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Clinical Characteristics of Patients who Developed Hepatocellular Carcinoma after Hepatitis C Virus Eradication with Interferon Therapy: Current Status in Japan

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Abstract

Objective We attempted to elucidate the clinical features of chronic hepatitis C patients who develop hepatocellular carcinoma (HCC) after achieving a sustained viral response (SVR) to interferon (IFN) therapy.

Methods The clinical features of 130 patients at 19 hospitals who developed HCC after obtaining an SVR were retrospectively reviewed.

Results Overall, 107 (82%) of the 130 patients were men, with 92 (71%) being ≥60 years of age and 76, 38 and 16 developing HCC within 5, 5-10 and 10-16.9 years after IFN therapy, respectively. Before receiving IFN therapy, 92 (71%) patients had cirrhosis and/or a low platelet count ($<15\times10^4$ cells/μL). Lower albumin (<3.9 g/dL) and higher alpha fetoprotein (AFP) (≥10 ng/mL) levels were identified in a multivariate analysis to be independent variables of the development of HCC within five years after IFN therapy. Among 4,542 SVR patients, HCC occurred in 109 (2.4%) during a 5.5-year follow-up period, thus resulting in an occurrence rate of 4.6% for men and 0.6% for women.

Conclusion SVR patients with lower albumin or higher AFP levels require careful assessments to prevent early HCC development after IFN therapy. HCC occurrence within >10 years of IFN therapy is not uncommon, and the risk factors remain uncertain, thus suggesting that all SVR patients should undergo long-term follow-up examinations for HCC development.

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

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Introduction

Chronic hepatitis C virus (HCV) infection is a common cause of chronic liver disease and hepatocellular carcinoma (HCC) worldwide (1). In Japan, HCC is the third leading cause of cancer-related death, with more than 30,000 deaths occurring in 2010 (2), approximately 70% of which were associated with HCV infection (3). In chronic HCV patients, the risk of HCC has been shown to increase in association with the degree of liver fibrosis, with an annualized rate of HCC developing within a 2-8% cirrhotic background (4-7). It has been reported that interferon (IFN) therapy not only improves hepatic inflammation and fibrosis, but also reduces the incidence of HCC, particularly in patients who achieve a sustained viral response (SVR) (4, 8-10). However, HCC sometimes develops in patients with an SVR, and cases of patients who have developed HCC more than 10 years after completing IFN therapy have been reported (11, 12). The risk factors for HCC in chronic HCV patients are a male sex, older age (13, 14) and the presence of advanced fibrosis (4, 5). Several cohort studies have indicated that these risk factors are also associated with the development of HCC among SVR patients (15-21). However, the number of patients who developed HCC after achieving an SVR in each of these previous studies was limited, and the clinical features of such patients have not been fully clarified. We investigated the clinical features of a large number of patients who developed HCC after undergoing HCV eradication using IFN therapy at a workshop held during the 47th annual meeting of the Liver Cancer Study Group of Japan in July 2011 (President: F. Ichida) on the clinical features of patients who develop HCC after obtaining an SVR in order to compile a more detailed background of such patients.

Materials and Methods

Patients

This study was conducted from February to June 2011 at institutes with which the internal medicine secretaries of the Liver Cancer Study Group of Japan are affiliated. We first investigated the number of SVR patients treated at each institute and, of these, investigated the number of patients who developed HCC after obtaining an SVR. Responses to the initial inquiry were obtained from 25 of 46 hospitals, 22 of which provided the numbers of both SVR and HCC patients. Second, we assessed the characteristics of the patients who developed HCC, and the maximum, minimum and mean follow-up periods of all SVR patients with or without HCC were investigated. Responses were obtained from all 22 hospitals. The characteristics of 144 patients at 22 hospitals were initially reviewed retrospectively; however, three patients who developed HCC before the completion of IFN therapy and 11 patients whose clinical data prior to IFN therapy were unavailable were excluded. Patients positive for the hepatitis B surface antigen were ineligible for this study. Ultimately, 130 patients treated at 19 hospitals were enrolled. Among these patients, 109 were treated at 13 hospitals that also provided follow-up data of SVR patients with or without HCC. Liver cirrhosis and diabetes mellitus were diagnosed based on the clinical data that we had collected. Obesity was defined as a body mass index of ≥25.0 kg/m^2 (22). The SVR patients (4,542) with or without HCC followed up at 13 hospitals at 0.5-21.9 years were analyzed to determine the disease incidence rates.

