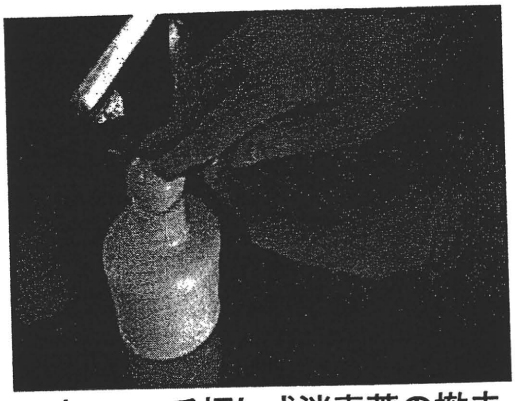

写真1-1　手押し式消毒薬の撤去

写真1-2　手押し式消毒薬の撤去

手を介して汚染の広がりを，わかりやすくずるため墨汁を使用して，示している．
このタイプの消毒薬は撤去する．
足踏み式や自動式の消毒薬に変更する．

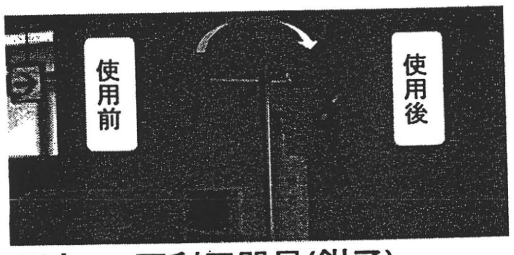

写真2　再利用器具(鉗子)

コッヘルは，使用前のものと使用後のものとをはっきり区別し，置く場所を移動して扱う．
使用後に洗浄，滅菌を行う．

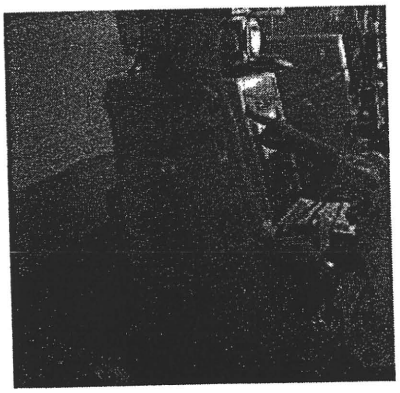

写真3　手袋を外すタイミング

手指を介した汚染の拡大を防止するために，手袋を外してから，透析装置を操作する．

＜巻頭カラー頁参照＞

施した．その後，改善効果をみるために1年間にわたってHCV感染に関する追跡調査（全数調査）を行った．

その結果，6ヵ月目にあたる2004年2月時点の調査では，HCVの新規感染例は1例もみられないことを確認し，1年後にあたる2004年8月の調査においても同様の結果を得ることができた[13]．

◆6. 介入による効果評価終了後に，新規に発生したHCV感染例とその原因

2004年8月以降は本調査，研究に参加した9つの全ての透析医療施設では，患者の同意に基づき，従前通りのスケジュールでそれぞれ自主的に継続して検査を行うこととした．

その結果，同一施設内において，2005年3月と2005年10月に各1例の新たなHCV感染事例が見出された．新たな感染の発生が確認された段階で，直ちに調査，検証を行なった結果，その年度途中に採用された看護師が前述の教育訓練を終えないまま透析現場の業務に加わっていたことが原因となっていた可能性を示唆する調査結果が得られた．

◆7. おわりに

日本透析医学会からの全国調査報告[14]や国際共同研究[3]の報告によれば，患者100名あたりのHCV抗体陽転化率は3.6人(日本)，同2.1人(米国)，同3.9人（伊）となっており，本稿で示した9つの透析医療施設における新規感染率は，かなり低い値を示しているといえる．このことは，今回の前向き全数調査へ自主的に参加した9つの透析医療施設は，県内の透析医会の幹事を務める施設が中心となっていたことによると考えられる．また，今回のパイロット的な調査，介入では，予防対策を講じた後，全施設において1年間にわたり前向きに追跡して，新たなHCV感染を防止できたことを確認した．

感染予防対策の基本は感染経路の遮断である．チンパンジーを用いた感染実験から，C型肝炎ウイルス（HCV）の感染成立に必要な最少のウイルス量は，感染早期のウイルス血症の血液では，in-vitroでの測定により得られるHCV RNA換算した絶対量で10 copy相当[15]，と極めて微量である．したがってこのことを十分に認識した上で対策を立てる必要があると言える．

また，感染予防対策が軌道に乗った後にも，特に，新たなスタッフを透析現場の業務に参加させる前にはあらかじめ感染予防のための教育，訓練を実施すること，さらに全スタッフに対して，定期的に教育，訓練を繰り返すことも大切であると言える．

〔引用文献〕

1) Sasaki F, Tanaka J, Moriya T, Katayama K, Hiraoka M, Ohishi K, Nagakami H, Mishiro S, Yoshizawa H.Very low incidence rates of community-acquired hepatitis C virus infection in company employees, long-term inpatients, and blood donors in Japan.*Journal of Epidemiology*, 1996; **6**: 198-203.
2) Tanaka J, Mizui M, Nagakami H, Katayama K, Tabuchi A, Komiya Y, Miyakawa Y, Yoshizawa H.Incidence rates of hepatitis B and C virus infections among blood donors in Hiroshima, Japan, during 10 years from 1994 to 2004.*Intervirology*, 2008; **51**: 31-41.
3) 秋葉隆，丸茂文昭，山崎親雄他：欧州・米国・日本の血液透析患者におけるC型ウイルス肝炎感染の現況と解析 —DOPPS研究より 第44回日本腎臓学会総会プログラム 75, 2001
4) 田辺泰登，佐々木富美子，守屋尚，田中純子，水井正明，中西敏夫，吉澤浩司，覚醒剤常用者におけるB型肝炎ウイルスおよびC型肝炎ウイルスの感染状況についての検討（速報），肝臓，1993; 34: 63.
5) Kumagai J, Komiya Y, Tanaka J, Katayama K, Tatsukawa Y, Yorioka N, Miyakawa Y, Yoshizawa H. Hepatitis C virus infection in 2,744 hemodialysis patients followed regularly at nine centers in Hiroshima during November 1999 through February 2003. *Journal of Medical Virology*, 2005; **76**: 498-502.
6) 「図説 わが国の慢性透析療法の現況 2007年12月31日現在」（社）日本透析医学会発行
7) 田中純子，厚生労働省老人保健課，片山惠子，

田渕文子，小宮裕，水井正明，山中烈次，吉澤浩司　肝炎ウイルス検診受診者 (2002.4-2007.3 受診群) を対象とした解析，厚生労働科学研究費補助金　肝炎等克服緊急対策研究事業．平成19年度　肝炎状況・長期予後の疫学に関する研究班　分担研究報告書 1-6.

8) Tanaka J, Kumagai J, Katayama K, Komiya Y, Mizui M, Yamanaka R, Suzuki K, Miyakawa Y, Yoshizawa H：Sex-and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995-2000. *Intervirology*, **47**, 32-40, 2004

9) 片山透，上沼優子，高祖飛佐子：輸血後肝炎の発生状況．日赤 / 輸血後肝炎に関する特定研究班　昭和58～60年度成果（経過）報告書，9-21.

10) Watanabe J, Matsumoto C, Fujimura K, Shimada T, Yoshizawa H, Okamoto H, Iizuka H, Tango T, Ikeda H, Endo N, et al. Predictive value of screening tests for persistent hepatitis C virus infection evidenced by viremia. Japanese experience. *Vox Sang*, 1993; **65**: 199-203.

11) Yoshizawa H. Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. *Oncology*,2002; **62** :8-17.

12) ウイルス肝炎研究財団編，透析施設における肝炎ウイルス感染防止のてびき，文光堂，2007.

13) 田中純子，頼岡徳在，熊谷純子，小宮裕，片山恵子，吉澤浩司，辰川自光，梶川憲治，川合淳，大上和行，高杉敬久，土谷晋一郎，浜口直樹，原田知，山下達博　血液透析施設におけるC型肝炎ウイルス感染防止のための介入とその効果の検証，厚生労働科学研究費補助金　肝炎等克服緊急対策研究事業　平成16年度　B型及びC型肝炎の疫学及び検診を含む肝炎対策に関する研究班分担研究報告書 35-42.

14) 秋葉隆：透析医療におけるウイルス肝炎の現況，治療，予防，厚生労働科学研究費補助金　新興・再興感染症研究事業　平成13年度　C型肝炎の自然経過及び介入による影響等の評価を含む研究班分担研究報告書 72-79.

15) Kątayama K, Kumagai J, Komiya Y, Mizui M, Yugi H, Kishimoto S, Yamanaka R, Tamatsukuri S, Tomoguri T, Miyakawa Y, Tanaka J, Yoshizawa H. Titration of hepatitis C virus in chimpanzees for determining the copy number required for transmission. *Intervirology*, 2004; **47**: 57-64.

