difference in serum total bilirubin level between the beginning and the end of the observation period [Dbilirubin level = (bilirubin level at the end) − (bilirubin level at the beginning)] in individual patients and compared it between the PI group and the non-PI group. The mean Dbilirubin level in the PI group was 0.5 ± 3.4 mg/dl and that in the non-PI group was −0.2 ± 1.6 mg/dl ($p = 0.250$). The Dbilirubin level in a patient in the PI group who was coinfected with HCV besides HIV/HBV as well was −27.4 mg/dl. Excluding this single outlier, the mean Dbilirubin level was significantly different between the PI and non-PI groups (mean Dbilirubin level 0.8 vs. −0.2; $p = 0.01$).

Discussion

We have summarized here the data from our comprehensive survey of HIV/HBV coinfection in Japan, focusing particularly on the clinical features of the patients and the effect of ART on liver function. As we reported earlier, HIV/HBV coinfection was observed in 6.3 % of Japanese HIV-positive patients [7]. Certain considerations for HBV coinfection are important in HIV patient care.

The major transmission route of HIV was male homosexual contact, which accounted for the infection in about 80 % of the patients; thus, male patients were the majority in the present cohort. The most frequently found genotype of HBV was genotype A, which is infrequent in HIV-negative patients in Japan. Genotype A is often found in the United States, Europe, India, and the west coast of Sub-Saharan Africa [25]. Although the data on HBV subgenotypes were not available in our study, some reports showed that most genotype A strains detected in HIV/HBV-coinfected individuals are of genotype Ae [26]. These findings suggest that HBV infection among Japanese HIV carriers is not caused by the spread of indigenous HBV, such as transmission in the perinatal period, but rather specific strains are circulating among the homosexual population in Japan. Genotypes B and C accounted for more than 96 % of the entire Japanese chronic HBV infection [27, 28]. These findings are compatible with the report that the presumed transmission route of HBV in HIV/HBV-coinfected patients is not from Japanese female partners but from male partners, as shown by Koibuchi et al. [29].

Seventy-five percent of HIV/HBV-coinfected patients received ART with two agents against HBV, and its efficacy against HBV as well as HIV is considered to be high. As recommended by the United States Department of Health and Human Services (DHHS) and the Japanese guidelines on HIV treatment, the initiation of ART with NRTIs with anti-HBV activity as the backbone is indicated for HIV/HBV-coinfected patients regardless of HIV viral load or CD4+ T lymphocyte count [30]. Nucleoside analogues can improve liver function in HBV-monoinfected patients [31]. Our study shows that ART decreased the levels of ALT and albumin in HIV/HBV-coinfected patients. It is noteworthy that the regimen used in ART includes multiple drugs with anti-HBV activity such as lamivudine plus abacavir, which is unusual for HBV-monoinfected patients.

When we compared the characteristics of patients on ART with those not on ART, there were some notable differences in their immune status and liver function. At the beginning of the observation period, patients on ART showed a lower CD4+ T-cell count and poorer liver function. Our study is a retrospective observation, and patients were not grouped randomly. These observations are rather understandable because those who had a low CD4+ T cell count were more likely candidates for ART. Additionally, patients on ART had a longer observation period and were more likely to develop AIDS. These findings are also understandable because the longer the duration of HIV infection, the more likely is the immune system of the patient to deteriorate. Moreover, once ART is started, patients need to visit clinics or hospitals regularly for a long period; in reality, for the rest of their life. Following current recommendations for the initiation of ART for HIV infection, patients with worse immune status are more likely to receive the treatment. These findings can explain our observation.

Our data show that the serum albumin level and platelet count improved in the patients who were on ART. As the regimen of ART usually contains two drugs against HBV, ART suppresses HBV replication, which may lead to an improved liver function, as observed in HBV-monoinfected patients treated with nucleoside analogues [31]. Long-term treatment with lamivudine was shown to regress the fibrosis of the liver [32, 33] and decrease the proportion of patients with hepatocellular carcinoma complication [34]. In view of these findings, ART for HIV/HBV-coinfected patients may markedly improve the prognosis of patients. In our study, only a small number of patients with advanced liver diseases associated with HBV infection such as cirrhosis or hepatocellular carcinoma were observed, which could be attributable in part to the short observation period and the short duration of HBV infection. If we had a longer observational period, we would be able to clarify the difference in clinical course between the ART and non-ART groups, and the actual significance of ART for HIV/HBV-coinfected patients should become clearer.

We found that some parameters related to liver function changed paradoxically, particularly in the ART group. Although the mean serum albumin level, ALT level, and platelet count improved, the mean serum bilirubin level worsened, from 0.5 to 0.9 mg/dl. On the other hand, the serum bilirubin level in the non-ART group decreased. Both changes are statistically significant, which suggests

that the observed hyperbilirubinemia was not associated with HBV activity. The increase in serum bilirubin level is presumably caused by PIs. Hyperbilirubinemia following PI administration was previously reported [35]. Although it is unclear whether hyperbilirubinemia itself may lead to liver injury, PIs should be used carefully particularly for patients with advanced liver diseases.

Our present study has one major limitation; that is, the effect of alcohol on liver function was not analyzed because the history of alcohol consumption could not be obtained in the majority of the studied patients. Excessive alcohol consumption has been found to be an important risk factor for the development of severe hepatic injury in HIV-infected patients with [3] or without HCV coinfection [5]. Our present study showed that among the 26 patients whose history of alcohol consumption was available, only 2 patients were habitual drinkers. The results suggested that the effect of alcohol on liver function is small in HIV/HBV-coinfected patients in Japan.

In conclusion, ART with anti-HBV drugs may retard the progression of liver diseases and prevent liver-related death in HIV/HBV-coinfected patients. Multiple agents with anti-HBV activity seem essential for the efficacy. PIs should be carefully used particularly for patients with advanced liver diseases.

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Table 1. Characteristics of the Randomized Cohorts and SVR Rates of Heterozygous Genotype rs12979860CT With Additional Genotyping of rs8099917

Random Sample Size	Sample Number	Mean Age ±SD	Male	HCV RNA ≥400.000 IU/mL	Severe Fibrosis	SVR rs12979680CT/ rs8099917TT	SVR rs12979680CT/ rs8099917TG	*P*-value
10%	96	47±11	58%	69%	55%	48%	36%	0.408
20%	192	48±11	59%	80%	43%	43%	32%	0.379
30%	295	48±11	60%	72%	48%	50%	38%	0.154
40%	396	47±11	63%	66%	55%	57%	39%	**0.012**
50%	474	47±11	60%	68%	53%	56%	37%	**0.003**
60%	588	48±11	58%	71%	52%	57%	35%	**0.0001**
70%	654	47±11	58%	72%	52%	56%	39%	**0.002**
80%	754	48±11	58%	70%	51%	55%	39%	**0.002**
90%	835	48±11	59%	71%	52%	56%	40%	**0.001**
100%	942	48±11	59%	70%	52%	55%	40%	**0.001**

SD, standard deviation; IU, international units; SVR, sustained virological response; $P < 0.05$ considered to be statistically significant.

fibrosis stage on the SVR rates of genotype rs12979860CT/rs8099917TT and rs12979860CT/rs8099917TG (Supporting Table 1). Again, it becomes obvious that the impact of additional genotyping of rs8099917 on the prediction of SVR is improved in patients with heterozygous genotype of rs12979860 who have high baseline HCV RNA levels ($P = 3.7 \times 10^{-5}$), HCV subtype 1a ($P = 3.3 \times 10^{-5}$), or severe fibrosis stages ($P = 0.001$), being female ($P = 0.023$), or of younger age ($P = 0.029$). Thus, the different patient characteristics most likely explain the differences in the SVR rates.

