Ⅳ．研究成果の刊行物・別刷

Question 6

C 型肝炎でみられる肝外病変にはどのようなものがあるのか？

Key point

- C 型肝炎ウイルス（HCV）は，肝臓病だけでなく全身に種々の病態（いわゆる肝外病変）を引き起こす．
- C 型肝炎ウイルス感染症は，全身性疾患であるとの認識で診療すべきである．
- 肝外病変は，患者の QOL や生命予後にも関わることを知っておかねばならない．

❶ C 型肝炎ウイルス（HCV）との関連性が指摘されている肝外病変

HCV は，肝細胞だけでなく全身の種々の細胞や臓器にも感染し，増殖する[1]．末梢血リンパ球，心筋，膵臓，副腎，甲状腺，骨髄，脾臓，唾液腺，口腔粘膜，皮膚などさまざまな細胞や臓器で HCV RNA が検出される．このことは，HCV 感染を全身感染症として捉える必要があること，さらに HCV が種々の肝外病変の発生に重要な役割を担うことを示唆する根拠となっている．これまでに報告された肝外病変や代表的な病態には，表 1 に示すようにクリオグロブリン血症，膜性増殖性糸球体腎炎，Sjögren 症候群，悪性リンパ腫，扁平苔癬（図 1）などがある．

HCV 感染者における肝外病変の有病率として，少なくとも 1 つ以上の肝外病変を合併する割合

表 1　C 型肝炎ウイルスの肝外病変

1. クリオグロブリン血症
2. 膜性増殖性糸球体腎炎
3. Sjögren 症候群
4. 悪性リンパ腫
5. 晩発性皮膚ポルフィリン症
6. 筋　炎
7. 心筋障害
8. 扁平苔癬
9. 口腔癌
10. Mooren 角膜潰瘍
11. 糖尿病
12. 間質性肺炎
13. 関節リウマチ
14. 慢性甲状腺炎

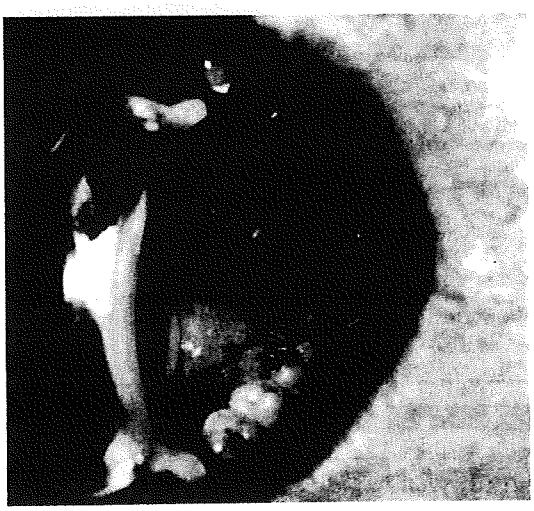

図 1 扁平苔癬

は，retrospective study では 74 %（1,202/1,604 人）[2]，prospective study では 38 %（122/321 人）であったと報告されている[3]．

一方，HCV はインスリン抵抗性や肝の脂肪化など肝関連の病態も惹起することがわかっている．これらの病態は，肝の線維化や発癌にも重要な役割を演じていることが推測されているだけでなく，C 型慢性肝炎に対するペグインターフェロン・リバビリン併用療法の治療効果を低下させる可能性としても注目されている．

❷ 肝外病変の発症機序

HCV が肝外病変の成立機序にどう関わっているのか，現状では完全に解明されているわけではないが，HCV エンベロープ蛋白発現トランスジェニックマウスでは涙腺や唾液腺に唾液腺炎を引き起こすことが証明されている[4]．また，糖尿病の発症機序に関するこれまでの検討では，インスリン抵抗性の出現にウイルスコア蛋白が重要な役割を担っており，insulin receptor substrate（IRS）に対して SOCS3 を介したプロテアゾームでの分解をコア蛋白が促進していることを我々は明らかにした[5]．さらに，HCV コア蛋白によるインスリン抵抗性発現には，プロテアゾームアクチベーター PA28γ の発現が必須であることも報告されている[6]．

