ウイルス肝炎検診と病診連携の重要性と進めかた

正木尚彦
国立国際医療研究センター 肝炎・免疫研究センター 肝炎情報センター／まさき・なおひこ

はじめに

厚生労働省の推定(2010年)によると，現在わが国には約350万人の肝炎ウイルスキャリアが存在する．その内訳は，B型肝炎ウイルスキャリアが約110～140万人，C型肝炎ウイルスキャリアが約190～230万人であるが，実際慢性肝炎以上に進行している患者数はB型肝炎で約7万人(慢性肝炎5万人，肝硬変・肝癌2万人)，C型肝炎で約37万人(慢性肝炎28万人，肝硬変・肝癌9万人)と見積もられており，それ以外の人は無症候性キャリアにとどまっているか，あるいは，肝炎ウイルスに感染していることすら自覚していないものと考えられる．いうまでもなく，ウイルス肝炎検診の主目的はこれら感染未自覚者を新たに掘り起こすことである．

肝炎総合対策のこれまでの概要

これまで国は数々の肝炎対策を打ち出してきた(表1)．その中でも特記すべき施策として，平成14年から18年までの5年間全国で行われた節目検診，節目外検診があり，肝炎ウイルス検査を無料で行うことにより，潜在的患者の掘り起こしを全国規模で展開した．その検診結果は厚生労働省による報道発表資料(http://www.mhlw.go.jp/houdou/2007/10/h1003-1.html)として公開されているが，この5年間にC型肝炎ウイルス検診受診者はのべ8,634,509人に達し，うち99,950人(1.16%)が「現在，C型肝炎ウイルスに感染している可能性がきわめて高い」と判定され，一方，B型肝炎ウイルス検診受診者はのべ8,704,587人でうち100,983人(1.16%)が「陽性」と判定された．しかし，その結果が検診受診者に通知されたにもかかわらず，厳密な意味での二次精検を目的とした医療機関への受診率は約40%にとどまったものと推定されており，インターフェロンなどの抗ウイルス療法まで受けた患者数はさらに少なく，検診

表1 これまでの国の肝炎対策

・昭和39年	「献血の推進について」閣議決定
・昭和47年	献血血液に対してHBs抗原検査導入
・昭和61年	B型慢性肝炎に対するインターフェロンの保険適用
・平成4年	C型慢性活動性肝炎に対するインターフェロンの保険適用(初回)
・平成13年	「肝炎に関する有識者会議」報告書取りまとめ
・平成14年	「C型肝炎緊急総合対策」を開始 保健所，老健事業，政管健保，健保組合，職域の検診に肝炎ウイルス検査を導入 (～平成18年)節目検診(老人保健事業)・節目外検診
・平成17年	「C型肝炎対策等に関する専門家会議」
・平成18年	「C型肝炎対策等の一層の推進について」取りまとめ 肝炎ウイルス検査の実施，検査体制の強化，診療体制の整備
・平成19年	「全国C型肝炎診療懇談会報告書―都道府県における肝炎検査後肝疾患診療体制に関するガイドライン―」 与党PT「新しい肝炎総合対策の推進について」取りまとめ 肝炎ウイルス検査の促進，インターフェロン治療のための環境整備，研究の推進
・平成20年1月	「薬害肝炎被害者救済特別措置法」の成立
・平成20年4月～	「B型・C型慢性肝炎に対するインターフェロン治療費助成の開始」
・平成21年11月	「肝炎対策基本法」の成立
・平成22年4月～	「B型・C型慢性肝疾患に対する医療費助成の拡充」

0910-1551/11/￥100/頁/JCOPY

◎平成14年度から行われた節目(外)検診における二次精検受診率は約40%であった.
○現在,全国47都道府県に70肝疾患診療連携拠点病院が指定されている.
◎各自治体では二次医療圏ごとに専門医療機関を指定している.

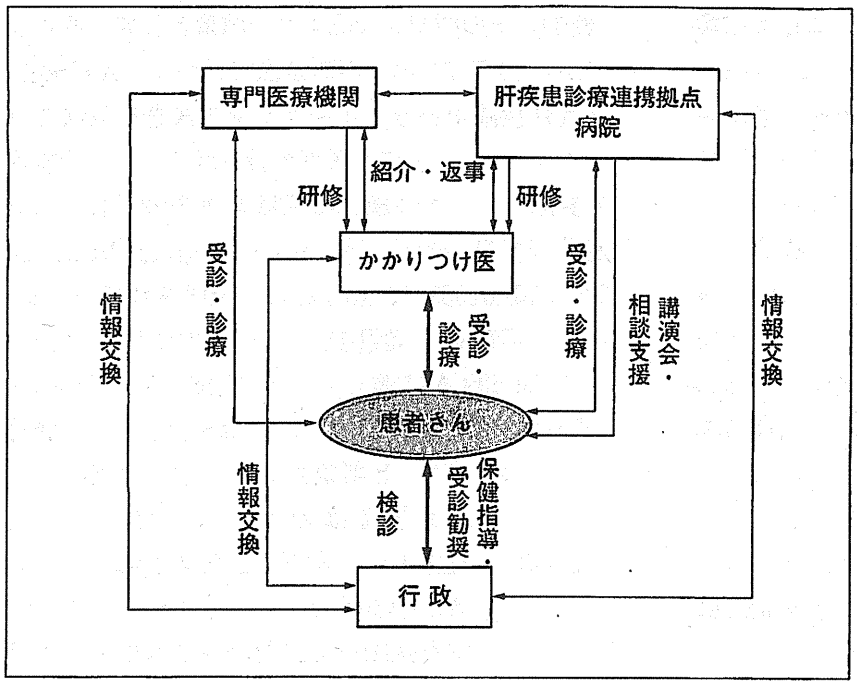


図1 都道府県における肝疾患診療ネットワーク
(都道府県における肝炎検査後肝疾患診療体制に関するガイドライン:2007年1月,厚生労働省)

表2 肝疾患診療連携拠点病院と専門医療機関が満たすべき資格要件

1)肝疾患診療連携拠点病院
① 肝疾患に係る一般的な医療情報の提供
② 都道府県内の専門医療機関などに関する情報の収集や提供
③ 医療従事者や地域住民を対象とした研修会や講演会の開催や肝疾患に関する相談支援
④ 肝疾患に関する専門医療機関と協議の場の設定
2)専門医療機関
① 専門的な知識を持つ医師による診断と治療方針の決定
② インターフェロンなどの抗ウイルス療法
③ 肝癌の高危険群の同定と早期診断

の効果は当初期待されたほどではなかった.さらに,解決されるべき課題として,肝疾患診療体制が全国において必ずしも同等のレベルではないという現状があった.これら諸問題に対処するために,平成19年1月「都道府県における肝炎検査後肝疾患診療体制に関するガイドライン」が厚生労働省により取りまとめられ,各都道府県においてかかりつけ医と患者を支援するネットワークを行政側,医療側含めて構築しようとする施策が打ち出された.「かかりつけ医と患者」は診療の最小単位であるが,かかりつけ医は必ずしも肝疾患診療に精通しているわけではない.これを支援するために,本ガイドラインでは,各都道府県に原則1ヵ所の肝疾患診療連携拠点病院を設置するとともに,二次医療圏ごとに専門医療機関を指定し,さらに行政側も参加するという診療ネットワークの構築を提言した(図1).これらの施設指定を受けるために必要とされる資格要件を表2に示す.特に,肝疾患診療連携拠点病院の資格要件を満たすためには複数名の専門医(特に肝臓専門医)が常勤する基幹病院であることが必然的に求められる.平成23年4月現在,全国47都道府県に70施設が肝疾患診療連携拠点病院の指定を受けているが

◎肝炎情報センターは都道府県における肝疾患診療ネットワークを支援する組織である.
◎今後の肝炎総合対策は肝炎対策基本法に基づいて決定される.

(国立国際医療研究センター肝炎情報センターホームページURL：http://www.ncgm.go.jp/center/index.html)，その内訳をみると，国立大学法人が34病院，公立・私立大学が24病院，その他(国立病院機構，県立病院，一般病院など)が12病院となっている．なお，肝疾患患者数が多く広域に分布しているなどの理由で，複数の拠点病院が指定されている自治体もある．さらに，都道府県単位の活動を支援するシステムとして，国立国際医療センター(現，国立国際医療研究センター)に平成20年11月肝炎情報センターが設置された(千葉県市川市)．その果たすべき役割として三つのミッションがある[1]．第一に「インターネットなどによる最新情報提供」であり，平成20年12月には肝疾患医療に関する診療ガイドライン，肝炎診療をめぐる国内外の情報などを「一般向け，医療従事者向け，および，肝臓専門医向け」に発信するためのホームページを立ち上げた．第二に「拠点病院間での情報共有を支援する」ことで，肝疾患診療連携拠点病院で構成する連絡協議会を年に2回開催し，拠点病院事業における問題点の解決を目指した話し合いを行っている．第三に，肝疾患診療連携拠点病院などに勤務する医療従事者(医師，看護師，相談員ほか)を対象とした「研修」の企画・立案・推進を行っている．

