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CLINICAL STUDIES

Extrahepatic metastasis of hepatocellular carcinoma: incidence and risk factors

Miho Kanda[1,2], Ryosuke Tateishi[1], Haruhiko Yoshida[1], Takahisa Sato[1], Ryota Masuzaki[1], Takamasa Ohki[1], Jun Imamura[2], Tadashi Goto[1], Hideo Yoshida[1], Keisuke Hamamura[1], Shuntaro Obi[2], Fumihiko Kanai[1], Shuichiro Shiina[1] and Masao Omata[1]

1 Department of Gastroenterology, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan
2 Department of Hepatology, Kyoundo Hospital, Tokyo, Japan

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Abbreviations
AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of AFP; CT, computed tomography; DCP, des-γ-carboxy prothrombin; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus antibody; MRI, magnetic resonance imaging; TACE, transcatheter arterial chemoembolization.

Correspondence
Ryosuke Tateishi, MD, PhD, Department of Gastroenterology, Graduate School of Medicine, the University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
Tel: +81 3 3815 5411
Fax: +81 3 3814 0021
e-mail: tateishi-tky@umin.ac.jp

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Abstract

Background: Extrahepatic metastasis of hepatocellular carcinoma (HCC) is of growing importance as the survival of patients has been improved owing to advances in treatments to intrahepatic lesions. *Methods:* To elucidate the incidence and risk factors of extrahepatic metastasis of HCC, we enrolled 1573 (1131 treatment-naïve and 442 previously treated on referral) patients with HCC without extrahepatic tumour spread treated at the authors' department between 1990 and 2003. Patients received medical treatment including percutaneous ablation and transcatheter arterial chemoembolization, and followed by dynamic computed tomography (CT) or magnetic resonance imaging (MRI) and tumour markers every 3–4 months. Extrahepatic metastasis was diagnosed by plain X-ray, CT, MRI and scintigraphy. Clinical parameters at the time of treatment to intrahepatic lesions were evaluated as a predictor of subsequent extrahepatic metastasis among the 1131 treatment-naïve patients by Cox's proportional hazard model. *Results:* During the average observation period of 3.9 years, extrahepatic metastasis was diagnosed in 123 in the treatment-naïve and 53 in the patients treated previously. The incidence rate of extrahepatic metastasis, as detected during the lifetime after medical treatment of HCC, was approximately 13% at 5 years. Multivariate analysis with Cox proportional hazard model revealed that positivity for viral markers, lager tumour diameter, multiple tumour nodules, presence of vascular tumour invasion and elevated tumour markers were associated with the development of extrahepatic metastasis. *Conclusion:* The incidence of extrahepatic metastasis of HCC diagnosed during clinical course was not frequent. Advanced intrahepatic lesions, presence of vascular tumour invasion, elevated tumour markers and presence of viral hepatitis were risk factors for extrahepatic metastasis.

Hepatocellular carcinoma (HCC) is a common malignancy worldwide, claiming approximately 600 000 deaths each year (1). Because HCC usually develops in patients with advanced chronic liver diseases (2, 3), efficient surveillance for HCC is feasible on high-risk patients by using advanced imaging diagnostics, facilitating detection of HCC at early stages (4–8). Together with advances in treatment modalities, such as surgical resection, medical ablation, transcatheter arterial chemoembolization (TACE) and liver transplantation, the prognosis of HCC has been much improved (4, 9–12).

Except for cases after transplantation, intrahepatic recurrence of HCC is very common (13–16) but this may be treated by modalities applicable to primary HCC. In contrast, extrahepatic metastasis of HCC is relatively rare at the time of initial diagnosis even with fairly advanced intrahepatic lesions (17–19). However, with prolonged survival of HCC patients, the incidence of extrahepatic metastasis seems to be increasing (20–22). Most of the previous studies on extrahepatic metastases of HCC were based on autopsy reports and few described extrahepatic metastases detected in the course of illness (17, 18, 23, 24). Risk factors for

extrahepatic metastases are not well known either (22). The diagnostic procedures for extrahepatic metastases have not been standardized. However, considering the substantial advances in treatment of intrahepatic lesions, appropriate diagnosis and treatment of extrahepatic lesions may be essential for further improvement of prognosis.

The authors' institution has been one of the leading tertiary centres for HCC treatment in Japan. The majority of patients received percutaneous medical ablation. One of the major merits of medical ablation is its repeatability for metachronous intrahepatic recurrence. As a result, we achieved the cumulative 5-year survival rate of 49.6% among overall HCC patients (25). The prolonged survival seems to be associated with increased incidence of extrahepatic metastasis. In the present study, we analysed the incidence of extrahepatic metastases of HCC among consecutive patients and evaluated its possible predictors.

Patients and methods

Patients

Between 1990 and 2003, the authors' institution received a total of 1619 patients with HCC. We enrolled 1573 of them excluding 46 patients who showed extrahepatic metastasis at the time of first visit. Among these patients, 1131 had naïve HCC and 442 had a previous history of HCC treatment before the first visit to our department. The previous treatments were hepatic resection in 107, percutaneous ablation in 169, TACE in 249 and radiation therapy in one (including overlap).

Diagnosis and treatment of hepatocellular carcinoma

The diagnosis of primary HCC was based on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), where hyperattenuation in the arterial phase and hypoattenuation in the late phase were considered definitely diagnostic. Elevation in HCC-specific tumour markers, i.e. α-fetoprotein (AFP), des-γ-carboxy prothrombin (DCP) and lectin-reactive fraction of AFP (AFP-L3), were considered suggestive of HCC. Ultrasound-guided tumour biopsy was performed when considered necessary.

The treatment of HCC consisted of percutaneous tumour ablation (83.2%), TACE (31.3%), intra-arterial chemotherapy (0.9%), systemic chemotherapy (1.5%) and irradiation (0.4%); some patients received combination treatments. The effects of primary treatments were evaluated with contrast-enhanced CT/MRI 1–2 months later. Intrahepatic recurrence was monitored with abdominal ultrasound and CT/MRI at an interval of 3–4 months. Other imaging examinations, such as chest X-ray or CT, and 99m-Tc or Ga-67 scintigraphy, were also performed when indicated.

Diagnosis of extrahepatic metastasis

The diagnosis of extrahepatic metastasis was based on abdominal ultrasonography, CT, MRI, chest X-ray or bone scintigraphy. Intra-abdominal metastasis was usually found on abdominal ultrasonography, CT or MRI regularly performed for the follow-up of intrahepatic HCC. Pulmonary metastasis was detected often with chest X-ray routinely performed before treatment for intrahepatic recurrence. Other examinations were indicated by the emergence of symptoms suggestive of respective metastasis, or an elevation of HCC-specific tumour markers that was not accounted for by the status of intrahepatic lesion. Differentiation from benign or malignant lesions other than metastatic HCC was based on findings on diagnostic imaging, changes in tumour markers and sequential changes in size.

Event occurrence was defined by the definite diagnosis of extrahepatic metastasis. Deaths without definite diagnosis of extrahepatic metastasis were handled as censored. Extrahepatic metastasis detected only at autopsy, consisting 7.5% of autopsied cases, was not considered as an event because the current study was focused primarily on the diagnosis and treatment of extrahepatic metastasis within the lifetime.

The characteristics of extrahepatic metastasis, recorded at the time of its diagnosis, included the method of diagnosis, symptoms, the status of intrahepatic lesions and the serum concentration of HCC-specific tumour biomarkers. The incidence of extrahepatic metastasis was recorded individually for its locations which consisted of the lung, bone, lymph nodes, adrenal glands and others. When metastases occurred to multiple locations during the observation period, each metastasis was distinctly handled as an event in each location. However, metachronous metastases to the same organ were represented by the first metastasis and clinical data at that period were recorded.

Statistical procedures

The observation period was defined as the interval between the first treatment of HCC at our department and the diagnosis of extrahepatic metastasis, death or

the last observation before 31 August 2006, whichever came first. Cumulative incidence rates of extrahepatic metastasis were calculated by the method of Kaplan–Meier (26). When a patient received only best supportive care as the first treatment, the time of definite diagnosis of HCC was regarded as the start of observation. In addition, we assessed the cumulative rate of intra- and extrahepatic recurrence in 885 patients who received medical ablation as their initial treatment and achieved complete response using cumulative incidence estimation with competing risks (27). Clinical data, at the time of first treatment, were tested for the prediction of extrahepatic metastasis by using Cox's proportional hazard model (28). Those factors with a P value < 0.1 in univariate analysis were retained in a multivariate analysis, where stepwise variable selection was used to estimate the best model. Factors included in the analysis were as follows: age, gender, hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCVAb), serum concentrations of albumin and total bilirubin, platelet count, serum levels of aspartate aminotransferase and alanine aminotransferase, Child–Pugh classification of liver function, the maximum size and the number of HCC nodules, the presence of vascular tumour invasion, the levels of AFP, DCP and AFP-L3. Data were expressed as the mean ± standard deviation (SD) unless otherwise specified. A P value < 0.05 was considered statistically significant. S-PLUS 2000 (Insightful Co., New York, NY, USA) was used in all statistical analyses.

Results

Patients

Among 1573 HCC patients, 1131 had naïve HCC and 442 had a previous history of HCC treatment. The average age was 65.7 ± 8.7 years in the former group and 64.6 ± 8.3 in the latter one. Male patients were dominant in both groups, constituting about two-thirds. HCVAb was positive in 77.8% in the former and 78.5% in the latter group. The mean ± SD diameter of HCC nodules was 3.2 ± 2.3 and 3.4 ± 2.6 cm respectively. Massive form of HCC constituted 0.5 and 1.1% respectively. Vascular tumour invasion was found in 2.2 and 3.6% respectively (Table 1).

Table 1. Patients' characteristics at entry

Variables	Naïve (n = 1131)	Treated previously (n = 442)
Age (years), mean ± SD	65.7 ± 8.7	64.6 ± 8.3
Male, n (%)	785 (69.4%)	322 (72.9%)
HBsAg/anti-HCVAb		
+/−	104 (9.2%)	56 (12.7%)
−/+	880 (77.8%)	347 (78.5%)
+/+	21 (1.9%)	7 (1.6%)
−/−	126 (11.1%)	32 (7.2%)
Child–Pugh classification, n (%)		
Class A	696 (61.5%)	256 (57.9%)
Class B	386 (34.1%)	169 (38.2%)
Class C	49 (4.3%)	17 (3.8%)
Tumour size, n (%)		
≤ 2.0 cm	339 (30.0%)	114 (25.8%)
2.1–5.0 cm	665 (58.8%)	275 (62.2%)
> 5.0 cm	127 (11.2%)	53 (12.0%)
Number of nodules, n (%)		
1	584 (51.6%)	147 (33.3%)
2–3	368 (32.5%)	158 (35.7%)
> 3	179 (15.8%)	137 (31.0%)
Vascular tumour invasion, n (%)	25 (2.2%)	16 (3.6%)
AFP > 100 (ng/ml), n (%)	318 (28.1%)	158 (35.7%)
DCP > 100 (mAU/ml), n (%)*	249 (23.1%)	115 (28.1%)
AFP-L3 > 15 (%), n (%)†	163 (21.1%)	96 (32.2%)
Treatment of HCC, n (%)‡		
Percutaneous ablation	957 (84.6%)	351 (79.4%)
Arterial chemoembolization	367 (32.4%)	126 (28.5%)
Arterial chemotherapy	10 (0.9%)	4 (0.9%)
Systemic chemotherapy	10 (0.9%)	14 (3.2%)
Radiation	3 (0.3%)	3 (0.7%)
Supportive care only	11 (1.0%)	3 (0.7%)

*Missing in 85.
†Missing in 502.
‡Including overlaps.
AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of AFP; DCP, des-γ-carboxy prothrombin; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; HCC, hepatocellular carcinoma; SD, standard deviation.

