

Interferon Therapy after Tumor Ablation Improves Prognosis in Patients with Hepatocellular Carcinoma Associated with Hepatitis C Virus

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Background: Even after the surgical or medical treatment of hepatocellular carcinoma, tumors frequently develop at new foci, leading to a poor prognosis.

Objective: To assess whether combined tumor ablation and interferon therapy can reduce the occurrence of new foci of hepatocellular carcinoma, thereby improving survival rate.

Design: Randomized, controlled study.

Setting: University hospital.

Patients: 74 patients with compensated cirrhosis, three or fewer nodules of hepatocellular carcinoma, and low hepatitis C virus RNA loads ($\leq 2 \times 10^6$ copies/mL).

Intervention: After all patients had complete ablation of lesions by percutaneous ethanol injection therapy, 49 patients were assigned to receive 6 million U of interferon three times weekly for 48 weeks and 25 did not receive treatment.

Measurements: Abdominal ultrasonography, computed tomography, and determination of blood biochemical measures.

Results: Of the 49 patients treated with interferon, 21 showed a sustained biochemical response and 14 showed a sustained virologic response. The rate of first recurrence of new foci of hepatocellular carcinoma was similar in patients treated with interferon and untreated patients; however, the rates of second or third recurrence seemed to be lower in the interferon group than in the untreated group. Patients treated with interferon had a survival rate of 68% at 5 years and 53% at 7 years; untreated patients had a survival rate of 48% at 5 years and 23% at 7 years.

Conclusion: After tumor ablation by ethanol injection, interferon therapy may enhance patient survival in selected patients with chronic hepatitis C.

Ann Intern Med. 2003;138:299-306.

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Chronic hepatitis C virus (HCV) infection is a common, frequently asymptomatic disease. Despite the clinically quiescent course of HCV infection, it may slowly progress to cirrhosis and, eventually, to hepatocellular carcinoma (1, 2). Cirrhosis is a major risk factor for the development of hepatocellular carcinoma (3, 4), and 70% to 80% of patients with hepatocellular carcinoma in Japan have HCV infection (5).

Current strategies for treating hepatocellular carcinoma include surgical resection, transarterial embolization, percutaneous ethanol injection therapy, radiofrequency wave ablation, and chemotherapy (6–9). Recent studies have shown that percutaneous ethanol injection therapy is effective for hepatocellular carcinoma when the tumors are small (<3 to 5 cm in diameter) and limited in number; survival rates are similar to those obtained with surgery (10–12). Five-year survival rates, however, are poor (30% to 60% for both hepatectomy and percutaneous ethanol injection therapy). Poor prognosis may be the result of the high incidence of tumor recurrence; the cumulative recurrence rate at 5 years is 60% to 100% (10–13).

Several studies have evaluated the factors that contribute to the recurrence of hepatocellular carcinoma (12, 13). Occasionally, early recurrence develops adjacent to the treated lesion (local recurrence, 6% to 33% depending on tumor size) (14), but most tumors (80% to 90%) recur at different sites (15). Because hepatocellular carcinoma recurrence and decompensation of underlying liver disease are major problems after medical or surgical treatment,

liver transplantation is another option for treating small, unresectable hepatocellular carcinomas in patients with cirrhosis. Studies report 5-year survival rates as high as 75% with liver transplantation (16–18).

Interferon therapy has beneficial effects in chronic HCV infection (19, 20). In long-term follow-up studies, sustained virologic responders have remained in remission with normal liver function and improved histologic features of inflammation; in some of these responders, fibrosis even regresses (21, 22). Recently, the frequency of hepatocellular carcinoma in patients receiving interferon therapy has substantially decreased, especially in patients with sustained virologic and biochemical responses (23–25). This decreased frequency has occurred even in patients with cirrhosis (25, 26). Our study evaluated whether complete ablation of neoplastic nodules and administration of antiviral therapy could increase survival rates.

METHODS

Study Design

Our prospective study was designed by an eight-member committee in December 1992. The Ethics Committee of the University of Tokyo approved the study. We obtained informed consent from each patient in accordance with the Helsinki declaration.

Patients with compensated cirrhosis, three or fewer nodules of hepatocellular carcinoma, and low HCV RNA loads were recruited after complete ablation of the lesions.

Context

Hepatocellular carcinoma often follows hepatitis C virus infection. Currently available treatments for hepatocellular carcinoma are unsatisfactory. Percutaneous ethanol injection therapy into tumor nodules shows some promise, but recurrence rates are high.