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特集 C型肝炎のすべて・2009
HCV疫学と病態Update

HCV感染の疫学の変化：現況と将来

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索引用語：C型肝炎ウイルス（HCV），HCVキャリア率，コホート効果，肝がん死亡

1 はじめに

本稿では，成因（原因ウイルス）別にみたわが国の肝がんによる死亡（人口10万対）の年次推移と出生年別にみた初回供血者集団（約350万人）におけるHCV抗体陽性率，および2002年から5カ年計画で実施された肝炎ウイルス検診の節目検診受診者集団（約620万人）における出生年別HCVキャリア率との関連性について示し，HCV感染の現況と将来について述べてみたい．

2 成因別にみたわが国の肝がん死亡の年次推移

わが国では，1975年を境に肝がんによる死亡実数，人口10万対の死亡数は増加の一途をたどり，2002年に至って，その数はようやく頭打ちの状態となった（2002年34,637人，2004年34,510人，2006年33,662人）[1]．1950年以来の肝がんによる死亡実数，人口10万人対の死亡数の推移を図1にまとめて示した．

この人口10万対の肝がんによる死亡数と日本肝癌研究会による調査成績をもとに，1977年から2003年までの成因別にみたわが国の肝がん死亡（人口10万人対）の年次推移をまとめると図2のようになる[1,2]．

まず，HBVの持続感染に起因する肝がん（B型の肝がん）による死亡は，1970年代後半から今日に至るまでほぼ増減がないままの状態で推移しており，HBVの持続感染によらない肝がん（非B型の肝がん）がわが国の肝がんによる死亡の増加に寄与していることがわかる．

次に，HCV感染の確定診断が可能になった1992年以降についてみると，それまで非B型の肝がんとされてきた集団の80%以上はHCVの感染に起因する肝がん（C型の肝がん）であることがわかる[3]．

Junko TANAKA et al: Transition of epidemiology on HCV infection - Current state and the future -
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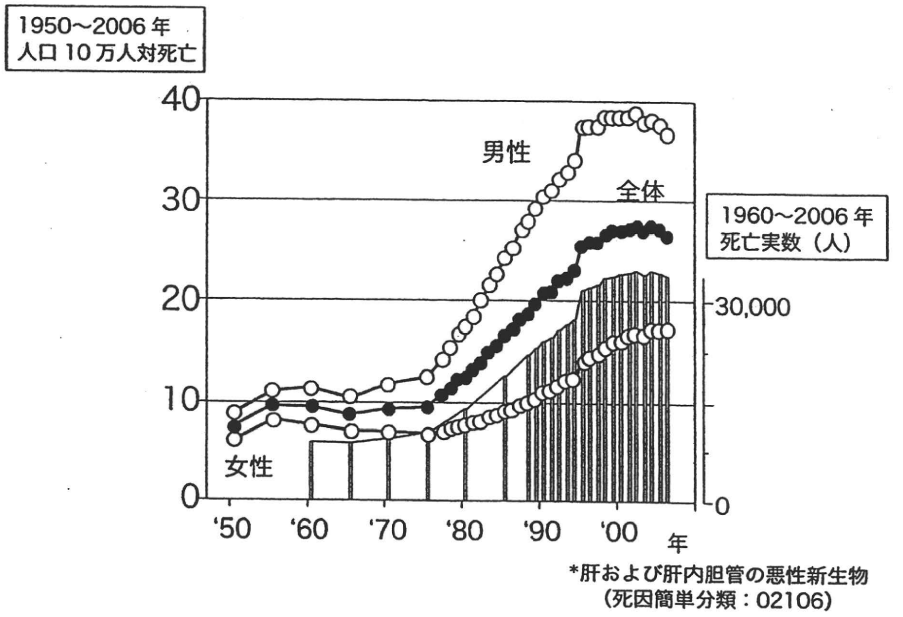


図1　わが国における肝がん*死亡率および死亡実数の推移

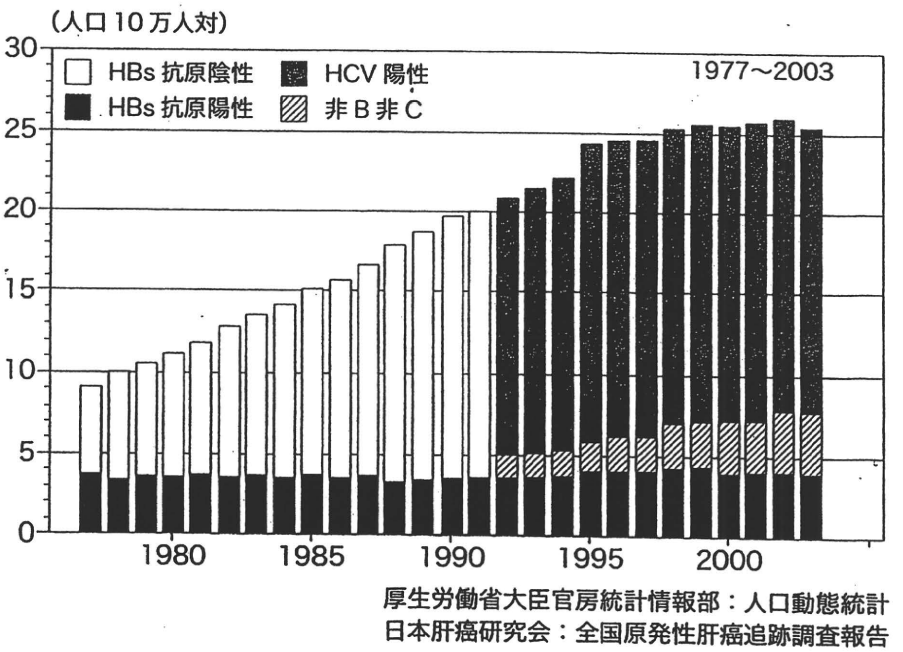


図2　わが国における成因別肝がん死亡の推移

初回供血者集団における年齢，地域別にみたHCV抗体陽性率

わが国の一般集団におけるHCVの感染率の近似値は，日本赤十字血液センターの献血者の資料をもとにして算出することができる．血液センターでは，毎年約600万本の献血された血液が，全国一律の精度により検査されてきた．

厚生労働省の「C型肝炎疫学研究班」が日本赤十字社の全面的な協力のもとにまとめた年齢別，地域別にみたHCV抗体陽性率を図3，図4に示す．解析の対象は，1995年から2000年までの6年間に全国の血液センターで初めて献血した3,485,648人（初回献血者）であり，年齢は2000年の時点に換算して記載し出生

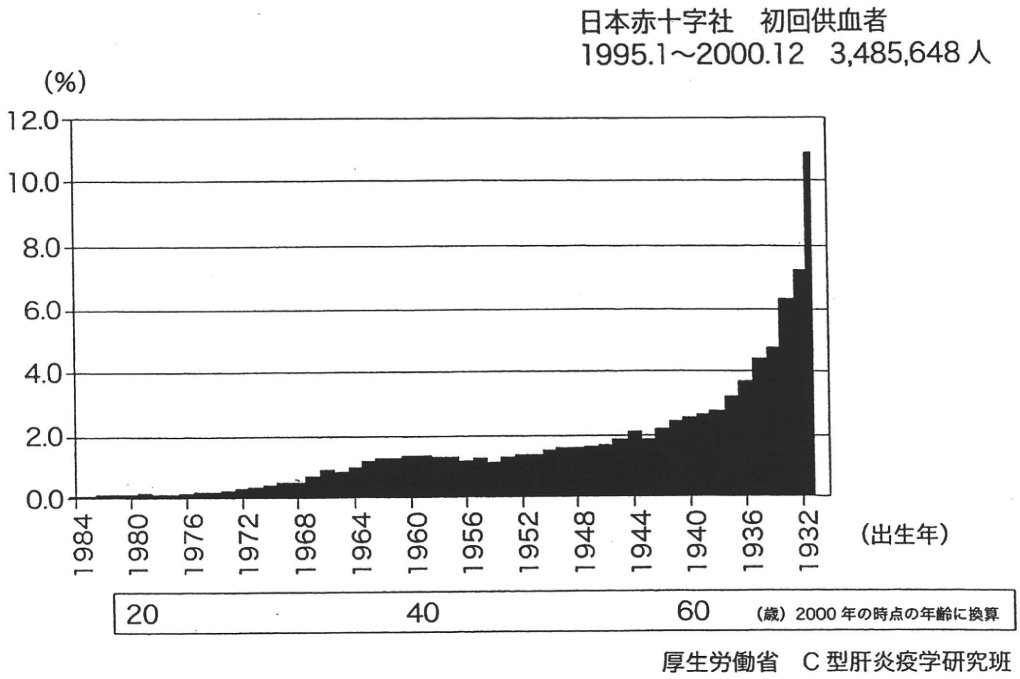


図3　1歳刻みの出生年別にみたHCV抗体陽性率

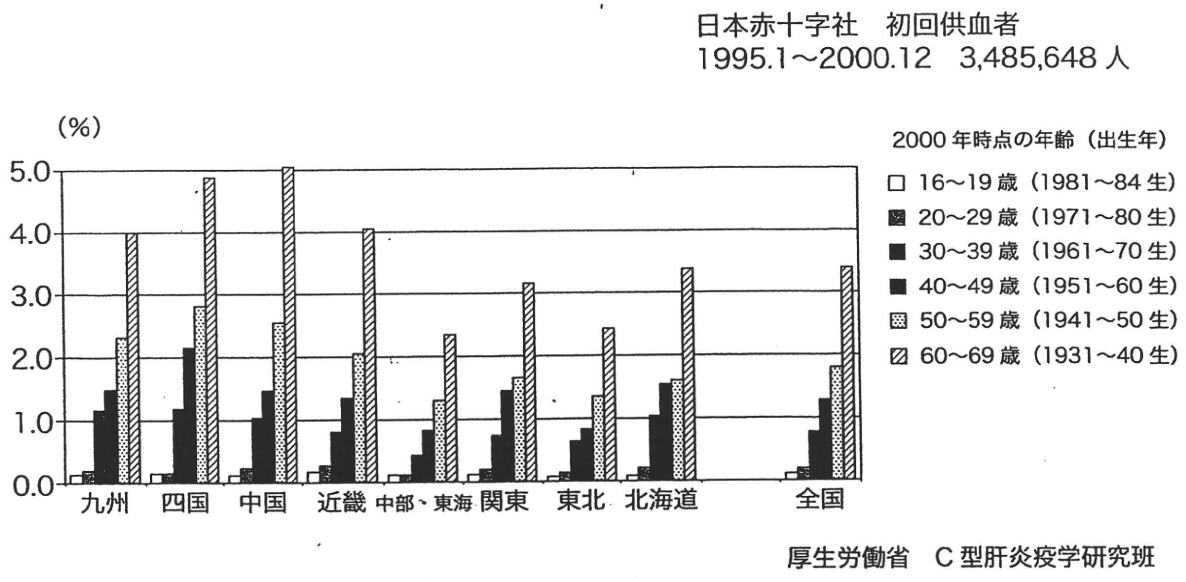


図4　地域別，年齢階級別にみたHCV抗体陽性率

年を併記した[4]．

HCV抗体陽性率を単純平均すると0.5%であるが，年齢が高い集団で高い値を示す傾向がみられる．20歳代以下すなわち1980年以降の出生群では0.2%以下と極めて低い値を示すが，1936年以前の出生群すなわち，2000年の時点における64歳以上の年齢集団では3%を超える高い値を示している．