Statistical analyses

All statistical analyses were performed using the SPSS software package (ver17.0 for Windows; SPSS, Chicago, IL, USA). Clinical differences were evaluated using the chi-square test, and a multivariate analysis was conducted with an ordinal logistic regression analysis using the forced entry method. A p value of <0.05 was considered to be statistically significant.

Results

Patient characteristics at the time of hepatocellular carcinoma occurrence

A total of 107 (82%) of the 130 patients were men; 72 (55%) patients developed HCC in their sixties and 34 (26%) developed HCC in their fifties. Ninety-seven patients (75%) had a solitary tumor at the time of HCC occurrence, and 117 (90%) had one or two tumors. The maximum tumor size was within 3 cm in 102 (78%) patients, and 110 (85%) patients underwent radical treatment.

Period between the completion of IFN therapy and the occurrence of hepatocellular carcinoma

Seventy-six (58%) patients developed HCC within five years of completing IFN therapy and 26 patients developed HCC within one year of completing IFN therapy (Figure). Although the number of patients who developed HCC after >5 years of IFN therapy completion gradually decreased over time (38 patients: >5 and ≤10 years, 16 patients: >10 years), four patients developed HCC 15 years after completing IFN therapy.

Patient characteristics at the start of IFN therapy

Sixteen patients had undergone IFN therapy before 50 years of age and 114 (88%) had undergone IFN therapy after 50 years of age (Table 1). Obesity, alcohol intake (more than 80 g/day for five years), diabetes mellitus and cirrhosis were observed in 34 (26%), 38 (29%), 26 (20%) and 46 (35%) patients, respectively. The platelet count was $<15\times10^4$ cells/μL in 88 (68%) patients, the serum albumin level was <3.9 g/dL in 53 (41%) patients and the alpha fetoprotein (AFP) level was ≥10 ng/mL in 60 (46%) patients. Ninety-two patients (71%) had either cirrhosis or a low platelet count ($<15\times10^4$ cells/μL), and 38 had neither of these fac-

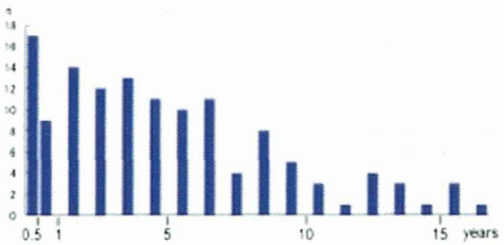

Figure. **Patient distribution according to the period between the completion of interferon therapy and the occurrence of hepatocellular carcinoma.**

Table 1. **Patient Characteristics at the Start of IFN Therapy**

	No. of patients
Age (yr)	
38-49	16
50-59	50
60-69	55
≥70	9
BMI (kg/m^2,) ≥25/<25	34/86
Alcohol intake (g/day), ≥80/<80	38/90
Diabetes mellitus, present/absent	26/104
Cirrhosis, present/absent	46/83
Platelet count (× 10^4 per μL), <10 /10- <15 /15-<20 /≥20	26/62/30/9
AST (IU/L), ≥100/<100	43/86
ALT (IU/L), ≥100/<100	54/75
AST/ALT, >1/≤1*	37/72
GGT (IU/L), ≥100/51-99/≤50	41/41/45
Albumin (g/dL), ≤3.5/3.6-3.8/≥3.9	26/27/74
AFP (ng/mL), ≥20/19-10/<10	37/23/49

* Cases with AST>39 IU/L

BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyltransferase, AFP: alpha fetoprotein

Table 2. **Univariate Analysis of Risk Factors Associated with the Development of HCC within Three Periods after Eradication of HCV with IFN**

Period since completion of IFN therapy	≤5 years	6-10 years	>10 years	p value
Sex, male/female	58/18	34/4	15/1	0.098
Age at IFN treatment (years), ≥60/<60	45/31	13/25	6/10	0.025
BMI (kg/m^2), ≥25/<25	18/53	11/27	4/12	0.830
Alcohol intake (g/day), ≥80/<80	21/54	13/25	4/12	0.725
Diabetes mellitus, present/absent	14 /62	11/27	1/15	0.142
Cirrhosis, present/absent	29/47	11/26	6/10	0.671
Platelet count (× 10^4 per μL), <15 /≥15	53/21	24/13	11/5	0.767
AST (IU/L), ≥100/<100	23/52	15/23	5/11	0.633
ALT(IU/L), ≥100/<100	28/47	18/20	8/8	0.463
GGT(IU/L), ≥100/<100	24/49	14/24	3/13	0.425
Albumin (g/dL), <3.9/ ≥3.9	38/35	12/26	3/13	0.016
AFP (ng/mL), ≥10/<10	43/20	10/21	7/8	0.003

BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyltransferase, AFP: alpha fetoprotein

tors. No significant differences in obesity, diabetes mellitus or alcohol intake were observed between the patients with and those without either of these background factors.

