14. Tian F, Appert HE, Myles J, Howard JM. Prognostic value of serum CA 19-9 levels in pancreatic adenocarcinoma. Ann Surg. 1992;215:350–5.
15. Tanaka K, Noura S, Ohue M, Seki Y, Yamada T, Miyashiro I, et al. Doubling time of carcinoembryonic antigen is a significant prognostic factor after the surgical resection of locally recurrent rectal cancer. Dig Surg. 2008;25:319–24.
16. Stamey TA, Kabalin JN, Ferrari M. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. III. Radiation treated patients. J Urol. 1989;141:1084–7.
17. Stamey TA, Kabalin JN, Ferrari M, Yang N. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. IV. Anti-androgen treated patients. J Urol. 1989;141:1088–90.
18. Stamey TA, Kabalin JN, McNeal JE, Johnstone IM, Freiha F, Redwine EA, et al. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. J Urol. 1989;141:1076–83.
19. Fabbro D, Manley PW. Su-6668. SUGEN. Curr Opin Investig Drugs. 2001;2:1142–8.
20. Pang RW, Poon RT. From molecular biology to targeted therapies for hepatocellular carcinoma: the future is now. Oncology. 2007;72(Suppl 1):30–44.
21. Kanai F, Yoshida H, Tateishi R, Sato S, Kawabe T, Obi S, et al. A phase I/II trial of the oral antiangiogenic agent TSU-68 in patients with advanced hepatocellular carcinoma. Cancer Chemother Pharmacol. 2011;67:315–24.
22. Eisenhauer EA. Phase I and II trials of novel anti-cancer agents: endpoints, efficacy and existentialism. The Michel Clavel Lecture, held at the 10th NCI-EORTC Conference on New Drugs in Cancer Therapy, Amsterdam, 16–19 June 1998. Ann Oncol. 1998;9:1047–52.
23. Eisenhauer EA. Response evaluation: beyond RECIST. Ann Oncol. 2007;18 Suppl 9:ix29–32.
24. Gelmon KA, Eisenhauer EA, Harris AL, Ratain MJ, Workman P. Anticancer agents targeting signaling molecules and cancer cell environment: challenges for drug development? J Natl Cancer Inst. 1999;91:1281–7.
25. Korn EL, Arbuck SG, Pluda JM, Simon R, Kaplan RS, Christian MC. Clinical trial designs for cytostatic agents: are new approaches needed? J Clin Oncol. 2001;19:265–72.
26. Ratain MJ, Eckhardt SG. Phase II studies of modern drugs directed against new targets: if you are fazed, too, then resist RECIST. J Clin Oncol. 2004;22:4442–5.
27. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205–16.
28. Dachman AH, MacEneaney PM, Adedipe A, Carlin M, Schumm LP. Tumor size on computed tomography scans: is one measurement enough? Cancer. 2001;91:555–60.

29. Schwartz M. A biomathematical approach to clinical tumor growth. Cancer. 1961;14:1272–94.
30. Chan SL, Mo FK, Johnson PJ, Hui EP, Ma BB, Ho WM, et al. New utility of an old marker: serial alpha-fetoprotein measurement in predicting radiologic response and survival of patients with hepatocellular carcinoma undergoing systemic chemotherapy. J Clin Oncol. 2009;27:446–52.
31. Riaz A, Ryu RK, Kulik LM, Mulcahy MF, Lewandowski RJ, Minocha J, et al. Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma: oncologic marker of radiologic response, progression, and survival. J Clin Oncol. 2009;27:5734–42.
32. Shao YY, Lin ZZ, Hsu C, Shen YC, Hsu CH, Cheng AL. Early alpha-fetoprotein response predicts treatment efficacy of antiangiogenic systemic therapy in patients with advanced hepatocellular carcinoma. Cancer. 2010;116:4590–6.
33. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378–90.
34. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10:25–34.
35. Bourhis J, Wilson G, Wibault P, Janot F, Bosq J, Armand JP, et al. Rapid tumor cell proliferation after induction chemotherapy in oropharyngeal cancer. Laryngoscope. 1994;104:468–72.
36. Davis AJ, Tannock JF. Repopulation of tumour cells between cycles of chemotherapy: a neglected factor. Lancet Oncol. 2000;1:86–93.
37. Kim JJ, Tannock IF. Repopulation of cancer cells during therapy: an important cause of treatment failure. Nat Rev Cancer. 2005;5:516–25.
38. Okazaki N, Yoshino M, Yoshida T, Suzuki M, Moriyama N, Takayasu K, et al. Evaluation of the prognosis for small hepatocellular carcinoma based on tumor volume doubling time. A preliminary report. Cancer. 1989;63:2207–10.

VOLUME 31 · NUMBER 6 · FEBRUARY 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Low Hepatitis C Viral Load Predicts Better Long-Term Outcomes in Patients Undergoing Resection of Hepatocellular Carcinoma Irrespective of Serologic Eradication of Hepatitis C Virus

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Published online ahead of print at www.jco.org on November 5, 2012.

Supported by Health and Labor Sciences Research Grant No. H21-015 for Clinical Cancer Research and by a grant from the Japanese Foundation for Multidisciplinary Treatment of Cancer.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/13/3106-766/$20.00

DOI: 10.1200/JCO.2012.44.3234

A B S T R A C T

Purpose
Hepatitis C virus (HCV) infection has been recognized as a potent risk factor for the postoperative recurrence of hepatocellular carcinoma (HCC). However, little is known about the impact of HCV viral load on surgical outcomes. The study objective was to investigate clinical significance of HCV viral load on long-term outcomes of HCC.

Patients and Methods
Three hundred seventy patients who were classified as Child-Pugh class A and underwent curative liver resections for HCV-related HCC were divided into low and high viral load groups (≤ or > 5.3 $\log_{10}$IU/mL) based on the results of a minimum *P* value approach to predict moderate to severe activity of hepatitis; the clinical outcomes were then compared.

Results
The 5-year recurrence-free survival rate was 36.1% in the low viral load group and 12.4% in the high viral load group ($P < .001$). The 5-year overall survival rate was 76.6% in the low viral load group and 57.7% in the high viral load group ($P < .001$). Multivariate analysis confirmed significant correlation between high viral load and tumor recurrence with a hazard ratio of 1.87 (95% CI, 1.41 to 2.48; $P < .001$). Subanalysis revealed that the favorable results in the low viral load group were not attributed to whether or not serologic eradication of HCV was obtained both in primary and recurrent lesions.

Conclusion
Low HCV viral load predicts better long-term surgical outcomes in patients with HCC regardless of the serologic eradication of HCV.

J Clin Oncol 31:766-773. © 2012 by American Society of Clinical Oncology

Recent developments in medical and surgical treatments have significantly improved the long-term outcomes of patients with hepatocellular carcinoma (HCC).[1] However, the cumulative recurrence rate remains as high as 50% to 60% at 3 years and 70% to 100% at 5 years, even after curative liver resection.[2-7]

Hepatitis C virus (HCV), a major cause of chronic hepatitis and liver cirrhosis, has been recognized as a potent risk factor of carcinogenesis[8] and/or the recurrence of HCC.[9,10] Because postoperative persistent viremia is thought to be the main cause of sustained liver dysfunction and the high tumor recurrence rate in patients with HCV, adjuvant antiviral therapy using interferon (IFN) has recently been attempted, and favorable outcomes have been reported in several studies.[11-13]

Conventionally, the eradication of HCV and a sustained status of undetectable HCV-RNA have been regarded as the most important factors for obtaining better clinical results after IFN therapy. In recent studies, however, possibly favorable effects of a reduced viral load on long-term outcomes have been suggested in patients with chronic hepatitis.[14,15]

Our hypothesis was that a correlation existed between the HCV viral load and long-term surgical outcomes. Simply labeling patient as having viremia did not sufficiently stratify those who had low viral load versus those who had high viral load. In this study, we tested this hypothesis by examining patients who had undergone curative

liver resection for HCV-related HCC and analyzed the impact of the HCV viral load on postoperative outcomes.

Study Population

This study was performed in accordance with the ethical guidelines for clinical studies at the University of Tokyo Hospital (Tokyo, Japan). The subject pool consisted of 508 consecutive patients who underwent curative liver resection for HCV-related HCC between January 2002 and December 2011. Patients classified as Child-Pugh class B (n = 49) or patients missing preoperative viral load data (n = 89) were excluded because the goal of this study was to reveal the prognostic impact of the HCV viral load in patients who were considered to be capable of tolerating antiviral therapies. The remaining 370 patients were included in the analysis.

Serum HCV-RNA Quantification

Serum HCV-RNA was quantified within 4 weeks before surgery using a conventional reverse transcriptase polymerase chain reaction (PCR) assay before 2007 and a new commercially available real-time PCR assay (TaqMan PCR; Roche Molecular Systems, Pleasanton, CA) in 2007 and thereafter. In this study, the viral load unit was standardized to a logarithm style ($\log_{10}$IU/mL) for the statistical analysis according to the following equation: Y ($\log_{10}$IU/mL) = $\log_{10}$ [X (kIU/mL) × 10^3].

Surgical Treatment and Histopathologic Assessments

The indications for hepatic resection and the types of operative procedures were determined as previously described.[16] Briefly, operative decisions were based on an algorithm consisting of the presence of ascites, the serum total bilirubin level, and the results of an indocyanine green tolerance test.[17] Because HCC has a high propensity to invade the portal veins and because intrahepatic metastasis via vascular invasion is one of the major forms of recurrence, tumor-bearing portal regions (ie, the segment or subsegment of the liver) were systematically removed (ie, an anatomic resection) to reduce the risk of local recurrence as long as such resections were feasible given the functional reserve of the liver.[18]

The histologic classifications of the tumor and background liver were described based on the system of the Liver Cancer Study Group of Japan.[19] The histologic differentiation of HCC (well, moderate, or poor) was determined according to the Edmondson grade.[19,20] Both the fibrotic stage and the activity of the hepatitis in the background liver were also recorded according the classification proposed by Desmet et al.[21]

Postoperative Antiviral Therapy

Postoperative adjuvant IFN therapy was performed only in patients who had a good performance status and were capable of tolerating a standard high-dose combination therapy with ribavirin. Specifically, patients who were younger than 65 years of age, had no evidence of cirrhosis, and had a sufficient platelet count ($> 9.0 \times 10^4/\mu L$) were considered good candidates for postoperative antiviral therapy.