全国を8つの地域に分けてみると，肝がん多発地域である西日本の各地域，すなわち九州，中国・四国，近畿地方の1960年以前の出生群，すなわち2000年の時点における年齢が40歳以上の群におけるHCV抗体陽性率が他の地域・年齢層に比べて高い値を示して

表1　HCV感染の新規発生率

	献血者			定期健康診断受診者	肝障害者・老人福祉施設入所者
地域	広島	大阪	広島	広島	岡山
	1992～1995	1992～1997	1994～2004	1992～1995	1988～1992
対象者	114,266	448,020	218,797	3,079	678
キャリア化	3	59*	16	0	0
観察人年	168,726	1,095,668	861,842	5,786	2,712
Incidence	1.8/10万人年	5.4/10万人年*	1.9/10万人年	0	0
95% CI	0.4 - 5.2	4.1 - 7.0	1.1 - 3.0	0 - 0.6	0 - 1.3

*抗体陽性

いる．一方，1980年以後の出生群(2000年の時点において20歳以下の群)では，いずれの地域においてもHCV抗体陽性率は0.2％以下と極めて低い値を示していることがわかる．

当時，日赤血液センターでは，凝集法(HCV PHA価，またはHCV PA法)を用いて一定の精度を維持しつつHCV抗体の検査を行っていた．この方法により「HCV抗体陽性」と判定された場合，その約70％がHCV RNA陽性(HCVキャリア：C型肝炎ウイルス持続感染者)であることが，献血者の年齢に関わりなく認められることが過去に行った基礎的調査により明らかにされている．このことから，HCVキャリア率は図3，図4のHCV抗体陽性率の約70％に相当すると考えればよい．

なお，日赤血液センターでは採血前の問診により，過去に輸血歴がある場合，肝炎(肝障害)の既往がある場合など，肝炎ウイルスに感染していると考えられるリスクが多少なりともある場合には献血辞退のお願いをしている．したがって，献血者のデータをもとに算出したC型肝炎ウイルスのキャリア率は，社会一般における実態よりもやや低めに捉えている可能性があることを認識しておく必要がある．

4　HCVの新規感染率の頻度

前項に示した年齢階級別にみたHCV抗体陽性率の分布が加齢効果，すなわち，若い年齢層における低いHCV抗体陽性率は，加齢とともに高くなるのか，あるいは，出生年ごとの集団には時代背景を含めた固有のHCVの曝露率があり，10年20年と加齢しても変わらずその値を保持するのか(コホート効果)を知るためには，一般集団における新規のHCV感染がどの程度起こっているのかを把握しておくことが必要となる．

このことを明らかにするために，広島および大阪の赤十字血液センターにおいて献血者集団を対象に行った前向き調査の成績[5,6,7]をまとめて表1に示す．

広島の献血者集団では，異なる期間に観察された調査であるにもかかわらず，新規のHCV感染率(新規のHCVキャリア発生率)は10万人年あたり1.8人(95％ CI：0.4-5.2)および10万人年あたり1.9人(95％ CI：1.1-3.0)とほぼ同等の，極めて低い値を示している．大阪の献血者集団においても，10万人年あたりのHCV抗体陽転者は5.4人(95％ CI：4.1-7.0)と低い値を示すに止まっていることが明

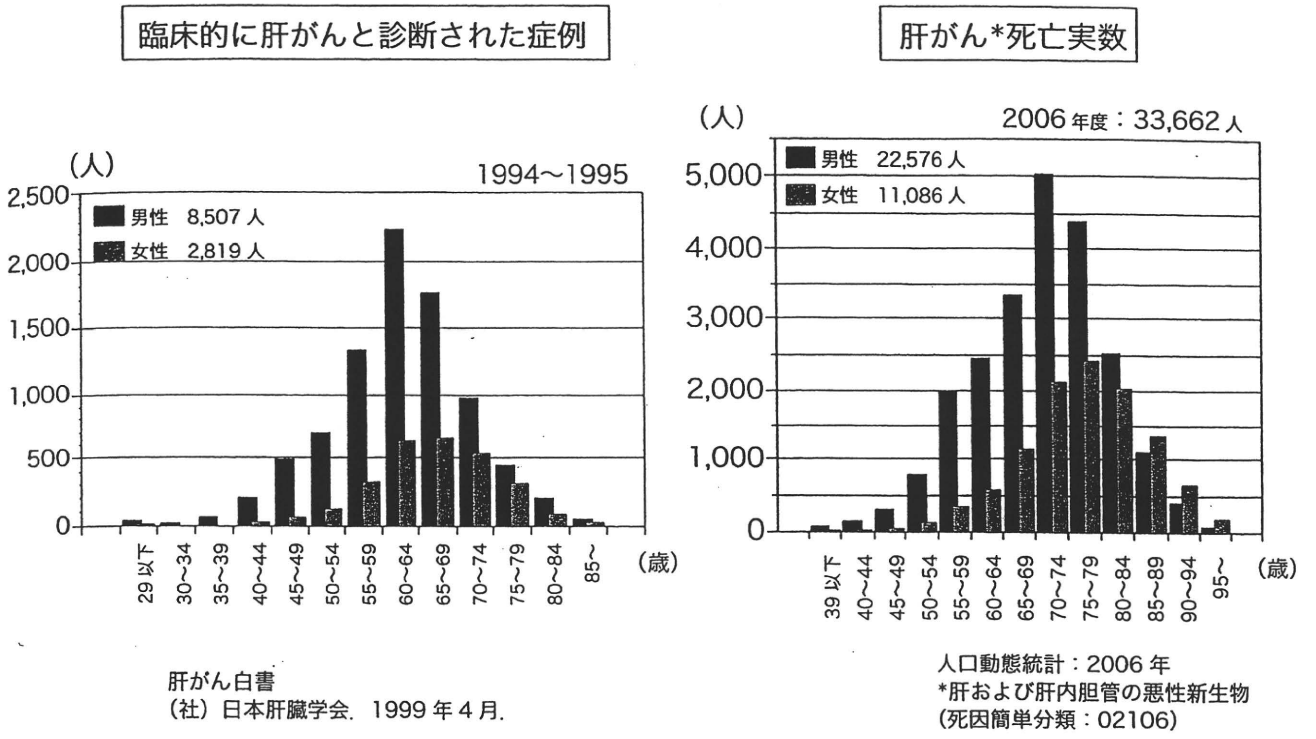


図5　性・年齢階級別にみた分布の比較

らかとなった．一方，企業内検診受診者集団およびHCVキャリアも同居している福祉施設での長期入所者における同様の前向き調査を行った成績からも，調査期間内におけるHCVの新規感染は0であることが示されている．これらの成績から，図3に示した年齢階級が高い集団においてHCV抗体陽性率が高い値を示すという現象は，いわゆるコホート効果によるものであると推察できる．

一方，透析医療施設など日常的に観血的処置を行っている医療現場におけるHCV感染のリスクは，国際的にみても高いことが知られており，HCV抗体陽転化率は，患者100名1年あたり3.6人(日本)，同2.1人(米国)，同3.9人(伊)と報告[8]されている．

厚生労働省「C型肝炎疫学研究班」と広島県の透析医会幹事施設との協力のもとに実施した前向き調査[9]においても，HCVの新規感染率は0.33人/100人年と，先に述べた一般健常者集団と比べ高い値を示しており，特定のハイリスク集団においては適切な感染予防対策を講じる必要性は現在も依然として残されていることは銘記しておく必要がある．

(5) 年齢階級別にみたHCV抗体陽性率と肝がん好発年齢との関係

肝がん白書(1999年)[10]から引用した，初めて肝がんと診断された患者数の年齢分布と，人口動態統計から得た年齢ごとの肝がんによる死亡実数を示す(図5)．1945年-1995年の調査時点における診断時の患者の年齢ピークは，男性では60歳代前半，女性では60歳代であるのに対し，2006年の時点における肝がんによる死亡実数は男性では70歳代前半，女性では70歳代であることがわかる．