From that, one possibly may conclude that two SNPs are good in large cohorts but not relevant for clinical practice. However, the idea of large studies is to inform individual clinical practice. Our results derived from a large cohort suggest that algorithms and models that include both rs12979860 and rs809917 as well as baseline parameters and viral factors are informative to guide therapeutic decision making.[3]

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Plasma Lysophosphatidic Acid Levels and Hepatocellular Carcinoma

To the Editor:

We read with interest the article by Mazzocca et al.,[1] showing that serum lysophosphatidic acid (LPA) levels are increased in hepatocellular carcinoma (HCC) patients correlated with tumor burden, while not enhanced in cirrhosis patients. However, we think that their LPA values in serum samples need to be carefully evaluated, because of some technical issues in the measurement of LPA levels in blood samples. First, because LPA is released from platelets, LPA has been measured in plasma but not in serum when evaluating its clinical significance.[2,3] Second, as we previously demonstrated,[4] LPA levels in plasma samples are markedly increased after sample preparation unless the temperature is kept under strict control, potentially because the synthetic enzyme autotaxin (ATX) and the substrate lysophosphatidyl choline coexist in plasma samples to abundantly produce LPA. LPA was once reported as a biomarker of ovarian cancer,[2] but contrary data were later demonstrated, in which a distinct sampling of plasma may explain this discrepancy.[3] Indeed, LPA levels in serum reported by Mazzocca et al. were approximately 10 times higher than the previously reported LPA levels in plasma.[2,3] If their LPA values in serum were increased after sampling similarly in each sample, plasma LPA levels might be correlated with HCC burden as reported. To clarify this, we have newly measured plasma LPA levels in HCC patients,

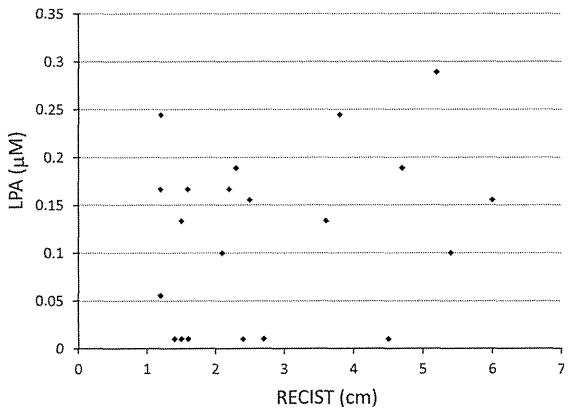

Fig. 1. Plasma LPA levels and HCC burden. Plasma LPA levels, measured in 21 HCC patients (13 males and 8 females; 2 patients with chronic hepatitis B, 15 with chronic hepatitis C, and 4 with non-B non-C chronic liver disease), were not significantly correlated with HCC burden as evaluated by RECIST (Response Evaluation Criteria in Solid Tumors; Spearman rank, $r = 0.158$, $P = 0.4937$). This study was approved by the Institutional Research Ethics Committee and informed consent was obtained for the use of the samples.

and found that they were not correlated with tumor burden, as shown in Fig. 1. Moreover, plasma LPA levels in HCC patients (0.12 ± 0.09 mM, mean $\pm$ SD, n = 21), were not different from the previously reported levels in non-HCC patients with chronic hepatitis C (0.10 ± 0.05 mM).[5] Although Mazzocca et al. reported no enhancement of serum LPA levels in cirrhosis patients, we[5] and others[6] previously showed that plasma LPA levels and serum ATX activity were increased in chronic liver diseases in association with fibrosis and cholestatic pruritus, from which HCC frequently arises. Collectively, a role of LPA in HCC should be cautiously analyzed.

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Potential conflict of interest: Nothing to report.

Reply:

Ikeda et al. remark that platelets are a main source of lysophosphatidic acid (LPA) and therefore the interpretation of LPA serum concentrations deserves careful attention. However, the same authors previously reported[1] an inverse correlation between plasma LPA concentrations and the number of platelets in patients with chronic C hepatitis. Therefore, it is possible that in physiologic conditions platelets remain the main source of LPA, while in chronic inflammation such as hepatitis C, liver cirrhosis, or hepatocellular carcinoma (HCC), the platelet contribution to LPA production may likely become less relevant. In our study we analyzed sera for LPA detection in healthy donors, liver cirrhosis, and HCC patients, performing well-standardized procedures of collection for each sample. Thus, the contribution of platelets to the LPA concentration was, in reality, normalized. On the contrary, the authors should consider that even in plasma or whole blood, platelet activation is an extremely difficult problem to deal with and control. For example, prolonged tourniquet application, or twisting of the needle in the vein, are major factors interfering with the function of platelets during blood withdrawal, as reviewed by Ruggeri.[2] Unfortunately, these limitations are common for a number of molecules involved both in cancer and in blood cell biology.[3]

Moreover, Ikeda et al. investigated patients with chronic hepatitis C, in whom the inflammatory response is a key component of the tissue microenvironment. In their study, the fibrotic status was also questionable, due to their choice of statistical method (comparison among groups should be done with Kruskal-Wallis tests), and because of the very limited number of patients (14), further stratified into four different groups, which means the conclusions were affected by low power.[1] In our study,[4] we compared liver cirrhosis versus HCC. In the former case, the inflammation is reduced while the fibrotic response is increased, consequently inducing a different microenvironment response.[5] This could explain why patients with liver cirrhosis display relatively low levels of LPA. In addition, it is conceivable that when HCC develops in cirrhotic liver, LPA levels rise once more, as in cases of active inflammatory states (i.e., viral hepatitis). Another key point is patient selection. Ikeda et al. do not provide any information with regard to the clinical features of the patients, i.e., etiology, BCLC stage, previous therapy, etc., as well as how they calculated the size of the tumor in patients with multifocal disease, for instance. Finally, some differences between Caucasian and Asian patients with HCC are to be expected, since the natural history is completely different in Western and Southeast Asian countries.[6] In our study,[4] we demonstrated that LPA has a role in promoting tumor progression and we did not attempt to speculate about the use of LPA as a clinical biomarker. To validate LPA as a potential biomarker for HCC a different study design is required, as well as first considering the power of the study. The enhancement of serum LPA levels reported by Watanabe et al.[1] referred to a relatively small number of patients with chronic hepatitis C. In addition, the

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Systemic combination therapy of intravenous continuous 5-fluorouracil and subcutaneous pegylated interferon alfa-2a for advanced hepatocellular carcinoma

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Abstract
Background In Japan, sorafenib is now the first-line therapy for individuals with advanced hepatocellular carcinoma (HCC), but no other treatment is available for such patients. The aim of this study was to assess the efficacy and safety of combination therapy with systemic continuous intravenous infusion of 5-fluorouracil (5-FU) and subcutaneous peginterferon alfa-2a, which was used before sorafenib was introduced to Japan.
Methods Two hundred and twenty-three HCC patients, who were not amenable to curative surgery, percutaneous ablation, or transarterial chemoembolization (TACE), and for whom intraarterial chemotherapy was not indicated because of the presence of extrahepatic metastasis or stenosis of the common hepatic artery, received peginterferon alfa-2a (90 μg subcutaneously on days 1, 8, 15, and 22) and 5-FU (500 mg/day intravenously given continuously on days 1–5 and 8–12). We assessed their response to treatment and survival, and treatment safety.
Results The response rate was 9.4 % (including six patients with complete response) and the disease-control rate was 32.7 %. The median time to progression was 2.0 months. The overall median survival time was 6.5 months (Child–Pugh class A: 9.2 months vs. Child–Pugh class B: 2.8 months). In a multivariate analysis, Eastern Cooperative Oncology Group (ECOG) performance status >0, Child–Pugh class B, and the presence of macroscopic vascular invasion were independent predictors of poor prognosis. The major grade 3–4 adverse events were leucopenia (13.9 %) and thrombocytopenia (5.8 %). No treatment-related deaths occurred.
Conclusions This combination therapy was well tolerated and showed promising efficacy. Further studies are needed to establish the usefulness of this treatment.

Keywords Hepatocellular carcinoma · Systemic chemotherapy · Survival analysis · Time to progression

Abbreviations

AIC	Akaike information criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CR	Complete response
CT	Computed tomography
DCP	Des-gamma-carboxy prothrombin
ECOG	Eastern Cooperative Oncology Group
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
MRI	Magnetic resonance imaging
MST	Median survival time
NA	Not assessable
PD	Progressive disease
PR	Partial response

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RECIST	Response to treatment in solid tumors
SD	Stable disease
TACE	Transcatheter arterial chemoembolization
TTP	Time to progression
5-FU	5-Fluorouracil

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death, with a particularly high incidence in Asian countries, including Japan [1, 2]. HCC usually develops in a liver already suffering from chronic disease, most notably due to hepatitis B virus (HBV) or hepatitis C virus (HCV) infection [3]. In the past, HCC was diagnosed often only at a very advanced stage, which was associated with a very poor prognosis [4]. Close surveillance of designated high-risk patients, using advanced diagnostic modalities, has now facilitated HCC detection at a much earlier stage. Together with the considerable advances in HCC treatment, such as surgical resection, percutaneous ablation, transcatheter arterial chemoembolization (TACE), and liver transplantation, the survival time of HCC patients has been much prolonged in recent years [5–10].

