Changes in hepatic functional reserve after percutaneous tumor ablation for hepatocellular carcinoma: long-term follow up for 227 consecutive patients with a single lesion

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Abstract

Background/Aims Percutaneous tumor ablation (PTA), such as ethanol injection, is currently accepted as a potentially curative treatment for hepatocellular carcinoma (HCC). Percutaneous tumor ablation is presumed to be relatively non-invasive, but there are few studies on long-term follow-up of liver function after tumor ablation.

Methods Changes in liver functions were monitored in 227 consecutive patients treated for a solitary HCC nodule by PTA between 1993 and 1997. The liver function evaluated based on Child-Turcotte classification prior to the initial treatment was Child A in 119 (52.4%) patients, B in 81 (35.7%), and C in 27 (11.9%). The follow-up period was 46 ± 21 months.

Results The five-year survival rates of patients in Child A, B, and C group after treatment were respectively 76%, 45%, and 43%. Annual shift rate of Child A to Child B was 7%, and that of Child B to Child C was 14%. Tumor

recurrence significantly affected aggravation of liver function in Child A ($P = 0.002$) but not in Child B patients ($P = 0.55$). Tumor size at initial treatment influenced changes of liver function in Child B group patients ($P = 0.009$).

Conclusions Preservation of liver function may be essential when treating HCC patients with impaired liver function.

Keywords Hepatocellular carcinoma · Hepatic functional reserve · Child Turcotte classification · Percutaneous tumor ablation · Percutaneous ethanol injection therapy · Percutaneous microwave coagulation therapy

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide with an increasing number of patients [1, 2]. Hepatectomy was once regarded as the only curative therapy for HCC [3], but surgery is not infrequently contraindicated by concomitant liver diseases, cirrhosis in particular. Fortunately, non-surgical percutaneous tumor ablation (PTA) therapies, namely, percutaneous ethanol injection therapy, percutaneous microwave coagulation therapy, and, most recently, percutaneous radio-frequency ablation (RFA), have been introduced and now play an important role in the treatment of HCC, especially in patients with impaired liver function [4, 5]. In general, PTA is preferred in the treatment of small HCC nodules [6]. However, complete tumor ablation is attainable also in large HCC nodules [7].

Percutaneous tumor ablation is feasible even in patients with relatively poor liver function. We previously showed

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that PTA, even when applied to large tumors, had little immediate adverse effects on liver function [8]. However, PTA may still predispose patients with poor functional reserve to liver failure by reducing functioning liver mass and worsen survival. Thus, information about long-term effects of PTA on liver function is indispensable, especially when PTA is considered in HCC patients with poor liver function. In this study, we analyzed changes in liver function of 227 patients who underwent curative PTA for HCC, placing special emphasis on liver function prior to PTA.

Patients and methods

Patients

Between January 1993 and December 1997, 516 patients with the first-time HCC development were treated at the Department of Gastroenterology, University of Tokyo Hospital, or its affiliates. Since one of the aims of this study was to assess changes in liver function after PTA with regard to the size of the HCC nodules, 277 patients having more than one nodule were excluded. Of the 239 patients with a solitary HCC, seven received hepatectomy and five received only palliative treatments. The remaining 227 patients who underwent curative PTA as described below constituted the subjects of this study. Informed consent was obtained from each patient before treatment in accordance with the Helsinki declaration.

Detection of HCC

HCC nodules were detected by abdominal ultrasonography, dynamic computed tomography, abdominal angiography, and/or magnetic resonance imaging. Diagnosis of HCC was confirmed by histologic examination of needle biopsy specimens in 180 patients (79%). In the remaining 47 cases, HCC was confirmed by hypervascularity of the tumor, typical of HCC, on angiography and/or contrast-enhanced computed tomography. Informed consent was obtained from each patient before treatment in accordance with the Helsinki declaration.

