Table III. Building of covariate population pharmacokinetic models for gemcitabine (dFdC) and 2′,2′-difluorodeoxyuridine (dFdU)

Model name	Parameter	Factor[a]	OFV	Model used for comparison	ΔOFV	p-Value
Gemcitabine						
1		Basic model	−532.19			
	CL_1	*CDA**3 (linear)	−2206.79	1	−1674.60	<0.000001
2	CL_1	***CDA**3 homozygous**	−2260.86	1	−1728.68	<0.000001
3	CL_1	***CDA**3 heterozygous**	−2276.14	2	−15.28	9.28E−05
4	CL_1	BSA	−2405.26	3	−129.12	
	V_1	BSA	−2204.71	3	71.43	
	CL_1	Bodyweight	−2276.05	3	0.094	
	V_1	Bodyweight	−2176.05	3	100.09	
	CL_1	Age	−2409.77	4	−4.51	0.034
	V_1	Age	−2410.98	4	−5.72	0.017
	CL_1	Sex	−2406.40	4	−1.14	0.29
	V_1	Sex	−2406.52	4	−1.26	0.26
	CL_1	Cisplatin	−2407.248	4	−1.99	0.16
5	CL_1	**S-1**	−2427.66	4	−22.40	2.21E−06
6	CL_1	***CDA*−31delC**	−2464.89	5	−37.23	1.05E−09
	CL_1	*CDA**2	−2441.21	5	−13.55	0.00023
	CL_1	*CDA* IVS1+37G>A	−2441.84	5	−14.18	0.00017
dFdU						
7		Basic model	91.694			
8	CL_m	**BSA**	45.958	7	−45.736	
	V_{m1}	BSA	10.795	7	−80.899	
9	V_{m1}	**BSA**	−31.64	8	−77.598	
	CL_m	Bodyweight	163.251	7	71.557	
	V_{m1}	Bodyweight	2.496	7	−89.198	
10	CL_m	**Creatinine**	−166.798	9	−135.158	3.05E−31
11	CL_m	**Age**	−197.342	10	−30.544	3.26E−08
12	V_{m1}	**Age**	−212.069	11	−14.73	0.000124
13	V_{m1}	**Sex**	−243.914	12	−31.845	1.67E−08
	CL_m	Sex	−253.677	13	−9.763	0.00178

a The factors indicated in bold type were selected as covariates for the final model.

BSA = body surface area; **CL_1** = clearance of gemcitabine; **CL_m** = clearance of the metabolite dFdU; **OFV** = objective function value; **S-1** = an oral product of tegafur with gimeracil and oteracil; **V_1** = apparent volume of distribution of the central compartment of gemcitabine; **V_{m1}** = apparent volume of distribution of the central compartment of dFdU.

covariate to the basic model to account for the effect of homozygosity of *3 (θ_{*3homo}) on the clearance of gemcitabine (equation 1):

$$CL = \theta_1 \times (1 - \theta_{*3homo} \times CDA*3homo) \quad \text{(Eq. 1)}$$

where CL is total gemcitabine clearance in a patient of interest; θ_1 is gemcitabine clearance in patients without *3/*3; and *CDA**3homo is 1 for *3/*3 and 0 for other patients (*3/non-*3 or non-*3/non-*3). This modification significantly reduced the OFV, as shown in table III (model 2).

Next, the effect of heterozygous *3 on gemcitabine clearance was examined by comparing equations 2 and 3:

$$CL = \theta_2 \times (1 - \theta_{*3homo} \times CDA*3) \quad \text{(Eq. 2)}$$

$$CL = \theta_2 \times (1 - \theta_{*3hetero} \times CDA*3hetero) \times (1 - \theta_{*3homo} \times CDA*3homo) \quad \text{(Eq. 3)}$$

where θ_2 is gemcitabine clearance for patients without *3, *CDA**3 is 0 for non-*3/non-*3, ½ for *3/non-*3 and 1 for *3/*3; $\theta_{*3hetero}$ is a parameter related to the effect of heterozygous *3 but independent of θ_{*3homo}; and *CDA**3hetero is 1 for *3/non-*3 and 0 for *3/*3 or non-*3/non-*3. Equation 3 assumes a nonlinear gene-dose effect of *CDA**3 on CL. The OFV of equation 3 (model 3) was slightly but significantly smaller than that of equation 2, which indicates that the *CDA**3 gene-dose effect is not linear.

The effects of the body surface area (BSA), bodyweight, age and sex on the CL and V_1 of gemcitabine were investigated. As shown in table III, while consideration of an effect of size on the V_1 did not improve the OFV, examination of proportionality between the CL and BSA (model 4) considerably reduced the OFV. Age and sex did not significantly affect the CL and V_1 of gemcitabine (table III), although they were significantly correlated with these parameters in our previous univariate analyses.[12] As shown in table I, 66 patients received a gemcitabine-based combination chemotherapy with either cisplatin, carboplatin, fluorouracil, S-1 (an oral anti-cancer multicomponent drug containing tegafur, gimeracil and oteracil) or vinorelbine. Among the coadministered drugs, only S-1 significantly increased CL (model 5).

The effects of genetic polymorphisms of *CDA* other than *3 on the pharmacokinetics of gemcitabine were also examined. *CDA*–31delC (rs3215400; previously described as *CDA*–33_–31delC [precisely *CDA*–33_–31 C3>C2]), *CDA* 79A>C (Lys27Gln, *2) and *CDA* IVS1+37G>A increased gemcitabine clearance, and their effects were all statistically significant (table III). A delC factor was adopted in the final model for gemcitabine because it gave the smallest p-value and OFV (model 6 in table III).

Although we previously reported that 29 genetic variations of *DCK* were detected in our patients, they were very rare except for *DCK*–360C>G and 364C>T (Pro122Ser) [the allele frequencies were 0.131 and 0.061, respectively, as shown in table II],[15] and their functions were reported to be altered.[19,20] We analysed the effects of *DCK*–360C>G and 364C>T (Pro122Ser) on gemcitabine population pharmacokinetics, but no effects were detected. Thirty-nine genetic polymorphisms of *SLC29A1* (*hENT1*), including two nonsynonymous ones, were also previously reported.[16] Although we analysed the effects of genetic polymorphisms of *hENT1* whose allele frequencies were higher than 0.05 (table II), no effects were observed in univariate analyses (data not shown).

Development of a Combined Population Pharmacokinetic Model for Gemcitabine and dFdU

Next, we added compartments for dFdU where its central compartment was connected with the central compartment of gemcitabine with a first-order metabolic rate constant (CL/V_1) (figure 2). The f_m was assumed to be 1 because >90% of administered gemcitabine was recovered in the urine as dFdU.[6] Since an extraordinarily large V_m for dFdU was obtained if the V_1 for gemcitabine was not fixed, the V_1 was fixed to the value estimated in the previous section (12.60 L). Although the sampling duration in this study was not sufficiently long for pharmacokinetic analysis of dFdU (which has a longer half-life than that of gemcitabine, as shown in figure 1b), a two-compartment model (model 7, the combined basic model for gemcitabine and dFdU) provided a better fit for the data than a one-compartment model (the ΔOFV was –3402.44). Inclusion of covariates such as the BSA, age, serum creatinine level and sex in the model significantly reduced the OFV, as shown in table III.

All covariates selected by the inclusion steps remained after the stepwise exclusion/deletion process. The final population pharmacokinetic model (model 13) for Japanese cancer patients is shown in table IV. This model indicated that gemcitabine clearance was decreased by 64% and 17% in the *3-homozygotes and heterozygotes, respectively, compared with patients without *CDA**3. The increases in gemcitabine clearance by delC were 7.5% for heterozygotes and 15% for homozygotes. If S-1 was coadministered, gemcitabine clearance increased by 19%. CL_m was reduced by 8.6% if a patient was 10 years older than the average age (62.67 years in our patient group) and by about 7.3% if the creatinine level of a patient was 0.1 mg/dL higher than the average level (0.7 mg/dL in our patient group). The V_{m1} for dFdU was decreased by 8.1%

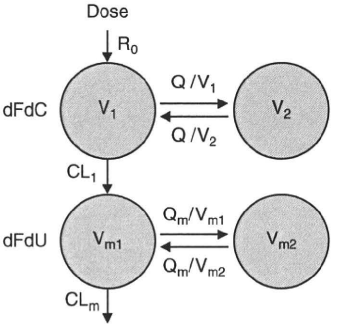

Fig. 2. Compartmental representation of gemcitabine (dFdC) and 2′,2′-difluorodeoxyuridine (dFdU) pharmacokinetics. **CL_1** = clearance of gemcitabine; **CL_m** = clearance of the metabolite dFdU; **Q** = intercompartmental clearance between the central and peripheral compartments of gemcitabine; **Q_m** = intercompartmental clearance between the central and peripheral compartments of dFdU; **R_0** = zero-order infusion rate constant; **V_1** = apparent volume of distribution of the central compartment of gemcitabine; **V_2** = apparent volume of distribution of the peripheral compartment of gemcitabine; **V_{m1}** = apparent volume of distribution of the central compartment of dFdU; **V_{m2}** = apparent volume of distribution of the peripheral compartment of dFdU.