However, the potentially curative treatment modalities described above are not indicated for patients with advanced HCC with extrahepatic metastasis or macroscopic vascular invasion , and their prognosis remains poor. In two recent large randomized controlled trials, sorafenib, a multi-kinase inhibitor, significantly prolonged survival in patients with advanced HCC, even when the primary lesion was associated with vascular invasion or extrahepatic metastases, and this agent is now widely regarded as the standard treatment for such patients [11, 12]. However, even with sorafenib, the median survival time (MST) of such patients is rather short, ranging from 6.5 to 10.7 months. Thus, the development of new drugs or new regimens that include cytotoxic and molecular-targeted agents still remains necessary.

Previously, we reported the efficacy of therapy using a combination of intrahepatic arterial 5-fluorouracil (5-FU) and subcutaneous interferon alfa for patients with advanced HCC with portal venous invasion [13]. Because most intraarterially administered 5-FU is taken up by the liver during the first pass, this combination chemotherapy would not be effective against extrahepatic metastasis. Nevertheless, the mechanism underlying the chemotherapy with intraarterial 5-FU would function if 5-FU could reach extrahepatic lesions via systemic administration. Therefore, we expected that a combination of systemic intravenous 5-FU and subcutaneous interferon would be effective against extrahepatic metastasis of HCC. We report the efficacy and safety of this treatment for advanced HCC, which we performed before sorafenib was introduced to Japan.

Patients, materials, and methods

Patients

The present study was conducted as a retrospective cohort study. We analyzed 223 consecutive patients who received combination therapy comprised of continuous intravenous infusion of 5-FU and subcutaneous pegylated interferon-alfa for advanced HCC at Kyoundo Hospital from January 1, 2004, to May 31, 2009, when sorafenib was licensed in Japan. The study population consisted of patients with advanced HCC who were not amenable to curative surgery, percutaneous ablation, or TACE, and for whom intraarterial chemotherapy was not indicated because of the presence of extrahepatic metastasis or stenosis of the common hepatic artery. Patients with a previous history of treatment, including systemic chemotherapy, were included. The eligibility criteria also included an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less [14], Child–Pugh liver function class A or B, adequate hematologic function (white blood cell count, $\geq$3000/μL; hemoglobin, $\geq$8.5 g/dL; platelet count >30000/μL; and prothrombin time international normalized ratio, $\leq$2.3), adequate hepatic function (albumin, $\geq$2.8 g/dL; total bilirubin, $\leq$3 mg/dL; and alanine aminotransferase [ALT] and aspartate aminotransferase [AST], $\leq$5 times the upper limit of the normal range), and adequate renal function (serum creatinine, $\leq$1.5 times the upper limit of the normal range). Patients were required to have at least one measurable target lesion according to the response to treatment in solid tumors (RECIST) guidelines ver. 1.0 [15]. All patients provided written informed consent before treatment. The treatment protocol was approved by the ethics committee of the institution.

Diagnosis of HCC

Intrahepatic lesions, vascular invasion, and extrahepatic metastasis of HCC were diagnosed with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), considering hyperattenuation in the arterial phase with washout in the late phase as the definitive sign of HCC [16, 17]. Ultrasound-guided tumor biopsy was also performed when radiological findings were atypical. Bone scintigraphy was added when bone metastasis was suspected because of symptoms but was not confirmed on CT or MRI.

Treatment

One cycle of this treatment consisted of 4 weeks (days 1–28). Peginterferon alfa-2a (90 μg) was administered subcutaneously on days 1, 8, 15, and 22, and 5-FU (500 mg/day) was systemically administered via continuous intravenous infusion, using a portable infusion pump, on days 1–5 and 8–12. Treatment was continued until disease progression, unacceptable toxicity, or patient refusal occurred. This protocol had no treatment interval, and the next cycle started on the day after day 28 of the previous cycle. The first one or two treatment cycles were provided during hospitalization and 5-FU was administered through a peripheral intravenous catheter. Patients who could be expected to survive for a relatively long period underwent implantation of an indwelling central intravenous catheter and were treated on an outpatient basis thereafter. Indwelling central intravenous catheters were inserted by ultrasound-guided subclavian vein puncture and the catheter tip was placed into the superior vena cava using a guidewire under fluoroscopic guidance. When adverse events caused by 5-FU became clinically important, the dose of 5-FU was reduced by 50 %. As prevention and treatment for stomatitis, sodium gualenate hydrate and sodium bicarbonate were used as a gargle. Dexamethasone ointment was also used for stomatitis. Antidiarrheal agents such as loperamide hydrochloride were used for diarrhea.

Response and toxicity assessment

To assess the response to treatment, contrast-enhanced CT or MRI was performed at the end of the first and second cycles and every two cycles thereafter. In principle, treatment responses were evaluated according to the RECIST guidelines ver.1.0 [15]. The best overall response was adopted in the analysis. Complete response (CR) was defined as the disappearance of both intrahepatic lesions and extrahepatic metastasis. CR was confirmed by repeat assessments performed 4 weeks or more after the criteria for response were first met. Patients who had not completed the first cycle were regarded as having progressive disease (PD) if radiological disease progression was confirmed at the time, and as "not assessable (NA)" if imaging was not performed at the time. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria version 3.0. During hospitalization, patients were interviewed about their symptoms and underwent a daily physical examination. Blood tests were performed every week. When treated as outpatients, they were required to visit the outpatient department at least once every 2 weeks.

Statistical analysis

We included in the analysis those patients who could not complete the first cycle. The categorical variables were compared by χ^2tests, whereas continuous variables were compared with an unpaired Student's *t*-test (parametric) or Mann–Whitney *U*-test (nonparametric). A P value of <0.05 was considered statistically significant. Overall survival and time to progression (TTP) were calculated using the Kaplan–Meier method. Patients were censored at the time of the last visit, when lost to follow up, or at the end of the study period. Follow up ended on June 30, 2010. The clinical data at baseline were assessed as predictors of survival using univariate and multivariate Cox proportional hazard regression analysis. The following variables were included in this analysis: age, sex, ECOG performance status, hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCVAb), Child–Pugh classification, platelet count, Barcelona-Clinic Liver Cancer (BCLC) staging classification [18], presence of viable intrahepatic lesions, macroscopic vascular invasion, extrahepatic metastasis, and a history of previous treatment. Stepwise variable selection with the Akaike information criterion (AIC) was used to find the best model in multivariate analysis. All analytical procedures were performed with S-plus Ver. 7.0 (Insightful, Seattle, WA, USA).

Results

Patients

A total of 223 patients, 176 male and 47 female, with an average age of 64.3 years, received this treatment. Patient characteristics are listed in Table 1. Child–Pugh classification was A in 166 patients (74.4 %) and B in 57 (25.6 %). Macroscopic vascular invasion was present in 103 patients (46.2 %). Extrahepatic metastasis was present in 166 (74.4 %) patients. Those patients without extrahepatic metastasis who were treated with this regimen had contraindications to intraarterial chemotherapy because of stenosis of the common hepatic artery, mainly due to repeated TACE. Two hundred and ten (94.2 %) patients had previously received some other treatment. The median number of cycles of the combination treatment was two (range 1–13). Four patients did not complete the first cycle because of deterioration of performance status, unacceptable toxicity, or patient refusal.