これらの基礎的報告に加えて他にも肝外病変に対する HCV の関与を示唆する多くの臨床および疫学研究報告がなされている．我々の研究によって口腔扁平苔癬の発症には HCV が重要な役割を担っていることが明らかになったが[7]，口腔癌の発生にも関連している可能性が高い．最近，米国の退役軍人を対象に行われた HCV 感染と肝外病変に関する大規模疫学研究において，クリオグロブリン血症やリンパ増殖性疾患そして，non−Hodgkin lymphoma の発症要因として HCV の重要性を示唆する報告がなされた[8]．今後発症機序の解明に関する研究だけでなく発症予防や治療法に関しての基礎ならびに臨床研究に拍車がかかるであろう．

❸ 肝外病変の治療

これまでにインターフェロン治療あるいはリバビリンとの併用療法による治療効果が確認された

肝外病変の病態として，膜性増殖性糸球体腎炎，クリオグロブリン血症，悪性リンパ腫，晩発性皮膚ポルフィリン症，扁平苔癬，Mooren 角膜潰瘍，インスリン抵抗性などが知られている．

一方，インターフェロン治療が肝外病変を増悪顕性化させることもあり，治療効果と増悪が表裏一体をなす場合があることを知っておかねばならない．インターフェロン治療前・中・終了後に，口腔扁平苔癬の出現率や病態変化を観察すると，口腔扁平苔癬は 24 例中 4 例（16.7 %の出現率）に認められ，治療中に出現した病変は症状が一時的に増悪したことがわかっている[9]．たとえ扁平苔癬が増悪しても，適切な対症療法を行えば，インターフェロン治療の継続が可能であることが多い．しかし，元来びらん型の扁平苔癬を合併している C 型慢性肝炎患者にインターフェロン治療を行うと，扁平苔癬が増悪し，インターフェロン治療の継続が不可能な場合も存在する[10]．このような症例では，口腔粘膜のびらん，出血，激痛を伴うため，摂食障害を訴え，QOL が著しく低下する．

肝外病変の治療対策のコツは，早期に種々の専門医に紹介し，診療科間あるいは病診連携を行うことである．

おわりに

HCV は，全身に種々の病気を引き起こす可能性をもったウイルスであることを常に念頭において，ウイルス感染者の経過を観察すべきである．

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サイドメモ　扁平苔癬

扁平苔癬とは，角化異常を伴った慢性炎症性疾患であり，病変が口腔粘膜に限局するもの（口腔粘膜苔癬）（図 1 参照）と口腔粘膜・皮膚の両方に生じる場合がある．口腔粘膜では頬粘膜や下唇に，皮膚では下腿や前腕に好発する．50 ～ 60 歳以上の年齢に好発し，女性に多い．粘膜に発現した場合，炎症の程度によって，線条，網状，環状，丘疹状，水疱など，さまざまな形態をとり，左右対称性もしくは多発する傾向にある．軽症の場合，治療は必要ないが，難治性の場合はステロイド剤が効果的である．鑑別診断として，白板症，早期浸潤癌，ニコチン性口内炎などがある．

〈長尾由実子　佐田通夫〉

Question 17

肝癌の発生に肥満，糖尿病は影響するか？

Key point

- 肥満・糖尿病は肝細胞癌の発症要因
- 管理栄養士による栄養評価に基づいた日常指導
- 体脂肪率，腹囲，食後血糖値を加味した肥満・糖尿病評価

❶ 肥満・糖尿病は肝細胞癌の発症要因である

肝細胞癌の多くはＢ型もくしはＣ型肝炎ウイルスの持続感染を背景とした慢性肝炎・肝硬変より発症する．飲酒や喫煙などの生活習慣が肝細胞癌の発症に促進的に作用することは知られているが，近年，肥満や糖尿病も慢性肝疾患患者からの肝癌の発症に影響を及ぼすことが明らかとなった．肥満や糖尿病を有する慢性肝疾患患者は有さない患者に比べ，肝細胞癌の発症は約２～４倍高率である．また，肝炎ウイルスに感染していない肥満・糖尿病患者においても，一般健常人に比べ肝細胞癌の発症は約２～５倍高率である．このように肥満・糖尿病は肝細胞癌発症において肝炎ウイルスとの相乗効果を有するだけでなく，単独でも発癌要因となりうる重要な病態である[1-3]．