Table IV. Population pharmacokinetic parameters for gemcitabine (dFdC) and 2′,2′-difluorodeoxyuridine (dFdU) in the final model

Pharmacokinetic parameter	Estimated value	CV%
Gemcitabine		
CL_1 (L/h/m^2)	$73.70 \times BSA \times (1 - 0.639 \times$ *3homo[a]$) \times (1 - 0.171 \times$ *3hetero[b]$) \times (1 + 0.0749 \times$ delC[c]$) \times (1 + 0.191 \times$ S-1[d]$)$	17.1
V_1 (L)	12.60 (Fixed)	58.9
Q (L/h)	37.50	Not estimated
V_2 (L)	9.54	25.3
dFdU		
CL_{m1} (L/h/m^2)	$11.00 \times BSA \times (1 - 0.00855 \times (AGE - 62.67)) \times (1 - 0.732 \times (Cre - 0.70))$	20.5
V_{m1} (L)	$15.00 \times BSA \times (1 - 0.00806 \times (AGE - 62.67)) \times (1 + 0.239 \times$ Sex[e]$)$	27.9
Q_m (L/h)	58.0	22.7
V_{m2} (L)	31.7	26.4
Residual error	SD (ε_3); 0.0844	
	CV (ε_1) and CV (ε_2); 0.200 and 0.0412, respectively	

a *3homo: 1 for homozygous *CDA**3 and 0 for others.

b *3hetero: 1 for heterozygous *CDA**3 and 0 for others.

c delC: number of *CDA*–31delC in a patient (delC = 0, 1 or 2).

d S-1: 1 for S-1 coadministered to patients and 0 for others.

e Sex: 1 for male and 0 for female.

ε = variance; **AGE** = age (years); **BSA** = body surface area (m^2); **CL_1** = clearance of gemcitabine; **CL_m** = clearance of the metabolite dFdU; **CL_{m1}** = clearance of the metabolite dFdU from central compartment; **Cre** = serum creatinine (mg/dL); **CV** = coefficient of variation (interindividual); **Q** = intercompartmental clearance between the central and peripheral compartments of gemcitabine; **Q_m** = intercompartmental clearance between the central and peripheral compartments of dFdU; **S-1** = an oral product of tegafur with gimeracil and oteracil; **V_1** = apparent volume of distribution of the central compartment of gemcitabine; **V_2** = apparent volume of distribution of the peripheral compartment of gemcitabine; **V_{m1}** = apparent volume of distribution of the central compartment of dFdU; **V_{m2}** = apparent volume of distribution of the peripheral compartment of dFdU.

if a patient was 10 years older than the average age, and was increased by 24% in males compared with females.

Evaluation of the Goodness of Fit

The observed plasma concentrations of gemcitabine and dFdU were plotted against concentrations predicted by the final model, as shown in figure 3a and b, respectively. Most gemcitabine concentrations distributed into two peaks: one peak with scattering around 25 mg/L (collected at the end of the gemcitabine infusion [30 minutes after initiation of the infusion]) and a second peak with scattering close to the point of origin. This dual peak plot was the result of very rapid gemcitabine metabolism. One point at an extremely high concentration represented the C_{max} obtained from a *3/*3 patient, who was administered 1000 mg/m^2 of gemcitabine.[12,13] For both gemcitabine and dFdU, higher plasma concentrations gave more widely scattered plots, indicating that the variation in the residual errors was proportional to the measured concentration (a constant coefficient of variation type). The slopes of the regression lines for gemcitabine and dFdU were very close to 1.0 (1.007 and 0.9908, respectively). Conditional weighted residuals (CWRES) were recently reported as a diagnostic tool for the FOCE approximation.[18] The slopes of the regression lines of CWRES for gemcitabine and dFdU against predicted plasma concentrations were very close to 0.0 (–0.00482 and –0.00926, respectively), indicating a very good fit for the constructed model. Further validation of the model by a visual predictive check or bootstrapping was not performed, because the distribution of some covariates, such as diplotypes of *CDA**3 (non-*3/non-*3 : non-*3/*3 : *3/*3 = 230 : 16 : 2), and coadministration of S-1 (in only 10 of the 248 patients) were unevenly distributed.

Discussion

Recently, Jiang et al.[21] performed population pharmacokinetic analyses on gemcitabine and dFdU, and they adopted two-compartment models for both plasma gemcitabine and dFdU pharmacokinetics. Likewise, in our study, the

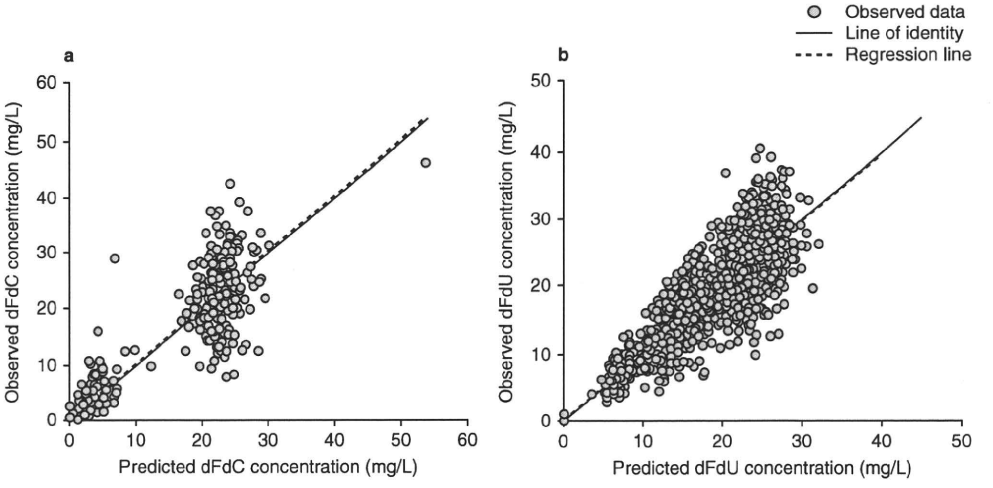

Fig. 3. Plots of observed concentrations against predicted concentrations of (**a**) gemcitabine (dFdC) and (**b**) 2′,2′-difluorodeoxyuridine (dFdU).

pharmacokinetics of gemcitabine and dFdU were effectively described by two-compartment models. The values of the estimated CL ([115.0 L/h] from a typical patient with an average BSA of 1.56 m^2), V_1 (12.60 L) and V_2 (9.54 L) were comparable to the values reported by Jiang et al.[21] (162 L/h, 15 L and 15 L, respectively). The estimated CL was slightly smaller and the V_1 was slightly larger than the values reported by Tham et al.[22] (222.8 L/h and 2.96 L, respectively). Although the reasons for these discrepancies are unknown, it should be noted that the population pharmacokinetic analyses performed by Tham et al.[22] included gemcitabine triphosphate (dFdCTP, an active form of gemcitabine) in addition to gemcitabine and dFdU, and the pharmacokinetic models applied in their study were completely different from ours.

The gemcitabine clearance in the *3/*3 patients, obtained from the model-independent analysis, was 80% less than the average clearance in patients without *3.[12,13] The effect of homozygous *3 on gemcitabine clearance, as estimated by the final population pharmacokinetic model, was a 64% decrease. This value, although slightly less than 80%, was the most significant among the covariates. Our current study also confirmed a finding from our previous report that the gene-dose effect of *CDA* was not linear. So far, we have encountered three patients with *3/*3, and all of them experienced life-threatening toxicities, including prolonged severe neutropenia.[12-14] Some of the non-*3/non-*3 and non-*3/*3 patients experienced transient grade 4 neutropenia, but only one patient required supportive treatment.[14] Thus, special attention to *3 homozygotes is advisable.

The effects of –31delC, 79A>C and IVS1+37G>A of *CDA* on gemcitabine clearance were found to be small but significant in this study (table III). All of these genotypes had slightly increased gemcitabine clearance (by <10%). The single nucleotide deletion –31delC is simultaneously present in both the haplotype *2 harbouring 79A>C and several *1 haplotypes (*1b, *1d, etc.) harbouring IVS1+37G>A in the Japanese population.[12] Thus it is reasonable that –31delC, rather than 79A>C or IVS1+37G>A, was selected as the covariate in the final model. This finding suggests that –31delC may be a functional SNP.

The haplotype analysis in our previous report[12] indicated that 208G>A, the tagging SNP of *CDA**3, is not present on a chromosome carrying –31delC, 79A>C or IVS1+37G>A. However, some patients simultaneously carried both haplotypes *2 and *3 (*2/*3). The median value of gemcitabine clearance observed in patients with *2/*3 was slightly higher than that observed in patients with *1/*3, although the difference was not statistically significant.[12]

The SNP 79A>C, a tagging SNP of the haplotype *2, results in the amino acid substitution, Lys27Gln.[12] A recent study[23] has suggested that the average enzymatic activity of CDA was significantly lower in cytoplasmic extracts of red blood cells obtained from patients with homozygous 79A (Lys27) than in those from patients with 79C (Gln27). Furthermore, it was reported that *CDA* 79A, the major allele, was a predictive marker of better response, more severe toxicity, longer time to disease progression and overall survival in Caucasian patients with advanced non-small-cell lung cancer who were treated with cisplatin and gemcitabine.[24] Haplotype *2 harbouring 79A>C also harbours –31delC, which has an incomplete association with the intron SNP IVS1+37. Our findings may explain the effects of 79A>C observed in Caucasian patients, since 79A>C is closely linked with –31delC, and the single nucleotide deletion –31delC in the 5′-untranslated region is responsible for increased clearance, a decreased AUC and less response to gemcitabine. This speculation warrants further study.