Response to treatment

Six patients had CR (2.7 %), 15 (6.7 %) had a partial response (PR), 52 (23.3 %) had stable disease (SD), and

Table 1 Demographic and baseline characteristics of patients ($n = 223$)

Variable, *n* (%)	
Age (years)[a]	64.3 ± 10.6
Male sex	176 (78.9)
ECOG performance status	
0	159 (71.3)
1	57 (25.6)
2	7 (3.1)
Viral infection	
HBsAg, positive	58 (26.0)
Anti HCVAb, positive	125 (56.1)
Both positive	4 (1.8)
Both negative	36 (16.1)
Child–Pugh classification	
Class A	166 (74.4)
Class B	57 (25.6)
Platelet count ($10^3/\mu l$)[b]	127 (34–840)
BCLC stage	
B	22 (9.9)
C	201 (90.1)
Viable intrahepatic lesion, present	213 (95.5)
Macroscopic vascular invasion, present[c]	103 (46.2)
Portal vein	73
Hepatic vein or vena cava	51
Maximum tumor size (cm)[b]	5.2 (1.0–20.0)
AFP >100 ng/mL	143 (64.1)
AFP-L3 >15.0 %[d]	147 (66.2)
DCP >100 mAU/mL[e]	152 (68.8)
Extrahepatic metastasis, present[c]	166 (74.4)
Lung	91
Lymph node	52
Bone	33
Adrenal gland	11
Dissemination	20
Others	5
Previous therapy[c]	
None	13 (5.8)
Surgical resection	78 (35.0)
Percutaneous ablation	95 (42.6)
Transarterial chemoembolization	150 (67.3)
Radiotherapy	32 (14.3)
Transarterial chemotherapy	65 (29.1)
Systemic chemotherapy	46 (20.6)
Cycles of systemic 5-FU + IFN therapy[b]	2 (1–13)

ECOG Eastern Cooperative Oncology Group, *HBsAg* hepatitis B surface antigen, *HCVAb* hepatitis C virus antibody , *BCLC* Barcelona-Clinic Liver Cancer, *AFP* alpha fetoprotein, *DCP* des-gamma-carboxy prothrombin, *5-FU* 5-fluorouracil, *IFN* interferon

[a] Mean ± SD

[b] Median (range)

[c] Including overlap

[d] Missing in one case

[e] Missing in two cases

Table 2 Summary of efficacy measures ($n = 223$)

Level of response, *n* (%)	
Complete response	6 (2.7)
Partial response	15 (6.7)
Stable disease	52 (23.3)
Progressive disease	132 (59.2)
Not assessable	18 (8.1)
Response rate (%)	9.4
Disease-control rate (%)	32.7
Time to progression (months)	
Median	2.0
95 % confidence interval (CI)	2.0–3.1
Overall survival (months)	
Median	6.5
95 % CI	5.13–9.13
1-year survival rate (%)	31.2
2-year survival rate (%)	12.7
3-year survival rate (%)	7.1

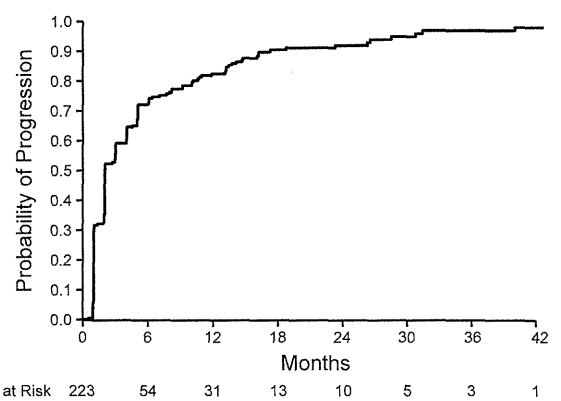

Fig. 1 Kaplan–Meier analysis of time to progression

132 (59.2 %) had PD. Treatment response was not assessable in the remaining 18 (8.1 %) patients due to symptomatic PD or their being lost to follow up before evaluation. The response rate was 9.4 % and the disease-control rate was 32.7 % (Table 2). The median TTP was 2.0 months (Fig. 1). There was no statistically significant difference in TTP between Child–Pugh class A and class B patients (median 3.0 vs. 2.0 months, $P = 0.19$).

Survival

The overall MST was 6.5 months (Fig. 2a). The survival rates at 1, 2, and 3 years were 31.2, 12.7, and 7.1 %, respectively (Table 2). MST was significantly longer in Child–Pugh class A as compared with class B patients (9.2 vs. 2.8 months, $P < 0.001$) (Fig. 2b). The MSTs of patients

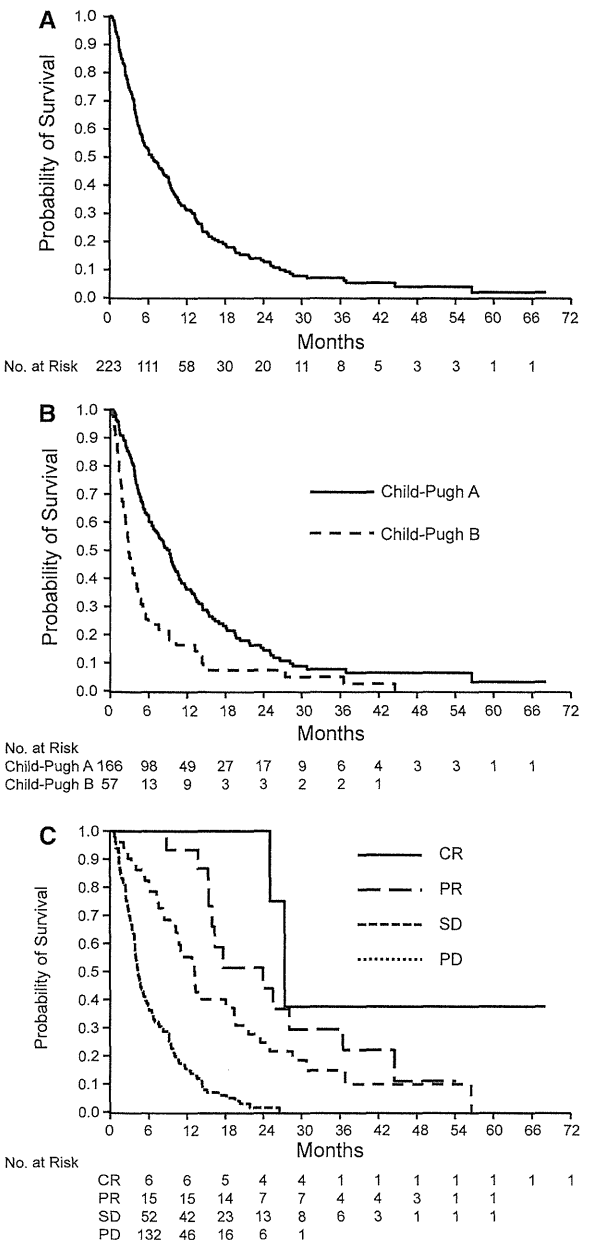

Fig. 2 Kaplan–Meier analysis of overall survival (**a**); stratified based on Child–Pugh classification (**b**) and response to treatment (**c**). *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

with CR, PR, SD, and PD were 27.4, 24.0, 13.2, and 4.4 months, respectively (Fig. 2c, $P < 0.001$). Based on a univariate analysis, the following factors were significantly associated with shorter survival time: ECOG performance status >0, Child–Pugh class B, and presence of macroscopic vascular invasion (Table 3). A multivariate analysis showed that all of these factors were also independent prognostic factors (Table 4).

Table 3 Predictors of overall survival: univariate analysis ($n = 223$)

Variable	Hazard ratio (95 % CI)	*P*
Age (years) >65	1.01 (0.76–1.35)	0.94
Male sex	1.03 (0.73–1.45)	0.87
ECOG performance status >0	1.73 (1.25–2.39)	<0.001
HBsAg, positive	0.87 (0.63–1.20)	0.38
Anti HCVAb, positive	1.06 (0.80–1.42)	0.68
Child–Pugh class B versus A	2.12 (1.54–2.92)	<0.001
Platelet count >127,000/μL	1.25 (0.94–1.67)	0.13
BCLC stage C	1.46 (0.89–2.41)	0.14
Viable intrahepatic lesion, present	1.85 (0.76–4.49)	0.17
Macroscopic vascular invasion, present	1.37 (1.03–1.83)	0.03
Extrahepatic metastasis, present	1.35 (0.97–1.87)	0.08
Previous chemotherapy, present	1.16 (0.86–1.55)	0.34

Table 4 Predictors of overall survival: multivariate analysis ($n = 223$)

Variable	Hazard ratio (95 % CI)	*P*
ECOG performance status >0	1.46 (1.04–2.05)	0.03
Child–Pugh class B	1.83 (1.31–2.55)	<0.001
Macroscopic vascular invasion, present	1.39 (1.03–1.88)	0.03
Extrahepatic metastasis, present	1.35 (0.96–1.92)	0.09

Table 5 Safety profile

	Grade 1–2, *n* (%)	Grade 3–4, *n* (%)
Leukopenia	25 (11.2)	31 (13.9)
Anemia	0 (0)	1 (0.4)
Thrombocytopenia	20 (9.0)	13 (5.8)
Stomatitis	11 (4.9)	3 (1.3)
Anorexia	2 (0.9)	1 (0.4)
Diarrhea	2 (0.9)	0 (0)
Skin rash	2 (0.9)	1 (0.4)

Safety

Adverse events graded as 3 or 4 were observed in 28 (12.6 %) patients. The incidence of major adverse events is presented in Table 5. The major grade 3–4 adverse events were leucopenia (13.9 %) and thrombocytopenia (5.8 %). A common non-hematological toxicity was stomatitis (6.2 %, any grade). Fever, which was mostly low-grade, occurred in about 90 % of the patients, usually after the first administration of peginterferon, and was gradually

attenuated during subsequent administrations. Elevations in bilirubin, AST, and ALT levels from baseline occurred in 7.6 % of patients, although most cases of such elevation occurred due to progression of the intrahepatic lesion, and not due to the treatment itself. There were no catheter-related problems, including infection or occlusion. No treatment-related deaths occurred.