肝発がんの好発年齢はB型肝炎ウイルス(HBV)の持続感染に起因する肝がんでは50歳代の前半から半ばに，またHCVの持続感染に起因する肝がんは50歳代の終わりから

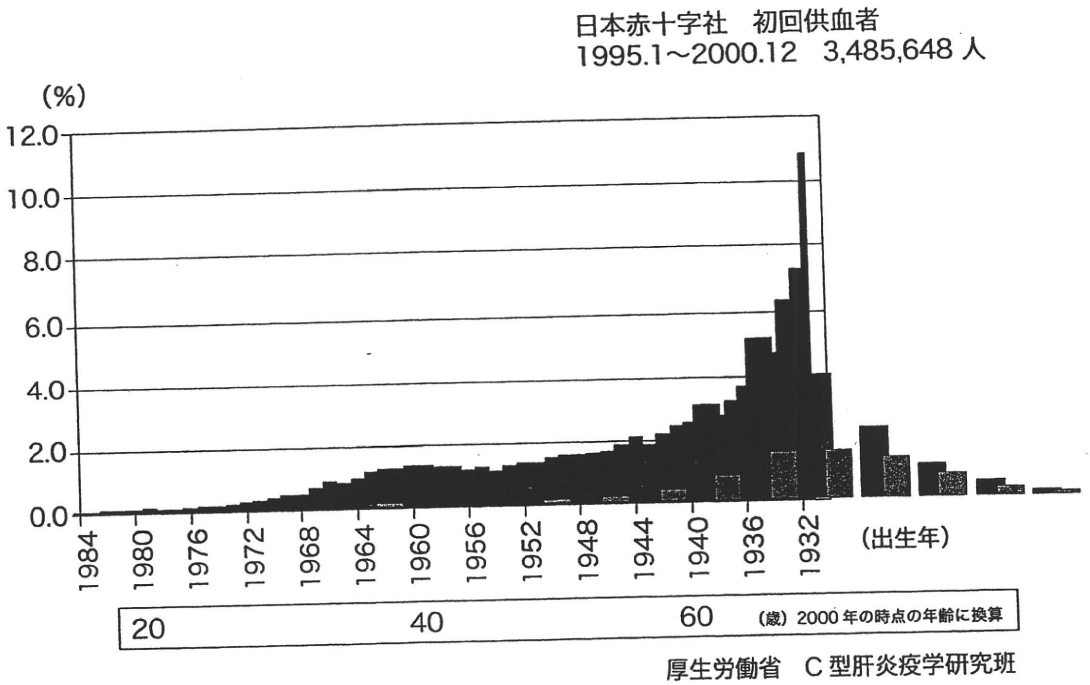
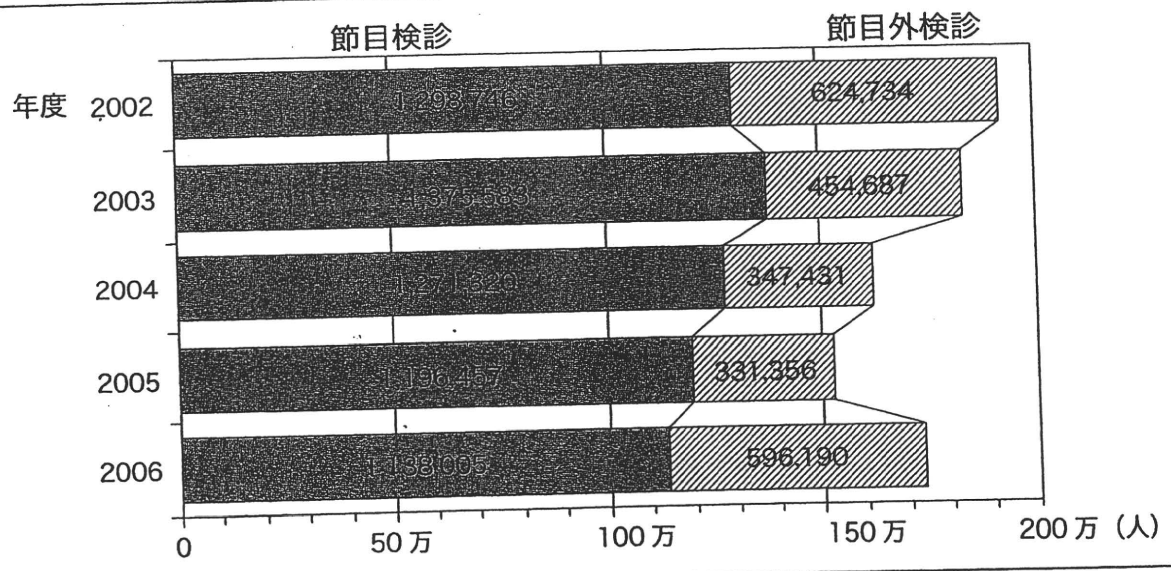


図6　HCV抗体陽性率と肝がん好発年齢

表2　C型肝炎ウイルス検査
節目・節目外検診別の受診者数およびキャリア率



	合計		節目検診		節目外検診	
	受診者数	HCV キャリア数(%)	受診者数	HCV キャリア数(%)	受診者数	HCV キャリア数(%)
2002	1,923,480	31,393 (1.6)	1,298,746	14,672 (1.1)	624,734	16,721 (2.7)
2003	1,830,270	23,491 (1.3)	1,375,583	13,324 (1.0)	454,687	10,167 (2.2)
2004	1,618,751	16,831 (1.0)	1,271,320	10,385 (0.8)	347,431	6,446 (1.9)
2005	1,527,813	13,976 (0.9)	1,196,457	8,909 (0.7)	331,356	5,067 (1.5)
2006	1,734,195	14.259 (0.8)	1,138,005	7,453 (0.7)	596,190	6,806 (1.1)
合計	8,634,509	99,950 (1.2)	6,280,111	54,743 (0.9)	2,354,398	45,207 (1.9)

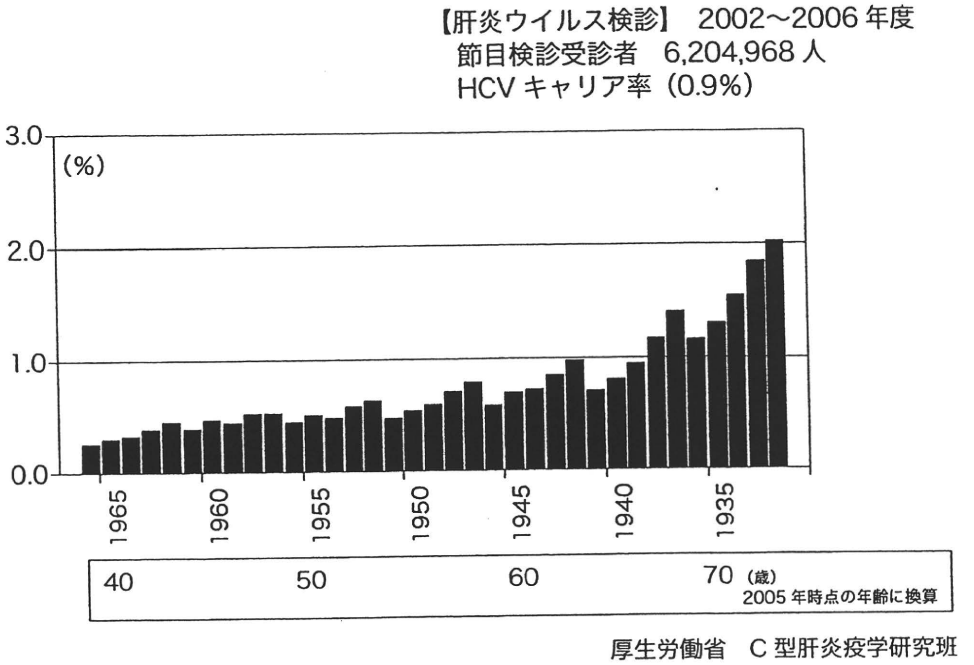


図7 地域別，年齢階級別にみたHCVキャリア率

60歳代にピークがあることが知られている．したがって，HCVの持続感染に起因する肝がんのみを考えた場合には，図に示した肝がんの好発年齢は僅かに右方に，すなわち高年齢層に移動させてみる必要がある．

図5に示した肝がん好発年齢の分布図と，前項図3に示した1歳刻みのHCV抗体陽性率の分布図を重ねてみると(図6)，2000年の時点はHCV抗体陽性率の最も高いコホート集団(1932年頃に出生した集団)は，肝がんの好発年齢のピークを経過した直後の時期にあたり，2008年の現在はHCV抗体陽性率のやや低いコホート集団(1936年頃に出生した集団)が，肝がんの好発年齢のピークを通過しつつある状態にあることを読み取ることができる．すなわち，わが国における肝がんの新規発生は，すでにピークを過ぎた状態に至っており，肝がんによる死亡は，ここ数年以内に下降線を辿り始めることを容易に読み取ることができる．

⑥ 肝炎ウイルス検診受診者における年齢，地域別にみたHCVキャリア率

わが国では，2002年度から肝炎・肝がん対策の一環として，肝炎ウイルス検診が5カ年間計画で実施に移された．この検診は，自覚症状がないまま社会に潜在している肝がんのリスク集団としてのHCVキャリア，およびHBVキャリアを組織的に見つけ出し，それぞれの地域単位で健康管理と適切な治療を行うことにより，肝がんによる死亡を減らすことを目的としたものである[11]．

厚生労働省によりまとめられた結果によれば，この5年間に，節目，節目外検診の両者を併せて合計8,634,509人がC型肝炎ウイルス検査を受け，99,950人(1.2%)のHCVキャリアが見いだされている(表2)．

「節目」と「節目外」検診受診群とに分けて，見出されたHCVキャリア率を比較すると，いずれの年度においても「節目外」検診受診群では「節目」検診受診群の2倍以上の値を示