Although the effects of sex and age on model-independent pharmacokinetic parameters of gemcitabine were detected in our previous univariate analysis,[12] they were not significant in the current multivariate analysis. On the other hand, a significant effect of coadministered S-1, an oral derivative of fluorouracil, was revealed (approximately 20% higher clearance than in patients treated with gemcitabine monotherapy). In this study, nine of ten patients were coadministered S-1 in the morning a couple of hours before gemcitabine treatment. It might be noted that thymidylate synthase inhibitors such as fluorouracil can upregulate expression of hENT1, a major transporter of gemcitabine.[25] Moreover, Nakahira et al.[26] recently reported that significant increases in hENT1 expression and gemcitabine uptake were observed after S-1 treatment in mice. However, since the study duration was too short for S-1 to reveal the effects on expression of hENT1 in our study, the clinical significance of coadministration of S-1 and gemcitabine should be further investigated. In this study, four patients received fluorouracil after treatment of gemcitabine, and no effects of fluorouracil on the pharmacokinetics of gemcitabine were observed.

The metabolite dFdU is inactive and is eliminated mostly by renal excretion.[27] However, its pharmacokinetic parameters can be surrogate biomarkers of gemcitabine exposure or CDA activity because they correlate well with pharmacokinetic parameters of gemcitabine (data not shown). Serum creatinine levels and age were shown to significantly affect the clearance of dFdU. The association between dFdU clearance and renal function was also reported by Jiang et al.[21]

Conclusion

We performed population pharmacokinetic analyses of gemcitabine and dFdU in Japanese cancer patients. Clearance of gemcitabine was decreased by *CDA* 208G>A (Ala70Thr, *3) and was slightly increased by *CDA*–31delC and coadministration with S-1. Clearance of dFdU was influenced by renal function and age.

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Liver Cancer Working Group Report

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Hepatocellular carcinoma is a highly prevalent disease in many Asian countries, accounting for 75–80% of victims worldwide. The incidence of hepatocellular carcinoma varies enormously across Asia, but tends to follow the incidences of hepatitis B infection and liver cirrhosis. The incidence and etiology of hepatocellular carcinoma in Japan are different from the rest of Asia, but similar to that in Western countries because hepatitis C infection is the main etiological factor in Japan. Hepatitis B virus vaccination programs are showing great success in reducing hepatitis B virus-related hepatocellular carcinoma. Screening program improves detection of early hepatocellular carcinoma and has some positive impact on survival, but the majority of hepatocellular carcinoma patients in Asia still present with advanced hepatocellular carcinoma. Long-term outcomes following treatment of even early/intermediate or advanced disease are often unsatisfactory because of a lack of effective adjuvant and systemic therapies. Various clinical practice guidelines for hepatocellular carcinoma have been established and are in use. Clinical diagnosis of hepatocellular carcinoma by imaging diagnosis is replacing diagnosis of hepatocellular carcinoma by pathological confirmation. New imaging and treatment techniques are continuously being developed and guidelines should be updated every 3 or 4 years, incorporating new evidence. New molecularly targeted therapies hold great promise. Sorafenib is the first systemic therapy to demonstrate prolonged survival vs. the placebo in patients with advanced hepatocellular carcinoma. Various other new molecularly targeted agents are currently under investigation.

Key words: liver cancer – epidemiology – etiology – diagnosis – treatment

INTRODUCTION

The Liver Cancer Working Group report was divided into seven topics: (i) epidemiology and etiology in Asian countries; (ii) proportions of early, intermediate and advanced stages of hepatocellular carcinoma (HCC); (iii) surveillance systems and prediction of HCC development; (iv) recent developments in imaging diagnosis; (v) pathological development of early HCC, especially consensus between Asia and the West; (vi) current status of treatment strategies; (vii) future perspectives, especially in regard to sorafenib; and other molecularly targeted agents.

Epidemiology and Etiology

Liver cancer, or HCC, is endemic in Asia. It is expected that around 75–80% of HCC cases worldwide develop in Asia (Fig. 1) (1). In most Asian countries, HCC is ranked from number 1 to number 5 among the leading causes of death. In

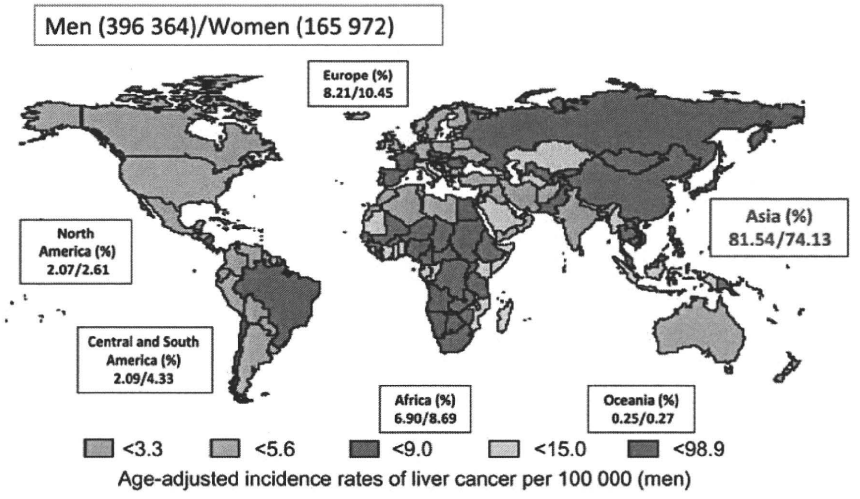

Figure 1. Liver cancer in the world (Curado et al. IARC Press, 2010).

Mainland China and Taiwan, the incidence of HCC has been increasing in the past 30 years, but in Japan, the incidence has been relatively stable during that period (2). In Korea, particularly in the male population, the incidence of HCC decreased slightly in the past 10 years. The primary etiological factor in Asia is hepatitis B. As exemplified by Korea, hepatitis B virus (HBV) accounts for 70–75% of HCC cases and hepatitis C virus (HCV) accounts for 10–15% (3). In Hong Kong, 80% of HCC cases are caused by HBV, and around 7% are caused by HCV. Japan is unique in the etiology of HCC in Asia because almost two-thirds of cases are caused by HCV and only 15% are related to HBV (2,4–6). Taiwan appears to be in between. In the early 1980s, HBV was the dominant cause of HCC in Taiwan, accounting for 88% (4), but in the past 30 years, HCV increased significantly and now accounts for more than 30%. HBV remains the predominant cause, but because of a vaccination program that was started in 1984, Taiwanese younger than 25 years old will have a carrier rate of around 1%. Thirty years from now, HBV-related HCC will decrease dramatically in Taiwan and in other countries that have adopted a nationwide HBV vaccination program (7). Regarding the age distribution of HCC, in all countries in which HBV is the dominant cause, the median age is around 55 years old. Statistics for Japan, which is characterized by HCV, show that the median age is about 10 years older.

In conclusion, HCC in the Asia-Pacific region accounts for 75–80% of victims worldwide. The incidence of HCC is on the rise in some countries, such as mainland China and Taiwan, but it is plateauing and decreasing slightly in some countries, like Japan. Except in Japan, HBV is the major etiology of HCC. The proportion of HCV has increased significantly in the past 30 years in Taiwan. Because of successful vaccination, the incidence of HBV-related HCC will decrease dramatically by 2040 (8).

Proportions of Early, Intermediate and Advanced HCC

There are various staging systems for HCC, with each system having its pros and cons and no consensus regarding which system is the best. The Barcelona Clinic of Liver Cancer, BCLC, system (9,10) is quite widely used in the West and in many clinical trials. The BCLC system stages patients into very early stage, early stage, intermediate stage, advanced stage and end stage according to the tumor size, vascular invasion, the tumor nodule number and the presence of metastasis. The BCLC system also provides a guideline for treatment according to the stage of HCC. Basically, patients with very early-stage or early-stage HCC are considered for curative treatment, either resection, liver transplantation or local ablation. Patients with intermediate-stage HCC, mainly those with multinodular disease, will be eligible for transarterial chemoembolization (TACE), and patients with advanced-stage disease showing portal invasion or distant metastasis will be considered for sorafenib or recruitment to clinical trials.

In addition to the BCLC, the Japanese TNM staging system (11) is quite widely used in Japan and Korea. This staging system takes into account three criteria for the T stage, i.e. whether the tumor is solitary or multiple, the tumor size, $\leq$2 cm or $>$2 cm, and the presence of any vascular or bile duct invasion. Patients are thus classified as T1, T2, T3 or T4. For N and M, it is similar to other TNM staging systems, based on the presence of lymph node or distant metastasis. By integrating Japanese TNM stage and Child–Pugh grade, Japan Integrated Staging system was developed (12) and widely used in Japan and Korea.