Contribution

In a carefully selected group of 74 patients with multicentric hepatocellular carcinoma, mild hepatitis C, and mild cirrhosis, patients randomly assigned to receive interferon in addition to ethanol injections showed improved survival at 5 and 7 years, particularly among patients with a sustained virologic response.

Cautions

Combined treatment of multicentric hepatocellular carcinoma offers the possibility of enhanced survival for carefully selected patients; this study is small, however, and enrolled only patients with low virus levels and mild cirrhosis.

—The Editors

Eligibility Criteria**Inclusion Criteria**

Hepatitis C virus infection was diagnosed on the basis of identification of anti-HCV antibody using the passive hemagglutination test (Dinabbot, Tokyo, Japan) or enzyme-linked immunosorbent assay (ELISA; Ortho Diagnostic Systems, Tokyo, Japan). Hepatitis C virus RNA was identified by reverse transcriptase polymerase chain reaction (RT-PCR). The serum HCV RNA level was measured by competitive reverse transcriptase (CRT)-PCR according to the method of Kato and colleagues (27); HCV genotype was determined by the method of Okamoto and colleagues (28).

Hepatocellular carcinoma was suspected on the basis of several imaging methods, including abdominal ultrasonography, dynamic computed tomography (CT), magnetic resonance imaging (MRI), and arteriography. We confirmed the diagnosis by histologic examination of tumor biopsy specimens obtained from all patients. Evaluation was based on the criteria of the International Working Party (29). In addition, we obtained and evaluated biopsy specimens from non-neoplastic lesions according to the methods of Desmet and colleagues (30).

Hepatocellular carcinoma was treated with percutaneous ethanol injection therapy (7, 8, 10). Real-time linear-array scanners were used with 3.5-MHz transducers for the sonographic guidance of needles (21-gauge with a 15-cm or 20-cm needle; Hanako, Tokyo, Japan) into the tumors. Two to 10 mL of 99.5% ethanol was injected into each lesion. Ethanol injection was repeated several times at different sessions. Complete destruction of the nodules was confirmed on dynamic CT 1 month after ethanol injection

according to the following criteria: 1) The destructive area was larger than the area of the tumor nodule shown on pretreatment dynamic CT and 2) dynamic CT showed no early-phase contrast enhancement of nodules (7, 8, 10).

Inclusion criteria were as follows: 1) hepatocellular carcinoma with three or fewer lesions (verified by histologic examination) and dynamic CT-confirmed complete ablation of hepatocellular carcinoma lesions by percutaneous ethanol injection therapy, 2) detection of HCV RNA by RT-PCR and an HCV RNA load of 2×10^6 copies/mL or less by CRT-PCR (the cutoff value was based on unpublished data indicating that interferon treatment was effective in patients with HCV RNA loads of 10^5 copies/50 μ L of serum by CRT-PCR [27]), 3) platelet count of 50×10^9 cells/L, 4) leukocyte count of 3×10^9 cells/L or greater, 5) compensated cirrhosis in Child-Pugh stage A, 6) age younger than 70 years, 7) no previous treatment with interferon, and 8) submission of informed consent.

Exclusion Criteria

Exclusion criteria were as follows: 1) liver diseases due to other causes, such as hepatitis B or primary biliary cirrhosis; 2) HCV RNA load of 2×10^6 copies/mL or greater by CRT-PCR; 3) severe comorbid diseases, such as heart disease, lung disease, or diabetes mellitus; 4) decompensated cirrhosis in Child-Pugh stage B or C; and 5) failure to obtain informed consent.

Randomization

Patients who enrolled in the study were randomly assigned in a 2:1 ratio to the interferon group or the control group by the controller. We assigned patients to the treatment group or control group by using a randomization list.

Interferon Therapy and Follow-up of Patients**Interferon Therapy**

We started interferon therapy with natural interferon- α (Sumitomo Pharmaceuticals, Tokyo, Japan) 2 to 3 months after tumor ablation was confirmed. Patients received 6 million U of interferon by intramuscular injection three times weekly for 48 weeks as outpatients. If patients could not tolerate this dose, the interferon dose was reduced to 3 million U. If HCV RNA in serum was still detected by RT-PCR (detection limit, 10^2 copies/mL) after 24 weeks of interferon therapy and serum alanine aminotransferase (ALT) levels were higher than pretreatment ALT levels, therapy was discontinued.