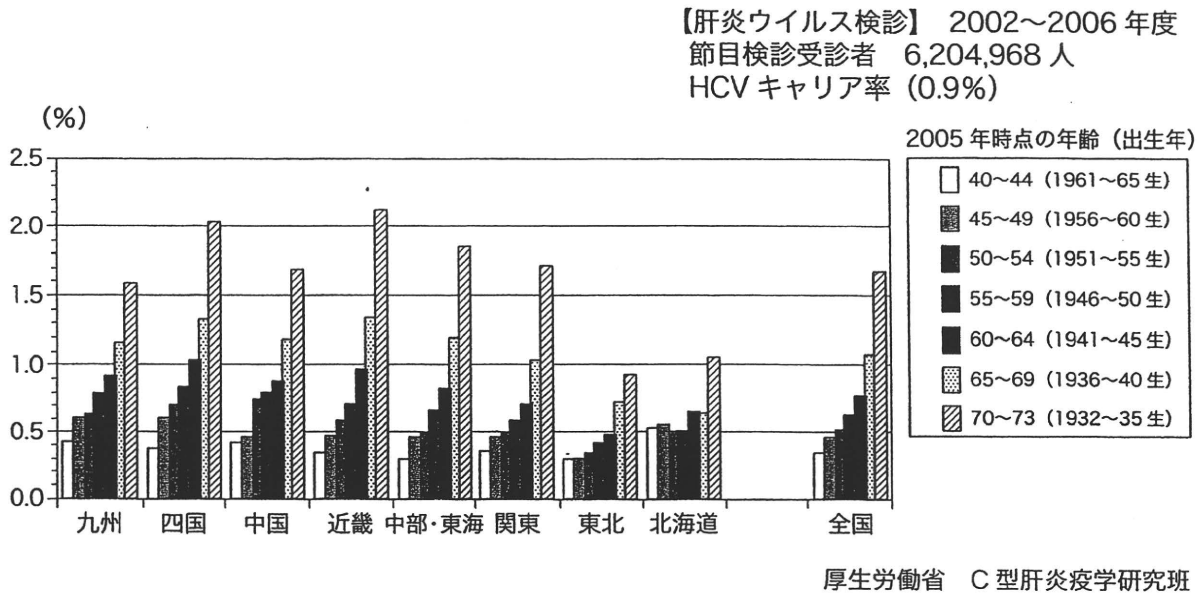


図8 地域別，年齢階級別にみたHCVキャリア率

し，また，全体の約45％は節目外検診により見いだされている．これは，「肝炎ウイルス感染のリスクが高いと考えられる集団」の設定が適切であったこと，また，各自治体において，対象とした節目外検診受診者集団の選別が適切に実施されていたことを示しているといえる．なお，この集団の中の一部には既に通院中の患者も紛れ込んできていた可能性は否定できないであろう．

節目検診は40歳以上の5歳刻みの年齢集団を対象に5カ年間実施され，最終的に2006年度における年齢が40歳から74歳までの全年齢が受診対象者となった．このうち，節目検診を受診した6,204,968人分のデータをもとに，2005年時点における年齢および出生年別にHCVキャリア率を算出し，図7に示した．

この成績は，わが国におけるHCVキャリア率の実態に最も近似するものであるといえる．さらにこのデータを8つの地域別にわけて再集計し，図8に示した．HCVキャリア率は，近畿以西の西日本の地域の高年齢層で高い値を示す傾向が認められている．

7 おわりに

本稿では，約350万人の初回献血者のデータをもととした年齢別にみたHCV抗体陽性率と，約620万人の節目検診受診者のデータをもとに年齢別にみたHCVキャリア率を提示，対比した．

両者は高年齢層では高いHCV抗体陽性率あるいはHCVキャリア率を示すこと，また，地理的にみると西高東低の分布を示すことで一致していた．一方，若い年齢層ではいずれの地域においても陽性率は低い値を示すに止まるという特徴が認められた．

この大規模集団を対象とした2つの成績と1990年代以降のわが国では，HCVキャリアの新規発生はごく稀にみられるに過ぎなくなっていることを併せると，現在のわが国の社会全般の衛生環境と医療環境が維持されれば，HCVキャリア率は減少の一途をたどることになると考えられる．

文　献

1) 厚生労働省大臣官房統計情報部：平成18年人口動態統計．上巻. 2006
2) 日本肝癌研究会：第4回–第17回全国原発性肝癌追跡調査報告（1977–2003）.
3) Yoshizawa H, Tanaka J : A National Project for the Management of Viral Hepatitis toward Prevention of Hepatocellular Carcinoma in Japan. International Kilmer Conference Proceedings 247–264, 2004
4) Tanaka J, Kumagai J, Katayama K et al : Sex-and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995–2000. Intervirology 47 : 32–40, 2004
5) Sasaki F, Tanaka J, Moriya T et al : Very low incidence rates of community-acquired hepatitis C virus infection in company employees, long-term inpatients, and blood donors in Japan. Journal of Epidemiology 6 : 198–203, 1996
6) Tanaka H, Tsukuma H, Hori Y et al : The risk of hepatitis C virus infection among blood donors in Osaka, Japan. J Epidemiol 8 : 292–296, 1998
7) Tanaka J, Mizui M, Nagakami H et al : Incidence rates of hepatitis B and C virus infections among blood donors in Hiroshima, Japan, during 10 years from 1994 to 2004. Intervirology 51 : 33–41, 2008
8) 秋葉隆：透析医療におけるウイルス肝炎の現況，治療，予防，平成13年度　C型肝炎の自然経過及び介入による影響等の評価を含む研究班分担研究報告書 72–79
9) Kumagai J, Komiya Y, Tanaka J et al : Hepatitis C virus infection in 2,744 hemodialysis patients followed regularly at nine centers in Hiroshima during November 1999 through February 2003. Journal of Medical Virology 76 : 498–502, 2005
10) 肝がん白書　平成11年度，日本肝臓学会発行
11) 吉澤浩司：肝がんの発生予防に資するC型肝炎検診の効果的な実施に関する研究，平成13年度厚生科学研究費補助金（21世紀型医療開拓推進研究事業）中間報告書，2000

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Regular surveillance by imaging for early detection and better prognosis of hepatocellular carcinoma in patients infected with hepatitis C virus

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Abstract
Purpose This study evaluated the usefulness of regular check-ups by ultrasonography and contrast-enhanced imaging for early detection of hepatocellular carcinoma (HCC) in a retrospective analysis.
Patients and methods From April 2001 to March 2007, 240 consecutive patients with HCC who were infected with hepatitis C virus (HCV) were divided into three groups. Patients diagnosed with HCC by repeated imaging constituted Group A (surveillance group). Group B comprised patients in whom HCC was detected during scheduled doctor visits for liver disease or other diseases such as diabetes. Group C comprised non-screened patients.
Results The prevalence of solitary tumors decreased from Group A through Group B to Group C (66, 48 and 24%, respectively, $P < 0.001$). The proportion of patients in stages I and II decreased from 83% (103/124) in Group A to 53% (42/79) in Group B and 24% (9/37) in Group C ($P < 0.001$). The proportion of patients who were treated with curative procedures, such as resection or ablation, was highest at 80% (99/124) in Group A, and lower at 53% (42/79) in Group B and 27% (10/37) in Group C ($P < 0.001$). The cumulative survival rate was better in Group A than B ($P < 0.05$), and in Group B than C ($P < 0.001$). Periodical medical check-ups without imaging did not necessarily detect early-stage disease, even when HCC-related markers including des-γ-carboxy prothrombin were tested.
Conclusions Regular surveillance with ultrasonography and contrast-enhanced imaging is useful for detecting early-stage HCC and increase chances for curative treatments in patients with HCV-related chronic liver disease.

Keywords Hepatocellular carcinoma · Early detection · Curative procedures · Survival rates · Surveillance

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide [1], and patients with HCC continue to suffer an unsatisfactory prognosis. Surveillance for HCC should aim at decreasing mortality, and early detection is vital for therapeutic success. Serum levels of alpha-fetoprotein (AFP) and ultrasonography are widely accepted screening tests for early diagnosis of HCC [2–11].

However, serological markers including des-γ-carboxy prothrombin (DCP) and glycosylated AFP have shown limited success in detecting HCC in early stages [12–14]. Recent advances in imaging technologies allow the detection of early HCC, as reported in the guideline of the American Association for the Study of Liver Diseases [14]. Patients need to be surveyed for HCC, taking into consideration the incidence of HCC and cost-effectiveness. The discovery of hepatitis B virus (HBV) and hepatitis C virus (HCV), responsible for the majority of HCC cases [15], has enabled providers to identify the population at risk for HCC.

In Japan, HBV and HCV infections are associated with HCC in 15 and 80% of the cases, respectively [16, 17]. This retrospective study focused on HCV-associated HCC in Japan, and compared the efficacy of three methods for diagnosing HCC diagnosis. As the results show, regular repeated imaging was useful for early detection of HCC in patients infected with HCV.

Patients and methods

Patients

From April 2001 to March 2007, 338 consecutive patients were diagnosed with HCC in our institution. Among them, 240 patients infected with HCV were enrolled in this study. We retrospectively examined the procedure of diagnosis from clinical records and classified patients into one of three groups according to the method for diagnosing HCC. A total of 124 patients were diagnosed with HCC by regular imaging procedures such as ultrasonography, and they were categorized into the surveillance group (Group A). Hepatic damages such as rough surface pattern of the liver and dullness on the liver edge, as well as the detection of obvious varices on the first ultrasonography, led them to receive repeated imaging procedures. In 82% (102/124) of Group A patients, the interval between the latest imaging and diagnosis of HCC was within 6 months. The average interval between the latest imaging and diagnosis of HCC was 4.3 months [median, 3.6 months (range 2–11 months)]. They also received tests for HCC-related markers at least every 3 months. Group B comprised 79 patients who had been diagnosed with HCC during scheduled doctor visits for HCV-related liver disease or other diseases such as diabetes. These patients were not enrolled in a surveillance program at the time, and had not undergone any imaging procedures for at least 1 year before the diagnosis of HCC, while they received tests for HCC-related markers at least every 3 months. Among them, 26 patients received imaging due to elevated levels of HCC-related markers, such as AFP and DCP. In the remaining 53 patients in Group B, imaging was performed incidentally; they had not received imaging over the previous 1 year. The 37 patients who had not been screened for HCC were classified into Group C. They were diagnosed with HCC when symptoms developed (32 patients) or incidentally during a diagnostic workout for unrelated medical conditions such as traffic accident (5 patients). The study conformed to the ethical guidelines of the declaration of Helsinki, and was approved by the Institutional Review Board.