Risk factors for the development of HCC within five years after IFN therapy

Because 58% of the patients developed HCC within five years of IFN therapy completion and the median period from IFN therapy completion to HCC occurrence was 4.2 years, we compared the background characteristics among the patients who developed HCC within 5, 5-10 and >10 years of IFN therapy completion.

A univariate analysis identified an advanced age (≥60 years) at IFN treatment and lower albumin (<3.9 g/dL) and higher AFP (≥10 ng/mL) levels as significant risk factors associated with HCC development within five years of IFN therapy completion (Table 2). A multivariate analysis of the predictive value of each variable for HCC development within five years identified lower albumin [<3.9 g/dL; odds ratio (OR), 2.604] and higher AFP (≥10 ng/mL; OR, 2.809) levels as being significant (Table 3). No significant factors for HCC development after 10 years of IFN therapy completion were identified.

Patients who started IFN therapy before 50 years of age

Of the 16 patients who received IFN therapy before 50 years of age, all were men (Table 4) and 12 had cirrhosis and/or a low platelet count, while three of the remaining four patients had a background of alcohol intake. Patients with obesity and/or diabetes mellitus were included in these 15 cases, and only one patient had no background of cirrhosis, a low platelet count, alcohol intake, obesity or diabetes mellitus.

Table 3. Multivariate Analysis of Risk Factors Associated with the Development of HCC within 5 Years after HCV Eradication

variable	Odds ratio (95% confidence interval)	p value
Age ≥60 years at IFN treatment	2.147 (0.957-4.816)	0.064
Male sex	0.663 (0.189-2.323)	0.521
Diabetes mellitus	1.303 (0.471-3.604)	0.610
Albumin <3.9 g/dL	2.604 (1.108-6.117)	0.028
AFP ≥10ng/mL	2.809 (1.221-6.456)	0.015

AFP: alpha fetoprotein

Table 4. Patient Characteristics at the Start of IFN Therapy among Patients who Started IFN Treatment before 50 Years of Age

	No.
Male/female	16/0
Age at start of IFN therapy, in years (median)	38–47 (46)
Interval between end of IFN therapy and HCC occurrence, in years (median)	0.1–13 (6.5)
Platelet count, $<15 \times 10^4$ per μL	11
Cirrhosis, present	6
Alcohol intake, ≥80 g/day	9
Diabetes mellitus, present	4
BMI, ≥25.0 kg/m^2	5
None of the above risk factors	1

BMI: body mass index

Table 5. Occurrence of HCC in SVR Patients

	SVR patients			Age in years at last IFN treatment		Follow-up period after IFN treatment (years)		HCC development		
Hospital	Total	Male	Female		Mean		Mean	Total	Male	Female
A	1,193	429	764	15-78	51.0	0.5-18.1	4.5	23	21	2
B	681	392	289	16-77	51.8	0.2-16.9	7.5	17	15	2
C	525	224	301	18-76	50.4	2.0-21.6	9.5	17	14	3
D	487	290	197	15-76	48.5	0.2-21.9	6.0	3	3	0
E	404	227	177	9-85	53.0	0.5-18.0	3.3	9	7	2
F	250	149	101	17-76	50.4	0.5-19.1	5.7	2	2	0
G	193	121	72	17-80	52.7	0.5-15.3	3.7	11	11	0
H	188	97	91	20-75	53.4	0.1-6.9	2.7	4	3	1
I	163	109	54	20-78	54.3	0.2-18.0	3.0	4	3	1
J	155	111	44	18-72	48.0	0.5-14.2	5.5	7	6	1
K	155	85	70	19-79	55.1	0.7-5.8	2.8	2	2	0
L	118	77	41	26-75	49.9	1.0-20.0	5.7	8	6	2
M	30	14	16	37-72	57.5	0.5-6.9	3.3	2	2	0
Total	4,542	2,325	2,217				5.5	109	95	14

Incidence of hepatocellular carcinoma among patients with a sustained response

Between 30 and 1,193 SVR patients were followed up at each of the 13 hospitals. The mean follow-up period was 2.7-9.5 years (Table 5). In 10 of the 13 hospitals, the mean patient age at the time of the last IFN treatment was in the 50s. Among the 4,542 SVR patients, 109 (2.4%) developed HCC within 5.5 years of the last IFN treatment. The HCC occurrence rates for the male and female SVR patients were 4.6% and 0.6%, respectively.