肝炎検診の重要性◎

平成22年1月に施行された肝炎対策基本法は肝炎対策に関してきわめて包括的な内容となっている．これを具体的施策として実現するために，平成22年6月から5回にわたって患者団体代表者ほか各界の有識者を交えた肝炎対策推進協議会が開催され，その肉づけが図られた．その結果が「肝炎対策の推進に関する基本的な指針[2]」としてまとめられている．その第3には「肝炎検査の実施体制及び検査能力の向上に関する事項」として取り上げられており，① 今後，肝炎ウイルス検査の受検者数把握のための調査・研究が必要であること，② 国民に対して肝炎に関する正しい知識の普及啓発，③ 肝炎検診の効果についての検証，さらに，④ 肝炎医療に携わる者に対して肝炎ウイルス検査に関する知見修得のための研修の機会を確保することなどを求めている．このように肝炎検診の重要性が強調される所以は，「一生に一度」肝炎検診を受けさえすれば肝炎ウイルスキャリアであることが判明し，そのことによって慢性肝炎から肝硬変・肝癌へ進展する患者の囲い込みが可能となるからである．筆者が所属する病院において2001～2006年の6年間に入院した544例の肝硬変患者の成因を調査したところ[3]，B型肝炎9.4%，C型肝炎69.8%，B＋C型肝炎2.6%とウイルス肝炎関連が80%以上を占め，特にC型肝炎関連が70%以上であった．さらに，この期間の肝癌371例の成因では，B型肝炎10.5%，C型肝炎75.5%，B＋C型肝炎3.0%と肝癌の90%は肝炎ウイルス感染が原因で，特にC型肝炎関連が75%を占めていた(図2)．したがって，肝疾患関連死を抑制するためには，肝炎ウイルス感染の有無を早期に把握することがきわめて重要であることは容易に理解されよう．

肝炎検診の実際●

肝炎検診を精密検査受診につなげ，さらには根本的な治療である抗ウイルス療法の施行率を上げることにより肝硬変・肝癌への進展を抑制せねばならない．その作業過程において，いかに地道な労力が要求されるものか，行政はもちろん病診連携の関与がいかに重要であるかについて，石川県における具体的事例[4]を紹介したい．

肝炎ウイルス検診が開始された平成14年度か

◎わが国における肝硬変，肝癌の成因の80～90%は肝炎ウイルス感染である．
○肝臓専門医数が少なく，かつ，偏在している地域では自治体全体の精検レベルの底上げが必要となる．

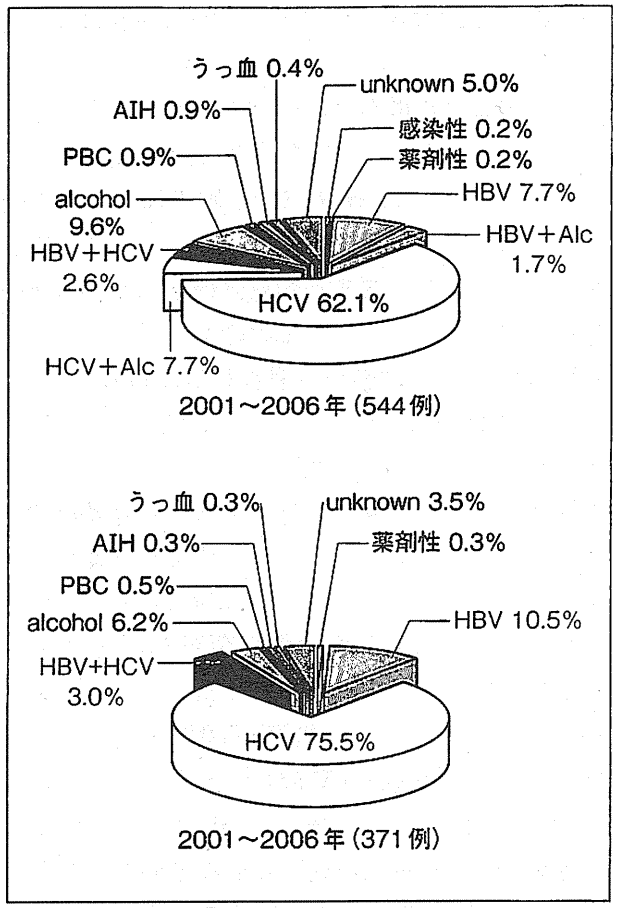


図2　肝硬変(上段)・肝癌(下段)の成因
(国立国際医療研究センター病院；2001～2006年)

表3　石川県肝炎ウイルス検診の7本の柱

1) 検診へ行政が関与することの通知と同意
2) 精密検査を全県下で統一
3) 住民，検診・精密検査担当医に対する手引きの作成
4) 精密検査での画像検査を義務づけ
5) 全症例に対する事例検討会の開催
6) 前年度陽性者に対する保健師による事後調査
7) 保健師などを対象とした研修会の開催

(文献4)より引用)

ら石川県では，県健康福祉部，保健所などの行政，検診を担当する医師会，学識経験者，検査センターをメンバーとして肝炎協議会を設置し，肝炎診療体制の確立に取り組んできた．石川県では消化器肝臓専門医が常勤する総合病院が都市部に集中しているため，精密検査受診率の低下が予想された．これを回避するために，精密検査を行う医療機関を敢えて指定せずに，県全体の精検レベルの底上げをするという画期的な方針をとった．具体的な7本の柱を表3に示す．初年度には画像検査未施行例11%，「追跡調査の必要なし」との診断例が4%存在したが，① 診断名の改訂(「異常なし」を「無症候性キャリア」へ変更)，② 1例ごとの事例検討会において画像検査の重要性を強調，③ 診断の手引きの作成などにより著明な改善を認めたという．特に，事例検討会については，その後石川県の肝疾患診療連携拠点病院に指定されている金沢大学医学部附属病院消化器内科スタッフの精力的な取り組みの賜物であると聞いている．その結果，インターフェロン施行率は平成14年度から18年度の5年間で4.6% → 7.9% → 23.5% → 35.3% → 31.0%と有意に上昇したことが報告されている．しかし，精検受診率が南加賀地方で低いこと，さらに，全地域において男性，特に65歳未満で低いことが問題点として指摘されている(図3)．このような疫学的解析を行うことによってはじめて，受診勧奨を推進すべき対象が明らかとなると同時に，行政に対する施策提言が可能になるものと考えられる．

おわりに

平成23年度政府予算では肝炎総合対策に238億円が割り当てられており，うち，肝炎ウイルス検査の促進分が55億円と前年度に比し倍増している．特定感染症検査等事業として，保健所における肝炎ウイルス検査の受診勧奨と検査体制の整備が図られるが，特に，出張型検診の実施に1億円が計上されている点は新たな試みとして注目に値する．さらに健康増進事業として，市町村にお

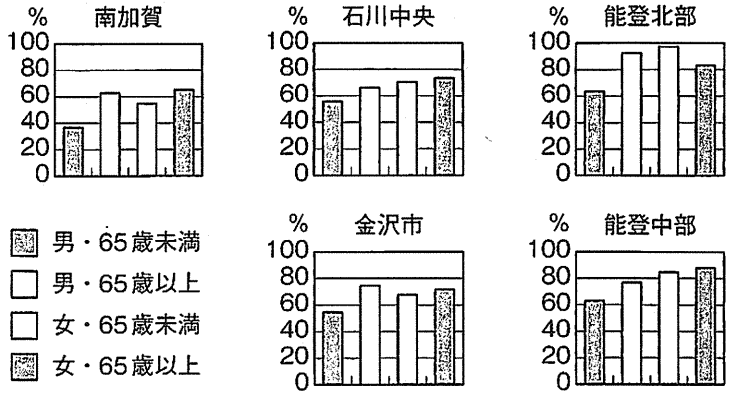
◎IFN治療を効率的に推進するためには，地域ごとの特性を考慮した肝炎対策の立案と運用が必要である．

◎ウイルス肝炎検診の推進には肝疾患診療ネットワークの活用が有効である．

図3　石川県肝炎ウイルス検診における精密検査受診状況(平成14～18年度分)
金沢大学附属病院消化器内科　酒井明人先生のご厚意による
(文献4)より引用)

精検受診率

	65歳未満	65歳以上	計(性別)
男性	70/131 (53.4%)	216/292 (74.0%)	286/423 (67.6%)
女性	205/285 (71.9%)	418/557 (75.0%)	623/842 (74.0%)
計	275/416 (66.1%)	634/849 (74.7%)	909/1,265 (72.0%)



ける肝炎ウイルス検診等(節目検診)の実施に32.3億円が計上されており，検査未受検者への受検促進の一層の強化が図られるものと期待される．これらの施策をわが国全体に浸透させるためには，これまで構築されてきた肝疾患診療ネットワークが有効に活用されるべきである．

文　献

1) 正木尚彦：肝炎情報センターの役割．特集　肝疾患の地域医療連携．肝胆膵 61 (5)：721-729, 2010
2) 肝炎対策の推進に関する基本的な指針．http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/hourei.html
3) 長沖祐子ほか：肝硬変の予後に関する実態調査—1990～1997年と2001～2006年との比較—．肝硬変の成因別実態2008，恩地森一ほか編，中外医学社，東京，p.116-120，2008
4) 酒井明人ほか：石川県の取り組み．特集　肝疾患の地域医療連携．肝胆膵 61 (5)：753-761，2010

Original article

Recurrence-free survival more than 10 years after liver resection for hepatocellular carcinoma

S. Eguchi[1], T. Kanematsu[1], S. Arii[2], M. Omata[3], M. Kudo[4], M. Sakamoto[5], K. Takayasu[6], M. Makuuchi[7], Y. Matsuyama[8] and M. Monden[9] for the Liver Cancer Study Group of Japan

[1]Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, [2]Department of Hepato-Biliary-Pancreatic Surgery, Tokyo Medical and Dental University, Graduate School of Medicine, [3]Department of Gastroenterology, Yamanashi Prefectural Central Hospital, Yamanashi, and [4]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kinki University School of Medicine, [5]Department of Pathology, University of Keio, [6]Department of Diagnostic Radiology, National Cancer Centre Hospital, [7]Department of Surgery, Japanese Red Cross Medical Centre, and [8]Department of Biostatistics, School of Health Sciences and Nursing, University of Tokyo, Tokyo, and [9]Department of Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

Correspondence to: Dr S. Eguchi, Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan (e-mail: sueguchi@nagasaki-u.ac.jp)

Background: High recurrence rates after liver resection with curative intent for hepatocellular carcinoma (HCC) remain a problem. The characterization of long-term survivors without recurrence after liver resection may help improve the therapeutic strategy for HCC.

