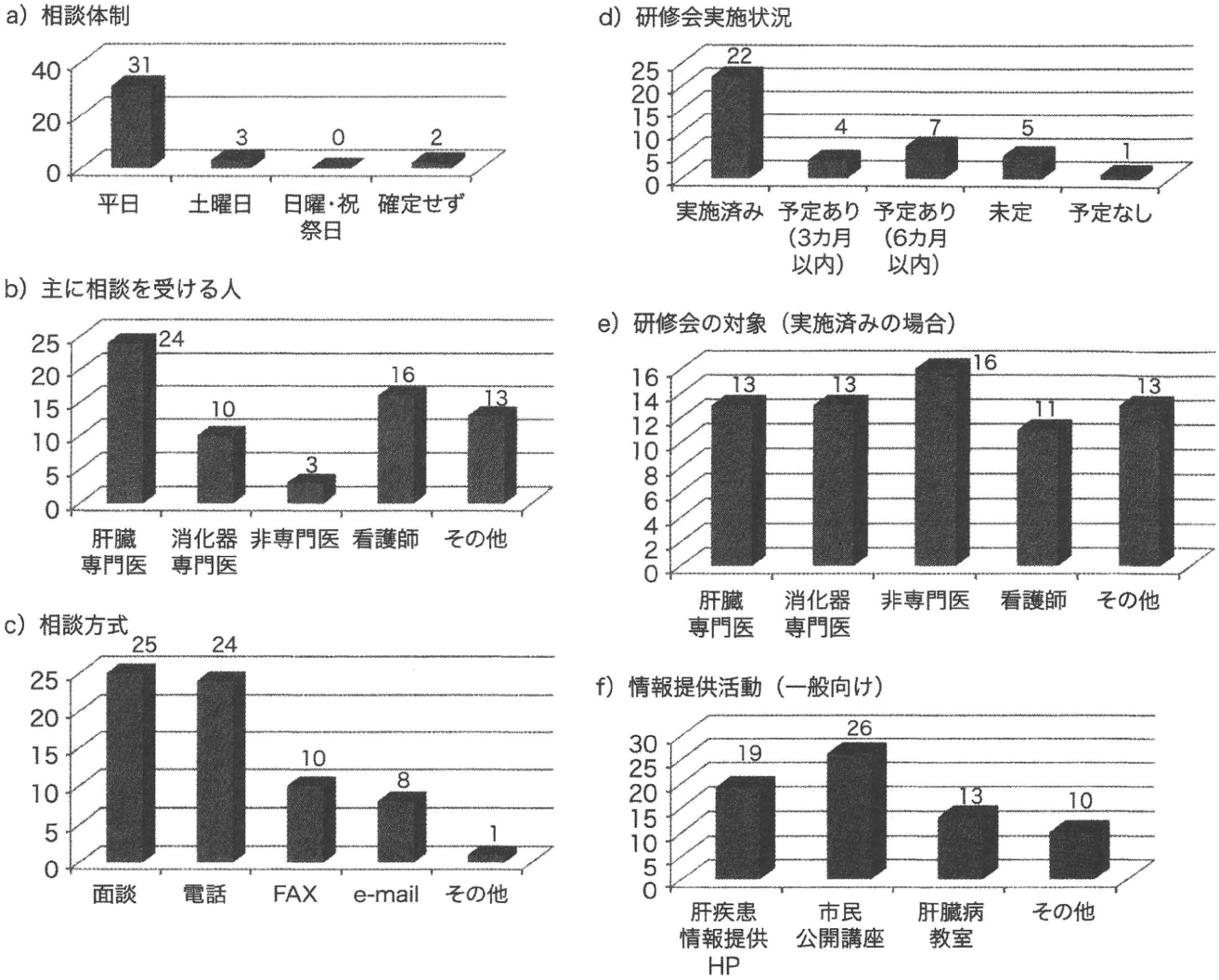

図4　肝疾患診療連携拠点病院の現状調査結果（平成21年6月実施）

のほか，ホームページ開設，肝臓病教室の実施など，情報の均霑化に努力されている現状が確認された（図4-f）．

5　おわりに

都道府県単位の拠点病院事業は順調なスタートを切ったと評価したい．さらに，国では拠点病院事業を支援するシステムとして，平成20年11月に国立国際医療センター（現国立国際医療研究センター）に肝炎情報センターを設置し，①インターネット等による最新情報提供（ホームページ http://www.ncgm.go.jp/center/index.html），②拠点病院間情報共有支援（肝疾患診療連携拠点病院で構成する協議会組織の事務局機能），③研修機能（肝疾患診療連携拠点病院等の医療従事者に対する研修の企画・立案・推進）の3つのミッションを担わせている．平成22年1月から肝炎対策基本法が施行されたこともあり，国，地方公共団体，医療保険者，国民および医師などの，すべての立場における関係者が肝炎撲滅を目指して一層の努力をすることが求められている．

肝炎情報センターの役割

正　木　尚　彦*

索引用語：肝炎情報センター，肝疾患情報提供検討委員会，
肝疾患相談支援センター研修会，データベース構築

1　はじめに

都道府県では肝疾患診療連携拠点病院を中心とした肝疾患診療ネットワークの構築が順調に進捗しているが，これらの諸活動を支援するシステムとして，国立国際医療センター（現独立行政法人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．その果たすべき役割として3つのミッションがある（図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（http://www.ncgm.go.jp/center/index.html）．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定期的に開催し，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を対象とした「研修会」の企画・立案・推進を行っている．本稿では，肝炎情報センター設置の経緯，ならびにその果たすべき3つのミッションについて概説するとともに，肝炎情報センターが「情報の発信」に加えて「情報の収集」についても取り組みつつある現状を紹介することとする．

2　肝炎情報センター設置の経緯

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纏められ，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．この施策に基づいて，本特集のテーマである「肝疾患診療連携拠点病院」構想が具体化されることになったわけである．その当初から，国（厚生労働

Naohiko MASAKI: An appointed task of hepatitis information center
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［〒272-8516 千葉県市川市国府台 1-7-1］

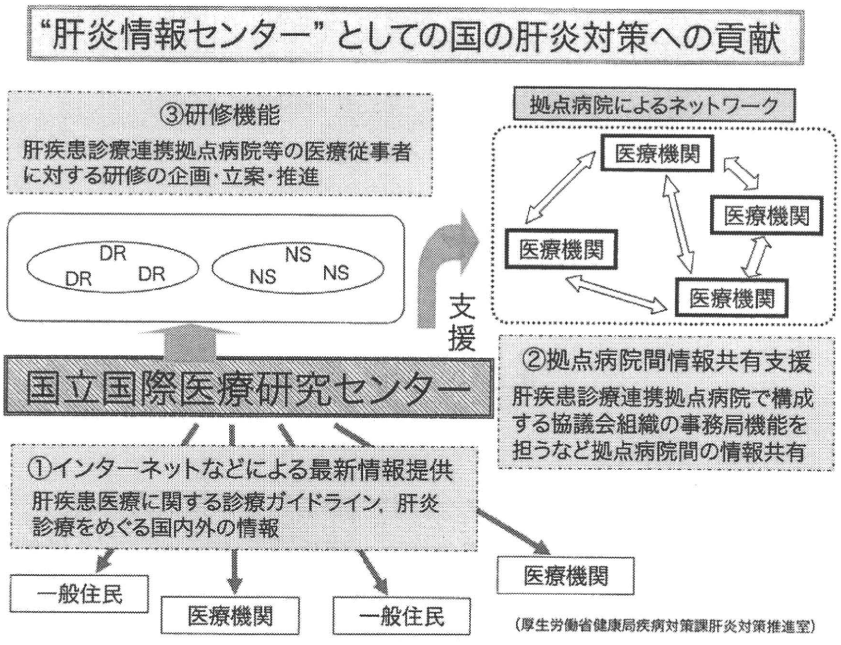

図1　肝炎情報センターに課せられた3つのミッション

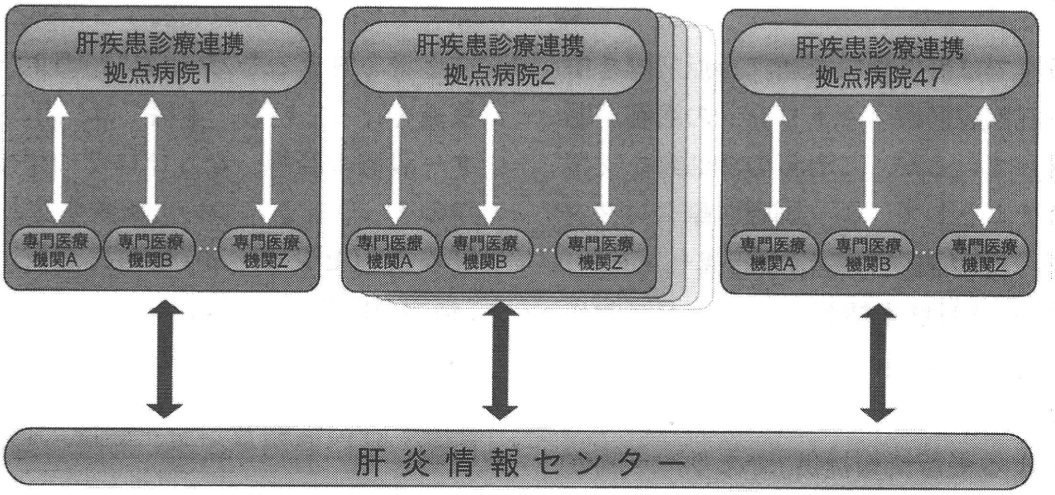

図2　拠点病院事業における肝炎情報センターの位置づけ

省)には，肝炎診療の均てん化・医療水準の向上をさらに全国的に推進するためには，特に情報提供機能について都道府県の肝疾患診療連携拠点病院を支援するシステムが必要であること，および，肝炎については国内外で基礎・臨床研究が急速に進行していることから，定期的に正確な情報をデータベース化し，広く発信するシステム作りが必要であるとの認識があった．そこで，平成19年度厚生労働科学研究費補助金特別研究事業「肝炎診療全国ネットワーク構築とその支援のための情報センターのあり方に係る研究」班(主任研究者:正木尚彦)において，肝疾患に関する基礎・臨床研究に関する情報収集，情報提供および研修システムについての基盤を構築することを目的とした開発研究が行われた．本研究班にはオブザーバーとして厚生労働省健康局疾病対策課の専門官も参加されたことから，行政側との意見交換も行われた．なお，後述する肝炎情報センターホームページの雛型版は