Treatment of HCC

Percutaneous ethanol injection was performed in 186 patients, 11 of them with transcatheter hepatic arterial embolization (THAE) prior to ethanol injection. Twenty-six patients received percutaneous microwave coagulation, which was introduced in 1996, and two of them received THAE before microwave coagulation. Fifteen patients underwent both ethanol injection and microwave coagula-

tion for the same solitary nodule. Percutaneous ethanol injection was performed using a 21-gauge needle 15 cm in length (Daimon, Saitama, Japan), which was introduced percutaneously into the tumor nodule under ultrasonographic guidance [9]. During each session, 3–15 ml of ethanol (99.5 w/v) was injected into the tumor and the surrounding liver tissue. For percutaneous microwave coagulation, a 14-gauge guide needle with 15 cm in length was introduced percutaneously into the lesion under ultrasonic guidance. The microwave electrode was then placed in the tumor through the guide needle [10]. For both percutaneous ethanol injection and microwave coagulation, treatments were performed once or twice a week until complete necrosis of HCC was confirmed by dynamic computed tomography, where complete necrosis was indicated when the ablated lesion showed a low-density area in both arterial and portal venous phases with a diameter larger than the pretreatment tumor size. Ablation was determined incomplete if there was a contrast-enhanced region or if the area of necrosis was not larger than the pretreatment tumor size [11].

Follow-up

All patients were monitored at outpatient clinics with biochemical and other laboratory tests every 1–2 months. Development of ascites or hepatic encephalopathy, if any, was recorded. Liver function was evaluated according to Child-Turcotte classification [12]. HCC recurrence was examined by ultrasonography every 3 months and computed tomography every 6 months. Patients received additional treatment for recurrence, whenever possible, mainly by PTA. THAE was performed prior to PTA when there were more than three tumor foci. The follow-up period was defined as the interval between the date of initial treatment and the date of event occurrence (deterioration in liver function or death) or the end of December 2000. The mean follow-up period was 46 ± 21 months (range 2–96 months).

Statistics

The primary endpoint of this study was deterioration of liver function as evaluated by Child-Turcotte classification, which was based on five factors, serum levels of albumin and total bilirubin, presence of ascites and hepatic encephalopathy, and state of nutrition. Cumulative survival curves and deterioration rates of liver function were calculated by the Kaplan–Meier method and difference among groups were assessed by the log-rank test. Risk factors for aggravation of liver function were analyzed by Cox proportional hazards regression, where candidate predictive factors included demographic data prior to the initial PTA

(age, gender, HBs antigen, HCV antibody, alcohol consumption >50 g daily), history of interferon treatment, stage of fibrosis in the background liver, serum alanine transaminase (ALT) level, platelet count, prothrombin time, levels of tumor markers (α -fetoprotein and des- γ -carboxy prothrombin), tumor characteristics (size, pathologic grading), and the mode of treatment (percutaneous ethanol injection, percutaneous microwave coagulation, with or without THAE). Continuous variables were transformed into dichotomous data divided by the median value, except that AFP and DCP were represented by positivity. Association between HCC recurrence and degradation of liver function was evaluated by χ^2 -test. A *P* value <0.05 was considered significant.

Results

Patient profile

The clinical profiles of 227 patients (158 men and 69 women, average age 64 years) on initial admission are shown in Table 1. As typical in Japan, 80% were positive for hepatitis C virus and 10% for hepatitis B virus. The size of the tumor was 26 ± 10 mm in diameter. Tumor cell differentiation was determined in 180 (79%) patients, as Edmondson I, II, III, and IV in 65, 85, 28, and 2, respectively. Adequate specimen could not be obtained in 27 patients and tumor biopsy was not performed in 20 patients. Stage of fibrosis in the background liver was evaluated in 202 (89%) patients, where 59% showed cirrhosis (F4) and 31% showed advanced fibrosis (F3). Seropositivity of tumor markers was 18% for AFP (cut off 100 ng/ml) and 12% for DCP (0.1 AU/L) Table 2.

Liver function was evaluated based on Child-Turcotte classification as Child A in 119, Child B in 81, and Child C in 27 patients. Age, gender, viral markers, and alcohol consumption did not differ among the three groups, while there was significant difference in the levels of albumin, bilirubin, ALT, platelet counts, prothrombin time, and stage of fibrosis. Tumor characteristics and the mode of treatment did not differ among the groups except that all patients in the Child C group received percutaneous ethanol injection Table 3.

Survival and changes in liver function

Cumulative survival rate among the overall 227 patients was 93, 76, and 61% at 1, 3, and 5 years, respectively. Compatible with previous reports, the 5-year survival rate was better in patients at Child A (76%) than in those at Child B (45%) or Child C (43%) ($P < 0.0001$, log-rank test, Fig. 1). Difference between Child B and Child C

patients was not significant ($P = 0.4$). Among 119 patients who were initially at Child A, 44 showed deterioration in liver function to Child B. Cumulative deterioration was found in 9, 19, and 38% at 1, 3, and 5 years, respectively (Fig 2). Similarly, 49 of 81 patients who were initially at Child B were shifted to Child C, with a rate of 13, 44, and 70% at 1, 3, and 5 years, respectively (Fig 3) Table 4.