The current distribution of HCC based on the BCLC system is quite similar in Hong Kong and Korea, with about 30–40% of patients having early-stage disease, about 20–30% having intermediate-stage disease and about 30% having advanced-stage disease. In Japan, the proportion of early-stage HCC is very high: about 65%, whereas only 5% of

patients present with advanced-stage disease (5). Japan is thus quite different from the rest of the Asia-Pacific region, probably because of its very well-established surveillance system.

But even within a country, there can be a significant variation between regions, as exemplified by Taiwan. In northern Taiwan, about 58% of patients have early-stage HCC, whereas in the southern part, the rate is only 35.2%. This is probably related to differences in the popularity of surveillance due to cultural, social and economic differences between the populations in the north and south of Taiwan. Data generated in Japan and Korea, using the Japanese TNM staging system, are similar to the BCLC staging results and show that Japan has a higher number of patients with early-stage HCC compared with Korea.

The disease stage obviously affects the treatment modality. For early-stage cancers, curative treatments like surgery or ablation are generally implemented, whereas TACE is performed for intermediate-stage disease and systemic therapy for advanced disease. Comparison between Hong Kong and Japan shows a dominance of ablation and surgery in Japan, whereas in Hong Kong, the percentage of patients amenable to ablation is limited. Even for TACE, the proportion of patients is higher in Japan than in Hong Kong, where a large proportion of patients have advanced disease and receive systemic therapy. For early-stage disease, curative treatment is the first choice, and about 38% of patients in Hong Kong and 65% in Japan are amenable to curative treatments. For intermediate-stage HCC, the rates are 22% in Hong Kong and 30% in Japan, and for advanced-stage disease, the rates are 40% in Hong Kong and 5% in Japan.

BCLC staging has important predictive power for overall survival. Data for more than 3000 patients in Hong Kong show very good stratification of overall survival in terms of the stage. Survival data from Yonsei University (Korea) show a very similar stratification. For patients with early HCC, the 5-year survival rate is now more than 50%, whereas for patients with advanced-stage disease, the 5-year survival is $<5\%$, showing a great difference in the survival outcomes. In some countries, like Korea, evidence points to some recent improvement in the overall survival of HCC patients: comparison between 1993 and 2005 shows that the 5-year survival has improved from 10.7% to 18.9% in the most recent 5-year period.

In conclusion, there is a significant variation in the distribution of early, intermediate and advanced stages of HCC among Asia-Pacific countries, with the highest proportion of early HCC in Japan. Curative treatment for early-stage HCC is associated with the 5-year survival $>50\%$, while the prognosis of advanced-stage HCC remains dismal. These results underscore the importance of early diagnosis by means of surveillance of high-risk patients.

Surveillance Systems and Prediction of HCC

A Hong Kong study proved that a screening program can improve survival by increasing the chance of treatment in the screened group (13). Unfortunately, in Hong Kong, the percentage of patients with HCC diagnosed by screening is low, but it has increased slightly, from 29% in 1991–1997 to 33% in 1998–2004 (14). There is no government-funded surveillance program for HCC in Hong Kong or other parts of China. Korea, however, established a national surveillance program in 2003, with the target population being those over 40 years of age, with liver cirrhosis or an HBV or HCV carrier (15). Taiwan has a similar surveillance program in place, and a different testing interval is applied depending on whether the subject has cirrhosis or not: 3–6 months for cirrhosis, but 6–12 months for non-cirrhosis. There is no age limitation for surveillance of HBV carriers in Taiwan, but in Korea, the government recommends over 40 years. The surveillance program in Japan is slightly different: it selects super high-risk patients, meaning liver cirrhosis B or C, and applies a shorter interval for examination, every 3 or 4 months, and test for more tumor markers (three tumor markers, including AFP, AFP-L3 and DCP) (16,17). The surveillance programs in Korea and China prefer a 6-month interval. Japanese surveillance program also recommends CT or MRI every 6–12 months for improving sensitivity. Thus, there are some differences in HCC surveillance among Asia-Pacific countries, including the candidates for surveillance and the age limit for HBV carriers. As surveillance tools, ultrasonography and AFP are still the standards, but there is a need to know whether more tumor markers will improve the sensitivity. A study investigated whether the surveillance interval is important for improving the survival. The group with a surveillance interval of within 6 months showed better survival than that of more than 6 months.

It is important to predict the development of HCC by quantitative risk estimation. An individualized prediction model is possible by combining multiple risk factors into a comprehensive risk expression. A study identified eight independent risk factors, and a special formula was established to calculate the relative risk factors. This model enables identification of the high- and low-risk groups.

In conclusion, HCC surveillance can detect early tumors and increase the chance of a curative approach. All patients at risk of developing HCC with potentially curative treatment available are recommended for regular surveillance. At present, ultrasonography and the serum AFP test at 6-month intervals are the standard surveillance tools. To improve the detection rate of early-stage HCC, the benefit of additional tests and a shorter surveillance interval should be confirmed by a randomized clinical trial in Asia. The application of individualized prediction model to surveillance programs may improve the cost-effectiveness by focusing on the high-risk group.

Recent Developments in Imaging Diagnosis

Various clinical practice guidelines for HCC are being implemented around the world, including in Europe, Korea, America, Japan and the Asia-Pacific region. In accordance

with those guidelines, the use of dynamic imaging, such as contrast-enhanced ultrasound (US), CT and MRI, is increasing and becoming more important, whereas application of biopsy is decreasing. Angiography and fusion imaging are other imaging tools that are available for the diagnosis of HCC. These tools are based on different imaging techniques. US is the first step for imaging diagnosis of HCC in accordance with the guidelines. If a nodule is found by US examination, the next technique to be used depends on the size of the mass. For a nodule that is <1 cm in diameter, follow-up study is usually recommended. If the nodule is >2 cm in diameter, one further imaging examination, such as contrast-enhanced US, CT or MRI, is sufficient to make a diagnosis of HCC with specific findings. Specific findings consist of a hypervascular nature in the arterial phase of imaging, and a washout pattern in the equilibrium phase. Diagnosis of HCC by dynamic imaging (contrast-enhanced ultrasonography, CT or MRI) is based on the enhancement pattern according to time sequence or phase. Overt HCC shows high attenuation in the arterial phase, indicating the hypervascular nature of the tumor, iso-attenuation in the portal-venous phase and low attenuation in the equilibrium phase, indicating a rapid washout pattern. These comprise very specific findings for the diagnosis of HCC.

In the APASL Guideline 2009 for imaging diagnosis of HCC, US is a screening test, not a diagnostic test for confirmation. US can detect a nodule but cannot characterize it. However, contrast-enhanced US is as sensitive as dynamic CT or dynamic MRI for the diagnosis of HCC (18). When using a US contrast agent for the diagnosis of HCC, the arterial phase and equilibrium phase show a rapid wash-in and washout pattern, which are characteristic findings for overt HCC. Dynamic CT or dynamic MRI is recommended as a first-line diagnostic tool for HCC when a screening test is abnormal. The hallmark of HCC in a CT scan or MRI is the presence of arterial enhancement followed by washout of the tumor in the portal-venous and/or delayed phases. In the diagnostic algorithm for hypervascular masses, typical HCC can be diagnosed by imaging regardless of the size of the detected tumor if a typical vascular pattern—arterial enhancement with portal-venous washout—is obtained on dynamic CT, dynamic MRI or contrast-enhanced US. In the diagnostic algorithm for hypervascular nodules, US is the initial screening method. If a nodule is detected by US, the nodule is then characterized by dynamic CT or MRI. Further characterization is usually performed by Kupffer cell imaging, including Sonazoid-enhanced US, or gadolinium-ethoxybenzyl-diethylene triamine pentaacetic acid (Gd-EOB-DTPA) MRI (Fig. 2) (19). In the diagnostic algorithm for hypovascular masses, nodular lesions showing an atypical imaging pattern, such as iso- or hypovascularity in the arterial phase, or arterial hypervascularity alone without portal-venous washout, should undergo further examination or close follow-up (Fig. 3). Recently, new imaging techniques are being developed, including volume US using various contrast agents, US elastography (20), volume CT, dual energy CT for perfusion CT, diffusion-weighted MRI, MRI elastography, etc. The efficacy of these techniques in diagnosing HCC is being evaluated.