Extrahepatic metastasis

During the average observation period of 3.9 years, extrahepatic metastasis was diagnosed in 176 patients (11.2%): 123 in the naïve group and 53 in the group treated previously. The cumulative incidence rates of extrahepatic metastasis at 1, 2, 3, 5 and 7 years were 2.3, 4.5, 7.4, 11.6 and 17.0%, respectively, in the former group and 4.9, 8.3, 11.3, 17.3 and 19.5%, respectively, in the latter (Fig. 1). However, if we focus on the first appearance of recurrence after curative medical ablation (n = 885), cumulative probabilities of intrahepatic recurrence at 1, 2, 3, 5 and 10 years were

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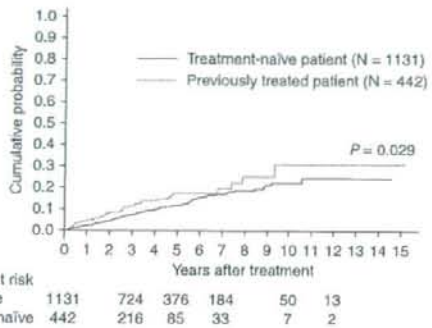

Fig. 1. Cumulative incidence of extrahepatic metastasis. The cumulative incidence of extrahepatic metastasis at 5 years was 11.6% in the naïve group and 17.3% in the group treated previously. There were significant difference between two groups ($P = 0.029$).

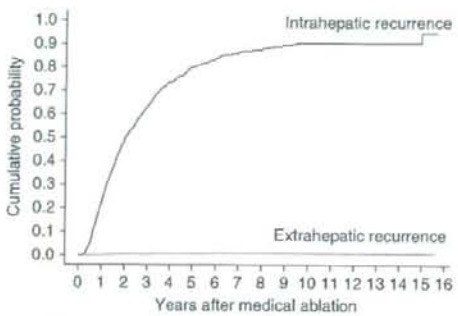

Fig. 2. Cumulative probabilities of intra- and extrahepatic recurrence in patients with complete response to medical ablation. Cumulative probabilities of intrahepatic recurrence at 1, 2, 3, 5 and 10 years were 22.7, 49.9, 63.3, 80.0 and 90.5% while those of extrahepatic recurrence (metastasis) were 0.2, 0.6, 0.6, 0.7 and 0.9% respectively.

22.7, 49.9, 63.3, 80.0 and 90.5% while those of extrahepatic recurrence (metastasis) were 0.2, 0.6, 0.6, 0.7 and 0.9% respectively (Fig. 2).

The location of the first extrahepatic metastasis was lung in 74 patients (42.0%), bone in 43 (24.4%), lymph node in 37 (21.0%), adrenal gland in 16 (9.1%) and others in 6 (3.4%). Total numbers of events were 243:92 for the lung, 60 for bone, 49 for lymph nodes, 23 for adrenal gland and 19 for other organs (Table 2). Among the other organs, metastasis to the brain was the most frequent ($n = 10$). Eight of 10 patients (80.0%) with brain metastasis had extrahepatic metastasis to other organs while on the whole 50 patients (39.7%) had metastases to more than one organ. The dominant location of bone metastasis was the vertebrae (37.5%). Regional lymph nodes were the site of metastasis in 75% cases. 82.5% of adrenal metastasis occurred to the right side gland.

At the time of diagnosis of extrahepatic metastasis, symptoms attributable to the corresponding lesions were present in 76.6% of patients with bone metastasis, manifesting itself as pain, motor or sensory nerve disturbance, or local bone swelling and 10.9% of those with pulmonary metastasis as dyspnoea, cough or pain; all symptomatic patients had metastases to bilateral lungs.

Predictors of extrahepatic metastasis

Clinical parameters at the time of HCC treatment were evaluated as a predictor of extrahepatic metastasis among the 1131 patients who were treated for naïve HCC by using Cox's proportional hazard model. In univariate analysis, the following parameters had a P value < 0.1: HBsAg seropositivity, anti-HCVAb seropositivity, maximum tumour diameter, the number of HCC nodules, the presence of vascular tumour invasion, levels of AFP, DCP and AFP-L3 (Table 3). Excluding AFP-L3 for which missing values were frequent, the remaining parameters were analysed in multivariate analysis with stepwise selection, in which all parameters retained statistical significance (Table 4). The presence of vascular tumour invasion showed the greatest relative risk, followed by HBsAg seropositivity and the diameter exceeding 5.0 cm.

Discussion

In this study, the incidence rate of extrahepatic metastasis, as detected during the lifetime after medical treatment of HCC, was approximately 2.5%/year. Although the applicability of this result may be limited by the fact that the study population were treated mainly by medical ablation, this is compatible with previous reports that metachronous heterotopic recurrence of HCC is relatively rare, as compared with other cancers (18). In the current study, the most frequent location of extrahepatic metastasis was the lung, followed by the bone, lymph node and adrenal gland. The lung was the most frequent site of metastasis also in other reports, followed by either the bone or the lymph nodes (21, 24, 29, 30).

Among the three modes of tumour extension, i.e. haematogenous metastasis, lymphatic metastasis and direct invasion, haematogenous metastasis is the most common with HCC (31), which contrasts clearly with lymph node-dominant metastasis from cholangiocellular

Table 2. Clinical data at diagnosis of extrahepatic metastasis

	Lung ($n = 92$)	Bone ($n = 60$)	Lymph node ($n = 49$)	Adrenal gland ($n = 23$)	P
Age (year)*†	65.6 ± 9.6	68.0 ± 7.9	67.5 ± 7.9	65.7 ± 9.3	0.47
Men, *n* (%)	72 (78.3%)	45 (75.0%)	37 (75.5%)	18 (78.3%)	0.96
Symptomatic, *n* (%)	10 (10.9%)	46 (76.7%)	3 (6.1%)	1 (4.3%)	< 0.001
Diagnostic modality, *n* (%)					
Plain X-ray	45 (48.9%)	2 (3.3%)	0 (0.0%)	0 (0.0%)	
CT/MRI	46 (50.0%)	29 (48.3%)	45 (91.8%)	22 (95.7%)	
Scintigraphy	1 (1.1%)	29 (48.3%)	1 (2.0%)	0 (0.0%)	
Ultrasound	0 (0.0%)	0 (0.0%)	3 (6.1%)	1 (4.3%)	
HBsAg/anti-HCVAb, *n* (%)					
+/−	19 (20.7%)	5 (8.3%)	3 (6.1%)	4 (17.4%)	0.054
−/+	63 (68.5%)	49 (81.7%)	41 (83.7%)	18 (78.3%)	0.133
+/+	4 (4.3%)	3 (5.0%)	3 (6.1%)	0 (0%)	0.70
−/−	6 (6.5%)	3 (5.0%)	2 (4.1%)	1 (4.3%)	0.93
Intrahepatic lesion, *n* (%)	82 (89.1%)	53 (88.3%)	39 (79.6%)	20 (87.0%)	0.43
Massive type	9 (9.8%)	1 (1.7%)	3 (6.1%)	3 (13.0%)	0.18
Vascular invasion	23 (25.0%)	9 (15.0%)	10 (20.4%)	5 (21.7%)	0.53
AFP > 100 ng/ml, *n* (%)	70 (76.1%)	33 (55.0%)	28 (57.1%)	13 (56.5%)	0.041
DCP > 100 mAU/ml‡, *n* (%)	60 (65.2%)	33 (57.9%)	20 (40.8%)	12 (52.2%)	0.046
AFP-L3 > 15%§, *n* (%)	57 (75.0%)	29 (61.7%)	25 (67.6%)	12 (66.7%)	0.47
Coexisting extrahepatic lesion					
Lung		17 (28.3%)	16 (32.7%)	6 (26.1%)	
Bone	19 (20.7%)	–	5 (10.2%)	5 (21.7%)	
Lymph Node	17 (18.5%)	6 (10.0%)	–	3 (13.0%)	
Adrenal Gland	7 (7.6%)	4 (6.7%)	3 (6.1%)	–	
Others	11 (12.0%)	3 (5.0%)	3 (6.1%)	1 (4.3%)	

*At diagnosis of extrahepatic metastasis.

†Mean+SD.

‡Missing in 3.

§Missing in 46, including overlaps.

AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of AFP; CT, computed tomography; DCP, des-γ-carboxy prothrombin; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; MRI, magnetic resonance imaging; SD, standard deviation.

carcinoma (29). HCC cells presumably reach the lungs through hepatic vein and reside in the capillary network. The vertebrae were the most frequent site of osseous metastasis (37.5%), to which vertebral venous plexus is reportedly responsible (32, 33). Vertebral metastasis bears clinical importance because it may cause paraplegia. Metastasis to the adrenal gland is theoretically through systemic circulation and thus chances of metastasis to right and left glands are equal (34). However, in the current study, as in previous reports, adrenal metastasis was much more frequent to the right gland than to the left (35, 36).

Opportunities for the diagnosis of extrahepatic metastases could be classified into three categories. The first category was chance detection by abdominal CT or chest X-ray that were routinely taken on each admission for the treatment of intrahepatic recurrence or other causes. Those examinations may not have been performed as meticulously at terminal stages, resulting in possible underestimation of overall incidence of extrahepatic metastasis. The second category was the detection by systemic scrutiny for elevated tumour biomarkers in spite of well-controlled intrahepatic lesions. In the current study, 9.1% cases of extrahepatic metastasis were diagnosed in the absence of viable intrahepatic lesions. The last category was the detection owing to specific symptoms such as local pain or dyspnoea. About 80% cases of osseous metastasis were detected based on subjective symptoms.

Response to treatment is undoubtedly a strong predictor for prognosis of HCC patients as well as other malignancies (37, 38). The complete response to treatment strongly reduces the risk for extrahepatic metastasis. However, the effect size was reduced in the multivariate analysis, although the variable retained significance in the final model after stepwise variable selection. This may be owing to the strong correlation between treatment response and tumour-related factors such as tumour size, number of tumour nodules and presence of vascular invasion.