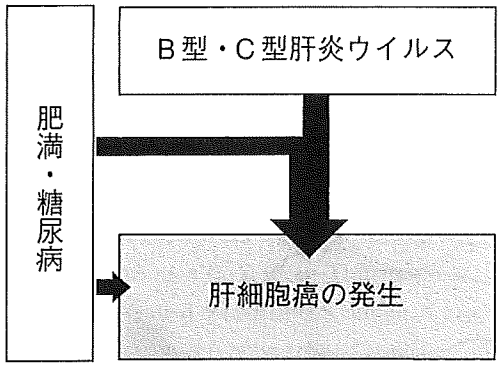

図１ 肥満・糖尿病と肝細胞癌発生の関係

❷ 肥満・糖尿病が肝癌を発症させるメカニズム

肥満・糖尿病は「インスリン抵抗性」を有している場合がほとんどである．インスリン抵抗性は脂肪性肝炎と肝線維化を介して肝細胞癌の発症を促進させると考えられる．また，インスリン抵抗性によって引き起こされるインスリン・インスリン様成長因子，性ホルモン，アディポカインなど

のホルモン変化が遺伝子異常や細胞増殖能亢進を介して肝細胞癌の発症を促進させると考えられる[1].

❸ 慢性肝疾患患者における肥満・糖尿病の評価

肥満・糖尿病の主な要因は過食と運動不足である．ただし，ライフスタイルは個人により大きく異なる．加えて，慢性肝疾患患者では味覚異常による偏食，C 型肝炎ウイルス，鉄・亜鉛などの微量元素異常，アミノ酸インバランス，脂質異常症などによって引き起こされるインスリン抵抗性が肥満・糖尿病に関与している場合も少なくない[4]．このため，管理栄養士による摂取エネルギー量と摂取栄養素評価を参考にし，日常生活指導を行うべきである．

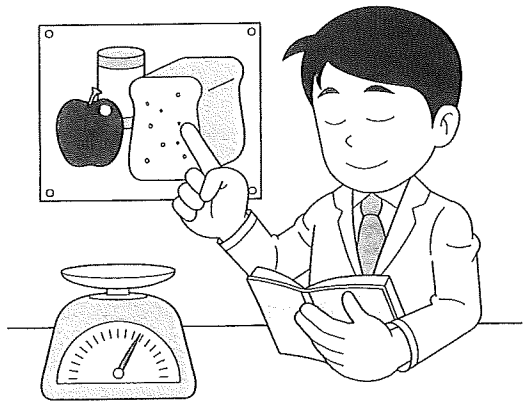

図 2 管理栄養士による栄養評価の重要性

肥満とは体脂肪が異常に増加した状態で，一般的には Body Mass Index（BMI）25 以上を肥満とする．BMI は身長と体重より簡便に算出でき，一般診療において有用な指標であることに違いはないが，脂肪量や筋肉量は加味されていない．体脂肪量，特に内臓脂肪量が肝細胞癌の発症と関係することから，体脂肪率や腹囲の測定も併せて評価すべきである．