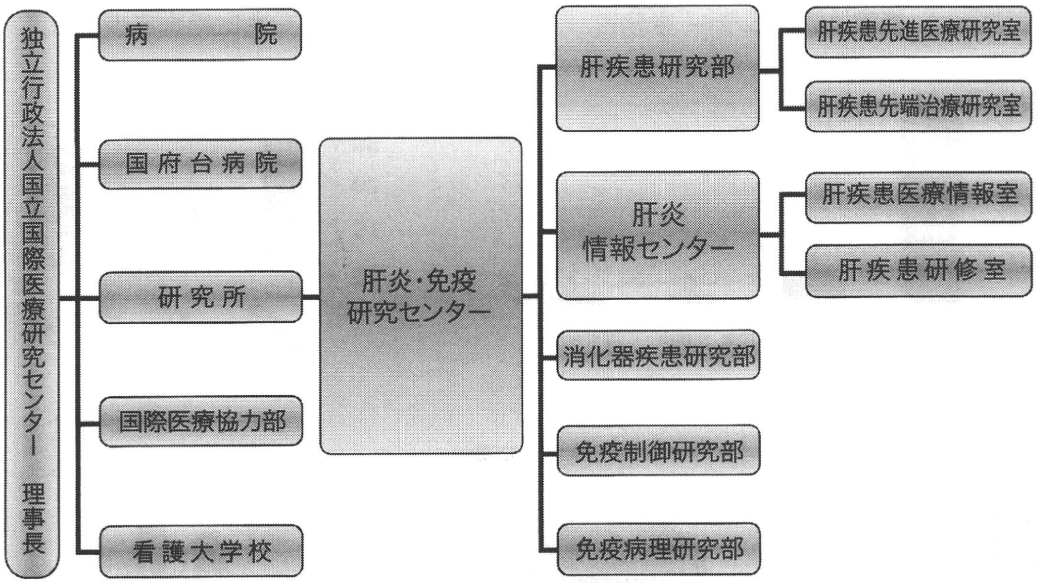

図3　肝炎情報センターに係わる組織図

表1　肝疾患情報提供検討委員会構成委員一覧

氏　名	所　属
林　紀夫	独立行政法人労働者健康福祉機構 関西労災病院 病院長
熊田　博光	国家公務員共済組合連合会 虎の門病院 分院長
小池　和彦	東京大学 大学院医学系研究科 消化器内科学教授
脇田　隆字	国立感染症研究所 ウイルス第二部部長
田中　純子	広島大学大学院 医歯薬学総合研究科疫学・疾病制御学講座教授
八橋　弘	独立行政法人 国立病院機構長崎医療センター臨床研究センター 治療研究部長
泉　並木	武蔵野赤十字病院 副院長
茶山　一彰	広島大学 大学院医歯薬学総合研究科 分子病態制御内科学教授
榎本　信幸	山梨大学 大学院医学工学総合研究部 第一内科教授
溝上　雅史	独立行政法人国立国際医療研究センター 肝炎・免疫研究センター長
正木　尚彦	独立行政法人国立国際医療研究センター 肝炎・免疫研究センター 肝炎情報センター長

本研究班の分担研究者の先生方によって作成されたものである．国立国際医療センターは6つあるナショナルセンターの中で唯一総合病院を有しており，これまでもエイズ(HIV)やSARSなどの感染症，糖尿病(さらには新型インフルエンザ)といった国民の健康に影響する重大な疾病に係る数々のミッションを担ってきた実績があることから，「肝炎」に関しても国の中核機関としての責務を果たすことが期待された．その後，平成20年10月に国立国際医療センター国府台病院(千葉県市川市)に肝炎・免疫研究センターが設置され，その一部門として同年11月に肝炎情報センターが設置された(図2)．なお，国立国際医療センターが平成22年4月に独立行政法人化されたため，組織図上，肝炎情報センターは研究所に所属することとなった(図3)．さらに，肝炎情報センターの活動を円滑に運用するための専門組織として肝疾患情報提供検討委員会を設置し，肝疾患領域における指導的

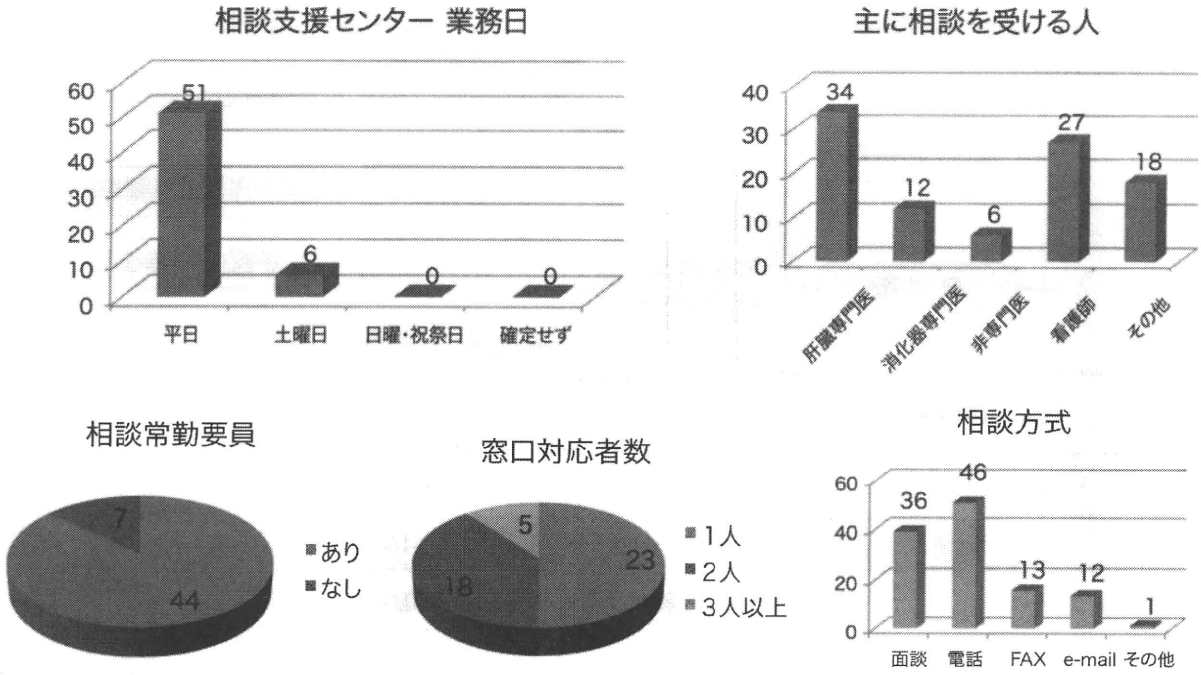

図4　平成21年度拠点病院事業活動に関する現状調査(平成22年5月実施) ～肝疾患相談支援センタ～

立場の先生方にもご協力いただいている．平成22年8月現在の構成委員を表1に示す．

3 インターネットなどによる最新情報提供

先述したように，肝炎情報センター構想は都道府県肝疾患診療連携拠点病院を情報提供機能面から支援するシステムということであった．しかし，薬害肝炎訴訟等を契機として，肝疾患に対する国民全体の認識が高まっていたことから，「肝炎診療全国ネットワーク構築とその支援のための情報センターのあり方に係る研究」班においても，肝臓専門医のみならず，非専門医，国民全般を対象にすべきとの議論が交わされた．その結果として，ホームページは「肝臓専門医向け」，「非専門医・医療従事者向け」，「患者さん向け」を対象とし，急性肝炎，B型肝炎，C型肝炎，肝硬変，および肝細胞がんに関して三者三様に解説することとした．拠点病院事業を支援する内容としては，各施設へのリンクに肝疾患相談支援センターを加え，さらに，専門医療機関に関する情報へもリンクさせた．また，自治体の中にはこれまでの拠点病院事業活動を出版物として纏める動きもみられることから，PDF形式で提供していただいた資料へリンクさせる試みも始めたところである．これらの資料は他の自治体や拠点病院にとっての極めて有用な情報源となることが期待される．

4 拠点病院間での情報共有への支援

平成22年4月現在，全国45道府県において65医療機関が拠点病院の指定を受け，肝疾患診療ネットワークの中心としてさまざまな事業活動を行っている．これら拠点病院間での情報共有の円滑化を図る目的で，肝炎情報センター主催の拠点病院間連絡協議会を原則として年2回開催している．協議会では，肝疾患情報の収集・提供に関すること，肝疾患診療などに係わる人材育成に関すること，その他協議会の運営に必要な事項に関する協