Criteria for Interferon Response

We defined the efficacy of interferon therapy virologically and biochemically. Patients who were negative for HCV RNA (as determined by RT-PCR; detection limit, 10^2 copies/mL) more than 6 months after the completion of interferon therapy were classified as showing a sustained virologic response. Patients with persistently normal ALT levels after the completion of interferon therapy were clas-

sified as showing a sustained biochemical response; patients with abnormal ALT levels were classified as showing a non-sustained biochemical response.

Follow-up

Patients attended a monthly medical consultation at the University of Tokyo Hospital outpatient clinic. Blood biochemical measures, including α -fetoprotein (AFP) tumor markers, were measured every 1 to 2 months; ultrasonography was performed every 2 to 3 months; and dynamic CT was performed every 6 months. Recurrence of hepatocellular carcinoma was detected by the finding of abnormal nodules with low or high echogenic appearance on abdominal ultrasonography or by the finding of abnormal density on dynamic CT. The diagnosis was confirmed histologically through ultrasonography-guided fine-needle biopsy of the tumor. Recurrent nodules were divided into two categories (14, 15): 1) local recurrence, in which the nodule appeared adjacent to the previously treated nodules, suggesting that residual tumor cells had not been completely ablated by percutaneous ethanol injection therapy, or 2) new foci developing at a distant site.

New foci of hepatocellular carcinoma, as well as local recurrent nodules at tumor, node, metastasis (TNM) stage I, II, and III, were mainly treated by a second course of percutaneous ethanol injection therapy; local recurrent nodules at TNM stage IV were treated with transarterial chemoembolization or chemotherapy. New development of hepatocellular carcinoma and survival of the patients (tumor recurrence rate and survival rate) were analyzed in relation to the time interval after initial treatment.

Statistical Analysis

When estimating the sample size, we assumed that 5-year survival in the control group would be 40% according to the data of our previous unpublished study. We predicted that 5-year survival would be increased by 35% as a result of treatment with interferon and calculated that 49 patients in the interferon group and 25 in the control group would be required to give the study a power of 80% with an α level of 0.05 (two-tailed) by the log-rank test (31). In May 1994, we extended the length of the mean follow-up period from 5 years to 7 or more years. This was done because we estimated that the change in survival rate in the interferon group would be lower than initially anticipated.

We used SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina), for the statistical analysis. Kaplan–Meier life tables were constructed to detect the new development of hepatocellular carcinoma and survival. The number of outcome events was insufficient to support multivariable analyses (32).

Role of the Funding Source

The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Patient Enrollment

Of 449 patients with hepatocellular carcinoma who were admitted to our hospital to receive percutaneous ethanol injection therapy for destruction of tumor nodules from January 1993 to December 1997, 233 patients who were positive for HCV RNA satisfied the initial inclusion criteria (≥ 3 nodules) (Figure 1). After confirmation of complete destruction of hepatocellular carcinoma nodules by dynamic CT, we excluded the following patients: 127 patients with greater than 2×10^6 HCV RNA copies/mL; 9 patients with advanced-stage liver disease and 7 with severe comorbid diseases (severe diabetes mellitus [$n = 3$], chronic obstructive pulmonary disease [$n = 3$], and myocardial infarction [$n = 1$]); and 14 patients who did not give informed consent because they were concerned about the adverse effects of interferon therapy. The remaining 76 patients gave informed consent and were enrolled in the study. The data sheets for these patients were submitted to a controller to confirm eligibility; 2 patients did not meet the inclusion criteria because hepatocellular carcinoma had not been histopathologically confirmed.

The remaining 74 patients were registered and randomly assigned to two groups: 49 patients to the interferon therapy group and 25 to the untreated group. These patients were defined as a full-analysis set (intention-to-treat sample). Six patients who were assigned to the interferon therapy group had difficulty receiving interferon three times weekly at the hospital; however, these patients were still considered to be in the interferon therapy group, and follow-up data were collected for them. Clinical, laboratory, and demographic characteristics were similar in the interferon group and the untreated group (Table). All patients were classified as having stage 4 fibrosis (cirrhosis). Patients in the treatment group received interferon therapy for a mean (\pm SD) of 38 ± 11 weeks; the total dose was 675 ± 294 million U. The mean follow-up period was 7.1 ± 1.3 years.