Discussion

Wadler et al. first reported combination therapy with intravenous 5-FU and subcutaneous interferon for a malignant neoplasm. They treated 30 patients with advanced colorectal cancer using this protocol [19]. However, the following phase III trial failed to establish the efficacy of the treatment [20]. Subsequently, Patt et al. [21] reported systemic combination therapy for HCC patients, reporting that the treatment induced a decrease of more than 50 % in the size of each measurable lesion in 18 % of the treated patients. Since then, several studies have demonstrated the efficacy of combination therapy of intraarterial 5-FU and subcutaneous interferon for patients with advanced HCC with portal venous invasion, reporting response rates of 44–63 % [13, 22, 23]. Furthermore, other studies have revealed the mechanism underlying the antitumor effects of this combination therapy [24–31]. However, only a case series of a small number of patients has reported on this systemic combination therapy in HCC patients [32]. The present study is the first report of this therapy in a large number of patients ($n = 223$).

In the past, systemic chemotherapy for advanced HCC using various cytotoxic agents, such as doxorubicin, 5-FU, cisplatin, and etoposide, has been investigated. However, few agents showed response rates above 20 %, and the number of patients included in those studies was small. Furthermore, no regimens demonstrated convincing survival benefits in phase III trials [33, 34]. Single-agent 5-FU [35–37] and related drugs such as eniluracil/5-FU [38, 39] and uracil/tegafur [40, 41] showed low response rates. An impressive result came from phase II and phase III studies of PIAF (combination of cisplatin, interferon alfa, doxorubicin, and 5-FU). The response rates of these studies were 26 and 20.9 %, respectively [42, 43], which were actually better than that of the present study, although the number of patients was small and the characteristics of the patients differed from those in our study.

At present, sorafenib is the standard treatment for advanced HCC with extrahepatic metastasis or vascular invasion. Before the availability of sorafenib, we treated such patients with a combination of systemic intravenous 5-FU and subcutaneous interferon. The MSTs in the SHARP study and the Asian-Pacific study of sorafenib (both randomized controlled trials) were 10.7 and 6.5 months, respectively, whereas the MST in the present study was 6.5 months. However, both these trials of sorafenib consisted only of Child–Pugh class A patients, and the MSTs in these two studies were comparable to the MST of the Child–Pugh class A patients in our study (9.2 months). The disease-control rate in our study was 32.7 %, which was comparable to that of sorafenib (43 % in the SHARP study; 35.3 % in the Asian-Pacific study). Moreover, there were no complete responders in either of these randomized controlled trials, and the response rates were also low (2 % in the SHARP study; 3.3 % in the Asian-Pacific study). On the other hand, in the present study, six (2.7 %) patients achieved a complete response, and the response rate of 9.4 % was higher than that in these two studies. Thus, the combination of intravenous 5-FU and subcutaneous interferon is worth consideration as a choice of treatment for advanced HCC.

The response rate of 52.6 % that we observed in our previous study where we treated HCC patients with portal venous invasion with a combination of intraarterial 5-FU and subcutaneous interferon [13] was much better than that observed here. This may be partly because the local concentration of 5-FU in the liver is higher after intraarterial infusion than after systemic administration. However, systemic rather than intraarterial administration is appropriate for patients with extrahepatic metastases because intraarterially administered 5-FU is substantially removed by the liver in the first pass [44, 45].

In our previous study [13], we combined interferon alfa, not pegylated, with the intraarterial administration of 5-FU. Here, we combined pegylated interferon alfa with the systemic administration of 5-FU mainly because of the convenience in an outpatient setting. Whereas non-pegylated interferon needs to be administered three times a week, pegylated interferon requires only once-a-week administration.

Cirrhotic patients have lower clearance rates of 5-FU than non-cirrhotic patients [46]. Thus, such patients with poor liver function may have more severe adverse events. However, there were few serious adverse events in the present study, although as many as 25.6 % of the patients were Child–Pugh class B. Although grade 3 or 4 leucopenia and thrombocytopenia were observed, the baseline white blood cell and platelet counts in the patients with these events were almost always low because of background cirrhosis, and they were able to continue to receive treatment. In addition, we did not observe any serious adverse events in relation to infection.

According to our data, ECOG performance status, Child–Pugh classification, and the presence of vascular invasion were independent prognostic factors. This is consistent with our previous study findings on the prognosis of patients with

extrahepatic metastasis of HCC [47]. In the present study, we also analyzed prognosis as stratified by treatment response, and better treatment response resulted in better prognosis. This point is to be confirmed in future prospective studies.

The combination therapy described in the present study was performed before the advent of sorafenib. It will now be important to evaluate the efficacy of this combination therapy in cases of sorafenib failure. It is also necessary to assess the efficacy and safety of this treatment, as well as that of sorafenib, for patients with poor liver function [48, 49].

In conclusion, the combination of continuous intravenous infusion of 5-FU and subcutaneous peginterferon alfa-2a was well tolerated and showed promising efficacy in a subset of patients with advanced HCC. Further studies; for example validating the efficacy of this treatment in patients with sorafenib failure and conducting a randomized controlled trial comparing this treatment with sorafenib, are needed to definitively establish the usefulness of this treatment.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Mortality and morbidity of hepatectomy, radiofrequency ablation, and embolization for hepatocellular carcinoma: a national survey of 54,145 patients

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Abstract
Background Reported mortalities and morbidities of therapeutic procedures for liver tumors vary between studies, because of different designs and small sample sizes. We investigated the mortalities and complication rates for hepatectomy, radiofrequency ablation (RFA), and trans-catheter arterial embolization (TAE) for hepatocellular carcinoma (HCC) in a large sample, using a nationwide Japanese database (the Diagnosis Procedure Combination database).
Methods Data from the Diagnosis Procedure Combination database were analyzed for July 1 to December 31, 2007 and the same period in 2008. We identified 54,145 patients with HCC who underwent hepatectomy ($n = 5{,}270$), RFA ($n = 11{,}688$), or TAE ($n = 37{,}187$). In-hospital mortality and morbidity were analyzed for each procedure. The relationships between mortality and factors including patient characteristics and procedural backgrounds were assessed.
Results In-hospital mortalities associated with hepatectomy, RFA, and TAE were 2.6 % [95 % confidence interval (CI) 2.2–3.1], 0.3 % (0.2–0.4), and 1.0 % (0.9–1.1), and post-procedural complication rates were 14.5 % (13.5–15.5), 4.5 % (4.2–4.9), and 4.5 % (4.3–4.7), respectively. Increased mortality following hepatectomy was significantly associated with older age, extended lobectomy (vs. partial hepatectomy; odds ratio [OR] 3.80, $p < 0.001$), lower hospital volume (OR 2.74, $p < 0.001$), and renal comorbidity (OR 3.01, $p = 0.02$). Older age and cardiac comorbidity (OR 5.14, $p = 0.001$) were significantly associated with RFA-related mortality, and lower hospital volume was significantly associated with TAE-related mortality (OR 1.60, $p < 0.001$).
Conclusions Mortalities and morbidities associated with therapeutic procedures for liver tumors were acceptably low in Japan, but were affected by patient and institutional characteristics.

Keywords Liver tumor · Hospital volume · Nationwide database

Abbreviations

RFA	Radiofrequency ablation
TAE	Trans-catheter arterial embolization
DPC	Diagnosis Procedure Combination
ICD-10	International Classification of Diseases and Related Health Problems, Tenth Revision

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Introduction

The liver is one of the commonest sites of primary and metastatic tumors [1, 2]. Hepatectomy has been considered as a treatment of choice in patients with liver tumors, and can offer survival for 5 years in 50–70 % of patients with early hepatocellular carcinoma (HCC) [3–7], and in

50–60 % with liver metastases of colorectal carcinoma [8–10]. However, image-guided minimally invasive techniques have been widely used for the treatment of HCC in the past decade, and radiofrequency ablation (RFA) has yielded promising clinical results, with survival rates comparable with those of hepatectomy. During the past decade, there has been growing interest in the use of RFA in patients with liver tumors considered to be unresectable because of impaired hepatic function [11–14]. Despite the fact that surveillance programs have reduced the proportion of HCC detected at an advanced stage in certain populations [15, 16], the majority of patients with HCC are still not eligible for curative treatments, such as hepatectomy and RFA, because of advanced features, and trans-catheter arterial embolization (TAE) has been widely used as a palliative treatment in such patients. A recent meta-analysis showed improved overall survival in patients with well-preserved liver function who were treated with TAE [17].