Discussion

Several studies have discussed the risk factors for hepatocarcinogenesis following HCV eradication using IFN therapy (19-25). In these studies, the risk factors for HCC development were investigated in SVR patients. In the present

study, we reviewed the clinical features of patients who developed HCC after undergoing HCV eradication. Although the risk factors for hepatocarcinogenesis were not statistically analyzed due to the lack of data for non-HCC patients with an SVR, the characteristics of a relatively large number of patients may provide general information regarding the clinical features and present state of patients who develop HCC after obtaining an SVR in Japan.

At the time of HCC diagnosis, 117 patients had one or two tumors, and the tumor size was ≤3 cm in 102 patients. A total of 110 patients received curative therapy, suggesting that SVR patients are receiving appropriate follow-up care (23) in most of the hospitals that participated in this study.

A majority of the patients were men, received IFN treatment at an older age and had an advanced stage of liver fibrosis, as previously reported (15-21). A considerable number of patients had a background of alcohol intake, obesity and diabetes mellitus prior to IFN treatment, irrespective of the stage of liver fibrosis. These background characteristics have synergistic effects on hepatocarcinogenesis in chronic HCV patients (24-27). Some studies have suggested that alcohol intake is also a risk factor for HCC development among SVR patients (16, 17). Arase et al. (28) recently reported that both alcohol intake and diabetes increase the risk of HCC development in SVR patients without cirrhosis and non-SVR patients with cirrhosis, consistent with the findings of this study. To clarify the associations between these factors, including obesity, prospective cohort studies involving a large number of patients and data on the clinical features of patients who have undergone HCV eradication and individuals with a relatively low volume of alcohol intake, especially female patients, are needed.

An advanced age at HCV eradication is considered to be a risk factor for HCC development in SVR patients (15-21, 29), and most patients in this study were >50 years when they received IFN therapy. Although 16 patients received IFN therapy before 50 years of age, 12 had advanced fibrosis with cirrhosis or a lower platelet count, and three patients were heavy alcohol drinkers before IFN treatment. The number of heavy alcohol drinkers in this group was higher than that of male patients >50 years old (56.3% versus 29.7%, p=0.038), which suggests that alcohol intake may influence hepatocarcinogenesis and the progression of liver fibrosis in this group.

Nagaoki et al. (30) reported an older age at HCV eradication and heavy alcohol intake as risk factors for HCC development within five years of HCV eradication. In this study, an older age at IFN treatment initiation tended to be associated with an increased risk of HCC, and the development of HCC within five years was significantly associated with lower albumin and higher AFP levels at IFN treatment initiation. Kurosaki et al. (31) reported lower albumin levels as one risk factor for HCC development within five years among non-SVR patients without cirrhosis. However, it is uncertain as to why lower albumin levels are correlated with the occurrence of HCC. Regarding the AFP level, Asahina et al. (32) recently reported that the posttreatment AFP level (≥6 ng/mL) is correlated with the development of HCC among IFN-treated patients; however, this is not the case with the pretreatment AFP level. This suggests that patients with a posttreatment AFP level of ≥6 ng/mL have a substantial risk of developing HCC and that, of these patients, those with a pretreatment AFP level of >10 ng/mL have a risk for early HCC development. Therefore, patients with these characteristics should be closely followed up during and after IFN therapy.

In conclusion, our investigation revealed that most patients who develop HCC after obtaining an SVR are men with advanced fibrosis and that lower albumin and higher AFP levels before IFN treatment may increase the risk for HCC development within five years of HCV eradication. In contrast, the risk factors for HCC development after 10 years of IFN treatment are uncertain, and such patients are not rare; therefore, all patients with chronic HCV should receive long-term follow-up care to monitor for the possible development of HCC following HCV eradication.

The authors state that they have no Conflict of Interest (COI).

Ethical Considerations

This study was approved by the Medical Ethics Committee of the St. Marianna University School of Medicine. The investigation conformed to the principles outlined in the Declaration of Helsinki.