Methods: A nationwide Japanese database was used to analyse 20 811 patients with HCC who underwent liver resection with curative intent.

Results: The 10-year recurrence-free survival rate after liver resection for HCC with curative intent was 22·4 per cent. Some 281 patients were recurrence-free after more than 10 years. The HCCs measured less than 5 cm in 83·2 per cent, a single lesion was present in 91·7 per cent, and a simple nodular macroscopic appearance was found in 73·3 per cent of these patients; histologically, most HCCs showed no vascular invasion or intrahepatic metastases. Multivariable analysis revealed tumour differentiation as the strongest predictor of death from recurrent HCC within 5 years.

Conclusion: Long-term recurrence-free survival is possible after liver resection for HCC, particularly in patients with a single lesion measuring less than 5 cm with a simple nodular appearance and low tumour marker levels.

Paper accepted 16 November 2010
Published online 25 January 2011 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.7393

Introduction

Hepatocellular carcinoma (HCC) is a common malignancy in Japan, and often develops in virus-infected cirrhotic liver[1]. The high incidence of recurrence following treatment renders it difficult to cure this disease completely. On the other hand, long-term survival has been reported even beyond 10 years, with or without recurrence, after potentially curative liver resection[2–4]. However, there have been few reports regarding recurrence-free survival (RFS) for more than 10 years after liver resection with curative intent for HCC[5].

The Liver Cancer Study Group of Japan (LCSGJ) has conducted a nationwide survey of patients with primary liver carcinoma since 1969 to evaluate the clinicopathological characteristics and outcomes of these patients[6]. The large-scale registration system of the LCSGJ was used here to evaluate the characteristics of patients who survived without recurrence for at least 10 years after curative liver resection. These patients were compared with patients who died from recurrent HCC within 5 years in order to gain insight into the demography and biological behaviour of HCCs. In addition, such data might be important in determining follow-up strategies, and encouraging patients to undergo treatment, including surgical resection.

Methods

A nationwide follow-up survey of all patients with primary HCC was conducted by the LCSGJ. All patients with

primary malignant liver tumours diagnosed by imaging, preoperative clinical data, and/or histopathological studies at approximately 800 institutions in Japan were registered and followed prospectively every 2 years.

At the time of this analysis, the LCSGJ database contained 142 900 patients diagnosed with a liver tumour and 130 748 patients ultimately diagnosed with HCC. The present study enrolled 20 811 patients with HCC who had undergone liver resection with curative intent before 1993, and were registered in the JCSGJ database between 1988 and 2003 (from the 10th to the 17th surveillance). The indications for hepatic resection and operative procedures were based on both anatomical location of the tumour and liver function. Follow-up ended on 31 December 2003.

Patients who survived more than 10 years without recurrence of HCC and those who died from recurrent HCC within 5 years of liver resection were identified. Patients were further examined according to the degree of background liver damage, as advocated by the JCSGJ as an alternative to the Child–Pugh score (*Table 1*)[7]. The serological presence of hepatitis B antigen was considered evidence of hepatitis B infection, and that of hepatitis C antibody as an indicator of hepatitis C infection. Hepatic resections were classified according to the terminology of the Liver Cancer Study Group of Japan[7]. The macroscopic appearance of HCC was classified into six types: type 1 (simple nodular type), type 2 (simple nodular type with extranodular growth), type 3 (confluent multinodular type), type 4 (multinodular type), type 5 (others, including infiltrative, mass and diffuse types) and unknown[6,8]. Serum levels of α-fetoprotein (AFP) and des-γ-carboxyprothrombin (DCP) were measured as tumour markers. Microscopic portal vein invasion was defined as the presence of tumour emboli within the portal vein. Intrahepatic metastasis was classified into four groups: 0 (no intrahepatic metastasis), 1 (intrahepatic metastasis to the segment in which the main tumour is located), 2 (intrahepatic metastases to two segments), 3 (intrahepatic metastases of the three or four segments). Non-cancerous liver was classified microscopically as normal, or as having chronic hepatitis, fibrosis or cirrhosis.

Hepatic recurrence of HCC was diagnosed at each centre by ultrasonography and/or dynamic computed tomography. Distant metastases were diagnosed by computed tomography (lung) and scintigraphy (bone)[9].

Table 1 Degree of liver damage according to the Liver Cancer Study Group of Japan

	Degree of liver damage		
	A	B	C
Ascites	None	Controllable	Uncontrollable
Serum bilirubin (mg/dl)	> 2·0	2·0–3·0	< 3·0
Serum albumin (g/dl)	> 3·5	3·0–3·5	< 3·0
ICG-R15 (%)	< 15	15–40	> 40
Prothrombin activity (%)	> 80	50–80	< 50

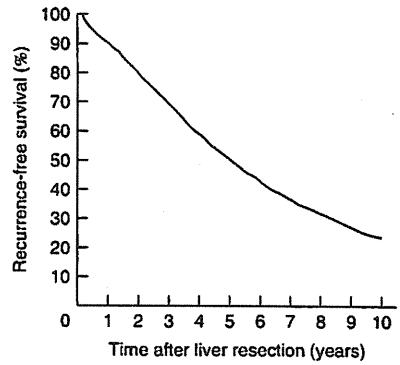
The degree of liver damage was classified as grades A, B and C based on the highest grade containing at least two of five items. Then, if two or more items scoring the same grade occur in the three grades, the higher grade is adopted as the degree of liver damage. ICG-R15, indocyanine green retention rate at 15 min.

Statistical analysis

Continuous data were expressed as mean(s.d.) and analysed by means of Student's t test. The χ^2 test was used to analyse the distribution of nominal variables, and the Wilcoxon rank sum test for analysis of ordered categorical variables. RFS curves were generated by the Kaplan–Meier method. A multivariable logistic regression model was used to investigate odds ratios. $P < 0{\cdot}050$ was considered statistically significant.

Results

Stratification according to the time of recurrence identified 281 patients who survived more than 10 years without recurrence of HCC (10-year RFS group), whereas 918 patients died from recurrent HCC within 5 years of liver resection. Median follow-up was 11·2 and 0·9 years respectively. The RFS rate at 10 years was 22·4 per cent after liver resection with curative intent (*Fig. 1*). Clinical



No. at risk	4977	3399	2253	1423	572	39
Cumulative recurrences	0	543	1047	1349	1533	1704
Cumulative deaths without recurrence	0	471	812	1110	1275	1339

Fig. 1 Recurrence-free survival after liver resection with curative intent for hepatocellular carcinoma

Table 2 Comparison of clinical data between recurrence-free survivors at 10 years and patients who died from recurrent hepatocellular carcinoma within 5 years

	10-year RFS ($n = 281$)	Died within 5 years ($n = 918$)	P§
Age (years)*	57·5(9·4)	60·8(8·5)†	< 0·001¶
Sex ratio (M : F)	219 : 62	755 : 162‡	0·115
Liver damage grade			< 0·001
A	212 (79·1)	553 (65·1)	
B	52 (19·4)	257 (30·3)	
C	4 (1·5)	39 (4·6)	
Unknown	13	69	
HBsAg-positive	82 of 255 (32·2)	179 of 812 (22·0)	< 0·001
HCV Ab-positive	103 of 198 (52·0)	356 of 474 (75·1)	< 0·001
AFP (ng/ml)			< 0·001#
< 20	140 (50·9)	272 (30·8)	
≥ 20 to < 400	73 (26·5)	345 (39·1)	
≥ 400 to < 1000	15 (5·5)	79 (9·0)	
≥ 1000	47 (17·1)	186 (21·1)	
Unknown	6	36	
DCP (mAU/ml)			< 0·001#
< 40	118 (69·4)	222 (50·5)	
≥ 40 to < 500	16 (9·4)	83 (18·9)	
≥ 500 to < 1000	36 (21·2)	135 (30·7)	
≥ 1000	0 (0)	0 (0)	
Unknown	111	478	
Operative method			0·270
> 1 segment	135 (48·2)	410 (44·9)	
Subsegment	71 (25·4)	216 (23·6)	
< 1 subsegment	74 (26·4)	288 (31·5)	
Unknown	1	4	

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). Data missing for †six and ‡one patients. RFS, recurrence-free survival; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C antibody; AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin. §χ^2 test, except ¶Student's t test and #Wilcoxon rank sum test.

Table 3 Comparison of histopathological data between recurrence-free survivors at 10 years and patients who died from recurrent hepatocellular carcinoma within 5 years

	10-year RFS ($n = 281$)	Died within 5 years ($n = 918$)	P*
Maximum tumour size (cm)			0·009
< 2	91 (32·5)	198 (21·7)	
2–5	142 (50·7)	480 (52·6)	
> 5	47 (16·8)	234 (25·7)	
Unknown	1	6	
No. of tumours			< 0·001
1	253 (91·7)	675 (74·1)	
2	20 (7·2)	145 (15·9)	
≥ 3	3 (1·1)	91 (10·0)	
Unknown	5	7	
Macroscopic type			< 0·001
1	198 (73·3)	521 (60·2)	
2	32 (11·9)	174 (20·1)	
3	28 (10·4)	69 (8·0)	
4	6 (2·2)	66 (7·6)	
5	6 (2·2)	35 (4·0)	
Unknown	11	53	
Tumour differentiation			< 0·001
Well	52 (24·0)	95 (13·7)	
Moderate	133 (61·3)	427 (61·4)	
Poor	31 (14·3)	167 (24·0)	
Unclassified	1 (0·5)	6 (0·9)	
Unknown	64	223	
Vascular invasion			0·281
Yes	4 (1·4)	23 (2·6)	
No	272 (98·6)	875 (97·4)	
Unknown	5	20	
Intrahepatic metastases			< 0·001
0	258 (92·5)	673 (75·3)	
1	15 (5·4)	154 (17·2)	
2	6 (2·2)	62 (6·9)	
3	0 (0)	5 (0·6)	
Unknown	2	24	< 0·001
Non-cancerous liver			
Normal	35 (14·4)	50 (6·6)	
Chronic hepatitis/fibrosis	105 (43·2)	189 (25·1)	
Cirrhosis	103 (42·4)	514 (68·3)	
Unknown	38	165	

Values in parentheses are percentages. RFS, recurrence-free survival. *χ^2 test.

and histopathological characteristics of the two groups are compared in *Tables 2* and *3* respectively.