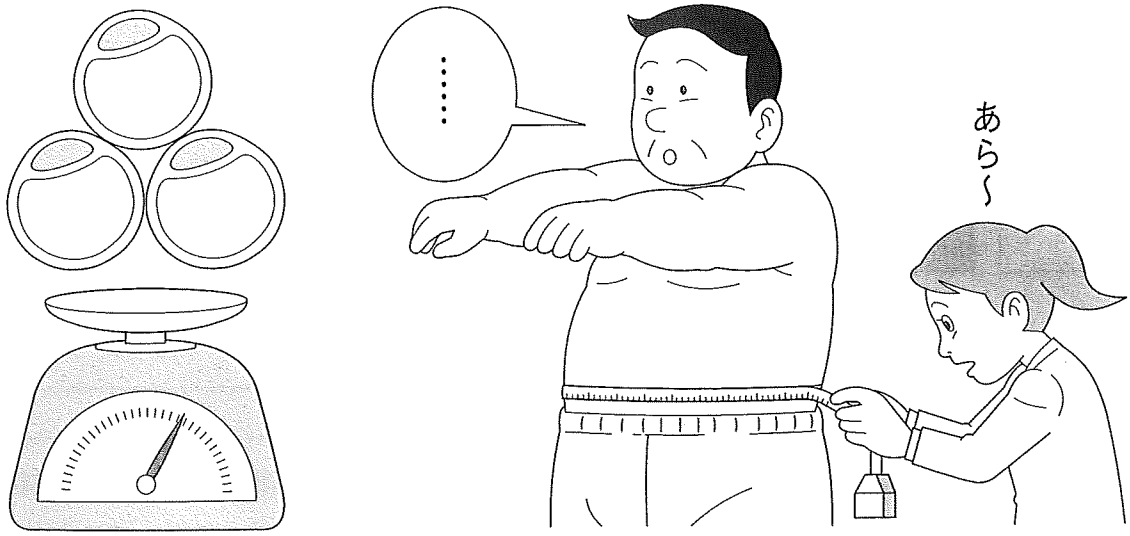

図 3 内臓脂肪は肝細胞癌の発症に関係する

慢性肝疾患患者は肝でのインスリン作用の減弱により高頻度に肝性糖尿病を合併する．肝性糖尿病では過栄養に基づく糖尿病と以下の 3 点が異なる．1）肝臓でのグリコーゲン貯蔵量が減少しているため，早朝空腹時では血糖は正常もしくは低血糖となる[5]．2）食後，血糖を十分に肝臓に取り込めないため，食後高血糖となりやすい．3）脾機能亢進のため，赤血球寿命が短縮していることからヘモグロビン A_{1c} が過栄養に基づく糖尿病と比較して低値となる．以上のことから，慢性肝疾患患者では食後の血糖測定も併せて耐糖能評価を行うべきである．

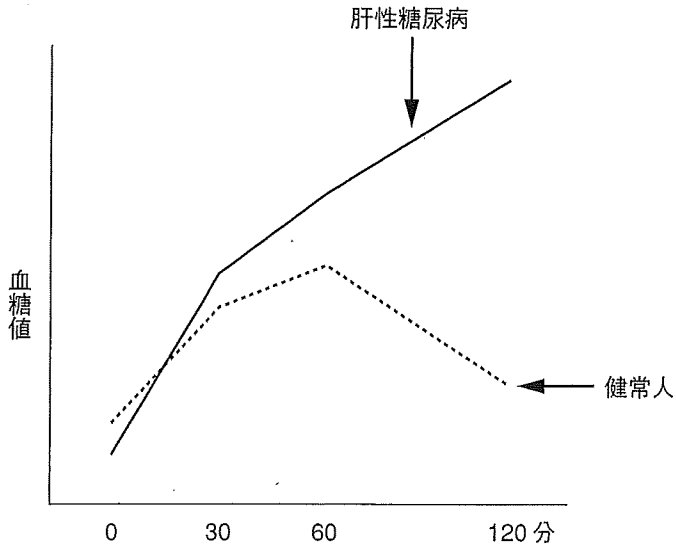

図 4 食後血糖測定の重要性

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サイドメモ 肥満と癌

近年，肥満が肝細胞癌だけでなく他の様々な癌の発症にも影響を及ぼすことが明らかとなった．90 万人以上の成人を 16 年間追跡した疫学研究（米国）の結果，肥満との関連を認めた癌は，食道癌，大腸癌，肝癌，胆嚢癌，膵臓癌，腎癌，胃癌，前立腺癌，乳癌，子宮癌，卵巣癌と多岐にわたっていることが報告されている[6]．また，米国癌研究協会と英国の世界癌研究基金による報告書 “Food, nutrition, physical activity, and the prevention of cancer: A global perspective” においても食道癌，膵癌，大腸癌，子宮内膜癌，腎癌，閉経後の女性の乳癌と肥満の関連が報告されている[7]．肥満患者を診療するにあたり，虚血性心臓病，脳血管疾患の発症に加えて，上記癌発症の危険性も念頭におく必要がある．

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A Study Design
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).

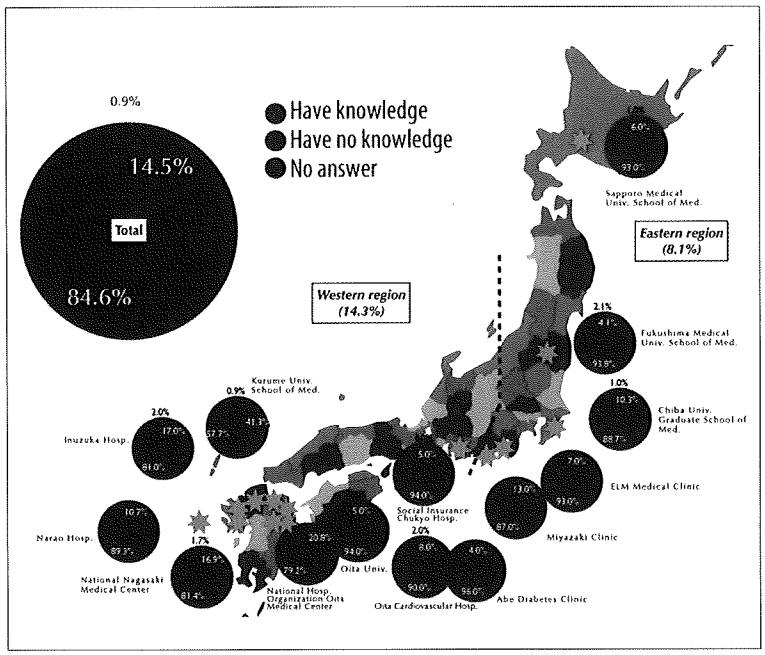

Figure 1. Knowledge of *V. vulnificus* infections among all patients with liver diseases. Only 14.5% of such patients had knowledge of this infection. Fourteen red stars indicate the location of each medical institution. Japan consists of 47 prefectures. Half of east of Japan, including Tokyo, where 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.