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Topics of HCC

わが国における肝細胞癌に対する肝移植の現状

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はじめに

再生医療が現実的でない現状では，肝移植医療に期待するものとして，非可逆的肝疾患に陥った病的肝臓を正常の肝臓に置換することにより，その生命を維持することにある。その対象となる疾患の多くは治療に不応性の劇症肝炎と非代償性肝硬変が主たる疾患である。一方，悪性腫瘍の肝細胞癌に対する肝移植の意義は，上述の肝疾患と少し異なる理論が必要である。肝細胞癌に対する肝移植は以下の考えによる。

B型肝炎ウイルス(HBV)あるいはC型肝炎ウイルス(HCV)陽性慢性肝疾患から見出された肝細胞癌はいくら早期発見し，完璧に局所制御しても再発は必至な高癌化状態(hypercarcinogenic state)である。したがって，適切な条件で肝移植により肝細胞癌はもとより背景の慢性肝疾患を含めて一挙に病的肝臓を正常肝臓に置き換えると，長期生存を得ることができると考えられる[1]。

本稿では，今までわが国で実施されてきた肝細胞癌に対する肝移植の実情を提示し，今後，脳死肝移植症例が増加するにつれて，脳死肝移植と生体肝移植が肝細胞癌の治療戦略の中心になると考え，詳述する。

生体肝移植の実施

1．日本肝移植研究会の登録

2011年末までの肝移植が施行された登録症例数は6,195例であり，そのうち98例が死体肝移植，6,097例が生体肝移植であった。そのなかで肝細胞癌は1,225例と全体の約20％を占めている。さらにその要因を検討するとHCV陽性が739例(60.3％)，HBV陽性が375例(30.6％)，アルコール性が44例，原発性胆汁性肝硬変11例で，その他は56例とされている。

その移植成績は1年，3年，5年，10年，15年生存率でそれぞれ79.7％，75.0％，72.5％，64.5％，56.9％であった(図1)[2]。しかし，これ以上の詳細な登録はされていないために，果たしてどれだけの症例がミラノ基準を満たしていたかは不明と言わざるを得ない。さらに，それらの再発様式や再発時の治療内容，さらには死亡原因なども一切不明で，この日本肝移植研究会の登録症例での解析は困難であることが判明した。

2．藤堂らの独自の集計

そこで北海道大学の藤堂らが独自に全国44施設で1988～2009年までに3度のアンケート調査を行った1,106例を対象にわが国における肝細胞癌に対する生体肝移植の実施状況を検討し，すでに2004年から海外，わが国の論文として数編にわたって記載され報告している[3)-6)]。日本肝移植研究会の1,225例と大差がないことより，この報告を中心に解析することとする。