In the 10-year RFS group, at the time of liver resection the background liver damage was grade A in 79·1 per cent, grade B in 19·4 per cent and grade C in 1·5 per cent. Some 32·2 per cent of these patients were positive for hepatitis B virus antigens, whereas 52·0 per cent were positive for hepatitis C virus antibody. Serum levels of AFP and DCP were normal in 50·9 and 69·4 per cent of patients respectively. Surgical procedures comprised resection of less than a subsegment in 26·4 per cent, subsegmentectomy in 25·4 per cent and resection of more than one segment in 48·2 per cent of patients.

The maximum size of HCC at resection was less than 5 cm in 83·2 per cent of patients in the 10-year RFS group. Some 91·7 per cent of these patients had a single HCC at resection. HCCs in this group were of the single nodular type in 73·3 per cent, and 61·3 per cent were moderately differentiated; most showed no vascular invasion (98·6 per cent) or intrahepatic metastases (92·5 per cent). The non-cancerous tissue was cirrhotic in 46·5 per cent.

Comparison of the characteristics of patients who survived for at least 10 years without disease recurrence and those who died from recurrent HCC within 5 years revealed significant differences in age, degree of liver damage, positivity for hepatitis B antigen and hepatitis C antibody, serum levels of AFP and serum levels of DCP

(*Table 2*). Indeed, the 10-year survivors were younger, less frequently positive for hepatitis C and more frequently positive for hepatitis B. Levels of tumour markers (AFP, DCP) were lower in this group, whereas HCCs were smaller and fewer in number. There were also statistically significant differences in macroscopic appearance, tumour differentiation, intrahepatic metastasis and non-cancerous liver histology.

Table 4 Multivariable logistic regression analysis for death from recurrent hepatocellular carcinoma within 5 years

	Odds ratio	*P*
Age (years)		
≥ 60	1·00	
< 60	1·67 (1·06, 2·61)	0·026
Maximum tumour size (cm)		
< 2	1·00	
2–5	1·10 (0·63, 1·93)	0·728
> 5	2·56 (1·16, 5·65)	0·020
No. of tumours		
1	1·00	
≥ 2	1·99 (0·85, 4·62)	0·111
Macroscopic type		
1	1·00	
2	1·44 (0·75, 2·75)	0·270
3	0·76 (0·36, 1·62)	0·473
4	1·31 (0·36, 4·78)	0·687
5	1·68 (0·50, 5·67)	0·405
Tumour differentiation		
Well	1·00	
Moderate	1·59 (0·86, 2·92)	0·138
Poor	3·33 (1·46, 7·60)	0·004
Unclassified	1·01 (0·08, 12·67)	0·995
Vascular invasion		
No	1·00	
Yes	1·21 (0·25, 5·74)	0·813
Intrahepatic metastasis		
No	1·00	
Yes	2·34 (1·02, 5·37)	0·046
Non-cancerous liver		
Normal	1·00	
Chronic hepatitis/fibrosis	0·71 (0·30, 1·72)	0·450
Cirrhosis	2·25 (0·93, 5·40)	0·071
Liver damage grade		
A	1·00	
B or C	1·58 (0·96, 2·62)	0·075
AFP (units/l)		
< 20	1·00	
≥ 20 to < 400	1·96 (1·19, 3·25)	0·009
≥ 400 to < 1000	2·88 (1·19, 6·94)	0·019
≥ 1000	1·63 (0·86, 3·08)	0·134
DCP (units/l)		
< 40	1·00	
≥ 40 to < 500	2·73 (1·28, 5·41)	0·004
≥ 500 to < 1000	0·90 (0·39, 2·08)	0·804
≥ 1000	1·42 (0·76, 2·68)	0·273

Values in parentheses are 95 per cent confidence intervals. AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin.

Multivariable analysis revealed that tumour differentiation had the highest odds ratio related to death from recurrent HCC within 5 years, followed by raised levels of AFP and DCP (*Table 4*). When both the size and number of HCCs were categorized, the frequency of single HCC was significantly higher for any diameter of HCC in the 10-year RFS group than in patients who died from recurrent HCC within 5 years (data not shown).

Among patients whose levels of AFP (400–1000 units/l) and DCP (500–1000 units/l) were moderately raised, those with a single HCC had a lower risk of death from recurrent HCC than those with multiple tumours (data not shown). The number of HCCs yielded a higher odds ratio than the diameter of HCC in this specific group.

Discussion

The present study characterized tumour and patient factors among patients who survived without recurrence for 10 years after liver resection with curative intent for HCC. Although the characteristics of 10-year survivors after liver resection have already been investigated, there are few reports on 10-year RFS[2–5,10]. The present research was conducted as a nationwide large-scale comprehensive study of long-term recurrence-free survivors of HCC following liver resection in Japan.

In the present study, patients in the 10-year RFS group were younger with less background liver damage than patients who died from recurrent HCC within 5 years after liver resection. This was probably because there was less inflammatory change resulting from hepatitis C infection in the 10-year RFS group. The importance of underlying liver disease has been noted previously with regard to the degree of liver fibrosis and cirrhosis[10]. Underlying liver disease has more impact on patient survival than tumour factors[11]. Although two extreme HCC groups were compared in the present study (long-term RFS and short-term relapse), the present findings are of importance in determining possible factors associated with long-term RFS after curative liver resection.

Failure to detect latent intrahepatic HCC before surgery has no prognostic impact on the outcome or recurrence of HCC after liver transplantation[12,13]. The explanted diseased liver may show early HCCs that could not be detected before surgery, which can therefore appear as multicentric HCC on later examination. In the present study, patients in the 10-year RFS group had better liver function, despite a higher rate of positivity for hepatitis B surface antigen. Although the inflammatory activity in the resected liver was not investigated here, it was likely to have been lower in the remnant liver of the long-term survivors.

Tumour markers such as AFP or DCP have been reported to predict the early recurrence of HCC, even in the absence of microvascular invasion in the resected specimen[14,15]. The documentation of microvascular invasion depends on the slice width of the resected specimen and the number of slices investigated. Therefore, early recurrence can occur despite the absence of documented microvascular invasion. However, AFP or DCP levels are raised in nearly 60 per cent of patients with HCC, reflecting the biological behaviour of malignant tumours. The present data indicate that patients with no increase in AFP and DCP levels before surgery have a higher chance of survival without recurrence. In multivariable analysis, both tumour markers were independently associated with death due to recurrence after liver resection with curative intent. Furthermore, patients with a single HCC who had moderately raised AFP and DCP levels still had the prospect of surviving for longer after liver resection than those with high levels of tumour markers.

Considering the number and size of HCCs, a considerable percentage of patients in the 10-year RFS group had a single HCC (91·7 per cent) at the time of liver resection. Even with a raised AFP or DPC level, the risk of early death from recurrent HCC increased when there was more than one lesion. In other words, if a single HCC is found, a patient has an increased chance of surviving for longer after liver resection with curative intent.

Macroscopic HCC appearance was valuable for predicting 10-year RFS after curative liver resection, as shown previously[8]. HCCs of a contiguous multinodular type with clustering of small and contiguous nodules, and simple nodular types with extranodular growth carry a worse prognosis, most likely owing to microvascular invasion. In line with this, patients with these macroscopic types of HCC had a lower chance of long-term survival after liver resection in the present series.

The authors' group previously reported that anatomical resection has therapeutic value for treating patients with HCCs of 2–5 cm in diameter[16]. However, in the present study, this benefit of curative resection was not confirmed, even for HCCs with a diameter of 2–5 cm. This may have been because two extreme patient groups were compared. For example, even for HCC of 2–5 cm in size, the macroscopic appearance, vascular invasion, inflammatory status and fibrosis in the tumour-bearing liver may have been largely different between the two groups.

Acknowledgements

The authors acknowledge Professor T. Ichida, Department of Gastroenterology and Hepatology, Shizuoka Hospital, University of Juntendo, Shizuoka, Japan, and Professor O. Nakajima, Department of Pathology, Kurume University School of Medicine, Kurume, Japan, for helping to evaluate the study data. The authors declare no conflict of interest.