Patient Follow-Up

All patients were regularly screened for recurrences through the evaluation of the HCC-specific tumor markers α-fetoprotein (AFP) and des-γ-carboxyprothrombin every 1 to 2 months, with ultrasonography every 2 months, and with dynamic computed tomography every 4 months, as previously reported.[22] The HCV viral load was re-examined after surgery in possible candidates for adjuvant antiviral therapy. The function of the background liver was monitored using the serum ALT levels. If the ALT levels increased beyond 100 IU/L, an appropriate dose of ursodeoxycholic acid and/or monoammonium glycyrrhizinate was administered expecting their liver protective effects.[23,24]

Recurrence was defined as the appearance of a new lesion with radiologic features compatible with HCC, as confirmed using at least two imaging modalities. When a recurrence was detected, the patient received further treatment using a repeated hepatectomy, radiofrequency ablation, transcatheter arterial chemoembolization (TACE), or other treatment options, as indicated. In the present study, recurrence-free survival (RFS) was defined as the interval between the operation and the date of the diagnosis of the first recurrence or the last follow-up examination, and overall survival (OS) was calculated based on the time from surgery to death or last follow-up.

Data Analysis

Statistical analysis was performed using SAS software, version 9.3 (SAS Institute, Cary, NC). Medians and ranges of continuous data were compared using the Mann-Whitney *U* test. Categorical data were compared using Pearson's χ^2 test or Fisher's exact test as appropriate. $P < .05$ was considered statistically significant.

High viral load was defined as HCV viral load to predict moderate to severe activity of hepatitis (grade 2 or 3 in Desmet classification[21]). The cutoff value was determined using the minimum *P* value approach, and clinical outcomes were compared between the patients with a high viral load and those with a low viral load. In addition, the low viral load group was further subclassified according to whether or not HCV-RNA was detectable, and clinical outcomes between these subgroups were also compared.

Survival curves for OS and RFS were generated using the Kaplan-Meier method and were compared using the log-rank test. To identify risk factors for tumor recurrence, multivariate regression analysis was performed with the Cox proportional hazards model using a backward elimination procedure. To prevent overfitting, only factors that showed statistically significant association with tumor recurrence with $P < .10$ were included in the final model. Prognostic value of HCV viral load was

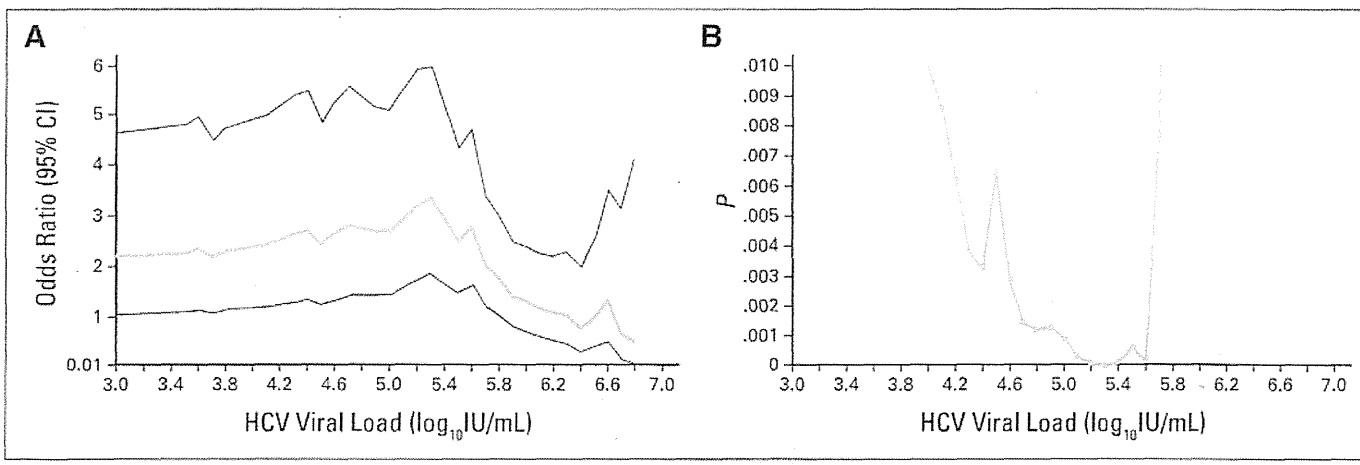

Fig 1. Optimal cutoff value of hepatitis C virus (HCV) RNA viral load to predict moderate to severe activity of hepatitis. (A) Plot of odds ratio. (B) Plot of *P* value in likelihood test (null hypothesis: odds ratio, 1).

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	Patients With Low Viral Load (n = 168)		Patients With High Viral Load (n = 202)		*P*
	No.	%	No.	%	
Age, years					.07
Median	69		70		
Range	47-83		39-85		
Sex					
Male	139	82.7	131	64.9	< .001
Female	29	17.3	71	35.1	
HBsAg					
Positive	7	4.2	4	2.0	.24
Negative	161	95.8	198	98.0	
HBcAb					
Positive	45	28.5	59	33.7	.30
Negative	113	71.5	116	66.3	
HCV genotype					
1b	40	69.0	87	81.3	0.07
Other	18	31.0	20	18.7	
HCV-RNA, $\log_{10}$IU/mL					< .001
Mean	3.0		6.0		
Standard deviation	1.9		0.4		
History of IFN therapy					
Positive	69	41.6	48	24.0	< .001
Negative	97	58.4	152	76.0	
No. of tumors					
Solitary	107	63.7	127	63.2	.87
Multiple	61	36.3	75	37.1	
Maximum diameter of the tumor, mm					.45
Median	24		25		
Range	8-130		6-200		
AST, IU/L					< .001
Median	34		49		
Interquartile range	24-56		36-63		
ALT, IU/L					< .001
Median	32		47		
Interquartile range	20-52		29-67		
Total bilirubin, mg/dL					.12
Median	0.7		0.7		
Interquartile range	0.5-0.9		0.6-0.9		
PT, %					.18
Median	82.9		82.9		
Interquartile range	73.1-94.9		75.6-98.3		
ICG-R15, %					< .001
Median	13.8		16.9		
Interquartile range	8.8-20.8		12.1-24.3		
Platelets, $10^4/\mu$L					.11
Median	14.4		14.0		
Interquartile range	11.4-19.0		10.1-17.1		
AFP, ng/mL					< .001
Median	9		15		
Interquartile range	4-42		7-99		
DCP, mAU/mL					.49
Median	32		35		
Interquartile range	17-177		19-146		

Abbreviations: AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; ICG-R15, indocyanine green retention rate at 15 minutes; IFN, interferon; LC, liver cirrhosis; PT, prothrombin time.

quantified by comparing Harrell's concordance statistics of prognostic models based on the results of the multivariate analysis.

Characteristics of High and Low HCV Viral Load Groups

The best cutoff value of HCV viral load to predict moderate to severe activity of hepatitis was more than 5.3 $\log_{10}$IU/mL in both the plots of odds ratio and *P* value in the likelihood test (Fig 1). The background characteristics are compared between the high viral load (n = 202) and low viral load (n = 168) groups in Table 1. Female sex was more frequent in the high viral load group than in the low viral load group. The rates of coinfection with hepatitis B were not significantly different between the two groups. A history of IFN therapy was more common in the low viral load group. Number and maximum diameter of lesions were comparable between the two groups. The serum ALT and AST levels, indocyanine green retention rate at 15 minutes, and AFP levels were significantly higher in the high viral load group, whereas the platelet count was almost the same between the groups.

As for surgical factors (Table 2), the initial hepatectomy rates were 51.8% and 67.3% in the low and high viral load groups, respectively ($P < .001$). The remaining patients had repeat hepatectomies for

Table 2. Surgical, Histopathologic, and Postoperative Factors

Factor	Patients With Low Viral Load (n = 168)		Patients With High Viral Load (n = 202)		*P*
	No.	%	No.	%	
Surgical factors					
Liver resection					< .001
First HX	87	51.8	136	67.3	
≥ Second HX	81	48.2	66	32.7	
Operation time, minutes					.06
Median	359		330		
Interquartile range	279-461		263-443		
Blood loss, g					
Median	700		660		.77
Interquartile range	370-1,059		350-1,050		
Transfusion	7	4.2	7	3.5	.79
Anatomic resection	73	43.5	80	39.6	.45
Surgical margin, mm					.20
Mean	3.1		3.6		
Standard deviation	5.4		4.9		
Histopathologic factors					
Tumor differentiation*					
Well	35	21.5	42	21.2	.86
Moderate	106	65.0	134	67.7	
Poor	22	13.5	22	11.1	
Major vascular invasion	10	5.9	5	2.6	.39
Microvascular invasion	59	35.3	64	32.0	.50
Fibrosis score†					
F0-2	52	49.1	56	37.1	.06
F3-4	54	50.9	95	62.9	
Postoperative factors					
Adjuvant IFN therapy	6	3.6	7	3.5	1.00
HCV-RNA at 1 year, $\log_{10}$IU/mL‡					< .001
Mean	3.3		6.0		
Standard deviation	2.0		0.4		
ALT after surgery, IU/L					.004
Median	33		42		
Interquartile range	20-56		28-64		
AFP at 1 month, ng/mL					< .001
Median	4		7		
Interquartile range	3-7		4-13		
DCP at 1 month, mAU/mL					.08
Median	14		15		
Interquartile range	10-16		10-19		

Abbreviations: AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; HCV, hepatitis C virus; HX, hepatectomy; IFN, interferon.
*Based on modification of the Edmondson grade.[19]
†Based on the classification by Desmet et al.[21]
‡Based on data from 31 and 28 patients with low viral load and high viral load, respectively.

recurrent lesions. Type of surgery (anatomic *v* nonanatomic), operating time, blood loss, and surgical margins were comparable between the groups. Histopathologically, no significant difference was observed in histologic grade of tumor or presence of vascular invasions. Fibrotic scores tended to be higher in the high viral load group.

