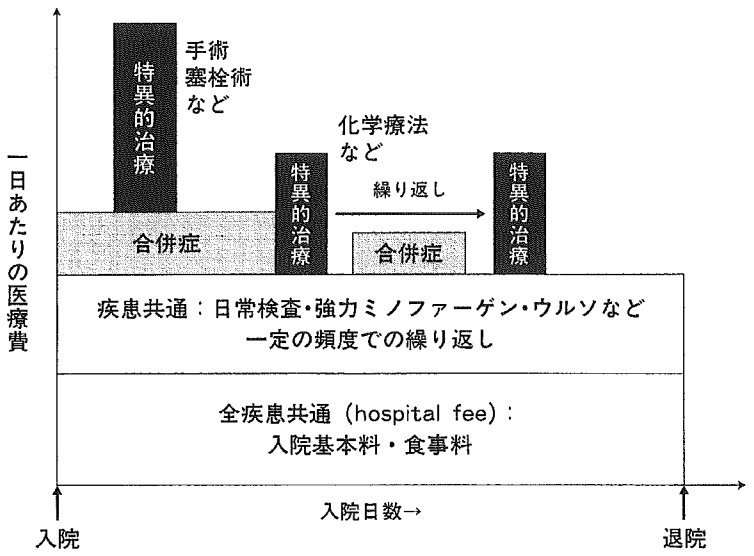


**入院医療費は，全疾患共通の入院基本料や食事料などのhospital feeや日々投与される一般的な処方・注射などを基盤として，肝細胞癌に対する特異的な治療としての手術や腫瘍塞栓術のような回数は少ないが1回あたりの点数の高い治療や繰り返しの注射・処置や合併症の治療などの項目から構成される．**

**図1　入院医療費の構成概念図**

のあるもの，さらに敗血症性ショックを合併し入院となった患者などを除いたのべ236例を最終的な解析対象とした．モデル検証群は，2002年7月1日から10月31日までの期間に同様に肝細胞癌の診断で入院したのべ92症例(実患者85名，うち男性63名，年齢は20～86歳で平均およびその標準偏差は68.7±9.0歳)であり，モデル作成群と同じ条件で対象外となった症例を除く80例を最終対象とした．

この検討における医療費は，保険支払いの立場での入院基本料や管理加算などのいわゆるhospital feeを含む診療報酬請求額および入院期間中に実施された一つ一つの診療行為に対応する医事点数のみを合計しhospital feeを含まない診療行為請求額とした．

データの集計および解析は次のような手順で行った．

1．個々の症例について入院中の診療行為の明細，最終的な診療報酬請求額をレセプト請求データから抽出した．さらに診療行為の明細と医事点数を掛け合わせ入院基本料などのhospital feeを除いた診療行為のみの診療行為請求額を算定した．

2．慢性肝炎および肝硬変症における抗炎症基礎治療，肝硬変症の非代償性合併症，すなわち，腹水・浮腫，肝性昏睡，食道静脈瘤に対する治療，さらには肝細胞癌の特異的治療，すなわち，手術，経皮的エタノール注入(PEIT療法)，抗がん剤とリピオドール(およびスポンゼル)による冠動脈化学栓術(Chemo-lipiodol療法)，化学療法(塞栓剤を用いない経動脈的あるいは経静脈的化学療法)に用いられる代表的な薬剤や診療行為に着目し(**表1**)，個々の症例の診療行為の明細から合併症に対する治療の有無，肝細胞癌治療実施の有無の判定を行った．なお，肝細胞癌の遠隔転移に対し放射線療法(体外照射)が実施された患者数は4人と少なく最終的な検討対象には入れなかった．

3．2で得られた合併症や肝細胞癌治療の有無により一入院期間における診療報酬請求額および診療行為請求額に差があるかどうかを検定するために単変量解析を行った．さらに，それらの請求額に対する入院日数および合併症の有無や肝細胞癌治療法の種別との関連を多変量解析にて検討した．

統計解析にはStatFlex ver.5(アーテック社)を用いた．単変量解析では合併症ならびに肝細胞癌の治療行為別(要因)に入院あたりの診療報酬請求額との関連をMann-Whitney検定を用いて$P<0.05$を有意水準として検討した．また，入院日数とそれぞれの請求額との相関についてはSpearman

表1　肝細胞癌および合併症に対する医療行為の特異的マーカー

| 合併症・治療 | | 診療行為・薬剤 |
|---|---|---|
| 抗炎症基礎治療 | | 強力ミノファーゲンC・ウルソ・プロヘパール等 |
| 合併症 | 腹水・浮腫 | ラシックス・アルダクトンなど利尿剤(＋アルブミン) |
| | 肝性脳症 | アミノレバン・モニラック・ラクツロース＋アンモニア測定 |
| | 食道静脈瘤 | 食道静脈瘤結紮術・食道静脈瘤硬化療法・オルダミン |
| 肝細胞癌治療 | 手術 | 手術術式(肝切除術) |
| | PEIT 療法 | エタノール局所注入 |
| | Chemo-lipiodol 療法 | 抗がん剤＋リピオドール（＋スポンゼル) |
| | 化学療法 | 抗がん剤－リピオドール（－スポンゼル) |
| | 放射線療法 | 放射線治療管理料・体外照射 |

診療行為明細の中で肝細胞癌に対する治療と非代償性肝硬変症に対する治療の実施の有無を判断するために指標とした薬剤，検査，処置行為，術式.

順位相関により検討を行った．多変量解析では診療報酬請求額および診療行為請求額を従属変数とし，入院日数に加えて非代償性肝硬変症の腹水・浮腫，肝性昏睡および食道静脈瘤の3種類の合併症，手術，PEIT 療法，Chemo-lipidol 療法および化学療法の肝細胞癌に対する4種類の治療法，そして抗炎症基礎療法の有(1)，無(0)を説明変数とした重回帰分析を行った．この際，あらかじめ変数の分布型解析を行い，入院中の診療報酬請求額と診療行為請求額に対しては 0.36 乗，入院日数に対しては 0.2 乗の Box-Cox 変換を行った．最適な重回帰モデルは変数増減法により，$P<0.05$ であればモデルに組み込み，$P<0.15$ であればモデル内に残す条件でより小さな赤池情報量基準が得られるように変数を取捨選択した．

## 4. 結　果

モデル作成群 236 例において入院日数のメジアンならびに 2.5，97.5 パーセンタイル値は 19 日，6 日，67 日であり，診療報酬請求額のそれらはそれぞれ 689,000 円，192,000 円，2,217,000 円であった．合併症および肝細胞癌に対して実施された治療頻度の内訳は**表2**の通りであった．単変量解析では，抗炎症基礎治療の実施群と非実施群の間で入院日数および診療報酬請求額に有意差を認めなかった．一方，合併症のある群および肝細胞癌の治療が実施された群は合併症や肝細胞癌の治療がされなかった群と比較して入院日数は長く，診療報酬請求額は高かった．特に，食道静脈瘤に対する治療および手術，化学療法が実施された群はメジアンが 100 万円を超える請求額となっていた．但し，Chemo-lipiodol 療法においては治療が実施された群で入院日数は逆に短く，また，PEIT 療法および Chemo-lipiodol 療法では実施，非実施群間で診療報酬請求額には有意差を認めなかった．

入院日数と診療報酬請求額の間では，Spearman の順位相関にて 0.78 と高い相関を示した．また，合併症および肝細胞癌の診療行為別に入院日数と診療報酬請求額あるいは診療行為請求額との間で，前者では 0.71～0.92 と高い相関を認め，後者でも 0.43～0.69 と中等度の相関を認めた(**表3**)．

診療報酬請求額に対する多変量解析(**表4**)では，入院日数は t 値が 20.81 と高く診療報酬請求額に影響する最も有意な要因であった．これは単変量解析で相関が高かったことと一致する結果であった．入院日数以外には，手術，Chemo-lipiodol 療法，化学療法などの肝細胞癌治療，肝硬変症の合併症である腹水・浮腫や食道静脈瘤では有意であったが，PEIT 療法，肝性脳症は有意な要因ではなかった．また，診療報酬請求額の推定に対する寄与度を有意度および回帰係数から見ると，入院日数を除いて肝細胞癌に対する治療の寄与度が高く，合併症に対する治療の寄与度は低いという結果であった．一方，入院日数に依存する入院基本料などの hospital fee を除いた診療行為請求額に対する多変量解析(**表5**)でも，診療報酬請求額と同様の要因が有意であったが，その寄与度は回帰係数から手術が最も高く，以下，Chemo-lipiodol 療法と

表2　診療行為の有無による入院日数，診療請求額(千円)

| 診療行為 | | あり | なし | p値 |
|---|---|---|---|---|
| 抗炎症基礎治療 | N* | 194 | 42 | |
| | 入院日数 | 19(12, 30)** | 17(10, 28) | NS |
| | 診療請求額 | 707(503, 1,107) | 524(354, 1,076) | NS |
| 合併症 | | | | |
| 腹水・浮腫 | N | 116 | 120 | |
| | 入院日数 | 23(14, 31) | 15(10, 29) | 0.002 |
| | 診療請求額 | 800(568, 1,397) | 600(431, 854) | <0.001 |
| 肝性脳症 | N | 58 | 178 | |
| | 入院日数 | 24(15, 39) | 17(11, 28) | <0.001 |
| | 診療請求額 | 998(635, 1,487) | 642(451, 999) | <0.001 |
| 食道静脈瘤 | N | 11 | 225 | |
| | 入院日数 | 35(28, 47) | 17(12, 30) | <0.001 |
| | 診療請求額 | 1,361(1,070, 1,737) | 654(476, 1,057) | <0.001 |
| 肝細胞癌治療 | | | | |
| 手術 | N | 19 | 217 | |
| | 入院日数 | 29(26, 33) | 17(11, 30) | 0.001 |
| | 診療請求額 | 1,476(1,374, 1,904) | 647(465, 1,005) | <0.001 |
| PEIT 療法 | N | 28 | 208 | |
| | 入院日数 | 31(17, 39) | 17(12, 29) | 0.005 |
| | 診療請求額 | 889(534, 1,136) | 655(482, 1,082) | NS |
| Chemo-lipiodol 療法 | N | 124 | 112 | |
| | 入院日数 | 15(10, 27) | 23(15, 33) | <0.001 |
| | 診療請求額 | 687(551, 920) | 693(366, 1,397) | NS |
| 化学療法 | N | 23 | 215 | |
| | 入院日数 | 36(16, 59) | 17(12, 28) | 0.001 |
| | 診療請求額 | 1,454(572, 1,963) | 654(484, 1,041) | 0.005 |

