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# Incidence Reduction Following Colonoscopic Polypectomy

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**To the Editor:** In Dr Sandler's editorial (1) in which he reviewed the current controversy in screening colonoscopy, he stated that the National Polyp Study (NPS) finding that colonoscopic polypectomy reduces colorectal cancer (CRC) incidence has not been replicated (2). This is an inaccurate statement. An incidence and mortality reduction similar to that observed by NPS was replicated in two other studies of post polypectomy patients that showed a 67% incidence reduction and an 88% mortality reduction, respectively (3,4). The studies that he cited as having a similar design to the NPS in fact had different designs with respect to the initial colonoscopy that identified the adenoma patients. In the NPS, all patients referred to participating clinical centers for initial colonoscopy prospectively had a protocol colonoscopy that reached the cecum, all polyps detected were removed, and all colonoscopies were performed by experienced endoscopy investigators. Those patients identified as having adenomas at this initial examination were eligible for the NPS. The studies cited by Sandler (1) had adenomas identified from community-based practices and then, 1 year later, had a clearing colonoscopy performed by experienced endoscopy investigators. Interval cancers attributable to missed lesions are not uncommon in community-based practice (5). When the missed cancers of the first non-protocol colonoscopy were excluded, the post-polypectomy CRC rate dropped from 1.8 to 0.96 per 1000 person years of follow-up, which is very similar to that of the NPS (0.6 per 1000). The CRC incidence reduction observed in the NPS compared with a simulated cohort of adenoma patients without their adenomas removed (90%) and compared with the general population Surveillance, Epidemiology and End Results rate (76%) was probably achieved as a result of the NPS design and methodology, which included rigorous baseline clearing with a 13% repeat for inadequate preparation.

There are three separate but related questions: first, does removal of adenomas reduce the incidence and mortality of CRC; second, what is the precise magnitude of this reduction; and third, what is the benefit of screening colonoscopy in the general population, of whom only a proportion have adenomas. The long-standing belief in the concept of the adenoma–carcinoma sequence and that its interruption reduces CRC incidence and mortality is supported by many studies, including the NPS (2–4,6). However, the precise magnitude of the colonoscopy effect in the general population has not been clearly established, and will not be established until completion 10 or 15 years hence of the European and American screening colonoscopy randomized controlled trials (RCTs). Data from the colonoscopy RCTs will also provide a comparison of the colonoscopy effect with the recently reported sigmoidoscopy effect (6). The NPS supports the importance of finding and removing adenomas with any screening method in addition to detecting early-stage cancers. The best method to do this needs to be established.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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# Appropriate Response to Influenza A (H1N1) Virus Vaccination in Patients With Inflammatory Bowel Disease on Maintenance Immunomodulator and/or Biological Therapy

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**To the Editor:** In April 2009 an outbreak of the novel influenza A (H1N1) virus infection occurred in Mexico and has assumed pandemic proportions soon. After initial controversial data, vaccines directed toward the influenza A (H1N1) virus have proven to be safe and efficient to prevent the complications of the infection.

Patients with inflammatory bowel diseases (IBD—Crohn's disease (CD), ulcerative colitis) on immunosuppressive therapy are at increased risk for various infections, some of which can be prevented by immunization. Inactivated influenza vaccination

Oncology

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# Highly Sensitive *Lens culinaris* Agglutinin-Reactive α-Fetoprotein: A New Tool for the Management of Hepatocellular Carcinoma

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**Key Words**

Hepatocellular carcinoma · Tumor biomarker · Highly sensitive *Lens culinaris* agglutinin-reactive α-fetoprotein · Sensitivity · Specificity · Prognosis

**Abstract**

***Objectives:*** The highly sensitive *Lens culinaris* agglutinin-reactive α-fetoprotein (hs-AFP-L3), measured using a newly developed method involving microfluidics-based separation technology, was evaluated as a new tool for the management of hepatocellular carcinoma (HCC) in clinical practice. ***Methods:*** The sensitivity and specificity of hs-AFP-L3 for the diagnosis of HCC and its ability to predict the outcome of patients with HCC were analyzed based on reported studies. ***Results:*** Compared to AFP-L3 measured using conventional methods, the sensitivity of hs-AFP-L3 was markedly higher and the specificity was comparable. In all studies, multivariate analysis found that elevation of hs-AFP-L3 was an independent factor that affected patient survival. ***Conclusions:*** The use of hs-AFP-L3 improves the true positive rate of patients with HCC at diagnosis, maintaining the high specificity of AFP-L3 and its indicative value for poor prognosis. The utility of this tumor marker for prediction of the development of HCC in high-risk patients under surveillance needs to be investigated. 

## Introduction

Tumor biomarkers are important tools in the management of patients with malignant tumors in clinical practice, with roles in diagnosis, evaluation of tumor progression, outcome prediction, and the evaluation of treatment efficacy. Several biomarkers have been reported as tumor markers of hepatocellular carcinoma (HCC), which is the sixth most common cancer in the world and the third most common cause of cancer-related deaths [1]. These biomarkers include α-fetoprotein (AFP) [2–4], *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3) [5, 6], and des-γ-carboxy prothrombin (DCP) [7, 8]. AFP is the most widely used marker for monitoring HCC development. However, increased total AFP is not always specific for HCC [9, 10], and conversely, elevation of the total AFP level is not typically observed in patients with early-stage HCC.

In contrast, a fucosylated fraction of AFP (AFP-L3) is highly specific for HCC [5, 11]. In addition, an elevated AFP-L3 reportedly correlates with tumor progression, poor tumor differentiation, and unfavorable prognosis [6, 12–15]. However, measurement of AFP-L3 with conventional assay systems has not always been of value in the management of HCC, especially in patients with low total AFP (less than 20 ng/ml), mainly due to low analytical sensitivity.

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**Table 1.** Sensitivity and specificity of hs-AFP-L3 for the diagnosis of HCC at low total AFP levels

| Reference | Total AFP ng/ml | Patients with HCC, n | Patients without HCC (control), n | Cutoff of AFP-L3 | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| Tamura et al. [17] | <20 | 112 | 320 | 1% | 67.9% | 80.6% |
| | | | | 7% | 41.1% | 91.9% |
| | | | | 10% | 21.4% | 96.9% |
| Hanaoka et al. [18] | <10 | 36 | 205[a] | 5.75% | 52.8% | 86.8% |
| Toyoda et al. [19] | <20 | 270 | 396 | 5% | 41.5% | 85.1% |
| | | | | 7% | 26.7% | 92.4% |
| | | | | 10% | 14.8% | 98.2% |
| | <10 | 199 | 357 | 5% | 36.2% | 88.5% |
| | | | | 7% | 23.6% | 93.8% |
| | | | | 10% | 11.6% | 98.3% |
| Nouso et al. [20] | ≤20 | 196 | 87[b] | 5% | 51.5% | 54.0% |
| | | | | 10% | 13.3% | 88.5% |
| | | | | 15% | 8.7% | 96.6% |
| Kobayashi et al. [21][c] | <20 | 154 | | 3% | 54.5% | |
| | | | | 5% | 40.3% | |
| | | | | 7% | 24.0% | |
| | | | | 10% | 12.3% | |

[a] Includes 92 patients who had a history of HCC treatment. [b] Only patients with cirrhosis. [c] Does not include control patients.

Recent technical improvements in the analytical methods of measuring AFP-L3 have employed novel and advanced microfluidics-based separation technology, thus improving the sensitivity of this assay [16]. This new generation of assays (micro-total analysis systems; μTAS) has enabled the accurate measurement of AFP-L3 with a high sensitivity and at very low AFP concentrations. In this review, we attempted to evaluate the value of this highly sensitive AFP-L3 (hs-AFP-L3) as a tool in the management of HCC based on previously reported data as well as our own.

### hs-AFP-L3 for the Diagnosis of HCC

Five reported studies have analyzed the diagnostic significance of hs-AFP-L3 at low total AFP levels [17–21]. The sensitivity and specificity of hs-AFP-L3 at different cutoff levels in these five studies are summarized in table 1. The sensitivity of hs-AFP-L3 for HCC was approximately 25–50% in patients with total AFP levels below 20 ng/ml, when the cutoff was fixed between 5 and 7%. The sensitivities of AFP-L3 measured by conventional methods in the serum samples of hs-AFP-L3 from two studies were 3.6 and 5.2% (cutoff of AFP-L3: 7%) [17, 19]. Thus, the sensitivity for HCC markedly increased with the use of a newly developed, highly sensitive measurement method.