Postoperative IFN therapy was performed in only six patients (3.6%) and seven patients (3.5%) in the low and high viral load groups, respectively. Because the median age of the patients in this study was 70 years and approximately 50% of the patients exhibited marked thrombocytopenia and/or cirrhotic changes in their background livers, the standard combination therapy of IFN with ribavirin was difficult to apply in most of the patients.

In 59 patients in whom postoperative viral load data were available, the HCV-RNA levels did not significantly change from baseline to 1 year after surgery ($4.5 \pm 2.0 \log_{10}$IU/mL before surgery *v* 4.6 ± 1.9 $\log_{10}$IU/mL after surgery; $P = .78$). HCV-RNA viral load at 1 year and postoperative mean ALT levels were higher in the high viral load group. Postoperative AFP levels were also higher in the high viral load group even after curative resection.

Patient Survival

The median follow-up time of the studied population was 38.4 months (range, 1 to 120 months), and no hospital deaths occurred. During the study period, recurrence was observed in 108 patients (60.7%) and 137 patients (71.4%) in the low and high viral load groups, respectively.

The 1-, 3-, and 5-year RFS rates were 66.1%, 37.4%, and 36.1% in the low viral load group and 60.2%, 25.8%, and 14.9% in the high viral load group, respectively ($P < .001$; log-rank test). The 3- and 5-year OS rates were 87.6% and 76.6% in the low viral load group and 77.2% and 57.7% in the high viral load group, respectively ($P < .001$; log-rank test; Fig 2). At the time of the first recurrence, multiple intrahepatic recurrences were more frequent in the high viral load group (47.5%) than in the low viral load group (33.8%; $P = .05$). Repeat hepatectomy, radiofrequency ablation, and TACE were performed for intrahepatic recurrence in 26.0% (n = 33), 19.7% (n = 25), and 42.5% (n = 54) of patients in the high viral load group, respectively, and 41.0% (n = 34), 20.5% (n = 17), and 30.1% (n = 25) of patients in the low viral load group, respectively ($P = .06$).

The median HCV viral load of the positive HCV-RNA subgroup in the patients with low viral load was 4.9 $\log_{10}$IU/mL (range, 2.3 to 5.3 $\log_{10}$IU/mL), and it was significantly lower than that in the high viral load group ($P < .001$). Clinicopathologic parameters were almost comparable between the two subgroups in the low viral group except that HCV-RNA titers and serum AST and ALT levels were significantly higher in positive HCV-RNA patients ($P < .001$). The 1- and 3-year RFS rates were similar between the two subgroups (65.6% and 38.8% for the negative HCV-RNA patients and 66.5% and 35.9% for the positive HCV-RNA patients, respectively; $P = .61$; Fig 3A). The RFS rate among the low viral load group with positive HCV-RNA was superior to that of the high viral load group ($P = .009$). A similar tendency was also observed in the OS rates. The positive HCV-RNA patients had relatively favorable results, similar to the negative HCV-RNA patients when the viral load was $\leq 5.3 \log_{10}$IU/mL. The 3- and 5-year OS rates were 85.8% and 78.1% for the negative HCV-RNA patients, respectively, and 89.0% and 75.8% for the positive HCV-RNA patients, respectively ($P = .94$; Fig 3B). The OS rate of the low viral load group with positive HCV-RNA was superior to that of the high viral load group ($P = .005$). These observations were constant when stratifying the study population according to hepatectomies for primary or recurrent lesions (Appendix Fig A1, online only).

Risk Factors for Postoperative Recurrence

Risk factors for postoperative recurrence were investigated in 357 patients without postoperative antiviral therapy. In the multivariate analysis, we chose 17 potential confounders considering their clinical significance and reported evidences,[4,25-31] as indicated in Table 3. There were no specific combinations of factors suggesting multicollinearity in scatter plots. In multivariate analysis, high HCV viral load ($> 5.3 \log_{10}$IU/mL), macroscopic vascular invasion, repeat resection for recurrent tumor, tumor exposure, and tumor size greater than 2 cm were selected in the final model. The concordance statistic of the four-factor model (macroscopic vascular invasion + repeat resection + tumor exposure + size > 2 cm) was 0.603 (95% CI, 0.559 to 0.647),

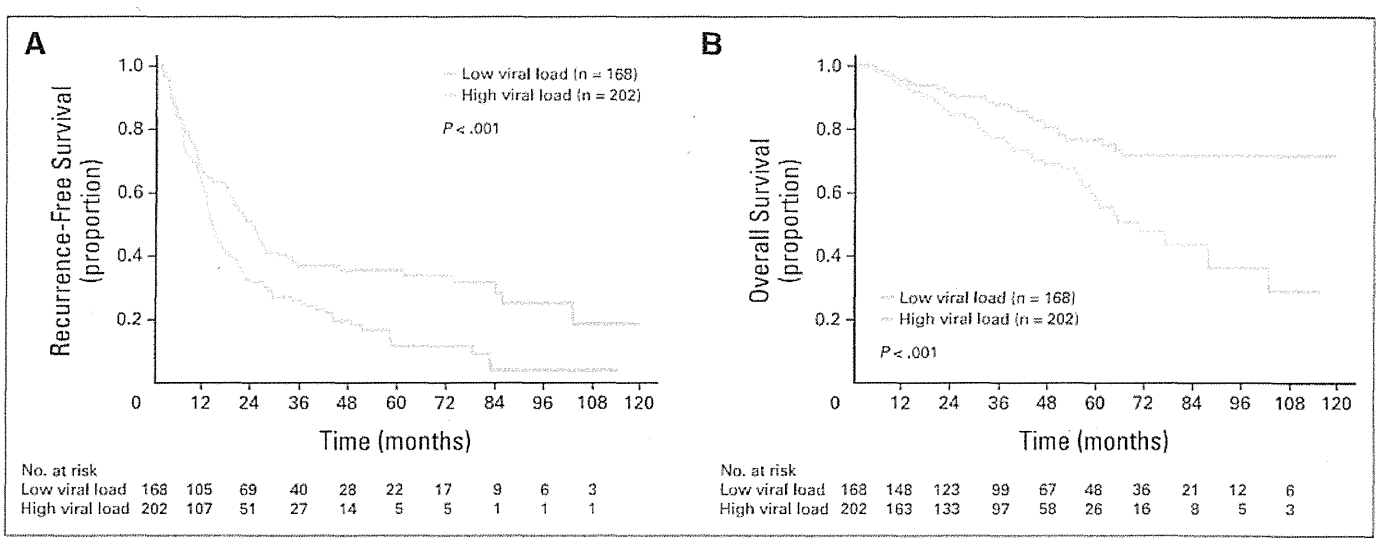

Fig 2. (A) Cumulative recurrence rate and (B) cumulative overall survival curves of low and high viral load groups.

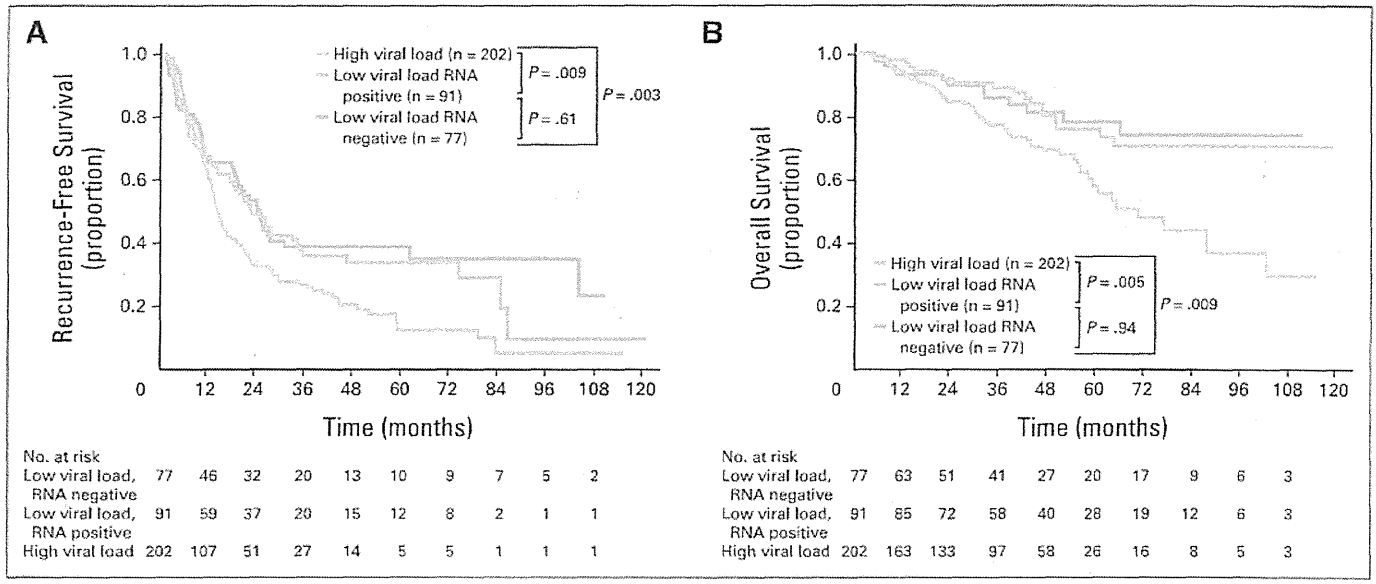

Fig 3. (A) Cumulative recurrence rate and (B) cumulative overall survival curves of low and high viral load groups stratified according to the results of hepatitis C virus RNA quantification.

and it improved to 0.627 (95% CI, 0.590 to 0.665) when including HCV viral load greater than 5.3 $\log_{10}$IU/mL in the prognostic model (Table 3).

In this study, we analyzed 370 patients who underwent curative liver resection for HCV-related HCC. The current study indicates that a low viral load ($\leq$ 5.3 $\log_{10}$IU/mL) is strongly associated with lower recurrence rate and better OS regardless of the serologic eradication of HCV. These observations were constant both in initial hepatectomy for primary lesions and repeat hepatectomy for recurrent lesions. Multivariate analysis confirms that a high HCV viral load (> 5.3 $\log_{10}$IU/mL) is an independent factor associated with a 1.84-fold greater risk of tumor recurrence after curative resection of HCC.