The choice of treatment modalities may affect the risk of extrahepatic metastasis (39–41). Indeed, it was

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Table 3. Predictors for extrahepatic metastasis: univariate analysis

Variables*	Relative risk (95% CI)	*P*
Age > 65 years	0.99 (0.97–1.01)	0.29
Men	1.12 (0.76–1.66)	0.57
HBsAg, positive	3.92 (1.30–11.82)	0.015
Anti-HCVAb, positive	2.91 (1.07–7.92)	0.036
Albumin (g/dl)		
< 2.8	1	
2.8–3.5	2.31 (0.57–9.35)	0.24
> 3.5	1.97 (0.49–7.95)	0.34
Bilirubin (mg/dl)		
≤ 1	1	
1.1–2.0	1.12 (0.74–1.71)	0.58
> 2	0.57 (0.14–2.30)	0.43
Platelet count > 10×10^4/μl	1.32 (0.92–1.90)	0.13
AST > 80 IU/l	1.12 (0.77–1.62)	0.55
ALT > 80 IU/l	1.29 (0.90–1.86)	0.17
Child–Pugh classification		
A	1	
B/C	0.90 (0.60–1.33)	0.59
Tumour diameter (cm)		
≤ 2.0	1	
2.1–5.0	2.04 (1.30–3.18)	0.002
> 5.0	4.11 (2.24–7.53)	< 0.001
Number of nodules		
Single	1	
2–3	1.63 (1.09–2.45)	0.019
> 3	3.20 (2.02–5.09)	< 0.001
Vascular tumour invasion	7.80 (3.14–19.4)	< 0.001
AFP (ng/ml)		
≤ 100	1	
101–400	1.74 (1.07–2.82)	0.026
> 400	4.14 (2.63–6.52)	< 0.001
DCP (mAU/ml)		
≤ 100	1	
101–400	2.77 (1.72–4.45)	< 0.001
> 400	2.63 (1.51–4.60)	< 0.001
AFP-L3 (%)		
≤ 15	1	
15.1–40	2.49 (1.05–5.92)	0.039
> 40	5.59 (3.21–9.72)	< 0.001
Complete response to treatment	0.307 (0.204–0.460)	< 0.001

*Data at initial treatment.

AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of AFP; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCP, des-γ-carboxy prothrombin; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody.

Table 4. Predictors for extrahepatic metastasis: multivariate analysis

Variables*	Relative risk (95% CI)	*P*
HBsAg, positive	2.58 (1.40–4.75)	0.002
Anti-HCVAb, positive	2.32 (1.24–4.34)	0.008
Diameter (cm)		
≤ 2.0	1	
2.1–5.0	1.76 (1.11–2.77)	0.015
> 5.0	2.46 (1.27–4.75)	0.008
Number of nodules		
1	1	
2–3	1.51 (1.00–2.29)	0.047
> 3	1.75 (1.00–3.08)	0.05
Vascular tumour invasion	3.20 (1.05–9.83)	0.04
AFP > 100 ng/ml	1.61 (0.87–2.95)	0.12
DCP > 100 mAU/ml	1.52 (0.93–2.49)	0.095
Complete response to treatment	0.600 (0.345–1.04)	0.071

*Data at initial treatment.

AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody.

extremely rare that the first recurrence occurred as an extrahepatic metastasis when curative ablation had been performed. However, because patients with HCC usually receive multimodality treatment during clinical course, it is difficult to determine which treatment is associated with extrahepatic metastasis. In the current study, the majority of patients had received TACE before extrahepatic metastasis was diagnosed. However, the choice of treatment modalities was highly dependent on tumour-related factors such as tumour size, number of tumour nodules and vascular invasion. Those treated with TACE had larger tumour and more tumour nodules than those treated with medical ablation, which makes analysis concerning treatment modality rather difficult.

The predictors for extrahepatic metastasis the current study revealed to be significant, such as the size and number of HCC nodules, the presence of vascular tumour invasion, or seropositivity of tumour biomarkers, are similar to the factors shown to be associated with prognosis in general in previous studies (42–44). Because we used in analysis the data obtained at the time of initial treatment, the relative importance of each factor may have changed through the course of disease. In particular, at least one of the three tumour biomarkers, AFP, DCP or AFP-L3, was positive in 92.7% of cases at the diagnosis of extrahepatic metastasis, in contrast to the positivity of 42.0% at the initial treatment. This may reflect the degree of malignancy enhanced during the time course of disease. Viral markers, HBsAg and anti-HCVAb, were associated with the risk of extrahepatic metastasis probably because they are also risk factors of intrahepatic HCC recurrence.

In contrast to the relatively rare incidence of extrahepatic metastasis, intrahepatic recurrence is quite frequent with HCC. Whereas some cases of intrahepatic recurrence are attributable to metachronous *de novo* carcinogenesis, the risk of intrahepatic

metastasis via the portal vein has been emphasized for HCC nodules > 2.0 cm in diameter. This is in marked contrast to the fact that recurrence of HCC after liver transplantation is rare if HCC meets the Milan criteria, i.e. a solitary nodule not > 5.0 cm in diameter or less than four nodules each not > 3.0 cm. The present study has shown that the commonest route of extrahepatic metastasis is via the hepatic vein. Metastasis through the hepatic vein seems to occur at later stages than does metastasis through the portal vein. Because most patients in the current study were treated for intrahepatic nodules more than once, we could not analyse the size of tumour critical to extrahepatic metastasis. However, the large seropositivity of tumour markers at extrahepatic metastasis suggests an advanced degree of malignancy.

In conclusion, this large-scale study has shown that the incidence of extrahepatic metastasis of HCC was approximately 13% in 5 years after medical treatment. The extent of hepatic HCC lesions, tumour biomarkers and the presence of viral hepatitis were revealed to be the significant predictors of extrahepatic metastasis. Elevation of tumour biomarkers in spite of well-controlled hepatic lesions may indicate extrahepatic metastasis, frequent location of which included lung, bone, lymph node and adrenal gland. Symptoms such as dyspnoea or bone pain may be caused by extrahepatic metastasis of HCC.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74–108.
2. Shiratori Y, Shiina S, Imamura M, *et al.* Characteristic difference of hepatocellular carcinoma between hepatitis B- and C-viral infection in Japan. *Hepatology* 1995; **22** (Part 1): 1027–33.
3. Shiratori Y, Yoshida H, Omata M. Management of hepatocellular carcinoma: advances in diagnosis, treatment and prevention. *Expert Rev Anticancer Ther* 2001; **1**: 277–90.
4. Mazzaferro V, Regalia E, Doci R, *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693–9.
5. Shapiro RS, Katz R, Mendelson DS, Halton KP, Schwartz ME, Miller CM. Detection of hepatocellular carcinoma in cirrhotic patients: sensitivity of CT and ultrasonography. *J Ultrasound Med* 1996; **15**: 497–502; quiz 03–4.
6. Spreafico C, Marchiano A, Mazzaferro V, *et al.* Hepatocellular carcinoma in patients who undergo liver transplantation: sensitivity of CT with iodized oil. *Radiology* 1997; **203**: 457–60.
7. Peterson MS, Baron RL, Marsh JW Jr, Oliver JH III, Confer SR, Hunt LE. Pretransplantation surveillance for possible hepatocellular carcinoma in patients with cirrhosis: epidemiology and CT-based tumor detection rate in 430 cases with surgical pathologic correlation. *Radiology* 2000; **217**: 743–9.
8. Stoker J, Romijn MG, De Man RA, *et al.* Prospective comparative study of spiral computer tomography and magnetic resonance imaging for detection of hepatocellular carcinoma. *Gut* 2002; **51**: 105–7.
9. Arii S, Yamaoka Y, Futagawa S, *et al.* Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. *Hepatology* 2000; **32**: 1224–9.
10. Lo CM, Ngan H, Tso WK, *et al.* Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; **35**: 1164–71.
11. Shiina S, Teratani T, Obi S, *et al.* A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005; **129**: 122–30.
12. Shiina S, Tagawa K, Niwa Y, *et al.* Percutaneous ethanol injection therapy for hepatocellular carcinoma: results in 146 patients. *Am J Roentgenol* 1993; **160**: 1023–8.
13. Ikeda K, Saitoh S, Tsubota A, *et al.* Risk factors for tumor recurrence and prognosis after curative resection of hepatocellular carcinoma. *Cancer* 1993; **71**: 19–25.
14. Okada S, Shimada K, Yamamoto J, *et al.* Predictive factors for postoperative recurrence of hepatocellular carcinoma. *Gastroenterology* 1994; **106**: 1618–24.
15. Koike Y, Shiratori Y, Sato S, *et al.* Risk factors for recurring hepatocellular carcinoma differ according to infected hepatitis virus – an analysis of 236 consecutive patients with a single lesion. *Hepatology* 2000; **32**: 1216–23.
16. Johnson RC. Hepatocellular carcinoma. *Hepatogastroenterology* 1997; **44**: 307–12.
17. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer* 1954; **7**: 462–503.
18. Anthony PP. Primary carcinoma of the liver: a study of 282 cases in Ugandan Africans. *J Pathol* 1973; **110**: 37–48.
19. Aramaki M, Kawano K, Kai T, *et al.* Treatment for extrahepatic metastasis of hepatocellular carcinoma following successful hepatic resection. *Hepatogastroenterology* 1999; **46**: 2931–4.
20. Lo CM, Lai EC, Fan ST, Choi TK, Wong J. Resection for extrahepatic recurrence of hepatocellular carcinoma. *Br J Surg* 1994; **81**: 1019–21.
21. Lam CM, Lo CM, Yuen WK, Liu CL, Fan ST. Prolonged survival in selected patients following surgical resection for pulmonary metastasis from hepatocellular carcinoma. *Br J Surg* 1998; **85**: 1198–200.
22. Uka K, Aikata H, Takaki S, *et al.* Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. *World J Gastroenterol* 2007; **13**: 414–20.
23. Kaczynski J, Hansson G, Wallerstedt S. Metastases in cases with hepatocellular carcinoma in relation to clinicopathologic features of the tumor. An autopsy study from a low endemic area. *Acta Oncol* 1995; **34**: 43–8.