成人の肝細胞癌に対する生体肝移植は1998年から始まり，2005年の年間172例をピークに少しずつその症例数の減少が目立つようになってきた(図2)[3]。

肝細胞癌の患者プロファイル

生体肝移植を受けた肝細胞癌症

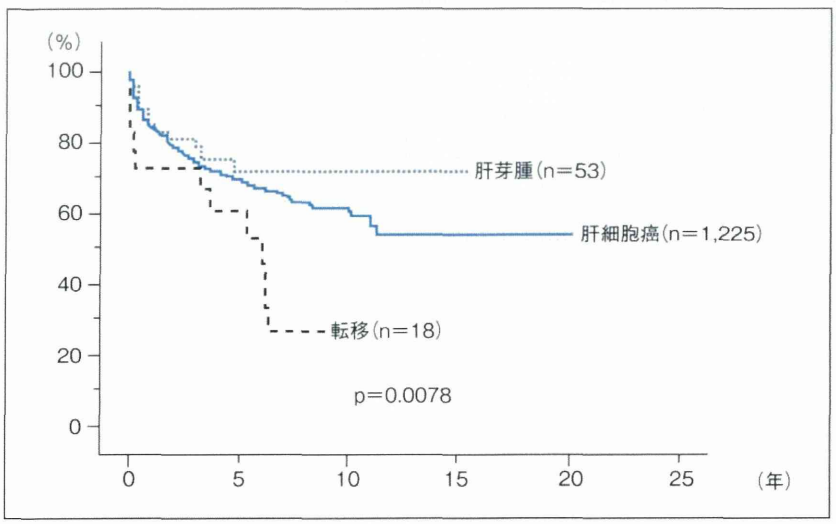

図1．日本肝移植研究会の登録肝細胞癌の累積生存率
文献2)より引用

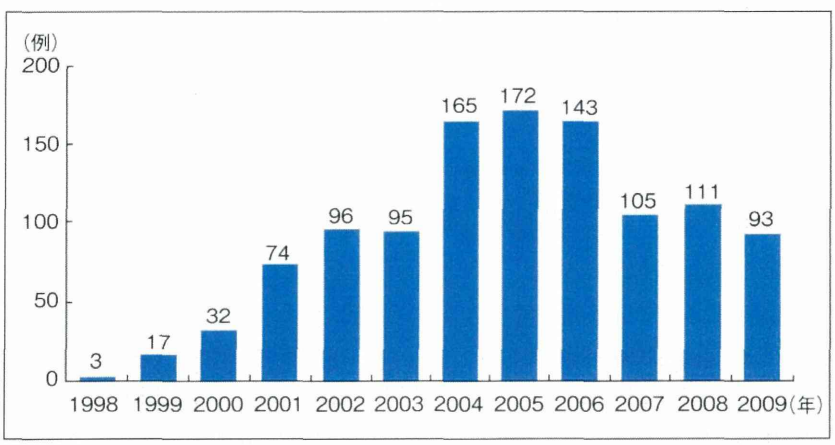

図2．わが国における肝細胞癌に対する生体肝移植数の年次推移
文献3)より引用

例の平均年齢は56歳で，男女比は2.6対1と男性優位であった。原因はHBV 327例(29.6％)，HCV 660例(59.7％)，その他100例とされ，圧倒的にHCV陽性肝細胞癌が多数を占めていた。

併存する肝疾患の肝障害度はA，B，Cそれぞれ121例，372例，553例と肝障害が進行した病変を有する肝細胞癌が肝移植を受けていたことが理解される。

さらに，model for end-stage liver disease(MELD)スコアを検討すると，その平均は13.0であり，短期死亡予測は比較的低率の状態で肝移植を受けていたようである。

ここで問題となる適応基準に関してはミラノ基準内が605例(54.7％)，基準外が501例(45.3％)と予想を覆してミラノ基準外の症例が多いことが特徴的であった。これは後述するが，わが国の移植施設が独自の適応基準で生体肝移植を実施し，必ずしも保険適応内での実施でないことを示すものである。

生体肝移植の肝細胞癌の生存率(図3)[3]

Kaplan-Meier法による肝細胞癌に対する生体肝移植の累積生存率を図3[3]に示す。1,106例の成績は1年，3年，5年，10年生存率はそれぞれ84.9％，74.2％，69.0％，61.0％であり，2009年の末時点で705例の生存をみている。さらに無再発生存率を検討してみると1年，3年，5年，10年無再発生存率はそれぞれ80.2％，68.7％，64.5％，56.7％であった。そして肝細胞癌の再発を検討すると，1年，3年，5年，10年再発率は8.0％，15.7％，17.7％，19.7％であった。

死亡例の検討(図4)[4]

それぞれの死亡原因を検討してみると，3ヵ月以内の死亡例76例では感染症と技術的な側面からの死亡例が多くを占め，再発例はほんの数例であった。1年以降の死亡例では肝細胞癌の再発が最大の因子となり，その年次推移は図4[4]で示す。

累積死亡例は363例であり，そのうち再発例が126例(34.7％)，次いで感染症78例(21.5％)，原因不明が73例(20.1％)とこれらが三大死因で，残りはHCVによる肝障害の進行やアルコール再飲酒による原疾患の再発による肝障害が挙げられている。そして，21例の拒絶を認