In patients with HCV-related HCC, virologic status of HCV has been thought to be a prognostic factor associated with high tumor recurrence rate.[9,10] Adjuvant antiviral therapy is performed with the aim of preventing tumor recurrence by improving the fibrotic status and/or activity of inflammation in the background liver through the reduction of the viral load. Several studies have shown favorable long-term outcomes of adjuvant IFN therapy after locoregional treatments or surgical resections.[11,32-34] However, the effectiveness of antiviral therapy has been discussed mainly from the view point of virus eradication,[11-13,34-36] and little is known about the significance of the viral load itself for tumor recurrence.

Akamatsu et al[37] previously reviewed 371 patients who had undergone locoregional treatments for HCV-related HCC and denied a correlation between the viral load and the recurrence rate of HCC. However, their study contained a heterogeneous population that underwent

Table 3. Factors Associated With Recurrence of Hepatocellular Carcinoma

Factor	P*	Coefficient†	SE	Wald χ^2	HR	95% CI
HCV-RNA > 5.3 $\log_{10}$IU/mL	< .001	0.627	0.144	19.1	1.87	1.41 to 2.48
Macrovascular invasion	< .001	1.384	0.327	17.9	3.99	2.10 to 7.57
Repeat resection for recurrence	< .001	0.505	0.150	11.4	1.66	1.24 to 2.22
Tumor exposure	.013	0.337	0.136	6.1	1.40	1.07 to 1.83
Tumor size > 2 cm	.093	0.252	0.150	2.8	1.29	0.96 to 1.83

NOTE. The concordance statistic for the four-factor model (macrovascular invasion + repeat resection + tumor exposure + size > 2 cm) was 0.603 (95% CI, 0.559 to 0.647). The concordance statistic for the full model (the four-factor model + HCV-RNA > 5.3 $\log_{10}$IU/mL) was 0.627 (95% CI, 0.590 to 0.665). Multivariate Cox regression was applied with stepwise backward selection. Initially, all factors were included in the model. Then factors that showed no or limited statistically significant association ($P > .01$) with tumor recurrence adjusted for the remaining factors in the model were deleted from the model in a stepwise fashion. The 17 factors tested were as follows: sex, primary versus repeat resection, tumor size (> *v* ≤ 2 cm), number of tumors (solitary *v* multiple), hepatitis B core antibody (yes *v* no), HCV viral load (> *v* ≤ 5.3 $\log_{10}$IU/mL), fibrotic status of the underlying liver (F3-4 *v* F0-2), serum ALT level (> *v* ≤ 40 IU/L), indocyanine green retention rate at 15 minutes (> *v* ≤ 15%), serum α-fetoprotein level (> *v* ≤ 20 ng/mL), plasma des-γ-carboxyprothrombin level (> *v* ≤ 40 mAU/mL), type of hepatectomy (anatomic *v* nonanatomic), perioperative transfusion (yes *v* no), tumor exposure (yes *v* no), microvascular invasion (yes *v* no), macrovascular invasion (yes *v* no), and tumor differentiation (well/moderate *v* poor).

Abbreviations: HCV, hepatitis C virus; HR, hazard ratio.

*Based on likelihood test adjusted for the other factors in the final model.

†Estimated coefficient for the variable and the associated SE.

various types of treatments including surgery, ablation, and TACE. Therefore, the true clinical influence of HCV viral load on long-term outcomes of HCV-related HCC is still unclear. In the current study, we carefully reviewed patients who underwent curative surgical resections under a consistent treatment strategy in a single high-volume hepatobiliary center. Major prognostic improvements were observed both in recurrence and survival when a low viral load was obtained according to the cutoff value (5.3 $\log_{10}$IU/mL) that was determined by the minimum *P* value approach to predict moderate to severe activity of hepatitis. Comparison of clinicopathologic factors revealed that high viral load was associated with higher serum ALT and AST levels (both before and after surgery) and higher fibrotic status. These correlations are consistent with previous reports[38,39] and suggest the higher carcinogenic potential in the background liver in patients with high HCV viral load.

Another noteworthy result is that the preferable outcomes in the low viral load group are not significantly influenced by whether or not the serologic eradication of HCV is obtained. As shown in Figure 3, when the survival curves were compared between the RNA-positive and RNA-negative patients, no significant difference was observed, although both curves represented apparently better outcomes than that for the high viral load group. We also confirmed a similar tendency both in initial hepatectomy and repeat hepatectomy in a subset analysis (Appendix Figure 1, online only). These results suggest that a lower viral load might be preferable even if the serologic eradication of HCV is not obtained, supporting the outcomes of previous studies[14,15] and a recent meta-analysis[40] studying the effectiveness of IFN therapy.

Recent introduction of combination therapy consisting of pegylated IFN and ribavirin has dramatically improved the sustained viral response rate in patients with HCV.[32,33] However, the postoperative use of IFN remains a major concern because HCC usually emerges in the liver that has been damaged over the course of decades, and accordingly, patients tend to be elderly and to exhibit cirrhotic changes. Therefore, a high-dose standard combination therapy is not always applicable because of the issue of tolerability. Furthermore, even if IFN therapy is available, a sustained viral response may not always be achievable, especially in female patients or patients infected with HCV genotype 1b, both of which have been reported as factors refractory to antiviral therapy.[41-44] In fact, the median age of the current population was 70 years, and 47.8% of the patients were clinically diagnosed with cirrhosis. The proportion of women was higher in the high viral load group, and 71.4% of the patients had genotype 1b.

Given the current results, a low HCV viral load can be a new clinical end point in adjuvant therapy for HCV-related HCC. In this context, a more tolerable antiviral therapy, including low-dose IFN therapy with prolonged therapeutic duration[45,46] or possibly a combination with protease inhibitors,[47-49] may be a therapeutic option for elderly patients or patients with liver cirrhosis. Given the fact that anatomic resection of the liver was also an independent predictor of recurrence in the multivariate analysis, combination of anatomic resection and adjuvant IFN therapy may enhance the postoperative outcomes in patients with HCV-related HCC by eradicating micrometastases and reducing the carcinogenic potential in the underlying liver.

Because this study was retrospective, prospective/randomized trials are needed to confirm the true influence of the HCV viral load and the effectiveness of adjuvant antiviral therapy on postoperative outcomes. In addition, the results of the Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM) trial, if sorafenib is found to be of benefit, will impact the selection of postoperative therapy in HCC in the near future. Given the possibility of drug interactions and competing toxicity between sorafenib and antiviral agents, further investigation on the selection of adjuvant treatment is needed, especially in patients with HCV-associated HCC.

In conclusion, a low viral load may predict lower recurrence and better survival in patients undergoing hepatic resection for HCV-related HCC irrespective of the serologic eradication of HCV. Postoperative antiviral therapy with individually adjusted intensity and incorporation of direct antiviral agents may warrant prospective study to characterize safety and impact on recurrence risk in patients undergoing surgical resection for HCV-associated HCC.

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** Norihiro Kokudo, Bayer, Dainippon Sumitomo **Expert Testimony:** None **Other Remuneration:** None

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Manuscript writing: All authors
Final approval of manuscript: All authors

1. Rahbari NN, Mehrabi A, Mollberg NM, et al: Hepatocellular carcinoma: Current management and perspectives for the future. Ann Surg 253:453-469, 2011
2. Belghiti J, Panis Y, Farges O, et al: Intrahepatic recurrence after resection of hepatocellular carcinoma complicating cirrhosis. Ann Surg 214: 114-117, 1991
3. Grazi GL, Ercolani G, Pierangeli F, et al: Improved results of liver resection for hepatocellular carcinoma on cirrhosis give the procedure added value. Ann Surg 234:71-78, 2001
4. Imamura H, Matsuyama Y, Miyagawa Y, et al: Prognostic significance of anatomical resection and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma. Br J Surg 86:1032-1038, 1999
5. Kakazu T, Makuuchi M, Kawasaki S, et al: Repeat hepatic resection for recurrent hepatocellular carcinoma. Hepatogastroenterology 40:337-341, 1993
6. Nakajima Y, Ko S, Kanamura T, et al: Repeat liver resection for hepatocellular carcinoma. J Am Coll Surg 192:339-344, 2001

7. Poon RT, Fan ST, Lo CM, et al: Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: Implications for a strategy of salvage transplantation. Ann Surg 235:373-382, 2002

8. Tsukuma H, Hiyama T, Tanaka S, et al: Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 328:1797-1801, 1993

9. Kumada T, Nakano S, Takeda I, et al: Patterns of recurrence after initial treatment in patients with small hepatocellular carcinoma. Hepatology 25:87-92, 1997

10. Yamanaka N, Tanaka T, Tanaka W, et al: Correlation of hepatitis virus serologic status with clinicopathologic features in patients undergoing hepatectomy for hepatocellular carcinoma. Cancer 79:1509-1515, 1997

11. Kubo S, Nishiguchi S, Hirohashi K, et al: Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. Br J Surg 89:418-422, 2002

12. Miyake Y, Takaki A, Iwasaki Y, et al: Meta-analysis: Interferon-alpha prevents the recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. J Viral Hepat 17:287-292, 2010

13. Singal AK, Freeman DH Jr, Anand BS: Meta-analysis: Interferon improves outcomes following ablation or resection of hepatocellular carcinoma. Aliment Pharmacol Ther 32:851-858, 2010

14. Kasahara A, Hayashi N, Mochizuki K, et al: Clinical characteristics of patients with chronic hepatitis C showing biochemical remission, without hepatitis C virus eradication, as a result of interferon therapy: The Osaka Liver Disease Study Group. J Viral Hepat 7:343-351, 2000

15. Yabuuchi I, Imai Y, Kawata S, et al: Long-term responders without eradication of hepatitis C virus after interferon therapy: Characterization of clinical profiles and incidence of hepatocellular carcinoma. Liver 20:290-295, 2000

16. Hasegawa K, Kokudo N, Imamura H, et al: Prognostic impact of anatomic resection for hepatocellular carcinoma. Ann Surg 242:252-259, 2005

17. Makuuchi M, Kosuge T, Takayama T, et al: Surgery for small liver cancers. Semin Surg Oncol 9:298-304, 1993

18. Nakashima T, Kojiro M: Pathologic characteristics of hepatocellular carcinoma. Semin Liver Dis 6:259-266, 1986

19. Liver Cancer Study Group of Japan: The General Rules for the Clinical and Pathological Study of Primary Liver Cancer (ed 5). Tokyo, Japan, Kanehara, 2008