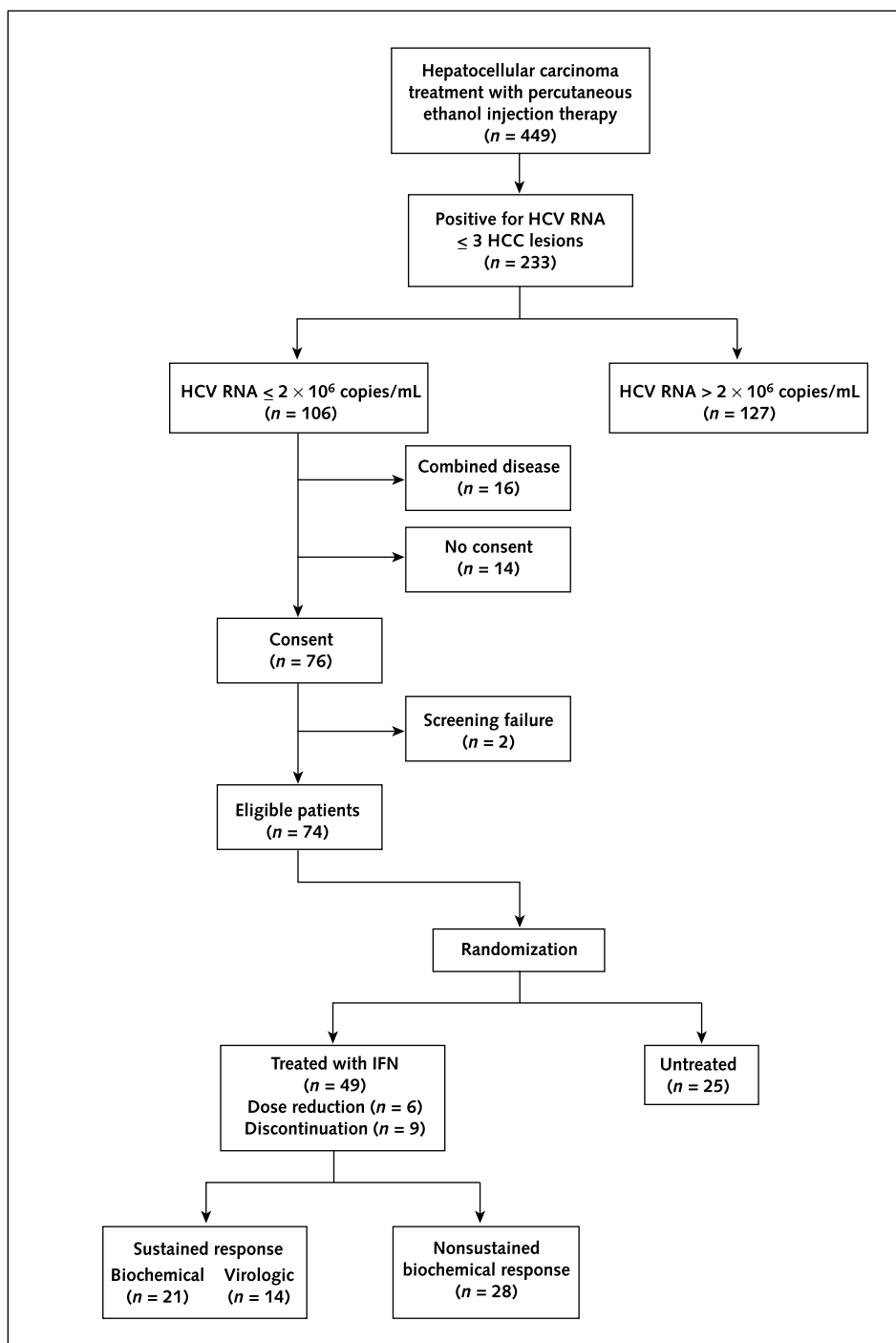
Response to Interferon Therapy

Of the 49 patients in the interferon group, 22 (45%) were negative for HCV RNA at the end of treatment. Sustained virologic response was demonstrated in 14 (29%) patients and sustained biochemical response in 21 (43%) patients. None of the 25 untreated patients was negative for HCV RNA or sustained a normal ALT level.

