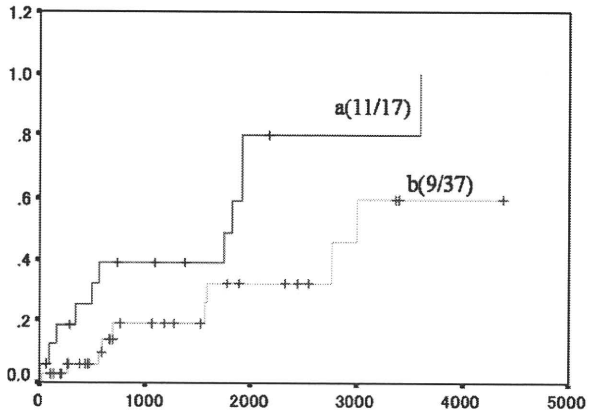

Fig. 3. Comparison of the cumulative bleeding rates of patients with reversed or "to and fro" SV flow and with forward SV flow. The cumulative bleeding rate at 3 and 5 years was significantly higher in patients with reversed or "to and fro" SV flow (38.8% at 3 years, 59.2% at 5 years) than in patients with forward SV flow (18.7% at 3 years, 32.2% at 5 years, $p = 0.0199$). a, patients with reversed or "to and fro" SV flow; b, patients with forward SV flow. SV, splenic vein.

3. Results

3.1. Hemodynamics of SGV in relation to the bleeding FV

Diameter, flow velocity and flow volume of SGV were significantly greater in bleeders (9.6 ± 3.1 mm, 11.4 ± 5.2 cm/s, 499 ± 250.1 ml/min) than non-bleeders (6.5 ± 2.2 mm, $p = 0.0141$; 7.9 ± 3.3 cm/s, $p = 0.022$; 205 ± 129.1 ml/min, $p = 0.0031$) at the latest observation. There were no significant differences of stratification of age and sex, Child-Pugh scoring, and endoscopic variceal size of FV between bleeders and non-bleeders. Inter-observer variability for the measurement results of SGV was 6.1% for diameter, 8.1% for flow velocity and 9.5% for flow volume in 14 patients.

3.2. Flow direction of SV in relation to the bleeding FV

SV had forward flow in 40 (74%), "to and fro" in 1 (1.9%) and reversed flow in 13 patients (24.1%) at the beginning of the observation. As the flow direction changed in three patients, from forward flow to "to and fro" in two patients and from forward flow to reversed flow in one patient, SV showed forward flow in 37 (68.5%), "to and fro" in 3 (5.6%) and reversed flow in 14 patients (25.9%) at the latest observation. None had reversed flow direction in the portal trunk during the clinical course. The frequency of FV bleeding was significantly higher in case with reversed or "to and fro" SV flow (11/17) than in case with forward SV flow (9/37, $p = 0.0043$, Table 1). Diameter, flow velocity and flow volume of SGV were significantly greater in patients with reversed SV flow (10.6 ± 4.4 mm, 13.1 ± 5.1 cm/s, 599 ± 388.9 ml/min) than in patients with forward SV flow (7.2 ± 2.4 mm, $p = 0.0018$; 8.8 ± 4.1 cm/s, $p < 0.0001$; 255.6 ± 171.9 ml/min, $p < 0.0001$). The cumulative bleeding rate at 3 and 5 years was significantly higher in patients with reversed or "to and fro" SV flow (38.8% at 3 years, 59.2% at 5 years) than in patients with forward SV flow (18.7% at 3 years, 32.2% at 5 years, $p = 0.0199$, Figs. 2, 3).

4. Discussion

The portal hemodynamics of patients with FV are quite different from those of patients with EV, the former being characterized by having dominant blood supply from SGV and/or PGV [11–14]. From this aspect, we investigated the blood flow in the SGV in patients with FV using Doppler US, which allowed the sufficient inter-observer variability of the measurement results. As diameter, flow velocity and flow volume of SGV were significantly greater in bleeders than in non-bleeders, it may be suggested that the hemodynamics of SGV on Doppler US were closely related to FV bleeding in patients with SGV as inflow vessel.

We also focused on another aspect, a flow direction of SV, and found that FV bleeding was significantly more frequent in patients without forward SV flow than in patients with forward SV flow. Furthermore, diameter, flow velocity and flow volume of SGV were significantly greater in reversed SV cases than in forward SV cases. Thus, reversed SV flow may reflect the presence of advanced blood supply from SGV into FV, and this may be supported by the fact that reversed SV flow was more common in patients with large gastric varices accompanied by chronic portal systemic encephalopathy [13]. Meanwhile, Kim et al. reported that the cumulative bleeding rate of FV was 16% at 1 year, 36% at 3 years, and 44% at 5 years [7], and other studies found bleeding from FV in 23.4% [5], and 25% [4]. However, the FV patients with reversed SV flow in the present study had quite a high risk of bleeding, the cumulative bleeding rate at 3 and 5 years being 38.8% and 59.2%, respectively. Therefore, reversed SV flow demonstrated by Doppler US may be a considerable risky sign for FV bleeding, and hemodynamic evaluation of SGV and SV by Doppler US might be predictive for FV bleeding.

Three patients had a "to and fro" appearance of SV, two patients of which flow direction changed from forward to "to and fro" being bleeders and the other being a non-bleeder. Although the precise mechanism for this flow direction is not clear, the authors have two hypotheses; one is that "to and fro" is a tentative flow direction in the process of change from forward SV flow to reversed SV flow, and the other is that "to and fro" is caused by fewer gradients between portal venous pressure and systemic venous pressure. The former may indicate risky sign, whereas the latter may indicate non-risky sign, though we could not conclude at this time. Further studies should be planed to examine the relationship between SV flow direction and portal venous pressure. Moreover, long-term follow-up with larger numbers of patients might clarify the clinical meaning of this "to and fro" appearance of SV blood flow.

There were three cases of which SV flow direction changed in the clinical course, from forward flow to "to and fro" or reversed flow. It should be noted that one of them bled 25 days after the observation of blood flow change on Doppler US. Repeated observation of portal hemodynamics is the advantage of Doppler US method, and our results suggest that change of flow direction in the SV might also be a risky sign for FV bleeding. An appropriate interval for US examination should be established to practice careful follow-up such FV patients.

Gastrorenal shunt is known as a major drainage pathway from FV and recent study has shown that its hemodynamics may reflect the grading and bleeding FV [13,21]. In fact, blood flow in the FV may be aggregated in this gastrorenal shunt because some FV have multiple inflow routes other than SGV. Our results based on the observation of SGV blood flow alone may be insufficient for the clinical management of all FV. Meanwhile, gastrorenal shunt might include blood flow derived from normal gastric wall other than FV. Further studies may be necessary to measure inflow routes against outflow routes as the preferable parameter reflecting FV bleeding.

There are certain limitations to the present study. First, our results were based on a retrospective study, and the interval of US examinations was not strictly defined in each patient. Practical role of the hemodynamic evaluation of SGV and SV on Doppler US for the management of FV bleeding should be elucidated in a prospective study. Next, our data did not include small-sized FV, because they might have low risk of bleeding. However, changes in the hemodynamics of SGV during the long-term clinical course of small-sized FV would also be an interesting aspect deserving attention in such a study. Third, our results lacked the information of the

intra-observer variability for measurement results in the SGV. Correspondence of the data of the different date in all subjects may not make sense, because this study had some emergent cases that might have dynamic changes in hemodynamics. However, this variance should be examined in the further studies.

In conclusion, advanced SGV blood flow and reversed SV flow direction may be a hemodynamic features closely related to the FV bleeding. Although, prospective study with a larger population of FV patient may be needed to confirm the clinical significance of our method, evaluation of the hemodynamics in the SGV and SV by Doppler US might be useful for predicting FV bleeding.

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B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Knowledge of *Vibrio vulnificus* infection among Japanese patients with liver diseases: A prospective multicenter study

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Summary

Background: *Vibrio vulnificus* (*V. vulnificus*) is a seafood-borne infectious pathogen that can be lethal to humans. The infection has been correlated with pre-existing liver disease, particularly liver cirrhosis. Awareness of *V. vulnificus* infection among Japanese citizens is low, despite the increasing number of patients with hepatocellular carcinoma (HCC). The present study was conducted to assess the level of knowledge of patients with liver disease regarding *V. vulnificus* infection.

Material/Methods: Questionnaires were sent to patients with chronic liver disease who had been treated by liver specialists at 14 medical institutes.

Results: Of 1,336 patients, 304 (22.8%) had liver cirrhosis, and 732 (54.8%) had comorbidities of this disease. Only 14.5% (194/1,336) of patients had knowledge of *V. vulnificus* infection. Of 304 patients with liver cirrhosis, 17.4% (53/304) of the patients had knowledge of *V. vulnificus* infection. Of 60 patients with liver cirrhosis and diabetes mellitus, 11 (18.3%) patients had knowledge of *V. vulnificus* infections. Even when the patients with high risk factors such as liver cirrhosis and diabetes mellitus had knowledge of *V. vulnificus* infections, most ate raw seafood without regard to season.

Conclusions: Patients with chronic liver diseases and their physicians need to be better educated about *V. vulnificus* infection and its prevention.

key words: ***Vibrio vulnificus*** • **liver diseases** • **hepatitis C virus (HCV)** • **hepatocellular carcinoma (HCC)**

Abbreviations: ***V. vulnificus*** – *Vibrio vulnificus*; **HCV** – Hepatitis C virus; **HBV** – Hepatitis B virus; **HCC** – Hepatocellular carcinoma; **PBC** – primary biliary cirrhosis; **AIH** – autoimmune hepatitis; **ICD** – International Classification of Diseases

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Background

Vibrio vulnificus (*V. vulnificus*), a gram-negative bacterium of the family *Vibrionaceae*, is a worldwide inhabitant of salt water [1,2]. These bacteria tend to be more common in warmer waters (17–20°C) [3,4]. *V. vulnificus* causes serious illness including necrotizing fasciitis and septicemia, and death in persons with preexisting liver disease or compromised immune systems [5–7]. People with chronic liver disease, particularly liver cirrhosis, are more prone to developing infection, and are at greatest risk for an adverse outcome [8,9]. Other predisposing factors are iron overload and hemochromatosis, and immunosuppression caused by steroid treatment, malignancy, human immunodeficiency virus (HIV) infection, renal failure and organ transplantation [10,11].