24. Katyal S, Oliver JH III, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahepatic metastases of hepatocellular carcinoma. *Radiology* 2000; **216**: 698–703.
25. Omata M, Tateishi R, Yoshida H, Shiina S. Treatment of hepatocellular carcinoma by percutaneous tumor ablation methods: ethanol injection therapy and radiofrequency ablation. *Gastroenterology* 2004; **127**(Suppl. 1): S159–66.
26. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc* 1958; **53**: 457–81.
27. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94**: 496–506.
28. Cox DR. Regression models and life-tables (with discussion). *J R Stat Soc* 1972; **34B**: 187–220.
29. Ikai I, Arii S, Okazaki M, *et al.* Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. *Hepatol Res* 2007; **37**: 676–91.
30. Natsuizaka M, Omura T, Akaike T, *et al.* Clinical features of hepatocellular carcinoma with extrahepatic metastases. *J Gastroenterol Hepatol* 2005; **20**: 1781–7.
31. Kondo Y, Niwa Y, Akikusa B, Takazawa H, Okabayashi A. A histopathologic study of early hepatocellular carcinoma. *Cancer* 1983; **52**: 687–92.
32. Onuigbo WI. Batson's theory of vertebral venous metastasis: a review. *Oncology* 1975; **32**: 145–50.
33. Batson OV. The function of the vertebral veins and their role in the spread of metastases. 1940. *Clin Orthop Relat Res* 1995; 4–9.
34. Yamashita N, Fukawa M, Imaizumi N, *et al.* Establishing a diagnosis of adrenal metastasis from hepatocellular carcinoma by 99mTc-PMT hepatobiliary scintigraphy. *Surg Today* 1992; **22**: 565–7.
35. Momoi H, Shimahara Y, Terajima H, *et al.* Management of adrenal metastasis from hepatocellular carcinoma. *Surg Today* 2002; **32**: 1035–41.
36. Zeng ZC, Tang ZY, Fan J, *et al.* Radiation therapy for adrenal gland metastases from hepatocellular carcinoma. *Jpn J Clin Oncol* 2005; **35**: 61–7.
37. Sala M, Llovet JM, Vilana R, *et al.* Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. *Hepatology* 2004; **40**: 1352–60.
38. Iwata M, Kaneko S, Terasaki S, *et al.* Importance of achieving complete necrosis during the first treatment for hepatocellular carcinoma to prevent bone metastasis: a prospective study. *J Gastroenterol Hepatol* 2001; **16**: 46–51.
39. Louha M, Poussin K, Ganne N, *et al.* Spontaneous and iatrogenic spreading of liver-derived cells into peripheral blood of patients with primary liver cancer. *Hepatology* 1997; **26**: 998–1005.
40. Sheen IS, Jeng KS, Shih SC, *et al.* Does surgical resection of hepatocellular carcinoma accelerate cancer dissemination? *World J Gastroenterol* 2004; **10**: 31–6.
41. Lin SC, Shih SC, Kao CR, Chou SY. Transcatheter arterial embolization treatment in patients with hepatocellular carcinoma and risk of pulmonary metastasis. *World J Gastroenterol* 2003; **9**: 1208–11.
42. Okuda K, Ohtsuki T, Obata H, *et al.* Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985; **56**: 918–28.
43. The Cancer of the Liver Italian Program (CLIP) Investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. *Hepatology* 1998; **28**: 751–5.
44. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329–38.

Review

Treatment of hepatocellular carcinoma

Ryota Masuzaki, Masao Omata

Department of Gastroenterology, University of Tokyo, Japan

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, and is the third highest cause of cancer-related mortality. HCC usually develops in patients with chronic liver disease, particularly in those who also have cirrhosis. The possibility of curative treatment depends on both the stage of tumor and liver function. Effective treatments for HCC include percutaneous ablation, surgical resection, and liver transplantation. Both percutaneous ablation and surgical resection provide a high rate of complete responses and are assumed to improve survival that should exceed 50% at 5 years. Liver transplantation results in a better survival rate, and is not contraindicated by advanced liver dysfunction. However, its application is limited by the scarcity of donor organs. Treatments for advanced HCC include transarterial chemoembolization and chemotherapy. Although short-term prognosis of HCC patients has improved recently due to advances in early diagnosis and treatment, long-term prognosis is as yet far from satisfactory due to frequent recurrence. Prevention of recurrence of HCC remains one of the most challenging tasks in current hepatology.

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Hepatocellular carcinoma (HCC), one of the most common cancers worldwide, usually develops in an already damaged, often cirrhotic liver. Although the etiology of background liver diseases differs geographically, chronic viral hepatitis due to either hepatitis B virus (HBV) or hepatitis C virus (HCV) is the main cause of HCC in most areas.[1,2,3] Comparison of treatment outcomes is difficult because there is no universally accepted staging system for HCC. The comparison is further complicated by the fact that the background liver function may also differ. In fact, not only HCC itself but also the background liver disease should be the target of complete treatment for HCC.

Underlying liver disease

Etiology

The incidence rate of HCC differs according to the geographical area, which is mostly due to varying prevalence of several carcinogenic factors in different populations.[4] The mortality from HCC has more than tripled in Japan since the mid-1970s. This increase in HCC incidence has been almost entirely due to HCV-related HCC.[5] HCV infection is currently responsible for 75%– 80% cases of HCC in Japan whereas HBV is responsible for 10%–15% cases.[6] About 40% of HCV-related HCC patients in Japan have a history of blood transfusion and typical patients received blood transfusion in the 1950s or 1960s. During that period, supply for blood transfusion was dependent on paid blood donors. Few of them were also injecting-drug users, mainly methamphetamine, among whom HCV is thought to have spread first. Infection through reused syringes and needles is also suspected. Commercial blood banks were entirely abolished by 1969, and the reuse of syringes and needles was strongly discouraged in the 1970s. The viral spread in Japan started to decline and was almost eliminated after the advent of sensitive HCV detection system in the early 1990s. Thus, there was an interval of 30 years between the peak of HCV spread and that of HCV-related HCC incidence in Japan, which can be considered as the incubation period for carcinogenesis. Countries where spread of HCV occurred more recently are now facing increasing incidence of HCC.[7,8]

Prevention of HCC

Since chronic viral hepatitis B and C are the predominant causes of HCC,[9,10] infection control will lead to primary prevention of HCC (Table 1). In fact, neonatal vaccination for HBV has decreased not only the prevalence of HBV carriers, but also the incidence of HBV-related HCC. HCV spread is currently declining in most countries due to increasing awareness of blood-borne infection control. The effect of interferon therapy on the prevention of development of HCC may be controversial. Studies in USA have failed to show the reduction in HCC incidence after interferon therapy. However, numerous clinical studies done in Japan have clearly demonstrated that HCC incidence was reduced among interferon-treated patients showing sustained virologic response.[11,12] Resolution of cirrhosis was also noted following sustained virologic response. These effects can be anticipated to be augmented by the advent of combination therapy with peg-interferon

Table 1: Strategies for prevention of HCC in patients with hepatitis B and C

Virus	*Hepatitis B*	*Hepatitis C*
New infection	Neonate vaccination	General infection control
Existing infection	Antiviral therapy (Suppression)	Antiviral therapy (eradication)
	Nucleos(t)ide analogs	Interferon plus ribavirin
Treatment*	Early diagnosis and curative treatment	
Prevent recurrence*	Transplantation	
	Antiviral therapy (?)	
	Molecular targeting drugs	

Strategies for treatment and prevention of recurrence are similar for both hepatitis B and C

and ribavirin. The discrepancy in the preventive effect of interferon therapy for HCC in studies from Japan and USA may be partly attributable to different characteristics of patients, such as the ages of HCV-infected patients, but certainly requires further elucidation.

Recent reports of a large-scale, long-term cohort study in Taiwan have shown that that the serum level of HBV DNA is the strongest risk factor for cirrhosis and HCC among HBV-positive patients, independently of serum HBe antigen/HBe antibody status or alanine aminotransferase (ALT) levels.[13,14] Since HBV-related hepatocarcinogenesis is related, at least in part, to viral duplication and integration of viral DNA into host genome, it is possible that anti-HBV nucleos(t)ide analogs, by suppressing viral duplication, can decrease the risk of HBV-related HCC among chronic hepatitis B patients.[15]

Diagnosis of HCC

Cost-effective surveillance is possible because risk factors for HCC are well known and this enables us to detect HCC at an early stage. There has been marked progress in treatment of HCC, as we describe later. However, the indication of effective treatments depends heavily on the stage of cancer, and detection at an early stage is still a prerequisite for improved prognosis.

A diagnostic approach to HCC has been developed based on available literature and expert consensus.[14,15] If the nodule is larger than 2 cm at initial diagnosis and has the typical features of HCC (hypervascular in arterial phase with washout in portovenous phase) on a dynamic imaging technique, biopsy is not necessary for the diagnosis of HCC. Alternatively, if the AFP is >200 ng/mL biopsy is also not required. Meanwhile, the recommended diagnostic approach for tumors ≤2 cm is that, when nodules within 1 cm – 2 cm on screening of a cirrhotic liver are typical of HCC on 2 imaging modalities, the lesion should be treated as HCC. In an atypical lesion where the vascular finding is not consistent among techniques, a biopsy of the lesion should be considered. Nodules which are smaller than 1 cm should be followed with US at 3- to 6-month intervals. If, over a period of 2 years, increase in size is not observed, a return to routine surveillance at 6-month intervals is suggested.

Imaging modalities

The detection of HCC primarily depends on imaging studies, where ultrasonography (US) has been playing an essential role. The resolution of US in detecting small intrahepatic nodules has been greatly improved with technological developments. Ultrasound examination detects HCC nodules because their echogeneity is different from the surrounding liver. Small tumor nodules are typically hypoechoic and become hyperechoic as they enlarge. The presence of a capsule may also be noted. Although confirmatory diagnosis of HCC usually depends on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), color Doppler US and US using contrast agents may provide additional qualitative information. Several new contrast agents are being evaluated as an aid to diagnose HCC or evaluate the effectiveness of ablation or assistance for US-guided ablation therapy.[18,19] In particular, Sonazoid, a new contrast agent commercially available in Japan since 2007, is very useful in detecting malignant liver tumors, including metastatic tumors, due to the long duration of Kupffer imaging (Figure 1).

Recent improvements in CT imaging of HCC include the use of spiral scanners that allow very rapid imaging of the liver following infusion of intravenous contrast agents. CT plays a pivotal role in detecting small HCC nodules.[20] MRI may be the diagnostic procedure of choice for HCC depending on its availability. Recent advances in MRI technology include scanner hardware, software, and new contrast agents.

Tumor markers

Several tumor markers are used in clinical setting for the diagnosis of HCC, evaluation of treatment efficacy and surveillance for recurrence. Alpha-fetoprotein (AFP) may be the best known among them. Serum AFP level is elevated above 20 ng/mL in >70% of patients with HCC. However, AFP levels may be also elevated in benign liver diseases, such as chronic hepatitis or cirrhosis, indicating a low specificity. Moreover, a small HCC is less likely to

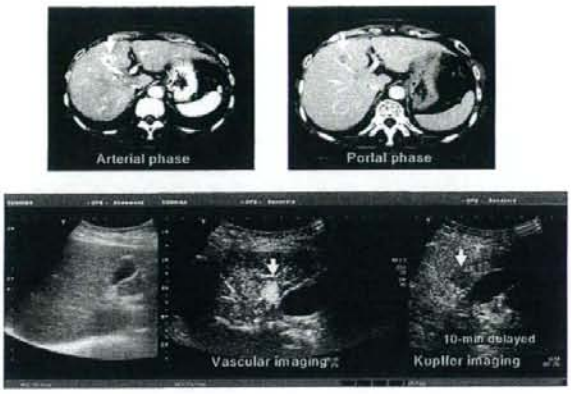

Figure 1: Sonazoid features of HCC. The left top panel shows an arterial phase CT examination of the liver and an enhancing mass in the right lobe. The right top panel shows a wash out on portal phase. This lesion is hardly detected at the B-mode image (left bottom panel). The middle bottom panel shows vascular imaging 30 seconds after intravenous injection of Sonazoid. The tumor is clearly detected as a hyperechoic lesion. The right bottom panel shows Kupffer imaging of Sonazoid and the tumor is detected as an anechoic lesion

be AFP-producing compared to large HCC detected decades before. Thus, the usefulness of AFP in the diagnosis of HCC is rather controversial.