Factors Associated with Sustained Response

The HCV genotype (1b versus others) was associated with greater sustained biochemical response (relative risk, 0.39 [95% CI, 0.20 to 0.76]) and greater sustained virologic response (relative risk, 0.25 [CI, 0.09 to 0.66]). Lower HCV RNA level was associated with sustained virologic response (relative risk, 3.8 [CI, 1.13 to 24.20]; $P = 0.02$) but not with sustained biochemical response ($P > 0.2$). Age; sex; levels of albumin, aspartate aminotransferase, ALT, and bilirubin; and platelet counts were not asso-

Figure 1. Schematic flow chart of enrolled patients.



HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IFN = interferon.

ciated with sustained biochemical response or with sustained virologic response (all $P > 0.2$).

Adverse Events and Tolerance

Of the 43 patients who received interferon therapy, interferon dose was reduced from 6 to 3 million U in 6 (14%) patients. Interferon therapy was discontinued in 9

(21%) patients as a result of adverse events of varying severity, such as thrombocytopenia ($n = 1$), depression or loss of appetite ($n = 5$), recurrence of hepatocellular carcinoma ($n = 3$), and patient's request ($n = 1$). Interferon therapy was discontinued for tumor treatment in 3 patients with recurring hepatocellular carcinoma, and the tumors were then completely ablated. One patient experienced

both hepatocellular carcinoma recurrence and depression. The 9 patients for whom interferon therapy was discontinued were analyzed as part of the interferon group, but they did not receive antiviral therapy after discontinuation.

Development of New Foci of Hepatocellular Carcinoma

We found local recurrence of hepatocellular carcinoma in 4 (5%) patients within 12 months of initial therapy; these nodules were then completely ablated by additional percutaneous ethanol injection therapy. **Figure 2** shows that the first occurrence of a new focus of hepatocellular carcinoma in the control group was detected during follow-up in 24% of patients after 1 year, in 76% of patients after 3 years, and in 92% of patients after 5 years. The rates of other outcomes at 1, 3, and 5 years were as follows: incidence of the first occurrence of a new focus of hepatocellular carcinoma in the interferon group—24%, 69%, and 80%; incidence of the second recurrence of a new focus of hepatocellular carcinoma in the control group—4%, 52%, and 88%; incidence of the second recurrence of a new focus of hepatocellular carcinoma in the interferon group—2%, 45%, and 63%; incidence of the third recurrence of a new focus of hepatocellular carcinoma in the control group and interferon group—4%, 32%, and 80% and 2%, 24%, and 53%, respectively.

Patient Survival

Forty-one patients died during the follow-up period as a result of cancer progression, not hepatic failure. Survival rates in the control group were 96% at 1 year, 84% at 3 years, 48% at 5 years, and 23% at 7 years; survival rates of patients treated with interferon were 98% at 1 year, 82% at 3 years, 68% at 5 years, and 53% at 7 years (**Figure 3**). In our study, the survival rate in the interferon group was

higher than in the control group. In addition, survival rates in sustained virologic responders were 86% at 3 years, 78% at 5 years, and 68% at 7 years, whereas survival rates in nonsustained virologic responders were 80% at 3 years, 65% at 5 years, and 47% at 7 years (data not shown).

DISCUSSION

Patients with hepatocellular carcinoma and HCV infection with low viral loads ($\leq 2 \times 10^6$ copies/mL) who underwent successful percutaneous ethanol injection therapy were enrolled in this study of combined tumor ablation and interferon therapy. Only patients with three or fewer lesions of hepatocellular carcinoma were included because complete necrosis of the nodules could be easily achieved (7, 8, 10). Of the 74 patients enrolled, 49 were assigned to receive interferon therapy and 25 served as the control group (untreated group). Clinical profiles were similar in the two groups.

We achieved sustained virologic response in 14 patients (29%) and biochemical response in 21 patients (43%). Because only patients with low viral loads were enrolled, HCV subtype, but not HCV RNA load, was associated with sustained biochemical response. However, both factors were associated with sustained virologic response. Interferon therapy was discontinued in 9 patients at the patients' requests or as a result of adverse events.