An important advantage of AFP-L3 is its high specificity for HCC. Therefore, attempts to increase the sensitivity of AFP-L3 for HCC should avoid a concomitant reduction in specificity. Based on the data from reported studies among patients with low total AFP levels, the specificity of hs-AFP-L3 for HCC was over 85% when the cutoff was fixed between 5 and 7%, except in one study. The original advantage of AFP-L3 produced by conventional methods, i.e. high specificity for HCC, appeared to be maintained in the case of hs-AFP-L3. The specificity was 54.0% when the cutoff was fixed at 5% in the study by Nouso et al. [20]. This was because the control group in their study included only patients with cirrhosis; patients with minute HCC that had not been detected by imaging examination might have been included in a control group.

With the improvement in the sensitivity of AFP-L3, we experienced cases in which elevation of AFP-L3 was a

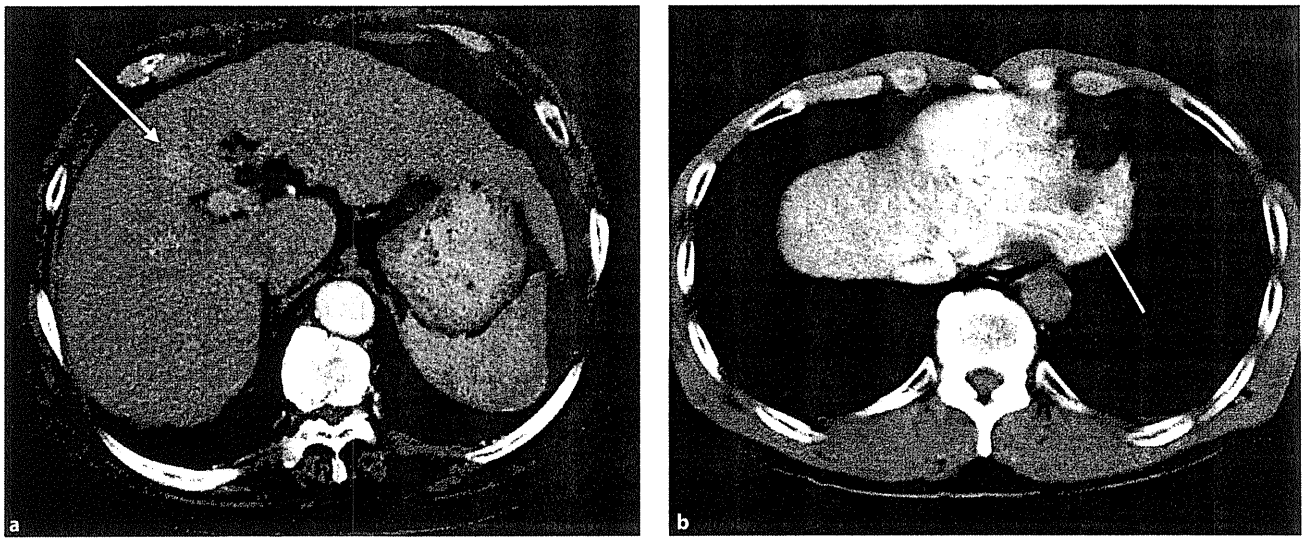

**Fig. 1.** A case of HCC in which the elevation of hs-AFP-L3 was a trigger for detection and diagnosis. **a** Seventy-year-old male. Despite the severe obesity and fatty liver on ultrasonography, his transaminase levels and platelet count were normal (ALT: 17 IU/l, AST: 18 IU/l, and platelets: 149 × $10^3$ /μl). He did not have hepatitis B or C virus infections. Although serum AFP and DCP levels were normal (AFP: 3.4 ng/ml and DCP: 35 mAU/ml) and AFP-L3 was not detected by conventional methods, hs-AFP-L3 had increased to 13.4%. CT examination revealed a small HCC (arrow) that could not have been identified by ultrasonography due to severe obesity and the patient's inability to hold his breath during sonographic examination. The patient was treated by radiofrequency ablation with CT guidance under general anesthesia. **b** Fifty-six-year-old male. This patient was a hepatitis B virus carrier with persistent normal transaminase levels. He did not have cirrhosis and had a platelet count of 282 × $10^3$/μl. An elevation of hs-AFP-L3 to 9.6% was observed despite normal AFP and DCP levels (AFP: 2.8 ng/ml and DCP: 19 mAU/ml) and undetectable AFP-L3 by conventional methods. CT during arterial portography examination revealed a small HCC nodule without hypervascularity (arrow). The tumor had not been identified by ultrasonography due to its location behind the stomach. The patient underwent hepatic resection and the diagnosis of HCC was confirmed pathologically.

trigger for the detection and diagnosis of HCC. Because of its convenience in clinical settings, ultrasonography is usually the routine baseline examination used to detect HCC in patients who are at high risk for HCC development and who are under surveillance. However, the quality of ultrasonographic findings varies with the specific ultrasonographic apparatus used as well as the skill of the sonographer, and we sometimes encounter difficulty obtaining reliable results because of patients' obesity or inability to hold their breath (fig. 1a). In addition, liver tumors are sometimes difficult to identify by ultrasonography due to their locations in the liver, including the top of the right hepatic lobe or positions covered by the gastrointestinal tract (fig. 1b). The measurement of hs-AFP-L3 is a laboratory test that can be easily performed in routine clinical settings and thus serves as a complimentary tool for the detection of HCC.

## hs-AFP-L3 for Evaluating the Prognosis of Patients with HCC

Another reported advantage of AFP-L3 in the management of patients with HCC is its ability to indicate the advanced nature of HCC and to identify cases with poor prognoses. Previous studies have reported that HCC with high AFP-L3 levels demonstrate characteristics of advanced HCC by pathologic [13] and imaging findings [22]. Higher recurrence rates [23] and lower survival rates [12, 14] after treatment have also been reported in patients with increased AFP-L3 at diagnosis. We sought to determine whether these benefits of AFP-L3 persist with hs-AFP-L3.

Table 2 shows the impact of hs-AFP-L3 elevation at diagnosis on the survival of patients with HCC as determined by multivariate analysis. Although there were minor differences in the variables analyzed by multivariate analysis between studies, the elevation of hs-AFP-L3 was an independent factor for the decreased survival of pa-

**Table 2.** Multivariate analysis-derived impact of increased AFP-L3 on the survival of patients with HCC

| Reference | Cutoff of AFP-L3 | Hazard ratio (95% CI) | p value |
|---|---|---|---|
| Tamura et al. [17][a] | ≥7% | 1.673 (1.079–2.594) | 0.021 |
| Hanaoka et al. [18][b] | ≥5.75% | 3.460 (1.08–11.1) | 0.036 |
| Toyoda et al. [19][c] | ≥5% | 1.697 (1.066–2.709) | 0.026 |
| Nouso et al. [20][d] | ≥10% | 8.36 (2.79–25.5) | <0.001 |

[a] Including patients with any total AFP level. [b] In patients with total AFP <10 ng/ml. [c] In patients with total AFP <20 ng/ml. [d] In patients with total AFP ≤20 ng/ml.

tients with HCC. In addition to these reports, Kobayashi et al. [21] recently demonstrated a higher likelihood of recurrence after treatment of HCC by hepatectomy or radiofrequency ablation with a curative intent in patients with elevated hs-AFP-L3 levels (≥5%) by multivariate analysis. With regard to evaluation of the prognosis, therefore, the advantages of AFP-L3 measured using conventional methods appeared to be maintained when its sensitivity is increased.

### hs-AFP-L3 for Predicting the Detection of HCC in High-Risk Patients under Surveillance

We recently studied the sensitivity and specificity of hs-AFP-L3 (with a 7% cutoff level for HCC) in 104 patients with hepatitis C virus (HCV)-related HCC that was detected during surveillance, using as a control 104 HCV-infected patients without HCC selected by propensity score matching. hs-AFP-L3 had a sensitivity of 39.4% and a specificity of 77.0% for the diagnosis of HCC. Surprisingly, a similar sensitivity and specificity was found with hs-AFP-L3 that was measured in stored serum samples obtained 1 year before the detection and diagnosis of HCC (data not shown).