AFP is heterogeneous in relation to the degree of sugar chain fucosylation,[21] which can be distinguished by the binding affinity to lectin (*Lens culinaris* agglutinin). Lectin fraction-3 of AFP (AFP-L3) is highly specific to HCC.[22,23] AFP-L3 is considered not only a very specific marker of HCC, but also an indicator of poorly-differentiated histology and unfavorable prognosis.[24]

Des-gamma-carboxy-prothrombin (DCP) is an abnormal prothrombin induced by vitamin K deficiency. Although its sensitivity for the detection of HCC is lower than that of AFP, the combination of DCP and AFP has the sensitivity of >80% among HCC 3 cm – 4 cm in diameter and 70% among HCC 2 cm – 3 cm diameter.[25,26,27] The positivity for DCP is reportedly associated with the risk of portal vein invasion, one of the main end-stage sequelae of HCC.[28]

Evaluation of liver function reservoir

Liver function is one of the decisive factors in considering the indication of treatment for HCC. Few treatments are applicable to HCC in patients with decompensated cirrhosis regardless of tumor stage. Several hepatic function tests have been developed and applied to patients in the 1980s and 1990s. Currently, the most frequently used assessment is the Child–Pugh classification.[29] In Europe and USA, the absence of clinically relevant portal hypertension, as reflected by a hepatic venous pressure gradient <10 mmHg, is often emphasized.[30] Blood coagulation factors, especially prothrombin activity, are used as a rapid turnover index of liver function. Galactose elimination capacity, indocyanine green elimination test and asialoscintigraphy may provide additional information. Patients under consideration for liver transplantation are evaluated based on the Model for End-stage Liver Disease (MELD) scoring system, which consist of serum creatinine, total bilirubin, and prothrombin INR.[31,32]

Treatment of HCC

Although anti-viral therapies may reduce the risk of HCC, secondary prevention, i.e. early diagnosis and treatment, is still essential. There have been great advances in diagnostic imagings such as CT and US. Simultaneously, much progress has been made in the treatments of HCC, some of which will be illustrated here. The choice of optimal treatment for individual patients may be sometimes controversial. Generally speaking, treatment options are broader when the cancer is detected at earlier stages. However, some treatments may be contraindicated due to accompanying liver diseases. Indeed, the prognosis of patients with HCC is dependent not only on the stage of tumor but also on the background liver function reservoir (Figure 2). Survival of HCC patients grouped based on treatment modality, as reported by the Liver Study Cancer Group of Japan, is shown in Table 2. The survival of patients who underwent RFA is not inferior to that of patients who received surgical resection, although the former group

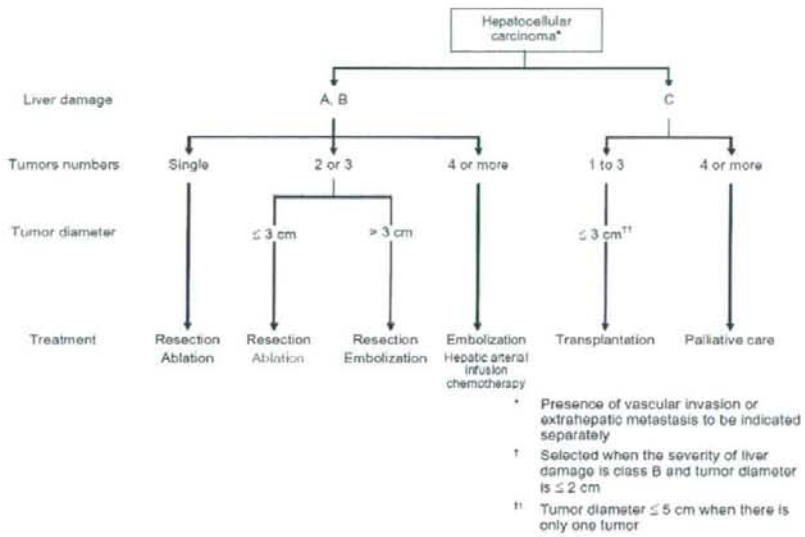

Figure 2. Flowchart of management of hepatocellular carcinoma based on degree of liver damage and tumor characteristics. Liver damage was assessed by the liver function classification reported by the Liver Cancer Study Group of Japan using the category indocyanine green retention rate at 15 min [ICG(R15)] instead of encephalopathy in the Child-Pugh classification

contains patients with poorer hepatic function reservoir.

Surgical resection

Ever since acceptable safety was achieved in hepatectomy, surgical resection has been considered as the sole potentially curative treatment for HCC, although currently it competes with transplantation and percutaneous ablation. Resection is usually indicated in patients with solitary HCC and preserved liver function. The liver function reservoir limits the extent of hepatic resection. This poses no difficulty when HCC arises in a normal liver. However, since HCC usually develops in cirrhotic liver, the preoperative evaluation of liver function is essential. Perioperative mortality can be less than 1%. The use of intraoperative ultrasonography (IOUS) allows precise localization and staging of the tumor. Anatomical resection is

Table 2: Survival of HCC patients according to treatment modality (1992–2003)

Treatment	*Number*	*Survival (years; %)*			*Liver damage* (N)*	*Survival (years; %)*		
		1	3	5		1	3	5
Resection	27062	87.8	69.2	52.1	A (17433)	89.9	73.4	58.4
					B (7260)	85.2	59.4	45.3
					C (631)	74.1	69.6	35.5
Radiofrequency ablation	5478 (1998–2003)	94.9	76.7	57.3	A (2927)	97.1	82.7	73.6
					B (2123)	94.4	72.2	-
					C (277)	80.7	52.4	-
Percutaneous ethanol injection	14726	91.3	63.0	39.4	A (7257)	94.7	72.2	48.4
					B (5243)	91.8	57.7	32.9
					C (1237)	76.8	36.7	19.2
Transcatheter arterial chemoembolization	30490	74.5	40.2	21.3	A (11094)	83.7	51.4	29.8
					B (8365)	75.4	37.5	18.2
					C (2303)	56.8	19.8	7.0

* The liver function classification reported by the Liver Cancer Study Group of Japan using the category indocyanine green retention rate at 15 min [ICG(R15)] instead of encephalopathy in the Child-Pugh classification

preferred by some surgeons, who perform segment-wise hepatectomy whenever possible. This is based on the idea that intrahepatic microscopic metastasis is likely to occur in the same segment as the original tumor via portal veins. Survival of properly selected patients receiving surgical hepatectomy exceeds 70% at 5 years, although the overall survival is substantially reduced without strict selection of patients.[33] Thus, hepatectomy plays a limited role in the treatment of overall HCC.[34] Only 20% – 30% of patients can be candidates for hepatectomy, with the other patients not being considered either because of severely impaired liver function or advanced tumor stage. Most importantly, even after apparently curative surgical resection, 80% of patients develop recurrent HCC within 5 years[35] because of latent intrahepatic metastasis or metachronous multicentric carcinogenesis.

Liver transplantation

The restriction on hepatic resection posed by poor liver function reservoir can be lifted in case of liver transplantation. Although extrahepatic comorbidity and old age can limit the indication for transplantation, the status of background liver will not be a contraindication, whatever the degree or severity of liver dysfunction, whatever the degree or severity of the underlying cirrhosis.[36,37] Indeed, the recovery of liver function is the chief object of liver transplantation for liver failure without HCC, and this is also applicable to patients with HCC. The restriction on resection posed by multiplicity of HCC lesions can be also conquered by liver transplantation when the restriction is due to the fact that the expected remnant liver volume is too small. Of course there is a certain limitation concerning the stage of tumor, beyond which post-transplant HCC recurrence is likely to occur. Post-transplant HCC recurrence is usually of aggressive nature and associated with poor prognosis, probably because of immunosuppressant use. Pre-transplant tumor invasion into large vessels is a definite contraindication for transplantation. Currently, the Milan criteria are widely accepted as indication criteria for liver transplantation with HCC: solitary tumor of 5 cm or less in diameter or three or fewer lesions each 3 cm or less in diameter.[37,38] However, the Milan criteria were not established on exhaustive evidence and there have been ceaseless efforts to extend the criteria. What is really needed is not a static anatomic description of the extent of HCC, but more sophisticated prognosticators of the behavior of an individual tumor, possibly obtainable through genomics or proteomics.

The waiting list of potential recipients continues to be long as the demand for donor liver keeps going up. The scarcity of donor organ is a universal issue. With a waiting list of 12 months, up to 25% of patients are estimated to be excluded from liver transplantation due to tumor advance, an unfortunate event that translates to 60% survival on intention-to-treat basis.[39] The lack of cadaveric donors is very intense in Japan, where cadaveric liver transplantation has been performed only in 52 cases in 9 years. Living donor liver transplantation has been adopted as the practical alternative for cadaveric transplantation.[40] After the first successful attempt,[41] more than 3000 living donor operations have been performed worldwide. Results from Asia[41,43] and a recent survey in Japan[44,45,46] suggest that living donor liver transplantation is accompanied by favorable outcomes comparable to cadaveric transplantation. A decision analysis indicated that, based on the risk for the donor as 0.3%–0.5% mortality, living donor transplant is a cost-effective approach if the waiting time exceeds 7 months.[47] However, this is a complex intervention that should be undertaken only by expert surgeons to ensure the lowest morbidity and best outcome to both the recipient and the donor.

Recrudescence of viral hepatitis is a substantial problem for liver transplantation in HCC patients because the majority of them have HBV or HCV infection pre-transplant. Measures have been taken to prevent post-transplant viral infection, such as nucleos(t)ide analogues and hepatitis B immunoglobulin (HBIG) for HBV and peginterferon-ribavirin combination for HCV.[48,49,50]

Local ablation therapies

Not only cadaveric liver transplantation, but also living donor liver transplantation is frequently infeasible because of the absence of an appropriate donor or the conditions of the recipient. Consequently, the clinical need for non-surgical therapies of HCC remains unmitigated. Among them, image-guided local ablation therapies, such as percutaneous ethanol injection[51,52] and radiofrequency ablation,[53–56] have been playing important roles, because they are potentially curative, less-invasive, and easily repeatable. At the authors' institution, about 90% of naïve HCC patients are treated with local ablation therapies. We treated a total of 2000 cases with ethanol injection starting in 1985, with satisfactory long-term results. The major treatment modality has been shifted to radiofrequency ablation (RFA) since 1999, which has been shown to be superior to ethanol injection in randomized controlled trials including ours.[57,58]

In an RFA procedure, an ablation electrode at the tip of a needle is placed percutaneously into the targeted tumor under ultrasound guidance. Radiofrequency electromagnetic waves are transmitted from a generator and converted to heat in tissues surrounding the electrode. There are several types of RFA electrode with distinct size and shape and the details of ablation procedure differ

according to the type of electrode.