20. Edmondson HA, Steiner PE: Primary carcinoma of the liver: A study of 100 cases among 48,900 necropsies. Cancer 7:462-503, 1954

21. Desmet VJ, Gerber M, Hoofnagle JH, et al: Classification of chronic hepatitis: Diagnosis, grading and staging. Hepatology 19:1513-1520, 1994

22. Takayama T, Makuuchi M, Hirohashi S, et al: Early hepatocellular carcinoma as an entity with a high rate of surgical cure. Hepatology 28:1241-1246, 1998

23. Combes B, Carithers RL Jr, Maddrey WC, et al: Biliary bile acids in primary biliary cirrhosis: Effect of ursodeoxycholic acid. Hepatology 29:1649-1654, 1999

24. Yamamura Y, Kotaki H, Tanaka N, et al: The pharmacokinetics of glycyrrhizin and its restorative effect on hepatic function in patients with chronic hepatitis and in chronically carbon-tetrachloride-intoxicated rats. Biopharm Drug Dispos 18:717-725, 1997

25. Fan ST, Ng IO, Poon RT, et al: Hepatectomy for hepatocellular carcinoma: The surgeon's role in long-term survival. Arch Surg 134:1124-1130, 1999

26. Vauthey JN, Lauwers GY, Esnaola NF, et al: Simplified staging for hepatocellular carcinoma. J Clin Oncol 20:1527-1536, 2002

27. Ikeda K, Marusawa H, Osaki Y, et al: Antibody to hepatitis B core antigen and risk for hepatitis C-related hepatocellular carcinoma: A prospective study. Ann Intern Med 146:649-656, 2007

28. Fuster J, García-Valdecasas JC, Grande L, et al: Hepatocellular carcinoma and cirrhosis: Results of surgical treatment in a European series. Ann Surg 223:297-302, 1996

29. Lee CS, Sheu JC, Wang M, et al: Long-term outcome after surgery for asymptomatic small hepatocellular carcinoma. Br J Surg 83:330-333, 1996

30. Yamamoto J, Kosuge T, Takayama T, et al: Recurrence of hepatocellular carcinoma after surgery. Br J Surg 83:1219-1222, 1996

31. Yamanaka N, Okamoto E, Toyosaka A, et al: Prognostic factors after hepatectomy for hepatocellular carcinomas: A univariate and multivariate analysis. Cancer 65:1104-1110, 1990

32. Ikeda K, Arase Y, Saitoh S, et al: Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor: A prospective randomized study of hepatitis C virus-related liver cancer. Hepatology 32:228-232, 2000

33. Shiratori Y, Shiina S, Teratani T, et al: Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. Ann Intern Med 138:299-306, 2003

34. Suou T, Mitsuda A, Koda M, et al: Interferon alpha inhibits intrahepatic recurrence in hepatocellular carcinoma with chronic hepatitis C: A pilot study. Hepatol Res 20:301-311, 2001

35. Uenishi T, Kubo S, Hirohashi K, et al: Relationship between response to previous interferon therapy and postoperative recurrence of hepatitis C virus-related hepatocellular carcinoma. Hepatol Res 24:404-412, 2002

36. Uenishi T, Nishiguchi S, Tamori A, et al: Influence of interferon therapy on outcome after surgery for hepatitis C virus-related hepatocellular carcinoma. Hepatol Res 36:195-200, 2006

37. Akamatsu M, Yoshida H, Shiina S, et al: Neither hepatitis C virus genotype nor virus load affects survival of patients with hepatocellular carcinoma. Eur J Gastroenterol Hepatol 16:459-466, 2004

38. Uenishi T, Nishiguchi S, Tanaka S, et al: Response to interferon therapy affects risk factors for postoperative recurrence of hepatitis C virus-related hepatocellular carcinoma. J Surg Oncol 98:358-362, 2008

39. Kubo S, Hirohashi K, Tanaka H, et al: Risk factors for recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. World J Surg 24:1559-1565, 2000

40. Miao RY, Zhao HT, Yang HY, et al: Postoperative adjuvant antiviral therapy for hepatitis B/C virus-related hepatocellular carcinoma: A meta-analysis. World J Gastroenterol 16:2931-2942, 2010

41. Kogure T, Ueno Y, Fukushima K, et al: Pegylated interferon plus ribavirin for genotype Ib chronic hepatitis C in Japan. World J Gastroenterol 14:7225-7230, 2008

42. Sezaki H, Suzuki F, Kawamura Y, et al: Poor response to pegylated interferon and ribavirin in older women infected with hepatitis C virus of genotype 1b in high viral loads. Dig Dis Sci 54:1317-1324, 2009

43. Hadziyannis SJ, Sette H Jr, Morgan TR, et al: Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: A randomized study of treatment duration and ribavirin dose. Ann Intern Med 140:346-355, 2004

44. Tsubota A, Chayama K, Ikeda K, et al: Factors predictive of response to interferon-alpha therapy in hepatitis C virus infection. Hepatology 19:1088-1094, 1994

45. Kudo M, Sakaguchi Y, Chung H, et al: Long-term interferon maintenance therapy improves survival in patients with HCV-related hepatocellular carcinoma after curative radiofrequency ablation: A matched case-control study. Oncology 72:132-138, 2007 (suppl 1)

46. Shimomura S, Ikeda N, Saito M, et al: Long-term interferon therapy after radiofrequency ablation is effective in treating patients with HCV-associated hepatocellular carcinoma. Hepatol Int 5:559-566, 2010

47. Hayashi N, Okanoue T, Tsubouchi H, et al: Efficacy and safety of telaprevir, a new protease inhibitor, for difficult-to-treat patients with genotype 1 chronic hepatitis C. J Viral Hepat 19:e134-e142, 2012

48. Poordad F, McCone J Jr, Bacon BR, et al: Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 364:1195-1206, 2011

49. Zeuzem S, Andreone P, Pol S, et al: Telaprevir for retreatment of HCV infection. N Engl J Med 364:2417-2428, 2011

Original article

Resection of segment VIII for hepatocellular carcinoma

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Background: Anatomical resection of segment VIII (SVIII) is technically demanding. Only two small studies have published short-term outcomes. The aim of the present study was to evaluate short- and long-term outcomes after anatomical resection involving SVIII for hepatocellular carcinoma (HCC), and to compare long-term outcomes with those after non-anatomical resection of SVIII.

Methods: Outcomes after anatomical resection of SVIII or its subsegments for HCC were compared with those in patients who underwent primary non-anatomical resection of SVIII during the same period.

Results: A total of 154 patients underwent anatomical resection involving SVIII and 122 had non-anatomical resection. In patients undergoing anatomical resection, the preoperative indocyanine green retention rate at 15 min ranged from 2·9 to 32·2 (median 13·6) per cent, and was 10 per cent or more in 109 patients (70·8 per cent). Median duration of operation and blood loss were 378 min and 705 ml respectively. There were no postoperative deaths, but major adverse events occurred in ten patients (6·5 per cent). The cumulative 5-year recurrence-free and overall survival rates were 28·5 and 79·6 per cent, which were significantly better than rates of 19·4 and 64·8 per cent respectively after non-anatomical resection ($P = 0·036$ and $P < 0·001$).

Conclusion: Complete resection of SVIII or its subsegments can be performed safely and the long-term outcomes seem acceptable. This can be a curative procedure for HCC, especially in patients with limited liver function reserve, in whom right hepatectomy or right paramedian sectorectomy might otherwise be needed.

Paper accepted 28 March 2012
Published online 14 June 2012 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.8790

Introduction

Right hepatectomy is the procedure of choice for most hepatic tumours located in the right liver in patients with normal liver function. Parenchyma-sparing resection may be required, however, in patients with impaired liver function and this is common in patients with hepatocellular carcinoma (HCC). Because HCC tends to metastasize via the portal vein[1,2], resection of the liver parenchyma fed by portal venous branches bearing the tumour seems logical to eradicate potential intrahepatic metastases.

Anatomical segmentectomy and subsegmentectomy have been proposed to accommodate both oncological advantage and preservation of liver parenchyma[1]. Previous studies have shown a survival benefit after anatomical resection in comparison with that following non-anatomical partial resection[3–7]. Anatomical segmentectomy is technically demanding. Operative technical details are inconsistent; identification of the segment borders is not standardized, the dissected surface is not a flat plane[8] and precise dissection of the correct Glissonian branches necessitates intraoperative ultrasonography[1]. In a strict sense, only complete removal of the corresponding portal territory should be called complete anatomical resection.

Segment VIII (SVIII) is the largest of the eight Couinaud segments[9], comprising 11–45 (median 24) per cent of the total liver volume[8]. It is located between the middle and right hepatic veins, and usually two major portal pedicles feeding the ventral and dorsal subsegments of SVIII branch out from the trunk (*Fig. 1*). From a technical point of view, among the various types of anatomical resection, segmentectomy or subsegmentectomy of SVIII may be the

most challenging, because of this location, surrounded by the trunk of the middle and/or right hepatic veins, and the absence of landmarks for the segmental border on the liver surface[10–12].

There are no large series describing the technical details and outcomes of anatomical segmentectomy and subsegmentectomy for SVIII. Only two studies, of ten and 18 patients, have reviewed the outcomes of SVIII anatomical resections[12,13]. The aim of this study was to describe the technical details of anatomical SVIII resection, evaluate the safety of the procedure by examining short-term outcomes, and to compare long-term outcomes with those in patients undergoing non-anatomical resection.

Methods

A prospectively maintained single-institution database of all patients undergoing hepatic resection for HCC between November 1994 and June 2007 was used to identify those who had undergone anatomical (based on portal vein anatomy) complete resection of SVIII, subsegmentectomy (usually the ventral or dorsal part of SVIII fed by the ventral or dorsal portal pedicles) and SVIII resection extending to adjacent segments (IV, V or VII), as well as patients who had undergone non-anatomical resection (wedge resection or more bulky excision ignoring the portal vein anatomy). Patients undergoing resection of two or more complete segments, such as right paramedian sectorectomy, were excluded. Choice of type of resection was made based on the location of the tumour(s) and the estimate of functional hepatic reserve.