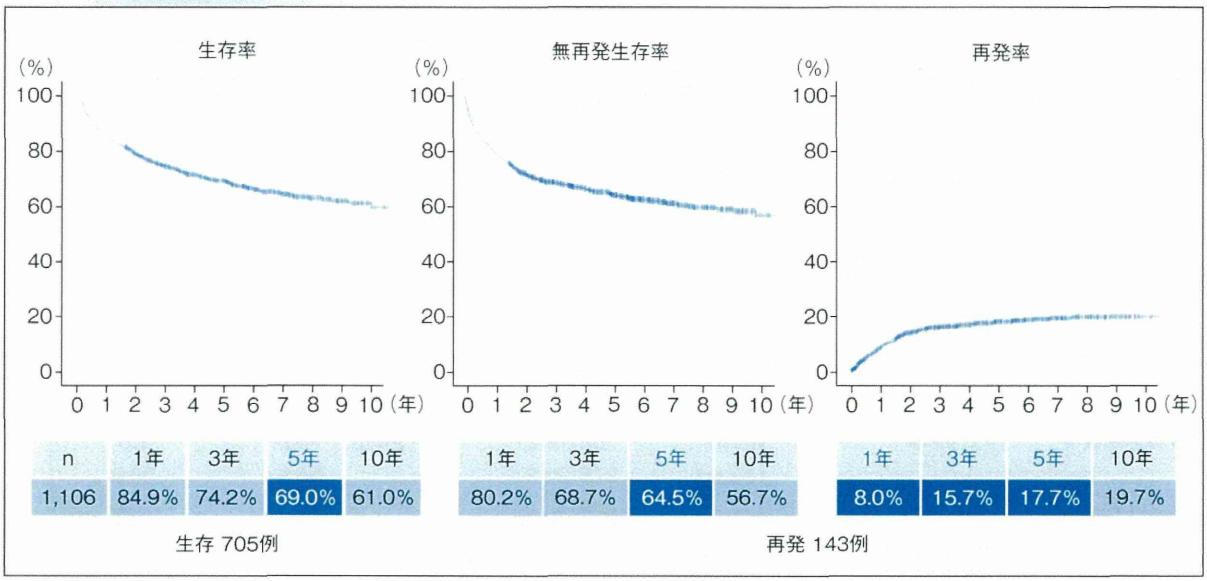

図3．わが国における肝細胞癌に対する生体肝移植の累積生存率，無再発生存率ならびに累積再発率（Kaplan-Meier法）

文献3）より引用

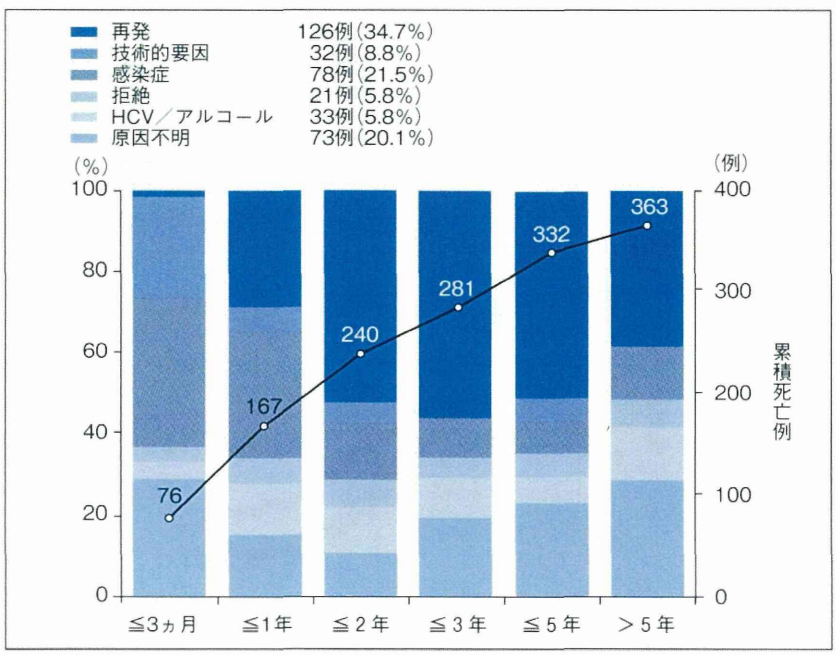

図4．生体肝移植後の死亡時期と死亡原因の内訳と頻度

文献4）より引用

めるのは，推測の域を脱し得ないが肝細胞癌の再発により免疫抑制剤を減量もしくはオフにすることによるものと考えることができる。

さらに，技術的な要因でグラフトロスをきたしているのは多分に胆管合併症が年余にわたって継続し，進行性の二次性胆汁うっ滞性肝硬変に進行することも考えられる。

各適応基準別成績

肝細胞癌に対する肝移植の適応基準は現在ミラノ基準がgolden standardとして用いられ，事実わが国の保険診療の肝細胞癌の適応基準にも用いられている。このミラノ基準に関する再検討が同じ筆者から15年間の論文を調査しMeta-Analysisで検討され，ミラノ基準逸脱の生存に寄与するハザード比1.76の脳死肝移植，同1.28の生体肝移植とされ，ミラノ基準を逸脱してもそれほど生存率のハザード比が高くないことが判明した[7]。このことはミラノ基準を逸脱してもその生存率が50%を超える臨床的事実から腫瘍の大きさや個数に関してわが国はもとより海外からミラノ基準を超える新しい基準が設定されることの妥当性を生み，事実，それぞれの成績を示し，その有用性を論じ，多くの患者に肝移植を受ける