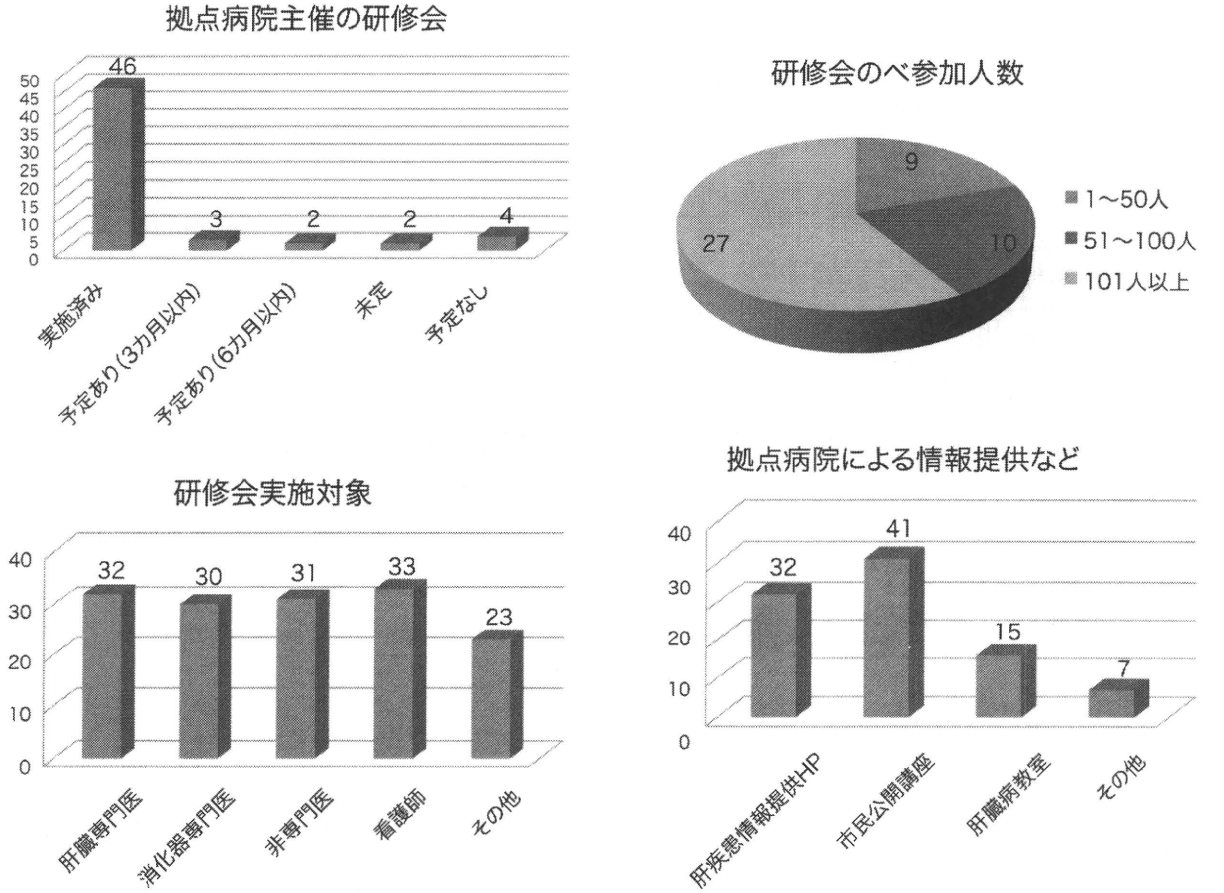

図5　平成21年度拠点病院事業活動に関する現状調査(平成22年5月実施) ～研修会と情報提供～

議を行っている．また，拠点病院事業活動に関する現状調査を年1回実施し，肝疾患相談支援センターの活動状況，研修会開催状況などについての情報収集を行っている．平成22年度は5月に実施し，55病院から回答を得た．図4に肝疾患相談支援センターの活動状況，図5に研修会の開催状況，情報提供活動の状況を示す．55病院中52病院がすでに相談支援センターを設置しており，平日のほか土曜日にも対応している施設が6病院あった．相談員は肝臓専門医，看護師が主に務めており，ほとんどの施設が常勤スタッフを置いていた．相談方式は電話，面談が大部分で，次いでファックス，メールの順であった．研修会については，ほとんどの施設がすでに実施ずみと回答しており，その対象として肝臓・消化器専門医のほか，非専門医，看護師も含まれており，当該地域の肝炎診療のレベルアップのために努力されている現状がうかがえた．情報提供の手段として，市民公開講座の開催，相談支援センターホームページの開設が積極的に行われていた．しかし，肝臓病教室の実施は約3割程度の施設に留まっており，今後の一層の取り組みが嘱望される結果であった．

5　研修会の企画・立案・推進

さて，肝炎情報センターの3番目のミッションが拠点病院などの医療従事者向けに行う研修会の開催である．平成20年11月以降，医師向け，および看護師向け研修会を開催してきた．医師向け研修会では，「診療ネットワーク構築に関するノウハウ」，「肝炎検診後のフォローアップ体制の拡充」など，拠点病

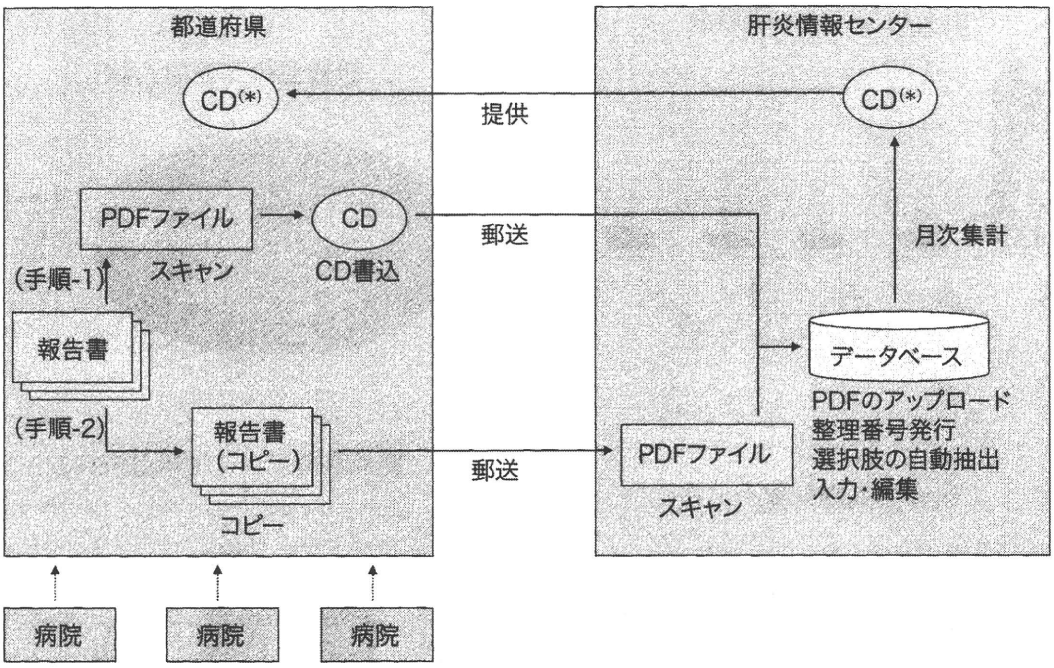

図6　情報の流れ

院事業の推進に必要な知識に加えて，「肝炎に関する最新の疫学」,「肝炎治療の最新情報」などのトピックをテーマとして取り上げてきた．また，看護師向け研修会では，肝疾患診療に関する一般的知識のみならず，「患者のメンタルケア」，看護師として係わることが期待されている「肝疾患相談センター相談員」や「肝臓病教室の運営」に関する情報の取得を目的としている．特に，看護師向け研修会は2日目にグループワークを行うため，分担するテーマに関する事前のレポート提出を必須とし，さらに，研修会当日の講師にはファシリテーターを務めていただくなど，極めて充実したプログラムになっている．今後は肝疾患相談センター相談員や病院栄養士などにも対象を拡げるべく調整を行っているところである．これらの研修会を修了した医療従事者には，各拠点病院が当該自治体において開催する研修会において中核的な役割を果たすことが期待されている．

6　肝疾患に関する情報収集と解析

さて，肝炎情報センターでは情報発信のみならず，肝炎患者に関する情報収集ならびに解析にも事業を拡大している．その一つとして，平成21年度から開始している「インターフェロン療法に係る公費助成を受けたB型・C型肝疾患患者の治療成績に関する全国規模のデータベース構築に関する研究」について紹介する．平成20年4月からB型・C型肝疾患のインターフェロン療法に対する医療費助成が開始され，さらに，平成22年4月からはさらなる拡充，すなわち，患者自己負担限度額の引き下げ，ならびにB型肝炎の核酸アナログ製剤に対する医療費助成追加が行われているところである．具体的数字では平成22年度の肝炎対策分政府予算236億円のうち180億円がインターフェロン・核酸アナログ治療費助成に充当されることになっている．このように多額の公的資金が投入されている以上，そのアウトカムについて検証すべきで