In conclusion, various clinical practice guidelines including diagnostic algorithm for HCC have been established and

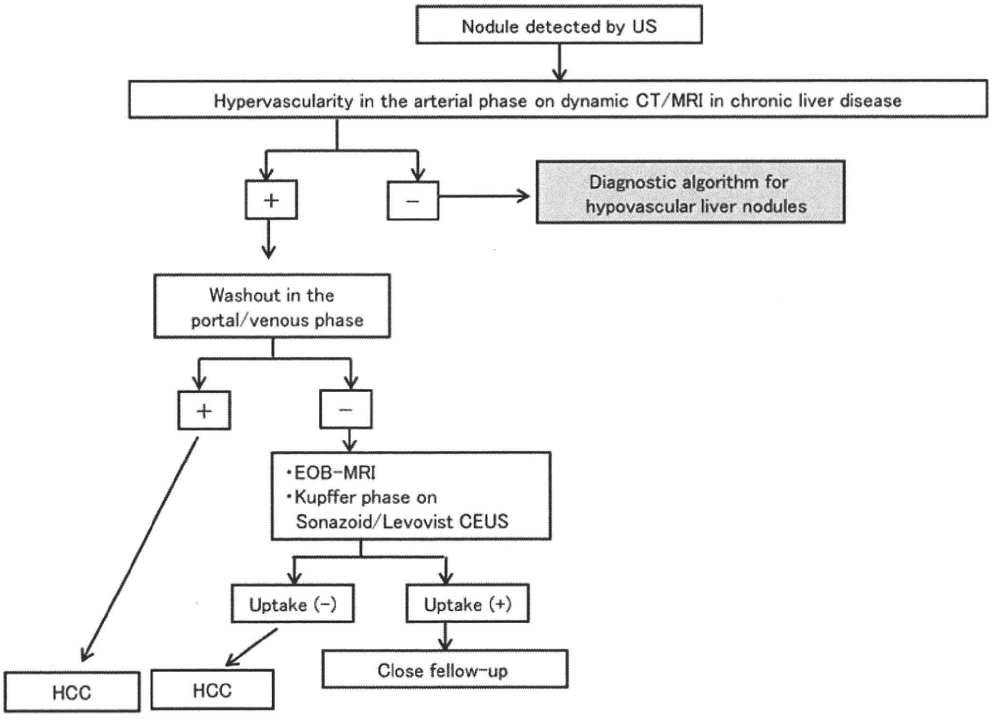

Figure 2. Diagnostic algorithm for hypervascular nodule (APASL Guideline). US, ultrasound; HCC, hepatocellular carcinoma.

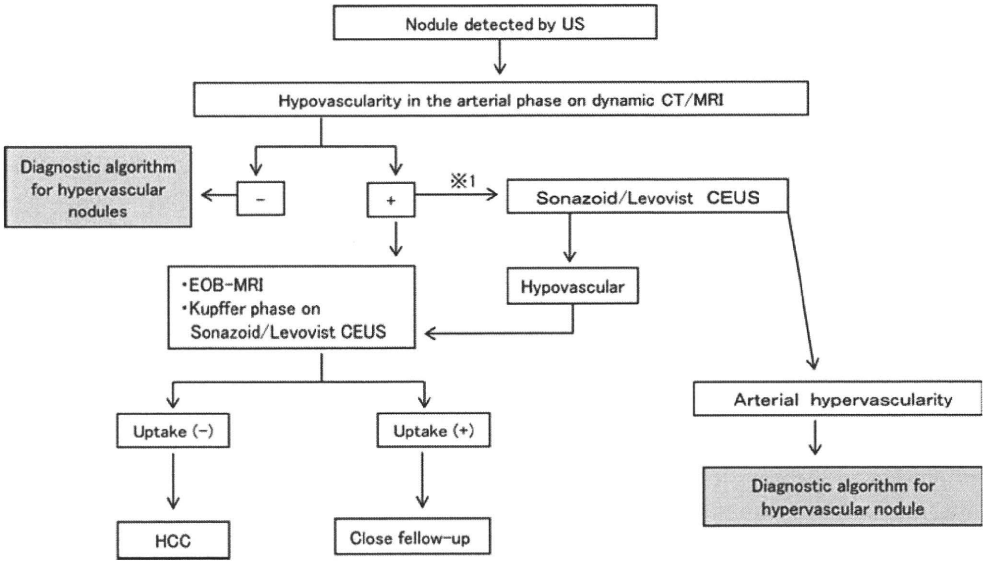

Figure 3. Diagnostic algorithm for hypovascular nodule (APASL Guideline). ※1: When the nodule is hypovascular on dynamic CT or dynamic MRI, Sonazoid-enhanced contrast US is recommended to confirm whether it is truly a hypovascular nodule.

are in use. Use of imaging diagnosis is increasing, whereas the use of biopsy is decreasing. New imaging techniques are continuously being developed. Practice guidelines should be updated to reflect the development of new imaging techniques.

Pathological Diagnosis of Early HCC

In 2009, pathologists from all over the world made great progress by reaching a consensus on the pathological diagnosis of early HCC. A consensus paper was published in the journal, *Hepatology* (21). The main topic of the consensus paper was histopathological definition of early HCC, together with premalignant lesions, dysplastic nodules and progressed HCC. Representative early HCC is a small, well-differentiated tumor, of vaguely nodular type. Microscopically, the border is unclear, and very well-differentiated cancer cells show a replacing growth pattern. They also frequently show stromal invasion, which is quite useful for making a diagnosis of cancer. However, histological atypia or histological alteration is usually very slight in early HCC, which is quite similar to the case of early cancers in other organs. Biopsy diagnosis of early HCC is especially difficult. In an example case, a slight increase in chromatin staining with substantial increase in the nuclear density is seen. Several standard techniques reveal slight changes or alterations in the tumor portion, such as a decrease in reticulin and a slight increase in proliferative activity. However, the use of some new markers, such as heat shock protein (HSP) 70, clearly highlights the tumor portion, making it more easily recognized. Greater use of tumor markers, including glypican 3 and HSP70, is likely and will increase the accuracy of diagnosis of early HCC.

Much has been learned about early HCC, but various problems remain. We know that cancer development is a multistep process, especially when there are cirrhotic changes. Early HCC grows very slowly and has a favorable outcome, whereas progressed, small HCC has a greater likelihood of showing intrahepatic spread and a worse prognosis. It is necessary to recognize that there is a gray zone between precancerous lesion and early HCC. Liver biopsy is recommended for small, equivocal lesions. Also, molecular markers are expected to raise the diagnostic accuracy, especially in the case of biopsy diagnosis of HCC. At the same time, controversy remains regarding which lesions should be examined by biopsy, and there is a risk of overdiagnosis of early cancer.

Current Treatment Strategies

Since 2001, when the Barcelona group published their consensus guideline, at least eight other guidelines have been released worldwide regarding the diagnosis and/or treatment of HCC. In 2003, the Korean guidelines were published, and in 2005, the Japanese guidelines for evidence-based clinical practice (Fig. 4) (16) were released. Clinical practice guidelines should be evidence-based, and they should represent the consensus of expert committees. Sometimes, it is very difficult to reach a consensus in the field of HCC. Guidelines must also take into consideration the socioeconomic status and current daily practice in the country or region. The socioeconomic background and daily practice regarding HCC were compared among Europe and the USA, Asia (Korea) and Japan. The major etiology of HCC is HCV in Europe, the USA and Japan, but HBV in Asia (Korea). A surveillance system has been established in Japan, is being

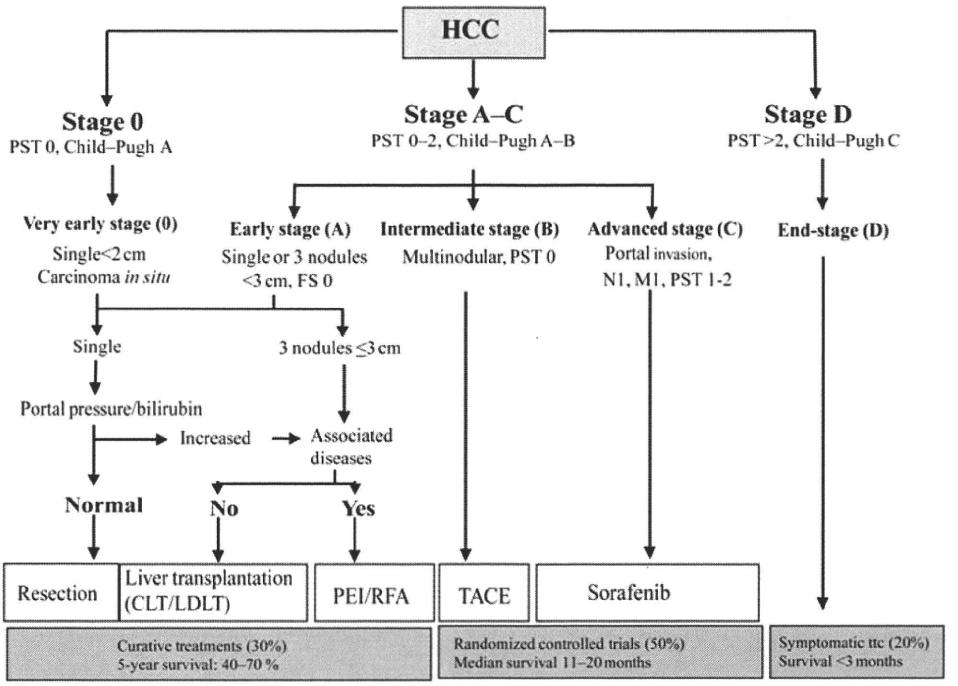

Figure 4. BCLC staging [Llovet et al. (10)]. BCLC, Barcelona Clinic of Liver Cancer; PST, performance status; CLT, cadaveric liver transplantation; LDLT, living donor liver transplantation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