Factors predictive of deterioration in liver function

Predictive factors for deterioration in liver function after PTA were assessed using Cox proportional hazards regression for the change from Child A to Child B among 119 patients who were initially at Child A, and for that from Child B to Child C among 81 patients who were initially at Child B, separately.

Univariate analysis revealed that aging, fibrosis of background liver tissue, high grade of tumor pathology (Ed. III/IV), and serum AFP levels were significantly associated with the aggravation of liver function in Child A group patients. Serum AFP levels were only significant in stepwise multivariate analysis. In Child B group patients, aging, alcohol consumption (>50 g daily), and size of tumor foci were significant by univariate analysis, and size of tumor foci was the only significant factor by stepwise multivariate analysis.

Recurrence of HCC

Recurrence of HCC was detected in 143 of 227 (63%) patients, of which 22 were adjacent to the primary lesion, 99 were elsewhere, and 22 were both. Cumulative recurrence rates did not differ when compared based on Child-Turcotte classification of liver function before the initial PTA (data not shown). Seventy-nine of 119 (66%) patients who were initially at Child A function developed HCC recurrence, and liver function deteriorated to Child B in 40 of those 79 patients (51%). In contrast, only 4 of 40 patients (10%) who had no HCC recurrence showed deterioration in liver function ($P = 0.002$). In contrast, deterioration to Child C from Child B occurred in 31 of 47 patients (66%) with HCC recurrence, and in 18 of 34 patients (53%) without ($P = 0.554$).

Discussion

PTA has become accepted as a potentially curative treatment for HCC, showing survival rates compatible with that of hepatectomy [13]. In fact, the present study showed a 5-year cumulative survival of 76% among Child A patients and that of 43% among Child C patients. It is noteworthy that hepatectomy might have been contraindicated in the

Table 1 Patients profiles at the time of initial treatment for HCC

Variables	All 227 patients	Child A group (n = 119)	Child B group (n = 81)	Child C group (n = 27)
Host-related factors				
Sex (male/female)	158/69	89/30	52/29	17/10
Age (y.o.)	64 ± 6.5 (63)	63 ± 7.0 (63)	66 ± 5.2 (66)	63 ± 8.8 (61)
Patients grouped according to viral marker (N)				
HBs-Ag(+),HCV-Ab(-)	22	17	3	2
HBs-Ag(-),HCV-Ab(+)	182	93	66	23
HBs-Ag(+),HCV-Ab(+)	1	1	0	0
HBs-Ag(-),HCV-Ab(-)	22	8	12	2
Previous IFN therapy (Yes)	49	34	15	0
Alcohol consumption >50 g/day n/n (%)	76/196 (39%)	41/107 (38%)	27/66 (41%)	8/23 (35%)
Albumin (g/dl)	3.6 ± 0.4 (3.5)	4.0 ± 0.2 (3.9)	3.3 ± 0.2 (3.3)	2.8 ± 0.3 (2.8)
Total bilirubin (mg/dl)	0.9 ± 0.4 (1.1)	0.7 ± 0.2 (0.7)	1.0 ± 0.4 (0.9)	1.5 ± 0.8 (1.4)
ALT (IU/l)	76 ± 41 (62)	81 ± 43 (68)	73 ± 38 (60)	61 ± 45 (49)
Platelet count (104/mm ³)	10.8 ± 4.0 (9.5)	12.9 ± 3.8 (12.8)	9.1 ± 3.1 (7.7)	6.9 ± 2.0 (7.2)
Prothrombin time (%)	71 ± 12 (70)	77 ± 10 (75)	68 ± 11 (66)	55 ± 14 (52)
Fibrosis staging of noncancerous tissue (F1/2/3/4)	3/17/62/120	3/11/42/51	0/6/16/49	0/0/4/20
Tumor-related factors				
Size of tumor (mm)	26 ± 10 (22)	26 ± 10 (21)	25 ± 10 (22)	27 ± 13 (24)
Pathological grading of tumors (Ed. I/II/III/IV)	65/85/28/2	39/40/17/2	19/30/10/0	7/15/1/0
Positivity of tumor markers n/n (%)				
AFP (>100 ng/ml)	38/216 (18%)	16/113 (14%)	17/79 (22%)	5/24 (21%)
DCP (>0.1 IU/l)	23/182 (12%)	9/93 (10%)	12/68 (18%)	2/20 (10%)
Treatment-related factors (n/n)				
THAE before PTA (With / Without)	11/216	7/112	3/78	1/26
Ethanol injection (with/without) ^a	201/26	105/14	69/12	27/0
Microwave coagulation (with/without) ^a	41/186	21/98	18/63	2/25
HCC recurrence				
Presence/Absence (n/n)	143/84	79/40	47/34	17/10