V. vulnificus infection was first reported by Roland in 1970 in a case of endotoxic shock with leg gangrene [12]. In Japan, Matsuo et al. reported the first case of *V. vulnificus* infection in 1978 [13]. There have since been case reports of approximately 200 patients over a period of about 30 years [14]. However, because the 200 cases represent only those that were published, the actual number of *V. vulnificus* infections is considered to be higher [14]. The annual number of *V. vulnificus* septicaemia cases in Japan has been estimated at 425 (95% CI 238–752) [15]. The prevalence of *V. vulnificus* septicaemia is estimated at 3.3 per million in Japan. The annual number of *V. vulnificus* infection in Japan is notably higher than in other countries, such as Korea and the USA [15]. The prevalence of *V. vulnificus* septicaemia is low in the general population, and estimated at 0.6 per million in USA [8]. A study of the epidemiological and clinical characteristics of *V. vulnificus* infections reported in Japan from 1975 to 2005 [14] found that about 90% of Japanese patients with *V. vulnificus* infection had liver disease such as liver cirrhosis, hepatocellular carcinoma (HCC), and chronic hepatitis.

It is estimated that approximately 2 million Japanese people are chronically infected with hepatitis C virus (HCV) [16]. Approximately 35,000 patients died due to HCC in Japan, and the number of deaths in Japan from HCC continues to increase. In Japan, approximately 80% of HCCs are caused by HCV and about 10% by hepatitis B virus (HBV). The increase in the number of HCC patients due to HCV in turn contributes to the increase in the number of deaths in Japan from HCC.

In Japan, patients with liver disease are not provided adequate educational opportunities. Therefore, in this study, we assessed knowledge about *V. vulnificus* infection in patients with chronic liver disease.

Material and Methods

Subjects

Between August 1, 2008 and October 31, 2008, anonymous questionnaires relating to general knowledge of *V. vulnificus* infections were given to all patients with chronic liver diseases who had been treated at 14 geographically-distinct institutions in Japan, as well as to their attending physicians. A physician at each participating institution completed a questionnaire with the patient's medical information and handed the questionnaire to the patient. Next the patient was interviewed about *V. vulnificus* infection. The questionnaire was conducted in one-to-one interview style by patient and physician. A physician at each medical institution returned the completed questionnaires to Kurume University of Medicine; 1,336 completed questionnaires were recovered, and the collection rate was 97.3% (1,336/1,373). The 14 medical organizations were those where many liver specialists authorized by the Japan Association for the Study of the Liver work full-time.

We mailed questionnaires directly to these 14 medical institutions through a collaborative study. A database for the results of our investigation was compiled at the Department of Digestive Disease Information & Research, Kurume University School of Medicine.

Items of investigation

Anonymous questionnaires asked patients and their attending physicians to respond to the following items; patient background (age, gender, diagnosis of liver diseases, comorbidities, and steroid use), patient awareness and understanding of *V. vulnificus* infection, frequency of eating raw fish and shellfish, raw shrimp and sushi, the season in which raw fish was eaten, and frequency of bathing in the sea and shellfish gathering. After the patients answered the questionnaires, we provided them with literature containing basic information about *V. vulnificus* infection.

The investigation was conducted in accordance with the "ethical guidelines on epidemiological studies" of the Ministry of Education and Science and the Ministry of Health, Labour and Welfare, and observed the spirit of the Helsinki Declaration. Physicians at study facilities explained to patients the content and significance of the study and obtained consent in accordance with each facility's regulations.

Statistical analysis

All data are expressed as mean ± standard error. Differences between the 2 groups were analyzed using the Welch's test and the Mann-Whitney U test. Differences were judged significant for $p<0.05$ (2-tailed). All statistical analyses were conducted using JMP Version 6 (SAS Institute, Cary, NC, USA).

Results

Patient's background

We analyzed 1,336 questionnaires in which 656 indicated they were males, 670 females, and 10 did not specify gender. Mean age was 61.4±12.3, as shown in Table 1.

Among the 1,336 patients, the distribution of diagnoses of liver disease was as follows: HCV-related liver diseases 760 (56.9%), HBV-related liver diseases 266 (19.9%), HCV & HBV-related liver diseases (simultaneous infection) 4 (0.3%), non-B non-C-related liver diseases 19 (1.4%), other liver diseases 273 (20.4%), and no answer 14 (1.0%). Some institutions differed significantly in patients' age, gender distribution, or liver diseases, compared to the overall averages (Table 1).

Table 1. Clinical information for 1,336 patients from whom questionnaires returned.

Prefecture	Medical institution	n	Collection rate of questionnaire	Age			Sex				Liver diseases													
				Mean	SD	P value	Male	Female	No answer	P value	HCV-related liver disease		HBV-related liver disease		HCV & HBV-related liver disease		NBNC-related liver disease		The other		No answer		P value
			(%)	year			n	n	n		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Hokkaido	Sapporo Medical University School of Medicine	100	(100.0)	59.4	13.4	NS	44	55	1	NS	48	(48.0)	27	(27.0)	0	(0.0)	4	(4.0)	19	(19.0)	2	(2.0)	NS
Fukushima	Fukushima Medical University School of Medicine	97	(97.0)	63.6	12.2	NS	38	52	7	NS	42	(43.3)	12	(12.4)	0	(0.0)	2	(2.1)	34	(35.1)	7	(7.2)	<0.05
Chiba	Chiba University Graduate School of Medicine	97	(97.0)	58.8	13.5	NS	47	50	0	NS	63	(65.0)	15	(15.5)	0	(0.0)	1	(1.0)	18	(18.6)	0	(0.0)	NS
Shizuoka	ELM Medical Clinic	100	(100.0)	57.2	12.2	0.001	71	29	0	<0.0001	38	(38.0)	36	(36.0)	0	(0.0)	0	(0.0)	26	(26.0)	0	(0.0)	<0.001
	Miyazaki Clinic	100	(100.0)	51.0	15.3	<0.000000001	53	47	0	NS	40	(40.0)	37	(37.0)	0	(0.0)	0	(0.0)	23	(23.0)	0	(0.0)	<0.001
Aichi	Social Insurance Chukyo Hospital	100	(100.0)	61.4	14.1	NS	44	55	1	NS	59	(59.0)	14	(14.0)	0	(0.0)	1	(1.0)	25	(25.0)	1	(1.0)	NS
Fukuoka	Kurume University School of Medicine	213	(100.0)	60.6	11.6	NS	86	127	0	0.01	135	(63.4)	38	(17.8)	0	(0.0)	1	(0.5)	39	(18.3)	0	(0.0)	NS
Saga	Inuzuka Hospital	100	(100.0)	64.4	11.0	<0.05	47	52	1	NS	85	(85.0)	6	(6.0)	1	(1.0)	0	(0.0)	8	(8.0)	0	(0.0)	<0.00001
Nagasaki	Narao Hospital	122	(81.3)	66.5	10.8	<0.00001	68	54	0	NS	71	(58.2)	42	(34.4)	0	(0.0)	1	(0.8)	7	(5.7)	1	(0.8)	<0.0001
	National Nagasaki Medical Center	59	(98.3)	64.5	10.5	NS	29	30	0	NS	47	(79.7)	6	(10.2)	1	(1.7)	0	(0.0)	5	(8.5)	0	(0.0)	<0.01
Oita	Oita University	100	(100.0)	59.6	13.4	NS	41	59	0	NS	53	(53.0)	16	(16.0)	2	(2.0)	3	(3.0)	25	(25.0)	1	(1.00	<0.05
	National Hospital Organization Oita Medical Center	48	(96.0)	64.9	12.5	<0.05	23	25	0	NS	31	(64.6)	8	(16.7)	0	(0.0)	4	(8.3)	4	(8.3)	1	(2.1)	0,001
	Oita Cardiovascular Hospital	50	(100.0)	67.0	10.9	<0.001	29	21	0	NS	36	(72.0)	8	(16.0)	0	(0.0)	2	(4.0)	4	(8.0)	0	(0.0)	NS
	Abe Diabetes Clinic	50	(100.0)	62.0	10.6	NS	36	14	0	0.001	12	(24.0)	1	(2.0)	0	(0.0)	0	(0.0)	36	(72.0)	1	(2.0)	<0.00000000000001
Total		1336	(97.3)	61.4	12.3		656	670	10		760	(56.9)	266	(19.9)	4	(0.3)	19	(1.4)	273	(20.4)	14	(1.0)	

Liver cirrhosis was observed in 304 (22.8%) patients, including those with HCV-related liver cirrhosis (177 cases), HBV-related liver cirrhosis (66), HCV & HBV-related liver cirrhosis (1), non-B non-C-related liver cirrhosis (11), and other liver diseases such as primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH) (49).

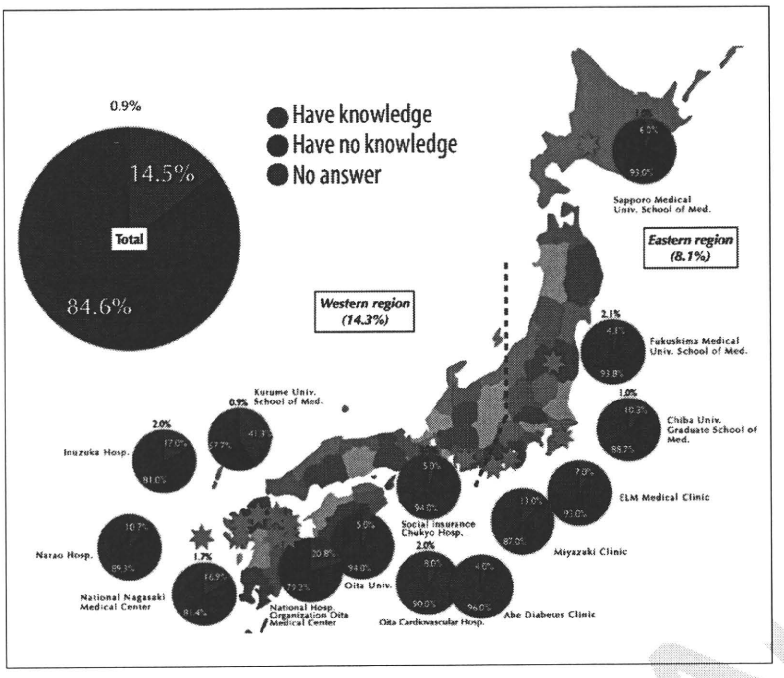

Figure 1. Knowledge of *V. vulnificus* infections among all patients with liver diseases. Only 14.5% of such patients had knowledge of this infection. Fourteen red stars indicate the location of each medical institution. Japan consists of 47 prefectures. Half of east of Japan, including Tokyo, where Japan is metropolitan, is called eastern Japan, and the western half of Japan is called western Japan. The broken line indicates the boundary between the 2 areas.