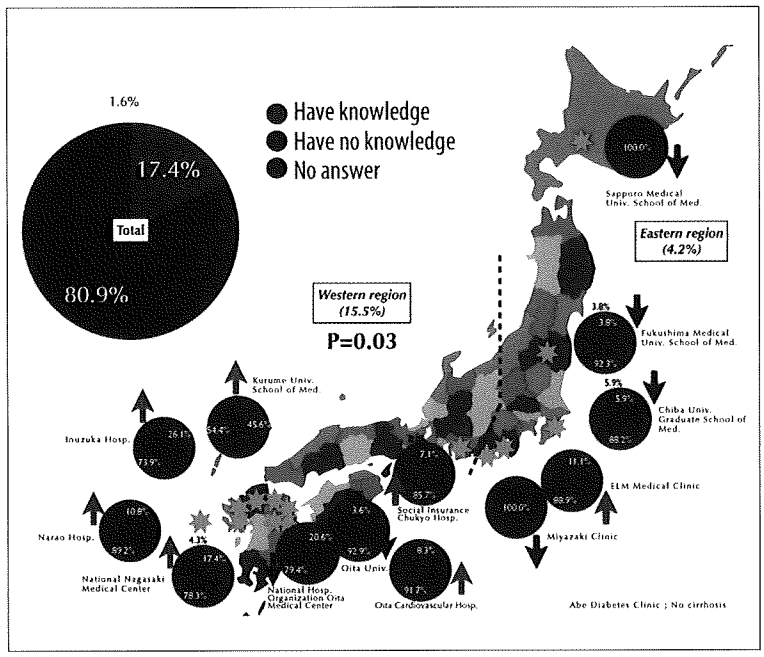

Figure 2. Knowledge of *V. vulnificus* infections in patients with liver cirrhosis. The rate of patient knowledge in the western region of Japan was significantly higher than in the eastern region. The upward pointing arrow indicates an increase in the rate of *V. vulnificus* infections in a given institution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

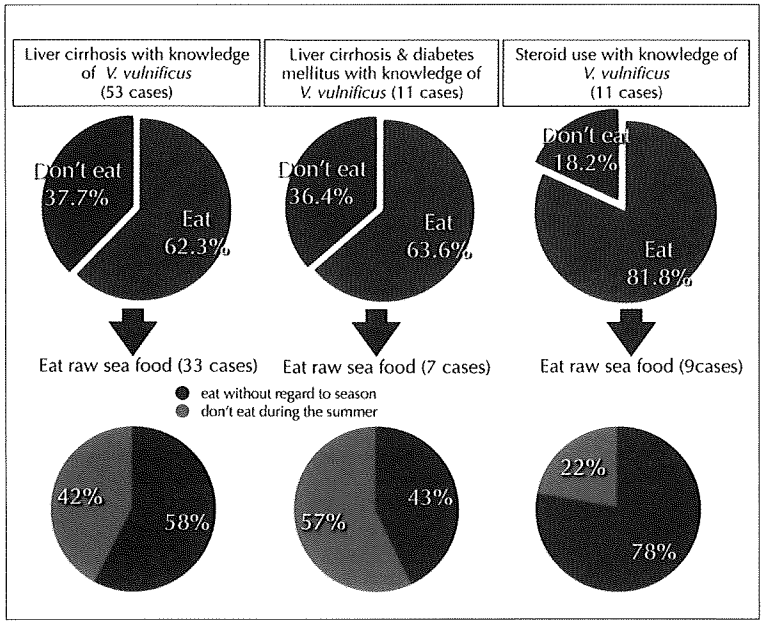

Figure 3. Frequency of eating raw seafood. Even if patients had high risk factors for infection, such as liver cirrhosis, diabetes mellitus, or steroid use, and had knowledge of *V. vulnificus* infections, most ate raw seafood without regard to season.

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 Deçember 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.

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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].