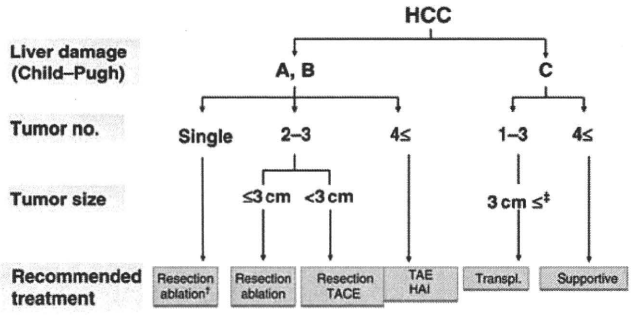

Figure 5. EBM-based algorithm for HCC treatment (J-HCC Guidelines 2009). Resection or transarterial chemoembolization (TACE) may be selected for liver damage A patients with vascular invasion. Chemotherapy may be selected for extrahepatic HCC. LT is only for ≤65 years old. †Recommended for Child B; ‡<2 cm for solitary lesion. HAI, hepatic arterial infusion.

developed in Asia (Korea), but does not exist in the Western countries. As a result, most HCC patients are diagnosed in an early stage in Japan, but at a very advanced stage in Western countries. As tumor markers, only AFP is measured in Western countries, whereas three tumor markers are measured in Japan. The risk of treatment of HCC must also be considered. The mortality of liver resection is as high as 4–5% in Western countries, but only 0.7% in Japan. Brain-dead donors for liver transplantation are very rare in Japan, but common in Western countries (22). These factors must be considered for development of treatment strategies for HCC.

The BCLC guidelines to staging and treatment of HCC are probably the most popular treatment algorithm in Western countries, but not in Asia. The Japanese guidelines were just revised in 2009, are very simple and cover a majority of early- and intermediate-stage HCC patients (Fig. 5). A Japanese consensus-based algorithm for HCC covers even very advanced-stage HCC, including patients with extrahepatic spread and vascular invasion (Fig. 6) (17,19). Sorafenib is recommended for such advanced disease with good liver function, and an ongoing trial is evaluating its use as an adjuvant therapy. The Korean guideline for management of HCC was initially published in 2003, after which they accumulated evidence, held a nationwide forum for revision of the guidelines and created a revision committee. As a result, their updated guidelines were published in 2009 (23). The algorithm for the Korean HCC treatment plan lists hepatic resection, liver transplantation, radiofrequency ablation and ethanol injection as curative treatments. There is no evidence showing which treatment is superior for cure of HCC in each patient, so the guideline recommends that the physician decide which treatment will be used. The APASL Consensus on Treatment of HCC (24) was published in 2010 and may be utilized in the Asian region.

In conclusion, several practice guidelines presenting treatment strategies for HCC in Asia have been developed. They were created based on evidence-based medicine methodology and consensus among experts in the region. They also reflect the socioeconomic status and current daily practice in the region. A number of ongoing clinical trials aim to

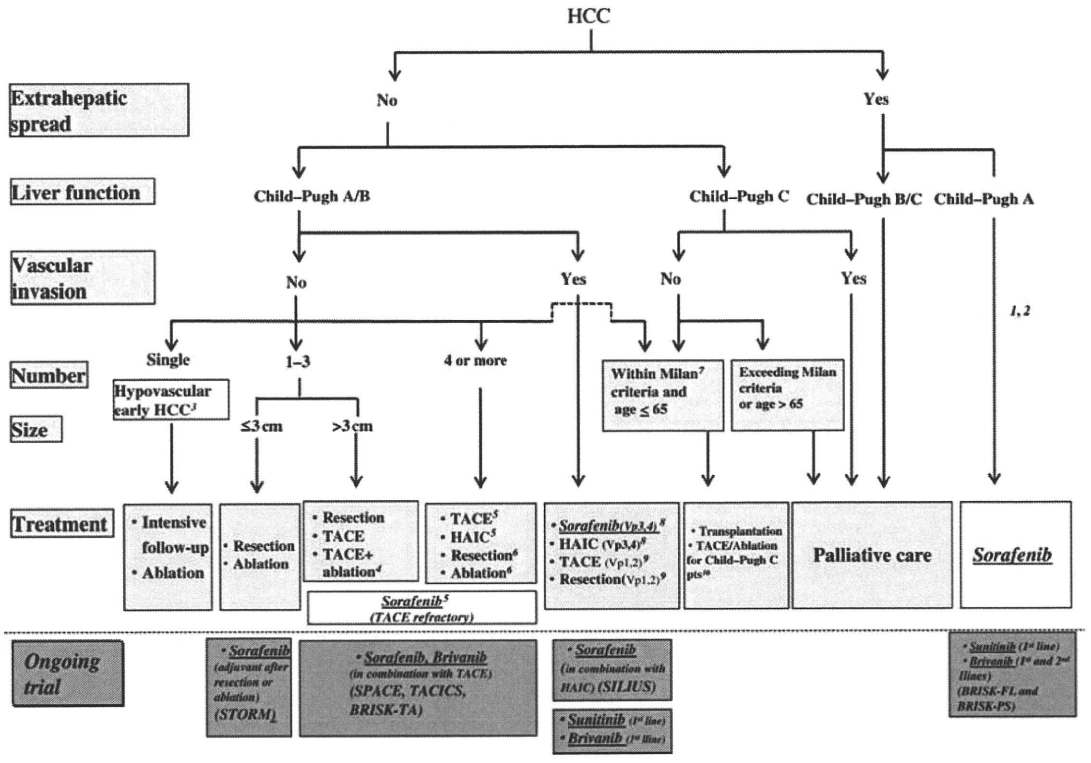

Figure 6. Consensus-based treatment algorithm for HCC proposed by Japan Society of Hepatology (JSH) 2009 revised in 2010. *1*, Treatment should be performed as if extrahepatic spread is negative, when extrahepatic spread is not regarded as a prognostic factor. *2*, Sorafenib is the first choice of treatment in this setting as a standard of care. *3*, Intensive follow-up observation is recommended for hypovascular nodules by the Japanese Evidence-Based Clinical Practice Guidelines. However, local ablation therapy is frequently performed in the following case: (i) when the nodule is diagnosed pathologically as early HCC, (ii) when the nodules show decreased uptake on gadolinium-ethoxybenzyl-diethylene triamine pentaacetic acid or (iii) when the nodules show decreased portal flow by CTAP, since these nodules are known to frequently progress to the typical advanced HCC. *4*, Even for HCC nodules exceeding 3 cm in diameter, combination therapy of TACE and ablation is frequently performed when resection is not indicated. *5*, TACE is the first choice of treatment in this setting. Hepatic arterial infusion chemotherapy (HAIC) using an implanted port is also recommended for TACE refractory patients. The regimen for this treatment is usually low-dose FP (5FU + CDDP) or intra-arterial 5FU infusion combined with systemic interferon therapy. Sorafenib is also recommended for TACE refractory patients. *6*, Resection is sometimes performed even when numbers of nodules are over 4. Furthermore, ablation is sometimes performed in combination with TACE. *7*, Milan criteria: Tumor size ≤3 cm and tumor numbers ≤3; or solitary tumor ≤5 cm. Even when liver function is good (Child–Pugh A/B), transplantation is sometimes considered for frequently recurring HCC patients. *8*, Sorafenib and HAIC are recommended for HCC patients with Vp3 (portal invasion at the first portal branch) or Vp4 (portal invasion at the main portal branch). *9*, Resection and TACE are frequently performed when portal invasion is minimum such as Vp1 (portal invasion at the third or more peripheral portal branch) or Vp2 (portal invasion at the second portal branch). *10*, Local ablation therapy or subsegmental TACE is performed even for Child–Pugh C patients when transplantation is not indicated when there is no hepatic encephalopathy, no uncontrollable ascites and a low bilirubin level (<3.0 mg/dl). However, it is regarded as an experimental treatment since there is no evidence of its survival benefit in Child–Pugh C patients. A prospective study is necessary to clarify this issue.

generate evidence for a better treatment algorithm. Guidelines should be updated every 3 or 4 years, incorporating new evidence.

Future Perspectives, Especially In Regard To Sorafenib

There was no established systemic chemotherapy for HCC. However, sorafenib has become a standard systemic treatment for advanced HCC. This section addresses the future perspectives for sorafenib and beyond sorafenib. Two randomized control studies have shown the survival benefit of sorafenib in advanced HCC patients with good liver function of Child–Pugh A. The SHARP trial (25), carried out mainly in European countries, and an Asia-Pacific trial (26) both showed that sorafenib provides a survival benefit in advanced HCC patients. Both trials yielded similar hazard ratio of 0.69 and 0.68, respectively, in favor of sorafenib over placebo. Other published reports on sorafenib for HCC include a Phase II trial conducted in Western countries (27), a Phase I Japanese study (28), a Korean study (29) and a Phase 2 Hong Kong study (30). The studies had various differences in patient background, such as involvement of HBV, HCV or others, liver function of Child–Pugh A and B, and the ECOG performance status. Those differences affected the survival outcomes in the four studies like outcomes after other treatment modalities.