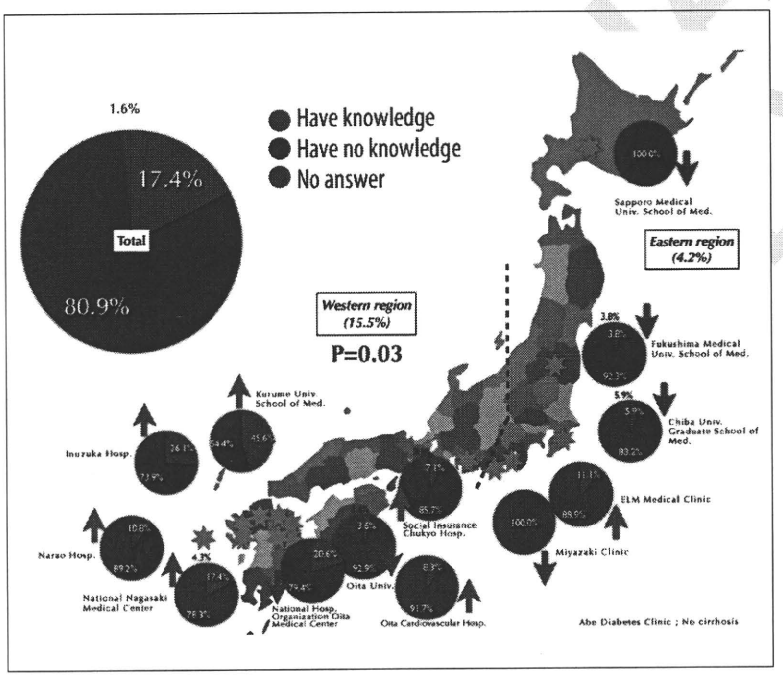

Figure 2. Knowledge of *V. vulnificus* infections in patients with liver cirrhosis. The rate of patient knowledge in the western region of Japan was significantly higher than in the eastern region. The upward pointing arrow indicates an increase in the rate of *V. vulnificus* infections in a given institution compared to Figure 1. A down-pointing arrow indicates a decrease compared to Figure 1.

There were associated comorbidities in 732 (54.8%) of all patients with liver disease. These were classified using International Classification of Diseases (ICD) criteria: diseases of the circulatory system (372 cases), endocrine, nutritional and metabolic diseases (316), diseases of the digestive system (73), malignant neoplasms (54), diseases of the genitourinary system (33), diseases of the nervous system (23), diseases of the musculoskeletal system and connective tissue (18), diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (17), diseases of the respiratory system (16), mental and behavioral disorders (7), diseases of the skin and subcutaneous tissue (4), diseases of the eye and adnexa (4), certain infectious and parasitic diseases (2), and other diseases (6).

There were 563 patients (42.1%) with no comorbidities, 40 patients provided no answer about comorbidities, and 1 patient was unassessable. There were 60 patients who took oral or topical steroids for their liver disease or comorbidities.

Knowledge of *V. vulnificus* infection in patients with liver diseases

Only 14.5% (194/1,336) of patients with liver disease had general knowledge regarding *V. vulnificus* infections. The level of patient knowledge varied widely among medical institutes, ranging from 4.0% to 41.3%. The mean rate (14.3%) of knowledge among patients who resided in the western re-

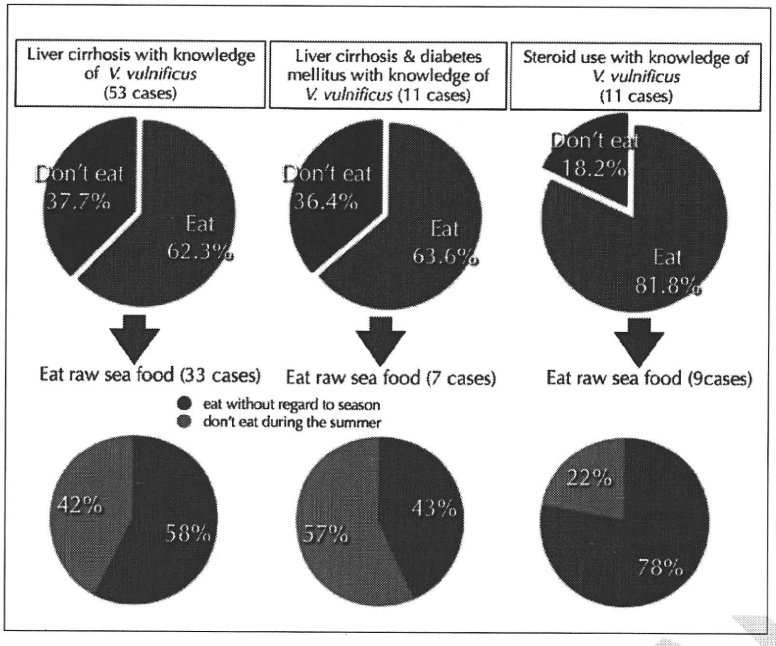

Figure 3. Frequency of eating raw seafood. Even if patients had high risk factors for infection, such as liver cirrhosis, diabetes mellitus, or steroid use, and had knowledge of *V. vulnificus* infections, most ate raw seafood without regard to season.

gion of Japan was higher than that (8.1%) in the eastern region (Figure 1).

Of 304 patients with liver cirrhosis, 17.4% (53/304) (minimum 0%, maximum 45.6%) had knowledge of *V. vulnificus* infection (Figure 2). This rate (17.4%) was higher than the mean rate (14.5%) of knowledge among all patients with liver diseases, but the proportion of those with knowledge was lower in 6 institutes. The rate (15.5%) of knowledge of *V. vulnificus* infection among those with liver cirrhosis in the western region was significantly higher than those (4.2%) in the eastern region (P=0.03).

Knowledge of *V. vulnificus* infection among patients with liver cirrhosis and diabetes mellitus

Sixty patients had liver cirrhosis and diabetes mellitus. Of these, 11 (18.3%) had knowledge of *V. vunificus* infections. Patients with liver cirrhosis and diabetes mellitus in 7 institutes had no knowledge of the infection.

Frequency of intake of raw seafood

A total 1,170 (87.6%) of 1,336 patients answered that they often eat raw seafood. Most (1,002 cases, 85.6%) of the patients answered that they eat raw seafood without regard to season. There was significant difference between patients with knowledge and without knowledge who eat raw seafood (P<0.00001).

Thirty-three of 53 patients who suffered from liver cirrhosis and who had knowledge of *V. vulnificus* infection ate raw seafood (19 cases ate raw seafood without regard to season; 14 did not eat raw seafood during the summer). Seven of 11 patients, who suffered from liver cirrhosis and diabetes mellitus and with knowledge of *V. vulnificus* infection, ate raw seafood (3 cases ate raw seafood without regard to season; 4 cases did not eat raw seafood during the summer). Nine of 11 patients who took steroids and who had knowledge of *V. vulnificus* infection ate raw seafood (7 cases ate raw seafood without regard to season, 2 cases did not eat raw seafood during the summer).

In these cases, even if patients with high risk factors, such as liver cirrhosis and diabetes mellitus, had knowledge of *V. vulnificus* infections, most ate raw seafood without regard to season (Figure 3). However, the rate of the patients with liver cirrhosis who did not eat raw seafood and who had knowledge was significantly lower than that of the patients with liver cirrhosis and without knowledge who did not eat raw seafood (37.7% vs. 14.8%, P=0.0001).

Frequency of bathing in the sea and shellfish gathering

The results of the patients who answered questionnaires about bathing in the sea and shellfish gathering were as follows: often (18 cases, 1.3%), sometimes (122, 9.1%), rarely (394, 29.5%), never (768, 57.5%), unassessable (4, 0.3%), and no answer (30, 2.2%). Most of the patients does not swim in the sea and did not go clamming.

Discussion

V. vulnificus causes severe human infections, and is acquired through wounds or contaminated seafood. In Japan, many cases of *V. vulnificus* infection have been reported to occur in the western region and more than half of the infections were reported to occur in Kyusyu [14,17]. Inoue et al. did a retrospective survey in which 1,693 hospitals from across Japan were surveyed, including advanced life saving emergency centers and dermatology institutions [17]. Ninety-four cases were confirmed as *V. vulnificus* infections over 5 years. The authors reported that many *V. vulnificus* infections occurred in Kyusyu, especially in the coastal areas of the Ariake and Yatsushiro Seas.

One reason for the high incidence of *V. vulnificus* infection in the western region in Japan is thought to be higher seawater temperature. *V. vulnificus* proliferates in areas where, or during months when, the water temperature exceeds

17–20°C [3,4]. The other reason is the greater number of HCV carriers in Kyusyu. Geographically, HCC is more frequent in western than eastern Japan [16].

The awareness of *V. vulnificus* infections among Japanese physicians is reported to be low [15]. Only 15.7% of emergency-physicians were reported to have a basic knowledge of *V. vulnificus* infections. In 2004, Osaka et al. reported that emergency-room physicians who work in the western region of Japan had more knowledge of *V. vulnificus* infections [15]. The Ministry of Health, Labour and Welfare warned of the risk of *V. vulnificus* infection on their website in 2006.

Our study demonstrates that awareness of *vulnificus* infections among patients with chronic liver diseases is low. Medical institutions in Japan, except for Kurume University of Medicine, did not provide educational opportunities for learning about *V. vulnificus* infections. Although the 15.5% rate of knowledge among patients with liver cirrhosis in the western region was significantly higher than that in the eastern region (P=0.03), this rate is far from adequate.

The most significant host factor contributing to virulence is chronic liver disease [8,9]. This may act in several ways including: portal hypertension, causing shunting of the bacteria around reticuloendothelial cells in the liver [18,19]; decreased clearance of bacteria from the portal circulation by Kupffer's cells in the diseased liver [19]; increased iron in the serum, as seen in patients with cirrhosis and hemochromatosis, which promotes growth of *V. vunificus* [7,20]; and achlorhydria occurring naturally or induced by medications [8,19,21].

Factors conferring high risk include: liver disease and other diseases with possible hepatic involvement or elevated serum iron levels (including cirrhosis, alcoholism, malignancy, hemochromatosis, or thalassemia major) [8,9,19,20]; therapeutically induced or naturally low gastric acid (achlorhydria or antacid or H2 blocker use) [8,19,21]; and conditions that compromise the immune system (HIV infection, diabetes mellitus, renal disease, or steroid dependency) [10,11,19].

