

Table 1. Baseline characteristics of the 685 Patients undergoing percutaneous ethanol injection for primary hepatocellular carcinoma

Variable	
Age (years)	64.0 ± 8.9
Males, <i>n</i> (%)	502 (73.3)
Viral infection*	
HBs-Ag positive, <i>n/N</i> (%)	64/685 (9.3)
Anti-HCV positive, <i>n/N</i> (%)	570/673 (84.7)
Both positive, <i>n/N</i> (%)	11/673 (1.6)
Both negative, <i>n/N</i> (%)	52/673 (7.7)
Alcohol consumption >80 g/day, <i>n</i> (%)	143 (20.9)
Ascites, <i>n</i> (%)	122 (17.9)
Encephalopathy, <i>n</i> (%)	44 (6.5)
Albumin (g/dl)	3.55 ± 0.50
Total bilirubin (mg/dl)	0.96 ± 0.536
Prothrombin time (%)	71.6 ± 15.9
Platelet count (×10 ⁴ /mm ³)	10.3 ± 4.6
AST (IU/L)	80.6 ± 48.2
ALT (IU/L)	79.2 ± 61.9
Child–Pugh class, <i>n</i> (%)	
A	425 (62.1)
B	228 (33.3)
C	32 (4.6)
Tumour size (cm)	2.83 ± 1.47
Tumour number	2.0 ± 1.7
Serum AFP (ng/ml), <i>n</i> (%)	
≤ 100	525 (76.6)
101–400	95 (13.9)
>400	65 (9.5)
Serum DCP (mA U/ml), <i>n</i> (%)†	
≤ 100	428 (82.8)
101–400	49 (9.5)
>400	40 (7.7)
Serum AFP-L3 (%), <i>n</i> (%)‡	
≤ 15	193 (86.2)
15.1–40	16 (7.1)
>40	15 (6.7)

*Anti-HCV was not tested in 12 patients.

†Serum DCP level was not measured in 168 patients.

‡Serum AFP-L3 level was not measured in 461 patients.

HBs-Ag, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, α -fetoprotein; DCP, des-gamma-carboxy-prothrombin; AFP-L3, lectin-reactive α -fetoprotein.

Data are expressed as mean ± standard deviation.

HCC recurrence and the number of ethanol injection sessions to survival was analysed by univariate and multivariate models. The prognostic relevance of baseline variables (Table 1), the combination of chemoembolization and the number of ethanol injection sessions to local tumour progression and distant recurrence was also analysed by univariate and multivariate models. In multivariate analysis, we evaluated models including Child–Pugh class and excluding its components to avoid multicollinearity. Serum DCP and AFP-L3 levels were excluded from the multivariate model because of absence of data from 168 and 461 patients respectively. Some continuous variables in which log-linearity could

not be assumed were transformed into categorical variables. Variables with a *P* value <0.05 determined by univariate comparison were subjected to multivariate analysis. A stepwise variable selection was performed with Akaike Information Criteria in multivariate analysis. Results were expressed as hazard ratios with corresponding 95% confidence intervals (CI), with *P* values from the Wald test. All significance tests were two-tailed, and differences with a *P* value <0.05 were considered statistically significant.

Complications were defined according to the guidelines of the Society of Interventional Radiology (16).

Results

Antitumour effect

We performed 2147 ethanol injection treatments, comprising 13 526 procedures. Thus, procedure number per treatment was 6.3 ± 2.6. The total volume of injected ethanol per treatment was 40.9 ± 16.3 ml. Many patients received iterative ethanol injection treatments for recurrence. A total of 108 patients underwent ethanol injection treatment once, 118 patients twice, 196 patients 3 times, 153 patients 4 times, 71 patients 5 times, 28 patients 6 times, 8 patients 7 times and 3 patients 8 times.