Although sorafenib has become a standard systemic treatment for advanced HCC, there are still issues to be investigated with regard to this agent, including its efficacy and safety in patients with Child–Pugh B moderate liver

function, combination therapy with other treatment methods, and the need to identify predictive factors and markers for sorafenib. Various studies are currently attempting to elucidate those issues. The Phase III STORM global trial will evaluate sorafenib as an adjuvant therapy after surgery or radiofrequency ablation. A Japanese Phase II study will evaluate the efficacy and safety of sorafenib in patients with Child–Pugh A and B, with investigation of biomarkers. A global trial of combination of sorafenib with TACE is ongoing, while two Japanese Phase I studies of combination of sorafenib with hepatic arterial infusion are in progress (19). Arterial infusion chemotherapy is a very common and useful treatment in Japan (31), and one of these studies combines sorafenib with cisplatin, whereas the other combines sorafenib with 5-FU and cisplatin. It is anticipated that these trials will lead to Phase III studies.

Other Molecularly Targeted Agents

Sorafenib is the first systemic therapy approved for advanced-stage HCC, and widely used. Sorafenib prolongs time to progression and overall survival in patients with advanced HCC; however, predictive factors are unknown at the present. Good responders show a good response, but how can they be identified in advance? Researchers are currently looking for biomarkers that will identify good responders and lead to modification of the treatment algorithm. Also, a 'good response' has limitations. How can a 'complete response' be attained? Combination therapy and some adjuvant treatment, after palliative or curative treatment, will be needed. There are also many poor responders. How can a poor response be overcome? Second-line agents are necessary, as is combination therapy. Various targeted agents in addition to sorafenib are under development for HCC. They include brivanib, bevacizumab, cediranib, erlotinib, gefitinib, lapatinib, RAD001, sunitinib, thalidomide and TSU-68. These agents have similar yet slightly different mechanisms of action. The results of various clinical studies of these molecular targeted therapy agents were summarized in *Hepatology* (32). The results look good, and many Phase II and Phase III trials are ongoing. The trials can be categorized into three types: first-line or combination studies, second-line studies and adjuvant studies.

First-line or combination studies are being carried out as Phase III trials of sunitinib vs. sorafenib (terminated in 2010 because of severe adverse effect); brivanib vs. sorafenib; lilifanib vs. sorafenib; erlotinib plus sorafenib vs. sorafenib; and erlotinib plus bevacizumab vs. sorafenib. The results of these trials should be available in 2 or 3 years. There are also many first-line Phase II studies. There are two second-line Phase II studies, of brivanib vs. the placebo and RAD001 vs. the placebo, for patients who failed to respond to sorafenib. There are three Phase III adjuvant studies. The STORM study investigates sorafenib vs. placebo after resection or ablation. A second adjuvant study investigated sorafenib vs. placebo after TACE; this is already finished and the results were presented at ASCO-GI in 2010 (33). The third Phase III adjuvant study compares brivanib vs. placebo after TACE. In a first-line Phase II study of brivanib, 46% of the patients showed stable disease, and in the second-line Phase II study, 43% showed stable disease (34,35). These results were promising, and at least three trials are now ongoing for brivanib.

In conclusion, molecularly targeted therapy (MTT) has emerged as a promising approach for advanced HCC. Sorafenib impacted on MTT agents in HCC, but the benefits of sorafenib were reported to be relatively modest. Several MTT agents for first- and second-line treatments are undergoing clinical trials. The advantages of MTT agents are being explored in combination treatments as well as adjuvant therapy with resection, local ablation, radiation, hepatic arterial infusion chemotherapy and TACE.

CONCLUSION

HCC is a highly prevalent disease in many Asian countries and incidence of HCC varies enormously across Asia, but tends to follow incidences of hepatitis B infection and liver cirrhosis. Incidence and etiology of HCC in Japan is different from the rest of Asia, but similar to Western countries since hepatitis C infection is the main etiological factor. Screening program improves detection of early HCC and has some positive impact on survival, but the majority of HCC patients in Asia still present with advanced HCC. Long-term outcomes following treatment of early, intermediate or advanced disease are still unsatisfactory because of lack of effective adjuvant or systemic therapies. Sorafenib is the first systemic therapy to demonstrate prolonged survival vs. placebo in patients with advanced HCC. New molecular targeting therapies hold great promise. Many new agents are under investigation and their results are awaited.

Conflict of interest statement

The author, Joong-Won Park, participated in phase II and phase III clinical studies sponsored by Bristol-Myers Squibb, Pfizer Inc., Bayer Healthcare and Bukwang Pharmaceutical Co. He is also a member of BMS Brivanib study steering committee, Pfizer Sunitinib advisory committee, and Bukwang Pharmacetutical Co. advisory committee.

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A Conundrum for Randomized Controlled Trials: Experience from a Small Hepatocellular Carcinoma Trial

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Objective: The aim of this study was to explore why patients accepted or declined to participate in a randomized clinical trial, which was subsequently discontinued because of a low recruitment rate.
Methods: Forty-one patients were invited to participate in a randomized clinical trial that aimed to compare local ablation therapies and surgery to treat small asymptomatic hepatocellular carcinomas. These patients were then asked to answer a questionnaire that assessed patient perception and reasons for accepting or declining to enroll in the randomized clinical trial. When patients had a strong preference for a specific treatment, the questionnaire assessed why, how and when they had chosen it.
Results: The response rate was 6/6 (100%) and 30/35 (86%) for the participant and non-participant groups, respectively. Among the 30 non-participants, 23 had a strong preference for local ablation therapies, which was less invasive and offered shorter hospitalization. Patient preference for a specific treatment often stemmed from their consultations with a clinician who referred them to a specialist hospital. Patients without strong preference for a specific treatment participated in the randomized clinical trial because of altruistic motivations.
Conclusion: When new treatments that are innovative and less burdensome become widespread, they are difficult to compare with standard therapy utilizing a well-designed randomized clinical trial. Consequently, when an innovative treatment is developed, investigators should consider designing a randomized clinical trial as early as possible.

Key words: small asymptomatic hepatocellular carcinomas – local ablation therapies – liver resection – randomized clinical trial

INTRODUCTION

Randomized clinical trials (RCT) are the gold-standard to evaluate the safety and efficacy of proposed new treatments (1–3). When a new treatment shows benefits, it is introduced into general practice and is expected to improve the quality of care. However, an appropriate evaluation of an unproven new treatment through a RCT is difficult when it becomes integrated into general clinical practice because of its innovative and minimally burdensome nature (3). Consequently, the co-existence of a new treatment and a standard therapy often leads to diminished patient access to beneficial treatments.

Small asymptomatic hepatocellular carcinomas (HCC) are increasingly recognized as a problem in Japan since the initiation of periodic surveillance of high-risk populations (4). Surgical resection has been accepted as the first-line treatment for HCC. In addition, several local ablation therapies (LAT) have been developed to treat HCC, including percutaneous ethanol injection (PEI) (5) and radiofrequency ablation (RFA) (6). They are minimally invasive and have been recognized as an alternative to surgery in small HCC patients. Retrospective studies have reported that the prognosis of patients undergoing PEI (7–10) or RFA (6,11) for small HCC was equivalent to that of patients selecting surgery. However, the optimal therapeutic strategy for small HCC is under debate. Patient decisions regarding treatment are often guided by the expertise of their consulting clinician, which is frequently affected by sectionalism that is predominant in the Japanese medical community.

In 2002, a RCT (the parent study) was organized to settle the longstanding debate comparing the benefits of LAT relative to surgery in treating small HCC (i.e. three or fewer tumors, where each tumor is 3 cm in diameter or smaller). Table 1 shows the study outline. The trial was carried out in three cancer hospitals (Institutions A, B and C) and a university hospital (Institution D), where physicians and surgeons had the opportunity to build a framework for cooperation. We reached a consensus on what to include in the informed consent form and how to obtain it from patients. Specifically, we explained the clinical equipoise by noting: (i) the probability of 5-year disease-free survival associated with the two treatments was 25 and 10% for surgery and LAT, respectively; and (ii) the probability of 5-year survival associated with the two treatments was 62 and 59% for surgery and LAT, respectively (10). The purpose of the parent study and difference between two treatments were explained in informed consent form as follows; the purpose of this study is to compare the effectiveness, risk, burden and cost between surgery and LAT. Surgery has been usually performed for your type of cancer. LAT has been found to be effective and spread widely, but there is no solid evidence that LAT has a similar benefit to surgery. Currently, the proportion of recurrence in surgery is lower than LAT. However, there is little difference in long-term survival between surgery and LAT. LAT imposes less burden and invasiveness on patients than surgery. The comparative table of benefit, burden and cost in two treatments also was put on the form.

Table 1. Outline of the parent study

	Contents
Purpose	To compare local ablation therapies (RFA, PEI) with surgical resection
Eligibility	Hepatocellular carcinoma, three or fewer tumors each 3 cm in diameter or smaller, Child-Pugh class: A or B
	Age: ≥20, <80
Endpoints	
Primary endpoints	Overall survival and disease-free survival
Secondary endpoints	Medical costs, hospitalization period, Toxicity
Sample size	120 patients
Recruit period	2 year
Institutions	Cancer hospitals (Institution A, B, C), University hospital (Institution D)

Between October 2002 and April 2003, 41 patients were invited to participate in this study. Among these patients, six agreed and 35 refused to participate. Although a similar study was completed in China (12), the steering committee decided to discontinue the trial because of the low recruitment rate. Within this context, the aim of this study was to explore why patients accepted or declined to participate in the trial, and to use this information to provide insights for future research.