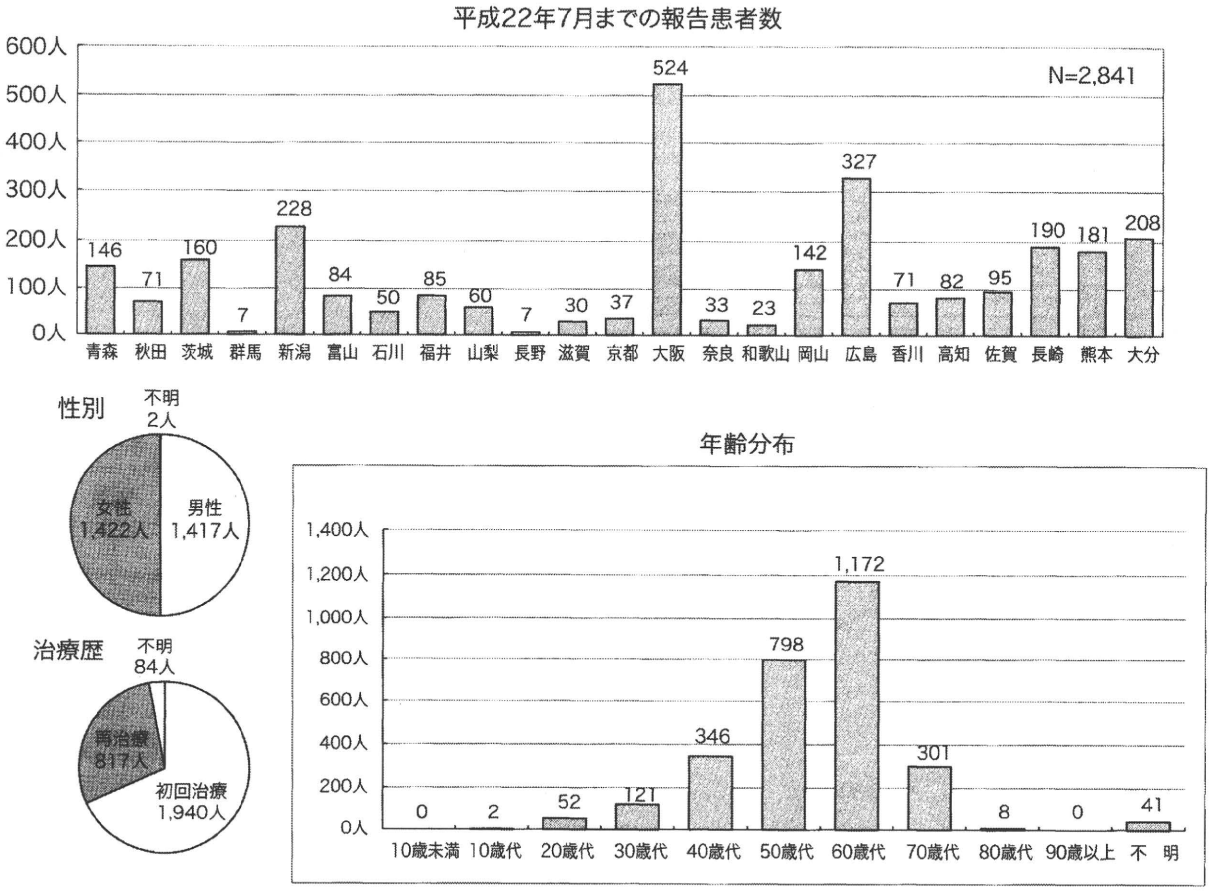

図7　患者背景

あることはいうまでもない．しかし，肝疾患患者が治療をより受けやすくなるように国と自治体が環境整備を図っているにもかかわらず，例えばインターフェロン医療費助成の交付を受けた患者数は平成20年度では44,731人，平成21年度では26,594人に留まったという現実がある．その原因として，肝疾患患者に対する啓発活動の不足，診療アクセス上の課題などが指摘されているが，わが国における肝炎治療の現状についての具体的情報が不足している可能性も想定される．そこで，筆者が研究代表者を務めている厚生労働科学研究費肝炎等克服緊急対策研究事業「肝炎に関する全国規模のデータベース構築に関する研究」の一環として，わが国でインターフェロン治療を受けているB型・C型肝疾患患者の年齢，性別，肝病変進行度，ウイルス型，ウイルス量，副作用の出現状況，および最終的治療効果などに関する臨床情報の収集を平成21年度から開始した．全体の情報の流れ(図6)を説明すると，①主治医が肝疾患インターフェロン治療効果判定報告書(以下，「報告書」)を記載する．②報告書は原則，自治体肝炎対策担当部署に提出される．③各自治体肝炎対策担当部署は報告書のオモテ面のみをスキャナによりCD-Rへ取り込むか，コピーを行い，肝炎情報センターへ郵送する．したがって，報告書のウラ面に記載された個人情報(住所，氏名など)は自治体の外には出ないことになる．なお，①と②は医療費助成事業として，③は研究事業として行われることになる．平成22年1月までに全国37都府県のご協力を得て，本研究事業を開始している．肝炎情報センターでは送付されたデータ

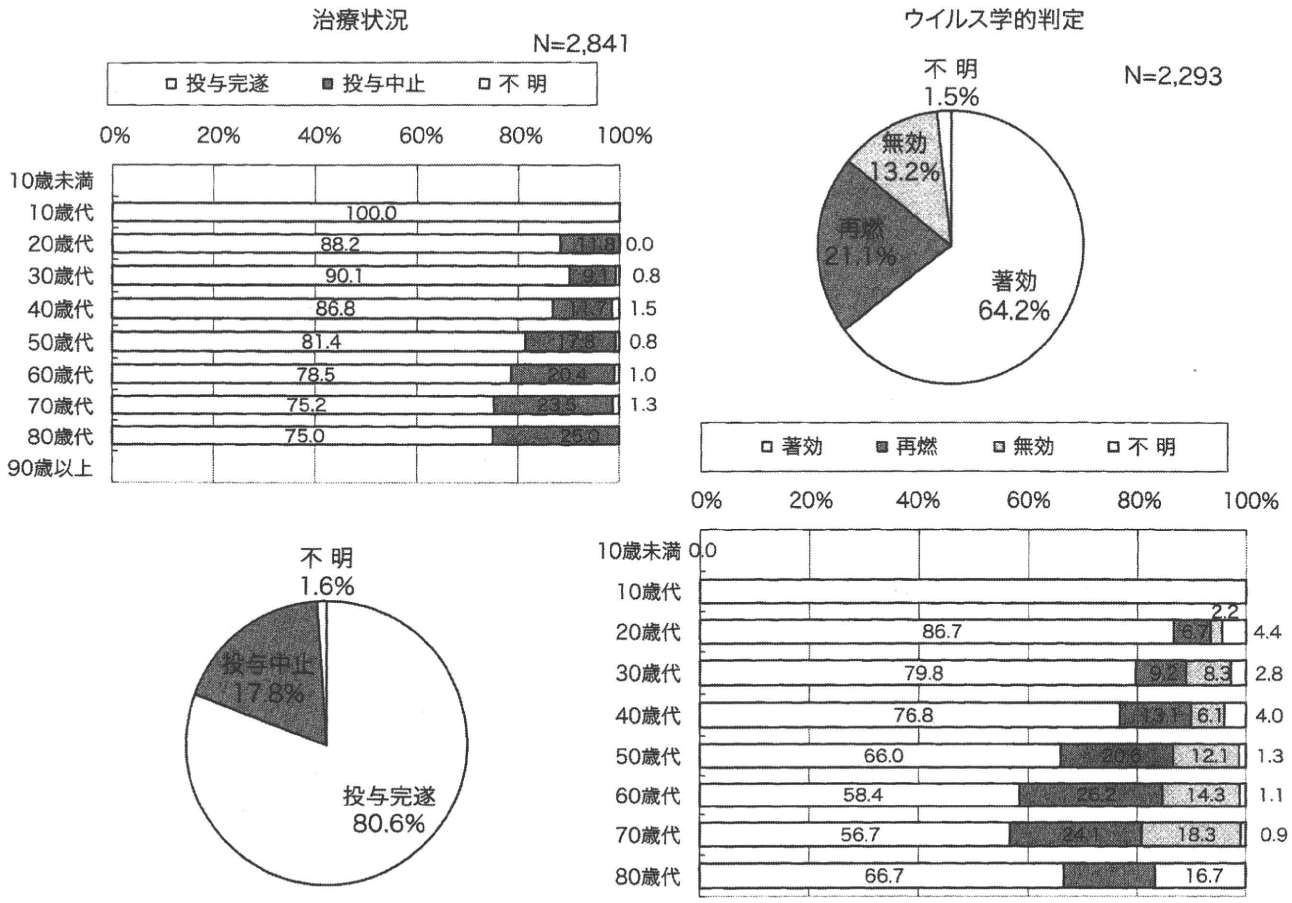

図8　治療状況とウイルス学的判定

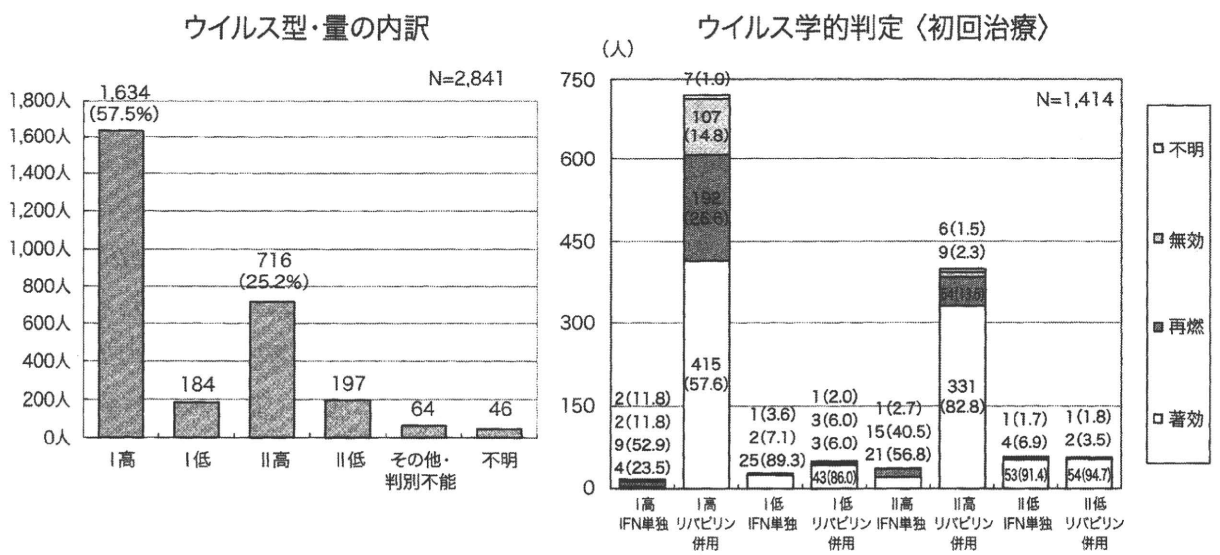

図9　ウイルス側因子と治療効果

を電子化し，エクセルファイル化するシステムをすでに構築しており，現在，2カ月ごとにデータの更新・解析を行い，その結果(全体分と当該自治体分)を各自治体へ送付している．これらのデータは各自治体で開催される連絡協議会などを介して，主治医へフィー

ドバックされることになる．平成22年7月までに23府県2,884例のデータを収集しているが，B型肝炎単独は43例に過ぎないことから，現時点ではC型肝炎中心の解析を行っている．紙面の都合上，本稿ではごく一部の結果を提示する．図7に示すように，男女比は1：1で，初回治療が7割を占め，年齢分布では60歳代がピークとなっている．図8にあるように，投与完遂率，著効率はともに高齢になるにつれて低下している．なお，ウイルス側因子(ウイルス量，型)と治療効果との関連については図9に示すように，ほぼ満足すべき成績をあげているものと考えられた．さらに，著効率，投与完遂率には地域差はみられないものの，高齢者の治療割合には有意な地域差の存在することが明らかとなっている．

今後，費用対効果などについても検討する予定である．

7 おわりに

肝炎情報センター設置の経緯，ならびに，その果たすべき3つのミッションと今後の方向性について述べた．平成22年1月から施行された肝炎対策基本法を実現させるために，現在，肝炎対策推進協議会を中心に具体的な施策の策定が進められているところであるが，肝炎情報センターとしても着実にその責務を全うしたいと考えている．そのためには，国，自治体，肝疾患診療連携拠点病院，そして患者さんとの連携をこれまで以上に密接に図って行く必要があるものと認識している．