* 症例数
**メジアン(25％値，75％値)を示す．

表3　診療行為別の入院日数と診療報酬請求額，診療行為請求額との相関

| 診療行為 | 診療報酬請求額 | 診療行為請求額 |
|---|---|---|
| 抗炎症基礎治療 | 0.783 | 0.502 |
| 合併症 | | |
| 腹水・浮腫 | 0.820 | 0.626 |
| 肝性脳症 | 0.841 | 0.622 |
| 食道静脈瘤 | 0.747 | 0.433 |
| 肝細胞癌治療 | | |
| 手術 | 0.718 | 0.612 |
| PEIT 療法 | 0.858 | 0.602 |
| Chemo-lipiodol 療法 | 0.897 | 0.475 |
| 化学療法 | 0.924 | 0.690 |

表4　診療報酬請求額*に対する多変量解析結果

| 治療・合併症 | 回帰係数(SE) | t値 | p値 |
|---|---|---|---|
| 入院日数** | 51.10 (2.46) | 20.81 | <0.001 |
| 手術 | 109.19 (10.53) | 10.37 | <0.001 |
| Chemo-lipiodol | 50.20 (5.80) | 8.66 | <0.001 |
| 化学療法 | 49.07 (9.69) | 5.06 | <0.001 |
| 腹水・浮腫 | 14.67 (5.32) | 2.76 | 0.006 |
| 食道静脈瘤 | 28.77 (12.48) | 2.31 | 0.022 |

R=0.89
*0.36 乗で Box-Cox(べき)変換後
**0.2 乗で Box-Cox 変換後

化学療法が同程度の寄与度になった．肝硬変症の合併症は診療報酬請求額の場合と同様に診療行為請求額においても寄与度は低い結果であった．

モデルの適合性については，**表4**に示したモデル作成群での診療報酬請求額の予測値と実際額との重相関係数は0.89であり，手術，Chemo-lipiodol 療法，化学療法における予測額と実際額の平均値の比較(**表6**)でも近似した値が得られた．

一方，モデル作成群とは異なる80例のモデル検証患者群のデータセットに得られた重回帰モデルを適用し，予測値と実際の診療報酬請求額の相関を見ると0.89(Spearman 順位相関係数)と高い結果が得られた(**図2**)．

表5　診療行為請求額*に対する多変量解析結果

| 治療・合併症 | 回帰係数(SE) | t値 | p値 |
|---|---|---|---|
| 入院日数** | 51.42 (7.99) | 6.44 | <0.001 |
| 手術 | 186.56 (18.80) | 9.92 | <0.001 |
| Chemo-lipiodol | 112.38 (10.36) | 10.85 | <0.001 |
| 化学療法 | 106.96 (17.16) | 6.23 | <0.001 |
| 腹水・浮腫 | 24.83 (9.49) | 2.62 | 0.010 |
| 食道静脈瘤 | 59.68 (22.25) | 2.68 | 0.008 |

R=0.74
*0.36乗でべき変換後　　**0.2乗でべき変換後

表6　モデルによる予測額と実際額の比較(モデル作成群)

| 治療 | 入院日数* | 実際額** | 予測額** |
|---|---|---|---|
| 手術 | 30 | 1,656 | 1,622 |
| Chemo-lipiodol療法 | 18 | 787 | 797 |
| 化学療法 | 42 | 1,372 | 1,274 |

*平均　　**平均(千円)

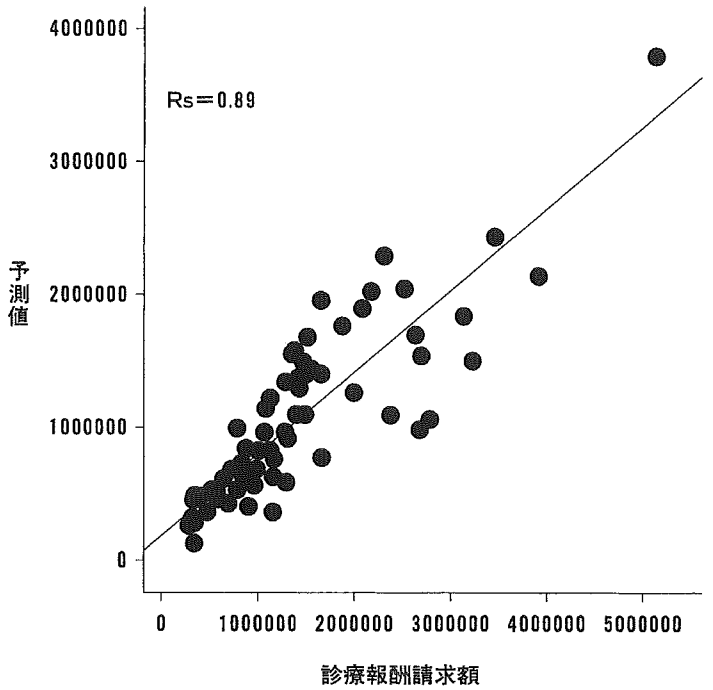


図2　検証用データにおけるモデルによる予測額と実際の診療報酬請求額との相関

## 5. 考　察

医療費の正確度の高い推定は，疾患が社会に与える影響の大きさを測る上でも，あるいは，費用効果分析などにより様々な治療における医療資源の配分を考える上でも不可欠である．しかし，我が国での疾患別の医療費についての正確な情報は少なく，医療経済の研究における重要な課題となっている．

一方，複数の病態が併存している患者では，それぞれの病態に特異的な検査や治療のみでなく複数の病態に共通の検査や治療がなされることからその病態毎に機械的に分けて医療費の算出を行うことは容易ではない．実際の症例を用いた検討でも，様々な合併症をもつ症例が多く含まれることから，その病態の純粋な医療費を推定するには，その中で層別化し，合併症が全くない，あるいは，特定の合併症だけを有する症例のみを集めて検討することが多い[5]．

そこで，本研究では，それぞれの合併症や特異的治療にかかる経費は医療費の中で部分的な独立したコンポーネントを構成するという仮定に立ち，

肝硬変症を基礎疾患として非代償性の合併症を伴うことが多い肝細胞癌を対象として，複合病態における医療費推定モデルを作成し，一入院あたりの医療費における肝細胞癌治療や合併症の寄与度およびモデルの適合性を検討した．

結果として診療報酬請求額に対して適合性の高いモデルが得られ，診療報酬請求額および診療行為請求額に対する変動要因としての合併症および治療の寄与度をみると，いずれも入院日数は有意であり，また，肝細胞癌治療の方が合併症より寄与度が大きい傾向を認めた．また，それぞれの治療はいずれも入院日数との相関が強かったが，有意な要因として上がらなかった抗炎症基礎治療，PEIT療法や肝性脳症に対する治療は，入院日数の増加に伴って増加する診療報酬請求額にそれらの医療費分が包含されてしまうのに対して，有意となった手術，Chemo-lipiodol療法等では，治療の有無により係数分の請求額が加わると理解できることから，**図1**のような医療費を構成するコンポーネントとしての考え方は妥当であると考えられた．

今回は従来から行われてきた診療録から肝硬変症の合併症，肝細胞癌に対する治療の情報を得るのではなく，診療請求上の行為明細から判定を行った．これは，レトロスペクティブな診療録の確認では実施された医療行為について十分な情報が得られない場合が多く，また，診療報酬請求の観点からは，実際に請求の対象となった診療行為に注目する方がより正確な推定が可能になると考えたからである．実際，診療行為明細には入っている処置などが診療録の記載からは確認できないケースが多くあり，有用な方法と考えられた．一方，診療行為明細には，患者毎に異なる様々な行為が含まれていることから，医療費推定の対象とする病態に直接関連すると考えられる診療行為を的確に把握することが重要であり，当然，その如何により推定の正確度が影響されることになる．

医療費の推定方法は医療費を考える立場(perspective)，すなわち，医療提供者，患者，保険支払者，社会などの立場で異なるが，一般的には個々の患者に実際に行われた医療行為に用いられた薬剤や医療材料，医師，看護師など医療提供者の費用，さらには施設や機器利用に伴う費用などをひとつひとつ積み上げるmicro-costingの手法がとられることが多い[2]．しかし，今回の医療費の推定は保険支払者の立場で行い，診療報酬請求に伴う保険償還額を医療費とした．我が国では，国民医療費の増大から近年，従来の出来高支払い制に加えて包括評価支払い制度が導入され，DPCに基づく診療報酬額の割り当てが行われているが，この基盤となっているのは，それぞれのDPC別の出来高による診療報酬額の調査であり，今回の検討もそれと同様のアプローチである．そのため，DPCをもとにした包括支払い制度の妥当性を評価する上でも今回の検討は意義あるものと考える．すなわち，DPCそのものが基本的に疾患と手術，処置，副傷病名の有無の組み合わせであり，今回の検討における手術，処置，そして，肝硬変症の合併症の寄与度の相対的な大きさの結果は，それに相似するものと考えられた．

さらに，肝硬変症の合併症である腹水・浮腫，肝性脳症，食道静脈瘤は，それぞれ治療により医療資源を消費するものであるが，肝細胞癌と複合した病態においては，入院日数と肝細胞癌に対する治療によって医療費のほとんどの部分が決定されるという結果は，例えば，費用効果分析などでは，肝細胞癌がある場合に肝硬変症の合併症別に分ける必要性があるかどうかを考える上で重要な情報と考えられた．

今回の検討の限界として，次の2点が挙げられる．1つは，食道静脈瘤やPEIT療法などで患者数が少ないことが解析に影響した可能性があり，今後，それらの患者数を増やしての検討が必要となる．2つには，推定モデル作成に線形回帰である重回帰分析を用いたが，有意とされた要因それぞれが入院日数と相関が強く，また，変数の正規化のためにBox-Cox変換を行ったことにより，モデルで有意とされた要因毎に単純なブロック組み立てのように加算できる形にはならなかった．一般的には医療費は分布が正規分布とはならないため，その歪度を考慮に入れる必要があるが，そのため，正規分布を前提としない一般化線形モデルなど，より適切な手法について検討する必要がある[6]．

## 6. 結　語

複合病態における医療費(診療報酬請求額・診療行為請求額)の推定の例として肝細胞癌患者を対象として入院日数とともに実施された診療行為に着目した多変量回帰モデルを作成した．モデルは入院日数が最も有意な因子であったが，肝細胞癌治療や非代償性肝硬変症の合併症がそれぞれ独立した有意な因子として挙げられ，その回帰係数から寄与度が推定できることが示唆された．この結果により，病態(合併症)，治療それぞれの因子をコンポーネントとして捉えて医療費を推定することが可能と考えられた．今後，適用するモデルの妥当性の検証が必要であるが，今回のアプローチは，従来の病態別，治療別に層別化された患者集団に基づく医療費推定に代わって，主要な変動要因の抽出およびその組み合わせでの平均的医療費の推定に有用と考えられた．

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### 参　考　文　献

1) Etzioni R, Riley GF, Ramsey SD, Brown M. Measuring costs. Administrative claims data, clinical trials, and beyond. *Med Care* 2002 ; **40** [Suppl. III] : 63-72.