Primary liver cancer, 95% of which is HCC, is ranked third among men and fifth among women as a cause of death from malignant neoplasms in Japan [22,23]. The number of deaths and death rate of HCC has been increasing. Geographically, HCC is more frequent in western than eastern Japan. Meanwhile, according to the Ministry of Internal Affairs and Communications, yearly per capita fish consumption in Japan was 63.2 kilograms on average for 2003–2005, about 4 times higher than the world average. The Japanese custom of eating raw fish and shellfish such as sashimi or sushi has become widely known throughout the world. Their traditional eating habits are attributed to the fact that patients with knowledge about *V. vulnificus* infections still ate raw seafood.

Therefore, it is important for physicians in Japan to expand their knowledge of *V. vulnificus* infections and become familiar with prevention methods. It is also important for patients with liver diseases to acquire the necessary knowledge of *V. vulnificus* infections and prevention methods, such as avoidance of eating raw seafood during the summer. Because of rapid aggravation and high mortality, patients should also keep an emergency contact number handy.

Conclusions

In conclusion, standardized guidelines for prevention of *V. vunificus* infections and education of patients with liver diseases should be required.

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High incidence of multiple primary carcinomas in HCV--infected patients with oral squamous cell carcinoma

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background: Hepatitis C virus (HCV) infection has been associated with several extrahepatic manifestations. Oral cancer is one of them. We investigated the association among oral squamous cell carcinoma (OSCC), multiple primary cancers (MPCs), insulin resistance and HCV infection.

Material/Methods: Upper gastrointestinal tract examination and determination of the presence of HCV infection were routinely done for 60 primary OSCC patients. Occurrence of MPCs was evaluated between 1992 and 2008.

Results: Of the 60 patients, 21 (35%: 15 males and 6 females; mean age 67.3±11.9 years) developed MPCs. Antibodies to HCV were found in 26.7% (16/60) of cases. The incidence of MPCs in HCV-infected OSCC cases was 62.5% (10/16 cases, $P<0.01$ vs the non-HCV-infected OSCC group); for cases without HCV infection it was 25% (11/44 cases). In HCV-infected cases, 10 MPCs with patients, hepatocellular carcinoma (HCC) was the most common outcome (5 cases), whereas gastric cancer was the most common outcome (6 cases) in non-HCV-infected 11 MPCs. In logistic regression analysis, the adjusted odds ratios on staging IV, anti-HCV positive, and over 70 years old were 15.50, 13.45, and 4.46, respectively, indicating that there were significant differences. Furthermore, the patients with HCV-infected MPCs had hyperinsulinemia.

Conclusions: HCV infection was strongly associated with the occurrence of MPCs as well as primary OSCC. HCV-infected OSCC patients in Japan should receive medical treatment to inhibit development of HCC. In patients with HCV infection, it is important to clinically examine organs other than the liver.

key words: **multiple primary cancers (MPCs) • oral squamous cell carcinoma (OSCC) • hepatitis C virus (HCV) • hepatocellular carcinoma (HCC) • lichen planus • insulin resistance • extrahepatic manifestations**

Abbreviations: **anti-HCV** – anti-bodies to HCV; **anti-HBc** – antibody to hepatitis B core antigen; **CLEIA** – chemiluminescent enzyme immunoassay; **HBsAg** – hepatitis B surface antigen; **HCC** – hepatocellular carcinoma; **HCV** – hepatitis C virus; **HOMA-IR** – homeostasis model assessment; **IFN** – interferon; **MPCs** – multiple primary cancers; **OSCC** – oral squamous cell carcinoma

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Background

The development of multiple primary cancers (MPCs) is frequently detected in patients with oral squamous cell carcinoma (OSCC). Patients with OSCC are at risk of developing second cancers or MPCs, particularly at sites within the upper digestive tract and airway [1,2]. Routine upper gastrointestinal panendoscopy identifies synchronous MPCs in 9–14% of patients [3].

In recent years in Japan, there has been an upward trend in MPCs in patients with head and neck cancer [4]. The reasons behind this are increases in carcinoma itself, progress in diagnostic techniques, improvements in treatment outcomes, and increased mean survival time.

Since 1981, malignant neoplasms have been the leading cause of death in Japan. During the past 20 years, primary liver cancer, 95% of which is hepatocellular carcinoma (HCC), has ranked third in men and fifth in women in Japan as the cause of death from malignant neoplasms [5]. The number of deaths from HCC is expected to increase by 2010–15 [6]. Of the HCC cases in Japan, ~16% are caused by hepatitis B virus (HBV) infection and~80% by hepatitis C virus (HCV) infection. The increase in incidence of HCC in Japan has largely been attributable to HCV infection. Geographically, HCC is more frequent in western than eastern Japan.

HCV infection has also been associated with extrahepatic manifestations and immune-mediated phenomena [7]. For example, HCV is associated with the development of OSCC. We reported for the first time an association between HCV and OSCC [8], and provided evidence, at the national level in Japan, for the high prevalence of HCV infection in patients with OSCC [9]. The subjects included 305 patients with OSCC and 276 patients with non-malignant disease (the control group) from five geographically-distinct institutions. The incidence of HCV infection in Japanese OSCC patients has been reported as 16.7–24.0% [8,9]. We also investigated the prevalence of HCV infection in oral cancer patients with MPCs [10]. Of 327 patients with OSCC, 59 (18.0%) exhibited MPCs. In the OSCC patients with MPCs, serum HCV antibodies (anti-HCV) and HCV RNA were detected in 36.7% and 28.6%, respectively [10].

Meanwhile, insulin resistance emerges as a very important host factor in patients with chronic hepatitis C. Hyperinsulinaemia is associated with accelerated HCC growth [11]. We concluded that HCV infection induces insulin resistance, which causes an increase in the incidence of extrahepatic manifestations such as lichen planus in HCV-infected individuals [12,13]. Lichen planus is an inflammatory disease of the skin and oral mucosa. The HCV infection rates in lichen planus patients are high especially in Japan [14]. Oral lichen planus should be considered as a precancerous lesion, particularly in patients presenting HCV infection [15]. Prevalence of smoking history, presence of hypertension, extrahepatic malignant tumor, and insulin resistance were significantly higher in 17 patients with lichen planus than in 70 patients without lichen planus [13].

In the current study, we surveyed the incidence of MPCs in OSCC patients with or without HCV infection and investigated the relationship between OSCC and insulin resistance.

Material and Methods

Subjects

This retrospective study included 60 primary OSCC patients who had visited our clinic at the Kurume University Hospital in Japan for the first time between November 1992 and December 1994. The 60 patients with OSCC included 39 males and 21 females. Their ages ranged from 32 to 85 years, with an average age of 64.8±13.7 years. These patients resided in the northern Kyushu region of Japan where the prevalence of HCV infection is the highest in the country [5,16]. The stages of OSCC were as follows; stage I (15 cases), II (24), III (6), and IV (15).

MPCs were identified according to the definition proposed by Warren and Gates: there must be histological evidence of malignancy in each tumor, they must be separated from each other by normal tissue, and one tumor must not be a metastasis of another [17]. Patients with multiple OSCCs were excluded from the study. MPCs detected <6 months after OSCC diagnosis were defined as synchronous; those detected >6 months after diagnosis were defined as metachronous [17].

Methods

Upper gastrointestinal tract examinations were routinely performed in all OSCC patients using an endoscope. This was done on the first visit or first day of medical treatment in order to confirm the presence of MPCs such as carcinomas of the larynx, pharynx, esophagus, and stomach regardless of whether symptoms were present.

Sera from all 60 OSCC patients were used for the following liver function tests at the time of the first visit to our hospital: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gammaglutamyl transpeptidase (γ-GTP), lactate dehydrogenase (LDH), total protein (TP), and albumin (Alb). Sera were also examined for the presence or absence of HCV or HBV infection. Anti-HCV antibodies and hepatitis B virus surface antigen (HBsAg) were measured by a chemiluminescent enzyme immunoassay (CLEIA) kit and a chemiluminescent immunoassay (CLIA), respectively. In 59 of 60 patients, HCV RNA in serum was detected using the Amplicore HCV test. In 58 of 60 patients, antibody to hepatitis B core antigen (anti-HBc) was found using a CLEIA kit. Ultrasonographic examination for all subjects was performed in order to examine the shape of the liver and lesions occupying the liver. Computed tomography and liver biopsy were performed in some patients.

Plasma glucose levels were measured by a glucose oxidase method for all subjects and serum insulin levels were measured using a sandwich enzyme immuno assay kit (EIKEN CHEMICAL, Tokyo, Japan). Insulin resistance was calculated on the basis of fasting levels of plasma glucose and insulin, according to the homeostasis model assessment (HOMA-IR) method [18]. The formula for the HOMA-IR is: HOMA-IR = fasting glucose (mg/dL) × fasting insulin (μU/mL)/405.

Their district, a history of liver dysfunction, blood transfusion, alcohol consumption, and smoking at the time of the first medical examination were collected as background information; OSCC was based upon their medical record cards.

Table 1. Incidence difference of MPCs depend on the presence or absence of HCV infection.

		Anti-HCV negative n=44 (%)		Anti-HCV positive n=16 (%)		P value A versus B
Age	Mean (year) ±SD	64.3±14.5		66.1±11.0		NS
Sex	Male	30	(68.2)	9	(56.2)	NS
	Female	14	(31.8)	7	(43.8)	
MPCs	Number	11	(25.0)	10	(62.5)	p<0.01
	Primary oral SCC					
	Tongue	2	(18.2)	6	(60.0)	
	Gingiva	5	(45.5)	3	(30.0)	
	Buccal mucosa	2	(18.2)	0	(0.0)	
	Sinus	1	(9.1)	0	(0.0)	
	Oropharynx	1	(9.1)	1	(10.0)	
	Number of MPCs					
	Double		(81.8)	10	(100.0)	
	Triple		(9.1)	0	(0.0)	
	Quadruple		(9.1)	0	(0.0)	
	Organ of MPCs	Stomach	6	Liver	5	
		Esophagus	2	Colon	2	
		Skin	2	Lung	1	
		Thyroid	1	Throid	1	
		Pharynx	1	Bone marrow*	1	
		Kidney	1			
		Liver	1			
		Total	14	Total	10	
	Occurrence time					
	Synchronus		6		5	
	Metachronus		6**		5	

* Acute myeloid leukemia (AML); ** One patient with quadruple cancer had cancer of the gingiva-esophagus (synchronous)-skin (synchronous)-hypopharynx (metachronous). SD – standard deviation; NS – no significance.