We analyzed new foci of hepatocellular carcinoma at a site different from the original location because locally recurrent hepatocellular carcinoma might have originated from residual neoplastic cells if tumor ablation had been incomplete. In fact, we identified four patients (5% only) with local recurrence within 12 months of initial treat-

Table. Demographic Characteristics of Enrolled Patients*

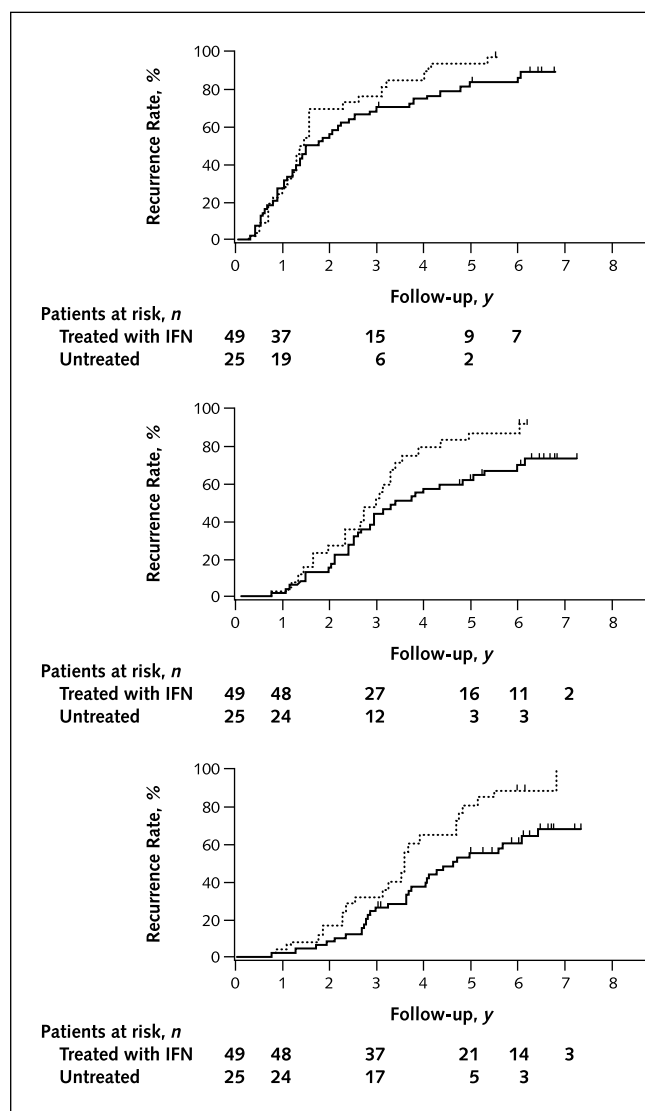
Characteristic	Treated Group	Untreated Group
Patients, <i>n</i>	49	25
Age (range), <i>y</i>	61 (37–70)	63 (51–69)
Sex, <i>n</i>		
Men	35	17
Women	14	8
Albumin level, <i>g/L</i> [<i>g/dL</i>]	35 (32, 38) [3.5 (3.2, 3.8)]	34 (32, 39) [3.4 (3.2, 3.9)]
Aspartate aminotransferase level, <i>IU/L</i>	91 (53, 112)	89 (61, 122)
Alanine aminotransferase level, <i>IU/L</i>	88 (47, 116)	95 (63, 127)
Bilirubin level, $\mu\text{mol/L}$ [<i>mg/dL</i>]	13.7 (10.3, 18.8) [0.8 (0.6, 1.1)]	13.7 (11.9, 20.5) [0.8 (0.7, 1.2)]
Platelet count, $\times 10^9$ <i>cells/L</i>	93 (72, 123)	97 (73, 131)
α -Fetoprotein level, <i>ng/mL</i>	18 (8, 45)	23 (13, 54)
HCV RNA level, 2×10^6 <i>copies/mL</i>	5 (4.5, 5.5)	5.5 (4.5, 6)
HCV genotype, <i>n</i>		
1b	30	19
2a	18	5
2b	1	1
Background fibrosis score of F4 (cirrhosis), <i>n</i>	49	25
Number of tumors, <i>n</i>		
1	32	16
2	8	7
3	9	2
Tumor size, <i>mm</i>	22 (17, 29)	23 (19, 30)

* Except where indicated, data are expressed as the median (25th, 75th percentile). HCV = hepatitis C virus.

ment; although these nodules were completely ablated after additional therapy, the number was too small to be analyzed. On the other hand, the rate of new development of hepatocellular carcinoma after 4 years seemed to be lower in the patients treated with interferon than in the untreated patients (Figure 2). It is possible that tumors had already recurred at the time of initial tumor ablation but may not have been seen because the imaging study lacked sensitivity. Thus, the difference in first recurrence between the treated and untreated groups was not great.