2) Luce BR, Manning WG, Siegel JE, Lipscomb J : Estimating costs in cost-effectiveness analysis. In : Gold MR, Russell LB, Siegel JE, Weinstein MC(eds) Cost-effectiveness in health and medicine. Oxford University Press : Oxford 1996.

3) Byford S, Barber JA, Fiander M, Marshall S, Green J. Factors that influence the cost of caring for patients with severe psychotic illness : report from the UK 700 trial. *Br J Psychiatry* 2001 ; **178** : 441-447.

4) Tu F, Anan M, Kiyohara Y, Okada Y, Nobutomo K. Analysis of hospital charges for ischemic stroke in Fukuoka, Japan. *Health Policy* 2003 ; **66** : 239-246.

5) 井上裕二, 石田　博, 手良向聡, 黒川典枝, 日野啓輔, 沖田　極. C型肝炎ウィルス感染症の各病態における年間医療費の推定. 医療情報学 2001 ; **21** (suppl.) : 330-331.

6) Kilian R, Matschinger H, Loeffler W, Roick C, Angermeyer MC. A comparison of methods to handle skew distributed cost variables in the analysis of the resource consumption in schizophrenia treatment. *J Ment Health Policy Econ* 2002 ; **5** : 21-31.

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# Risk factors for development of hepatocellular carcinoma in patients with chronic hepatitis C after sustained response to interferon

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***Background.*** Interferon (IFN) is expected to prevent the progression of hepatitis C virus infection to cirrhosis and the development of hepatocellular carcinoma (HCC), but there have been several reports of the development of HCC after a sustained response to IFN. Our aim was to elucidate the incidence and clinical features of, and risk factors for, HCC in sustained responders to IFN, taken for the treatment of chronic hepatitis C. ***Methods.*** We designed a retrospective cohort study conducted at 16 major Hospitals. The subjects were a total of 1056 patients showing sustained responses, 29 of whom developed HCC. ***Results.*** The incidence of HCC per 100 person-years was 0.56 (95% confidence interval, 0.35–0.76) in sustained responders. By the Cox proportional hazard model, we found that older age, higher serum aspartate aminotransferase level, and lower platelet count before IFN therapy were independent risk factors associated with the development of HCC. A risk index of HCC development, based on the coefficients of these risk factors, was used to classify patients into three groups, with low, intermediate, and high risk. The incidence rates of HCC for these three groups were 0.11, 0.44, and 1.98 per 100 person-years, respectively. The median period to the development of HCC was 4.6 years (range, 1.4–9.0 years), and there were no other specific clinical features of the HCC that developed in these patients. ***Conclusions.*** This study suggests that the risk of development of HCC is not completely eliminated in sustained responders to IFN. These findings may be useful in determining a follow-up strategy after a sustained response to IFN.

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**Key words:** hepatitis C virus, hepatocellular carcinoma, interferon, sustained response

## Introduction

Hepatitis C virus (HCV) infection is one of the most common causes of chronic hepatitis, and it is also a major risk factor for hepatocellular carcinoma (HCC).[1,2] Chronic hepatitis C is often asymptomatic and mild, but may slowly progress to liver cirrhosis and eventually to HCC.[3–5] Therefore, it has been assumed that eradication of HCV would provide the most effective means of preventing HCC.

Currently, interferon (IFN) represents the mainstay of treatment for chronic hepatitis C.[5–9] IFN therapy can lead to a decrease in serum transaminase activity, and to the disappearance of serum HCV RNA in patients with chronic hepatitis C. These patients appear to benefit by the prevention of progression to cirrhosis and HCC.[5,7,10–14] However, HCC can still occur in patients who are treated successfully with IFN, i.e., those showing a sustained response to the therapy.[5,10–25] The incidence and clinical features of HCC, and the risk factors for carcinogenesis, have not yet been investigated, although they have been documented in individuals and in small numbers of patients.[5,10–25] We investigated a large cohort of patients showing a sustained response to IFN therapy given for chronic hepatitis C. Our aims were to assess the incidence of HCC in these patients and to discover the clinical variables that may be associated with the development of HCC. Our study also focused on the clinical features of HCC. We designed a multicenter retrospective cohort study, because a single-institution study would have provided inadequate numbers of sustained responders who developed HCC.

## Patients and methods

### *Patients*

This study was conducted at 16 major hospitals belonging to the Japanese Society of Gastroenterology, Kyushu Division. A large cohort of sustained responders to IFN therapy given for chronic hepatitis C, in whom HCC had, or had not, been detected, was assembled consecutively by means of data collection instruments. All sustained responders included in the study were positive for HCV RNA before IFN therapy, and were followed up for more than 1 year after termination of IFN therapy, during the period July 1988 to August 2001. Sustained response was defined as the presence of HCV RNA negativity (determined by using qualitative HCV RNA assay) more than 6 months after the termination of IFN therapy. Diagnosis of HCC was based either on histological examination or on typical computed tomographic and/or angiographic findings at each institution. Patients were excluded if HCC was detected within 1 year after the termination of IFN therapy, because in such cases it was highly likely that the cancer had been present at the end of the IFN therapy. In Japan, at the time of the study, the standard schedule was 6–10 MU IFN-α every day for the first 2–4 weeks and then the same dose given three time a week for the following 20–22 weeks, or 6 MU IFN-β every day for 6–8 weeks.

During the study period at the 16 hospitals, a total of 3504 patients with chronic hepatitis C had received IFN therapy and had been followed up for more than 1 year thereafter, and a sustained response was obtained in 1091 (31.1%) of them. Among the sustained responders, 30 patients (2.7%) developed HCC. By means of the data collection instrument, we requested individual clinical data before IFN therapy for all sustained responders, as well as clinical data at the time of diagnosis of HCC for patients who had developed HCC. The clinical data for all 1091 sustained responders identified were obtained from the 16 hospitals (8 university hospitals and 8 regional hospitals) listed in the appendix. Of these patients, 35 were excluded from the analysis because of the development of HCC within 1 year after IFN therapy (1 patient) or insufficient clinical records before commencement of IFN therapy (34 patients). The final study population comprised a total of 1056 patients showing sustained response to IFN therapy given for chronic hepatitis C, 29 of whom had developed HCC.

## Methods

To identify risk factors for the development of HCC in sustained responders to IFN therapy, we used univariate analysis and multivariate analysis to investigate 23 variables before IFN therapy for their relationship to the development of HCC. These variables were chosen by considering possible factors involved in the development of HCC, as indicated by previous investigations,[1–5,10–25] or suggested from our own clinical experience. Each variable, which was classified as host-related or treatment-related, was divided into one of two subgroups on the basis of clinically meaningful values. HCV RNA load was determined quantitatively by competitive reverse-transcription polymerase chain reaction (RT-PCR), branched-DNA probe assay, or Amplicor-HCV monitor assay.[26–28] When the serum HCV RNA level was more than $10^6$ equivalents/ml by branched DNA assay, more than $10^6$ copies/ml by competitive RT-PCR, or more than $10^5$ copies/ml by Amplicor-HCV monitor assay, it was designated as a high viral load; an HCV RNA level of $10^5$ copies/ml by the Amplicor-HCV monitor assay has already been demonstrated to correspond to approximately $10^6$ equivalents/ml by the branched DNA probe assay or $10^6$ copies/ml by competitive RT-PCR.[26–28] HCV subtype was classified by either the method of Okamoto et al.,[29] or Tanaka et al.'s method.[30] Genotypes 1a and 1b corresponded to serological group 1, and genotypes 2a and 2b corresponded to serological group 2, according to the Simmonds et al.[31] classification.[31] The data from liver biopsies that were done within 6 months before IFN therapy were included in this study. Assessments of the staging of liver fibrosis and the grade of inflammatory activity were based on the classification of Desmet and colleagues,[32] in which staging is defined as follows: F0 (no fibrosis), F1 (fibrous portal expansion). F2 (bridging fibrosis), F3 (bridging fibrosis with architectural distortion), and F4 (cirrhosis), and grading is defined as follows: A0 (no activity), A1 (mild activity), A2 (moderate activity), and A3 (severe activity).

To elucidate the clinical features of HCC that developed in sustained responders, 17 variables at the time of diagnosis of HCC were investigated. Number of tumors, maximum tumor size, portal vein invasion, hepatic vein invasion, and bile duct invasion were examined by ultrasonography, computed tomography, and/or angiography. The period to the development of HCC was measured from the day of termination of IFN therapy to the day when HCC was first diagnosed by imaging modalities, such as ultrasonography or computed tomography. The follow-up period for the detection of HCC after termination of IFN therapy was defined as the interval during which checks for HCC were done using tumor markers and/or imaging modalities.

### *Statistical analysis*

Follow up ended with the last recorded visit before August 31, 2001. Incidences were calculated in person-

**Table 1.** Patient characteristics of 1056 sustained responders to interferon therapy given for chronic hepatitis C

| | | Number of patients |
|---|---|---|
| **Host-related variables** | | |
| Age (years) | Median (range) | 50 (11–76) |
| Sex | Male | 711 (67%) |
| History of blood transfusion | Positive | 266 (27%) |
| Alcohol abuse[a] | Positive | 78 (8%) |
| Smoking habit[b] | Positive | 248 (38%) |
| HCV viral load | High ($\geq 10^6$) | 159 (21%) |
| HCV serologic group | Group 1 | 372 |
| | Group 2 | 466 |
| Hepatitis B surface antigen | Positive | 17 (2%) |
| **Treatment-related variables** | | |
| Interferon type | α | 829 (79%) |
| | β | 166 (16%) |
| | α + β | 61 (6%) |
| Total amount of interferon (MU) | Median (range) | 480 (42–1740) |
| Treatment period (weeks) | Median (range) | 22 (2–56) |
| Prior interferon therapy | Positive | 87 |

HCV, hepatitis C virus
[a] Alcohol intake, ≥80 g/day × 5 years
[b] Smoking habit, ≥20 cigarettes/day for ≥10 years

years; incidence curves of HCC were calculated by the Kaplan-Meier method; and differences in survival were evaluated by log rank tests. Hazard ratios and trend *P* values were calculated by treating the categories as ordinal variables. The Cox proportional hazard model was used to determine the most significant variables related to the development of HCC. All patients were then assigned a risk index value for the development of HCC, as follows: the value of each factor in the final model was multiplied by its corresponding regression coefficient, and these values were totaled to obtain the risk index for each patient. Stratification of the patients was conducted on the basis of this risk index. All *P* values were two-tailed and were considered significant when less than 0.05.