We observed the occurrence of MPCs from the first medical examination day to the last check-up day or nearest day preceding October 17, 2008. MPCs were diagnosed based on histopathology by the pathology laboratory which collected samples from all other medical departments of our hospital; or the diagnosis was made at other medical institutions.

Furthermore, the 60 patients whom we followed were divided into four groups: (i) MPCs with HCV infection, (ii) MPCs without HCV infection, (iii) non-MPCs with HCV infection, (iv) non-MPCs without HCV infection. We examined insulin resistance in these four groups.

Statistical analysis

All data are expressed as mean ± standard error. Differences between two groups were analyzed using the Mann-Whitney U test and the Chi-square test. Differences were judged significant for $p<0.05$ (two-tailed). Adjusted odds ratios were calculated using logistic regression analysis. All statistical analyses were conducted using JMP Version 6 (SAS Institute, Cary, NC, USA). The level of statistical significance was defined as 0.05.

Results

Incidence of MPCs

The details of the 60 patients studied are shown in Table 1. The mean period of follow-up was 2914.6±1536.7 days. Of the 60 patients with OSCC, 21 (35%: 15 males and 6 females; mean age 67.3±11.9 years) developed MPCs. Among the 21 patients, there were a total of 24 affected organs. The affected organs were: 6 liver cases (25%), 6 stomach (25%), 2 esophagus (8.3%), 2 colon (8.3%), 2 thyroid (8.3%), 2

Table 2. Background factors of 60 patients in onset of OSCC.

		Total n=60 (%)	Group A MPCs n=21 (%)	Group B Non-MPCs n=39 (%)	P value A versus B
Age	Mean (year) ±SD	64.8 ± 13.7	67.3 ± 11.9	63.4 ± 14.4	NS
Age group	20-69 years old	35 (58.3)	10 (47.6)	25 (64.1)	NS
	70 years or older	25 (41.7)	11 (52.4)	14 (35.9)	
Sex	Male	39 (65.0)	15 (71.4)	24 (61.5)	NS
	Female	21 (35.0)	6 (28.6)	15 (38.5)	
Stage	I	15 (25.0)	4 (19.0)	11 (28.2)	NS
	II	24 (40.0)	6 (28.6)	18 (46.2)	
	III	6 (10.0)	2 (9.5)	4 (10.3)	
	IV	15 (25.0)	9 (42.9)	6 (15.4)	
Period of follow-up	Mean (days) ±SD	2914.6±1536.7	3512.3±1355.0	2675.5±1457.9	NS
History of liver dysfunction	Yes	16 (26.7)	10 (47.6)	6 (15.4)	p<0.01
	No	41 (68.3)	9 (42.9)	32 (82.1)	
	Unknown	3 (5.0)	2 (9.5)	1 (2.6)	
History of blood transfusion	Yes	7 (11.7)	5 (23.8)	2 (5.1)	p<0.05
	No	48 (80.0)	13 (61.9)	35 (89.7)	
	Unknown	5 (8.3)	3 (14.3)	2 (5.1)	
Alcohol consumption	Yes	29 (48.3)	11 (52.4)	18 (46.2)	NS
	No	29 (48.3)	10 (47.6)	19 (48.7)	
	Unknown	2 (3.3)	0 (0.0)	2 (5.1)	
Smoking history	Yes	24 (40.0)	10 (47.6)	14 (35.9)	NS
	No	34 (56.7)	11 (52.4)	23 (59.0)	
	Unknown	2 (3.3)	0 (0.0)	2 (5.1)	

OSCC – oral squamous cell carcinoma; MPCs – multiple primary cancers; SD – standard deviation, NS: no significance.

skin (8.3%), 1 pharynx (4.2%), 1 kidney (4.2%), 1 lung (4.2%), and 1 bone marrow (leukemia, 4.2%). Nineteen patients had second primary cancers: one patient had three, and one patient had four primary cancers.

Incidence of HCV infection

Anti-HCV were detected in sera from 16 of the 60 patients with oral cancer (26.7%). The diagnosis of liver disease following the development of primary OSCC included: asymptomatic HCV carrier 6.3% (1/16), past HCV infection 6.3% (1/16), chronic hepatitis C 25% (4/16), liver cirrhosis 37.5% (6/16), HCC with liver cirrhosis 18.8% (3/16), and HCC post interferon (IFN) treatment for chronic hepatitis C 6.3% (1/16). Just after we succeeded in eliminating HCV by IFN treatment, a 38-year-old man developed simultaneous HCC and OSCC. The incidence of MPCs in an HCV-infected OSCC or in a non-HCV-infected OSCC patient was 62.5% (10/16 cases, P<0.01 vs the non-HCV-infected OSCC group) and 25% (11/44), respectively. In 10 MPC patients who were HCV-infected, HCC was the most common carcinoma (5 cases); In 11 MPC patients who were not HCV-infected, gastric cancer was the most common (6 cases).

Risk factors by univariate analysis

We compared characteristics of 21 subjects who had MPCs (group A) and 70 subjects who did not have MPCs (group B). The average age in group A was 67.3±11.9 years; there were 15 males and 6 females. The average age in group B was 63.4±14.4 years; there were 24 males and 15 females. Table 2 shows clinical features of groups A and B. A history of liver dysfunction in group A was found in 10 (47.6%, p<0.01 vs group B); a history of blood transfusion in group A was found in 5 (23.8%, p<0.05 vs group B).

We analyzed for differences between these two groups in AST, ALT, ALP, γGTP, LDH, TP, Alb, insulin, blood glucose level, and HOMA-IR. The laboratory data of both groups are shown in Table 3. Prevalence of anti-HCV antibodies was significantly higher in group A than in group B (p<0.01).

Significant differences in the development of MPCs included a history of liver dysfunction, blood transfusion, and anti-HCV positivity.

Table 3. Laboratory data of 60 patients in onset of OSCC.

		Total n=60	Group A MPCs n=21	Group B Non-MPCs n=39	P value A versus B
AST (IU/L)	(Mean ± SD)	31.1±23.5	34.6±22.4	29.1±24.1	NS
ALT (IU/L)	(Mean ± SD)	19.5±18.5	22.7±15.4	17.7±19.9	NS
ALP (IU/L)	(Mean ± SD)	15.6±2.0	33.2±2.1	7.1±1.9	NS
γ-GTP (IU/L)	(Mean ± SD)	23.4±20.5	25.5±18.7	22.3±21.3	NS
LDH (IU/L)	(Mean ± SD)	337.1±66.8	351.1±56.5	330.4±70.8	NS
TP (g/dL)	(Mean ± SD)	7.6±0.5	7.7±0.5	7.6±0.5	NS
Alb (g/dL)	(Mean ± SD)	4.0±0.4	3.9±0.3	4.0±0.4	NS
Insulin (μU/L)	(Mean ± SD)	11.9±9.4	14.1±9.0	10.8±9.5	NS
Blood glucose level (mg/dL)	(Mean ± SD)	90.9±40.6	89.8±19.3	91.5±47.7	NS
HOMA-IR	(Mean ± SD)	3.0±3.7	3.3±2.3	2.9±4.2	NS
Anti-HCV	Positive	16 (26.7%)	10 (47.6%)	6 (15.4%)	p<0.01
	Negative	44 (73.3%)	11 (52.4%)	33 (84.6%)	
HCV RNA	Positive	13 (21.7%)	7 (33.3%)	6 (15.4%)	
	Negative	46 (76.7%)	13 (61.9%)	33 (84.6%)	NS
	Uncertain	1 (1.7%)	1 (4.8%)	0 (0.0%)	
HBsAg	Positive	1 (1.7%)	0 (0.0%)	1 (2.6%)	NS
	Negative	59 (98.3%)	21 (100.0%)	38 (97.4%)	
Anti-HBc	Positive	39 (65.0%)	14 (66.7%)	25 (64.1%)	
	Negative	19 (31.7%)	5 (23.8%)	14 (35.9%)	NS
	Uncertain	2 (3.3%)	2 (9.5%)	0 (0.0%)	

SD – standard deviation; NS – no significance; AST – serum aspartate aminotransferase; ALT – alanine aminotransferase; γ-GTP – gammaglutamyl transpeptidase; LDH – lactate dehydrogenase; TP – total protein; Alb – albumin; HOMA IR – homeostasis model assessment.

Multivariate analysis

According to multivariate analysis, three factors – stage IV, anti-HCV positivity, and over 70 years old – were identified as factors associated with OSCC patients having an increased chance of developing MPCs. The adjusted odds ratios for these three factors were 15.50, 13.45, and 4.46, respectively, and each was statistically significant (Table 4).

Table 4. Results of multivariate analysis.

	Adjusted odds ratio (95% confidence interval)		P value
Stage IV	15.50	(0.39–2.58)	P=0.0124
Anti-HCV positive	13.45	(0.50–2.30)	P=0.0039
70 years or older	4.46	(0.04–1.56)	P=0.0480

Insulin resistance for the four groups

Of the 60 subjects (16 anti-HCV antibody positive and 44 anti-HCV negative), 10 had MPCs with HCV infection (group 1), 11 had MPCs without HCV infection (group 2), 6 lacked MPCs but had HCV infection (group 3), and 33 lacked MPCs and HCV infection (group 4). Fasting insulin levels at the time of the first visit to our hospital were: 16.3±7.9, 12.1±9.5, 13.5±12.6, or 10.3±8.7, in groups 1, 2, 3 and 4, respectively. Fasting insulin levels for group 1 was significantly higher than for group 4 (p=0.01, Figure 1A). HOMA-IR values seven years prior in groups 1, 2, 3, and 4 were, respectively, 3.5±1.6, 3.0±2.7, 3.1±3.0, and 2.9±4.4. A HOMA-IR value for group 1 was significantly higher than for group 4 (p=0.01, Figure 1B).

Discussion

We have already reported a high incidence of HCV among patients with OSCC [8,9]. Furthermore, we investigated the characteristics and incidence of MPCs in patients with OSCC treated between 1974 and 1995, suggesting that HCV infection increases the risk of developing MPCs [10].