We have adopted the following indication criteria for RFA: (i) HCC lesions are unresectable or patient refuses surgery; (ii) three or fewer lesions, each 3 cm or less in diameter; (iii) no extrahepatic metastasis or vascular invasion; (iv) no excessive bleeding tendency, platelet count must be greater than 50 X 10^9/L and prothrombin activity must be better than 50%; (v) no refractory ascites; and (vi) total bilirubin level of <3.0 mg/dL.[58,59]

Reportedly complete tumor necrosis can be achieved by RFA in 80%–100% of cases. The difference in complete necrosis rates seems to represent not only the difference in patients' characteristics but also the difference in expertise among institutions. According to the authors' experience in RFA for HCC, viable lesions remained only in 14 (0.6%) out of 2350 sessions (1219 patients), although we put no restriction on the location of tumor.[60] To accomplish these outcomes, we have used artificial pleural effusion technique, artificial ascites technique[61] and guide-needle method. The therapy has not been compromised if the target lesions were at so-called difficult locations, i.e. on the surface of liver, beneath the diaphragm, near the large vessels, or adjacent to other organs. We have treated 652 patients with naïve HCC by RFA. The overall survival rates among these patients at 1, 2, 3, 4, 5, and 6 years were 96%, 88%, 80%, 69%, 58%, and 53%, respectively.

Transcatheter arterial chemoembolization

Transcatheter arterial chemoembolization (TACE) has been widely performed for unresectable HCC. TACE is based on the fact that HCC derives its blood supply predominantly from the hepatic artery, whereas surrounding liver receives portal-dominant blood supply. TACE is effective for multiple or large lesions and can be performed in cases of impaired liver function. The catheter tip was advanced at the nearest site of the feeding artery as possible. The emulsion of anticancer agent and lipiodol followed by gelatin sponge particles was carefully injected under fluoroscopic monitoring. The dose of emulsion of anticancer agent and lipiodol and the pieces of embolic materials used for TACE were determined based on the tumor size and extension of the lesions. The patients were followed by dynamic CT or MRI every 3–4 months, and repeated TACE was determined when the local recurrence, intrahepatic metastases, and/or second primary HCC was found. The effects of TACE are limited in cases with capsular invasion, extracapsular growth, or vascular invasion. Complete necrosis of whole lesions is rarely achieved and the indication should be limited to advanced HCC that cannot be treated by resection nor ablations. At present, options such as radio-labeled yttrium glass beads and radio-labeled lipiodol remain experimental. Despite huge efforts in this area, beneficial effects on survival are not clear.[34,62] However, two recently published trials have shown a survival benefit of TACE using either doxorubicin or cisplatin compared with best supportive care only, and deserve attention.[63,64] From Japan, Takayasu *et al* reported that TACE demonstrated a 5-year survival rate of 26%, a mortality rate of 0.5% in 8510 patients with unresectable HCC and the hepatic function, tumor characteristics (size, number, and presence of portal vein tumor thrombus), and AFP value were independent predictors of survivals of patients.[65]

Conventional chemotherapy

Although a huge number of randomized and non-randomized clinical trials have been published to evaluate the usefulness of a single agent or a combination of agents as chemotherapy to highly advanced HCC, current outcomes are dismal.[66–69] Recently, a combination therapy with subcutaneous interferon and intra-arterial infusion of 5-FU was reported with promising results in 116 HCC patients with portal vein invasion.[70] One cycle of treatment consisted of 4 weeks, where 5,000,000 U (5 MU) IFN (*OIF*; Otsuka Pharmaceutical, Tokyo, Japan) was administered intramuscularly on days 1, 3, and 5 of each week, resulting in a total dose of 60 MU in a cycle. 5-FU (500 mg/day, Kyowa Hakko, Tokyo, Japan) was administered into the hepatic artery over 5 hours using a portable infusion pump on days 1–5 of the first and second weeks through the intra-arterial catheter (5 g in a cycle). Nineteen (16%) patients showed complete response and other 42 (36%) showed partial response. Adverse events were limited to nausea and appetite loss. The overall survival rates at 12 and 24 months among patients were 34% and 18%, respectively, and those among complete responders were 81% and 59%, respectively.

Molecular-targeted chemotherapy

Antiangiogenic molecular-targeted chemotherapy usually uses antibodies to an extracellular growth factor receptor, or inhibitors to a receptor tyrosine kinase. Epidermal growth factor receptor (EFGR) and vascular endothelial growth factor receptor (VFGFR) are usual targets of new drugs intended to suppress tumor-related angiogenesis. The EGFR-inhibiting agents gefinitib and erlotinib are approved for lung cancer and cetuximab is for irinotecan–refractory metastatic colorectal cancer. Gefinitib inhibited cell proliferation and metastatic properties of HCC both in vitro and in an animal model.[71] Recent data from two clinical trials suggested some prolongation of progression-free survival in HCC patients by erlotinib.[72,73]

A variety of agents that interfere with VEGFR signaling are being investigated. The monoclonal antibody bevacizumab is approved for metastatic colorectal cancer in

combination with fluorouracil-based chemotherapy. Recent data for bevacizumab indicate that bevacizumab can be administered safely in carefully selected HCC patients.[74] Caution must be exercised in using antiangiogenic agents in HCC patients with esophageal varices, vascular thrombi, and coagulation disorders. A novel inhibitor of raf kinase and VEGFR signal transduction sorafenib showed promising clinical activity in HCC, median time to progression of 4.2 months, and median overall survival of 9.2 months in phase II trial.[75] In phase III trial, sorafenib hepatocellular carcinoma assessment randomized protocol (SHARP) trial, the median time to radiologic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group ($p<0.001$) and median overall survival was 10.7 months in the former and 7.9 months in the latter.[76] However, 96.7% of patients were Child–Pugh class A and median survival was not satisfactory even in the sorafenib group. Moreover, since molecular-targeted drugs are costly, a cost–benefit analysis might be needed.

Other options

Radionuclide yttrium-90, a pure beta emitter, is a form of hepatic artery-directed therapy. Microspheres of approximately 25 im in diameter containing yttrium-90 are lodged via a catheter insertion into the lobar or segmental level of either hepatic artery and emit local radiation with limited exposure to adjacent healthy tissue.[77] Recently, there are no data to suggest its superiority over ablative therapies.

High-intensity focused ultrasound (HIFU) therapy has been developed for the treatment of tumors of solid organs.[78] HIFU focuses an extracorporeal source of US to a target lesion inside the body. The US energy passes harmlessly through overlying tissues en route to a tightly focused target area. The rapid rate of energy deposition generates a rapid rise in temperature, which results in irreversible cell death with defined region of tissue necrosis. The disadvantages of HIFU therapy are: it is a time-consuming procedures (average 3–4 hours) and sometimes needs rib resection when the tumor is located behind the rib bone. There are a few reports about the long-term efficacy of HIFU for advanced HCC.

Prevention of recurrence

Short-term prognosis of HCC patients has been much improved recently due to advances in early diagnosis and treatment as shown above. However, long-term prognosis is as yet far from satisfactory, as indicated by the fact that overall survival at 10 years after apparently curative treatment of HCC is as low as 22%–35%.[79,80] In a typical cumulative survival curve of HCC patients after treatment, the slope of curve does not level out over time in contrast to the slope of cumulative survival curves after relatively curative treatment of most other malignancies. In other words, HCC is rarely treated curatively, with the exception of successful liver transplantation. The primary reason for poor long-term survival is extremely frequent intrahepatic recurrence of HCC even after apparently curative treatment, either local ablation or surgical resection.[81] These are locoregional therapies and in contrast to liver transplantation, may not remove microscopic metastasis in the remaining liver. However, this does not explain the fact specific to HCC that the risk of recurrence does not decline over time, which continues to occur at a rate of 10%–20% per year. This continual recurrence of HCC is considered to be mostly due to multicentric *de novo* carcinogenesis. Also in this respect liver transplantation exceeds locoregional therapies.

However, strategies similar to those of primary prevention of HCC may be applicable to HCC recurrence due to multicentric carcinogenesis. Interferon therapies have been performed on HCV-related HCC patients after initial treatment and there was a possible reduction in recurrence incidence.[82,83] Liver function did not deteriorate in patients who achieved sustained virologic response by interferon therapy, among whom there was no death due to liver failure. Consequently, overall survival was improved in patients treated with interferon. For HBV-related HCC, recently developed oral nucleos(t)ide analogs are also promising, particularly because the relation between serum viral load and the risk of HCC has been recently shown. In contrast to interferon, these anti-HBV drugs can be given to patients with advanced cirrhosis. Although the effects of these drugs on the prevention of HBV-related HCC recurrence are yet to be shown, we can expect at least that the anti-HBV drugs prevent further deterioration of liver function by suppressing hepatitis.

Early diagnosis and complete removal of primary HCC lesions are prerequisities for tertiary prevention. For moderately-advanced HCC where microscopic metastasis can be suspected safe and effective chemotherapeutic agents would be useful as adjuvant or neoadjuvant. However, conventional chemotherapeutic agents are not satisfactorily effective against HCC, nor safe enough for long-term use. Hasegawa *et al* reported that the administration of uracil-tegafur (UFT) as an adjuvant chemotherapy for hepatic resection offered no evidence to support potential benefits and overall survivals appeared to be worse in the treatment group.[84] They suggested that a reason for the poor survival in the treatment group was the adverse effects of UFT on liver function. Some agents appears promising in terms of safety, but the effects remain yet to be confirmed.[85,86] Prevention of recurrence of HCC, or tertiary prevention, is one of the most challenging tasks in current hepatology.