Before the 1980s, hepatectomy-related mortality was reported to be as high as 10 %. In recent years, however, this has decreased to less than 5 % at some surgical centers, and several recent studies have reported large series of successful hepatectomies with no mortality [18, 19]. On the other hand, although the safety of image-guided therapies has been generally accepted, various complications have been reported. The reported complication rates vary substantially, primarily because of the small sample sizes used in most studies. Published studies may also be liable to publication bias, i.e., authors may be less enthusiastic about reporting studies with higher complication rates.

The Diagnosis Procedure Combination (DPC) database is a discharge abstract and administrative claims database of inpatient admissions to secondary and tertiary care hospitals in Japan [20–22], representing approximately 40 % of inpatient admissions to such hospitals. This database represents a large number of samples, and can thus be used to investigate the mortalities and morbidities associated with different treatment modalities, on an objective basis. The aim of this study was to investigate the mortalities and complication rates associated with hepatectomy, RFA, and TAE for HCC in a large patient sample, using the DPC database.

Subjects, materials, and methods

Data source

The DPC database includes the following information: location of hospital; patient demographics; diagnosis, comorbidities at admission and complications after admission recorded with text in Japanese and the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes; therapeutic procedures coded by the Japanese original K-code; length of stay; and discharge status, including in-hospital death. The survey of the DPC hospitals is conducted by the DPC Research Group between July 1 and December 31 each year, and is funded by the Ministry of Health, Labour and Welfare, Japan. All 82 university teaching hospitals are obliged to adopt the DPC system, but adoption by community hospitals is voluntary. The survey started in 2003 with 82 teaching hospitals; 926 hospitals participated in 2007, and 855 in 2008. Data for 2.99 and 2.86 million patients were included in 2007 and 2008, respectively. The number in 2008 represented approximately 40 % of all the inpatient admissions to secondary and tertiary care hospitals in Japan.

The requirement for informed consent was waived in this study, because of the anonymous nature of the data. Study approval was obtained from the institutional review board of the University of Occupational and Environmental Health, Fukuoka.

Samples

The data used in this survey were derived from the DPC database for July 1 to December 31, 2007 and the same period in 2008. Patients with a diagnosis of HCC (ICD-10 code C220) were identified. We then selected patients who underwent hepatectomy (DPC procedure code K695), RFA (K697-3), or TAE (K615). Hepatectomy (K695) patients were divided into five sub-categories (K695-1, partial hepatectomy; K695-2, hepatic segmentectomy; K695-3, hepatic lobectomy; K695-4, extended hepatic lobectomy; K695-5, extended hepatic lobectomy with revascularization procedure). Finally, patients who underwent two or more types of the above procedures, and those who underwent TAE for controlling tumor bleeding during emergency hospitalization were excluded.

Endpoints

The primary endpoint was the in-hospital mortality after each procedure. The secondary endpoint was the occurrence of post-procedural complications during hospitalization, including hemorrhage, pneumothorax, liver abscess, gastrointestinal perforation, peritonitis, and hepatic infarction.

Statistical analysis

Patient characteristics were analyzed in terms of sex, age, and comorbidities. The characteristics of patients who underwent hepatectomy were analyzed in terms of each operative method. Hospital volume for each therapeutic procedure during the survey period was determined using the unique identifier for each hospital, and categorized into

three (low-, intermediate-, and high-volume) groups, such that the numbers of patients in each group were almost equal. We assessed the relationships between mortality and various factors, including patient characteristics and hospital volume. The univariate association between each factor and in-hospital mortality was evaluated using the χ^2 test or analysis of variance, as appropriate. Stepwise logistic regression analysis was used to model the concurrent effects of procedures and other factors on in-hospital mortality. Statistical analyses were performed using PASW version 18.0 (SPSS, Chicago, IL, USA). The threshold of reported p values for significance was accepted as <0.05.

Results

Patient characteristics

Of 118,524 patients with HCC, 54,145 eligible patients at 808 hospitals were finally enrolled. Among these, 5,270, 11,688, and 37,187 patients underwent hepatectomy, RFA, and TAE, respectively. Approximately 70 % were male and the mean ages ranged from 67.7 to 71.2 years, according to the mode of treatment. Patients who underwent hepatectomy were younger, and had a higher probability of having diabetes or cardiac disease (Table 1).

Procedural outcomes

The numbers of in-hospital deaths among patients who underwent hepatectomy, RFA, and TAE were 137 (2.60 %), 29 (0.25 %), and 383 (1.03 %), respectively.

Table 2 shows the in-hospital mortality associated with each procedure, and the univariate association between patient characteristics and procedural backgrounds. The in-hospital mortality associated with hepatectomy was higher in older patients ($p = 0.002$), those treated with more invasive procedures ($p < 0.001$), those in hospitals with lower procedure volumes ($p < 0.001$), and patients with chronic renal disease ($p = 0.02$) (Table 2). The results of multivariate logistic regression analysis of in-hospital mortality for hepatectomy, RFA, and TAE are shown in Fig. 1. Multivariate logistic regression analysis revealed that lobectomy and partial lobectomy were significantly associated with higher mortalities. Segmentectomy was associated with higher in-hospital mortality than partial hepatectomy, but the difference was not statistically significant [adjusted odds ratio (OR) 1.21, $p = 0.38$] (Fig. 1a).

The in-hospital mortality associated with RFA was significantly higher in older patients ($p = 0.001$) and those with cardiac diseases ($p < 0.001$) (Table 2). Both of these features were identified as significant factors associated with increased mortality (Fig. 1b).

The in-hospital mortality associated with TAE was 1.03 % (Table 2). Univariate comparison showed that in-hospital mortality was significantly higher in hospitals with lower procedure volumes ($p < 0.001$) and in younger patients ($p = 0.04$). Multivariate logistic regression analysis identified higher procedure volume as a significant factor associated with lower mortality (OR 0.62, $p < 0.001$) (Fig. 1c).

The mean intervals between the date of procedure and death in fatal cases were 43.1 days (range 0–167 days) for hepatectomy, 42.1 days (range 0–178 days) for RFA, and 40.5 days (range 0–204 days) for TAE. The mortalities within the 30 days following the procedure were 1.08 % for hepatectomy, 0.14 % for RFA, and 0.45 % for TAE.

Table 1 HCC patient characteristics and details of procedures

	Total (n = 54,145)	Hepatectomy (n = 5,270)	RFA (n = 11,688)	TAE (n = 37,187)	p value
Sex, n (%)					<0.001
Female	15,266 (28.2)	1,250 (29.3)	3,831 (32.8)	10,185 (27.4)	
Male	38,879 (71.8)	4,020 (70.7)	7,857 (67.2)	27,002 (72.6)	
Age (years), mean ± SD	70.7 ± 8.8	67.7 ± 9.5	70.7 ± 8.6	71.2 ± 8.6	
Age (years), n (%)					<0.001
≤59	5,498 (10.2)	883 (16.8)	1,197 (10.2)	3,418 (9.2)	
60–69	14,662 (27.1)	1,703 (32.3)	3,162 (27.1)	9,797 (26.4)	
70–79	25,247 (46.6)	2,261 (42.9)	5,471 (46.8)	17,515 (47.1)	
≥80	8,738 (16.1)	423 (8.0)	1,858 (15.9)	6,457 (17.3)	
Comorbidities, n (%)					
Diabetes mellitus	9,878 (18.2)	1,162 (22.0)	1,945 (16.6)	6,771 (18.2)	<0.001
Cardiac diseases	2,138 (3.9)	317 (6.0)	365 (3.1)	1,456 (3.9)	<0.001
Chronic renal diseases	771 (1.4)	72 (1.4)	161 (1.4)	538 (1.5)	0.8

RFA radiofrequency ablation, *TAE* trans-catheter arterial embolization, *HCC* hepatocellular carcinoma