*　　*　　*

Effect of Aging on Risk for Hepatocellular Carcinoma in Chronic Hepatitis C Virus Infection

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An increase in the aging population is an impending problem. A large cohort study was carried out to determine the influence of aging and other factors on hepatocarcinogenesis in patients treated with interferon. Biopsy-proven 2547 chronic hepatitis C patients registered at our referral center since 1992 were included. Of these, 2166 were treated with interferon-based therapy. Incidences of hepatocellular carcinoma (HCC) associated with interferon were analyzed by Kaplan-Meier and person-years methods for an average follow-up of 7.5 years. Factors associated with HCC risk were determined by Cox proportional hazard analysis. HCC developed in 177 interferon-treated patients. The risk for HCC depended on age at primary biopsy and increased more than 15-fold after 65 years of age. Even when stratified by stage of fibrosis, the cumulative and annual incidences of HCC were significantly higher in older patients than in younger patients ($P < 0.001$) at the same stage of fibrosis, except for cirrhosis. Progression of fibrosis over time was significantly accelerated in older patients. The impact of viral eradication on HCC prevention was less significant in older patients than in younger patients. Multivariate analysis confirmed that age, gender, liver fibrosis, liver steatosis, total cholesterol level, fasting blood sugar level, baseline and postinterferon alpha-fetoprotein level, and virological response to interferon were independent risk factors associated with HCC. Aging was the strongest risk factor for a nonvirological response to interferon-based antiviral therapy. *Conclusion:* Elderly patients are at a higher risk for HCC. Hepatitis C viral eradication had a smaller effect on hepatocarcinogenesis in older patients. Patients should therefore be identified at an earlier age and treatment should be initiated. (HEPATOLOGY 2010;52:518-527)

Primary liver cancer is the third most common cause of cancer mortality worldwide,[1] and hepatocellular carcinoma (HCC) is one of the most frequent primary liver cancers.[2,3] Infection with hepatitis C virus (HCV) is a common cause of chronic hepatitis, which progresses to HCC in many patients.[4] The prevalence of older patients has been increasing in Japan, and this is an impending problem in other countries where viral spread has occurred more recently.[5] The number of Americans older than 65 years is expected to double by the year 2030.[6] In Western Europe, people older than 65 years already constitute 15%-18% of the population[7]; thus, aging patient who is chronically infected with HCV is

Abbreviations: AFP, alpha-fetoprotein; HBc, hepatitis B core; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; SVR, sustained virological response.

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one of the most important issues confronted by physicians.

Viral eradication with interferon-based therapy for chronic hepatitis C has been shown to prevent HCC by studies conducted in Japan and Italy.[8-11] However, this finding is controversial according to another study conducted in Europe and Canada,[12] in which viral eradication did not significantly reduce the risk for HCC in 479 consecutively treated patients. The likelihood of development of HCC among interferon-treated patients is difficult to determine because of the paucity of adequate long-term cohort studies. Moreover, in patients who are treated with interferon the effect of certain factors, including aging, on the risk for HCC remains unclear. Furthermore, the benefit of viral eradication with interferon-based therapy, including pegylated interferon and ribavirin combination therapy, in older patients remains unknown. To further clarify this, we conducted a large-scale, long-term cohort study and analyzed the influence of aging and other host and virological factors in patients treated with interferon.

Patients and Methods

Patients. Consecutive patients (n = 2547) chronically infected with HCV who underwent liver biopsy between 1992 and January 2008 at our referral center were enrolled. Of these, 2166 patients were treated with interferon-based antiviral therapy, whereas 381 patients did not receive interferon treatment (Fig. 1). All patients had histologically proven chronic hepatitis or cirrhosis. HCV infection was proven in all patients by identification of HCV RNA. Patients with a history of HCC, autoimmune hepatitis, or primary biliary cirrhosis were excluded. We also excluded patients who had a history of excessive alcohol consumption (50 g/day) and confirmed alcohol abstinence during follow-up. No patient was positive for hepatitis B surface antigen or antihuman immunodeficiency virus antibody. Written informed consent was obtained from all patients. The study was approved by the Ethical Committee of Musashino Red Cross Hospital in accordance with the Declaration of Helsinki.

Histological Evaluation. A liver biopsy specimen was obtained laparoscopically using 13G needles. When laparoscopy was impossible, ultrasound-guided liver biopsy was performed with 15G needles (n = 254). The mean length of the specimen was 18 mm (range 12-40 mm), and the mean number of portal tracts was 17 (range 8-34). Liver biopsy specimens

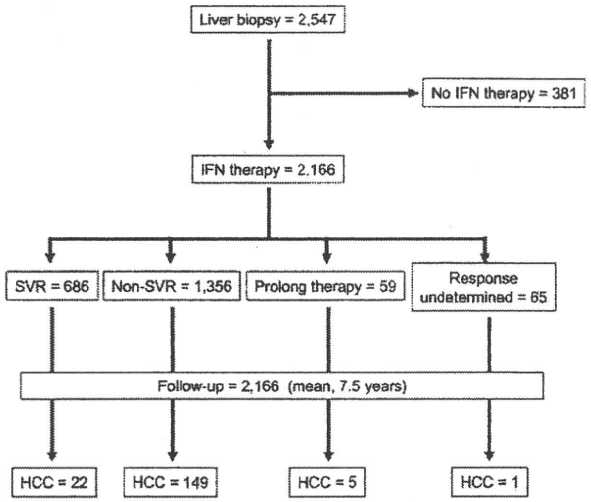

Fig. 1. Clinical outcomes of the patients enrolled in the present study. HCC, hepatocellular carcinoma; SVR, sustained virological response.

were scored by board-certified pathologists for stage of fibrosis and grade of inflammatory activity according to the classification of Desmet et al.[13] Additional macroscopic pathological information was obtained from laparoscopic findings. The percentage of steatosis was quantified by determining the average proportion of hepatocytes affected by steatosis. In this study, superimposed nonalcoholic steatohepatitis (NASH) was defined as a central pattern of colocalization of hepatic steatosis and hepatocyte ballooning with pericellular/perisinusoidal fibrosis or Mallory hyaline.

Interferon Treatment. Among the 2166 patients treated with interferon-based antiviral therapy, 1062 patients received interferon-alpha or beta monotherapy either for 24 weeks (n = 1003) or for 2 to 5 years (n = 59); 386 patients received interferon-alpha and ribavirin combination therapy for 24 weeks; 306 received pegylated interferon-alpha monotherapy for 48 weeks; and 412 received pegylated interferon-alpha and ribavirin combination therapy for 48 weeks. All interferon treatment was initiated within 48 weeks after liver biopsy.

Definitions of Response to Interferon Therapy. A patient negative for serum HCV RNA after the first 6 months of completion of interferon-based therapy was defined as a sustained viral responder. HCV RNA was determined by the qualitative Amplicor or TaqMan HCV assay (Roche Molecular Diagnostics, Tokyo, Japan).

Data Collection and Patient Follow-up. Data on patient characteristics, biochemical data, hematological

data, virological data, histological data, and treatment details were collected at enrollment. Age was determined at primary liver biopsy. Patients were examined for HCC with abdominal ultrasonography, dynamic computed tomography, and/or magnetic resonance imaging every 3-6 months. Serum alpha-fetoprotein (AFP) levels were measured every 1-2 months. This screening program constitutes the standard of care in Japan. To evaluate the effect of interferon-induced AFP reduction on hepatocarcinogenesis, the average AFP level after interferon treatment was calculated in each patient. HCC diagnosis was confirmed with needle biopsy, surgically resected specimens, or typical radiological findings diagnosed by board-certified radiologists. Figure 1 shows the schema for patient follow-up and clinical outcomes.

The start date of follow-up was the date of primary liver biopsy and the endpoint of follow-up was the development of HCC or the latest medical attendance until January 2009. The mean follow-up period was 7.5 years (range 0.5-17 years). The factors associated with development of HCC were retrospectively analyzed.

Change in Fibrosis Staging Over Time. To evaluate change in fibrosis staging over time, 271 patients who had not achieved a sustained virological response (SVR) with interferon therapy underwent a sequential biopsy after the initial biopsy. The interval between the paired biopsies was on average 4.8 years (range 0.7-14 years). The yearly rate of progression of fibrosis was calculated as the change in fibrosis staging divided by the time between paired biopsies.

Statistical Analysis. Categorical data were compared by the chi-square test and Fisher's exact test. Distributions of continuous variables were analyzed with Student's t test or the Mann-Whitney U test for two groups. All tests of significance were two-tailed and a P value of <0.05 was considered statistically significant. The cumulative incidence curve was determined with the Kaplan-Meier method and differences among groups were assessed using the log-rank test. Factors associated with HCC risk and virological response to interferon therapy were determined by the Cox proportional hazard model and logistic regression analysis, respectively. To depict the role of aging in developing risk for HCC, the multivariate Cox proportional hazard model was used after adjusting for stage of liver fibrosis, steatosis, and virological response to interferon. A polynomial regression was used to fit risk ratios for segments of the age distribution. Statistical analyses were performed using the Statistical Package for the Social Sciences software version 11.0 (SPSS, Chicago, IL).

Results

Patient Characteristics. Patient characteristics at the time of enrollment are shown in Table 1. The distribution of stages of liver fibrosis differed between younger and older patients, indicating the need to adjust for stage of liver fibrosis when comparing the two subgroups.

Response to Interferon Therapy. The response to interferon therapy was determined in 2042 (97.2%) of the interferon-treated patients, excluding those who received prolonged interferon treatment at the endpoint. SVR rates are shown in Table 1. The percentage of patients showing SVR was significantly lower in older patients (≥65 years) than in younger patients (<65 years) ($P < 0.001$). Overall response rates to the different types of interferon therapy were as follows: interferon monotherapy, 31.5% (312/992); interferon-alpha and ribavirin combination therapy, 28.6% (108/378); pegylated interferon-alpha monotherapy, 37.9% (108/285); and pegylated interferon-alpha and ribavirin combination therapy, 41.1% (159/387). Response rates in genotype-1 patients (n = 1347) were 20.6% (114/554), 17.9% (29/162), 18.9% (56/297), and 36.8% (123/334), and those in nongenotype-1 patients (n = 565) were 52.2% (163/312), 63.1% (77/122), 65.0% (52/80), and 70.6% (36/51). Overall response rates of interferon and pegylated interferon monotherapy seem to be high because of the high response rates in the nongenotype-1 patients treated with these regimens.