Previous studies including our own have suggested that mild elevations of total AFP indicate a high potential for the development of HCC [24, 25]. With regard to the high specificity of AFP-L3 for HCC, the elevation of hs-AFP-L3 levels 1 year before the detection of HCC might have indicated the presence of minute HCC unidentifiable by current imaging modalities. The potential of hs-AFP-L3 for predicting the development of HCC (or for indicating the presence of minute 'occult' HCC that is unidentifiable by current imaging modalities) should be further investigated.

## Conclusion

Hs-AFP-L3 increased the sensitivity of HCC at diagnosis, maintaining its high specificity and indicative value for poor prognosis. This biomarker can be used as a new tool in clinical practice for the management of patients with HCC. The utility of hs-AFP-L3 for the prediction of HCC development in high-risk patients under surveillance should be further investigated.

## Disclosure Statement

None disclosed.

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# Letter to the Editor

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## Incidence of hepatocellular carcinoma and response to interferon therapy in HCV-infected patients: effect of factors associated with the therapeutic response and incidence of HCC

To the Editor:

Several previous studies reported a significantly lower incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients who showed sustained virological response (SVR) to or relapsed on antiviral therapy with interferon (IFN) or peginterferon (PEG-IFN), with or without ribavirin compared with no responders (NR; i.e. partial response, viral breakthrough, or null-response) (1, 2). The reduction in HCC incidence was especially marked in patients with SVR. These results have been taken as evidence that antiviral therapy has an effect of suppressing the development of HCC.

Recently reported viral and host factors that are strongly associated with response to anti-HCV therapy (3, 4) may also be associated with the pathogenesis of HCC. Amino acid substitution in the HCV core region, a viral factor reportedly associated with response to PEG-IFN and ribavirin therapy (3), is also associated with the development of HCC (5). Regarding host factors associated with response to anti-HCV therapy (4), genetic polymorphisms near the *IL28* gene are reportedly associated with hepatic steatosis (6) and interact with amino acid substitutions in the HCV core region (7), both of which are associated with the development of HCC (5, 8).

We analysed the incidence of HCC in 448 patients who completed anti-HCV therapy with IFN or PEG-IFN and in whom the genetic polymorphisms near *IL28B* gene were analysed after the approval of the hospital ethics committee and obtaining written informed consent. We found significant differences in the incidence of HCC between patients with SVR ($n = 247$), relapse ($n = 122$), and NR ($n = 79$) (Fig. 1A, $P < 0.0001$ by Log-rank test). However, the prevalence of patients having TT genotype at rs8099917 near the *IL28B* gene, which is associated with favourable response to anti-HCV therapy, was significantly lower in patients with NR (SVR, 85.8%; relapse, 80.3%; NR, 39.2%; $P < 0.0001$ by Chi-square test). In addition, we found significant differences in the incidence of HCC also according to the genotype of rs8099917 (Fig. 1B, $P = 0.0156$). Although multivariate analysis using Cox proportional hazard model including age, gender, HCV genotype, and the outcome of therapy, but not *IL28B* polymorphisms identified SVR ($P = 0.0083$) and relapse ($P = 0.0493$) as independent factors that were associated with lower incidence of HCC, it failed to detect an independent factor that was associated with the incidence of HCC when *IL28B* polymorphisms were included. These results suggested that the previously reported differences in the incidence of HCC by anti-HCV response may not have been due to the ability of antiviral therapy to suppress HCC, but rather simply they may reflect the ability of such treatment to better identify patients at high-risk for HCC based on response to anti-HCV therapy.

It is not elucidated whether the results in our present analyses were simply due to the small number of

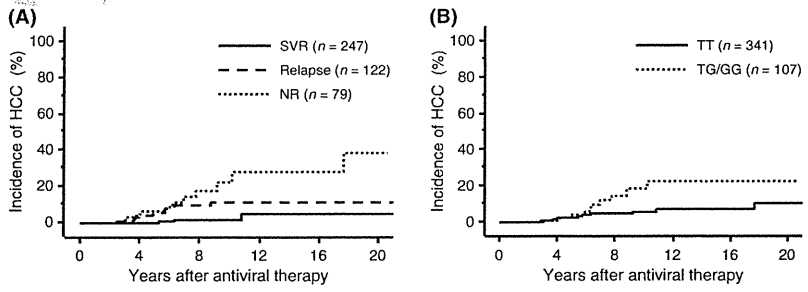


**Fig. 1.** Cumulative incidence of hepatocellular carcinoma (HCC) after antiviral therapy with interferon or peginterferon. (A) Incidence of HCC is significantly lower in patients with sustained virological response (SVR), those with relapse, and those with no response (NR) that includes partial response, viral breakthrough, or null-response, in that order. (B) Incidence of HCC is significantly lower in patients with TT genotype at rs8099917 near the *IL28B* gene, which is associated with the favourable response to antiviral therapy.

patients analysed or the incidence of HCC after antiviral therapy is similar regardless of response, when they are stratified by host and viral factors. In addition, our present analyses failed to examine the association between amino acid substitutions in the HCV core region and the incidence of HCC due to the small number of patients in whom the information of this substitution was available. Nonetheless, with the emergence of factors that can be independently associated with both the response to antiviral therapy and the development of HCC, the effect of response to antiviral therapy with IFN or PEG-IFN on the incidence of HCC will require re-examination taking *IL28B* polymorphisms and amino acid substitutions in the HCV core region into consideration.

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CLINICAL STUDY

# Transarterial Chemoembolization for Hepatitis B Virus–Associated Hepatocellular Carcinoma: Improved Survival after Concomitant Treatment with Nucleoside Analogues

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## ABSTRACT

**Purpose:** To determine whether nucleoside analogue therapy is associated with improved survival in patients with hepatitis B virus (HBV)–associated hepatocellular carcinoma (HCC) who are treated solely with transarterial chemoembolization.

**Materials and Methods:** A retrospective chart review of patients diagnosed with HBV-associated HCC was performed to identify patients treated solely with chemoembolization. Relevant demographic and clinical data were extracted and recorded. The influence of therapy with nucleoside analogues (lamivudine, adefovir dipivoxil, or entecavir) was determined by estimating the survival function using the Kaplan-Meier product-limit method.

**Results:** The inclusion criteria for chemoembolization were met by 81 patients (67 men and 14 women, mean age 60.6 years ± 9.2); 21 (25.9%) of these patients had been treated with nucleoside analogues. The number of chemoembolization treatments was significantly greater in the patients who were treated with nucleoside analogues (3.43 ± 2.32) than in the patients who did not receive nucleoside analogues (1.82 ± 0.95; $P = .0022$). The 1-year, 3-year, and 5-year survival rates were 89.5%, 66.8%, and 40.5% in the patients treated with nucleoside analogues and 72.6%, 27.5%, and 14.3% in the patients not treated with nucleoside analogues. The survival rate was significantly higher in the patients who received nucleoside analogues ($P = .0051$). Nucleoside analogue intake was an independent factor that was associated with increased survival ($P = .0063$).

**Conclusions:** Administration of nucleoside analogues was associated with longer survival in patients with HBV-associated HCC who were treated with transarterial chemoembolization.


## ABBREVIATIONS

AFP = alpha-fetoprotein, HBV = hepatitis B virus, HCC = hepatocellular carcinoma

Transarterial embolization was initially used to treat hepatocellular carcinoma (HCC) by Doyon et al (1) in 1974, and chemoembolization with gelatin sponge particles and anticancer agents was subsequently developed in Japan to treat inoperable HCC (2). Despite the increase in the number of patients who undergo complete curative treatments such as hepatectomy or radiofrequency ablation (3), transarterial chemoembolization continues to have an important role, both as an initial treatment and as a therapeutic alternative for recurrent disease (4) because of the advanced nature of HCC at diagnosis and the high rate of recurrent disease (5). The benefits resulting from chemoembolization have long been a subject of debate (6–10), but two randomized trials found that chemoembolization was associated with higher survival compared with symptomatic treatment (4,11,12).