Table 2 In-hospital mortality of hepatectomy, RFA, and TAE

	Hepatectomy			RFA			TAE		
	n/N	% (95 % CI)	*P*	*n/N*	% (95 % CI)	*P*	*n/N*	% (95 % CI)	*P*
Overall	137/5,270	2.60 (2.19–3.10)		29/11,688	0.25 (0.17–0.36)		383/37,187	1.03 (0.93–1.14)	
Sex			0.26			0.08			0.17
Female	38/1,250	3.04 (2.16–4.15)		14/3,831	0.37 (0.20–0.61)		93/10,185	0.91 (0.73–1.12)	
Male	99/4,020	2.46 (2.01–3.00)		15/7,857	0.19 (0.11–0.31)		290/27,002	1.07 (0.95–1.20)	
Age (years)			0.002			0.001			0.04
≤59	10/883	1.13 (0.54–2.07)		0/1,197	0.0 (0.00–0.30)		45/3,418	1.32 (0.96–1.76)	
60–69	40/1,703	2.35 (1.68–3.18)		2/3,162	0.06 (0.01–0.23)		112/9,797	1.14 (0.94–1.37)	
70–79	76/2,261	3.36 (2.66–4.19)		19/5,471	0.35 (0.21–0.54)		163/17,515	0.93 (0.79–1.08)	
≥80	11/423	2.60 (1.31–4.61)		8/1,858	0.43 (0.19–0.85)		63/6,457	0.98 (0.75–1.25)	
Procedure type			<0.001						
Partial hepatectomy	42/2,163	1.94 (1.40–2.62)		–			–		
Segmentectomy	45/1,921	2.34 (1.71–3.12)		–			–		
Lobectomy	31/869	3.57 (2.44–5.03)		–			–		
Extended lobectomy	19/317	6.00 (3.65–9.20)		–			–		
Hospital volume[a]			<0.001			0.26			<0.001
High	27/1,744	1.55 (1.02–2.24)		8/3,875	0.21 (0.09–0.41)		97/12,101	0.80 (0.65–0.98)	
Intermediate	38/1,742	2.18 (1.55–3.00)		8/3,896	0.21 (0.09–0.40)		126/12,497	1.01 (0.84–1.20)	
Low	72/1,784	4.04 (3.17–5.06)		13/3,917	0.33 (0.18–0.57)		160/12,589	1.27 (1.08–1.48)	
Comorbidities									
Diabetes mellitus			0.97			0.68			0.76
No	107/4,108	2.60 (2.14–3.14)		25/9,743	0.26 (0.17–0.38)		311/30,416	1.02 (0.91–1.14)	
Yes	30/1,162	2.58 (1.75–3.67)		4/1,945	0.21 (0.06–0.53)		72/6,771	1.06 (0.83–1.34)	
Cardiac diseases			0.93			<0.001			0.79
No	129/4,953	2.60 (2.18–3.09)		24/11,323	0.21 (0.14–0.32)		369/35,731	1.03 (0.93–1.14)	
Yes	8/317	2.52 (1.10–4.91)		5/365	1.37 (0.45–3.17)		14/1,456	0.96 (0.53–1.61)	
Chronic renal diseases			0.02			0.52			0.29
No	132/5,198	2.54 (2.13–3.00)		29/11,527	0.25 (0.17–0.36)		375/36,649	1.02 (0.92–1.13)	
Yes	5/72	6.94 (2.29–15.5)		0/161	0.0 (0.00–2.27)		8/538	1.49 (0.00–1.70)	

CI confidence interval, *RFA* radiofrequency ablation, *TAE* trans-catheter arterial embolization

[a] Hospital volume was defined according to the number of cases per year. High hospital volume represents hospitals with more than 57 cases per year for hepatectomy, 105 cases per year for RFA, and 183 cases per year for TAE. Low hospital volume represents hospitals with fewer than 21 cases per year for hepatectomy, 38 cases per year for RFA, and 76 cases per year for TAE

In-hospital complications occurred in 763 (14.48 %), 531 (4.54 %) and 1,668 (4.49 %) for hepatectomy, RFA, and TAE patients, respectively. The details of the complications are listed in Table 3. Postoperative hemorrhage was the commonest complication of hepatectomy and was seen in 361 (6.85 %) admissions. The most significant complication of both RFA and TAE was related to bile duct stenosis, which occurred in 152 (1.30 %) and 657 (1.77 %) cases, respectively.

Discussion

Hepatectomy, RFA, and TAE are widely applied therapeutic procedures which account for more than 90 % of all procedures performed in patients with primary HCC in Japan [23]. When deciding on a treatment strategy, both therapeutic efficacy and the risks associated with each treatment modality should be considered. Whereas the effectiveness of a procedure can be evaluated based on established criteria such as survival, local recurrence, and tumor necrosis, the complication rate as an index of safety varies greatly among reports, mainly because of differences in the definitions used. In-hospital mortality is a more reliable indicator of safety, but a large number of samples are required to obtain an accurate estimate of mortality, because death is a relatively rare event. In the present study, we investigated the mortalities and morbidities associated with various therapeutic procedures for HCC, using information from the nationally representative Japanese DPC database. It is particularly worth noting that the data for in-hospital mortality were expected to be 100 %

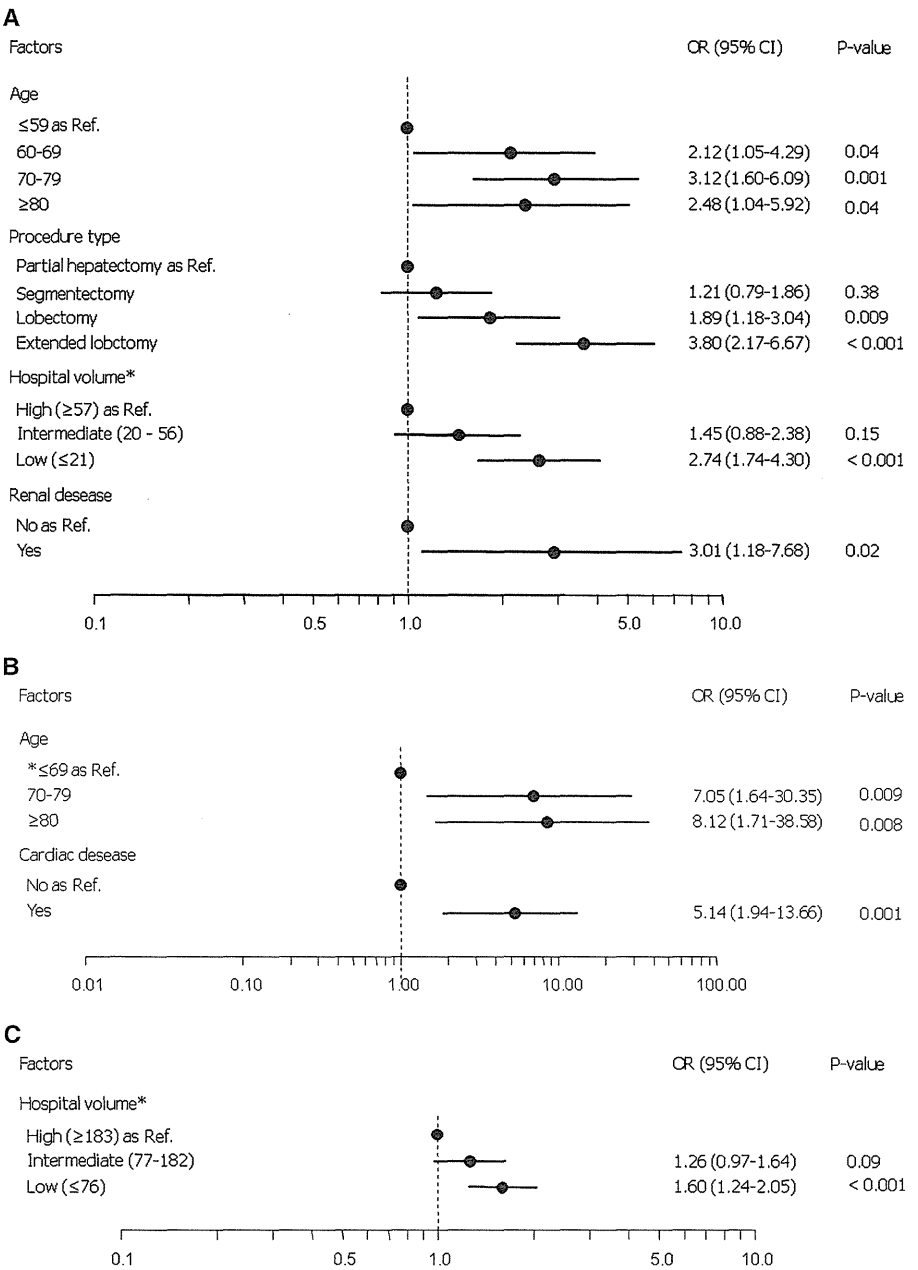

Fig. 1 **a** Multivariate logistic regression analyses for in-hospital mortality of hepatectomy. **b** Multivariate logistic regression analyses for in-hospital mortality of radiofrequency ablation (RFA). *Asterisk* indicates that patients aged 60–69 years and those aged ≤59 years are combined because the mortality of the patients aged ≤59 years was 0. **c** Multivariate logistic regression analyses for in-hospital mortality of trans-catheter embolization (TAE). *OR* odds ratio, *CI* confidence interval, *Ref.* reference value

reliable and free from recall bias because outcome was a required item on discharge.