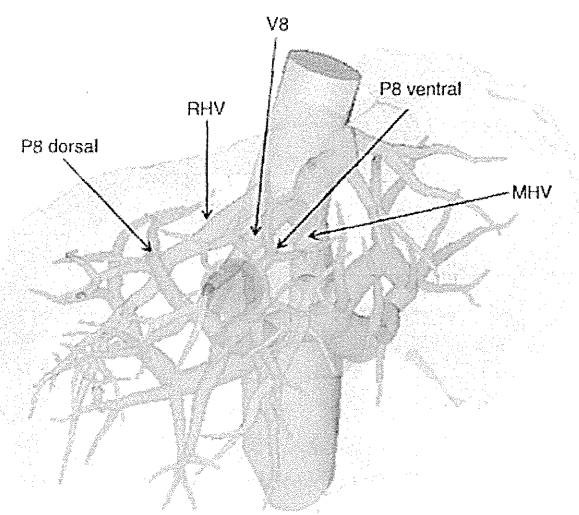
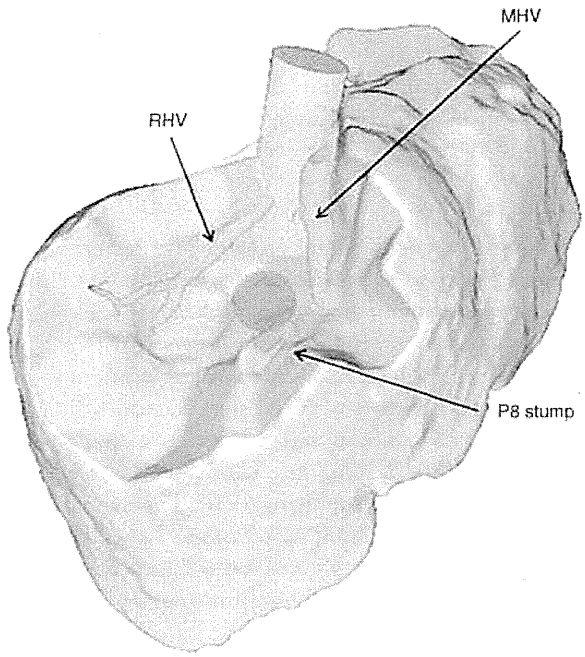


Fig. 1 Schema of the normal portal and hepatic vein anatomy. Segment VIII (SVIII) is located between the middle (MHV) and right (RHV) hepatic veins, and usually two major pedicles feeding the ventral (P8 ventral) and dorsal (P8 dorsal) branch out from the SVIII portal trunk. A tributary of the MHV (V8) is located between the two pedicles

Anatomical segmentectomy or subsegmentectomy was performed as reported previously[1]. In brief, after laparotomy and thoracotomy along the ninth intercostal space with a J-shaped incision, the entire liver was scanned by intraoperative ultrasonography and tumour locations were mapped. Portal branches of SVIII were identified by following the right paramedian sectoral branch in a peripheral direction. Branches heading in a cranial direction represented the portal pedicle supplying SVIII. Thoracophrenolaparotomy facilitated mobilization of the right liver and provided excellent views of the insertion of the hepatic veins into the vena cava[14]. Under ultrasonographic guidance, about 5 ml indigo carmine dye (Indigocarmine Injection 20 mg/5 ml; Daiichi Sankyo, Tokyo, Japan) was injected into portal venous branches at sites distal to the point at which they needed to be ligated during parenchymal dissection after clamping of the hepatic artery. Additional branches were punctured, as necessary, depending on the location of the tumour. If puncture of the tumour-bearing portal branch was difficult, the counterstaining identification technique was used, puncturing the adjacent portal branches[15]. The stained surface of the liver was marked by electrocautery. Under intermittent inflow occlusion by clamping of the hepatoduodenal ligament or hemihepatic inflow occlusion, the parenchyma was dissected using the clamp and crush method[1,16].

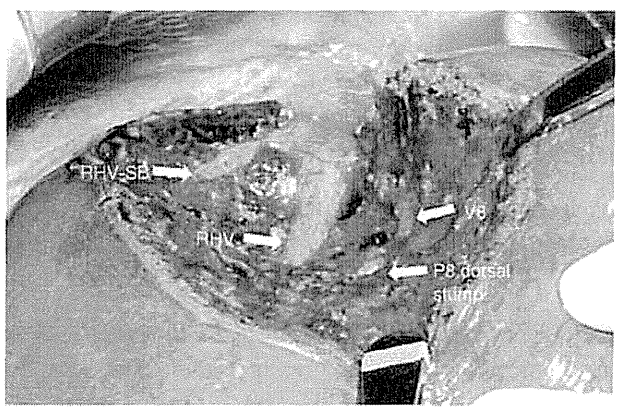
After complete SVIII resection, the trunks of the middle and right hepatic vein appeared on the dissected surface (*Fig. 2*). After resection of the ventral or dorsal parts of SVIII, a tributary of the middle hepatic vein running along the border appeared (*Fig. 2*). Drains were inserted in the transection surface of the liver and right subphrenic space. Drainage tubes were removed when there was no visible bile staining of the effluent, the fluid bilirubin level was less than 85·5 μmol/l and bacteriological culture was negative, from day 7 onwards after operation[17]. An intercostal drain was left in the pleural space. This was usually removed on day 2 after surgery or when the daily drainage volume was less than 200 ml.

After discharge, all patients were examined for evidence of recurrence: monthly using measurements of α-fetoprotein and des-carboxy prothrombin, every 2 months by ultrasonography, and every 4 months by dynamic

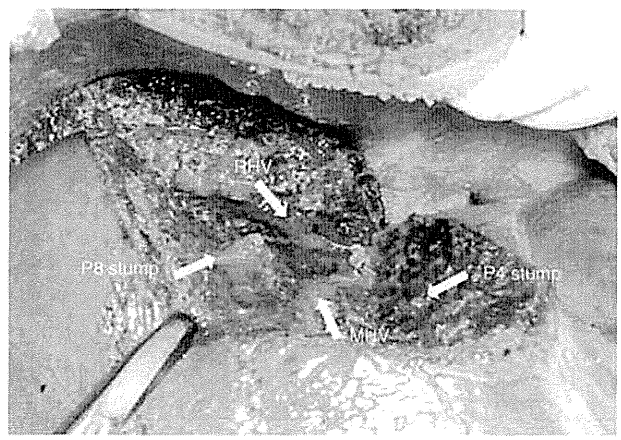


a Complete SVIII resection

b Complete SVIII resection



c SVIII subsegmentectomy



d Extended SVIII resection

Fig. 2 Dissected surface after **a**,**b** complete resection of segment VIII (SVIII), **c** subsegmentectomy of the dorsal portion of SVIII and **d** extended SVIII resection including adjacent segment IV. MHV, middle hepatic vein; RHV, right hepatic vein; P8, portal vein branch of SVIII; SB, superficial branch; V8, tributary of MHV draining SVIII; P4, portal vein branch of segment IV

computed tomography, as described previously[18]. Short-term outcomes were evaluated by maximal postoperative serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin, and by morbidity and mortality defined according to the Clavien–Dindo classification[19]. Grade I or II adverse events were defined as minor, and those of grade III or above as major. Hepatic insufficiency was defined as maximal postoperative serum bilirubin level exceeding 119·7 μmol/l[20].

For evaluation of long-term outcomes, recurrence-free and overall survival in patients who had anatomical SVIII resection were compared with those of patients who underwent macroscopically curative non-anatomical partial resection of SVIII with or without additional non-anatomical resection of other portions of the liver during

the same period. For the survival analysis, patients were censored at the date of last follow-up, designated to be no later than December 2010. Tumour stage was classified in accordance with the Liver Cancer Study Group of Japan (LCSGJ) system[21].

Statistical analysis

Continuous data are expressed as median (range), and were compared using the Mann–Whitney *U* test or Kruskal–Wallis test. Categorical data were compared by means of Pearson's χ^2 test or Fisher's exact test, as appropriate. Survival curves were prepared by the Kaplan–Meier method, and compared by the log rank test. $P < 0{\cdot}050$ was considered statistically significant for all analyses.

Results

The database included 966 patients who had undergone hepatic resection for HCC. Of these, 154 had anatomical resections involving SVIII and 122 patients had non-anatomical resections. Preoperative clinical profiles are summarized in *Table 1*. The most common aetiology of background liver disease was hepatitis C virus (HCV) infection. Three patients (2·0 per cent) in the anatomical resection group and two patients (1·6 per cent) in the non-anatomical resection group were positive for both hepatitis B surface antigen and HCV antibody, whereas 31 (20·1 per cent) and 18 patients (14·8 per cent), respectively, were negative for both. All patients were classified as Child–Pugh A or B. The median indocyanine green retention rate at 15 min (ICG-R15) was 13·6 (2·9–32·2) per cent among patients undergoing anatomical resection compared with 22·3 (5·8–67·0) per cent in patients having non-anatomical resections ($P < 0{\cdot}001$). In the anatomical resection group, the ICG-R15 value was normal (less than 10 per cent), 10–19·9 per cent and 20 per cent or more in 45 (29·2 per cent), 86 (55·8 per cent) and 23 (14·9 per cent) patients respectively.

SVIII segmentectomy or subsegmentectomy was used less often than non-anatomical resection in patients with recurrent HCC (35 of 154 *versus* 48 of 122; $P = 0{\cdot}003$). Anatomical resection was carried out for recurrence after previous hepatectomy in 23 patients (14·9 per cent), and for recurrence after percutaneous ethanol injection, radiofrequency ablation or transarterial chemoembolization in 12 (7·8 per cent).

Subsegmentectomy of SVIII was performed in 44 patients (28·6 per cent), resection of the entire segment in 52 (33·8 per cent) and extended resection in 58 (37·7 per cent). The subsegments and extended segments resected are shown in *Table 2*. Additional non-anatomical wedge resection of other liver sites owing to the presence of more than one tumour was performed in 30 patients (19·5 per cent). Five patients had other procedures in addition to the liver resection; these were subtotal gastrectomy, enucleation of gastric tumour, partial resection of the colon, videoscopy-assisted lung resection, and splenectomy with lymph node resection. The median duration of operation was 378 (147–655) min, with a median intraoperative blood loss of 705 (60–4830) ml. Blood transfusion was required in 17 patients (11·0 per cent). The median weight of the resected SVIII specimen was 120 (12–1090) g; this differed between the three types of resection (75 g for SVIII subsegmentectomy, 140 g for entire SVIII removal and 223 g for extended SVIII resection; $P < 0{\cdot}001$). The median surgical margin was 2 (0–30) mm. The tumour capsule was exposed in 42 patients (27·3 per cent), but no macroscopic tumour was left behind in any patient.