Surveillance strategy

Figure 1 outlines the surveillance program. Briefly, detection of any mass on ultrasonography instigated repeated imagings if the nodule diameter was up to 1 cm, or a dynamic study if the diameter exceeded 1 cm. HCC nodules are characterized by an intense contrast uptake during the arterial phase of dynamic computed tomography (CT) or magnetic resonance imaging (MRI), with the contrast washed away during the delayed or venous phase [12–14]. In the present study, the specific pattern of arterial uptake followed by venous washout was considered to represent HCC, since the value of "washout" in the venous phase has been recognized recently. If the vascular pattern on CT or MRI was not specific for HCC in a nodule with a diameter >1.5 cm, angiographically assisted CT or biopsy was undertaken to establish the diagnosis. Patients with nodules <1.5 cm in diameter who did not reveal HCC by angiographically assisted CT or biopsy underwent repeated surveillance procedures, and subsequent enlargement of the nodule during follow-ups indicated shifting to a dynamic study.

Diagnosis of cirrhosis

The diagnosis of chronic liver disease was made at the time of HCC detection by the following procedures.

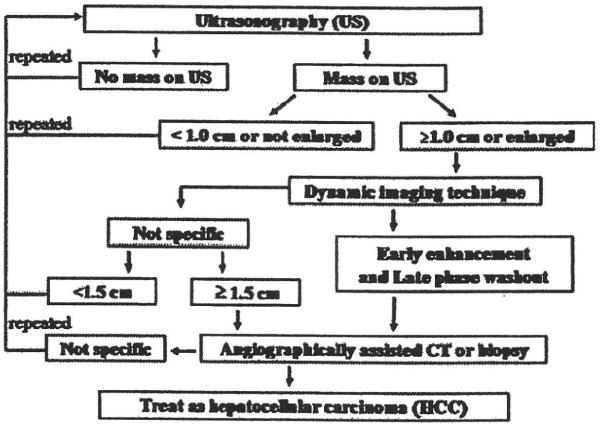

Fig. 1 Flow chart for the surveillance program including repeated imaging procedures

Histological findings were obtained in surgical specimens from 85 patients, and cirrhosis was diagnosed in 61 and chronic hepatitis or liver fibrosis in the remaining 24. Gastrointestinal varices in an additional 24 patients were considered diagnostic of cirrhosis. The remaining 131 patients were diagnosed to have cirrhosis according to the histologic scoring system [18].

Staging

Cancer stage was assessed by ultrasonography and dynamic CT or MRI. A total of 193 patients (80%) underwent angiography and/or angiographically assisted CT to obtain further details prior to resection, ablation or transarterial chemoembolization. In those patients, staging was also assessed by imaging on angiography and/or angiographically assisted CT. All patients underwent a chest X-ray, while additional investigations to detect metastases were performed only when extrahepatic involvement was suspected. Staging was not assessed by histologic findings on surgically resected specimens, even when they were available. Staging was determined according to the Liver Cancer Study Group of Japan classifications [19]. Staging was made also by the Milan criteria [20].

Treatment selection

Hepatic resection was indicated particularly to the patients with localized HCC who had maintained hepatic reserve capacity. When resection was contraindicated or refused by patients, the most appropriate treatment was selected according to the tumor status and liver function preserved [21]. Percutaneous ablation by ethanol injection [22] or radiofrequency ablation (RFA) [23] was considered in patients who had 1–3 nodules <3 cm in diameter, and were without vascular invasion or extrahepatic metastases. Transarterial chemoembolization [24] was offered to patients with either a paucifocal nodule not treatable by percutaneous ablation or multiple tumors not accompanied by thrombosis in main portal veins or extrahepatic metastasis. For the patients in Child-Pugh class C, transarterial chemoembolization was not recommended. In this study, resection and ablation were considered curative procedures based on their high efficacy.

Statistical analysis

The following 11 parameters were analyzed: age, sex, AFP, DCP, prothrombin activity, serum albumin level, total bilirubin level, liver state, tumor stage, HCC treatment and survival. Efficacy of the imaging program was evaluated by comparing clinical manifestation and prognosis among patients in the three groups. Differences in the distributions of tumor stage, tumor markers, and HCC treatment were evaluated by chi-squared test or Student's *t* test. Survival was calculated from the time of treatment start in patients who received it, and from the time of cancer diagnosis in patients without treatment. Data were censored at the time of death or the last follow-up visit. Survival was calculated according to the Kaplan–Meier method, and survival curves were compared by log-rank test. *P* values less than 0.05 were considered statistically significant.

Results

Background characteristics

There is no difference between Groups A and B in background of the patients except the programs with or without imaging. Table 1 details the background characteristics of all patients. Although the prevalence of cirrhosis was similar among the three groups, patients in Group C had poorer hepatic reserve with respect to albumin and total bilirubin levels ($P < 0.001$). The prevalence of non-cirrhotic liver in patients under 74 years was 26% (42/161), and 42% (33/79) in patients over 75 years. These differences were statistically significant ($P < 0.01$).

Features of HCC

The majority of HCC nodules were diagnosed by dynamic study including angiographically assisted CT, while HCC nodules in only 4 (1.7%) were confirmed by fine needle biopsy. Table 2 compares characteristics of HCC among the three groups. The frequency of solitary tumors was 66% (82/124) in Group A, 48% (38/79) in Group B, and 24% (9/37) in Group C, with a significant difference among three groups ($P < 0.001$). Nodules measuring less than 2 cm were detected in 64% (80/124) of patients in Group A, 25% (20/79) of those in Group B, and only 5% (2/37) of those in Group C ($P < 0.001$). The frequency of non-advanced tumor state decreased from 88% (109/124) in Group A, to 52% (41/79) in Group B, and to 27% (10/37) in Group C ($P < 0.001$). Cut-off values were set at 200 ng/ml and 40 mAU/ml, respectively, on AFP and DCP. In Group A, 47% (58/124) of the cases were negative for both, 46% (57/124) were positive for either, and 7% (9/124) were positive for both. In Group B, 11% (9/79) of the patients were negative for both, while 65% (51/79) were positive for ether, and 24% (19/79) were positive for both. In Group C, 11% (4/37) of the patients were negative for both, 57% (21/37) were positive for either, and 32% (12/37) were positive for both. These differences were statistically significant ($P < 0.001$). Thus, most patients in Groups B and C were positive for

Table 1 Background characteristics of patients

	Group A (surveillance) ($n = 124$)	Group B (scheduled doctor visits) ($n = 79$)	Group C (non-screened) ($n = 37$)	*P* value
Age at diagnosis of HCC (years)				
Median (range)	69.7 (49–89)	72.8 (49–87)	69.6 (50–87)	<0.05[b]
Gender				
Men	79 (64%)	52 (66%)	28 (76%)	NS
Women	45 (36%)	27 (34%)	9 (24%)	
History of blood transfusion	28 (22%)	19 (24%)	6 (16%)	NS
Excessive alcohol intake[a]	25 (20%)	20 (25%)	15 (49%)	NS
Liver state				
Not cirrhotic	34 (27%)	31 (39%)	10 (27%)	NS
Cirrhosis	90 (73%)	48 (61%)	27 (73%)	
Prothrombin activity (%)				
Median (range)	86 (48–125)	88 (57–135)	83 (39–124)	NS
Albumin (g/dl)				
Median (range)	3.6 (2.1–4.6)	3.8 (2.8–5.1)	3.4 (2.5–4.5)	<0.001[c]
Total bilirubin (mg/dl)				
Median (range)	0.9 (0.3–2.7)	0.8 (0.2–6.8)	1.4 (0.3–6.8)	<0.001[c]

NS not significant

[a] Excessive alcohol intake was defined as consumption of more 86 g alcohol/day

[b] Significant difference between Group B and Group A or Group C

[c] Significant difference between Group C and Group A or Group B

Table 2 Characteristics of the HCC nodule

	Group A (surveillance) ($n = 124$)	Group B (scheduled doctor visits) ($n = 79$)	Group C (non-screened) ($n = 37$)	*P* value
Solitary	82 (66%)	38 (48%)	9 (24%)	<0.001[b]
Size of main nodule				
–2 cm	80 (64%)	20 (25%)	2 (5%)	<0.001[b]
2.1–3 cm	31 (25%)	14 (18%)	6 (16%)	
3.1–5 cm	12 (10%)	33 (42%)	8 (22%)	
5.1 cm–	1 (1%)	12 (15%)	21 (57%)	
Vascular thrombus	4 (3%)	9 (11%)	10 (27%)	<0.001[b]
Distant metastases	1 (1%)	1 (1%)	5 (14%)	<0.001[c]
Tumor marker[a]				
Both negative	58 (47%)	9 (11%)	4 (11%)	<0.001[d]
Either positive	57 (46%)	51 (65%)	21 (57%)	
Both positive	9 (7%)	19 (24%)	12 (32%)	
Within the Milan criteria	109 (88%)	41 (52%)	10 (27%)	<0.001[b]

[a] HCC related tumor marker: AFP, DCP. Arbitrary cutoff values of 200 ng/ml and 40 mAU/ml were used for AFP and DCP, respectively

[b] Significant difference among all three groups

[c] Significant difference between Group C and Group A or Group B

[d] Significant difference between Group A and Group B or Group C

either or both AFP and DCP. Most patients in Group C who were in early tumor stages were diagnosed with HCC incidentally.