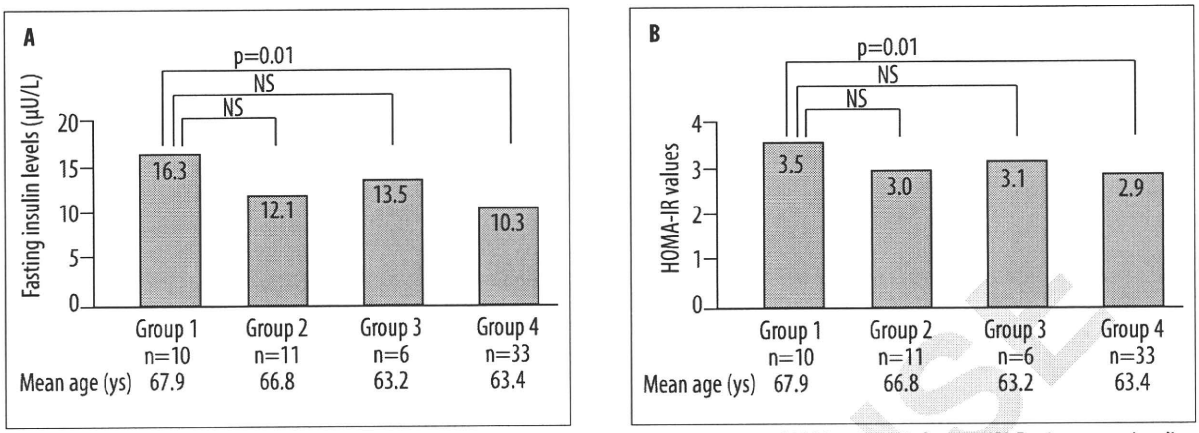

Figure 1. Association of carcinomas with insulin resistance depend on the presence or absence of OSCC and HCV infection. (**A**) Fasting serum insulin levels and (**B**) HOMA-IR values.

In the present study, the incidence of MPCs in patients with OSCC was 35% (21/60 patients) during 2914.6±1536.7 days of follow-up. The incidence of anti-HCV positivity was 26.7% (16/60 patients). The incidence of MPCs in an OSCC patient that was HCV-infected was significantly higher than in one that was not infected (62.5% vs 25%, $p<0.01$). HCC was the most common form of HCV-infected MPCs, and gastric cancer was the most common form of non-HCV-infected MPCs. These findings suggest a strong association between HCV infection and OSCC. The incidence of MPSc with the exclusion of 5 HCC in an OSCC patient that was HCV-infected was also higher than in one that was not infected (45.1% vs 25%). The affected carcinomas in extrahepatic organs of OSCC patients with HCV infection were: 2 colons, 1 lung, 1 thyroid, and 1 bone marrow (leukemia). Even excluding HCC, HCV-infected patients were at a high risk of developing extrahepatic MPCs.

Multivariate analysis demonstrated that stages of OSCC, being anti-HCV positive, and being over 70 years old increased the risk that patients with OSCC would develop MPCs. In OSCC patients who are HCV-infected, it is important to clinically examine the liver other than the oral cavity and gastrointestinal regions.

HCV infection induces not only chronic liver disease but also extrahepatic manifestations. Indeed, we experienced and reported five head and neck SCC among HCV-infected patients: (i) the patient who developed buccal mucosa cancer after IFN therapy for chronic hepatitis C [19], (ii) the patient who had simultaneous double primary cancers, including tongue cancer and HCV-related HCC [20], (iii) the patient who developed tongue cancer during the treatment of HCV-related liver disease [20], (iv) the patient with chronic hepatitis C, who developed worsening of lichen planus lesions during treatment with IFN plus ribavirin [21] and subsequently developed larynx cancer, and (v) the patient who developed tongue cancer during treatment for chronic hepatitis C [22].

It is presumed that between 1 and 2 million Japanese people are chronically infected with HCV. Because many such people are unaware that they are infected, carriers may develop liver cirrhosis and HCC, and this poses a serious problem. HCV-related HCC has increased and is now the cause of a majority of cases in Japan. Thus, the increased rates of death due to primary liver cancer in Japan appear to reflect the increase in numbers of HCV-related HCC [5]. IFN therapy, an antiviral agent, contributes to the prevention of occurrence of HCC and to improvement in long-term prognosis [23,24]. HCV-infected OSCC patients should also receive medical treatment to inhibit development of HCC, especially in Japan where the average life expectancy has increased year after year. In 2006, the life expectancies at birth were 79.0 years for males and 85.8 for females (Abridged Life Table, Ministry of Health, Labour and Welfare). Meanwhile, in patients with HCV infection, it is important to clinically examine organs other than the liver.

Satoh et al reported autopsy cases collected from the Annual of the Pathological Autopsy Cases in Japan, which is issued by the Japanese Society of Pathology for the past five years 1997–2001 [4]. A total of 134,997 cases had autopsies in Japan over five years. Of these, 321 were tongue cancer. The incidence of MPCs, affecting both the tongue and other organs, was reported to be 35.2% (113/321). In cases of double cancers including tongue cancer, commonly occurring cancers were reported to be lung, liver, esophagus, and thyroid. We think that there is a strong relation between OSCC and HCV infection, as can be seen from the fact that the second most common MPCs with tongue cancer, according to the results of autopsies, is liver cancer (reported by Satoh et al).

Several studies and our previous reports suggest that HCV infection antedates insulin resistance [25,26]. We showed molecular mechanisms for HCV core-induced insulin resistance [26]. Meanwhile, in a large population-based cohort study, Park et al. reported that among male cancer survivors, prediagnosis smoking, alcohol consumption, obesity, and insulin resistance (all risk factors for cancer development) affected cancer prognosis [27]. Previous studies in breast, prostate, and colorectal cancers demonstrated that insulin resistance can influence outcomes through systemic consequences of hyperinsulinemia [28–30]. Insulin receptors are overexpressed in those cancer tissues, so high insulin levels could promote the selective growth advantage of cancer cells [28–30]. We conclude that HCV infection induces insulin resistance and may cause lichen planus, a precancerous lesion [12,13]. In the present study,

the MPC patients who were HCV-infected had hyperinsulinemia. Insulin resistance may be involved in the development of MPCs in patients with HCV infection, although the mechanisms are unclear.

Conclusions

We demonstrated a high incidence of MPCs in HCV-infected OSCC patients. Risk factors for MPCs developing in OSCC patients are high stage of primary cancer, HCV infection, and older age. Our study emphasizes the importance of periodic examination of the oral cavity among patients with HCV infection. Success in the detection and treatment of MPCs at early stages requires close cooperation between different medical specialists.

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MEDICAL TREND
医療トレンド－3

C型肝炎ウイルス感染者における医療連携の在り方

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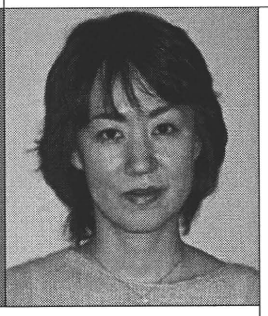

略歴

2005年4月より久留米大学医学部消化器疾患情報講座准教授に就任。専門領域はオーラルメディスン、特に肝炎ウイルスによる肝外病変。口腔外科専門医。肝臓をはじめとする消化器疾患に関する医療情報の発信と医療連携を目的とした啓発活動として消化器病教室を定期的に開催するとともに、分岐鎖アミノ酸（BCAA）食品（アミノフィール®）の開発と商品化に従事。（URL: http://www.med.kurume-u.ac.jp/med/joho/ 参照）。

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はじめに

近年、病気に関する知識や情報の共有化は、インターネットの普及により今まで以上に進み、一方では治療の変遷と標準化治療により医療現場は目まぐるしく変化している。このようなわが国の医療環境の変化に伴い、「患者の視点に立って考える医療」が重要視されている。医師にすべてを委ねる従来の医師中心の医療ではなく、患者の意思と判断を尊重した、いわゆる患者中心の医療である。患者中心の医療が、医療の在り方を見直すものとして注目されている。

厚生労働省は、2003年8月に「医療提供体制の改革のビジョン」を公表し、予防から治療までのニーズに応じた医療サービスが提供される患者主体の医療を確立するための具体的施策を提言した。

日本製薬工業協会医薬産業政策所の調査によると、医療消費者は患者中心の医療を望み、治療の意思決定に主体的に関与したいと考えているとともに、医療に関してある程度の知識を持っていることが明らかにされた[1]。しかしながら、病気の有無や世代間あるいは、患者会という準拠集団に所属しているか否かにより、医療への関与や知識、行動プロセスが大きく異なっているなど医療消費者の多様性が指摘されている。従って、患者中心の医療の実現には、医療消費者のエンパワーメントが必要であり、そのための3つの促進術が提示されている。すなわち、❶医療消費者の自立、❷医療消費者のヘルスリテラシー（医療を理解する能力）の向上、❸医療消費者と医療従事者との情報共有と相互信頼をベースにした信頼関係の構築である。

患者中心の医療を実現するためには、患者自身も医療に参加する必要がある。その医療を選択する根拠として、EBM（Evidenced Based Medicine）すなわち科学的根拠にもとづいた医療の実践が求められる時代を迎えている。

日本の肝臓がん

日本における急速な高齢化は、死亡原因の変化をもたらしている。1981年以降、悪性新生物の死因が第1位となり、以後悪性新生物の死亡率は増え続けている。なかでも国民病と呼ばれている肝臓がんは、発症者の95%以上がB型肝炎ウイルス（HBV）もしくはC型肝炎ウイルス（HCV）感染者であるため、他の悪性新生物と異なり、ハイリスクグループを絞り込むことができる唯一のがんである。しかし、肝炎ウイルス感染者の多くは自覚症状がない。そこで、感染者を発見するために、厚生労働省は2002年度から、肝炎等緊急総合対策の一環として、地域住民を対象とした肝炎ウイルス検診を開始した。本事業は5年間実施されたが、肝炎ウイルス感染者が発見されても、そのすべてが治療に結びつくわけではないという問題点が浮き彫りになった。

現在、HCV感染者の治療に用いられるインターフェロン治療は、ウイルスの駆除に留まらず、肝線維化の改善、肝臓がんの発生阻止、肝外病変への治療効果、更に生命予後の改善が明らかにされるなどの効果を上げている[2-4]。すなわち、肝臓がんの撲滅にはC型肝炎に対する治療戦略が重要な意義を持つ。インターフェロン治療は、さまざまな副作用はあるものの治療効果の向上はめざましく、C型肝炎の第一選択薬として高く評価されている。ただし、肝炎ウイルス感染者のインターフェロン治療の効率化には、医療連携システムが重要であり、患者の視点に立った医療が求められる。