References

1. Okuda K. Hepatocellular carcinoma: recent progress. *Hepatology* 1992;15:948–63.
2. Sherlock S. Viruses and hepatocellular carcinoma. *Gut* 1994;35:828–32.
3. Omata M, Ashcavai M, Liew CT, Peters RL. Hepatocellular carcinoma in the USA., etiologic considerations. Localization of hepatitis B antigens. *Gastroenterology* 1979;76:279–87.
4. Bosch FX, Ribes J, Diaz M, Cleries R. Primary liver cancer: worldwide incidence and trends. *Gastroenterology* 2004;127:S5–S16.
5. Okuda K, Fujimoto I, Hanai A, Urano Y. Changing incidence of hepatocellular carcinoma in Japan. *Cancer Res* 1987;47:4967–72.
6. Omata M, Yoshida H, Shiratori Y. Prevention of hepatocellular carcinoma and its recurrence in chronic hepatitis C patients by interferon therapy. *Clin Gastroenterol Hepatol* 2005;3:S141–S143.
7. Tanaka Y, Hanada K, Mizokami M, Yeo AE, Shih JW, Gojobori T, Alter HJ. Inaugural Article: A comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. *Proc Natl Acad Sci USA* 2002;99:15584–9.
8. El-Serag HB, Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med* 2003;139:817–23.
9. Simonetti RG, Camma C, Fiorello F, Cottone M, Rapicetta M, Marino L, *et al.* Hepatitis C virus infection as a risk factor for hepatocellular carcinoma in patients with cirrhosis. A case–control study. *Ann Intern Med* 1992;116:97–102.
10. Colombo M, de Franchis R, Del Ninno E, Sangiovanni A, De Fazio C, Tommasini M, *et al.* Hepatocellular carcinoma in Italian patients with cirrhosis. *N Engl J Med* 1991;325:675–80.
11. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, *et al.* Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann Intern Med* 1999;131:174–81.
12. Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, *et al.* Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995;346:1051–5.
13. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, *et al.* Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*2006;295:65–73.
14. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006;130:678–86.
15. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, *et al.* Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004;351:1521–31.
16. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208–36.
17. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, *et al.* Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001;35:421–30.
18. Minami Y, Kudo M, Chung H, Kawasaki T, Yagyu Y, Shimono T, *et al.* Contrast harmonic sonography-guided radiofrequency ablation therapy versus B-mode sonography in hepatocellular carcinoma: prospective randomized controlled trial. *AJR Am J Roentgenol* 2007;188:489–94.
19. Morimoto M, Shirato K, Sugimori K, Kokawa A, Tomita N, Saito T, *et al.* Contrast-enhanced harmonic gray-scale sonographic-histologic correlation of the therapeutic effects of transcatheter arterial chemoembolization in patients with hepatocellular carcinoma. *AJR Am J Roentgenol* 2003;181:65–9.
20. Coin CG, Chan YS. Computed tomographic arteriography. *J Comput Assist Tomogr* 1977;1:165–8.
21. Taketa K, Sekiya C, Namiki M, Akamatsu K, Ohta Y, Endo Y, Kosaka K. Lectin-reactive profiles of alpha-fetoprotein characterizing hepatocellular carcinoma and related conditions. *Gastroenterology* 1990;99:508–18.
22. van Staden L, Bukofzer S, Kew MC, Savage N. Differential lectin reactivities of alpha-fetoprotein in hepatocellular carcinoma: diagnostic value when serum alpha-fetoprotein levels are slightly raised. *J Gastroenterol Hepatol* 1992;7:260–5.
23. Yamashita F, Tanaka M, Satomura S, Tanikawa K. Prognostic significance of Lens culinaris agglutinin A-reactive alpha-fetoprotein in small hepatocellular carcinomas. *Gastroenterology* 1996;111:996–1001.
24. Tateishi R, Shiina S, Yoshida H, Teratani T, Obi S, Yamashiki N, *et al.* Prediction of recurrence of hepatocellular carcinoma after curative ablation using three tumor markers. *Hepatology* 2006;44:1518–27.
25. Izuno K, Fujiyama S, Yamasaki K, Sato M, Sato T. Early detection of hepatocellular carcinoma associated with cirrhosis by combined assay of des-gamma-carboxy prothrombin and alpha-fetoprotein: a prospective study. *Hepatogastroenterology* 1995;42:387–93.
26. Shimada M, Takenaka K, Fujiwara Y, Gion T, Kajiyama K, Maeda T, *et al.* Des-gamma-carboxy prothrombin and alpha-fetoprotein positive status as a new prognostic indicator after hepatic resection for hepatocellular carcinoma. *Cancer* 1996;78:2094–100.
27. Aoyagi Y, Oguro M, Yanagi M, Mita Y, Suda T, Suzuki Y, *et al.* Clinical significance of simultaneous determinations of alpha-fetoprotein and des-gamma-carboxy prothrombin in monitoring recurrence in patients with hepatocellular carcinoma. *Cancer* 1996;77:1781–6.
28. Koike Y, Shiratori Y, Sato S, Obi S, Teratani T, Imamura M, *et al.* Des-gamma-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. *Cancer* 2001;91:561–9.
29. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal

varices. *Br J Surg* 1973;60:646–9.

30. Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, *et al.* Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology* 1996;111:1018–22.
31. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000;31:864–71.
32. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;33:464–70.
33. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 2005;25:181–200.
34. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003;362:1907–17.
35. Balsells J, Charco R, Lazaro JL, Murio E, Vargas V, Allende E, *et al.* Resection of hepatocellular carcinoma in patients with cirrhosis. *Br J Surg* 1996;83:758–61.
36. Iwatsuki S, Starzl TE, Sheahan DG, Yokoyama I, Demetris AJ, Todo S, *et al.* Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg* 1991;214:221–8; discussion 228–9.
37. Pichlmayr R, Weimann A, Oldhafer KJ, Schlitt HJ, Tusch G, Raab R. Appraisal of transplantation for malignant tumours of the liver with special reference to early stage hepatocellular carcinoma. *Eur J Surg Oncol* 1998;24:60–7.
38. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693–9.
39. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999;30:1434–40.
40. Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med* 2002;346:1074–82.
41. Kawasaki S. Living-donor liver transplantation for hepatocellular carcinoma. *Hepatogastroenterology* 2002;49:53–5.
42. Steinmuller T, Pascher A, Sauer I, Theruvath T, Muller A, Settmacher U, *et al.* Living-donation liver transplantation for hepatocellular carcinoma: time to drop the limitations? *Transplant Proc* 2002;34:2263–4.
43. Gondolesi GE, Roayaie S, Munoz L, Kim-Schluger L, Schiano T, Fishbein TM, *et al.* Adult living donor liver transplantation for patients with hepatocellular carcinoma: extending UNOS priority criteria. *Ann Surg* 2004;239:142–9.
44. Todo S, Furukawa H. Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan. *Ann Surg* 2004;240:451–9; discussion 459–61.
45. Sugawara Y, Tamura S, Makuuchi M. Living donor liver transplantation for hepatocellular carcinoma: Tokyo University series. *Dig Dis* 2007;25:310–2.
46. Sugawara Y, Makuuchi M. Advances in adult living donor liver transplantation: a review based on reports from the 10th anniversary of the adult-to-adult living donor liver transplantation meeting in Tokyo. *Liver Transpl* 2004;10:715–20.
47. Sarasin FP, Majno PE, Llovet JM, Bruix J, Mentha G, Hadengue A. Living donor liver transplantation for early hepatocellular carcinoma: a life-expectancy and cost-effectiveness perspective. *Hepatology* 2001;33:1073–9.
48. Sugawara Y, Makuuchi M, Matsui Y, Kishi Y, Akamatsu N, Kaneko J, *et al.* Preemptive therapy for hepatitis C virus after living-donor liver transplantation. *Transplantation* 2004;78:1308–11.
49. Chalasani N, Manzarbeitia C, Ferenci P, Vogel W, Fontana RJ, Voigt M, *et al.* Peginterferon alfa-2a for hepatitis C after liver transplantation: two randomized, controlled trials. *Hepatology* 2005;41:289–98.
50. Sugawara Y, Makuuchi M. Liver transplantation for hepatitis B-related cirrhosis: recent advances. *J Hepatobiliary Pancreat Surg* 2006;13:378–81.
51. Livraghi T, Festi D, Monti F, Salmi A, Vettori C. US-guided percutaneous alcohol injection of small hepatic and abdominal tumors. *Radiology* 1986;161:309–12.
52. Shiina S, Yasuda H, Muto H, Tagawa K, Unuma T, Ibukuro K, *et al.* Percutaneous ethanol injection in the treatment of liver neoplasms. *AJR Am J Roentgenol* 1987;149:949–52.
53. Rossi S, Di Stasi M, Buscarini E, Cavanna L, Quaretti P, Squassante E, *et al.* Percutaneous radiofrequency interstitial thermal ablation in the treatment of small hepatocellular carcinoma. *Cancer J Sci Am* 1995;1:73–81.
54. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology* 1999;210:655–61.
55. Shiina S, Teratani T, Obi S, Hamamura K, Koike Y, Omata M. Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. *Oncology* 2002;62 Suppl 1:64–8.
56. Omata M, Tateishi R, Yoshida H, Shiina S. Treatment of hepatocellular carcinoma by percutaneous tumor ablation methods: Ethanol injection therapy and radiofrequency ablation. *Gastroenterology* 2004;127:S159–S166.
57. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or =4 cm. *Gastroenterology* 2004;127:1714–23.
58. Shiina S, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, *et al.* A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005;129:122–30.
59. Tateishi R, Shiina S, Teratani T, Obi S, Sato S, Koike Y, *et al.* Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. *Cancer* 2005;103:1201–9.
60. Teratani T, Yoshida H, Shiina S, Obi S, Sato S, Tateishi R, *et al.* Radiofrequency ablation for hepatocellular carcinoma in so-called high-risk locations. *Hepatology* 2006;43:1101–8.