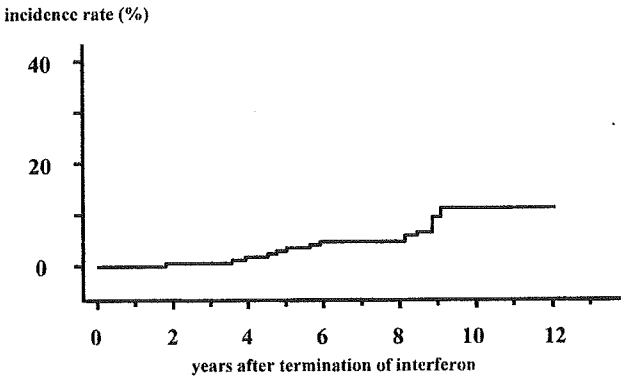


**Fig. 1.** Cumulative incidence of hepatocellular carcinoma in 1056 sustained responders to interferon therapy given for chronic hepatitis C

## Results

### *Patient characteristics*

Table 1 summarizes the patient characteristics of the 1056 sustained responders to IFN therapy given for chronic hepatitis C. The median age was 50 years (range, 11–76) years, and there were 711 men and 345 women ( sex ratio, 2.1 : 1). Hepatitis B surface antigen was positive in 17 patients (2%). The HCV serological group was group 1 in 372 patients and group 2 in 466 patients, and thus a higher proportion of patients were in serological group 2. A total of 829 patients (79%) received IFN-α, 166 patients (16%) received IFN-β, and 61 patients (6%) received both. The median dose and duration of IFN administration were 480 MU and 22 weeks, respectively. No patients received peginterferon or combination therapy with ribavirin, and 87 patients (8%) received more than two cycles of IFN therapy.

### *Incidence of HCC*

Twenty-nine of the 1056 sustained responders developed HCC, with a median follow-up period of 4.7 years. The incidence of HCC per 100 person-years was 0.56 (95% confidence interval, 0.35–0.76), and the incidences of HCC at 3, 5, 7, and 10 years after the termination of IFN therapy were 0.5%, 3.3%, 4.9%, and 11.1%, respectively (Fig. 1).

*Univariate analyses*

On univariate analysis (Table 2), age more than 60 years, positive smoking habit, platelet count less than $15 \times 10^4/mm^3$, aspartate aminotransferase (AST) more than 100 IU/l, prothrombin time less than 80%, and higher fibrosis stage (incidence of HCC per 100 person-years: F0, 0.00; F1, 0.27; F2, 0.47; F3, 0.62; F4, 1.31) were significant risk factors associated with the development of HCC. Alcohol abuse, total bilirubin, albumin, alanine aminotransferase, virological variables (viral load, serological group), tumor markers (alpha-fetoprotein, protein induced by vitamin K absence or antagonist-II), and treatment-related variables (treatment period, IFN type, total amount of IFN) were not significant risk factors.

*Multivariate analyses*

All variables whose $P$ values were less than 0.20 on the univariate analyses were entered into the multivariate analyses (Table 3). However, history of blood transfusion, smoking habit, prothrombin time, and indocyanine green retention rate at 15 min (ICG R15) were not included in the model because inadequate data were available. Multivariate regression analysis, which assessed the independent predictive importance of each variable studied for the development of HCC, showed that older age, higher serum AST level, and lower platelet count were significantly related to the development of HCC.

*Risk groups based on the regression model*

For the clinical application of these findings, a risk index was calculated based on the regression coefficients derived from the three variables identified by multivariate analysis. The index equation was as follows: $1.14 \times$ (0, age $\leq$ 60 years; 1, age $>$ 60 years) + $1.13 \times$ (0, AST $\leq$ 100 IU/l; 1, AST $>$ 100 IU/l) + $1.02 \times$ (0, platelet count $\geq 15 \times 10^4/mm^3$; 1, platelet count $< 15 \times 10^4/mm^3$). The risk index was $\ln[hi(t)/h_0(t)]$, where $hi(t)/h_0(t)$ was the relative risk of the development of HCC for the $i$-th patient. The index values ranged from 0.00 to 3.29. The patients were then classified into three groups according to the risk index, as follows: low risk, risk index less than 1.00 (equivalent to patients with none of the three risk factors); intermediate risk, risk index from 1.00 to 2.00 (equivalent to patients with one of the three risk factors); and high risk, risk index greater than 2.00 (equivalent to patients with two or more of the three risk factors). The incidence curves for the three groups are shown in Fig. 2. The incidence rates of HCC per 100 person-years (95% confidence interval) in the low-, intermediate-, and high-risk groups were 0.11 (0.00–0.26), 0.44 (0.11–0.77), and 1.98 (1.09–2.87), respectively. There was a significant difference in survival time among the three groups ($P < 0.0001$).

*Clinical features of HCC*

The characteristics of the 29 patients in whom HCC developed after sustained response are shown in Table 4. All patients were HCV RNA-negative (determined by using qualitative HCV RNA assay), at the time of diagnosis of HCC. Twenty-five patients (86%) were aged 60 years or more, and 24 patients (83%) were men. Among the 13 patients in whom liver biopsy was done at the time of diagnosis of HCC, A0, A1, and A2 histological activity was observed in 5 (38%), 6 (46%), and 2 (15%) patients, respectively. F0, F1, F2, F3, and F4 histological stages were observed in 1 (8%), 1 (8%), 7 (54%), 2 (15%), and 2 (15%) patients, respectively. The median period from the termination of IFN therapy to the development of HCC was 4.6 years (range, 1.4–9.0 years), and there were 11 patients (38%) in whom HCC was detected more than 5 years after the termination of IFN therapy. The periods and methods of medical follow-up examination after the end of IFN therapy varied among the patients, and 8 patients did not receive a sufficient post-treatment medical examination. Among them, HCC of 5 cm or more in size was detected in 5 patients (63%).

## Discussion

IFN is already widely used as a standard therapeutic modality for chronic hepatitis C.[5–9] It is generally assumed that eradication of HCV by IFN halts the progression of the disease and prevents clinical complications, including the development of HCC.[5,7,10–14] However, there have been reports of several patients in whom HCC developed after successful IFN therapy.[5,10–25] The incidence and clinical features of HCC, the risk factors for the disease, and the mechanism of carcinogenesis in these patients have not been fully elucidated, because the development of HCC is very rare in sustained responders to IFN therapy. This prompted us to perform a multicenter retrospective cohort study to gather clinical data on such patients.

Of all 1056 sustained responders to IFN therapy in the 16 hospitals in the study, 29 developed HCC, with a median period to development of 4.7 years, and the incidence of HCC was 0.56 (95% confidence interval, 0.35–0.76) per 100 person-years. This value was consistent with the results of previous studies of small numbers of sustained responders to IFN who developed HCC.[5,11–14,20,21–25] This rate was considerably lower than that in IFN-refractory patients or HCV-positive pa-

**Table 2.** Univariate analysis of 1056 sustained responders in relation to development of HCC

| Variables | | No. of patients | No. of patients developing HCC | Incidence (95% CI) (/100 person-years) | Hazard ratio (95% CI) | *P* value (log rank) |
|---|---|---|---|---|---|---|
| **Host-related variables** | | | | | | |
| Age | ≤60 years | 840 | 13 | 0.32 (0.14–0.49) | | |
| | >60 years | 216 | 16 | 1.43 (0.73–2.13) | 4.23 (2.04–8.80) | 0.001 |
| Sex | Male | 711 | 24 | 0.67 (0.40–0.94) | — | |
| | Female | 345 | 5 | 0.30 (0.04–0.57) | 0.47 (0.18–1.23) | 0.12 |
| History of blood transfusion | Positive | 266 | 11 | 0.80 (0.33–1.28) | — | |
| | Negative | 723 | 16 | 0.45 (0.23–0.67) | 0.60 (0.28–1.30) | 0.19 |
| Alcohol abuse[a] | Positive | 78 | 2 | 0.53 (0.00–1.26) | — | |
| | Negative | 946 | 26 | 0.56 (0.34–0.77) | 1.05 (0.25–4.42) | 0.95 |
| Smoking habit[b] | Positive | 248 | 14 | 1.16 (0.55–1.77) | — | |
| | Negative | 405 | 7 | 0.36 (0.09–0.62) | 0.30 (0.12–0.75) | 0.009 |
| HCV viral load | High (≥$10^6$) | 159 | 1 | 0.15 (0.00–0.45) | — | |
| | Low (<$10^6$) | 593 | 11 | 0.42 (0.17–0.66) | 2.68 (0.35–20.77) | 0.35 |
| HCV serological group | Group 1 | 372 | 5 | 0.27 (0.03–0.52) | — | |
| | Group 2 | 466 | 10 | 0.47 (0.18–0.76) | 1.78 (0.60–5.26) | 0.30 |
| Hepatitis B surface antigen | Positive | 17 | 0 | 0.00 | | |
| | Negative | 1008 | 27 | 0.54 (0.34–0.75) | [c] | 0.56 |
| Platelet count (×$10^4$/mm$^3$) | ≥15 | 568 | 7 | 0.27 (0.07–0.46) | — | |
| | <15 | 358 | 21 | 1.15 (0.66–1.65) | 3.95 (1.68–9.30) | 0.002 |
| Total bilirubin (mg/dl) | ≥1.0 | 207 | 8 | 0.75 (0.23–1.27) | — | |
| | <1.0 | 824 | 21 | 0.52 (0.30–0.75) | 0.37 (0.32–1.65) | 0.45 |
| Albumin (g/dl) | >4.0 | 564 | 17 | 0.59 (0.31–0.87) | — | |
| | <4.0 | 396 | 8 | 0.42 (0.13–0.72) | 0.78 (0.34–1.80) | 0.56 |
| Aspartate aminotransferase (IU/l) | >100 | 196 | 13 | 1.26 (0.57–1.94) | — | |
| | ≤100 | 844 | 16 | 0.39 (0.20–0.58) | 0.35 (0.17–0.73) | 0.005 |
| Alanine aminotransferase (IU/l) | >100 | 459 | 17 | 0.73 (0.38–1.07) | — | |
| | ≤100 | 591 | 12 | 0.42 (0.18–0.66) | 0.63 (0.30–1.32) | 0.22 |
| Prothrombin time (%) | ≥80 | 493 | 9 | 0.39 (0.14–0.65) | — | |
| | <80 | 158 | 10 | 1.19 (0.45–1.93) | 2.72 (1.10–6.74) | 0.03 |
| ICG R15 (%) | ≥10 | 322 | 9 | 0.52 (0.18–0.86) | — | |
| | <10 | 274 | 1 | 0.08 (0.00–0.23) | 0.18 (0.02–1.44) | 0.11 |
| Alpha-fetoprotein (ng/ml) | >20 | 66 | 2 | 0.58 (0.00–1.39) | — | |
| | <20 | 554 | 16 | 0.58 (0.30–0.87) | 1.10 (0.25–4.81) | 0.78 |
| PIVKA-II (AU/ml) | >0.063 | 42 | 0 | 0.00 | | |
| | ≤0.063 | 235 | 8 | 0.66 (0.20–1.12) | [c] | 0.63 |
| Histological activity grade | A0 (No) | 12 | 0 | 0.00 | | |
| | A1 (Mild) | 309 | 6 | 0.40 (0.08–0.73) | | |
| | A2 (Moderate) | 359 | 11 | 0.64 (0.26–1.01) | | |
| | A3 (Severe) | 169 | 5 | 0.61 (0.07–1.14) | 1.28 (0.74–2.21) | 0.39 |
| Histological fibrosis stage | F0 (No) | 26 | 0 | 0.00 | | |
| | F1 (Mild) | 405 | 5 | 0.27 (0.03–0.50) | | |
| | F2 (Moderate) | 301 | 7 | 0.47 (0.12–0.82) | | |
| | F3 (Severe) | 170 | 6 | 0.62 (0.12–1.11) | | |
| | F4 (Cirrhosis) | 97 | 4 | 1.31 (0.03–2.60) | 1.56 (1.03–2.36) | 0.03 |
| **Treatment-related variables** | | | | | | |
| Treatment period (weeks) | >24 | 472 | 17 | 0.73 (0.38–1.08) | | |
| | <24 | 584 | 12 | 0.41 (0.18–0.65) | 0.56 (0.27–1.16) | 0.11 |
| Interferon type | α | 829 | 25 | 0.61 (0.37–0.85) | — | |
| | β | 166 | 4 | 0.55 (0.01–1.10) | 0.99 (0.34–2.86) | 0.98 |
| | α + β | 61 | 0 | 0.00 | [c] | |
| Total amount of interferon (MU) | >500 | 491 | 10 | 0.42 (0.16–0.68) | — | |
| | ≤500 | 534 | 16 | 0.60 (0.31–0.89) | 1.34 (0.61–2.95) | 0.47 |
| Prior interferon therapy | Positive | 87 | 2 | 0.46 (0.00–1.10) | — | |
| | Negative | 955 | 27 | 0.57 (0.36–0.79) | 1.17 (0.28–5.00) | 0.82 |