Because of poor liver function, patients with HCC do not always receive chemoembolization. Repeated chemoembolization treatments for HCC may cause liver function to deteriorate despite the fact that the deterioration of liver function by each chemoembolization treatment would be mild (13). If repeated chemoembolization treatments are to be used in cases of HCC recurrence, it is important to

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Tables E1 and E2 are available online at *www.jvir.org.*



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prevent the worsening of liver function in the intervals between the treatments for longer survival (14).

Nucleoside analogues against hepatitis B virus (HBV) have been used since the late 1990s to suppress the replication of HBV and to normalize transaminase levels. Therapy with nucleoside analogues against HBV is known to arrest the progression of hepatic dysfunction in patients with chronic hepatitis B. More recent studies have shown that these drugs prevent the development of liver failure, even in the patients with advanced liver fibrosis (15–19). However, it is unknown whether this beneficial effect of antiviral therapy translates into longer survival for patients with concomitant HCC who undergo chemoembolization. We conducted a retrospective review of our experiences using chemoembolization to treat HCC in patients with chronic HBV infection.

## MATERIALS AND METHODS

### Patients

The complete study protocol was approved by the institutional review board of our hospital and was performed in compliance with the Helsinki Declaration. Between July 1997 and December 2010, 1,359 patients were diagnosed with primary HCC at our institution. Chronic HBV infection was confirmed in 260 of these patients, and 95 of these 260 patients were treated with chemoembolization. Of these 95 patients, 14 underwent treatments other than chemoembolization for recurrent HCC (4 underwent hepatectomy and 10 underwent radiofrequency ablation), and the remaining 81 patients had been treated with chemoembolization alone for recurrent HCC tumors. Our study retrospectively examined these 81 patients.

HCC was diagnosed based on clinical criteria (20) in all 81 patients. Specifically, the patients had a pertinent clinical background (chronic HBV infection) and typical imaging results. The tumor usually was detected by B-mode ultrasonography with typical HCC imaging features, including a hypoechoic tumor or a tumor with a mosaic pattern with a halo. HCC was diagnosed when a high-density mass was detected on arterial phase dynamic computed tomography (CT) images combined with a low-density mass on portal phase dynamic CT images obtained with a single or multidetector helical CT scanner. All of the patients with possible HCC tumors underwent angiography using a unified CT-angiography system (Interventional-CT; Toshiba, Tokyo, Japan) (21,22). CT during arterial portography and CT during hepatic arteriography were also performed to evaluate the progression of HCC (23).

The patients included 67 men (82.7%) and 14 women (17.3%), with a mean age of 60.6 years ± 9.2. The liver function at diagnosis was Child-Pugh class A in 49 patients (60.5%). At the time of diagnosis, 52 patients (64.2%) had multiple initial HCC tumors. HCC was accompanied by branch portal vein invasion in 18 patients (22.2%), but no patients had HCC invasion of the main portal vein trunks or the left or right main portal vein (**Table E1**).

### Chemoembolization for Hepatocellular Carcinoma and Follow-Up after Treatment

The treatment decisions were based principally on the Japanese HCC treatment guidelines (24). The patients were initially assessed for their eligibility for hepatic resection and subsequent local ablative therapies, including percutaneous ethanol injection, percutaneous microwave thermocoagulation, and radiofrequency ablation. The patients who were not eligible for curative treatment with surgery, local ablative therapies, or a combination of both were offered chemoembolization. The patients with Child-Pugh class C (25) liver function and the patients with HCC invasion of the main portal vein trunks and left or right main portal vein were not offered chemoembolization. Chemoembolization was performed by injecting an emulsion of 50 mg of farmorubicin hydrochloride (Epirubicin; Adria Laboratories, Columbus, Ohio) or 100 mg of cisplatin (IA-Call; Nihon-Kayaku, Tokyo, Japan) dissolved in 5 mL of iopamidol (Iopamiron, 370 mg I/mL; Schering, Tokyo, Japan) and mixed with 5 mL of iodized oil (Lipiodol Ultra Fluid; Guerbet, Paris, France). This procedure was followed by an injection of gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, Michigan). The total dose of the injected emulsion was determined by the volume of the liver that would be embolized. An unenhanced CT scan was obtained to confirm complete deposition of the iodized oil in the lesion and to complete the treatment.

After the first chemoembolization treatment, the patients were followed for 2.39–118.6 months (median follow-up period 19.3 months) at our institution with ultrasonography and CT or magnetic resonance imaging performed every 3–6 months. Serum tumor markers (alpha-fetoprotein [AFP], *Lens culinaris* agglutinin-reactive AFP, and des-gamma-carboxy prothrombin) were monitored every 3 months. When elevated tumor markers were detected, an additional imaging examination (usually CT or magnetic resonance imaging) was performed to check for recurrence or progression of HCC. If recurrence or progression was confirmed, retreatment was considered. Retreatment decisions were also based on the Japanese HCC treatment guidelines. Repeat chemoembolization was considered as a retreatment option in patients who had HCC recurrence or progression.

### Statistical Analyses

The intergroup differences were analyzed using $\chi^2$ and Mann-Whitney *U* tests for categorical and quantitative data. The date of the initial HCC treatment (chemoembolization) was defined as time zero when calculating the patient survival rates. Surviving patients and patients who died from causes other than liver disease were censored in the survival analysis. Patients whose death was caused by HCC

**Table 1. Clinical Characteristics of Patients Who Did and Did Not Receive Nucleoside Analogues**

| | Nucleoside Analogues (+) (n = 21) | Nucleoside Analogues (−) (n = 60) | *P* Value |
|---|---|---|---|
| Age (mean ± SD, y) (range) | 60.3 ± 8.9 (46–81) | 60.6 ± 9.3 (37–78) | .7957 |
| Sex ratio (female/male) | 3 (14.3%)/18 (85.7%) | 11 (23.3%)/49 (76.7%) | .9274 |
| Child-Pugh class (A/B) | 14 (66.7%)/7 (33.3%) | 35 (58.3%)/25 (41.7%) | .6773 |
| Albumin (mean ± SD, g/dL) | 3.65 ± 0.45 | 3.33 ± 0.79 | .0372 |
| Total bilirubin (mean ± SD, mg/dL) | 1.22 ± 0.72 | 0.98 ± 0.85 | .0844 |
| 15-minute retention rate of ICG (%)* | 24.8 ± 12.3 | 19.6 ± 13.8 | .0691 |
| Prothrombin (%) | 81.1 ± 19.5 | 79.7 ± 20.4 | .8209 |
| Platelet count (× 1,000/mL) | 112 ± 52 | 143 ± 82 | .1867 |
| Tumor size (mean ± SD, cm) (range) | 4.30 ± 2.94 (1.2–11.5) | 4.40 ± 3.24 (1.0–16.0) | .8083 |
| Tumor size (≤ 2 cm/> 2 cm and ≤ 5 cm/> 5 cm) | 4 (19.0%)/11 (52.4%)/6 (28.6%) | 17 (28.3%)/25 (41.7%)/18 (30.0%) | .6282 |
| Tumor number (single/multiple) | 9 (42.9%)/12 (57.1%) | 20 (33.3%)/40 (66.7%) | .4333 |
| Portal vein invasion (absent/present) | 18 (85.7%)/3 (14.3%) | 45 (75.0%)/15 (25.0%) | .4744 |
| AFP (median, ng/mL) (range) | 56.7 (0.9–3,132) | 61.4 (0.8–1,304,200) | .7836 |
| AFP (≥ 20 ng/mL/< 20 ng/mL) | 13 (61.9%)/8 (38.1%) | 35 (58.3%)/25 (41.7%) | .9746 |
| AFP-L3 (median, %) (range) | 0.5 (0–64.0) | 6.2 (0–60.7) | .3658 |
| AFP-L3 (≥ 10%/< 10%) | 7 (33.3%)/14 (66.7%) | 24 (40.0%)/36 (60.0%) | .7769 |
| DCP (median, mAU/mL) (range) | 94.0 (16–8,000) | 62.0 (10–75,000) | .7997 |
| DCP (≥ 40 mAU/mL/< 40 mAU/mL) | 13 (61.9%)/8 (38.0%) | 41 (68.3%)/19 (31.7%) | .7854 |

AFP = alpha-fetoprotein; AFP-L3 = *Lens culinaris* agglutinin-reactive AFP; DCP = des-gamma-carboxy prothrombin; ICG = indocyanine green test.
* ICG test was not performed in 14 patients.

or liver failure were not censored. The survival function was estimated using the Kaplan-Meier product-limit method (26), and the log-rank test (27) was used to analyze the differences in survival.