References

1 Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997; **349**: 1269–1276.
2 Tsunoda T, Segawa T, Eto T, Izawa K, Tsuchiya R. Long-term survivors after hepatectomy for hepatocellular carcinoma. *J Gastroenterol Hepatol* 1990; **5**: 595–600.
3 Zhou XD, Tang ZY, Ma ZC, Fan J, Wu ZQ, Qin LX *et al.* Twenty-year survivors after resection for hepatocellular carcinoma-analysis of 53 cases. *J Cancer Res Clin Oncol* 2009; **135**: 1067–1072.
4 Fukuda S, Itamoto T, Amano H, Kohashi T, Ohdan H, Tashiro H *et al.* Clinicopathologic features of hepatocellular carcinoma patients with compensated cirrhosis surviving more than 10 years after curative hepatectomy. *World J Surg* 2007; **31**: 345–352.
5 Poon RT, Ng IO, Fan ST, Lai EC, Lo CM, Liu CL *et al.* Clinicopathologic features of long-term survivors and disease-free survivors after resection of hepatocellular carcinoma: a study of a prospective cohort. *J Clin Oncol* 2001; **19**: 3037–3044.
6 The Liver Cancer Study Group of Japan. Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. *Ann Surg* 1990; **211**: 277–287.
7 The Liver Cancer Study Group of Japan. *General Rules for the Clinical and Pathological Study of Primary Liver Cancer* (4th edn). Kanehara: Tokyo, 2000.
8 Shimada M, Rikimaru T, Hamatsu T, Yamashita Y, Terashi T, Taguchi K *et al.* The role of macroscopic classification in nodular-type hepatocellular carcinoma. *Am J Surg* 2001; **182**: 177–182.
9 Kokudo N, Makuuchi M. Evidence-based clinical practice guidelines for hepatocellular carcinoma in Japan: the J-HCC guidelines. *J Gastroenterol* 2009; **44**(Suppl 19): 119–121.
10 Bilimoria MM, Lauwers GY, Doherty DA, Nagorney DM, Belghiti J, Do KA *et al.* Underlying liver disease, not tumor factors, predicts long-term survival after resection of hepatocellular carcinoma. *Arch Surg* 2001; **136**: 528–535.
11 Chen JY, Chau GY, Lui WY, Tsay SH, King KL, Wu CW. Clinicopathologic features and factors related to survival of patients with small hepatocellular carcinoma after hepatic resection. *World J Surg* 2003; **27**: 294–298.
12 Hidaka M, Eguchi S, Okudaira S, Takatsuki M, Soyama A, Tokai H *et al.* Multicentric occurrence and spread of hepatocellular carcinoma in whole explanted end-stage liver. *Hepatol Res* 2009; **39**: 143–148.
13 Eguchi S, Hidaka M, Tomonaga T, Miyazaki K, Inokuma T, Takatsuki M *et al.* Actual therapeutic efficacy of

pre-transplant treatment on hepatocellular carcinoma and its impact on survival after salvage living donor liver transplantation. *J Gastroenterol* 2009; **44**: 624–629.
14 Shimada K, Sano T, Sakamoto Y, Kosuge T. A long-term follow-up and management study of hepatocellular carcinoma patients surviving for 10 years or longer after curative hepatectomy. *Cancer* 2005; **104**: 1939–1947.
15 Shirabe K, Shimada M, Kajiyama K, Gion T, Ikeda Y, Hasegawa H *et al.* Clinicopathological features of patients with hepatocellular carcinoma surviving > 10 years after hepatic resection. *Cancer* 1998; **83**: 2312–2316.
16 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.

Digestive Diseases

Dig Dis 2011;29:339–364
DOI: 10.1159/000327577

Management of Hepatocellular Carcinoma in Japan: Consensus-Based Clinical Practice Guidelines Proposed by the Japan Society of Hepatology (JSH) 2010 Updated Version

Masatoshi Kudo[a] Namiki Izumi[b] Norihiro Kokudo[c] Osamu Matsui[d]
Michiie Sakamoto[e] Osamu Nakashima[f] Masamichi Kojiro[g]
Masatoshi Makuuchi[h] for the HCC Expert Panel of Japan Society of Hepatology

[a]Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka, [b]Musashino Red Cross Hospital, Musashino, [c]Department of Hepatobiliary and Pancreatic Surgery, University of Tokyo Graduate School of Medicine, Tokyo, [d]Department of Radiology, Kanazawa University Graduate School of Medical Science, Kanazawa, [e]Department of Pathology, Keio University School of Medicine, Tokyo, [f]Department of Pathology, Kurume University School of Medicine, Kurume, [g]Department of Kurume University School of Medicine, Kurume, and [h]Department of Surgery, Japanese Red Cross Medical Hospital, Tokyo, Japan

Key Words
Clinical practice guidelines, evidence-based · Clinical practice manual, consensus-based · Hepatocellular carcinoma, prevention · Hepatocellular carcinoma, staging · Hepatocellular carcinoma, surveillance · Hepatocellular carcinoma, diagnostic algorithm · Hepatocellular carcinoma, treatment algorithm

Abstract
Hepatocellular carcinoma (HCC) is one of the leading causes of cancer death not only in Japan but also worldwide. Clinical practice guidelines for HCC were first published in 2001 by the European Society of Study of the Liver (EASL) followed by the American Association for the Study of Liver Disease (AASLD) published in 2005 and updated in 2010. However, these guidelines have proven to be somewhat unsuitable for Japanese patients. In 2005, supported by the Japanese Ministry of Health, Labour and Welfare, evidence-based clinical practice guidelines for HCC were compiled in Japan. In 2009, a revised version of evidence-based guidelines was published. Based on both 'evidence-based' guidelines and the consensus of an expert panel on HCC, the Japan Society of Hepatology (JSH) published the Consensus-Based Clinical Practice Manual in 2007 and updated in 2010. In this article, the 2010 updated version of this manual, especially issues on prevention, surveillance, pathology, diagnosis, staging, and treatment algorithm are summarized.

Introduction

Following the publication by the European Society of Study of the Liver (EASL) in 2001 [1], the American Association for the Study of Liver Disease (AASLD) published the Clinical Practice Guidelines of hepatocellular carcinoma (HCC) in *Hepatology* in November 2005 [2] and updated in 2010 [3].

In Japan, the original Evidence-Based Clinical Practice Guidelines of HCC were published in 2005 [4] and updated in 2009 [5], disclosed on the website of the Japan Society of Hepatology (JSH) [www.jsh.or.jp/], and then widely used for liver cancer treatment in Japan. An ex-

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0257–2753/11/0293–0339$38.00/0

Accessible online at:
www.karger.com/ddi

Masatoshi Kudo, MD, PhD
Department of Gastroenterology and Hepatology
Kinki University School of Medicine
377-2, Ohno-Higashi, Osaka-Sayama, Osaka 589-8511 (Japan)
Tel. +81 72 366 0221 ext. 3149, E-Mail m-kudo@med.kindai.ac.jp

Table 1. JSH expert panel on Consensus-Based Clinical Practice Manual of the HCC, 2010 revised version (alphabetical order)

Hepatologists	
Norio Hayashi	Kansai Rosai Hospital
Naoki Hiramatsu	Osaka University
Takafumi Ichida	Juntendo University, Shizuoka
Akio Ido	Kagoshima University
Kenji Ikeda	Toranomon Hospital
Tatsuo Inoue	Kinki University
Takao Iwasaki	Tohoku University
Namiki Izumi	Musashino Red Cross Hospital
Shuichi Kaneko	Kanazawa University
Akinori Kasahara	Osaka University
Kazuhiko Koike	Tokyo University
Masatoshi Kudo	Kinki University
Takashi Kumada	Ogaki Municipal Hospital
Yasushi Matsuzaki	Tokyo Medical University
Masahito Minami	Kyoto Prefectural University of Medicine
Yasunori Minami	Kinki University
Takeshi Okanoue	Saiseikai Suita Hospital
Masao Omata	Yamanashi Prefectural Hospital
Yukio Osaki	Osaka Red Cross Hospital
Shuichiro Shiina	Tokyo University
Masatoshi Tanaka	Kurume University Medical Center
Hidenori Toyoda	Ogaki Municipal Hospital
Yoshihide Ueda	Kyoto University
Tatsuya Yamashita	Kanazawa University
Hepato-Biliary-Pancreatic and Transplant Surgeons	
Shigeki Arii	Tokyo Medical and Dental University
Hiroto Egawa	Murakami Memorial Hospital Asahi University
Takumi Fukumoto	Kobe University
Kiyoshi Hasegawa	Tokyo University
Toshimi Kaido	Kyoto University
Seiji Kawasaki	Juntendo University
Norihiro Kokudo	Tokyo University
Yonson Ku	Kobe University
Masatoshi Makuuchi	Japanese Red Cross Medical Center
Morito Monden	Osaka University
Hiroaki Nagano	Osaka University
Tadatoshi Takayama	Nihon University
Ryosuke Tateishi	Tokyo University
Shinji Uemoto	Kyoto University
Shintaro Yamasaki	Nihon University
Pathologists	
Masamichi Kojiro	Kurume University
Osamu Nakashima	Kurume University
Michiie Sakamoto	Keio University
Radiologists	
Osamu Matsui	Kanazawa University
Takamichi Murakami	Kinki University
Kenichi Takayasu	National Cancer Center Hospital
Medical Statistician	
Kenichi Yoshimura	Translation Research Center, Kyoto University

cerpted version has also been published in an English journal by Makuuchi and Kokudo et al. [5–7]. These guidelines were prepared after critical evaluations based on about 100 reports with a high evidence level in each field selected from 7,118 reports on HCC published between 1966 and 2002. In the 2009 revised version, 2,950 articles were reviewed and 532 articles were incorporated into the new version. Since the guidelines were prepared based as much as possible on highly evidenced data, some points may slightly deviate from actual practices related to HCC routinely performed based on the experience and consensus of HCC experts in Japan.

Considering this situation, the JSH summarized HCC treatment as performed in Japan with the consensus opinions of many experts, even though clear evidence was not available, and published a simple manual in 2007 [8] and updated in 2010 [9]. This was an experience- or consensus-based manual based on evidence-based guidelines with respect to the evidence level, and summarized the consensus of expert opinions – widely reflecting the actual state of HCC treatment in Japan.

The manual was prepared in accordance with the Evidence-Based Clinical Practice Guidelines reported by Makuuchi and Kokudo et al. [5–7], and thus contains no conflict with those guidelines. Points that slightly differ are a more detailed explanation of liver cancer treatments based on expert opinions, and a summary of the consensus by the expert panel [10]. Although it may seem unusual that two different guidelines are available and followed in Japan, both have different roles and are not contradictory.