HCC, hepatocellular carcinoma; CI, confidence interval; HCV, hepatitis C virus; ICG R15, indocyanine green retention rate at 15 min; PIVKA II, protein induced by vitamin K absence or antagonist-II; —; reference category

[a] Alcohol intake ≥80 g/day + 5 years

[b] Smoking habit, >20 cigarettes/day for >10 years

[c] not estimated

tients who did not receive IFN therapy, which has been reported to be 1.4%–7% yearly,[4–7,10–13,21–24] and it was obvious that IFN therapy decreased the risk of HCC in sustained responders. However, the incidence of HCC gradually increased over a period of at least 9 years after the termination of IFN therapy (Fig. 1). This suggests that the risk of HCC is not completely eliminated in patients who have a sustained response to IFN therapy,

at least for up to 9 years following cessation of the treatment.

Identification of the risk factors for the development of HCC in sustained responders is important, so that high-risk patients can be screened carefully for early detection of HCC and given potentially curative treatments such as hepatic resection; such patients generally have a good hepatic reserve after the elimination of HCV. Among the variables we investigated, multivariate analysis showed age to be an independent risk factor. As the patient ages, the period of HCV infection becomes longer, and the liver becomes more severely cirrhotic. Therefore, advanced age may simply represent the progression of associated liver disease. These findings are compatible with previous reports of the development of HCC in patients with chronic hepatitis C.[11–14,20–22]

Serum AST level and platelet counts were also independent risk factors in the present study. Some studies have reported that increased AST level and decreased platelet count are correlated with the progression of liver fibrosis,[33–34] which has been reported to be one of the most important risk factors for the development of HCC in patients with chronic hepatitis C.[5,11–13,21] Progression of liver fibrosis may reduce the clearance of AST,[35] leading to increased serum AST levels.[36] This progression is also associated with decreased production of thrombopoietin by hepatocytes[37] and progressive hypersplenism with worsening portal hypertension;[38] and, hence, reduced platelet production and increased platelet destruction. Moreover, in the present study, these factors were strongly associated with histological stage (Pearson's correlation coefficient; $P < 0.0001$). Therefore, increased AST level and decreased platelet count may reflect more progressive liver fibrosis.

For the clinical application of these findings, we proposed a risk index based on the independent risk factors. Patients were classified into three groups, with low, intermediate, and high risk ($P < 0.0001$ for difference in survival time among the three groups; Fig. 2). This index can be easily calculated, because it is based on variables obtained during routine laboratory examinations before IFN therapy is begun. This index, therefore, may be helpful in assessing the risk of development of HCC after sustained response to IFN therapy, although it is also important to validate this risk index by applying it to other populations of patients. Patients in the high-risk group (incidence rate, 1.98 per 100 person-years) may benefit from regular diagnostic imaging for the early detection of HCC.

In the analysis of the clinical features of HCC there were no specific findings. The period to the development of HCC after IFN therapy (median, 4.6 years; 1.4–9.0 range, years) was variable. HCC developed even in two patients whose liver showed improvement to mild fibrosis (stage F0 or F1) and in five patients whose liver improved to no activity (A0) after IFN therapy. The follow-up periods and methods for the detection of HCC after the termination of IFN therapy varied among the patients, and in some patients HCC was detected at far more advanced stages than in others, because of insufficient follow up after IFN therapy. This finding may suggest the need for regular follow up by diagnostic imaging, even after sustained response to IFN therapy for chronic hepatitis C, especially in the high-risk group.

Our study involved some uncertainties. First, because the study was retrospective, many data items were missing from the replies to the data collection instrument, and we had to ignore unmeasured or unrecorded data when conducting the statistical analyses. In the multivariate analysis, therefore, only variables whose $P$ values were less than 0.20 on the univariate analysis were entered. Also, history of blood transfusion, smoking habit, prothrombin time, and ICG R15, whose $P$ values were lower than 0.20, had to be excluded from the model because of missing data; these factors were potentially significant on multivariate analysis. Secondly, we sought information on serum hepatitis B virus DNA

**Table 3.** Significant risk factors identified in 1056 sustained responders, as determined by multivariate analysis with the Cox proportional hazard model

| Variable | Hazard ratio (95% confidence interval) | $P$ value |
|---|---|---|
| Age | 3.13 (1.32–7.42) | 0.01 |
| Aspartate aminotransferase | 3.10 (1.31–7.31) | 0.01 |
| Platelet count | 2.78 (1.07–7.20) | 0.04 |

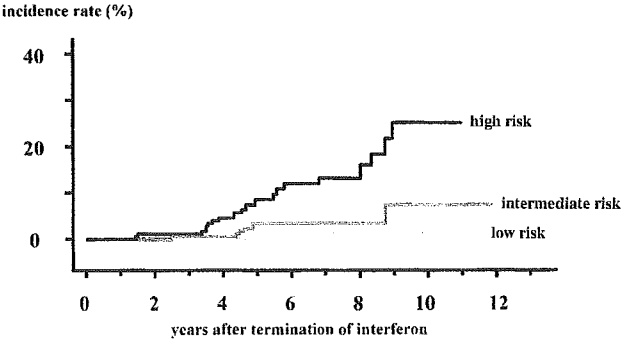


**Fig. 2.** Cumulative incidence of hepatocellular carcinoma for the three groups determined by a risk index based on the results of multivariate analysis. Low risk (risk index < 1.00); intermediate risk (risk index from 1.10 to 2.00); high risk (risk index, ≥2.00)

**Table 4.** Clinical features at the time of diagnosis of HCC in 29 patients who developed hepatocellular carcinoma after sustained response to interferon therapy given for chronic hepatitis C

| Age (years) | Sex | HCV RNA | HBs Ag | Histological fibrosis stage | Histological activity grade | AFP (ng/ml) | PIVKA II (AU/ml) | Number of tumors |
|---|---|---|---|---|---|---|---|---|
| 64 | Male | Negative | Negative | NA | NA | 2 | 0 | 4 |
| 60 | Male | Negative | Negative | NA | NA | 51 | 0.211 | 1 |
| 38 | Male | Negative | Negative | NA | NA | 4.3 | NA | >5 |
| 67 | Male | Negative | Negative | F4 | A0 | 4.2 | 0.033 | 1 |
| 75 | Male | Negative | Negative | F1 | A1 | 5 | 0.054 | 1 |
| 65 | Female | Negative | Negative | NA | NA | 5 | 0.029 | 1 |
| 62 | Male | Negative | Negative | NA | NA | 3 | NA | 1 |
| 61 | Male | Negative | Negative | F2 | A0 | 3 | 0.001 | 1 |
| 64 | Male | Negative | Negative | F2 | A0 | 4 | 0.426 | 1 |
| 70 | Male | Negative | Negative | NA | NA | 46 000 | NA | 1 |
| 64 | Male | Negative | Negative | NA | NA | 146 | 0.049 | 1 |
| 54 | Female | Negative | Negative | F3 | A1 | 2165 | 6690 | 1 |
| 65 | Male | Negative | Negative | F4 | A2 | 25.9 | 0.015 | >5 |
| 61 | Male | Negative | Negative | F2 | A1 | 4 | 1.79 | 1 |
| 64 | Male | Negative | Negative | F2 | A0 | NA | NA | 1 |
| 63 | Male | Negative | Negative | NA | NA | 135.3 | 0.06 | 1 |
| 67 | Male | Negative | Negative | NA | NA | 3.5 | 0.013 | 1 |
| 75 | Male | Negative | Negative | NA | NA | 2 | NA | 1 |
| 62 | Male | Negative | Negative | F2 | A1 | 1026 | 13.32 | 1 |
| 62 | Male | Negative | Negative | F2 | A1 | 2.3 | 1.79 | 1 |
| 68 | Female | Negative | Negative | F3 | A2 | 9.1 | 0.016 | 1 |
| 59 | Male | Negative | Negative | F0 | A0 | 29 | 0.029 | 1 |
| 70 | Male | Negative | Negative | NA | NA | 488.3 | 601 371 | 1 |
| 54 | Male | Negative | Negative | NA | NA | 258 | 2.1 | 1 |
| 68 | Female | Negative | Negative | NA | NA | 2.8 | 0.023 | 1 |
| 60 | Male | Negative | Negative | F2 | A1 | 3.2 | 0.023 | 1 |
| 70 | Male | Negative | Negative | NA | NA | 5463 | 6.566 | 2 |
| 70 | Female | Negative | Negative | NA | NA | 464.2 | NA | 1 |
| 77 | Male | Negative | Negative | NA | NA | 72 | 0.136 | 2 |