Overall Cumulative Incidence of HCC. During follow-up, HCC developed in 177 interferon-treated patients (Fig. 1). The cumulative incidence of HCC 5, 10, and 15 years after interferon therapy was 4.7%, 11.6%, and 15.5%, respectively. The cumulative incidence in SVR patients was 2.1%, 4.3%, and 4.3%, respectively, which was significantly lower than that in non-SVR patients (5.8%, 14.9%, and 20.2%, respectively; log-rank test, $P < 0.001$).

Effect of Aging on Risk for HCC. The risk ratio determined by multivariate Cox proportional hazards analysis after adjustment for stage of liver fibrosis, degree of liver steatosis, and virological response to interferon demonstrated that the risk for HCC after interferon treatment was age-dependent and increased predominantly when the age at primary liver biopsy was >65 years (Fig. 2A). Hence, we defined older patients as those ≥65 years of age at primary liver biopsy and younger patients as those aged <65 years. As shown in Fig. 2B, the cumulative incidence of HCC was significantly higher in older patients than in younger patients (log-rank test, $P < 0.001$).

Table 1. Characteristics of Patients Enrolled in the Present Study

Characteristics	Total	<65 year	≥65 year	*P* Value*
Patients, n	2166	1614	552	
Sex, n (%)				<0.001†
Male	1080 (49.9)	840 (52.0)	240 (43.6)	
Female	1086 (50.1)	774 (48.0)	312 (56.4)	
Age (SD), year	55.4 (12.1)	51.1 (10.8)	68.4 (2.9)	<0.001‡
BMI (SD), kg/m^2	23.3 (3.1)	23.4 (3.0)	23.3 (3.1)	0.9‡
Fibrosis stage, n (%)				<0.001†
F0	27 (1.3)	24 (1.5)	3 (0.5)	
F1	860 (39.7)	704 (43.6)	156 (28.2)	
F2	733 (33.8)	515 (31.9)	218 (39.5)	
F3	444 (20.5)	301 (18.6)	143 (25.9)	
F4	102 (4.7)	70 (4.3)	32 (5.8)	
%Severe steatosis (≥10%)	27.6	27.1	29.3	0.4†
ALT level (SD), IU/L	95 (18)	101 (119)	76 (58)	<0.001‡
HCV load (SD), KIU/mL	880 (1046)	861 (1016)	924 (1116)	0.2‡
HCV genotype, n (%)				<0.001†
1a	7 (0.3)	5 (0.3)	2 (0.4)	
1b	1414 (69.6)	1036 (68.9)	378 (71.3)	
2a	373 (18.3)	273 (18.2)	100 (18.9)	
2b	211 (10.4)	164 (10.9)	47 (8.9)	
Others	28 (1.4)	25 (1.7)	3 (0.6)	
Duration (SD), year	7.5 (4.4)	8.1 (4.4)	5.8 (3.7)	<0.001‡
IFN regimen, n (%)				<0.001†
IFN mono	1062 (49.0)	833 (51.6)	229 (41.5)	
PEG-IFN mono	306 (14.1)	200 (12.4)	106 (19.2)	
IFN + RBV	386 (17.8)	291 (18.0)	95 (17.2)	
PEG-IFN + RBV	412 (19.0)	290 (18.0)	122 (22.1)	
SVR, n (%)	686 (33.6)§	565 (36.6)‖	121 (24.3)¶	<0.001‡

Unless otherwise indicated, data are given as the mean (SD).

ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus; IFN, interferon; N/A, not applicable; PEG, pegylated; RBV, ribavirin; SVR, sustained virological response.

*Comparison between <65 years and ≥65 years.

†Chi-squared test.

‡Student *t* test.

§Virological responses were determined in 2042 patients.

‖Virological responses were determined in 1545 patients.

¶Virological responses were determined in 497 patients.

As shown in Fig. 2C-E, even when stratified by stage of fibrosis the cumulative incidences among patients at stages F0/F1, F2, and F3 were significantly greater in older patients than in younger patients (log-rank test, $P < 0.001$). These differences were not significant among patients with cirrhosis (Fig. 2F, log-rank test, $P = 0.7$).

The annual incidence of HCC after interferon treatment was calculated by the person-years method (Table 2); it increased with the degree of liver fibrosis from 0.2% (F0 or F1) to 4.6% (F4) and was higher among older patients at the same stage of liver fibrosis.

Among the 177 patients with HCC, 92 showed evidence of a single blood transfusion. We analyzed the relationship between duration of infection and age in these 92 patients. A significant and strong negative correlation was found between the interval from blood transfusion to development of HCC and the age of the patients at the time of blood transfusion ($r = -0.74$, $P < 0.001$) (Fig. 3A). The mean duration of chronic infection was 22.0 years in patients who had received blood transfusion at >40 years of age, which was significantly shorter than that in patients who received it at ≤40 years of age (40.6 years, $P < 0.001$).

The presence of cirrhosis at the time of development of HCC, which was defined as having any of the following criteria, was evaluated: (1) histological evidence for cirrhosis, (2) findings of cirrhosis in any radiological study, or (3) presence of marked portal hypertension (i.e., presence of esophagogastric varices). Following this, 142 of the 177 with HCC (80.2%) were diagnosed as having cirrhosis, of which 42 were diagnosed histologically, 69 radiologically, and 31 based on the presence of marked portal hypertension. No significant difference was found in the proportion of patients with cirrhosis between older and younger patients, at the rate of 78.3% (94/120) in older

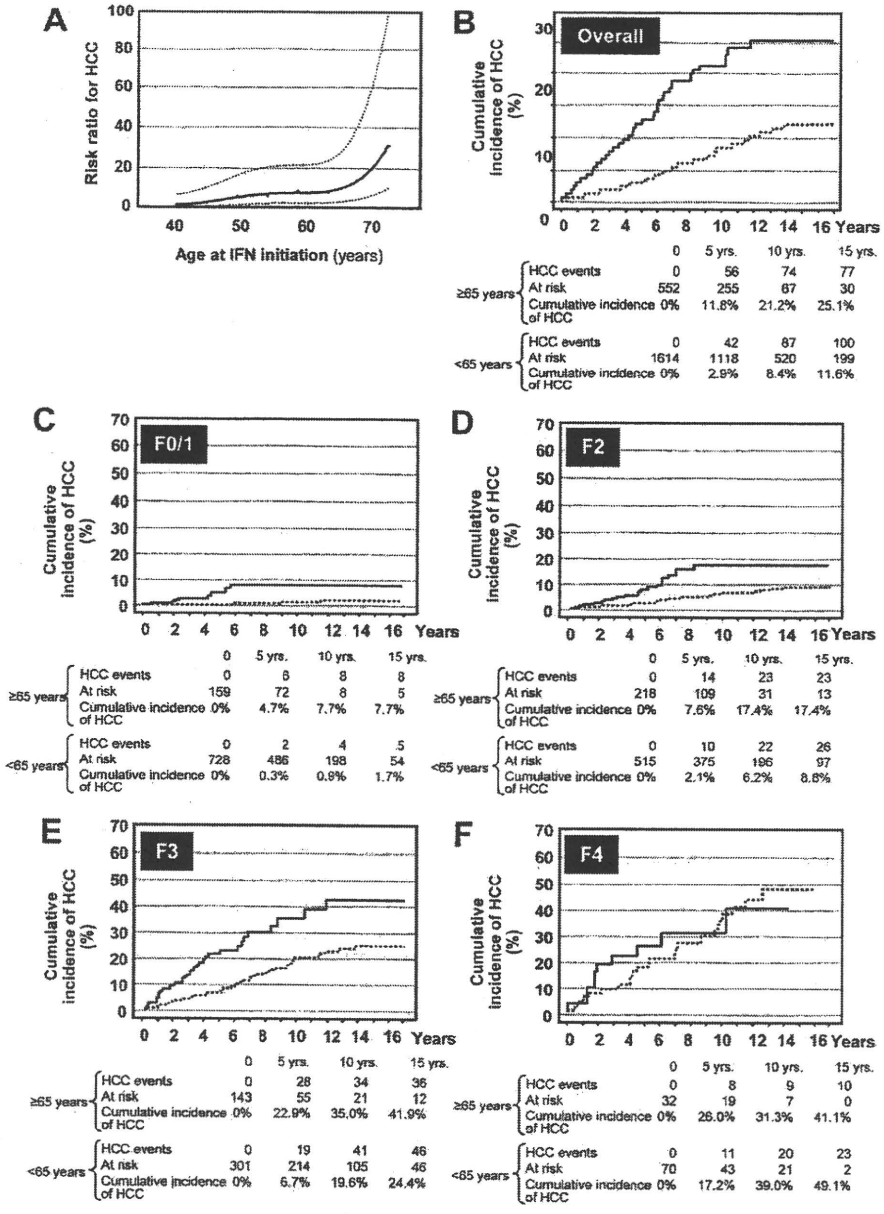

Fig. 2. Effect of aging on the risk for HCC. (A) Risk ratio (solid line) and 95% CI (dotted lines) for the risk of HCC according to age. To show the age-dependent relationship, a multivariate Cox proportional hazard model was used after adjustment for gender, stage of liver fibrosis, body mass index, and virological response to interferon therapy. Curves were fitted using polynomial regression. (B-F) Cumulative incidence of HCC after interferon therapy among younger (<65 years, n = 552, dotted line) and older patients (≥65 years, n = 1614, solid line). (B) Overall data, $P < 0.001$. (C) Patients with stage F0 or F1 liver fibrosis (no or mild fibrosis with portal expansion), $P < 0.001$. (D) Patients with stage F2 liver fibrosis (bridging fibrosis without architectural distortion), $P < 0.001$. (E) Patients with stage F3 liver fibrosis (bridging fibrosis with architectural distortion), $P < 0.001$. (F) Patients with stage F4 liver fibrosis (cirrhosis), $P = 0.7$. All P values were obtained by the log-rank test. The numbers of HCC events and patients at risk at each timepoint are shown below the graphs.

patients and 84.2% (48/57) in younger patients ($P = 0.36$, comparison at the age of HCC development).