肝臓がん多発地域での医療連携

私どもは、HCVの高浸淫地域について、1990年より長期的な疫学調査を行ってきた[5-12]。住民のHCV抗体陽性率は23%と極めて高く、肝臓がんの死亡率は全国平均に比し約3倍高い地域である。この地域における肝臓がんの撲滅を目指して、行政機関や地域医師会との協力で定期的な肝臓病検診を実施してきた。私どもは、地域住民に対してはウイルス肝炎に対する啓発活動を、医師会に対してはウイルス肝炎に対する知識の普及と医療連携の重要性を訴えてきた。地域住民の中でHCVキャリアと診断された方々が、その後どのような経過観察や治療を受けてきたかを示したものが**表1**である。つまり、HCV抗体もしくはHBs抗原が陽性で、しかも1990年より2002年までの肝疾患の病期の追跡と治療法が可能であった町在住の慢性肝疾患生存住民53名について、現在の治療法や肝疾患の病態（血液検査、画像検査、カルテを分析）をかかりつけ医より聴取した。

C型慢性肝炎と診断された22名の中で、肝臓専門医に少なくとも1回以上紹介されたことのある者は4名のみであった。またインターフェロン治療を受けた住民は3名で、このうち2名は肝臓専門医のもとで経過観察がなされていた。かかりつけ医だけで経過観察を受けていた18名の中でインターフェロン治療を受けた患者は1名のみであり、他はかかりつけ医からはインターフェロン治療の説明もなされていなかった[12]。

このような現状はまさに役割分担を明確にしたこの地域での医療連携の更なる重要性を示したものといえる。

肝臓がんの早期発見と治療に対する医療連携の重要性

C型肝炎の問題点は、肝組織の進展に伴う発がんリスクにある。日本に200万人は存在するといわれているHCV感染者の多くが、がん年齢に達し、今後も肝臓がん患者は増えると予想される。ただ前述したように、肝臓がんは、他の悪性新生物と異なりハイリスクグループを絞り込むことができる唯一のがんで

表1　HCV高浸淫地区におけるウイルス性慢性肝疾患を有する住民53名の治療法　文献12)より改変

—1990年から2002年まで肝疾患の追跡調査が可能で、病態と治療法が明らかにできた生存住民—

治療法 / 2002年の肝疾患名	経過観察 32名	肝庇護療法 10名	インターフェロン治療 4名	肝臓がんの治療 3名	未治療 4名
無症候性HCVキャリア（1名）	●				
HCV感染既往（15名）	✹✹✹●●● ●●●●●● ●●				●
C型慢性肝炎（22名）	✹✹●●●● ●●●●●●	●●●●●	✹✹●		●●
C型肝硬変（6名）	●	●●●●	✹		
C型慢性肝炎+肝臓がん（2名）				●	●
C型肝硬変+肝臓がん（3名）		●		✹✹	
無症候性HBVキャリア（4名）	●●●●				

✹ 肝臓専門医　● 肝臓専門医ではない

図1　アンケート実施方法
―医師と患者による1対1のアンケート―
(アンケート実施期間：2005年10月1日～2006年2月28日)
文献14）より改変

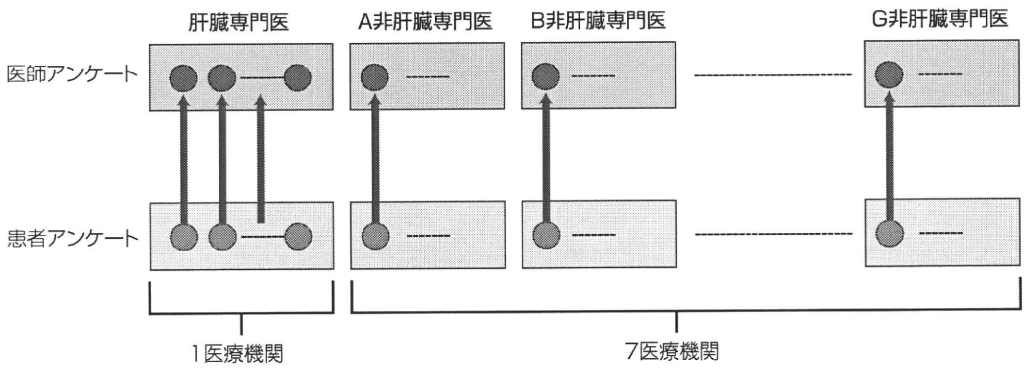


図2　インターフェロン治療の諾否に影響を与える要因（ロジスティック解析による）
文献15）より改変

医師が、患者にインターフェロン治療を勧めても、拒否する患者はどんなことに影響されるのか?

1	通院先	非専門医にかかっている患者は、専門医にかかっている患者に比べ、**治療を拒否する倍率が18.06倍高い**
2	性　別	女性は、男性より、**治療を拒否する倍率が3.65倍高い**
3	合併症	合併症を持つ患者は、持たない患者に比べ、**治療を拒否する倍率が3.63倍高い**

ある。従って肝疾患の病期の把握と腫瘍マーカーの測定や腹部超音波検査、CT・MRIなどの画像検査を用いた肝臓がんの発見と治療法の選択が、C型肝炎患者では常に重要となる。すなわち、肝臓がんの発症者の多くは、予想が可能であり、早期発見と治療が行えるわけである。

しかし、早期の肝臓がんを診断し、治療方針を決定するには、より優れた専門知識と技術が要求される。1995年から2006年まで久留米大学で肝臓がんと診断された1,074例について、肝臓がんの長期予後に対して専門病院での肝臓がんサーベイランスの有用性を検討した[13]。1,074例を3つにグループ化した。すなわち、当院でのサーベイランスにより肝臓がんが発見された211例（Aグループ）、他院でのサーベイランスにより肝臓がんが発見された544例（Bグループ）、偶発的に肝臓がんが発見された319例（Cグループ）である。

Aグループは、他の2グループに比べ、がん発見時の最大腫瘍径が有意に小さく、初回治療の侵襲も小さく、かつ生存率が高いことも明らかとなった。つまり、肝臓専門医による肝臓がんの治療は、一般の医療機関に比べて早期にがんを発見することが可能で、結果的に治療成績も向上する。そのためには、かかりつけ医と専門医間の医療連携システムが重要な鍵となる。

肝臓がんのリスクが上がる50歳以上のC型慢性肝疾患患者に対して、ただ漫然と経過観察するだけでは、肝臓がんの早期発見は遅れる。同時に、食道や胃静脈瘤の出現にも注意を払い、上部内視鏡検査が必要なことも知っておく必要がある。

インターフェロン治療の更なる普及を目指して
～患者と医師双方のアンケート調査から得られたもの

肝臓がんに至る前に、インターフェロン治療を施すことが不可欠であるが、国の検診事業は効率よく行われておらず、十分なインターフェロン治療が行われていないことが問題となっている。わが国では、2008年4月よりインターフェロン治療に関する医療費助成をはじめとした総合対策が推し進められているものの、インターフェロン治療の申請者数は伸び悩んでいる。

私どもは、2005年10月より全国に先駆けて、なぜインターフェロン治療が普及しないのかについて、その問題点の解析と解決策の確立を求めて検討してきた。インターフェロン治療を受けるべき患者、すなわち治療の適応患者がインターフェロン治療を受けない要因を分析し、治療の導入を妨げる要因を明らかにするための解析を行ったのである[14]。

ある地域で開業しているすべての8医療機関（肝臓専門医ではない内科、外科、脳神経外科などの7医療機関、肝臓専門医が常勤する1医療機関）と、そこに通院しているHCV慢性肝疾患患者らに同意を取得し、担当医師と患者に1対1のアンケート調査を実施した（**図1**）。これにより254組の回答を回収した。医師が患者にインターフェロン治療の推奨を行ったと回答した139例（インターフェロン治療の適応患者とみなす）の患者群を本研究の検討対象群とし、患者のインターフェロン治療の諾否に影響を与える要因を分析した[15]。

医師が患者にインターフェロン治療を推奨した139例のうち、92例（66.2%）が治療を受諾した。肝臓専門医の病院では86例中74例（86.0%）が、非肝臓専門医の診療所では53例中18例（34.0%）がインターフェロン治療を受諾した。またロジスティック回帰分析の結果、通院先、性別、および合併症の調整オッズ比が各々18.06、3.65、3.63となり、統計学的に有意であった（**図2**）。インターフェロン治療を断る理由としてインターフェロン治療の副作用を心配するのは、男性よりも女性の方が多かった。

インターフェロン治療をはじめとする薬物療法が適切に普及するためには、専門医と非専門医間で医療の在り方を協議し、医療連携の仕組みを整備すること、そして一方では患者と医師のコミュニケーションの向上を図るための施策を考えることが不可欠である。患者がインターフェロン治療を受諾しないリスクと関連する因子は、通院先、性別、合併症の有無であった。地域の専

門医と非専門医が協議し、病院と診療所が連携できる仕組みづくりが求められている。

肝外病変と医療連携の重要性

HCVは、肝障害のみならず種々の臓器障害を引き起こす。いわゆる肝外病変として、クリオグロブリン血症、膜性増殖性糸球体腎炎、晩発性皮膚ポルフィリン症、シェーグレン症候群、悪性リンパ腫、筋炎、心筋障害、扁平苔癬、口腔癌、糖尿病、間質性肺炎、モーレン角膜潰瘍、慢性関節リウマチ、慢性甲状腺炎などが報告されている（**表2**）[16]。**図3**に示すように、口腔領域に高頻度に出現する扁平苔癬は、慢性肝疾患患者のQOLの低下につながるだけでなく、インターフェロン治療により増悪することがあるため注意が必要な疾患である[17]。しかし、このような肝外病変についての知識は、医療従事者でさえ必ずしも認知しているわけではない。私どもは、某医師会に所属する医師を対象に、HCVが引き起こす肝外病変の存在を認知しているかどうかを検討した。**図4**に示すように、内科医であっても、4人のうち1人は肝外病変の知識がない。また、各肝外病変の疾患についても認知度は低い（**図5**）。

引き起こされる病態が多岐に及ぶという特徴が肝外病変の早期発見を遅らせる。特に臓器別診療体制の傾向が強い医療施設では、各診療科間の十分な連携のもとで、C型肝炎ウイルス感

表2　肝外病変の種類

●悪性リンパ腫	●甲状腺機能異常症
●クリオグロブリン血症	●関節リウマチ
●膜性増殖性糸球体腎炎	●糖尿病
●シェーグレン症候群	●筋炎
●晩発性皮膚ポルフィリン症	●間質性肺炎
●扁平苔癬	●モーレン角膜潰瘍
●口腔癌	●心筋障害