NA, not available; HBs Ag, hepatitis B surface antigen; AFP, alpha-fetoprotein; PIVKA II, protein induced by vitamin K absence or antagonist-II; Vp, portal vein invasion; Vv, hepatic vein invasion; B, bile duct invasion; US, ultrasonography; CT, computed tomography

in sustained responders in whom HCC developed after successful IFN therapy, but data could be obtained for only two patients, who were negative for hepatitis B virus DNA. We cannot rule out the presence of occult hepatitis B virus in the other patients, although all patients were negative for hepatitis B antigen. In spite of these uncertainties, this study represents a comprehensive analysis of HCC developing after sustained response to IFN therapy, because we were able to collect clinical data for a large number of sustained responders at 16 major hospitals.

In this study, we encountered 29 patients in whom HCC developed after successful IFN therapy, but the reason why HCC developed in these sustained responders is unclear. The existence of a small undetected HCC at the time of IFN therapy may have been responsible for the appearance of HCC after the sustained response to IFN therapy. However, in 11 patients (38%), HCC was detected more than 5 years after IFN therapy, and the incidence of HCC gradually increased for at least 9 years after IFN therapy. Considering the late onset of HCC in these patients, we cannot neglect the possibility of the de-novo development of HCC after the eradication of HCV. HCV is a single-stranded RNA virus without a DNA intermediate in its replicative cycle, so that the integration of HCV nucleic acid sequences into the host genome seems unlikely. Therefore, it is difficult to believe that HCV itself is a causative factor of HCC in the absence of chronic inflammation, liver cell necrosis and regeneration, and extensive fibrosis. It is probable that carcinogenesis is not a single-step event, but a complex multistep process. Future studies should aim to define the basic oncogenic mechanisms by which sustained responders to IFN develop HCC. Exploration of these mechanisms may point the way toward new strategies for the prevention of HCC.

In conclusion, some patients showing a sustained response to IFN therapy given for chronic hepatitis C demonstrated potential for the development of HCC for up to 9 years following cessation of the treatment. This suggests that the risk of HCC in sustained responders is not completely eliminated. The establishment of risk factors and an index for the development of HCC may be useful in determining follow-up strategy in patients after a sustained response to IFN therapy given for chronic hepatitis.

**Table 4.** *Continued*

| Maximum tumor size (mm) | Vp | Vv | B | Differentiation of HCC | Period to development Of HCC (years) | Medical follow-up period (months) | Diagnostic modality |
|---|---|---|---|---|---|---|---|
| 18 | 0 | 0 | 0 | Moderately | 1.43 | 3 | US |
| 16 | 0 | 0 | 0 | NA | 1.51 | 1 | US |
| >20 | 3 | 0 | 0 | NA | 1.79 | None | US |
| 15 | 0 | 0 | 0 | Moderately | 2.52 | 1 | US |
| 25 | 0 | 0 | 0 | Moderately | 3.32 | 2 | CT |
| 20 | 0 | 0 | 0 | Well | 3.39 | 3 | US |
| 34 | 2 | 1 | 2 | Well | 3.54 | 2 | US |
| 20 | 0 | 0 | 0 | Well | 3.59 | 3 | Laparoscopy |
| 40 | 0 | 0 | 0 | NA | 3.70 | None | US |
| 50 | 2 | 2 | 2 | NA | 3.89 | None | US |
| 30 | 0 | 0 | 0 | Well | 4.35 | 1 | US |
| 110 | 0 | 0 | 0 | Poorly | 4.38 | 6 | US |
| 15 | 0 | 0 | 0 | Well | 4.48 | 6 | US |
| 50 | 1 | 0 | 1 | Moderately | 4.58 | 12 | US |
| 80 | 0 | 0 | 0 | Moderately | 4.60 | None | CT |
| NA | 0 | 0 | 0 | NA | 4.70 | 6 | US |
| 44 | 0 | 0 | 0 | NA | 4.88 | 6 | US |
| 28 | 0 | 0 | 0 | NA | 4.97 | 3 | US |
| 60 | 1 | 1 | 1 | Moderately | 5.52 | None | US |
| 50 | 1 | 0 | 1 | Moderately | 5.58 | 6 | US |
| 51 | 0 | 0 | 0 | Combined type | 5.80 | 3 | US |
| 40 | 0 | 0 | 0 | Moderately | 5.86 | None | US |
| >20 | 2 | 0 | 0 | NA | 6.61 | 3 | US |
| 150 | 3 | 0 | 0 | Poorly | 6.86 | None | US |
| 15 | 0 | 0 | 0 | NA | 8.05 | 3 | US |
| 15 | 0 | 0 | 0 | Well | 8.39 | 6 | US |
| 60 | 0 | 0 | 0 | Well | 8.78 | None | US |
| 16 | 0 | 0 | 0 | NA | 8.79 | 3 | US |
| 42 | 0 | 0 | 0 | NA | 8.98 | 1 | CT |

## Appendix

In addition to the study authors' hospitals (the four institutions listed on the title page), data were supplied by the following hospitals and clinics in the Kyushu Division of the Japanese Society of Gastroenterology: Shinnittetsu Yahata Memorial Hospital; Yame General Hospital; First Department of Internal Medicine, Ryukyu University School of Medicine; Second Department of Internal Medicine, Kagoshima University School of Medicine; Hayato Town Medical Association Medical Center; Department of Internal Medicine, Saga Medical School; Department of Medicine and Biosystemic Science, Kyushu University School of Medicine; Nishinihon Hospital; Kagoshima Kouseiren Hospital; Miyata Memorial Hospital; Second Department of Internal Medicine, Nagasaki University School of Medicine; and Yonabaru Central Hospital.

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## References

1. Bruix J, Barrera JM, Calvet X, Ercilla G, Costa J, Sanchez-Tapias JM, et al. Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. Lancet 1989;II:1004–6.
2. Colombo M, Kuo G, Choo QL, Donato MF, Del Ninno E, Tommasini MA, et al. Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. Lancet 1989;II:1006–8.
3. Kew MC, Houghton M, Choo QL, Kuo G. Hepatitis C virus antibodies in southern African blacks with hepatocellular carcinoma. Lancet 1990;355:873–4.
4. Takano S, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. Hepatology 1995;21:650–5.
5. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: National Surveillance Program of Cirrhotic and Noncirrhotic Patients with Chronic Hepatitis C in Japan. IHIT Study Group. Ann Intern Med 1999;131:174–81.
6. Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC Jr, Perrillo RP, et al. Treatment of chronic hepatitis C with recombinant interferon alfa. A multicenter randomized, controlled trial.