This report introduces the revised version of Consensus-Based Clinical Practice Manual of HCC published by the JSH in 2010, and focuses on prevention, surveillance, pathology, diagnosis, staging, and treatment algorithm. This constitutes a 'practice manual' summarized by the expert panel of the JSH (table 1), and is different from the Clinical Practice Guidelines. The contents of this report may be considered as the current state of the most advanced HCC treatment practices in Japan.

Prevention

Antiviral Therapy

Hepatitis B Virus-Related HCC

Preventive therapy for HCC should be indicated for these patients. In Japan, HBe antigen-positive chronic hepatitis B patients with an ALT level of ≥31 IU/l and an HBV DNA level of ≥5 log IU/ml, HBe antigen-negative

chronic hepatitis B patients with an HBV DNA level of ≥4 log IU/ml, and liver cirrhosis patients with an HBV DNA level of ≥3 log IU/ml are recommended for antiviral therapy.

Previously, a randomized controlled trial (RCT) examined the inhibitory effects of interferon (IFN) therapy on carcinogenesis in patients with chronic hepatitis B. In 1999, Lin et al. [11] randomly divided 101 HBe antigen-positive patients with type B chronic liver disease into three groups: placebo (n = 31), placebo + IFN (n = 34), and prednisolone + IFN (n = 36) groups, and continued follow-up, with a mean follow-up of 8.4 (1.1–11.5) years. HCC was detected in 1 of 67 patients treated with IFN and in 4 of 34 patients receiving a placebo. They reported that carcinogenesis was significantly inhibited in the IFN-treated groups (p = 0.013). However, when investigating only chronic hepatitis patients, excluding 12 with liver cirrhosis, there were no significant differences in the incidence of HCC between the IFN-treated and non-IFN-treated groups.

On the other hand, the incidence of HCC was compared between 233 IFN-treated and 233 untreated patients in a case-control study involving 466 HBe antigen-positive patients with type B chronic liver disease. In the IFN-treated group, carcinogenesis was significantly inhibited (p = 0.011) [12].

Camma et al. [13] conducted a meta-analysis involving seven articles, and examined whether IFN therapy reduces the risk of compensatory liver cirrhosis B-derived carcinogenesis. IFN therapy decreased the absolute risk of liver carcinogenesis by 6.4%. However, the values markedly differed among the studies. A study involving groups in Europe with slight differences reported that there were no differences.

Prevention of Chronic Hepatitis/Liver Cirrhosis B-Derived Liver Carcinogenesis with Nucleoside Analogues

Two RCTs investigated the effectiveness of nucleoside analogue on preventing liver carcinogenesis in patients with chronic hepatitis/liver cirrhosis B. One of these involved 651 patients with marked hepatitis B-related fibrosis or compensatory liver cirrhosis. During the follow-up period (32.4 months), HCC was noted in 17 (3.9%) of 436 patients treated with lamivudine and in 16 (7.4%) of 215 patients treated with a placebo. In the former, carcinogenesis was significantly inhibited [14]. The other trial involving 222 patients with liver cirrhosis B compared lamivudine-treated and additionally adefovir-treated groups with a non-treated group, and reported that HCC incidence was significantly inhibited in the former two groups (p = 0.003) [15]. Furthermore, a non-randomized, comparative study also indicated that lamivudine and additional adefovir treatments significantly inhibited carcinogenesis compared to control group [16]. Thus, antiviral therapy with nucleoside analogues is useful for preventing HCC in patients with chronic hepatitis B or compensatory liver cirrhosis B.

Hepatitis C Virus-Related HCC

Primary Prevention of Chronic Hepatitis C-Derived Liver Carcinogenesis with IFN

The risk of HCC in patients in whom IFN therapy achieved sustained viral response (SVR) was one-fifth of that in untreated patients. In non-SVR group it was significantly inhibited to one-fourth to one-half in comparison with patients with ALT normalization at the end of IFN therapy and biochemical responders (BR) with ALT normalization for ≥6 months after the completion of such therapy [17]. A meta-analysis involving 4,614 patients examined the relationship between the presence or absence of IFN therapy in patients with type C chronic liver disease, including those with liver cirrhosis, and the incidence of HCC indicated that IFN therapy decreased the risk of HCC by 13%. The effects were more marked in BR [18]. These results suggest that IFN therapy inhibits the development of HCC in comparison with untreated patients, and that not only SVR but also BR are related to the prevention of HCC. Furthermore, a retrospective cohort study regarding the inhibitory effects of combination therapy with IFN and ribavirin on HCC in patients with chronic hepatitis C showed that the risk of HCC development was significantly lower in responders to this combination therapy [19]. Based on these findings, it is recommended that antiviral therapy with IFN be performed to prevent HCC incidence in patients with chronic hepatitis C. The primary goal of IFN treatment is virus eradication (SVR). When it is impossible, the liver function should be normalized as much as possible (BR).

Recently long-term follow-up of the HALT-C study confirmed this observation [20].

Two RCTs investigated the effectiveness of IFN therapy for liver cirrhosis C on preventing liver carcinogenesis. Of these, one reported that there was no difference in the incidence of HCC between IFN-treated and non-treated groups. However, the other study indicated that IFN therapy inhibited the development of HCC. Seven non-randomized, comparative studies, in which a non-IFN-treated group was set as a control group, have been

published. In six of these, IFN therapy inhibited the development of HCC in patients with liver cirrhosis C. Two meta-analyses also affirmed the preventive effects of IFN therapy on the development of HCC in patients with liver cirrhosis C. These effects were marked in patients who achieved SVR. Previously, one study examined the inhibitory effects of combination therapy with IFN and ribavirin on HCC in liver cirrhosis C patients, and reported that, in the combination therapy group, the development of HCC was inhibited in comparison with the non-treated group.

Anti-Inflammation Therapy

Glycyrrhizin Preparations

The intravenous administration of glycyrrhizin for chronic hepatitis/liver cirrhosis is commonly performed to improve the transaminase level. No RCT has investigated whether glycyrrhizin preparations inhibit liver carcinogenesis. However, a retrospective cohort study reported that the intravenous administration of glycyrrhizin preparations for chronic hepatitis C decreased the risk of liver carcinogenesis [21]. It is recommended that glycyrrhizin be intravenously administered for prevention of HCC development in patients with chronic hepatitis C when IFN therapy is not effective or indicated.

Ursodeoxycholic Acid

When administering ursodeoxycholic acid (UDCA) to patients with chronic hepatitis C, cytotoxic bile acid may be substituted for UDCA, protecting the hepatocyte membrane. Furthermore, a study suggested that the immunity-regulating and apoptosis-inhibiting actions of UDCA are involved in the protection of the hepatic cell membrane.

To date, no study has reported the preventive effects of long-term UDCA administration on liver carcinogenesis. However, UDCA administration at 600–900 mg/day improved the serum ALT level [22].

Phlebotomy Therapy

Phlebotomy therapy decreases the serum ALT level, suggesting the usefulness of phlebotomy for the treatment of chronic hepatitis C. Kato et al. [23] reported that long-term iron chelation significantly inhibited the development of HCC. In the future, a large-scale comparative study should be conducted.

Consensus Statements

1 Among patients with type B chronic liver disease, the incidence of HCC is high in those with a high HBV DNA level.
2 Nucleoside analogues are useful for preventing HCC in patients with chronic hepatitis B or compensatory liver cirrhosis B.
3 Among patients with chronic hepatitis C, the incidence of HCC is higher in those with marked fibrosis or liver cirrhosis.
4 It is recommended that antiviral therapy with IFN be performed to prevent HCC in patients with chronic hepatitis C. Firstly, virus elimination is important. When it is impossible, the liver function must be normalized.

Surveillance of Hepatocellular Carcinoma

Definition of the Population at High Risk for HCC

Persistent infections with hepatitis B and C viruses (HBV and HCV, respectively) are the highest risk factors for liver carcinogenesis. The carcinogenesis risk for HBV carriers is about 200 times higher than that for non-carriers, and the risk is higher in patients with type C liver cirrhosis than in those with hepatitis B-related cirrhosis. The HCV-associated risk is about 5 times higher than that associated with HBV. The characteristics of HCV-associated carcinogenesis are carcinogenesis in the F4 step in which liver cirrhosis is completed in most cases, and its occurrence in many cases at 60 years of age or older. The yearly carcinogenesis rate of cirrhosis type C is 7–8% in Japan, which is higher than that in Europe or North America; it might be that the mean age of carriers is closely involved. Liver cirrhosis induced by various causes, even though HBV and HCV are negative, is a risk for liver carcinogenesis. Since carcinogenesis occurs in some cases of liver cirrhosis associated with non-alcoholic steatohepatitis (NASH), alcoholic liver disease, primary biliary cirrhosis (PBC), and autoimmune hepatitis (AIH), the course of the disease should be followed paying close attention to carcinogenesis as in cases of viral liver cirrhosis. Alcohol increases the risk of chronic hepatitis B- and C-associated liver carcinogenesis.

Based on the above, patients with chronic hepatitis B and C and non-viral liver cirrhosis are defined as high-risk populations for HCC in both the Consensus-Based Clinical Practice Manual and Evidence-Based Practice Guidelines. Patients with liver cirrhosis types B and C are defined as a super-high-risk population (table 2). Risk factors other than hepatitis virus or liver cirrhosis are also proposed (table 3).