61. Kondo Y, Yoshida H, Shiina S, Tateishi R, Teratani T, Omata M. Artificial ascites technique for percutaneous radiofrequency ablation of liver cancer adjacent to the gastrointestinal tract. *Br J Surg* 2006;93:1277–82.
62. Camma C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, *et al.* Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology* 2002;224:47–54.
63. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, *et al.* Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359:1734–9.
64. Garcia-Retortillo M, Forns X, Feliu A, Moitinho E, Costa J, Navasa M, *et al.* Hepatitis C virus kinetics during and immediately after liver transplantation. *Hepatology* 2002;35:680–7.
65. Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, *et al.* Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology* 2006;131:461–9.
66. Patt YZ, Hassan MM, Aguayo A, Nooka AK, Lozano RD, Curley SA, *et al.* Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma and gallbladder carcinoma. *Cancer* 2004;101:578–86.
67. Lencioni M, Falcone A, Allegrini G, Pfanner E, Masi G, Brunetti I, *et al.* Oral doxifluridine in advanced hepatocellular carcinoma: a phase II study. *Oncology* 2000;59:204–9.
68. Chow PK, Tai BC, Tan CK, Machin D, Win KM, Johnson PJ, *et al.* High-dose tamoxifen in the treatment of inoperable hepatocellular carcinoma: a multicenter randomized controlled trial. *Hepatology* 2002;36:1221–6.
69. Llovet JM, Ruff P, Tassopoulos N, Castells L, Bruix J, El-Hariry I, *et al.* A phase II trial of oral eniluracil/5-fluorouracil in patients with inoperable hepatocellular carcinoma. *Eur J Cancer* 2001;37:1352–8.
70. Obi S, Yoshida H, Toune R, Unuma T, Kanda M, Sato S, *et al.* Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. *Cancer* 2006;106:1990–7.
71. Matsuo M, Sakurai H, Saiki I. ZD1839, a selective epidermal growth factor receptor tyrosine kinase inhibitor, shows antimetastatic activity using a hepatocellular carcinoma model. *Mol Cancer Ther* 2003;2:557–61.
72. Philip PA, Mahoney MR, Allmer C, Thomas J, Pitot HC, Kim G, *et al.* Phase II study of Erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol* 2005;23:6657–63.
73. Thomas MB, Chadha R, Glover K, Wang X, Morris J, Brown T, *et al.* Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma. *Cancer* 2007;110:1059–67.
74. Zhu AX, Blaszkowsky LS, Ryan DP, Clark JW, Muzikansky A, Horgan K, *et al.* Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006;24:1898–903.
75. Abou-Alfa GK, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, *et al.* Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006;24:4293–300.
76. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, *et al.* Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–90.
77. Kulik LM, Atassi B, van Holsbeeck L, Souman T, Lewandowski RJ, Mulcahy MF, *et al.* Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. *J Surg Oncol* 2006;94:572–86.
78. Yang R, Sanghvi NT, Rescorla FJ, Galliani CA, Fry FJ, Griffith SL, *et al.* Extracorporeal liver ablation using sonography-guided high-intensity focused ultrasound. *Invest Radiol* 1992;27:796–803.
79. Sasaki Y, Yamada T, Tanaka H, Ohigashi H, Eguchi H, Yano M, *et al.* Risk of recurrence in a long-term follow-up after surgery in 417 patients with hepatitis B- or hepatitis C-related hepatocellular carcinoma. *Ann Surg* 2006;244:771–80.
80. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg* 2002;235:373–82.
81. Sakon M, Umeshita K, Nagano H, Eguchi H, Kishimoto S, Miyamoto A, *et al.* Clinical significance of hepatic resection in hepatocellular carcinoma: analysis by disease-free survival curves. *Arch Surg* 2000;135:1456–9.
82. Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Yamazaki O, *et al.* Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized, controlled trial. *Ann Intern Med* 2001;134:963–7.
83. Shiratori Y, Shiina S, Teratani T, Imamura M, Obi S, Sato S, *et al.* Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. *Ann Intern Med* 2003;138:299–306.
84. Hasegawa K, Takayama T, Ijichi M, Matsuyama Y, Imamura H, Sano K, *et al.* Uracil-tegafur as an adjuvant for hepatocellular carcinoma: a randomized trial. *Hepatology* 2006;44:891–5.
85. Muto Y, Moriwaki H, Ninomiya M, Adachi S, Saito A, Takasaki KT, *et al.* Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. Hepatoma Prevention Study Group. *N Engl J Med* 1996;334:1561–7.
86. Habu D, Shiomi S, Tamori A, Takeda T, Tanaka T, Kubo S, *et al.* Role of vitamin K2 in the development of hepatocellular carcinoma in women with viral cirrhosis of the liver. *JAMA* 2004;292:358–61.

Correspondence to: Professor Omata, Department of Gastroenterology, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; Fax: 81 (3) 3814 0021.

E-mail: *omata-2im@h.u-tokyo.ac.jp*

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Systemic Therapy for Hepatocellular Carcinoma: Cytotoxic Chemotherapy, Targeted Therapy and Immunotherapy

Melanie B. Thomas, MD,[1] James P. O'Beirne, MD,[2] Junji Furuse, MD,[3] Anthony T. C. Chan, MD,[4] Ghassan Abou-Alfa, MD,[5] and Philip Johnson, MD[6]

[1]Department of Gastrointestinal Medical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 426, Houston, Texas 77030-4009, USA
[2]Department of Liver Studies and Transplantation, Kings College, London, UK
[3]Division of Hepatobiliary and Pancreatic Medical Oncology, National Cancer Center Hospital East, Chiba, Japan
[4]Department of Clinical Oncology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China
[5]Department of Gastrointestinal Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York
[6]UK Institute for Cancer Studies, University of Birmingham, Birmingham, UK

Conventional cytotoxic chemotherapy has not provided clinical benefit or prolonged survival for patients with advanced HCC. This review summarizes the results of prospective clinical trials of several categories of systemic therapy, with emphasis on the more promising results from recent trials of biologically targeted therapeutic agents in HCC.

Key Words: Hepatocellular—Hepatoma—Chemotherapy—Chemoresistance—Clinical trials—Biologic therapy.

Hepatocellular carcinoma (HCC) is currently the fifth most common solid tumor worldwide, and the fourth leading cause of cancer-related death.[1] It is a lethal disease, as the annual incidence roughly equals the annual mortality.[2,3] Eighty percent of new cases occur in developing countries, but the incidence is rising in economically developed regions including Japan, Western Europe, and the United States.[4] More than 80% of patients present with advanced or unresectable disease, and for those patients who do undergo resection, the recurrence rates can be as high as 50% at 2 years.[5–7] Thus, many patients will seek systemic therapy. A 1997 meta-analysis evaluating the results of 37 randomized clinical trials of systemic and regional chemotherapy in 2803 HCC patients concluded that nonsurgical therapies were ineffective or minimally effective at best.[8] Most HCC patients have underlying cirrhosis and hepatic dysfunction, which complicates safely administering systemic therapy and conducting trials of new agents in this patient population.

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Address correspondence and reprint requests to: Melanie B. Thomas, MD; E-mail: methomas@mdanderson.org

CYTOTOXIC CHEMOTHERAPY FOR HCC: REASONS FOR LACK OF EFFICACY

Most published studies of systemic chemotherapy report response rates of 0% to 25%, and there is no published evidence that systemic chemotherapy improves overall survival in any subset of HCC patients.[9–11] HCC comprises clinically chemotherapy-resistant tumors, and this observation is supported by low response rates across a wide variety of cytotoxic agents (Table 1). The most widely used agent has been doxorubicin, both as a single agent and in

TABLE 1. *Selected clinical trials in patients with advanced hepatocellular carcinoma*

Study	Regimen	Phase	Sample size	Response rate (%)	Median survival (mo)
Cytotoxic chemotherapy					
Yeo et al.[15]	PIAF vs. Adriamycin	3	94/94	20.9 vs. 10.5	8.6 vs. 6.83
Mok et al.[66]	Nolatrexed vs. doxorubicin	2	37/17	0	4.9 vs. 3.7
Posey et al.[67]	TI38067 vs. Adriamycin	2/3	169/170	NA	5.7 vs. 5.6
Gish et al.[16]	Nolatrexed vs. doxorubicin	3	444	1.4 vs. 4.0	5.5 vs. 8 (P = .0068)
Patt et al.[68]	Thalidomide	2	37	6%	6.8
Pastorelli et al.[69]	Pegylated doxorubicin + gemcitabine	2	35	23%	8.8
Immunotherapy/hormonal therapy					
Barbare et al.[70]	Tamoxifen vs. BSC	2	210/210	NA	4.8 vs. 4.0
O'Neil et al.[71]	Octreotide LAR	2	17		TTTF 3.5; OS 10
Lee et al.[61]	Dendritic cells	2	31	12.9%	1-y survival 40%
Targeted biologic therapy					
Llovet et al.[33]	Sorafenib vs. placebo	3	602	2.3%	10.7 vs. 7.9 (P = .00058)
Abou-Alfa et al.[32]	Sorafenib	2	137	2.2	9.3
Philip et al.[44]	Erlotonib	2	38	9%	13
Thomas et al.[43]	Erlotonib	2	40	0%	10.75
Thomas et al.[50]	Bevacizumab + erlotonib	2	34	20.6%	19 (PFS 9)
Zhu et al.[72]	Cetuximab	2	30	0%	PFS 6 wk; OS 22 wk
O'Dwyer et al.[73]	Gefitinib	2	31	3%	PFS 2.8; OS 6.5
Combination cytotoxic + biologic therapy					
Sun et al.[74]	Capecitabine, oxaliplatin, bevacizumab	2	30	11%	PFS 5.4
Zhu et al.[75]	Gemox + bevacizumab	2	33	20	9.6

PIAF, cisplatinum, interferon, doxorubicin, and 5-fluorouracil; OS, overall survival; PFS, progression-free survival; TTTF, time to treatment failure.

combination with other drugs.[12–14] An early randomized trial against best supportive therapy showed greatly increased survival, but this was only in the order of weeks. A pivotal phase 3 trial of doxorubicin combination chemotherapy (cisplatinum, interferon, doxorubicin, and 5-fluorouracil, PIAF) showed a statistically significant difference in response rate favoring PIAF, but no survival difference.[15] Another study in which doxorubicin was the control arm in a randomized phase 3 trial against nolatrexed showed a highly statistically significant survival benefit in favor of the control doxorubicin arm.[16] The variable results from trials summarized in Table 1 have contributed to the lack of consensus regarding "standard" chemotherapy for patients with advanced HCC; they have also resulted in ongoing debate regarding the best control arm for future randomized trials.

Furthermore, the definition of *drug activity* has changed over the years. It is now well recognized that the conventional markers of radiographic response (World Health Organization [WHO] or RECIST criteria) are poorly related to tumor cell kill in liver tumors and that end points other than radiographic tumor shrinkage, such as time to tumor progression, progression-free survival, and certainly overall survival, are more meaningful measures of therapeutic benefit.[17]

The third set of reasons is related to HCC tumor biology and intrinsic or acquired drug resistance. Large HCCs commonly develop areas of central necrosis, which may inhibit drug delivery to actively growing parts of the tumor. Topoisomerase IIa encodes an enzyme that is the target for anticancer chemotherapeutic agents such as doxorubicin, and mutations are associated with resistance.[18] There is upregulation of topoisomerase IIa in doxorubicin-resistant HCC cell lines, and its expression is associated with an aggressive tumor phenotype.[19] Cancer cells, including HCC cells, often have intrinsic drug resistance mediated by enhanced cellular drug efflux of several cytotoxic agents. This phenomenon is associated with increase in a drug transporter family, the adenosine triphosphate–binding cassette proteins that include MDR1, p-glycoprotein (p-gp), and the multidrug resistance protein (MRP).[20,21] Both these are overexpressed in HCC.[21,22] Overexpression of MDR1 accompanied by a decrease in doxorubicin accumulation levels has been observed in certain HCC cell lines.[23] The *H19* gene is believed to induce p-gp expression and MDR1-associated drug resistance in HCC cells through regulation of MDR1 promoter methylation.[23] Coexpression of p53 and p-gp may contribute to HCC drug resistance in HCC cell lines.[24] In addition, recent evidence suggests that hypoxia, MDR1 expression, and an angiogenic HCC phenotype may be linked.[25,26]

Clearly, to improve the outcome for patients with advanced HCC, alternatives to traditional cytotoxic chemotherapy agents must be explored.