The Cox proportional hazards model (28) was used to perform a multivariate analysis of the factors related to survival. The following variables were analyzed: patient age and sex, Child-Pugh class (A/B), tumor size (≤ 2 cm/> 2 cm and ≤ 5 cm/> 5 cm), number of tumors (single/multiple), portal vein invasion (absent/present), and treatment with nucleoside analogues against HBV. The data analyses were performed using JMP statistical software, version 6.0 (Macintosh version; SAS Institute, Cary, North Carolina). All *P* values were derived from two-tailed tests; $P < .05$ was considered statistically significant.

## RESULTS

### Comparison of Patient Characteristics According to Nucleoside Analogue Intake

The anti-HBV nucleoside analogues had been administered to 21 of the 81 patients (25.9%). Among the 21 patients who had received nucleoside analogues, 7 patients had already been taking nucleoside analogues at the initial HCC diagnosis, and the remaining 14 patients started nucleoside analogues after diagnosis of HCC. Seven patients were taking 100 mg of lamivudine (Zefix; GlaxoSmithKline, Tokyo, Japan), eight patients were taking 0.5 mg of entecavir (Baraclude; Bristol-Myers Squibb, Tokyo, Japan), and six patients were taking lamivudine and 10 mg of adefovir dipivoxil (Hepsera, GlaxoSmithKline) because of the emergence of lamivudine-resistant HBV. **Table 1** compares the background characteristics of the patients who had and had not been treated with nucleoside analogues. There were no significant differences between these two groups in patient age and sex, liver function, and tumor progression, although the serum albumin levels were higher in the patients who received nucleoside analogues.

### Influence of Nucleoside Analogue Treatment on Survival and Progression-Free Survival

**Table 2** shows the number of chemoembolization treatments that were performed for initial and recurrent HCC with respect to the nucleoside analogue intake. Chemoembolization could not be performed more than four times in the patients who had not received nucleoside analogues; however, it was performed more than four times in one-third of patients who did receive them. The number of chemoembolization treatments was significantly higher in the patients who had received nucleoside analogues than in the patients who were not treated with nucleoside analogues ($P = .0022$). In the patients who underwent chemoembolization treatments repeatedly, the interval between two chemoembolization treatment sessions did not differ significantly between the patients who were and were not treated with nucleoside analogues (6.27 months ± 2.66 in patients without nucleoside analogues vs 6.71 months ± 2.71 in

**Table 2.** Number of Transarterial Chemoembolization Procedures Performed as a Function of Treatment with Nucleoside Analogues

| No. Transarterial Chemoembolization Procedures | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Nucleoside analogues (−) (n = 60) | 28 (46.7%) | 20 (33.3%) | 7 (11.7%) | 5 (8.3%) | 0 | 0 | 0 | 0 |
| Nucleoside analogues (+) (n = 21) | 5 (23.8%) | 4 (19.0%) | 5 (23.8%) | 0 | 3 (14.3%) | 1 (4.8%) | 1 (4.8%) | 2 (9.5%) |

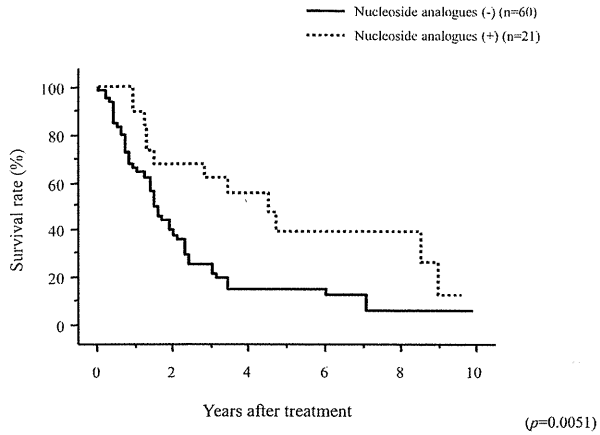


**Figure 1.** Plot of the Kaplan-Meier product-limit functions for survival after transarterial chemoembolization for initial HCC in the patients who did and did not receive nucleoside analogues.

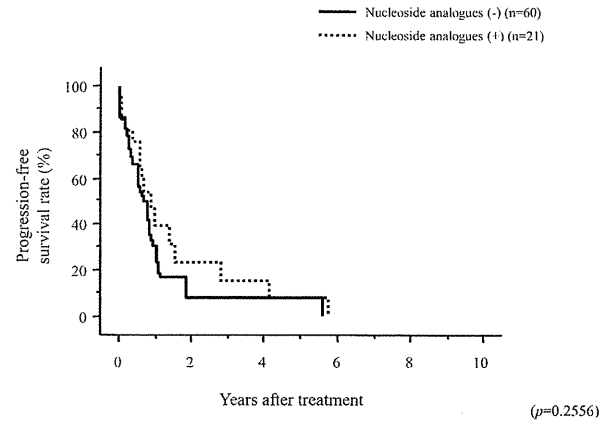


**Figure 2.** Plot of the Kaplan-Meier product-limit functions for progression-free survival after transarterial chemoembolization for initial HCC in the patients who did and did not receive nucleoside analogues.

patients with nucleoside analogues; $P = .3893$). The reasons for not offering further chemoembolization treatments to patients who did not receive nucleoside analogue therapy were emerging signs of liver failure (including ascites, jaundice, and hepatic coma) in 29 (48.3%) patients, progression to Child-Pugh C liver function in 18 (30.0%) patients, and progression of HCC (including extrahepatic metastases and invasion of the main portal vein trunks and left or right main portal vein) in 13 (21.7%) patients. The reasons for not offering further chemoembolization to the patients who did receive nucleoside analogue therapy were emerging signs of liver failure in 6 (28.6%) patients, progression to Child-Pugh C liver function in 4 (19.0%) patients, and HCC progression in 11 (52.4%) patients. Further chemoembolization was denied because of HCC progression more frequently in patients who were treated with nucleoside analogues ($P = .0174$).

**Figure 1** shows the survival curves for the two patient groups. The 1-year, 3-year, and 5-year survival rates were 89.5%, 66.8%, and 40.5% in the patients treated with nucleoside analogues and 72.6%, 27.5%, and 14.3% in the patients who did not receive nucleoside analogues. The survival rate was significantly higher in the patients who were treated with nucleoside analogues ($P = .0051$). By contrast, there was no difference in the progression-free survival rates between the two groups ($P = .2556$) (**Fig 2**).

A multivariate analysis was performed to examine the factors that influenced survival after chemoembolization for the initial HCC (**Table 3**). Multiple tumors and portal vein invasion at the initial HCC diagnosis independently reduced the survival rate, and nucleoside analogue intake was an independent factor that increased the survival rate. When multivariate analysis included the number of chemoembolization treatments as an independent variable, the number of chemoembolization treatments was an independent factor associated with improved survival, and the statistical significance of nucleoside analogue intake disappeared (**Table E2**).

## DISCUSSION

The results of the present study showed an association of nucleoside analogue therapy with longer survival in patients with HBV-associated HCC who were treated with chemoembolization for initial and recurrent disease. A multivariate analysis showed that nucleoside analogue intake was an independent factor that affected patient survival. However, the statistical significance of nucleoside analogue intake for improved survival disappeared when the multivariate analysis included the number of chemoembolization treatments as an independent variable, and the number of chemoembolization treatments was the factor that most affected survival. The patients who had received nucleoside analogues underwent a significantly greater number of chemoembolization treatments for HCC than the patients who were not treated with nucleoside analogues. Taken together, these results suggest that the association between nucleo-