Table 2. Definition of populations at high risk for HCC

A. Super-high-risk population
1. Hepatitis B-related liver cirrhosis
2. Hepatitis C-related liver cirrhosis
B. High-risk population
1. Chronic hepatitis B
2. Chronic hepatitis C
3. Liver cirrhosis (causes other than HBV or HCV)

Table 3. Risk factors other than hepatitis virus infection or liver cirrhosis

Older age
Male gender
Diabetes mellitus
High body mass index (BMI)
High AST
High ALT
Low platelet count (PLT)
Heavy alcohol drinker
High viral load (HBV carrier)

Table 4. Surveillance protocol for early detection of HCC

1. Super-high-risk patients
Every 3–4 months
Ultrasound examination
AFP/PIVKA-II/AFP-L3 measurements
Every 6–12 months
Dynamic CT or dynamic MRI/EOB-MRI
2. High-risk patients
Every 6 months
Ultrasound examination
AFP/PIVKA-II/AFP-L3 measurements

EOB-MRI = Ethoxybenzyl-MRI.

Surveillance Protocol for Early Detection of HCC

For HCC screening, the HCC detection sensitivity of ultrasonography (US) is higher than that of α-fetoprotein (AFP) measurement, but specificities are not markedly different. For liver cirrhosis, a combination of the two methods has been reported to increase detection frequency compared to detection by US or AFP measurements alone.

No clear evidence is available to determine the optimum interval for periodic screening, but HCCs detected in periodic screenings by AFP, a protein induced by vitamin K absence or antagonist-II (PIVKA-II), and AFP lectin fraction (AFP-L3) measurement, and US are solitary and small in many cases, as compared to those detected in symptomatic patients. Thus, the Evidence-Based Clinical Guidelines [4, 5] proposed performing US and tumor marker measurements every 3–4 months in the super-high-risk population and every 6 months in high-risk populations. Based on HCC doubling times, these intervals appear appropriate (table 4). At present, AFP, PIVKA-II, and AFP-L3 are covered under the Japanese national health insurance as HCC tumor markers. Measurement of two or more tumor markers increases the sensitivity, while minimizing the specificity reduction, for small liver cancer, but alternate measurements of the AFP and PIVKA-II combination or the AFP and AFP-L3 combination is proposed according to the coverage under the current Japanese health insurance. For cases with a very rough background liver parenchyma because of cirrhosis and obesity with difficulty for US evaluation, periodic imaging screening by dynamic CT (multidetector-row CT (MDCT)) or dynamic MRI/EOB-MRI (ethoxybenzyl-MRI) every 6–12 months is proposed [9] (table 4), which is identical to the protocol in the Evidence-Based Clinical Practice Guidelines.

Consensus Statements

5 Patients at high risk for developing HCC should be entered into surveillance programs. The high-risk population and risk factors are identified in tables 2 and 3.
6 Surveillance for HCC should be performed using both US and tumor markers.
7 In Japan, three tumor markers (AFP, PIVKA-II, AFP-L3) are covered by the national health insurance in clinical settings for HCC surveillance.
8 Patients should be screened at 3- to 6-month intervals based on their risk of developing HCC.
9 The surveillance interval needs to be shortened for patients at higher risk for HCC, as described in table 4.

Pathology of Hepatocellular Carcinoma

For the diagnosis and treatment of HCC, it is important to understand the pathology of HCC growth/progression pattern. Clinicians should know the entity of early HCC and the association between pathological features of liver cancer growth/progression and malignancy.

The liver does not have any epithelial structure, different from the digestive tract; therefore, it is impossible to

evaluate the invasive stage of HCC based on the grade of infiltration. In addition, simultaneous/metachronal multicentric development is relatively frequent, making the definition of early HCC difficult. However, several studies showed that the pathological morphology and biological malignancy grade of HCC changed with an increase in the tumor diameter, suggesting the presence of lesions corresponding to early cancer of other organs [24, 25].

Definition of Early HCC with Respect to Pathological Morphology

According to the 'General Rule of Clinical and Pathological of Primary Liver Cancer', HCC is macroscopically classified into five types: vaguely nodular with indistinct margin-, simple nodular-, simple nodular type with extratumor growth-, and multinodular confluent type [26]. In addition, macroscopic findings of small HCCs are classified into two types: simple nodular and vaguely nodular type with indistinct margin. Histologically, most simple nodular type lesions are composed of moderately differentiated carcinoma, whereas vaguely nodular type with indistinct margin consist of well-differentiated carcinoma without severe atypia. In addition to findings such as small cells with an increase in the N/C ratio, an increase in the cell density, 2- to 3-thin layer arrangement, and a small pseudo-glandular structure, these lesions include the several original portal areas. At the boundary of the tumor, cancer cells proliferate to replace the normal hepatocellular cords in the non-cancerous region; therefore, macroscopically, the tumor border becomes unclear. Nodules with indistinct margin, which reflect the earliest change of hepatocarcinogenesis that can be clinically diagnosed, are defined as 'early HCC'. In patients with early HCC, vascular invasion is very exceptional, and there is no intrahepatic metastasis [24]. It is often difficult to differentiate early HCC from high-grade dysplastic nodules. However, the presence or absence of the infiltration of cancer cells in the portal area involved (stromal invasion) [27, 28] should be evaluated for differentiation.

Vascular Structure of Early HCC

It is well known that advanced HCC is completely supplied by arteries. However, early HCC is supplied by the portal venous flow at various levels, i.e. early HCC is supplied by both portal and arteries. However, the number of portal regions in cancer tissue accounts for approximately 25% of that in the non-cancerous region. In addition, arterial tumor vessels are undeveloped; portal and arterial blood may be decreased. On the other hand, arterial tumor vessels develop with an increase in the tumor diameter. However, tumors measuring approximately 10 mm in diameter show insufficient development, and vascularization of the tumor stroma, that is, the capillarization, is also insufficient. Therefore, early HCC does not show hypervascularity on angiography or contrast-enhanced CT.

Fatty Change of Early HCC

Although early, small liver cancer is often visualized as a hyperechoic nodule on US, most lesions reflect the fatty change of the nodule. The fatty change of HCC was the most frequent (approx. 40%) in lesions measuring 10–15 mm in tumor diameter, and the incidence decreases with an increase in the diameter and a reduction in the grade of differentiation. Based on this, fatty change is regarded as a morphological characteristic of early HCC. As previously described, with respect to the pathogenesis of such fatty change, portal blood flow and arterial blood flow may reduce via a decrease in the portal area in lesions measuring 10–15 mm in tumor diameter, and cancer may transiently show ischemia due to the insufficient development of arterial tumor vessels, causing fatty change [29].

Diagnostic Imaging of Early HCC

As many lesions of early HCC are hypovascular, they are difficult to demonstrate on CT through a hemodynamic basis; the correct diagnosis rate is not high. Recently, diagnostic imaging of intrahepatic nodular lesions by contrast-enhanced MRI with Gd-EOB-DTPA has been introduced. For Gd-EOB-MRI to be used to evaluate the hepatocellular function, lesions with a decreased intense at the hepatocyte phase are regarded as HCC. The CT diagnosis rate (including CTHA and CTAP) when lesions with a decrease in portal blood flow were regarded as HCC was approximately 60–70%, whereas the diagnosis rate of HCC by EOB-MRI is approximately 90% [30]; MRI may improve the diagnostic accuracy of early HCC. However, the presence of HCC with isointense and dysplastic nodule with low intense on hepatocyte phase of Gd-EOB-MRI has been indicated.

Macroscopic Classification of HCC and Malignancy Grade

The association between macroscopic findings and malignancy grade depends on the grade of tissue differentiation. When investigating resected specimens of HCC

Table 5. Pathology of small HCC: relationship between macroscopic classification, histological differentiation and tumor size (all resected cases, nodule diameter ≤3 cm) [cited from 9, with permission]

	n (%)	Well	Well + mod.	Mod.	Mod .+ poor	Tumor size, mm
SNIM	22	19 (86.4)	3 (13.6)	0	0	13.6 ± 5.4
SN	123	6 (4.9)	24 (19.5)	92 (74.8)	1 (0.8)	22.8 ± 5.6
SNEG	45	0	5 (11.1)	40 (88.9)	0	23.1 ± 5.4
CM	19	0	6 (31.6)	11 (57.9)	2 (10.5)	23.9 ± 5.3

SNIM = Small nodule with indistinct margins; SN = simple nodular type; SNEG = simple nodular type with extranodular growth; CM = confluent multinodular type. Percent values are shown in parentheses.

Table 6. Pathology of small HCC: macroscopic classification and microscopic findings (all resected cases) [cited from 9, with permission]

	fc	fc-inf	sf	vp	vv	im
SNIM	0	0	2 (9.1)	0	0	0
SN	90 (73.2)	79 (64.2)	65 (52.8)	23 (18.7)	3 (2.4)	5 (4.1)
SNEG	38 (84.4)	35 (77.8)	35 (77.8)	20 (44.4)	2 (4.4)	12 (26.7)
CM	1 (5.3)	1 (5.3)	14 (73.7)	12 (63.2)	3 (15.8)	5 (26.3)

fc = Capsular formation; fc-inf = capsular infiltration; sf = septum formatin; vp = portal vein invasion; vv = hepatic vein invasion; im = intrahepatic metastasis; SNIM = small nodule with indistinct margins; SN = simple nodular type; SNEG = simple nodular type with extranodular growth; CM = confluent multinodular type.
Percent values are shown in parentheses.

measuring ≤3 cm, approximately 85% of vaguely nodular type with indistinct margin lesions (early HCC) consisted of uniform, well-differentiated cancer tissue. The remaining 15% contained an area consisting of moderately differentiated HCC tissue, in which dedifferentiation was noted, showing unclear/clear 'nodule-in-nodule lesion' (table 5). In vaguely nodular type lesions, intrahepatic metastasis and portal tumor invasion are extremely rare. The mean tumor diameter is approximately ≤15 mm, and these lesions are significantly smaller than other macroscopic types of nodular lesions. Approximately 75% of simple nodular type lesions are classified as moderately differentiated HCC. Histologically, portal invasion is observed in 20%, and intrahepatic metastasis in 4%, suggesting advanced HCC. Simple nodular type with extratumor growth and multinodular confluent type lesions suggest advanced HCC. Most lesions consist of moderately to poorly differentiated HCC tissues. Portal invasion and intrahepatic metastasis are more frequently seen than in simple nodular type lesions (table 6). The number of intrahepatic metastatic foci and distance from the primary nodular are greater than in simple nodular type lesions [30] (table 7). In other words, lesions with high-level biological malignancy may be macroscopically evaluated as simple nodular type with extratumor growth or multinodular confluent type lesions. Therefore, curative treatment to avoid intrahepatic metastasis and recurrence must be kept in mind in these lesions in comparison with vaguely nodular type and simple nodular type HCCs.