PATIENTS AND METHODS

We invited 41 patients, who were originally asked to participate in the parent study, to take part in this study. These patients were then asked by an attending clinician to respond to a questionnaire accompanied by an envelope. Patients were directed to place the completed questionnaire into the envelope and deliver it to the hospital staff. This study was approved by the National Cancer Center Hospital research ethics committee.

The questionnaire contained both multiple-choice and open-ended questions that aimed to assess the reasons behind patient decisions to participate in the study. We also examined views of non-participants towards random allocation. When non-participants had a strong preference towards a specific treatment, we assessed their perception by inquiring why, how and when they developed this preference. The questionnaire, developed by the investigators, was pilot-tested with laypersons to ensure clarity and comprehensibility of the questions. The questionnaires are shown in the Supplementary data, Appendix, available at http://www.jjco.oxfordjournals.org.

RESULTS

The survey was performed between May and July of 2003. Among the six participants and 35 non-participants, 6 (100%) and 30 (86%) patients, respectively, responded to the questionnaire. Table 2 shows the number of patients who accepted or declined participation in the parent-trial. Table 2 also shows the number of non-participants who chose surgery or LAT. Only 15% of patients participated in the parent-trial. There were no differences among institutions. Among the 30 respondents who declined trial entry, four had surgery, 25 had LAT and the remaining one was unknown.

Table 2. Number of patients (Pt) who accepted or declined participation

	Pt invited to RCT	Participant (%)	Non-participant		
			Total	Surgery	Local ablation therapies
Institution A	10	3 (30)	7	1	6
Institution B	8	1 (12)	7	1	6
Institution C	12	1 (8)	11	0	11
Institution D	11	1 (9)	10	4	6
Total	41	6 (15)	35	6	29

Reasons for Participation or Non-participation

Table 3 summarizes participants' reasons for deciding to participate in the parent-trial. All participants answered that they thought participation in the trial would contribute to the development of medicine. When asked about their major reason for participation, three participants marked 'the contribution to medical development' and two participants noted 'clinicians asked me to participate'.

Table 4 shows non-participants' reasons for refusing to enroll in the parent-trial. Four patients (13%) answered that they preferred surgery to LAT whereas 23 (77%) noted that they preferred LAT. One of two patients who received LAT stated 'I disliked surgery'; although the other stated 'clinicians did not ask strongly to participate'. Twelve patients (40%) stated that they were not satisfied with the random allocation into a treatment group. Among these 12 patients, 7 (58%) answered that patients should decide their own treatment whereas 3 (25%) answered that clinicians should decide. Two patients (17%) answered that randomization was inhumane. One patient (8%) stated that random allocation was problematic when two treatments were very different. One patient (8%) stated that he/she could not understand randomization.

Table 3. The frequency of agreement to each statement according to participation among six patients

Statement[a]	Number of respondents (%)
I thought participation in the trial would contribute to the development of medicine	6 (100)
Clinician asked me to participate	2 (33)
I thought there were no differences between two treatments	1 (17)
Other	
I had no preference because my tumors were small	1 (17)
I could not decide which treatment to have	1 (17)

[a]More than one response was allowed.

Table 4. The reasons of 30 non-participants for refusal

Statement[a]	Number of respondents (%)
I was not satisfied to be assigned to the treatment by randomization	12 (40)
Patient should decide the treatment	7 (58)
Clinician should decide the treatment	3 (25)
Randomization was inhumane	2 (17)
Two treatments were very different	1 (8)
I could not understand randomization	1 (8)
I wanted to receive local ablation therapies	23 (77)
I wanted to receive surgery	4 (13)
Other	
Clinician did not ask me to participate	1 (3)
I disliked surgery	1 (3)

[a]More than one response was allowed.

Reasons for Refusing Trial Entry Among Non-participants

Table 5 shows non-participants' reasons for why they subsequently decided to undergo surgery or LAT. All four patients who received surgery and one patient who receive LAT answered that they had thought the probability of recurrences would be lower. Among the patients who had LAT, the majority (20/25, 75%) stated that LAT imposed a lower amount of burden and invasiveness to their body than surgery. In addition, about half of the non-participants (12/25, 48%) stated that the hospitalization period would be shorter with LAT than with surgery. One patient stated that the medical cost of LAT was fewer.

Table 6 summarizes the results of how non-participants made their treatment decisions. Among these four patients who had surgery, three answered that they followed their surgeons' recommendation and one answered he/she followed physicians' recommendation. Among these 25 patients who had LAT, 2 (8%) answered that they referred to their surgeons, 21 (84%) answered that they relied on their attending physicians' recommendation and 9 (36%) answered that they relied on general practitioners' recommendation. Thirteen out of 25 patients who had LAT answered they had already decided to obtain this treatment before they were invited to the trial.

DISCUSSION

In this study, we found that patients who declined trial entry had a strong preference for LAT, which was less invasive and offered a shorter hospitalization course. We also found that this patient preference had stemmed from patient consultations with either a clinician or general practitioner who

Table 5. The reasons of 30 non-participants for preferring surgery or local ablation therapies

Statements[a]	Number of respondents (%)	
	Pt with surgery ($n = 4$)	Pt with local ablation therapies ($n = 25$)
I thought the probability of recurrences would be lower	4 (100)	1 (4)
I thought the survival period would be longer	0	0
I thought the treatment was less burdensome	0	20 (80)
I thought the hospitalization period was shorter	0	12 (48)
I thought the medical cost was fewer	0	1 (4)
Other	0	
I heard that the prognosis were the same		1 (4)
I did not want to increase wound any more		1 (4)

[a]More than one response was allowed.

Table 6. What non-participants referred to when they made a decision

	Number of respondents (%)	
	Pt with surgery ($n = 4$)	Pt with local ablation therapies ($n = 25$)
What non-participants referred to[a]		
Informed consent form	0	13 (52)
Consultation with surgeon in charge	3 (75)	2 (8)
Consultation with physician in charge	1 (25)	21 (84)
Consultation with general practitioner	0	9 (36)
Opinion of other patients	0	2 (8)
Opinion of my family	1 (25)	3 (12)
Other		
My close friend who was clinician suggested	1 (25)	
My friend suggested		1 (4)
The explanation about the prognosis		1 (4)
The information from internet		1 (4)
The information from newspaper		2 (8)
When they made a decision		
Before invitation to the study	1 (25)	13 (52)
After invitation to the study	1 (25)	8 (32)
Do not know or no answer	2 (50)	4 (16)

[a]More than one response was allowed.

referred them to a specialist hospital. Non-participants who received surgery believed in the survival benefits from surgery and relied on surgeon recommendations. On the other hand, patients without strong preference participated in the trial largely because of altruistic motivations. In summary, we found that patients tended to choose less invasive treatment methods even if there is a lack of superiority evidence or an inferiority possibility compared with the standard treatment. Many studies have reported a number of complex barriers in appropriately conducting RCTs (13–18), and we found a couple of these factors that contributed to the incompletion of this trial.

One barrier is that LAT, which had been performed in patients with unrespectable hepatic malignancies, has become popular in treating patients with small HCC due to its superiority in local tumor control and minimal invasiveness. It has become so popular that even without appropriate evidence that LAT has equivalent survival benefits compared with surgery, many general practitioners have recommended it to their patients as an alternative therapy.

Another barrier was patient fear towards a possible allocation into a treatment group that they did not prefer. Although some studies reported that a barrier to trial entry was patient difficulty in understanding the randomization concept and associated patient uneasiness (19–21), our study did not find this as an issue. Only one in 12 respondents that disliked randomization could not understand the randomization concept. Consequently, unbiased and objective explanations by clinicians are crucial in the consent process. However, in our study, we found that the more we stressed the clinical equipoise, the more the patients preferred LAT.

Although the lack of participation was based on these simple reasons, the solution is not simple. In order to increase the number of participants, there are a few possible study designs. One is a randomized consent design, where patients are randomly allocated into a specific treatment group before they provide consent (22,23). If patients decline the allocated treatment, they are then possibly allocated to the other treatment. Even if we apply this design, apart from its ethical problems, the effort will likely fail because most patients allocated to the surgery group will decline. Another possible solution is a randomized trial with a non-randomized part. Specifically, consenting patients are randomized into the two treatment groups, and those that refuse their allocated treatment are enrolled into a non-randomized study. At the conclusion of such a study, the endpoints of the randomized group and the non-randomized group are compared. In such a design, the results may include biases. Moreover, if there is an imbalance in the number of patients between the treatment groups in the non-randomized study, it is difficult to obtain appropriate results.

Furthermore, when there is a discrepancy in results between the randomized and non-randomized study groups, there is difficulty in the interpretation of the results.

In conclusion, when innovative and less burdensome treatments become widespread, they are difficult to compare with standard therapy utilizing a RCT. In light of the increasing number of organ preserving therapies, investigators should evaluate the efficacy and safety of innovative treatments with RCTs as early as possible (24).

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Conflict of interest statement

None declared.

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