Figure 2a shows the distribution of tumor stages according to the Liver Cancer Study Group of Japan [19]. Proportions of patients in stages I and II were highest in the

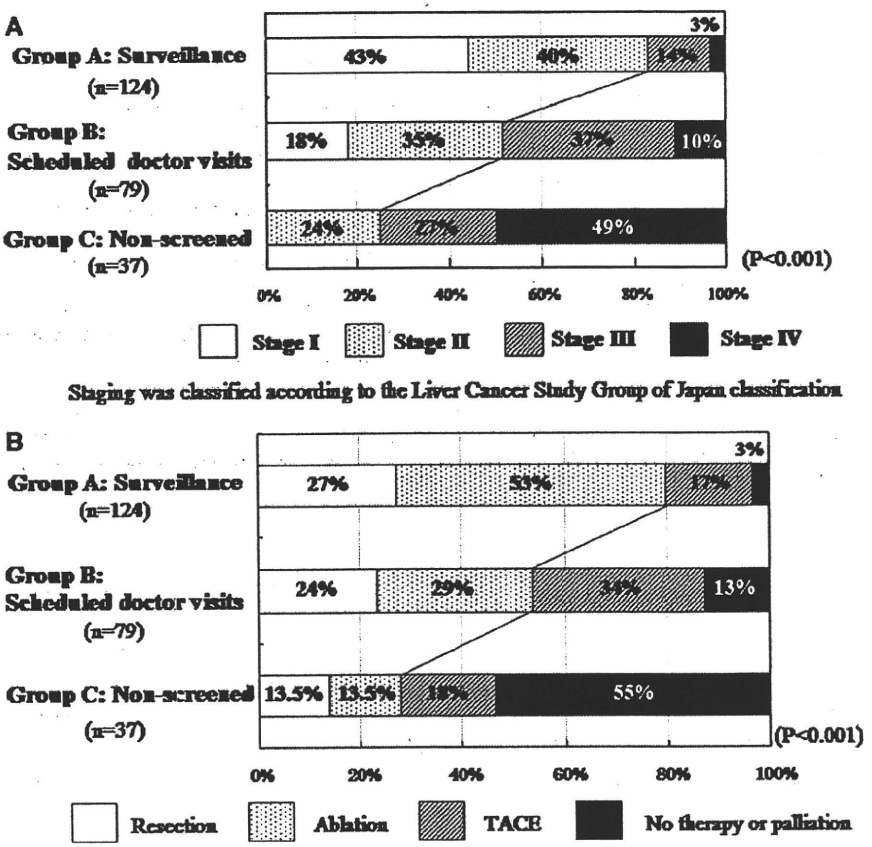

Fig. 2 a distribution of tumor stage according to the Liver Cancer Study Group of Japan [19]. b Distribution of treatment selected based on tumor stage and hepatic reserve

surveillance group (Group A); they decreased progressively through Group B to Group C ($P < 0.001$). The incidence of vascular thrombosis increased from 3% (4/124) in Group A to 11% (9/124) in Group B, and to 27% (10/37) in Group C ($P < 0.001$). Distant metastases were more frequent in Group C [14% (5/37)] than in Groups A and B [1% (1/124) and 1% (1/79), respectively] ($P < 0.001$). In Group A, the proportions of stages I and II was comparable between the patients with an interval between the latest imaging and diagnosis of HCC within 6 months and those with that of longer than 6 months [84% (86/102) vs. 77% (17/22)].

Treatment selection

Figure 2b shows the distribution of treatments selected based on the tumor stage and hepatic reserve. The proportion of patients treated with curative procedures, such as resection and ablation, was highest in Group A, and was lower in Groups B than C ($P < 0.001$). In Group C, the majority of patients received systemic chemotherapy or conservative care in hospice (palliation); most patients treated with curative procedures were diagnosed incidentally.

Survival

The median follow-up period was 35 months (range 3–94 months). During follow-ups, 148 patients died. Causes of death were cancer-related in 110 cases, liver failure in 6 (unrelated to treatment), gastrointestinal bleeding in 8, and others in the remaining 24. The distribution was similar between Groups A and B, while cancer-related causes were most prevalent (96%) in Group C. Figure 3a compares overall survival rates among the three groups. The cumulative survival rate was higher in group A than B ($P < 0.05$), and higher in group B than C ($P < 0.001$). Although survival rates of patients treated by curative procedures, such as resection and ablation, tended to be higher than the overall survival rate, there were no significant differences in the survival rates among patients in the three groups (Fig. 3b).

Discussion

For achieving better outcomes in patients with HCC, it is necessary to increase their eligibility for curative treatment. In the present study, 83% of patients under regular

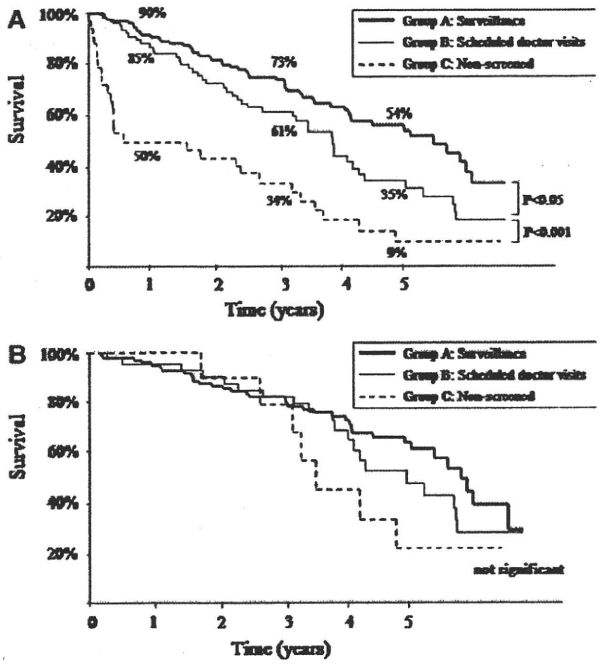

Fig. 3 a Survival rates in the three groups with different surveillance procedures. b Survival rates of the patients in three groups who had received curative treatments, such as resection and ablation

surveillance (Group A) were diagnosed with HCC at stage I or II, and the majority of them were indicated to curative treatments including surgical resection and RFA. As the results, patients in the surveillance group had a significantly better prognosis than those in the other groups without regular imaging screening (Group B) or none at all (Group C). Other reasons for the difference in prognosis among the three groups may include the following. Since the severity of underlying liver disease is a critical factor influencing the efficacy of surveillance programs, surveillance is reported to have few effects on improving the prognosis of patients with advanced cirrhosis [4, 10]. Although prevalence of cirrhosis was no different among the three groups, hepatic reserve was poorer in Group C than Group A or Group B. The dismal prognosis of patients in Group C, therefore, was attributed to either or both advanced tumor stage and poorer hepatic function. Indeed, analysis of only the patients who had received curative treatments, such as resection or ablation, revealed no significant differences in the survival among the three groups. However, the proportion of patients who had received curative treatment differed among the three groups with distinct diagnostic procedures.

Performance of surveillance would depend on the treatment selected and its efficacy. The 5-year survival of patients with a solitary HCC < 5 cm or up to 3 nodules <3 cm (Milan criteria [20]) exceeds 70% after transplantation, and that after resection surpasses 50% [12–14]. In general, transplantation offers the best long-term survival, and should be considered. In Japan, however, it is quite difficult for HCC patients to receive liver transplantation due to the shortage of donors [16], and liver resection is regarded as safe with less than 1% mortality [25]. Due to these background considerations, transplantation was not performed in the present study.

Should patients within the Milan criteria have undergone transplantation, differences in the outcome between Group A and Group B would have been reduced. In actuality, differences in the proportion of patients within the Milan criteria were lower that those in the distribution of stage I or II between them. The 5-year survival after resection was accomplished by 61% of patients with stage-II HCC and 73% of those with stage-I HCC; the staging was in accord with the definition of the Liver Cancer Study Group of Japan [16]. Thus, survival after resection in patients in Group A was comparable to that reported in transplanted patients within the Milan criteria. Indeed, the 5-year survival of patients in Group A who received curative treatments reached 63%. At present, the lack of sufficient liver donation is a worldwide problem in performing liver transplantation. Our results may indicate that surveillance by regular imaging can gain an excellent outcome where and when transplantation is hardly feasible, especially in patients with small HCC that can be treated by RFA or surgical resection.

With respect to HCC-related serological markers, most patients in Group A were negative for either AFP or DCP when they were diagnosed with HCC, in remarkable contrast to the majority of patients in Group B or C who were positive for either or both markers. In Group B, one-third of patients were tested for tumor markers during their scheduled doctor visits. However, the distribution of tumor stages was comparable between the patients with and without tumor-marker testing. Although yearly office visits would be helpful in early detection of HCC, periodical medical check-ups without screening by imaging may not necessarily detect early-stage disease, even if HCC-related markers such as AFP and DCP are tested for. This is the first report of poor performance of tumor markers including DCP in detecting early-stage HCC, and it suggests that various imaging procedures help detect HCC at a stage before levels of tumor markers elevate. Our results support the AASLD guideline that AFP alone should not be used for HCC screening when ultrasonography is not available [14]. On the other hand, it should be noted that 17% of patients in Group A in this study were diagnosed with HCC in stage III or IV, and 86% (18/21) of them were positive for either AFP or DCP. We therefore propose that HCC surveillance by regular imaging should be complemented with intermittent tests for tumor-markers, insofar as their elevated levels may reflect invisible nodules. As an

extension to this, repeated imaging with intermittent measurements of two different HCC-related tumor markers are included in the algorithm of the HCC surveillance program; it is described in Evidence-Based Clinical Practice Guidelines for HCC supported by the Japanese Ministry of Health, Labor and Welfare [26].