Hepatitis Interventional Therapy Group. N Engl J Med 1989;321: 1501–6.
7. Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, et al. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet 1995;346:1051–5.
8. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 1998;339:1485–92.
9. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 2000;343:1666–72.
10. Ikeda K, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1643 patients using statistical bias correction with proportional hazard analysis. Hepatology 1999;29:1124–30.
11. Okanoue T, Itoh Y, Minami M, Sakamoto S, Yasui K, Sakamoto M, et al. Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage: a retrospective study in 1148 patients. Viral Hepatitis Therapy Study Group. J Hepatol 1999; 30:653–9.
12. Kasahara A, Hayashi N, Mochizuki K, Takayanagi M, Yoshioka K, Kakumu S, et al. Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Osaka Liver Disease Study Group. Hepatology 1998;27:1394–402.
13. Imai Y, Kawata S, Tamura S, Yabuuchi I, Noda S, Inada M, et al. Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka Hepatocellular Carcinoma Prevention Study Group. Ann Intern Med 1998;129: 94–9.
14. Yoshida H, Arakawa Y, Sata M, Nishiguchi S, Yano M, Fujiyama S, et al. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. Gastroenterology 2002;123:483–91.
15. Hirashima N, Mizokami M, Orito E, Koide T, Itazu I, Kumada K, et al. Case report: development of hepatocellular carcinoma in a patient with chronic hepatitis C infection after a complete and sustained response to interferon-alpha. J Gastroenterol Hepatol 1996;11:955–8.
16. Tong MJ, Lai LP, Murakami-Mori K. Development of hepatocellular carcinoma after clearance of hepatitis C virus with interferon therapy. West J Med 1997;167:103–5.
17. Miyano S, Togashi H, Shinzawa H, Sugahara K, Matsuo T, Takeda Y, et al. Case report: occurrence of hepatocellular carcinoma 4.5 years after successful treatment with virus clearance for chronic hepatitis C. J Gastroenterol Hepatol 1999;14:928–30.
18. Toyoda H, Kumada T, Honda T, Hayashi K, Katano Y, Nakano I, et al. Analysis of hepatocellular carcinoma tumor growth detected in sustained responders to interferon in patients with chronic hepatitis C. J Gastroenterol Hepatol 2001;16:1131–7.
19. Yamada M, Ichikawa M, Matsubara A, Ishiguro Y, Yokoi S. Development of small hepatocellular carcinoma 80 months after clearance of hepatitis C virus with interferon therapy. Eur J Gastroenterol Hepatol 2000;12:1029–32.
20. Shindo M, Hamada K, Oda Y, Okuno T. Long-term follow-up study of sustained biochemical responders with interferon therapy. Hepatology 2001;33:1299–302.
21. Yoshida H, Tateishi R, Arakawa Y, Sata M, Fujiyama S, Nishiguchi S, et al. Benefit of interferon therapy in hepatocellular carcinoma prevention for individual patients with chronic hepatitis C. Gut 2004;53:425–30.
22. Kashiwagi K, Furusyo N, Kubo N, Nakashima H, Nomura H, Kashiwagi S, et al. A prospective comparison of the effect of interferon-alpha and interferon-beta treatment in patients with chronic hepatitis C on the incidence of hepatocellular carcinoma development. J Infect Chemother 2003;9:333–40.
23. Suzuki K, Ohkoshi S, Yano M, Ichida T, Takimoto M, Naitoh A, et al. Sustained biochemical remission after interferon treatment may be closely related to the end of treatment biochemical response and associated with a lower incidence of hepatocarcinogenesis. Liver Int 2003;23:143–7.
24. Yoneyama K, Yamaguchi M, Kiuchi Y, Morizane T, Shibata M, Mitamura K. Analysis of background factors influencing long-term prognosis of patients with chronic hepatitis C treated with interferon. Intervirology 2002;45:11–9.
25. Komorizono Y, Sako K, Yamasaki N, Hiwaki T, Sakurai K, Shibatou T, et al. Outcome of patients with hepatitis C virus-related hepatocellular carcinoma occurring after interferon therapy. Anticancer Res 2002;22:3573–8.
26. Hagiwara H, Hayashi N, Mita E, Takehara T, Kasahara A, Fusamoto H, et al. Quantitative analysis of hepatitis C virus RNA in serum during interferon alfa therapy. Gastroenterology 1993;104:877–83.
27. Yuki N, Hayashi N, Kasahara A, Hagiwara H, Takehara T, Oshita M, et al. Pretreatment viral load and response to prolonged interferon-alpha course for chronic hepatitis C. J Hepatol 1995;22:457–63.
28. Shiratori Y, Kato N, Yokosuka O, Imazeki F, Hashimoto E, Hayashi N, et al. Predictors of the efficacy of interferon therapy in chronic hepatitis C virus infection. Tokyo-Chiba Hepatitis Research group. Gastroenterology 1997;113:558–66.
29. Okamoto H, Sugiyama Y, Okada S, Kurai K, Akahane Y, Sugai Y, et al. Typing hepatitis C virus by polymerase chain reaction with type-specific primers: application to clinical surveys and tracing infectious sources. J Gen Virol 1992;73:673–9.
30. Tanaka T, Tsukiyama-Kohara K, Yamaguchi K, Yagi S, Tanaka S, Hasegawa A, et al. Significance of specific antibody assay for genotyping of hepatitis C virus. Hepatology 1994;19:1347–53.
31. Simmonds P, Alberti A, Alter HJ, Bonino F, Bradley DW, Brechot C, et al. A proposed system for the nomenclature of hepatitis C viral genotypes. Hepatology 1994;19:1321–4.
32. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19:1513–20.
33. Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. Gastroenterology 1988;95:734–9.
34. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518–26.
35. Kamimoto Y, Horiuchi S, Tanase S, Morino Y. Plasma clearance of intravenously injected aspartate aminotransferase isozymes: evidence for preferential uptake by sinusoidal liver cells. Hepatology 1985;5:367–75.
36. Okuda M, Li K, Beard MR, Showalter LA, Scholle F, Lemon SM, et al. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. Gastroenterology 2002;122:366–75.
37. Adinolfi LE, Giordano MG, Andreana A, Tripodi MF, Utili R, Cesaro G, et al. Hepatic fibrosis plays a central role in the pathogenesis of thrombocytopenia in patients with chronic viral hepatitis. Br J Haematol 2001;113:590–5.
38. Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia. J Clin Invest 1996;45: 645–57.

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# Interferon therapy for aged patients with chronic hepatitis C: improved survival in patients exhibiting a biochemical response

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***Background.*** In Japan, generally, patients with chronic hepatitis C are aged. The aim of this study was to investigate the effect of interferon (IFN) therapy on the mortality of chronic hepatitis C patients over age 60. ***Methods.*** Seven-hundred and seven patients with histologically proven chronic hepatitis C were enrolled in this study; 649 received IFN therapy (IFN group) and 58 did not (control group). The standardized mortality ratio (SMR) and Cox proportional hazard regression analysis were used to evaluate the effect of IFN on the survival of the patients. ***Results.*** Mean follow-up periods in the IFN and control groups were 5.7 and 6.7 years, respectively. During follow-up, 13 patients in the control group died (7 of liver-related diseases) and 42 in the IFN group died (29 of liver-related diseases). The SMRs of the control and IFN groups were 1.40 (95% confidence interval [CI], 0.76–2.45) and 0.73 (95% CI, 0.52–0.98) for overall death, and 10.70 (95% CI, 4.29–22.05) and 5.05 (95% CI, 3.38–7.26) for liver-related death, respectively. Sustained and transient biochemical responders in the IFN group (SMR, 0.53; 95% CI, 0.01–2.97 and SMR, 3.25; 95% CI, 0.87–8.32, respectively) showed lower liver-related mortality compared with the control group. In patients with sustained virological response, liver-related mortality was also very low (SMR, 0.65; 95% CI, 0.01–3.61). The risk for liver-related death of sustained and transient biochemical responders was also low compared with that of the control group (adjusted risk ratios 0.10 [95% CI, 0.01–0.95] and 0.50 [95% CI, 0.11–2.21], respectively). ***Conclusions.*** These results suggest that IFN treatment could reduce liver-related mortality in chronic hepatitis C patients over age 60, notably in patients showing a biochemical response and in those showing a sustained virological response.

**Key words:** interferon, chronic hepatitis C, aged, liver-related mortality, standardized mortality ratio

## Introduction

A high prevalence of hepatitis C virus (HCV) infection is observed in patients with hepatocellular carcinoma (HCC) in Japan.[1–4] In the early 1990s, interferon (IFN) was introduced, and it is now widely used worldwide, as well as in Japan, for the treatment of patients with chronic hepatitis C. Hitherto, many studies, including our own reports, have shown that IFN therapy reduced the incidence of HCC in patients with chronic hepatitis C.[5–10]

Recently, several groups have studied the effect of IFN therapy on survival in patients with chronic hepatitis C. Most of these studies reported that IFN therapy improved the survival of HCV-related chronic hepatitis and cirrhosis, although some studies did not find any efficacy of IFN therapy on survival.[10–19] We also reported the beneficial effect of IFN therapy on survival in chronic hepatitis C patients. In that report, we also

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showed that the effect of IFN therapy on survival was notable in the patients exhibiting sustained and transient biochemical responses, as well as in those showing sustained virological response.[20]

Many clinical trials showed that IFN therapy resulted in normalization of serum aminotransferase levels and eradication of serum HCV RNA, although a sustained virological response was achieved in a limited number of patients.[21–25] Recently, a combination therapy of ribavirin and IFN, or pegylated IFN, has been shown to have efficacy superior to IFN monotherapy for chronic hepatitis C.[26–28]

Patients in Japan with chronic hepatitis C are, generally, aged.[29,30] Also, patients with HCV-related HCC have been shown to be old, with a peak around age 70.[31] Despite the beneficial effects of IFN therapy or combination therapy of IFN and ribavirin for chronic hepatitis C patients, these treatments have several adverse effects which are not tolerable, especially for aged patients who have illnesses other than liver disease.[32] If IFN therapy does not prolong life expectancy in aged patients with chronic hepatitis C, the indications for IFN therapy in these patients may be very limited. Therefore, it is very important to investigate whether IFN therapy could improve survival in aged patients with chronic hepatitis C.

The aim of this study was to evaluate the effect of IFN therapy on mortality in aged patients with chronic hepatitis C. We conducted a multicenter, large-scale, retrospective cohort study of chronic hepatitis C patients over 60 years of age.

## Patients and methods

### *Patients*

We found previously that IFN therapy improved the survival in patients with chronic hepatitis C.[20] Of the 2954 patients with chronic hepatitis C in that study, we enrolled 707 patients over age 60 in the present study, to investigate the effect of IFN therapy on mortality in aged patients. Accordingly, the inclusion criteria were the same as those of the previous study: (1) histological diagnosis of chronic hepatitis or cirrhosis; (2) no history of clinical signs, at entry into the study, of complications of cirrhosis, i.e., ascites, jaundice, encephalopathy, or variceal bleeding; (3) no evidence of HCC at entry into the study, as assessed by ultrasonography and/or computed tomography; (4) absence of serum hepatitis B surface antigen; (5) absence of coexisting liver diseases, such as autoimmune hepatitis or primary biliary cirrhosis; (6) absence of excessive alcohol consumption (>80g/day); and (7) absence of human immunodeficiency virus antibodies.[20]

The IFN group comprised 649 patients who had started IFN therapy between 1992 and 1997 and had received a 4- to 12-month course of IFN, which was initiated within 1 month after liver biopsy. None of the patients had received IFN therapy before entry into this study. The control group consisted of 58 patients who had received liver biopsies between 1986 and 1997, but who did not undergo IFN therapy.

Biochemical responses to IFN therapy were categorized as follows. Patients whose alanine aminotransferase (ALT) levels decreased to the normal range during therapy and remained normal for up to 24 weeks after the end of the therapy were considered to have a sustained biochemical response. Patients whose ALT levels decreased to the normal range by the end of therapy, remained normal during therapy, but returned to abnormal levels during the 24 weeks following the end of the IFN therapy were considered to have a transient biochemical response. All other ALT patterns were classified as showing biochemical non-response. A sustained virological response was defined as persistent HCV RNA negativity during IFN therapy and follow-up. Patients showing positive HCV RNA after IFN therapy were classified as virological non-responders.

### *Follow-up*

Abdominal ultrasonography or computed tomography and biochemical examinations, including α-fetoprotein, were carried out before a liver biopsy and every 3 to 6 months during follow-up, equally in the IFN and control groups. The starting date of follow-up for patients in the control and IFN groups was defined as the date of liver biopsy. Follow-up data that were not available were collected from the resident registry of the local municipal office. In the patients residing in Osaka whose follow-up data were not obtained, the Osaka Cancer Registry was used, and the data were available until the end of 1999.[6] Therefore, it was decided to use the date of death or the end of 1999 as the end of follow-up. Because the longest observation period of the patients in the IFN group was 96 months, only the follow-up data for the first 96 months were considered in the control group. Causes of death were divided into liver-related and liver-unrelated deaths. Causes of liver-related death included HCC, liver failure, and esophageal variceal bleeding.

Informed consent was obtained from each patient included in the study. The study protocol was in accordance with the Helsinki Declaration of 1975 (revised in 1983) and was approved by the Ethics Committee of the Osaka University Graduate School of Medicine.