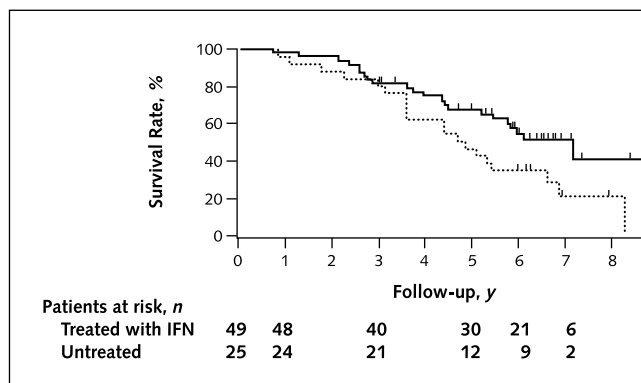
Most important, our study shows that if the primary tumor is treated by percutaneous ethanol injection therapy

Figure 2. Cumulative rate of development of new foci of hepatocellular carcinoma with respect to interferon (IFN) therapy (Kaplan–Meier method).



Top. Rates of first new foci of hepatocellular carcinoma. Middle. Rates of second recurrence of new foci of hepatocellular carcinoma. Bottom. Rates of third recurrence of new foci of hepatocellular carcinoma. Censoring times are indicated by the short vertical line segments.

Figure 3. Survival rate of patients with hepatocellular carcinoma with respect to interferon (IFN) treatment (Kaplan–Meier method).



Censoring times are indicated by the short vertical line segments.

and the underlying cirrhotic condition is treated with interferon therapy, the survival rate of patients treated with interferon seems to be markedly higher than that of untreated patients. Because the small size of this study precludes multivariable analysis, we cannot rule out alternative explanations for the longer patient survival in patients receiving interferon. Additional investigation in larger studies is required.

Our study may contain potential biases because patients, clinicians, and observers were not blinded to treatment received. To reduce such biases, we tried to separate the roles of physicians as follows: randomization by an independent investigator, interferon treatment by two other investigators, and treatment for hepatocellular carcinoma and patient follow-up by the remaining five investigators. All patients received regular follow-up at an outpatient clinic, and no patients withdrew from the study. Furthermore, during the study period, the 5-year survival rate of the 381 patients who were excluded from our study was 38%, which is similar to the survival rate of the control group in our study.

Our study has several limitations. These include the fact that interferon therapy was given to patients with low viral loads and at a mild stage of cirrhosis (Child–Pugh stage A). Because patients receiving liver transplantation may present with more severe end-stage liver disease (stage C) or high HCV RNA loads, we cannot compare the difference in survival among patients receiving liver transplantation. As our recent study showed the possibility of resolution of fibrosis in sustained virologic responders (22), the liver condition of sustained responders could be improved and might become similar to that of patients undergoing liver transplantation. On the other hand, recent studies of cirrhosis (33–36) suggest that response to interferon may be reduced in patients with higher baseline HCV RNA loads. Thus, more efficient therapies for cirrhotic patients with hepatocellular carcinoma, such as combination ther-

apy using ribavirin and interferon (36–38) or pegylated interferon (39, 40), may provide higher eradication rates, leading to an improved prognosis.

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I told him that congestion of the lungs was an old-fashioned term for pneumonia, and he told me I knew nothing about it and was absolutely wrong. Congestion of the lungs was a malady that was indigenous to Europe and I could not possibly know anything about it even if I had read my father's medical books, since they dealt with diseases that were strictly American. I said that my father had studied in Europe too. But Scott explained that congestion of the lungs had only appeared in Europe recently and my father could not possibly know anything about it. He also explained that diseases were different in different parts of America, and if my father practiced in New York instead of the Middle West, he would have known an entirely different gamut of diseases. He used the word gamut . . . I said he had a good point of the prevalence of certain diseases in one part of the United States and their absence in others and cited the amount of Leprosy in New Orleans and the low incidence in Chicago. But I said that doctors had systems of exchange of knowledge and information among themselves and now that I remembered it after he had brought it up, I had read the authoritative article on congestion of the lungs in Europe in the *Journal of the American Medical Association*, which had traced its history back to Hippocrates himself. This held him for awhile and I urged him to take another drink of Macon, since a good wine, moderately full-bodied but with a low alcohol content, was almost a specific against the disease.

Ernest Hemingway
A Moveable Feast
 New York: Penguin Books; 1964:120-1

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