Note. The value represents mean ± SD (median)

Abbreviations: HCC, hepatocellular carcinoma; N, number of patients; ALT, alanin transaminase; Ed, Edmondson classification; AFP, α -fetoprotein; DCP, des- γ -carboxy prothrombin; THAE, transcatheter hepatic arterial embolization; PTA, percutaneous tumor ablation

^a 15 patients received combined therapy of ethanol injection and microwave coagulation

Table 2 Occurrence rate of degradation in hepatic functional reserve with or without development of HCC recurrence

	HCC recurrence (+)	HCC recurrence (-)	P value
Child A group % (n/n)	50% (40/79)	10% (4/40)	0.002
Child B group % (n/n)	66% (31/47)	53% (18/34)	0.554

Abbreviations: HCC, hepatocellular carcinoma; HCC recurrence (+), patients who developed HCC recurrence during follow-up period; HCC recurrence (-), patients who did not develop HCC recurrence during follow-up period

latter group due to poor liver function. We have previously shown that PTA does not result in immediate deterioration in liver function. However, it was not known whether or not PTA affects liver function in a longer-term follow-up.

Since most patients with HCC have chronic liver diseases, usually chronic hepatitis and cirrhosis, changes in liver function are not easily attributed separately either to the progression of background liver disease or to the effect

Table 3 Risk factors contributing to degradation of functional reserve of the liver in Child A group

	Univariate analysis	
	Risk ratio (95% CI)	P
Host-related factors		
Age (>70 y.o.)	1.91 (0.96–3.82)	0.07
Sex (male)	0.88 (0.45–1.73)	0.71
HCV Ab positive	1.36 (0.60–3.05)	0.46
Previous interferon therapy (Yes)	0.77 (0.42–1.44)	0.42
Alcohol consumption (≥ 50 g/day)	1.30 (0.24–1.85)	0.40
ALT level (>80 IU/L)	1.47 (0.81–2.63)	0.20
Platelet count ($>12.8 \times 10^4$)	0.84 (0.47–1.52)	0.57
Prothrombin time (>68%)	0.73 (0.39–1.36)	0.32
Fibrosis staging (F4 vs. F1-3)	2.03 (0.74–3.86)	0.31
Tumor-related factors		
Size of tumor (>21 mm)	1.26 (0.70–2.28)	0.44
Ed. Classification (ed. III/IV vs. I/II)	2.18 (1.08–4.42)	0.03*
Positivity of tumor markers		
AFP (>100 ng/ml)	3.36 (1.62–6.94)	0.001*
DCP (>1.0 IU/L)	1.54 (0.47–5.10)	0.48
Treatment-related factors		
THAE before PTA	0.83 (0.20–3.48)	0.81
Ethanol injection	0.78 (0.31–2.03)	0.62
Microwave coagulation	0.76 (0.42–1.43)	0.42
Multivariate analysis		
Fibrosis staging (F4 vs. F1-3)	0.76 (0.74–3.86)	0.21
Ed. Classification (ed. III/IV vs. I/II)	1.70 (0.76–3.13)	0.19
AFP (>100 ng/ml)	2.69 (1.16–6.21)	0.02*

Abbreviations: HCC, hepatocellular carcinoma; ALT, alanin transaminase; Ed, Edmondson classification; AFP, α -fetoprotein; DCP, des- γ -carboxy prothrombin; THAE, transcatheter hepatic arterial embolization; PTA, percutaneous tumor ablation

* $P < 0.05$

Fig. 1 Cumulative survival rates of patients after percutaneous tumor ablation (PTA) according to Child-Turcotte classification prior to initial PTA

of intervention. We presumed in this study that the degree of untoward effect of PTA, if any, is correlated with the size of the HCC nodules. The results showed that the size

Fig. 2 Incidence of deterioration in liver function from Child A to Child B after percutaneous tumor ablation

of tumor was associated with deterioration in liver function among patients at Child B but not among patients at Child A. It appears that damage to liver function caused by PTA can be fully recovered in patients with good liver functional reserve while it may not be negligible in patients with poorer-functional reserve.