Table 7. Pathology of small HCC: distance between main nodule and intrahepatic metastasis [cited from 9, with permission]

	n (%)	Distance, mm			
		≤2	2.1–5	5.1–10.0	>10.1
SN	9	6 (66.7)	1 (11.1)	0 (0.0)	2 (22.2)
SNEG	75	23 (30.7)	12 (16.0)	17 (22.7)	23 (30.7)
CM	65	27 (41.5)	19 (29.2)	13 (20.2)	6 (9.2)
Total	149	56 (37.6)	32 (21.5)	30 (20.1)	31 (20.8)

SN = Simple nodular type; SNEG = simple nodular type with extranodular growth; CM = confluent multinodular type.
Percent values are shown in parentheses.

Table 8. Pathology of small HCC: rate of portal venous invasion/intrahepatic metastasis and size of nodule (all resected specimens) [cited from 9, with permission]

	Nodule size, cm				
	0–1	1.1–2.0	2.1–3.0	3.1–5.0	5.1–10.0
PVI	0	28.3%	33.3%	49%	58.5%
IM	0	6.7%	17.1%	29.6%	43.9%

PVI = Portal venous invasion; IM = intrahepatic metastasis.

Differentiation and Malignancy Grade of HCC

Most early HCC lesions appear as well-differentiated lesions. Macroscopically, they are detected as nodules with an unclear border. However, the tumor diameter increases with dedifferentiation. Moderately to poorly differentiated HCCs, contained in the well-differentiated cancer tissue after dedifferentiation, are more malignant than the peripheral well-differentiated HCC tissue, showing expansive growth, completely replacing the well-differentiated cancer tissue, and leading to classical HCC with clear margin. When examining small HCC with 'nodule-in-nodule', p53 overexpression is detected in approximately 40% of moderately to poorly differentiated cancer tissues in the internal area. In addition, a Ki-67 labeling index, which reflects the proliferative capacity, indicates that the malignancy is advanced when the peripheral well-differentiated HCC (early HCC) shows 'nodule-in-nodule' pattern. This is consistent with the finding that an increase in the tumor diameter was accelerated with the appearance of 'nodule-in-nodule' during clinical follow-up. 'Nodule-in-nodule' type HCC is recognized as being in the dedifferentiation process from early to advanced HCC; clinical management similar to advanced HCC is necessary.

In 'nodule-in-nodule' type HCC, there is a marked difference in vascularity between the marginal well-differentiated and internal moderately to poorly differentiated HCC tissues. On contrast-enhanced US or CT, the marginal well-differentiated cancer tissue is visualized as a hypovascular area, because the development of arterial tumor vessels and the capillarization is insufficient. However, moderately to poorly differentiated cancer tissues in the internal area are visualized as hypervascular area due to sufficient neovascular development. Briefly, the vascular structure of liver cancer is closely correlated with the grade of differentiation. The malignancy of early liver cancer may be predicted to some degree based on hemodynamic findings.

Nodule Size and Malignancy Grade of HCC

The size of HCC is associated with the macroscopic morphology, grade of histological differentiation, and intrahepatic metastasis/portal invasion rates. Most vaguely nodular type lesions measure ≤2 cm, and lesions measuring ≥3 cm are rare. However, simple nodular type with extratumor growth and multinodular confluent type lesions become more frequent with an increase in the tumor diameter. Concerning the grade of histological differentiation, the proportion of lesions consisting of uniform, well-differentiated cancer tissue markedly decreases when the tumor diameter exceeds 2 cm. Most lesions consist of moderately to poorly differentiated HCC tissues. The portal invasion/intrahepatic metastasis rates also increase in proportion to the tumor diameter (table 8). Usually, there is a correlation between an increase in the tumor diameter and malignancy grade. However, exceptionally, large, well-differentiated, slowly expanding HCC is present [32].

Consensus Statements

10 Vaguely nodular type HCCs, which are composed of very well-differentiated HCC, are defined as 'early hepatocellular carcinoma'.

11 Early HCC does not show hypervascularity on angiography or dynamic CT/MRI.

12 Fatty change and stromal invasion are regarded as the morphological characteristics of early nodular HCC.

13 In simple nodular type with extranodular growth and multinodular confluent type HCCs, intrahepatic metastasis and recurrence are more frequent than in lesions with vaguely nodular type and simple nodular type HCCs. This must be kept in mind on the curative treatment.

14 'Nodule-in-nodule' findings of very well-differentiated carcinoma (early HCC) reflect higher malignancy grade than early HCC.

Diagnosis of Hepatocellular Carcinoma

Diagnostic Criteria

The diagnosis of HCC is determined by three factors: the background chronic liver disorder, tumor markers, and imaging diagnosis. When the liver has hepatitis B- and C-related cirrhosis, tumor marker levels are increased, and typical imaging findings are detected, HCC can be definitely diagnosed. Typical imaging findings are hypervascularity in the arterial phase and washout in the portal equilibrium phase on dynamic CT or dynamic MRI. Hypervascularity on CTHA and a perfusion defect on CTAP also leads to a diagnosis of typical HCC. How-

ever, HCC cannot be definitely diagnosed based on a combination of tumor markers and chronic liver disorder alone, or on the elevation of tumor markers alone. Moreover, hypervascular nodules in the arterial dominant phase without washout in the portal equilibrium phase are not typical and more precise investigations are necessary. Hypovascular nodules in the arterial dominant phase also require further examination. Cases meeting all A, B, and C criteria in table 9 are definitely diagnosable as HCC in Japan. Cases not accompanied by the typical imaging findings are diagnosed and treated by the examinations detailed in figures 1 and 2.

Table 9. Diagnostic criteria of typical HCC[1]

A. Background liver disease (one positive factor)
Hepatitis B-related liver disease
Hepatitis C-related liver disease
Liver cirrhosis
B. Tumor markers (at least one positive study)
AFP ≥200 ng/ml associated with a rising trend over time
PIVKA-II (≥40 mAU/ml) with a rising trend over time
AFP-L3 (>15%)
C. Typical imaging findings (one positive study)[2]
Arterial phase hypervascularity with portal-venous phase washout on dynamic CT, dynamic MRI or CEUS
Hypervascularity on CTHA with perfusion defect on CTAP

[1] A+B+C, A+C, B+C, C: HCC confirmed A+B, B: HCC highly suspicious, thus, dynamic CT/MRI is required.

[2] Nodules with atypical imaging study, namely, hypervascularity without portal/venous washout or hypovascular nodule on arterial phase should undergo further study (as shown in fig. 1 and 2).

Multistep Development of HCCs and Abnormal Blood Flow

Many cases of HCCs originate from HBV and HCV infections via multistep development. Premalignant lesions and early HCCs are mainly fed by a portal venous flow in contrast to overt HCCs, which are supplied by an arterial flow. Thus, there may be no objection to indicating a hypervascular HCC for treatment.

However, how to diagnose a typical HCC is the most problematic issue when the hemodynamic pattern is not typical for a HCC. Although the Guidelines for Evidence-Based Clinical Practice for the Treatment of Liver Cancer [4, 5] do not suggest any detailed imaging diagnostic criteria for atypical nodules, a more detailed algorithm referring to these issues has been proposed in the new practice manual (fig. 1).

Diagnostic Modalities of HCC

Dynamic CT

Dynamic CT using MDCT acquires images within several seconds during a single respiratory pause if the slice thickness is about 5 mm and is superior for detection of hypervascular HCC. On dynamic CT of the liver, 100–120 ml of contrast medium is rapidly infused within 30 s. The arterial dominant phase is generally acquired at around 30–45 s following the initiation of the injection of contrast medium [33]. A characteristic of HCC is a corona-shaped enhancement in the late arterial phase or portal venous dominant phase [34]. The vascular and extracellular contrast medium concentrations reach equilibrium about 200 s after infusion; scanning at this time point is called the equilibrium or parenchymal phase. In a typical HCC, attenuation decreases in the equilibrium phase.

In MDCT, time resolution is high and acquisitions of the arterial, portal, and equilibrium phases have markedly increased the ability to qualitatively diagnose tumorous lesions. The diagnosis of a typical hypervascular HCC is easy because the lesion is detected as a high attenuation area in the arterial phase, corona enhancement is noted in the late arterial or the portal phase, and this becomes a low attenuation area in the equilibrium phase. However, the frequency of obtaining typical findings varies depending on CT equipment and acquisition conditions. Diagnostic accuracy of hypervascular HCCs by CT has been reported to be 68–91% [35–37].

Contrast-Enhanced US

Sonazoid-enhanced US are classified into the two phases: the vascular and Kupffer phases (fig. 3).

Vascular Phase

The sensitivity of contrast-enhanced US with Sonazoid to detect intranodular blood flow in liver tumors is extremely high. The sensitivity of 4-phase imaging (plain, arterial, portal, and equilibrium phases) by MDCT, as a gold standard, for detecting intranodular blood flow is similar to or superior to that of MDCT. In addition, in most patients in whom there is no intranodular blood flow in the arterial phase on contrast-en-