Pathological findings in the anatomical and non-anatomical resection groups are summarized in *Table 3*. Tumour diameter was generally greater in the anatomical resection group (30 (8–115) *versus* 21 (1–110) mm; $P < 0{\cdot}001$) and the maximum tumour diameter was more than 20 mm in 109 patients (70·8 per cent) in this group.

Table 1 Preoperative profiles of patients who underwent either anatomical or non-anatomical resection involving segment VIII

	Anatomical resection ($n = 154$)	Non-anatomical resection ($n = 122$)	P†
Age (years)*	64 (13–83)	68 (28–90)	0·056‡
Sex ratio (M : F)	127 : 27	94 : 28	0·263
Hepatitis B surface antigen-positive	29 (18·8)	16 (13·1)	0·202
Hepatitis C virus antibody-positive	97 (63·0)	90 (73·8)	0·057
Albumin (g/l)*	38 (27–47)	35 (26–47)	< 0·001‡
Total bilirubin (μmol/l)*	12·0 (5·1–32·5)	13·7 (5·1–32·5)	0·003‡
Prothrombin time (%)*	78·9 (50·7–100)	76·2 (50·9–100)	0·024‡
Child–Pugh grade			0·045
A	136 (88·3)	97 (79·5)	
B	18 (11·7)	25 (20·5)	
C	0 (0)	0 (0)	
ICG-R15 (%)*	13·6 (2·9–32·2)	22·3 (5·8–67·0)	< 0·001‡
α-Fetoprotein (ng/ml)*	22 (2–45 934)	22 (1–23 901)	0·987‡
Des-carboxy prothrombin (milliarbitrary units/ml)*	61 (10–48 571)	49 (10–20 400)	0·440‡
Recurrent HCC	35 (22·7)	48 (39·3)	0·003

Values in parentheses are percentages unless indicated otherwise; *values are median (range). ICG-R15, indocyanine green retention rate at 15 min; HCC, hepatocellular carcinoma. †χ^2 test, except ‡Mann–Whitney *U* test.

Table 2 Resected subsegments in subsegmentectomy and segments resected with segment VIII in extended segmentectomy

	No. of patients
Subsegmentectomy	44 (28·6)
Resected subsegment	
Dorsal	23 (52)
Ventral	17 (39)
Lateral	1 (2)
Ventral extended to dorsal	1 (2)
Lateral extended to ventral	1 (2)
Lateral extended to dorsal	1 (2)
Extended segment VIII resection	58 (37·7)
Extended segment	
VII	23 (40)
IV	18 (31)
V	7 (12)
IV + V	5 (9)
VII + I	3 (5)
IV + I	1 (2)
VII + V	1 (2)

Values in parentheses are percentages. The other 52 patients underwent complete segment VIII resection. Note that patients who underwent resection of two or more complete segments are not included.

None of the patients had lymph node or extrahepatic metastases. Among patients who underwent anatomical resection, tumour stage according to the LCSGJ staging system was I, II, III and IVA in 24 (15·6 per cent), 67 (43·5 per cent), 51 (33·1 per cent) and 12 (7·8 per cent) respectively. Although there were significant differences in the number of tumours and proportion of patients with multiple tumours between the two patient groups, the distribution of tumour stage was comparable. The background liver was cirrhotic in a smaller proportion of patients in the anatomical resection group (70 (45·5 per cent) *versus* 86 (70·5 per cent); $P < 0·001$).

Short-term outcomes

There was no postoperative death in either group. Following anatomical resection, maximum postoperative serum levels of AST, ALT and total bilirubin were 240 (78–1876) units/l, 196 (57–1347) units/l and 20·5 (6·8–94·1) μmol/l respectively. Peak bilirubin values in the range 35·9–51·3 μmol/l were measured in eight patients (5·2 per cent) and were greater than 51·3 μmol/l in only one patient. The increase in bilirubin level was always transient, and no patient suffered from hepatic insufficiency.

Minor adverse events occurred in 57 patients (37·0 per cent) after anatomical resection, consisting mainly of pleural effusion with atelectasis in 27 patients and biliary leakage in 15. Grade 3 events occurred in ten patients (6·5 per cent), mainly percutaneous drainage for intra-abdominal abscess and biliary leakage. Relaparotomy was needed in three patients (1·9 per cent), one for biliary leakage, one for remnant biliary tumour thrombus and the other for duodenal perforation. The median length of postoperative hospital stay was 17 (10–90) days.

Table 3 Pathological findings of resected tumours and background liver

	Anatomical resection ($n = 154$)	Non-anatomical resection ($n = 122$)	P†
Maximum tumour diameter (mm)*	30 (8–115)	21 (1–110)	< 0·001‡
No. of tumours*	1 (1–5)	2 (1–19)	< 0·001‡
Patients with multiple (≥ 2) tumours	53 (34·4)	68 (55·7)	< 0·001
Portal vein invasion	31 (20·1)	20 (16·4)	0·427
Hepatic vein invasion	5 (3·2)	6 (4·9)	0·481
Biliary invasion	2 (1·3)	3 (2·5)	0·658
Differentiation grade			0·128§
Necrosis	0 (0)	4 (3·3)	
Well	30 (19·5)	20 (16·4)	
Moderate	103 (66·9)	92 (75·4)	
Poor	17 (11·0)	6 (4·9)	
Combined	4 (2·6)	0 (0)	
Background liver			< 0·001
Normal	8 (5·2)	2 (1·6)	
Chronic hepatitis or fibrosis	76 (49·4)	34 (27·9)	
Cirrhosis	70 (45·5)	86 (70·5)	
Tumour stage defined by pathological findings			0·922
I	24 (15·6)	16 (13·1)	
II	67 (43·5)	57 (46·7)	
III	51 (33·1)	39 (32·0)	
IVA	12 (7·8)	10 (8·2)	
IVB	0 (0)	0 (0)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †χ^2 test, except ‡Mann–Whitney U test. §Excluding necrosis and combined subgroups.

Long-term survival

Median follow-up for patients who underwent anatomical and non-anatomical SVIII resection was 66 and 49 months respectively. Survival curves after anatomical and non-anatomical resection are compared in *Fig. 3*. Cumulative recurrence-free and overall survival rates were significantly higher after anatomical resection ($P = 0·036$ and $P < 0·001$ respectively).

Five-year recurrence-free survival rates after anatomical resection for patients with stage I, II, III and IVA HCC were 42, 33, 21 and 8 per cent respectively. Corresponding 5-year overall survival rates were 95, 78, 80 and 56 per cent.

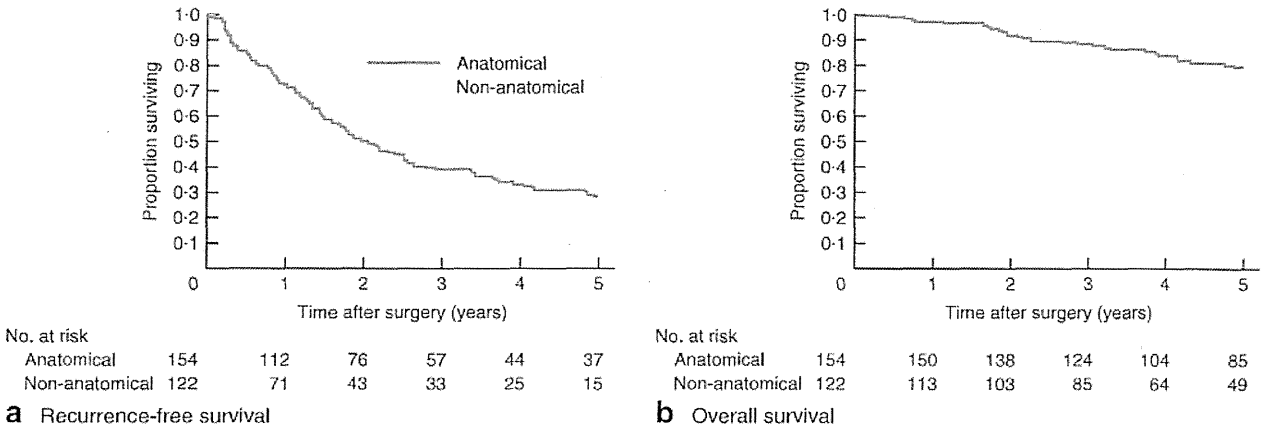


Fig. 3 a Recurrence-free and b overall survival curves for patients who underwent anatomical and non-anatomical resection of segment VIII for primary hepatocellular carcinoma. a $P = 0{\cdot}036$, b $P < 0{\cdot}001$ (log rank test)

Among the subgroup of patients with solitary HCC, the cumulative 1-, 3- and 5-year recurrence-free survival rates in the anatomical group (101 patients) were 78·0, 47·4 and 33·7 per cent, compared with 68, 32 and 19 per cent respectively among 54 patients in the non-anatomical group ($P = 0{\cdot}034$). The corresponding overall survival rates were 97·0, 88·8 and 80·8 per cent in the anatomical group, and 91, 79 and 63 per cent in the non-anatomical group ($P = 0{\cdot}005$).

Discussion

The present study has confirmed the feasibility of SVIII resection in a large patient cohort. Operating time was long, reflecting the complexity of the procedure, although blood transfusion was needed in only 11·0 per cent of patients. Although most patients had chronic hepatitis, liver fibrosis or cirrhosis, postoperative increases in serum bilirubin level were minor and no patient developed hepatic insufficiency. The incidence of biliary fistula (15 of 154, 9·7 per cent) was comparable to that in a previous study of over 1000 patients undergoing hepatic resection at this institution[17]. The present series has also demonstrated the feasibility of this procedure for advanced-stage and recurrent HCC.