Influence of Aging on Progression in Fibrosis Staging Over Time. In 271 patients who underwent paired biopsies, fibrosis staging progressed in 69 patients (25.5%), remained unchanged in 154 (56.8%), and regressed in 48 patients (17.7%). The overall rate of progression of fibrosis in these patients was 0.06 ± 0.02 fibrosis stages per year. Progression of fibrosis over time was significantly accelerated in older patients than in younger patients (0.21 ± 0.10 versus 0.03 ± 0.21 fibrosis stages per year, $P = 0.03$, Mann-Whitney U test) (Fig. 3B).

Effect of Viral Eradication on Risk for HCC in Older Patients. As shown in Fig. 4, the effect of viral eradication on the prevention of HCC was less significant in older patients than in younger patients. The annual incidence was higher among older patients than among younger patients with the same virological response (Table 2).

Influence of Liver Steatosis on Risk for HCC. The cumulative incidence of HCC after interferon therapy was significantly higher in patients with severe steatosis (≥10%) than in those with milder steatosis (at 5, 10, and 15 years: 8.6%, 19.1%, 32.0% versus 1.8%, 4.8%, 7.0%, respectively, log-rank test, $P < 0.001$).

Table 2. Annual Incidence of HCC After IFN Treatment

Factors	Total	<65 Years	≥65 Years
Fibrosis stage			
F0/F1	0.2%	0.1%	0.9%
F2	0.8%	0.6%	1.7%
F3	2.5%	1.8%	4.6%
F4	4.6%	4.4%	5.1%
Total	1.1%	0.8%	2.4%
Degree of liver steatosis			
<10%	0.5%	0.2%	1.4%
≥10%	2.0%	1.8%	3.0%
Virological response			
SVR	0.4%	0.2%	1.3%
Non-SVR	1.4%	1.0%	2.9%

Data were calculated by the person-years method. IFN, interferon; SVR, sustained virological response.

The annual incidence was higher in older patients than in younger patients with the same degree of liver steatosis (Table 2). In patients with severe steatosis (≥10%), superimposed NASH was diagnosed in 6.0% (26/435). Overall, superimposed NASH was significantly associated with hepatocarcinogenesis on univariate analysis (risk ratio, 4.1; 95% confidence interval [CI], 1.8-9.4; $P < 0.001$), but not on multivariate analysis. Superimposed NASH was significantly associated with high body mass index (27.2 ± 4.6 kg/m^2 versus 23.0 ± 3.1 kg/m^2, $P < 0.001$), hyperglycemia (186 ± 67 mg/dL versus 115 ± 39 mg/dL, $P < 0.001$), and advanced fibrosis (F3) (risk ratio, 2.9; 95% CI, 1.4-6.0; $P = 0.005$).

Factors Associated with Hepatocarcinogenesis After Interferon Therapy. Univariate analysis demonstrated factors that increase the risk ratio for the development of HCC (Table 3). Multivariate analysis using Cox proportional hazards regression confirmed that aging was one of the most significant independent factors associated with the development of HCC after interferon therapy. In this analysis, advanced fibrosis, presence of steatosis, male gender, lower total cholesterol level, higher fasting blood sugar level, higher baseline AFP level, insignificant improvement of mean AFP level after interferon therapy, and nonresponse to interferon therapy were also significantly associated with risk for HCC (Table 3).

We identified 22 patients in whom HCC developed even after achieving SVR. Univariate and multivariate logistic regression analyses indicated that both liver steatosis and aging were independently associated with the development of HCC among patients who achieved SVR (n = 686) (Table 4). Anti-HBc was detected in only 4 out of 22 patients and the age distribution was similar among anti-HBc-positive and anti-HBc-negative patients.

Response to Interferon Therapy in Older Patients. Multivariate logistic regression analysis confirmed that aging, female gender, severe liver fibrosis, extremely severe liver steatosis, genotype-1, high HCV load, and nonuse of pegylated interferon and ribavirin were independent risk factors for non-SVR (Supporting Table 1). The odds ratio, determined by multivariate logistic regression analysis after adjustment for these factors, demonstrated that the risk for non-SVR was age-dependent (Supporting Fig. 1). It was also ≈2.5 times higher in patients aged ≥65 years than in those aged <35 years.

In patients with genotype-1b and a high viral load who were treated with pegylated interferon and ribavirin combination therapy, the SVR rate was significantly lower in older patients than in younger patients (<49 years, 59.3%; 50-59 years, 50.5%; 60-65 years, 27.3%; ≥65 years, 25.2%; intention-to-treat analysis). Multivariate logistic regression analysis showed that

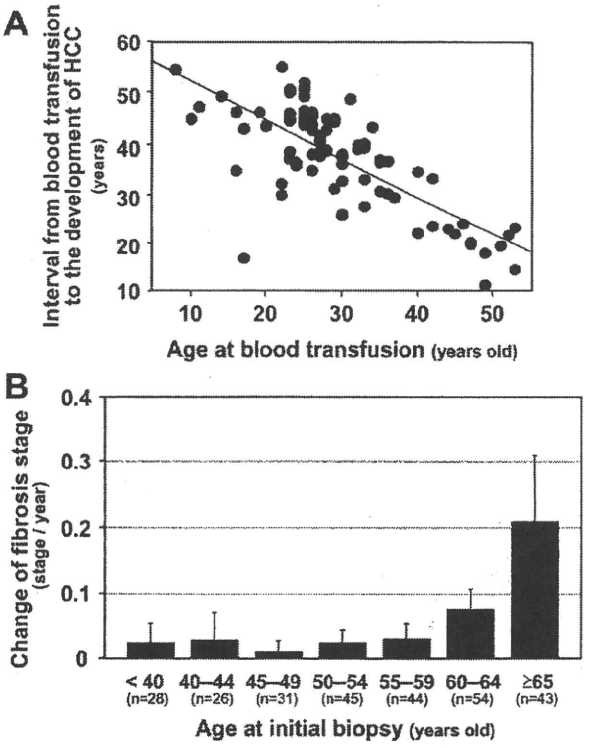

Fig. 3. (A) Relationship between the interval from blood transfusion to development of HCC and the age at blood transfusion (n = 92). A significant and strong negative correlation was observed ($r = -0.74$, $P < 0.001$). (B) Change in fibrosis staging over time. A total of 271 patients who had not achieved SVR by interferon therapy underwent a sequential biopsy after the initial biopsy. The yearly rate of progression of fibrosis was calculated as the change in fibrosis stage divided by the time between the paired biopsies. The yearly rate of progression of fibrosis was significantly higher in older patients (≥65 years) than in younger patients (<65 years) ($P = 0.03$, Mann-Whitney U test).

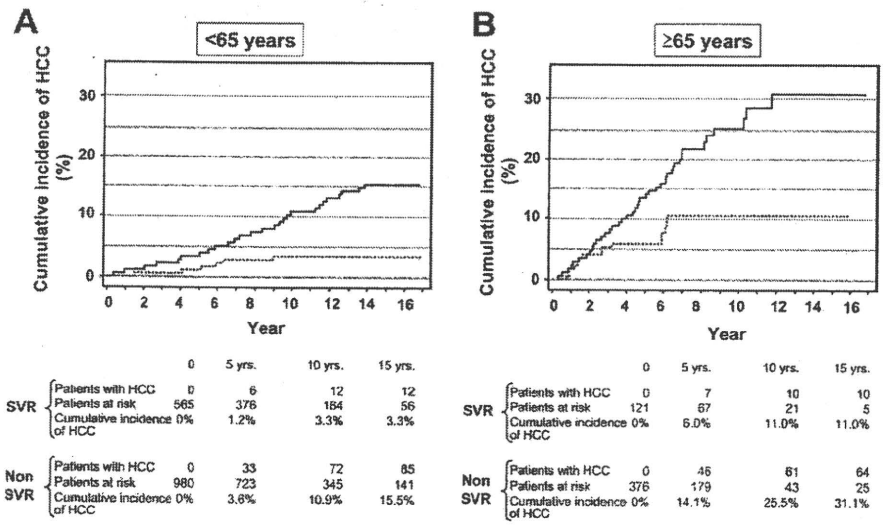

Fig. 4. Cumulative incidence of HCC after interferon therapy among SVRs (dotted lines) and non-SVRs (solid lines) according to age. (A) Younger patients (<65 years). The cumulative incidence of HCC was significantly higher in SVR than in non-SVR (log-rank test, $P < 0.001$). (B) Older patients (≥65 years). The cumulative incidence of HCC was significantly higher in SVR than in non-SVR (log-rank test, $P = 0.02$). However, the difference between SVR and non-SVR was less in older patients than in younger patients. The number of HCC events and patients at risk at each timepoint are shown below the graphs.

aging was the strongest independent factor contributing to SVR in these patients (data not shown). The odds ratio for the risk of non-SVR was 1.8 for each additional 10 years of age (95% CI, 1.5-2.3, $P < 0.001$).

Discussion

In this large cohort study we demonstrated that aging is significantly associated with the development of HCC in patients treated with interferon. The risk ratio increased predominantly in patients older than 65 years, which was more than 15 times that in patients in their 20s. Aging is becoming the most critical risk factor for the development of HCC. Although liver fibrosis was also an important risk factor, we clearly demonstrated that the risk for hepatocarcinogenesis after interferon treatment was significantly higher in older patients at each stage of liver fibrosis except for cirrhosis. Hence, physicians should be aware that older patients can develop HCC regardless of the stage of fibrosis.