Fig. 3 Incidence of deterioration in liver function from Child B to Child C after percutaneous tumor ablation

Analysis of changes in liver function was further complicated by frequent recurrence of HCC. Recurrence of HCC is associated with deterioration in liver function in patients who were initially at Child A but not in those

initially at Child B by χ^2 -test. Cox proportional hazards regression using recurrence as a time-dependent covariate also showed the same results (data not shown). More precisely, liver function was relatively preserved in Child A patients in the absence of HCC recurrence while deterioration was common in Child B patients regardless of the presence or absence of HCC recurrence. In fact, HCC was still under control in 15 of 34 patients (44%) when they died. These data suggest that preservation of liver function is at least as important as ablation of HCC nodules in patients with already impaired liver function. Since the efficacy of antiviral therapies such as pegylated interferon plus ribavirin for HCV and entecavir etc. for HBV has been recently improved, they may be beneficial also in improving prognosis of hepatitis virus-related HCC patients by preventing further deterioration in liver function.

Multivariate analysis showed serum AFP levels significantly affected the liver function in Child A group patients. We have already showed that serum AFP levels prior to PTA were closely related to HCC recurrence [14]. There-

Table 4 Risk factors contributing to degradation of functional reserve of the liver in Child B group

	Univariate analysis	
	Risk ratio (95% CI)	P
Host-related factors		
Age (>70 y.o.)	1.94 (1.07–3.52)	0.03
Sex (male)	0.89 (0.49–1.62)	0.71
HCV Ab positive	1.10 (0.53–2.26)	0.81
Previous interferon therapy (Yes)	0.69 (0.31–1.53)	0.36
Alcohol consumption (≥ 50 g/day)	1.61 (0.86–2.99)	0.14
ALT level (>80 IU/L)	0.61 (0.33–1.11)	0.10
Platelet count ($>7.7 \times 10^4$)	1.05 (0.60–1.83)	0.86
Prothrombin time (>68%)	1.07 (0.61–1.87)	0.81
Fibrosis staging (F4 vs. F1-3)	1.90 (0.94–3.79)	0.07
Tumor-related factors		
Size of tumor (>21 mm)	2.35 (1.31–4.21)	0.004
Ed. Classification (ed. III/IV vs. I/II)	1.56 (0.69–3.52)	0.29
Positivity of tumor markers		
AFP (>100 ng/ml)	1.12 (0.56–2.26)	0.74
DCP (>1.0 IU/L)	1.91 (0.91–4.07)	0.09
Treatment-related factors		
THAE before PTA	1.57 (0.48–5.15)	0.46
Ethanol injection	0.88 (0.39–2.00)	0.76
Microwave coagulation	1.51 (0.74–3.07)	0.25
Multivariate analysis		
Age (>70 y.o.)	1.25 (0.70–2.23)	0.44
Tumor size (>21 mm)	2.23 (1.23–4.07)	0.009*

Abbreviations: HCC, hepatocellular carcinoma; ALT, alanin transaminase; Ed, Edmondson classification; AFP, α -fetoprotein; DCP, des- γ -carboxy prothrombin; THAE, transcatheter hepatic arterial embolization; PTA, percutaneous tumor ablation

* $P < 0.05$

fore, it is possible that the significance of serum AFP levels should reflect the feasibility of HCC recurrence.

Since we did not assign patients to untreated controls, we cannot directly assess the long-term untoward effects of PTA on liver function. Nevertheless, the untoward effects were shown to be negligible in patients with relatively preserved liver function. On the other hand, the volume of ablation affected changes in liver function in patients with already impaired function. We have currently adopted strict criteria, based on dynamic computed tomography, regarding the complete ablation of HCC nodules. Prospective studies will be required in the future to clarify whether the complete ablation as such is beneficial in regard to the prognosis of patients with poor liver function.

To evaluate long-term prognosis of patients after ablation therapy, we did not include in this study patients treated with RFA, which has been recently shown to surpass ethanol injection as treatment of HCC. It will be important to assess long-term prognosis of patients treated with RFA especially in terms of preservation of liver function.

In conclusion, we showed that PTA did not affect long-term liver function in patients with preserved liver function regardless of the size of the HCC nodules. Recurrence of HCC determined their prognosis. In contrast, the size of the HCC was a significant risk factor for deterioration in liver function, while recurrence of HCC was not, in patients with already impaired liver function. Preservation of liver function may be essential when treating patients in the latter group.

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