**Table 1.** Baseline characteristics of the interferon and control groups

| | Interferon group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Virological response | | Biochemical response | | | Total ($n$ = 649) | Control group ($n$ = 58) | $P$ value |
| | Sustained response ($n$ = 161) | Non-response ($n$ = 484) | Sustained response ($n$ = 206) | Transient response ($n$ = 144) | Non-response ($n$ = 299) | | | |
| Age (years; mean ± SD) | 63.6 ± 3.0 | 63.3 ± 2.9 | 63.8 ± 3.1 | 63.0 ± 2.8 | 63.1 ± 2.8 | 63.3 ± 2.9 | 64.1 ± 3.1 | 0.06 |
| Age distribution (years; %) | | | | | | | | |
| 60–64 | 67.7 | 71.1 | 63.6 | 75.0 | 72.9 | 70.4 | 56.9 | 0.03 |
| ≥65 | 32.3 | 28.9 | 36.4 | 25.0 | 27.1 | 29.6 | 43.1 | |
| Male/Female | 110/51 | 272/212 | 134/72 | 80/64 | 171/128 | 385/264 | 31/27 | 0.38 |
| Histologic staging score (%) | | | | | | | | |
| 0 | 0.6 | 0.2 | 0.5 | 0.0 | 0.3 | 0.3 | 5.2 | 0.06 |
| 1 | 24.8 | 18.2 | 27.7 | 25.0 | 12.4 | 20.0 | 31.0 | |
| 2 | 29.2 | 27.7 | 26.7 | 28.5 | 28.8 | 28.0 | 20.7 | |
| 3 | 39.8 | 46.9 | 40.3 | 39.6 | 50.5 | 44.8 | 31.0 | |
| 4 | 5.6 | 7.0 | 4.9 | 6.9 | 8.0 | 6.8 | 12.1 | |
| ALT (IU/l; mean ⌜ SD) | 113 ⌜ 82 | 107 ⌜ 68 | 110 ⌜ 86 | 87 ⌜ 45 | 117 ⌜ 69 | 108 ⌜ 71 | 105 ⌜ 80 | 0.75 |

*Histological evaluation*

In all patients, liver biopsy was undertaken before IFN therapy. Sections were stained with hematoxylin-eosin and Azan-Mallory and analyzed by two pathologists in a blinded manner. For the assessment of liver histology, the classification of Desmet et al.[33] was used.

*Statistical analysis*

To compare the distribution of age at liver biopsy and histological staging between the IFN and control groups, the Wilcoxon rank-sum test was used. Differences in age at liver biopsy and ALT between the two groups was assessed for significance by Student's $t$-test. The $\chi^2$ test was used to compare sex differences. The Kaplan-Meier method was used to compare the cumulative survival rates in the IFN and control groups.

We compared the observed number of deaths with the expected number of deaths, which was calculated by applying sex-, 5-year age, 5-year calendar time, and cause-specific mortality rates for the general population in Japan, as prepared by the Statistics and Information Department, Japan Ministry of Health and Welfare.[34] The standardized mortality ratio (SMR) was expressed by dividing the observed number of deaths by the expected number of deaths. Survival was also analyzed by Cox proportional hazards regression. For analysis, age, sex, stage of liver fibrosis (stages 0,1/2/3/4), time of liver biopsy (until 1992/after 1993), and IFN therapy were used as variables. SMRs and hazard risk ratios were expressed with 95% confidence intervals (CIs).

Data analysis was performed with the SAS/PC statistical package (SAS Institute, Cary, NC, USA). All reported $P$ values were two-sided, and a $P$ value of less than 0.05 was considered to be significant.

## Results

*Baseline characteristics*

In the IFN group, 206 patients (31.7%) had a sustained biochemical response, 144 (22.2%) had a transient biochemical response, and 299 patients (46.1%) were biochemical non-responders. Four sustained biochemical responders whose serum HCV RNA was not examined during follow-up were excluded from the analysis. Accordingly, 161 patients (25.0%) of the 645 IFN-treated patients were classified as sustained virological responders. Table 1 shows the baseline characteristics of the IFN and control groups. Age at entry, sex, histologic staging score, and serum ALT level did not differ between the two groups. The proportion of patients more than 65 years of age in the control group was higher than that in the IFN group ($P$ = 0.03).

**Table 2.** Cumulative survival rate calculated from overall deaths

| | Interferon group | | | | | | |
|---|---|---|---|---|---|---|---|
| | Virological response | | Biochemical response | | | | |
| | Sustained response | Non-response | Sustained response | Transient response | Non-response | Total | Control group |
| Mean follow-up period (years: mean ± SD) | 5.7 ± 1.6 | 5.7 ± 1.7 | 5.6 ± 1.7 | 5.7 ± 1.8 | 5.8 ± 1.6 | 5.7 ± 1.7 | 6.7 ± 1.7 |
| 4-Year survival rate | 99.3% | 96.2% | 98.4% | 99.2% | 95.0% | 97.0% | 93.0% |
| 8-Year survival rate | 94.6% | 86.8% | 94.3% | 93.0% | 83.4% | 88.7% | 73.9% |
| *P* Value[a] | <0.001 | 0.0197 | <0.001 | 0.0036 | 0.1212 | 0.0031 | |

[a] The log rank test was used to determine the difference against the control group




**Fig. 1.** Cumulative survival rates in the interferon (*IFN*; *dotted line*) and control (*solid line*) groups. Log-rank test of the two curves showed a significant difference between the two groups (*P* 0.003)

*Cumulative survival and cause of death*

The mean follow-up periods of the IFN and control groups were 5.7 and 6.7 years, respectively. The mean follow-up periods of the patients with each response in the IFN group are shown in Table 2. Figure 1 shows the cumulative survival rates of the IFN and control groups, estimated by the Kaplan-Meier method. The 8-year survival rates of the IFN and control groups were 88.7% and 73.9%, respectively (log-rank test; $P = 0.003$; Table 2). The cumulative survival rates of sustained virological responders were significantly higher than those for virological non-responders (log-rank test; $P = 0.02$). The 8-year survival rates of sustained virological responders and virological non-responders were 94.6% and 86.8%, respectively (Table 2). The cumulative survival rates of both the sustained and transient biochemical responders were significantly higher than that of the biochemical non-responders (log-rank test; $P = 0.007$ and $P = 0.049$; Fig. 2). The 8-year survival rates of sustained and transient biochemical respon-ders and biochemical non-responders were calculated to be 94.3%, 93.0% and 83.4%, respectively (Table 2).

During follow-up, 42 of the 649 IFN-treated patients and 13 of the 58 control patients died. The numbers of liver-related and liver-unrelated deaths in the IFN and control groups are shown in Table 3. Liver-related deaths corresponded to 69% of all deaths (29/42) in the IFN group and 54% of all deaths (7/13) in the control group. HCC was the major cause of liver-related deaths in both groups. Only one liver-related death (17%) was found in the deaths of sustained biochemical respond-

**Table 3.** Causes of death in the interferon and control groups

| | Interferon group | | | | | | |
|---|---|---|---|---|---|---|---|
| | Virological response | | Biochemical response | | | | |
| | Sustained response ($n$ = 161) | Non-response ($n$ = 484) | Sustained response ($n$ = 206) | Transient response ($n$ = 144) | Non-response ($n$ = 299) | Total ($n$ = 649) | Control group ($n$ = 58) |
| All deaths ($n$) | 4 | 38 | 6 | 6 | 30 | 42 | 13 |
| Liver-related deaths ($n$) | 1 | 28 | 1 | 4 | 24 | 29 | 7 |
| Hepatocellular carcinoma | 1 | 25 | 1 | 3 | 22 | 26 | 5 |
| Other causes | 0 | 3 | 0 | 1 | 2 | 3 | 2 |
| Liver-unrelated deaths ($n$) | 3 | 10 | 5 | 2 | 6 | 13 | 6 |

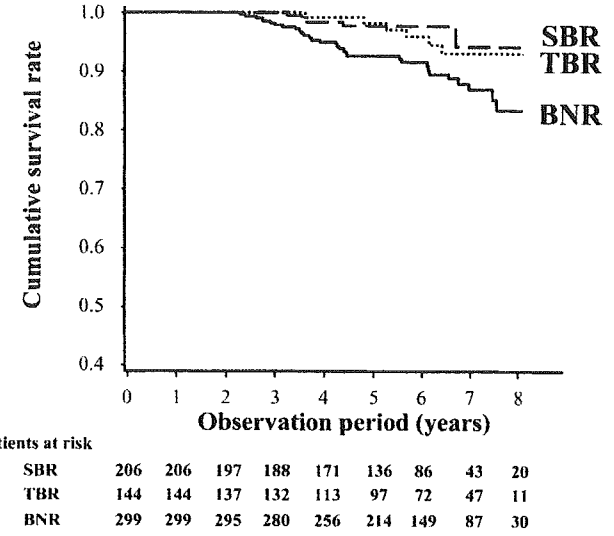


**Fig. 2.** Cumulative survival rates in the IFN-treated patients, categorized by sustained biochemical response (*SBR*; *dashed line*), transient biochemical response (*TBR*; *dotted line*), and biochemical non-response (*BNR*; *solid line*). Log-rank test showed significant differences between SBR and BNR ($P$ = 0.007) and between TBR and BNR ($P$ = 0.049)

ers. In the control group, 6 patients died of causes other than liver disease; 2 patients died of stomach cancer; 1 patient each died of lung cancer, colon cancer, and cerebral infarction; and in 1 patient, the cause of death was a traffic accident. In the IFN group, we identified 13 liver-unrelated deaths; 4 patients died of stomach cancer; 3 died of lung cancer; and 1 each died of breast cancer, colon cancer, esophageal cancer, pneumonia, chronic renal failure, and multiple myeloma.

### *Cox proportional hazard regression analysis*

Cox proportional hazard regression analysis revealed that the risk of overall death in the IFN group was lower than that in the control group, with a marginally significant difference (risk ratio, 0.37; 95% CI, 0.13–1.05; Table 4). The patients with a sustained virological response had a low risk of overall death (risk ratio, 0.15; 95% CI, 0.04–0.59) compared with the control group. Sustained and transient biochemical responders also showed low risks of overall death (risk ratio, 0.18; 95% CI, 0.05–0.65; and risk ratio, 0.24; 95% CI, 0.07–0.87). The risk of liver-related death in the IFN group was similar to that in the control group (Table 4). However, the patients with sustained virological and biochemical response had a low risk of liver-related death compared to the control group (risk ratio, 0.12; 95% CI 0.01–1.16 and risk ratio, 0.10; 95% CI, 0.01–0.95, respectively). In transient biochemical responders, the risk ratio for liver-related deaths was 0.50 (95% CI, 0.11–2.21).