**Table 3. Multivariate Analyses of Factors Associated with Patient Survival**

| Factor | | Parameter Estimate | Standard Error | Chi | Risk Ratio (95% Confidence Interval) | *P* Value |
|---|---|---|---|---|---|---|
| Age | | −0.0188 | 0.0158 | 1.41 | 0.9814 (0.9512–1.0122) | .2342 |
| Sex | Male | | | | 1 | |
| | Female | 0.0378 | 0.1804 | 0.04 | 1.0385 (0.7096–1.4504) | .8353 |
| Child-Pugh class | A | | | | 1 | |
| | B | 0.1316 | 0.1428 | 0.84 | 1.1406 (0.8580–1.5057) | .3602 |
| Tumor size | ≤ 2 cm | | | | 1 | |
| | > 2 cm and ≤ 5 cm | 0.2868 | 0.1688 | 2.98 | 1.3322 (0.9625–1.8733) | .0842 |
| | > 5 cm | 0.0282 | 0.1939 | 0.02 | 1.0286 (0.7029–1.5113) | .8843 |
| Tumor number | Single | | | | 1 | |
| | Multiple | 0.3492 | 0.1516 | 5.71 | 1.4179 (1.0631–1.9331) | .0169 |
| Portal vein invasion | Absent | | | | 1 | |
| | Present | 0.3970 | 0.1852 | 4.31 | 1.4874 (1.0232-2.1235) | .0379 |
| Nucleotide analogue | No | | | | 1 | |
| | Yes | −0.4420 | 0.1727 | 7.46 | 0.6428 (0.4483–0.8871) | .0063 |

Note–Data on Child-Pugh class, tumor size, tumor number, and portal vein invasion refer to the status at initial diagnosis of hepatocellular carcinoma.

side analogue intake and improved patient survival was likely mediated by the increased number of chemoembolization treatments. The use of nucleoside analogues may have slowed the progressive decline in liver function that occurs even with repeated chemoembolization treatments, potentially allowing more sessions of chemoembolization treatment in patients who would otherwise have been excluded from chemoembolization treatment because of progressive liver dysfunction. Additional chemoembolization sessions may have explained the improved patient survival, although not the improved progression-free survival. Several groups have reported on the beneficial survival effects nucleoside analogues exert by preserving liver function in patients with HCC and HBV who undergo curative treatment (29,30). Our experience may suggest that this finding also applies to patients receiving chemoembolization as palliative therapy.

Although previous studies reported that nucleoside analogues can suppress the development of HCC (17,31), it has not been confirmed that nucleoside analogues can suppress HCC recurrence after treatment (30,32–34). Because the patients in the present study had been treated for both initial and recurrent HCC solely by chemoembolization, which is not a curative treatment, it is difficult to determine the extent to which nucleoside analogues prevent HCC progression or recurrence. Although there was no difference in the progression-free survival rate after the initial HCC treatment based on nucleoside analogue intake, further studies are needed to investigate whether the suppressive effects of nucleoside analogues on HCC recurrence or progression play a role in improving the survival of HBV-infected patients with HCC.

There are several limitations to this study. This was a retrospective study, and the patients were not randomly assigned to treatment arms. There may have been selection bias toward the patients who were administered nucleoside analogues. In addition, the data on liver function deterioration during the course of HCC recurrence and retreatment were insufficient, and the mechanisms behind the effect of nucleoside analogues on patients with HCC treated with chemoembolization were not elucidated. Additional studies are necessary to elucidate these mechanisms.

In conclusion, administering nucleoside analogues for chronic hepatitis B was associated with longer survival and more chemoembolization treatments in patients with HCC who were treated solely with chemoembolization. Additional studies are needed to examine these findings further and to clarify the mechanisms underlying this association.

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**Table E1. Pretreatment Characteristics of Study Patients (n = 81)**

| | |
|---|---|
| Age (mean ± SD, y) (range) | 60.6 ± 9.2 (37–81) |
| Sex ratio (female/male) | 14 (17.3%)/67 (82.7%) |
| Child-Pugh class (A/B) | 49 (60.5%)/32 (39.5%) |
| Albumin (mean ± SD, g/dL) | 3.42 ± 0.73 |
| Total bilirubin (mean ± SD, mg/dL) | 1.04 ± 0.82 |
| 15-minute retention rate of ICG (%)* | 20.0 ± 13.5 |
| Prothrombin (%) | 80.1 ± 20.0 |
| Platelet count (× 1,000/mL) | 135 ± 77 |
| Tumor size (mean ± SD, cm) (range) | 4.38 ± 3.15 (1.0–15.9) |
| Tumor size (≤ 2 cm/> 2 cm and ≤ 5 cm/> 5 cm) | 21 (25.9%)/36 (44.5%)/24 (29.6%) |
| Tumor number (single/multiple) | 29 (35.8%)/52 (64.2%) |
| Portal vein invasion (absent/present) | 63 (77.8%)/18 (22.2%) |
| AFP (median, ng/mL) (range) | 61.4 (0.8–1,304,200) |
| AFP (≥ 20 ng/mL/< 20 ng/mL) | 48 (59.3%)/33 (40.7%) |
| AFP-L3 (median, %) (range) | 6.1 (0–64.0) |
| AFP-L3 (≥ 10%/< 10%) | 31 (38.3%)/50 (61.7%) |
| DCP (median, mAU/mL) (range) | 62.0 (10–75,000) |
| DCP (≥ 40 mAU/mL/< 40 mAU/mL) | 54 (66.7%)/27 (33.3%) |

AFP = alpha-fetoprotein; AFP-L3 = *Lens culinaris* agglutinin-reactive AFP; DCP = des-gamma-carboxy prothrombin; ICG = indocyanine green test.
* ICG test was not performed in 14 patients.

**Table E2. Multivariate Analyses of Factors Associated with Patient Survival (including Number of Chemoembolization Treatments)**

| Factor | | Parameter Estimate | Standard Error | Chi | Risk ratio (95% Confidence Interval) | *P* Value |
|---|---|---|---|---|---|---|
| Age | | −0.0250 | 0.0150 | 2.79 | 0.9753 (0.9469–1.0047) | .0949 |
| Sex | Male | | | | 1 | |
| | Female | −0.0013 | 0.1794 | 0.00 | 0.9987 (0.6836–1.3912) | .9943 |
| Child-Pugh class | A | | | | 1 | |
| | B | −0.0173 | 0.1476 | 0.01 | 0.9828 (0.7329–1.3106) | .9064 |
| Tumor size | ≤ 2 cm | | | | 1 | |
| | > 2 cm and ≤ 5 cm | 0.2361 | 0.1668 | 2.06 | 1.2662 (0.9183–1.7740) | .1512 |
| | > 5 cm | 0.0940 | 0.1920 | 0.24 | 1.0986 (0.7529–1.6069) | .6242 |
| Tumor number | Single | | | | 1 | |
| | Multiple | 0.4285 | 0.1562 | 8.23 | 1.5350 (1.1415–2.1140) | .0041 |
| Portal vein invasion | Absent | | | | 1 | |
| | Present | 0.3841 | 0.1843 | 4.05 | 1.4683 (1.0107–2.0898) | .0440 |
| Nucleotide analogue | No | | | | 1 | |
| | Yes | −0.1040 | 0.1903 | 0.31 | 0.9013 (0.6067–1.2859) | .5793 |
| No. chemoembolization procedures | | −0.3658 | 0.1194 | 10.00 | 0.6936 (0.5450–0.8720) | .0016 |

Note–Data on Child-Pugh class, tumor size, tumor number, and portal vein invasion refer to the status at initial diagnosis of hepatocellular carcinoma.

特集 C型肝炎のすべて2012

HCVと発癌

# HCV療法後発癌

豊田秀徳* 熊田 卓*

索引用語：HCV療法，インターフェロン，肝細胞癌，発癌抑制，予後

## 1 はじめに

インターフェロンを用いた抗C型肝炎ウイルス(HCV)治療とその後の肝細胞癌(HCC)の発生との関連については，以前から数多くの研究がなされてきた．しかしながら，その後の治療法の変遷，また新たな治療効果関連因子の発見により，抗HCV療法とその後の肝細胞癌の発生との関連にはこれらの因子を加えた再検討が必要になっている可能性がある．抗HCV療法の最終的な目的が肝硬変への進展，そして主には肝細胞癌発生の抑制であることから考えても，現時点で改めてインターフェロンを用いた抗HCV療法の肝発癌に対する影響，また肝細胞癌発生例での抗HCV療法(治療歴)の予後に対する影響を検証しておくことは必要であろう．

本稿では，現在までに得られた新しい情報を含めて現時点におけるHCV療法後の肝細胞癌の発生と，HCV療法後に発生した肝細胞癌の特徴・予後について検討した．なお本稿においては，トランスアミナーゼの正常化目的でのインターフェロン長期投与例(maintenance IFN症例)は割愛し，あくまでもHCV排除の目的で抗HCV療法を行った症例を対象とした．