In a cirrhotic liver, small lesions detected by ultrasonography are likely to represent HCC. Even lesions not typical of cancer might transform into bona fide HCC during subsequent follow-ups. Generally, the incidence of HCC increases with the nodule size. In the present study, lesions >1 cm in diameter were examined by dynamic study, together with follow-ups by imaging at 3–6 month intervals, even when the appearance was atypical of HCC. Lesions >1.5 cm should be evaluated by dynamic study, preferably in combination with angiographically assisted CT or biopsy. Since the incidence of hypervascularity and moderately or poorly differentiated histology increases in HCC >1.5 cm [27–30], a 1.5-cm threshold in diameter may improve early diagnosis of HCC.

The AASLD guidelines recommend at-risk patients be screened by ultrasonography at 6–12-month intervals [14]. In our study, patients in Group B who had not undergone imaging for at least one year before the diagnosis often presented with advanced disease. A surveillance interval <12 months is therefore desirable. Although most patients in Group A were diagnosed with HCC within 6 months after the latest imaging, the proportion of stage I or II was similar between patients with the interval between the latest imaging and diagnosis of HCC below and above 6 months. However, optimal frequency of imaging was not determined in the present study. Further studies are required to determine the optimal screening interval.

Surveillance with imaging is feasible only in populations at risk for HCC, because radiological procedures are highly labor-intensive in comparison with serological testing. Major causes of cirrhosis in patients with HCC include HBV, HCV, alcoholic liver disease, exposure to aflatoxin, and possibly nonalcoholic steatohepatitis (NASH). Persistent infection with HBV or HCV is the most common cause of chronic liver disease including HCC, and increases the risk of HCC by approximately 20-fold. Heavy alcohol use and aflatoxin ingestion are environmental carcinogenic factors, and act synergistically with other risk factors [12–15]. In evaluating risks for HCC, geographic variations in incidence has to be taken into account. A recent study suggested an increased risk of HCC among patients with metabolic diseases such as diabetes or NASH [31–35]. However, the rate of HCC development in patients with NASH-related cirrhosis was significantly lower than that in those with HCV-related cirrhosis [33]. Thus, it remains uncertain how to assign surveillance programs to patients with metabolic disease.

In conclusion, surveillance programs including regular ultrasonography are useful for identifying HCC in early stages. HCC detected early is frequently indicated to curative treatments, such as resection and RFA, and is associated with better survival. Recently, several studies demonstrated that elderly patients infected with HCV developed HCC despite low-grade fibrosis stages [36, 37]. Elderly patients with HCV would be at high risk for the development of HCC, even though they do not show progression to cirrhosis. In the present study, most patients over 75 years were non-cirrhotic. Management of HCC should include early detection programs in all patients with HCV-related chronic liver disease including elderly patients in Japan.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
2. Oka H, Kurioka N, Kim K, Kanno T, Kuroki T, Mizoguchi Y, et al. Prospective study of early detection of hepatocellular carcinoma in patients with cirrhosis. Hepatology. 1990;12:680–7.
3. Colombo M, de Franchis R, Del Ninno E, Sangiovanni A, De Fazio C, Tommasini M, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med. 1991;325:675–80.
4. Yuen MF, Cheng CC, Lauder IJ, Lam SK, Ooi CG, Lai CL. Early detection of hepatocellular carcinoma increases the chance of treatment: Hong Kong experience. Hepatology. 2000;31:330–5.
5. Tong MJ, Blatt LM, Kao VW. Surveillance for hepatocellular carcinoma in patients with chronic viral hepatitis in the United States of America. J Gastroenterol Hepatol. 2001;16:553–9.
6. Trevisani F, De NS, Rapaccini G, Farinati F, Benvegnù L, Zoli M, et al. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol. 2002;97:734–44.
7. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130:417–22.
8. Yu EW, Chie WC, Chen TH. Does screening or surveillance for primary hepatocellular carcinoma with ultrasonography improve the prognosis of patients? Cancer J. 2004;10:317–25.
9. Mok TS, Yeo W, Yu S, Lai P, Chan HL, Chan AT, et al. An intensive surveillance program detected a high incidence of hepatocellular carcinoma among hepatitis B virus carriers with abnormal alpha-fetoprotein levels or abdominal ultrasonography results. J Clin Oncol. 2005;23:8041–7.
10. Trevisani F, Santi V, Gramenzi A, Di Nolfo MA, Del Poggio P, Benvegnù L, et al. Italian Liver Cancer group. Surveillance for early diagnosis of hepatocellular carcinoma: is it effective in intermediate/advanced cirrhosis? Am J Gastroenterol. 2007;102:2448–57.
11. Davila JA, Weston A, Smalley W, El-Serag HB. Utilization of screening for hepatocellular carcinoma in the United States. J Clin Gastroenterol. 2007;41:777–82.
12. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35:421–30.

13. Llovet JM, Beaugrand M. Hepatocellular carcinoma: present status and future prospects. J Hepatol. 2003;38:S136–49.
14. Bruix J, Sherman M, Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology. 2005;42:1208–36.
15. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology. 2007;132: 2557–76.
16. Ikai I, Arii S, Ichida T, Okita K, Omata M, Kojiro M, et al. Report of the 16th follow-up survey of primary liver cancer. Hepatol Res. 2005;32:163–72.
17. Ohishi W, Kitamoto M, Aikata H, Kamada K, Kawakami Y, Ishihara H, et al. Impact of aging on the development of hepatocellular carcinoma in patients with hepatitis C virus infection in Japan. Scand J Gastroenterol. 2003;38:894–900.
18. Ikeda K, Saitoh S, Kobayashi M, Suzuki Y, Tsubota A, Suzuki F, et al. Distinction between chronic hepatitis and liver cirrhosis in patients with hepatitis C virus infection. Practical discriminant function using common laboratory data. Hepatol Res. 2000;18: 252–66.
19. Liver Cancer Study Group of Japan. General rules for the clinical and pathological study of primary liver cancer. 2nd English ed. Tokyo: Kanehara; 2003.
20. 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;334:693–9.
21. Schwartz M, Roayaie S, Konstadoulakis M. Strategies for the management of hepatocellular carcinoma. Nat Clin Pract Oncol. 2007;4:424–32. Review.
22. Kamada K, Kitamoto M, Aikata H, Kawakami Y, Kono H, Imamura M, et al. Combination of transcatheter arterial chemoembolization using cisplatin-lipiodol suspension and percutaneous ethanol injection for treatment of advanced small hepatocellular carcinoma. Am J Surg. 2002;184:284–90.
23. Kitamoto M, Imagawa M, Yamada H, Watanabe C, Sumioka M, Satoh O, et al. Radiofrequency ablation in the treatment of small hepatocellular carcinomas: comparison of the radiofrequency effect with and without chemoembolization. AJR Am J Roentgenol. 2003;181:997–1003.
24. Kamada K, Nakanishi T, Kitamoto M, Aikata H, Kawakami Y, Ito K, et al. Long-term prognosis of patients undergoing transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: comparison of cisplatin lipiodol suspension and doxorubicin hydrochloride emulsion. J Vasc Interv Radiol. 2001; 12:847–54.
25. Makuuchi M, Kokudo N, Arii S, Futagawa S, Kaneko S, Kawasaki S, et al. Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan. Hepatol Res. 2008;38:37–51.
26. Group formed to establish "Guidelines for evidence-based clinical practice for the treatment of liver cancer". Clinical practice guidelines for hepatocellular carcinoma (in Japanese). Tokyo: Kanehara & Co., Ltd.; 2005.
27. Takayasu K. Hepatic angiography. In: Okuda K, Tabor E, editors. Liver cancer. New York: Churchill Livingstone; 1997. p. 347–59.
28. Nakashima Y, Nakashima O, Hsia CC, Kojiro M, Tabor E. Vascularization of small hepatocellular carcinomas: correlation with differentiation. Liver. 1999;19:12–8.
29. Kojiro M, Nakashima O. Histopathologic evaluation of hepatocellular carcinoma with special reference to small early stage tumors. Semin Liver Dis. 1999;19:287–96.
30. Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology. 2008;47:97–104.
31. Adami HO, Chow WH, Nyrén O, Berne C, Linet MS, Ekbom A, et al. Excess risk of primary liver cancer in patients with diabetes mellitus. J Natl Cancer Inst. 1996;88:1472–7.
32. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology. 2004;126:460–8.
33. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol. 2006;4:369–80.
34. Sanyal AJ, Banas C, Sargeant C, Luketic VA, Sterling RK, Stravitz RT, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. Hepatology. 2006;43:682–9.
35. Ohishi W, Fujiwara S, Cologne JB, Suzuki G, Akahoshi M, Nishi N, et al. Risk factors for hepatocellular carcinoma in Japanese population: a nested case-control study. Cancer Epidemiol Biomarkers Prev. 2008;17:846–54.
36. Miki D, Aikata H, Uka K, Saneto H, Kawaoka T, Azakami T, et al. Clinicopathological features of elderly patients with hepatitis C virus-related hepatocellular carcinoma. J Gastroenterol. 2008;43:550–7.
37. Saneto H, Kobayashi M, Kawamura Y, Yatsuji H, Sezaki H, Hosaka T, et al. Clinicopathological features, background liver disease, and survival analysis of HCV-positive patients with hepatocellular carcinoma: differences between young and elderly patients. J Gastroenterol. 2008;43:975–81.