Because the present study included a large cohort, it was difficult to determine the duration of infection in all patients, and this might have affected the risk determination for HCC development. Therefore, we analyzed the relationship between duration of chronic infection and HCC development in patients who underwent a single blood transfusion. We found a significant and strong negative correlation between the interval from blood transfusion to development of HCC and the age of the patients at the time of blood transfusion. Consistent with our results, a previous report with posttransfusion HCV demonstrated that the age of patients, rather than the duration of HCV infection, was more significant for HCC development.[14-16] Therefore, older age and not duration of infection is more likely to influence hepatocarcinogenesis. Moreover, our analysis of sequential biopsy specimens demonstrated that the progression rate of liver fibrosis significantly accelerated in patients aged >65 years. Hence, the progression of fibrosis along with aging may also contribute to the increased risk for hepatocarcinogenesis in older patients.

We further demonstrated that liver steatosis was an independent risk factor for the development of HCC, which was not mentioned in previous reports.[8-11] The presence of steatosis is related to both viral (genotype-3 or HCV core protein) and host metabolic factors.[17,18] In our cohort, most superimposed NASH was associated with host metabolic factors such as high body mass index and hyperglycemia, whereas infection of genotype-3 was only noted in two patients. In vitro experiments have suggested an association between liver steatosis induced by HCV core protein and hepatocarcinogenesis,[19] and have proposed virus-associated steatohepatitis as a new aspect of chronic hepatitis C.[20,21] Because steatosis was likely to be related to hepatocarcinogenesis, patients with chronic hepatitis C, whose liver histology shows superimposed NASH,

Table 3. Factors Associated with HCC After IFN Therapy

	Univariate Analysis		Multivariate Analysis	
Risk Factor Value	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value
Age (by every 10 year)	2.2 (1.8-2.7)	<0.001	3.0 (1.9-4.8)	<0.001
Sex				
Female	1		1	
Male	1.2 (0.9-1.6)	0.2	2.0 (1.0-3.8)	0.04
BMI (by every 10 kg/m^2)	2.0 (1.2-1.3)	0.005	1.1 (0.4-3.5)	0.8
Fibrosis stage				
F0/F1/F2	1		1	
F3/F4	5.4 (3.9-7.5)	<0.001	2.5 (1.2-4.9)	0.01
Degree of steatosis				
<10%	1		1	
≥10%	4.5 (3.0-6.9)	<0.001	3.5 (1.9-6.4)	<0.001
Esophagogastric varices				
No	1		1	
Yes	3.3 (2.0-5.3)	<0.001	1.6 (0.6-4.4)	0.3
Virological response				
SVR	1		1	
Non-SVR	3.3 (2.1-5.2)	<0.001	2.6 (1.2-5.5)	0.001
Genotype				
Non-1	1		1	
1	1.7 (1.2-2.5)	0.006	1.0 (0.5-2.3)	0.9
Albumin (by every 1 g/dL)	0.2 (0.1-0.3)	<0.001	0.6 (0.2-2.2)	0.3
ALT (by every 100 IU/L)	1.0 (0.9-1.0)	0.8	0.4 (0.1-1.8)	0.6
AST (by every 100 IU/L)	1.2 (1.1-1.3)	0.001	1.1 (0.6-1.8)	0.8
γ-GTP (by every 100 IU/L)	1.3 (1.1-1.6)	0.009	0.6 (0.3-1.6)	0.3
ALP (by every 100 IU/L)	1.3 (1.2-1.5)	<0.001	0.6 (0.3-1.2)	0.2
Total bilirubin (by every 1 mg/dL)	1.6 (1.3-2.1)	<0.001	1.2 (0.6-2.7)	0.6
Total cholesterol (by every 100 mg/dL)	0.3 (0.2-0.6)	<0.001	0.2 (0.1-0.6)	0.006
Triglyceride (by every 100 mg/dL)	0.8 (0.5-1.1)	0.2	0.1 (0.02-1.1)	0.08
Fasting blood sugar (by every 100 mg/dL)	1.8 (1.5-2.2)	<0.001	1.1 (1.0-1.1)	0.04
WBC (by every 100/μL)	0.1 (0.03-0.3)	<0.001	0.1 (0.01-2.2)	0.2
RBC (by every 10^6/μL)	0.5 (0.4-0.7)	<0.001	1.8 (0.7-4.4)	0.2
Platelet counts (by every 10^6/μL)	0.3 (0.2-0.4)	<0.001	0.6 (0.3-1.5)	0.3
Baseline AFP (by every 10 ng/mL)	1.0 (0.9-1.1)	0.2	1.3 (1.0-1.7)	0.04
Post IFN AFP (by every 10 ng/mL)	1.2 (1.1-1.3)	<0.001	1.9 (1.5-2.4)	<0.001
HCV load (by every 100 KIU/mL)	1.0 (0.9-1.0)	0.4	1.0 (1.0-1.1)	0.06
IFN regimen				
IFN monotherapy	1		1	
IFN + RBV (24 W)	1.2 (0.8-1.8)	0.4	1.5 (0.7-3.2)	0.3
PEG-IFN monotherapy (48 W)	1.1 (0.6-1.9)	0.8	1.5 (0.4-5.5)	0.6
PEG-IFN + RBV	0.4 (0.2-0.9)	0.03	1.0 (0.3-3.1)	0.9

Risk ratios for development of HCC were calculated by Cox proportional hazards regression analysis. AFP, alpha fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspirate aminotransferase; BMI, body mass index; γ-GTP, gamma-glutamyltranspeptidase; HCC, hepatocellular carcinoma; IFN, interferon; PEG, pegylated; RBC, red blood cell counts; RBV, ribavirin; SVR, sustained virological response; WBC, white blood cell count.

may be at a higher risk of developing HCC. Further study is necessary to confirm this association in a clinical situation. Because several developed countries are in the midst of a growing obesity epidemic, the risk related to obesity cannot be ignored in patients with chronic hepatitis C who are treated with interferon.

Several retrospective cohort studies have been conducted to evaluate the effect of interferon on the incidence of HCC among patients with chronic hepatitis C.[8-11] Our results, obtained from one of the largest cohort studies, confirm the efficacy of viral eradication in preventing HCC. In one study conducted in a Western population, no statistically significant reduction was found in the development of HCC among patients with SVR compared with those without SVR (adjusted hazard ratio, 0.46; 95% CI, 0.12-1.70; $P = 0.25$).[12] Because relatively few occurrences of HCC were observed in this cohort, and the duration of follow-up was shorter, the differences in HCC development between patients with and without SVR might be less pronounced.

Interestingly, our results demonstrated that the risk for HCC remains even after achieving SVR in older patients, confirming the findings of previous studies conducted with a smaller number of patients.[22,23] The cumulative incidence of HCC during the first 5 years

Table 4. Factors Associated with Development of HCC After Achieving SVR

Risk Factor	Odds Ratio (95% CI)	*P*-value
Univariate analysis		
Age (by every 10 year)	3.2 (1.8-5.5)	<0.001
Sex		
Female	1	
Male	3.0 (1.0-8.8)	0.04
Fibrosis stage		
F0/F1/F2	1	
F3/F4	5.9 (2.5-14.0)	<0.001
Degree of steatosis		
<10%	1	
≥10%	5.5 (2.0-15.2)	0.001
BMI (by every 10 kg/m^2)	3.2 (0.8-12.6)	0.09
ALT (by every 10 IU/L)	0.9 (0.7-1.3)	0.7
AST (by every 10 IU/L)	1.1 (0.9-1.4)	0.3
Genotype		
Non-1	1	
1	1.2 (0.6-3.0)	0.5
HCV load (by every 100 KIU/mL)	0.9 (0.8-1.0)	0.2
IFN regimen		
IFN monotherapy	1	
IFN + RBV (24 W)	0.7 (0.2-2.3)	0.5
PEG-IFN monotherapy (48 W)	0.8 (0.2-3.6)	0.8
PEG-IFN + RBV	0.3 (0.03-2.0)	0.2
Multivariate analysis		
Age (by every 10 year)	2.7 (1.5-5.1)	0.002
Sex		
Female	1	
Male	4.1 (0.9-18.9)	0.06
Fibrosis stage		
F0/F1/F2	1	
F3/F4	2.6 (0.9-7.5)	0.08
Degree of steatosis		
<10%	1	
≥10%	5.6 (1.9-16.5)	0.002

Odds ratios for SVR were calculated by logistic regression analysis.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HCV, hepatitis C virus; IFN, interferon; HCC, hepatocellular carcinoma; PEG, pegylated; RBV, ribavirin; SVR, sustained virological response.

after completion of interferon therapy was similar between SVR and non-SVR patients in the older age group, and the risk for HCC remained for 9 years after eradication of HCV in our patients. Therefore, HCC patients with SVR who have a risk factor should be screened for at least 5-10 years after the completion of interferon therapy.

It has been reported that coffee consumption has a protective effect against hepatocarcinogenesis[24,25] and liver disease progression in patients with chronic HCV infection.[26] Because we could not review coffee consumption in all the patients and fewer data were available in the previous literature as to whether a habitual change of reducing coffee consumption occurs in older patients, it is unclear whether increased risk for HCC in older patients is an effect of this habitual change in older patients. However, the majority (68%) of Japanese patients who have HCV (n = 1058) drink less than 1 cup of coffee per day, and only 7.6% consume more than 3 cups of coffee per day.[27] Therefore, it is unlikely that a habitual change in older patients affects the increased risk for hepatocarcinogenesis in older patients.

Recently, it was reported that interferon therapy might be less effective in preventing HCC among patients with chronic hepatitis C who are positive for anti-HBc antibody,[28] but this finding is still controversial.[29,30] In the present study, anti-HBc was only detected in 4 of 22 patients in whom HCC developed after viral eradication, and age distribution was similar among anti-HBc-positive and anti-HBc-negative patients. Because no significant difference in mean age was found between anti-HBc-positive and anti-HBc-negative patients in the recent study conducted in Japan,[28] it is unlikely that previous exposure to hepatitis B virus or occult hepatitis B virus infection is responsible for the difference in risk for HCC between younger and elderly patients found in the present study.

In conclusion, aging has become one of the most important risk factors for HCC. Even after stratification by stage of fibrosis, the risk for HCC after antiviral treatment was significantly higher in older patients, and HCV eradication had a smaller effect on HCC-free survival in older patients. Patients with HCV should therefore be identified at an earlier age and antiviral treatment should be initiated. The present results have potentially important clinical implications for physicians that may influence their decisions about the treatment strategy in individual patients.

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