Right hepatectomy or extended right hepatectomy is often used for large or deeply located HCCs in SVIII, but these major resections may not be tolerated by patients with poor liver reserve. The local criterion for right hepatectomy is ICG-R15 less than 10 per cent[22]; in the present series 109 patients (70·8 per cent) undergoing anatomical resection had an ICG-R15 value of 10 per cent or more and were therefore unsuitable candidates for (extended) right hepatectomy. The present results suggest that these patients with impaired liver function, in whom right hemihepatectomy cannot be performed safely, can benefit from anatomical SVIII resection with the hope of long-term survival. Although liver transplantation would be an option for patients satisfying the Milan criteria[23], this is usually restricted to patients with decompensated cirrhosis. Previous studies have reported comparable 5-year survival rates after hepatic resection and liver transplantation (70–78 per cent) in patients with Child–Pugh A cirrhosis[24,25], and a similar rate (79·6 per cent) was achieved in the present series of SVIII resections. Anatomical SVIII resection therefore seems an acceptable option as a first-choice treatment for such patients.

Central hepatectomy for tumours located in segment IV, segment V (SV) or SVIII was proposed by McBride and Wallace[26] in 1972. The procedure has never gained great popularity because of its technical complexity[27]. Previous studies of SVIII resection have approached the Glissonian sheath from the hepatic hilum[12,13]. The right paramedian Glissonian branch is encircled via an extrahepatic approach exposing the bifurcation between SVIII and SV. The SVIII Glissonian pedicles are then divided[13]. However, it is rare to see the SV portal vein branch as a single main trunk. More often there are three to five branches originating from the right paramedian trunk or more peripheral SVIII portal branches[9]. The branching site of the ventral branch for SV and SVIII is deep within the hepatic parenchyma, so approaching the ventral branch of SVIII from the hepatic hilum is impossible. Hu and co-workers[13] reported that isolation of the SVIII Glissonian pedicle by this approach was not possible in four of 18 patients. Torzilli *et al.*[28–30] proposed ultrasound-guided finger countercompression as

a simple but valid technique to identify the discoloured area, and applied this method to right paramedian sectorectomy or segmentectomy including SVIII. They also reported that the ventral and dorsal branches of SVIII could not be compressed separately, but this drawback is overcome by use of the dye injection technique[30]. The site to be resected is easily recognized by this method and, if puncture of the tumour-bearing portal branch is found to be difficult owing to the location of the tumour, the counterstaining identification technique is useful[15].

The present study has several weaknesses. Only patients who actually underwent anatomical resection of SVIII were selected. The survival analyses must be interpreted with caution, specifically the comparison of patients who underwent anatomical *versus* non-anatomical resection, because the clinical and pathological profiles were different. The background state of the liver was generally worse, the patients had less functional reserve and more patients had multiple tumours in the non-anatomical resection group. Anatomical resection did, however, yield better overall survival outcomes than non-anatomical resection for tumours with a comparable distribution of LCSGJ stages. The survival rates in the anatomical resection group in the present study were also better than those in a nationwide survey that included both anatomical and non-anatomical resections, in which the 5-year survival rates after hepatectomy for stage I, II, III and IVA disease were 71·3, 60·1, 41·9 and 22·9 per cent respectively[31].

Quality control is important in SVIII surgery. The resection can be described as anatomical only when the anatomical landmarks of the hepatic veins and the portal pedicles of segments have been defined clearly, and marked on the raw surface of the liver. SVIII segmentectomy and subsegmentectomy are technically demanding, but can be performed safely. Long-term survival can be obtained in appropriately selected patients, irrespective of whether the HCC is recurrent, advanced or associated with impaired liver function.

Acknowledgements

The authors express their appreciation to Dr Takeshi Takamoto for his contribution in improving the quality of *Figs 1* and *2a*. This work was supported by Grant-in-Aid for Young Scientists (B) (no. 23791518) from the Ministry of Education, Culture, Sports, Science and Technology. Y.K. had full access to all of the data in the study, and takes responsibility for its integrity and the accuracy of the data analysis.

Disclosure: The authors declare no conflict of interest.

References

1 Makuuchi M, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. *Surg Gynecol Obstet* 1985; **161**: 346–350.
2 Nakashima T, Kojiro M. Pathologic characteristics of hepatocellular carcinoma. *Semin Liver Dis* 1986; **6**: 259–266.
3 Imamura H, Matsuyama Y, Miyagawa Y, Ishida K, Shimada R, Miyagawa S *et al.* Prognostic significance of anatomical resection and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma. *Br J Surg* 1999; **86**: 1032–1038.
4 Yamamoto M, Takasaki K, Ohtsubo T, Katsuragawa H, Fukuda C, Katagiri S. Effectiveness of systematized hepatectomy with Glisson's pedicle transection at the hepatic hilus for small nodular hepatocellular carcinoma: retrospective analysis. *Surgery* 2001; **130**: 443–448.
5 Hasegawa K, Kokudo N, Imamura H, Matsuyama Y, Aoki T, Minagawa M *et al.* Prognostic impact of anatomic resection for hepatocellular carcinoma. *Ann Surg* 2005; **242**: 252–259.
6 Eguchi S, Kanematsu T, Arii S, Okazaki M, Okita K, Omata M *et al.* Comparison of the outcomes between an anatomical subsegmentectomy and a non-anatomical minor hepatectomy for single hepatocellular carcinomas based on a Japanese nationwide survey. *Surgery* 2008; **143**: 469–475.
7 Kamiyama T, Nakanishi K, Yokoo H, Kamachi H, Matsushita M, Todo S. The impact of anatomical resection for hepatocellular carcinoma that meets the Milan criteria. *J Surg Oncol* 2010; **101**: 54–60.
8 Shindoh J, Mise Y, Satou S, Sugawara Y, Kokudo N. The intersegmental plane of the liver is not always flat – tricks for anatomical liver resection. *Ann Surg* 2010; **251**: 917–922.
9 Couinaud C. *Le Foie: Études Anatomiques et Chirugicales.* Masson: Paris, 1957.
10 Makuuchi M, Hashikura Y, Kawasaki S, Tan D, Kosuge T, Takayama T. Personal experience of right anterior segmentectomy (segments V and VIII) for hepatic malignancies. *Surgery* 1993; **114**: 52–58.
11 Billingsley KG, Jarnagin WR, Fong Y, Blumgart LH. Segment-oriented hepatic resection in the management of malignant neoplasms of the liver. *J Am Coll Surg* 1998; **187**: 471–481.
12 Mazziotti A, Maeda A, Ercolani G, Cescon M, Grazi GL, Pierangeli F. Isolated resection of segment 8 for liver tumors: a new approach for anatomical segmentectomy. *Arch Surg* 2000; **135**: 1224–1229.
13 Hu JX, Dai WD, Miao XY, Zhong DW, Huang SF, Wen Y *et al.* Anatomic resection of segment VIII of liver for hepatocellular carcinoma in cirrhotic patients based on an intrahepatic Glissonian approach. *Surgery* 2009; **146**: 854–860.
14 Ishizawa T, Kokudo N, Makuuchi M. Right hepatectomy for hepatocellular carcinoma: is the anterior approach superior to the conventional approach? *Ann Surg* 2008; **247**: 390–391.
15 Takayama T, Makuuchi M, Watanabe K, Kosuge T, Takayasu K, Yamazaki S *et al.* A new method for mapping

hepatic subsegment: counterstaining identification technique. *Surgery* 1991; **109**: 226–229.
16 Cunningham JD, Fong Y, Shriver C, Melendez J, Marx WL, Blumgart LH. One hundred consecutive hepatic resections. Blood loss, transfusion, and operative technique. *Arch Surg* 1994; **129**: 1050–1056.
17 Kyoden Y, Imamura H, Sano K, Beck Y, Sugawara Y, Kokudo N *et al.* Value of prophylactic abdominal drainage in 1269 consecutive cases of elective liver resection. *J Hepatobiliary Pancreat Sci* 2010; **17**: 186–192.
18 Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Yamamoto J, Shimada K *et al.* Early hepatocellular carcinoma as an entity with a high rate of surgical cure. *Hepatology* 1998; **28**: 1241–1246.
19 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD *et al.* The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; **250**: 187–196.
20 Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S *et al.* Hepatic insufficiency and mortality in 1059 noncirrhotic patients undergoing major hepatectomy. *J Am Coll Surg* 2007; **204**: 854–862.
21 Liver Cancer Study Group of Japan. *General Rules for the Clinical and Pathological Study of Primary Liver Cancer* (2nd edn). Kanehara: Tokyo, 2003.
22 Miyagawa S, Makuuchi M, Kawasaki S, Kakazu T. Criteria for safe hepatic resection. *Am J Surg* 1995; **169**: 589–594.
23 Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693–699.
24 Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg* 2002; **235**: 373–382.
25 Margarit C, Escartin A, Castells L, Vargas V, Allende E, Bilbao I. Resection for hepatocellular carcinoma is a good option in Child–Turcotte–Pugh class A patients with cirrhosis who are eligible for liver transplantation. *Liver Transpl* 2005; **11**: 1242–1251.
26 McBride CM, Wallace S. Cancer of the right lobe of the liver: a variety of operative procedures. *Arch Surg* 1972; **105**: 289–296.
27 Machado MA, Herman P, Machado MC. Intrahepatic Glissonian approach for pedicle control during anatomic mesohepatectomy. *Surgery* 2007; **141**: 533–537.
28 Torzilli G, Makuuchi M. Ultrasound-guided finger compression in liver subsegmentectomy for hepatocellular carcinoma. *Surg Endosc* 2004; **18**: 136–139.
29 Torzilli G, Procopio F, Palmisano A, Cimino M, Del Fabbro D, Donadon M *et al.* New technique for defining the right anterior section intraoperatively using ultrasound-guided finger counter-compression. *J Am Coll Surg* 2009; **209**: e8–e11.
30 Torzilli G, Procopio F, Cimino M, Del Fabbro D, Palmisano A, Donadon M *et al.* Anatomical segmental and subsegmental resection of the liver for hepatocellular carcinoma: a new approach by means of ultrasound-guided vessel compression. *Ann Surg* 2010; **251**: 229–235.
31 Ikai I, Arii S, Okazaki M, Okita K, Omata M, Kojiro M *et al.* Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. *Hepatol Res* 2007; **37**: 676–691.