## 2 インターフェロンを用いた抗HCV療法と治療後の発癌率

インターフェロンを用いた抗HCV療法による治療後のHCC発生への影響については，現在までに，特に1990年代後半ににおいてわが国から多くの報告がなされた[1~4]．これらの研究においては，インターフェロン療法を施行することによるHCCの抗発癌効果，とりわけインターフェロン療法によるHCV排除例(著効例)における著明なHCC発生抑制効果が示されている．さらにはHCV排除が得られなかった症例においても，治療中に血中HCV RNAが陰性化した再燃例や，治療後トランスアミナーゼ値が正常範囲で経過する生化学的著効例において，治療無効例に比

*Hidenori TOYODA et al*: Incidence, characteristics, and prognosis of hepatocellular carcinoma in patients treated by antiviral therapy with interferon
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表1　抗HCV療法症例における治療効果別の治療開始時の背景因子とHCV遺伝子型・rs7099917遺伝子多型性

| | 著効例 (n = 609) | 再燃例 (n = 293) | 無効例 (n = 225) |
|---|---|---|---|
| 年齢(歳) | 50.0 ± 12.2 | 53.8 ± 10.7 | 54.4 ± 9.5 |
| 性別(男性／女性) | 353 (58.0) /256 (42.0) | 167 (57.0) /126 (43.0) | 129 (57.3) /96 (42.7) |
| 体重 (kg) | 60.0 ± 10.7 | 59.8 ± 10.1 | 60.7 ± 10.1 |
| AST (IU/L) | 65.0 ± 55.4 | 65.7 ± 53.7 | 68.7 ± 46.0 |
| ALT (IU/L) | 92.0 ± 81.3 | 80.5 ± 66.0 | 80.6 ± 55.1 |
| γ-GTP (IU) | 54.5 ± 62.4 | 52.6 ± 48.8 | 69.2 ± 58.4 |
| ALB (g/dL) | 276.8 ± 91.7 | 319.4 ± 161.0 | 319.4 ± 161.0 |
| 血小板 ($\times 10^4/\mu L$) | 18.7 ± 5.7 | 17.0 ± 9.9 | 16.6 ± 6.3 |
| AFP (ng/mL) | 4.6 ± 8.7 | 6.6 ± 10.2 | 15.8 ± 29.6 |
| 肝組織-活動性 (A0-1/A2-3) | 367 (64.2) /205 (35.8) | 162 (58.9) /113 (41.1) | 122 (57.5) /90 (42.5) |
| 肝組織-線維化 (F0-1/F2-3) | 397 (69.4) /175 (30.6) | 177 (64.4) / 98 (35.6) | 122 (57.5) /90 (42.5) |
| HCV遺伝子型(1b/2a or 2b) | 273 (45.7) /324 (54.3) | 185 (63.6) /106 (36.4) | 191 (85.7) /32 (14.3) |
| Rs7099917遺伝子多型 (TT/TG or GG) | 202 (85.2) / 35 (14.8) | 94 (80.3) / 23 (19.7) | 30 (40.5) /44 (59.5) |

()内は%

べてその後の発癌率が低いことが報告されている．これらはHCV排除に加えて，インターフェロンを用いた抗ウイルス療法そのものがその後の発癌を抑制する可能性を示唆するものであった．

しかしながら，近年インターフェロンを用いた抗HCV療法の効果を規定するウイルス側・宿主側の因子が報告され[5,6]，最近ではさらに進んでこれらの因子がHCCの発生に関連する可能性が示唆されている．遺伝子型1b型のHCV感染症例においてインターフェロンを用いた抗HCV療法の効果を強く規定するウイルス側の因子であるHCV Core領域の遺伝子変異については，治療抵抗性であるCore領域アミノ酸70番・91番のmutant例においてその後の発癌率が高いことが報告されており[7]，また宿主側因子では*IL28B*近傍の遺伝子多型性で極めて強い治療抵抗性を示す遺伝子型(rs8099917のTG/GGタイプ)の症例において治療後のALT値やAFP値が高く，その後のHCCの発生率が高い可能性も示唆されている[8~10]．さらにはHCVが排除された著効例においてさえも，その後の肝発癌にHCV Core領域の遺伝子変異が関係している可能性も報告されている[11]．これらの報告は，かつての研究において抗HCV療法無効例で著効例・再燃例に比べて有意にその後のHCCの発生率が高かったのには治療抵抗性にかかわるウイルス側・宿主側の因子が関与していたのではないか，すなわち抗HCV療法著効例・再燃例において無効例に比べて発癌が抑制されていたのではなく，単にインターフェロンを用いた抗HCV療法を行いその効果をみることにより，発癌しやすい症例を分別していただけではないかという疑問を惹起する．

われわれの施設でインターフェロンを用いた抗HCV療法を施行し，その後経過を追えた1,127例についてその後のHCCの発生につき検討した．抗HCV療法の治療効果は著効例609例，再燃例293例，無効例225例であった．表1に示すように，無効例では治療

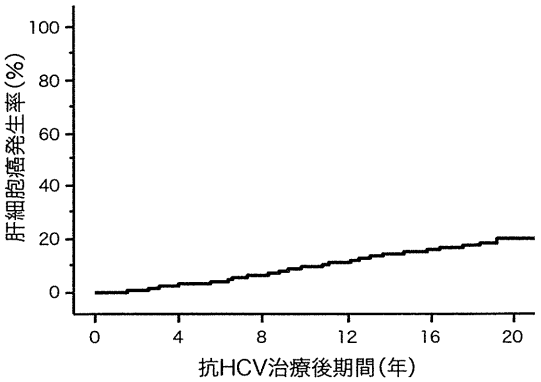


図1　インターフェロンを用いた後発癌率

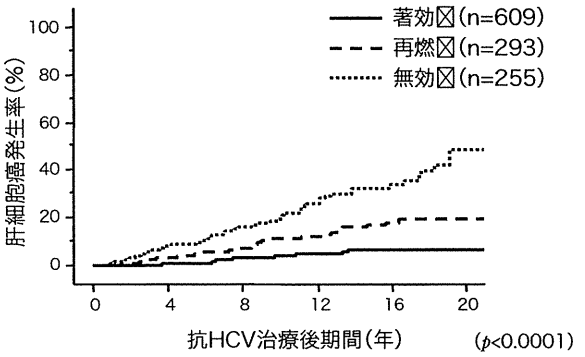


図2　インターフェロンを用いた抗HCV療法の治療効果別の治療後発癌率

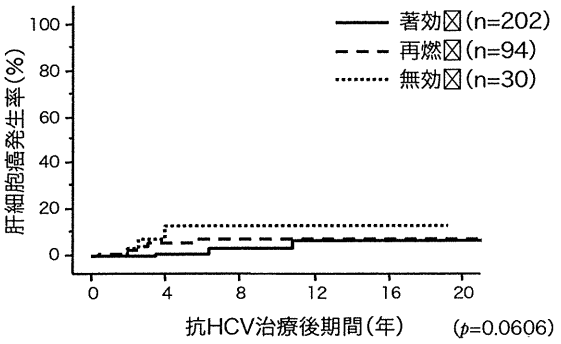


図3　rs8099917がTTタイプの症例における，インターフェロンを用いた抗HCV療法の治療効果別の治療後発癌率

前に線維化の進展している症例が多い傾向にあり，また治療前から著効例・再燃例に比べてAFP値が高かった．rs8099917の遺伝子多型性については一部の症例しか検討されていないが，治療抵抗性であるTG/GGタイプの割合が有意に高かった．治療後の発癌については，図1にみられるように治療後20年の観察で約20％にHCCの発生がみられた．これを抗HCV療法の効果別にみると，図2に示すように治療後の発癌率は著効例・再燃例・無効例の順に低く(p<0.0001)，特にHCVが排除された著効例ではその後の肝細胞癌の発生率は極めて低値であった．しかしながら，*IL28B*近傍の遺伝子多型性rs8099917を測定してTTタイプであった326症例に限ってその後の発癌率を抗HCV療法の効果別にみると，全体でみられた著効例・再燃例・無効例の発癌率の差は著明でなくなり，有意差がみられなくなった(p=0.0606)．これが単にrs8099917遺伝子多型の測定例が少なかったためなのか，もしくはTTタイプであれば抗HCV療法の効果にかかわらず発癌率は類似するのかは不明である．また今回の検討では検討可能症例数がさらに少なかったためにHCV Core領域の遺伝子変異の有無で層別化しての抗HCV療法効果別の発癌率は比較不能であった．今後，多施設・多症例でのこれら治療抵抗性に関連するウイルス側・宿主側因子，さらには肝線維化や年齢[12]を含めた補正を行ったうえでの治療後肝発癌に対する抗HCV療法の治療効果の関係を評価し直す必要があると思われる．