表1．各施設における肝細胞癌に対する肝移植の適応基準別累積 5 年生存率と再発率

適応基準			n (%)		5年生存率 (%)	5年再発率 (%)
ミラノ基準	単発，＜5 cm	within	571 (55.6)		77.5	4.5
	n＜3，s＜3 cm	beyond	456 (44.4)		61.6	30.9
Up Seven 基準	n+size (cm)＜7	within	707 (68.9)	13.3	76.8	6.4
		beyond	320 (31.1)		56.8	38.1
Asan大学基準	n＜6，s＜5 cm	within	783 (76.2)		75.5	8.0
	Vp0 or Vp1	beyond	244 (23.8)*		54.7	42.0
京都大学基準	n＜10, s＜5 cm	within	776 (76.3)		75.2	9.0
	PIVKA-Ⅱ＜400IU/L	beyond	239 (23.7)*		55.6	39.5
東京大学基準	5×5 rule	within	752 (73.2)	24.3	75.9	7.8
		beyond	275 (26.8)*		55.9	38.9
九州大学基準	s＜5 cm	within	811 (79.9)		73.7	10.3
	PIVKA-Ⅱ＜300IU/L	beyond	204 (20.1)*		57.8	39.2

＊：p<0.05 vs. ミラノ基準，除外＞Vp2

文献 3）より引用

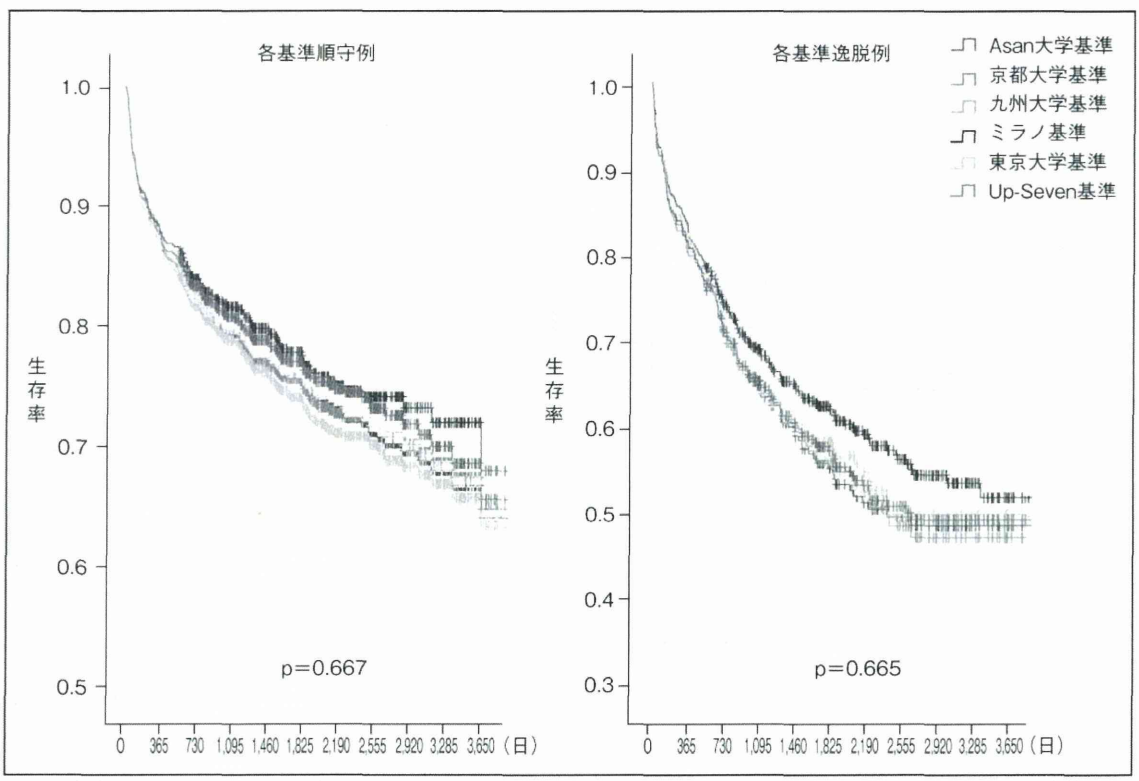

図5．各施設における肝細胞癌に対する肝移植の適応基準別累積生存率
（巻頭カラーグラビア p. 6 参照）

左：適応内症例，右：適応逸脱症例
文献 3）より引用