In this study, the mortality following hepatectomy was 2.60 %, out of a total of 54,145 patients with HCC. Previously reported in-hospital mortalities following hepatectomy for primary and metastatic liver tumors at major high-volume centers were 3.8–8 and 0–7.0 % [4, 5, 24–30], respectively. For example, one report from the United States, using data from a nationwide inpatient sample over a 9-year period, showed a mortality of 6 % [31]. However, the background of that study may be different from that of the present study; for example, lower invasive procedures such as partial hepatectomy and segmentectomy accounted for the major part of the present study. This kind of factor may have influenced the lower mortality rate in the present study.

The mortality associated with RFA in the present study was 0.25 %, which was similar to that noted in previous reports (0.2–0.6 %) [32–39]. Multivariate analysis identified older age and cardiac comorbidity as factors

Table 3 Complications related to each procedure

	Hepatectomy (n = 5270)	RFA (n = 11688)	TAE (n = 37187)
Overall, n (%)[a]	763 (14.48)	531 (4.54)	1,668 (4.49)
Hemorrhage, n (%)	361 (6.85)	56 (0.48)	102 (0.27)
Bile duct stenosis, n (%)	59 (1.12)	152 (1.30)	657 (1.77)
Liver abscess, n (%)	19 (0.36)	36 (0.31)	201 (0.54)
Pneumothorax, n (%)	1 (0.02)	16 (0.14)	–
Perforation of gastrointestinal tract, n (%)	2 (0.04)	3 (0.03)	–
Peritonitis, n (%)	98 (1.86)	98 (0.84)	–
Heat burn, n (%)	–	7 (0.06)	–
Hepatic infarction, n (%)	–	7 (0.06)	3 (0.00)
Liver failure, n (%)	122 (2.31)	131 (1.12)	617 (1.66)
Cardiac complication, n (%)	35 (0.66)	15 (0.13)	37 (0.10)
Ruptured suture, n (%)	40 (0.76)	2 (0.02)	2 (0.00)
Renal failure, n (%)	26 (0.49)	2 (0.02)	35 (0.09)
Pulmonary embolism, n (%)	7 (0.13)	4 (0.03)	14 (0.04)
Wound infection, n (%)	12 (0.23)	11 (0.09)	11 (0.03)
Pneumonia, n (%)	57 (1.08)	30 (0.26)	117 (0.31)
Allergy to anesthetic agents, n (%)	2 (0.04)	5 (0.04)	86 (0.23)

[a] More than one complication during hospitalization was counted as one

significantly related to high mortality in patients undergoing RFA.

A recent systematic review of the safety of TAE, based on 37 trials with 2,858 patients, reported a median periprocedural mortality (≤30 days) of 2.4 % (range 0–9.5 %) [40], which was higher than the in-hospital mortality for TAE in the present study (1.03 %). Some previous reports defined mortality as death within the 30 days following the procedure. In the present study, the 30-day mortalities for hepatectomy, RFA, and TAE were 1.08, 0.14, and 0.45 %, respectively.

A number of studies identified hospital procedure volume as an important determinant of postoperative mortality following advanced surgical procedures [31, 41–46]. In the present study, hospital procedure volume was significantly associated with in-hospital mortality for hepatectomy and TAE, but although the RFA-associated in-hospital mortality tended to be lower in high-volume hospitals, the difference was not significant. Despite the large sample size, it is still possible that this study was too underpowered to show any significant association between hospital volume and RFA mortality, because of the exceptionally low mortality rate of RFA. These results suggest that concentrating patients indicated for hepatectomy in high-volume centers should be considered on safety grounds.

In the present study, the mortality rate for hepatectomy was lower in patients over 80 years old. The indication for hepatectomy is determined on the basis of several factors. Although there is no specific age limitation for hepatectomy in Japan, older patients have shorter long-term survival after hepatectomy compared to younger patients, because of their expected life span. Thus, the indication for hepatectomy in older patients, especially those over 80, is stricter in clinical practice. Taking these factors into consideration, it is possible that the patients over 80 years old from the DPC database who did undergo hepatectomy were in generally better than average health. That could explain the lower mortality associated with hepatectomy in patients of 80 years and over in the present study. Similarly, the in-hospital mortality rate for TAE was significantly lower in older patients according to the univariate analysis. This result also may be related to the indications for TAE in Japan. Moreover, the intensity and area of embolization for TAE can be regulated, and embolization is likely to be less intensive in older patients, possibly accounting for the lower mortality in older patients who underwent TAE. Cardiac comorbidity was significantly associated with in-hospital mortality for RFA. According to the database, three out of the five deceased patients with cardiac comorbidities were speculated to have died as a result of cardiac complications (e.g., myocardial infarction, angina pectoris, and heart failure). RFA is thought to be less invasive than hepatectomy, and is sometimes considered as an alternative therapy to hepatectomy in patients with relatively severe cardiac comorbidities. The cardiac comorbidities were thus likely to have been severe in the RFA group, which could account for the higher mortality after RFA in the present study.

The complication rates for hepatectomy, RFA, and TAE in the present study were 14.48, 4.54, and 4.49 %, respectively. Previously reported complication rates have varied among studies, ranging from 28.4 to 47.7 % [47–

52], from 0 to 12.7 % [32–38], and from 4.3 to 10.8 % [53–55] for hepatectomy, RFA, and TAE, respectively. Our multivariate logistic regression analysis demonstrated that the complication rate was significantly higher after more invasive procedures in patients treated in hospitals with lower procedure volumes, in patients with diabetes mellitus, and in patients with cardiac diseases in the case of hepatectomy; and in patients treated in hospitals with higher procedure volumes, patients with diabetes mellitus, and patients with cardiac diseases for RFA and TAE (data not shown). However, complications are usually reported in the DPC database in relation to the reimbursement of medical fees, and the reported complications were therefore less objective than the reported mortality, and could have been underestimated. The complication rate was relatively low for hepatectomy, and the rates for the other procedures were similar to those in previous reports.

The present study had several limitations. First, although the DPC database represents approximately 40 % of all admissions to secondary and tertiary care hospitals in Japan, participating hospitals tend to be medium-to-large-sized institutions. The mortality could therefore have been underestimated by potentially excluding low-procedure-volume hospitals. Second, some important clinical data that may affect the risk of death related to treatments, such as the size and location of the tumor, and severity indexes of liver disease [e.g., the Child–Pugh and model for end-stage liver disease (MELD) scores] were unavailable in this database. Third, data on late-onset complications that appeared after discharge (i.e., biloma, biliary injury, or hepatic abscess) were also unavailable, because the database covers only inpatient data. This may have led to an underestimation of the complication rate in this study. However, according to previous reports, late-onset complications appear to have minimal effects on the mortality rates. Fourth, as noted above, as the DPC system was basically designed for assessing reimbursement, co-existing diseases are usually reported when a specific treatment is needed,; e.g., the proportion of patients with diabetes was higher in the hepatectomy group than that with the other procedures. This may be because patients who underwent hepatectomy were more likely to have been treated with intensive insulin therapy before surgery. Fifth, the immediate cause of death is not a required item in the DPC database. Accordingly, the in-hospital deaths recorded in this database have room for treatment unrelated deaths, the procedure-related mortality could therefore have been overestimated. However in-hospital mortality is more robust in terms of objectivity compared to treatment-related mortality assessed by operators. Finally, some complications, such as tumor seeding, were not covered by the ICD codes and could therefore not be evaluated.

In conclusion, this study confirmed that the therapeutic procedures used to treat liver tumors in Japan were associated with low mortalities and low complication rates. However, procedure-related mortality can be affected by patient and therapeutic backgrounds.

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Conflict of interest The authors declare that they have no conflict of interest.

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