## 3　インターフェロンを用いた抗HCV療法の治療後発癌症例の特徴と予後

次に，抗HCV療法後に発生したHCC症例の特徴と予後について検討した．1990年以降に当院で経験したHCV陽性・HBV陰性の

表2　発癌前抗HCV治療歴の有無による肝細胞癌診断時の臨床背景の比較

| | 抗HCV治療歴あり (n = 120) | 抗HCV治療歴なし (n = 1102) | *P* value |
|---|---|---|---|
| 年齢(歳) | 64.0 ± 6.5 | 68.3 ± 8.4 | <0.0001 |
| 性別(男性/女性) | 92 (76.7) /28 (23.3) | 757 (68.7) /345 (31.3) | 0.0897 |
| サーベイランスの有無(当院/他院/なし) | 95 (79.2) /18 (15.0) /7 (5.8) | 440 (40.5)/414 (38.2)/231 (21.3) | <0.0001 |
| 残存肝機能(Child-Pugh A/B/C) | 94 (79.7) /21 (17.8) /3 (2.5) | 667 (60.6) /333 (30.2) /101 (9.2) | 0.0002 |
| 腫瘍径(～2 cm/2～5 cm/5 cm～) | 59 (49.2)/51 (42.5)/10 (8.3) | 389 (35.4)/429 (39.0)/281 (25.6) | <0.0001 |
| 腫瘍個数(単発/多発) | 79 (65.8) /41 (34.2) | 545 (49.5) /555 (50.5) | 0.0010 |
| 門脈腫瘍浸潤(なし/あり) | 115 (95.8) /5 (4.2) | 893 (81.4) /204 (18.6) | 0.0001 |

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表3　発癌前抗HCV治療歴の有無による肝細胞癌診断時の臨床背景の比較
(当院でのサーベイランス症例・HCV非排除例)

| | 抗HCV治療歴あり (n = 78) | 抗HCV治療歴なし (n = 440) | *P* value |
|---|---|---|---|
| 年齢(歳) | 64.6 ± 6.5 | 68.7 ± 7.9 | <0.0001 |
| 性別(男性/女性) | 56 (71.8) /22 (28.2) | 272 (61.8) /168 (38.2) | 0.1193 |
| 残存肝機能(Child-Pugh A/B/C) | 57 (73.1) /18 (23.1) /3 (3.8) | 288 (65.6)/119 (27.1)/32 (7.3) | 0.3464 |
| 腫瘍径(～2 cm/2～5 cm/5 cm～) | 45 (57.7) /30 (38.5) /3 (3.8) | 245 (55.8)/171 (39.0)/23 (5.2) | 0.8600 |
| 腫瘍個数(単発/多発) | 51 (65.4) /27 (34.6) | 283 (64.5) /156 (35.5) | 0.9774 |
| 門脈腫瘍浸潤(なし/あり) | 77 (98.7) /1 (1.3) | 419 (95.7) /19 (4.3) | 0.3321 |

()内は%

初発肝細胞癌1,222例中，肝細胞癌発生前にインターフェロンを用いた抗HCV治療歴があったのは120例(著効例25例・再燃例32例・無効例63例)であった．これらの症例の診断後の生存率を抗HCV治療歴のなかった1,102例と比較すると(図4)，抗HCV治療歴のある症例で初発HCC診断後の生存率は有意に良好であった(p<0.0001)．しかしながら抗HCV治療歴の有無により臨床背景を比較すると(表2)，抗HCV治療歴のない症例において年齢が高く，HCCはサイズ・個数・門脈浸潤いずれの点からも進行しており，かつ残存肝機能は悪かった．これらは抗HCV治療歴のある症例の多くがその後にHCCのサーベイランスに入っているのに対して，抗HCV治療歴のない症例においては相当数がサーベイランスされていない状態でHCCが発見されていることに起因するものと思われた．

そこで診断時当院においてサーベイランスされていた症例に絞り，さらに抗HCV療法例のうちHCVが排除された著効例17例を除いて抗HCV治療歴の有無により臨床背景を比較すると(表3)，依然抗HCV治療歴のない症例において年齢が高かったが，両群で残存肝機能や腫瘍の進展度に差はみられなくなった．診断後の生存率を比較すると(図5)，両

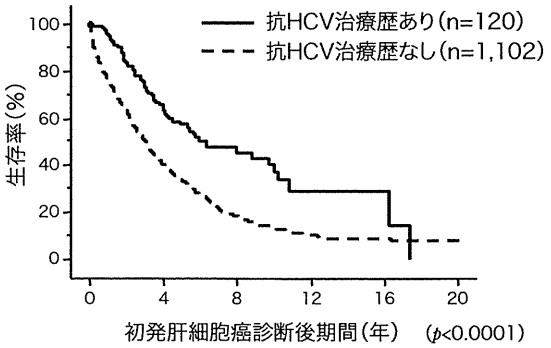


図4　抗HCV治療歴の有無による，HCV肝細胞癌診断後の生存率

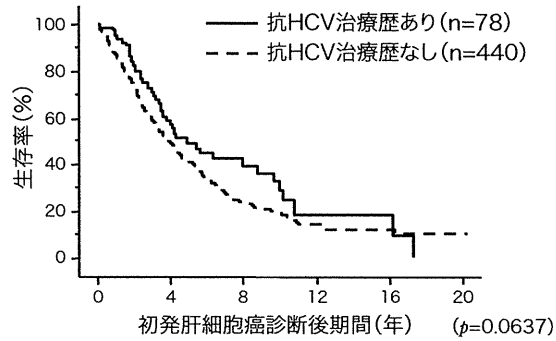


図5　当院でのサーベイライスで発見された，HCV排除例を除いたHCV肝細胞癌の診断後の生存率

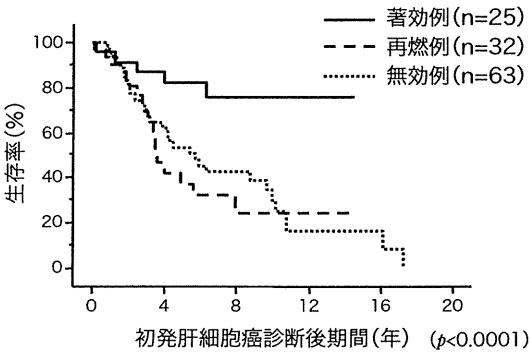


図6　インターフェロンを用いた抗HCV治療歴を有する症例における，治療効果別の肝細胞癌診断後の生存率

群の発癌率の差は著明でなくなり，有意差がみられなくなった(p=0.0606)．今後さらにpropensity score matching等を用いて背景因子を揃え，過去の抗HCV治療歴のHCC発生後の予後への関与を検証すべきであると思われる．

一方抗HCV治療歴のあるHCC発生症例において抗HCV療法の治療効果別に診断後の生存率を比較すると(図6)，再燃例・無効例に比べて著効例の生存率は有意に高く(p<0.0001)，HCV排除例はかりにその後に発癌しても非排除例に比べて予後は良好である可能性が示唆された．治療後の肝発癌だけでなく発癌後の生存も含めて，C型慢性肝炎患者の予後の改善のためには抗HCV療法はやはりまずHCVの排除を第一目標とすべきであろう．

## 4　おわりに

1992年にインターフェロンを用いた抗HCV療法が保険認可されてほぼ20年が経過し，現在新たに発生するHCV陽性HCC患者の多くが過去に抗HCV療法の施行歴のある症例となってきている．インターフェロンを用いない抗HCV療法が現実のものとなりつつある現時点において，インターフェロンを用いた抗HCV療法が発癌の抑止効果および発癌症例における発癌後の予後にどのように利益をもたらしてきたのか，今一度検証していく必要があると思われる．

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