図3　口腔領域に高頻度に出現する扁平苔癬　文献17）より改変

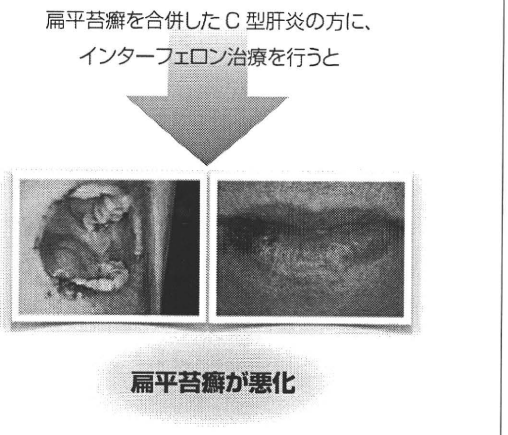


図4　診療科別の肝外病変の認識（某医師会で実施）
（アンケート実施期間：2003年10月1日〜11月30日／回答数82）

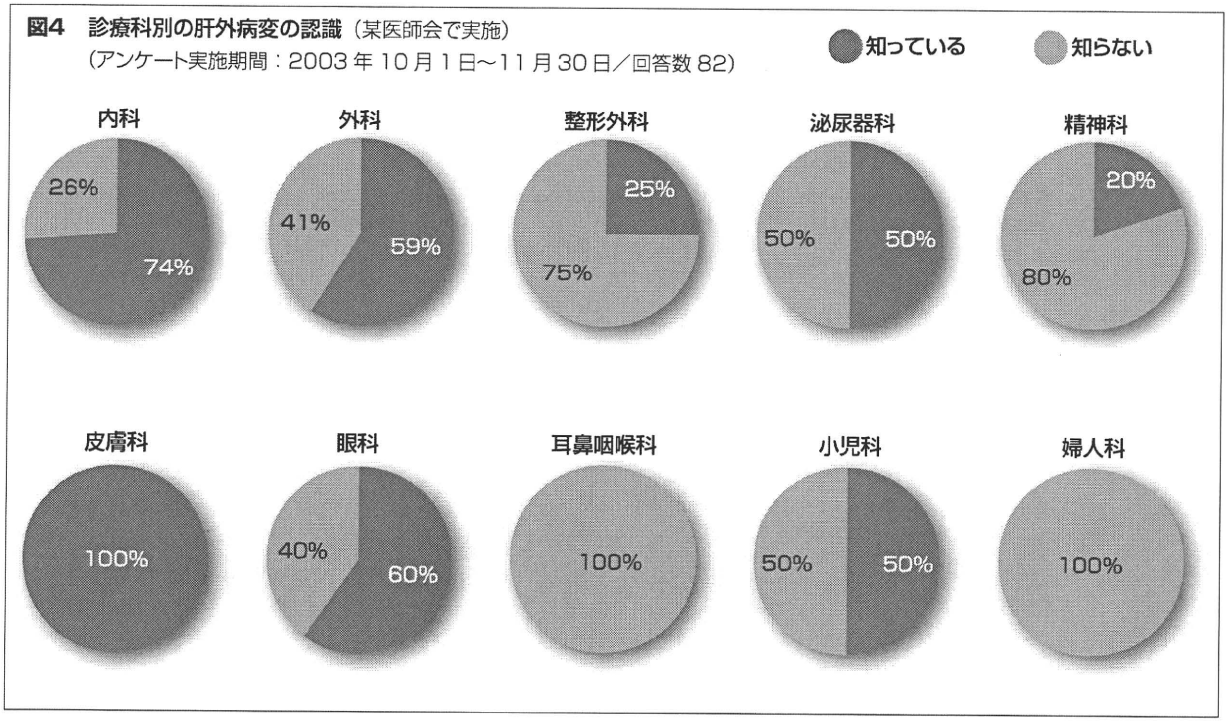
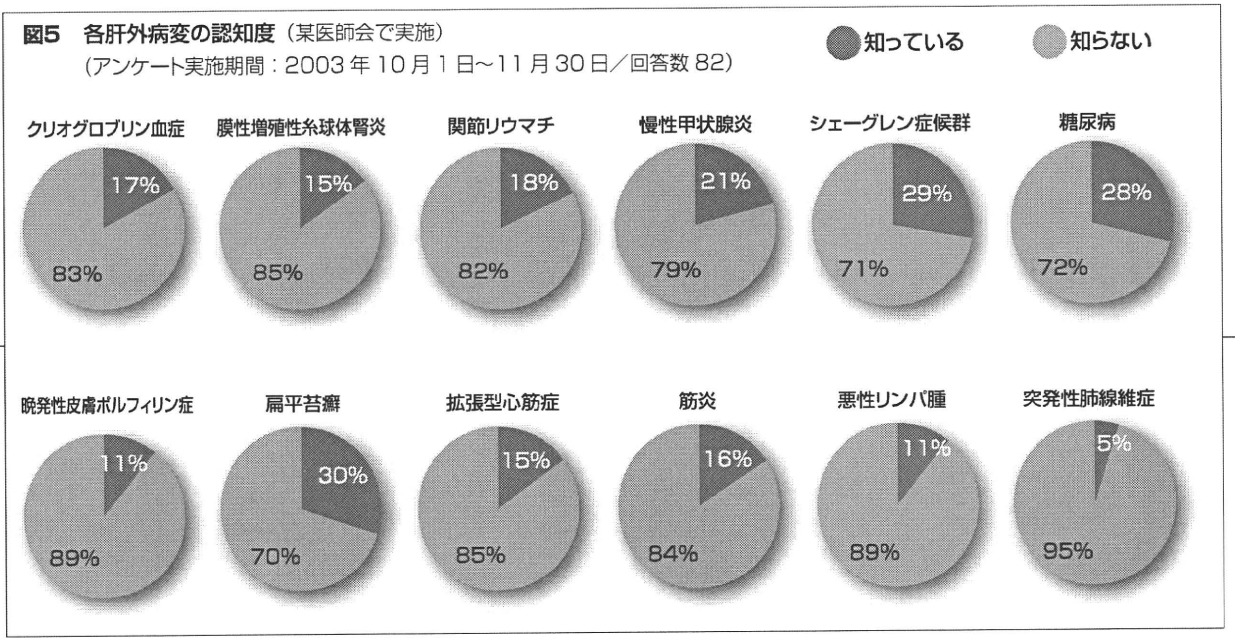


図5　各肝外病変の認知度（某医師会で実施）
（アンケート実施期間：2003年10月1日～11月30日／回答数82）



染者の経過観察が必要となる。

久留米大学では、インターフェロン治療を受ける患者は、循環器内科医、眼科医、精神科医、それに口腔外科医による精査を受けることがクリニカルパスになっている。事前に検査を受けることで、インターフェロン治療中の副作用発現時にも、診療科間の連携がスムーズに行うことができる長所を持ち、このことは結果的にインターフェロン治療の完遂率を上げると推測している。肝外病変からみた医療連携も今後更に重要になるはずである。

消化器病教室の活動を通して医療連携の効率化を目指す

各々の専門医と専門医ではない医師の間で、情報を共有する環境作りや適切な治療を患者に行うためには、地域の特徴に沿った仕組みを考える必要がある。医療連携の環境整備によって、患者が受ける医療の質を向上させられるはずである。

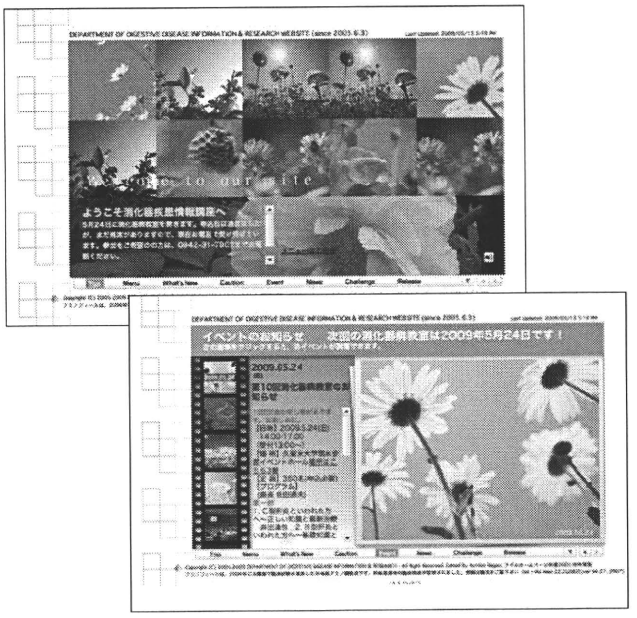
医療消費者である患者が、治療の意思決定に主体的に関わりたいと望むなら、患者自身も積極的に医師とコミュケーションを図る必要がある。そのために、私どもでは、2005年より患者と家族そして医療従事者を対象に、肝臓を中心とした消化器の病気について理解を深めていただくために、定期的に勉強会（消化器病教室）を開催している（**図6**）。この勉強会が、地域の医療連携のシステム作りや医師と患者のコミュニケーションに関する質の向上につながればと考えている。

私どもが消化器病教室を開催する背景には、次のような根拠にもとづいている。

❶1990年より長期的に実施してきたHCV高浸淫地区のさまざまな疫学調査（検診）を通じて、十数年前から医療連携の重要性を訴えてきたこと

❷医師と患者を対象にインターフェロン治療の実態を把握し、薬物療法の更なる普及に向けた医療の在り方を考察したこと（http://www.jpma.or.jp/opir/research/article32.html にてダウンロード可）

❸インターフェロン治療の適応患者が医師から治療を推奨されても治療を拒絶する因子は、「通院先」と「性別」と「合併症の有無」に規定されること（「非肝臓専門医に通院中の患者は、専門医に通院中の患者に比べ、インターフェロン治療の拒絶率が18倍高い」→つまり、患者がどの医療機関を選択するかによって、治療法が異なる）



なお、消化器病教室の活動の趣旨と予定については、ウエブサイトを参照していただきたい（http://www.med.kurume-u.ac.jp/med/joho/）。

おわりに

どんなに優れた薬物療法であったとしても、それは医療現場で使用されなければ意味がない。このことは、インターフェロン治療に限らず、すべての薬物療法に通じる。優れた治療法や医薬品が普及するためには、かかりつけ医と専門医間の医療連携が不可欠である。無駄のない効率的な医療体制を構築するためには、診療所と病院の具体的な役割分担を明確化するとともに、行政のサポートも必要である。また、患者の視点に立って考える医療の進展には、患者が治療を受ける際に、診療のアクセスを