Technique effectiveness rate was 98.2% (2108/2147 treatments). It was similar between the initial ethanol injection treatments and the other ethanol injection treatments for recurrence (*P* = 0.397). Complete ablation of the tumour was achieved in 675 (98.5%) of the 685 initial treatments and in 1433 (98.0%) of the 1462 other treatments. However, technique effectiveness rate significantly differed with tumour size (*P* = 0.002). No apparent viable portions remained in 758 (99.0%) of 766 treatments for tumours ≤ 2.0 cm in diameter, in 704 (98.4%) of 717 treatments for tumours 2.1–3.0 cm, in 570 (97.9%) of 582 treatments for tumours 3.1–5.0 cm and in 76 (92.7%) of 82 treatments for tumours >5.0 cm.

Survival

Table 1 shows clinical characteristics of the 685 patients. A total of 136 patients (19.9%) were older than 75 years. In all, 180 patients had tumours ≤ 2.0 cm in diameter, 274 had tumours 2.1–3.0 cm, 192 had tumours 3.1–5.0 cm and 39 had tumours >5.0 cm. A total of 367 patients had one tumour, 238 patients had 2 or 3 tumours and 80 had 4 or more tumours.

As of December 2010 (with a median follow-up of 51.6 months), 70 patients (10.2%) remained alive, 52 (7.6%) were lost to follow-up and 563 (82.2%) had died. Of the 685 patients, two were transplanted. The number of patients who survived longer than 5, 10 and 20 years after the first ethanol injection treatment was 305, 97 and 3 respectively. The cause of death was HCC

in 297 patients (52.8%), liver failure in 129 (22.9%), upper gastrointestinal bleeding in 30 (5.3%), complications related to the procedure in 2 (0.4%), liver-unrelated diseases in 84 (14.9%) and undetermined in 21 (3.7%).

The 1-, 3-, 5-, 10-, 15- and 20-year survival rates of all 685 patients were 91.0% (95% CI = 88.9–93.2%), 67.6% (95% CI = 64.1–71.3%), 49.0% (95% CI = 45.3–53.0%), 17.9% (95% CI = 15.0–21.2%), 8.6% (95% CI = 6.4–11.7%) and 7.2% (95% CI = 4.5–11.5%) respectively (Fig. 2; Table 2). Survival rates significantly differed with tumour number ($P = 0.0001$), tumour size

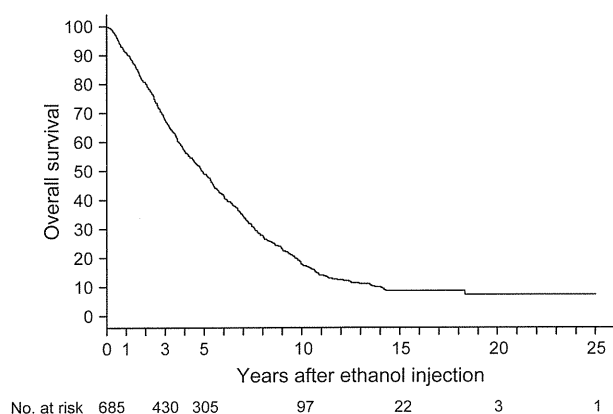


Fig. 2. Overall survival in 685 primary hepatocellular carcinoma patients who underwent ethanol injection.

($P = 0.0001$) and Child–Pugh class ($P = 0.0001$). In patients with 1–3 tumours, all ≤ 3 cm, and in Child–Pugh class A or B, the 5-year survival rate was 59.5% (95% CI: 54.7–64.7%).

Univariate analysis indicated that 13 of the 22 variables were relevant to survival. In multivariate analysis, a model that contained age, antibody to hepatitis C virus (anti-HCV), Child–Pugh class, tumour size, tumour number and serum AFP level was selected (Table 3).

Survival rates significantly differed with the time period in which the first ethanol injection was performed ($P < 0.0001$; Fig. 3). In 109 patients who underwent ethanol injection between 1985 and 1991, the 5-year survival rate was 30.3% (95% CI = 22.7–40.5%), whereas it was 51.2% (95% CI = 46.8–55.9%) in 476 patients between 1992 and 1998, and 61.1% (95% CI = 51.3–72.8%) in 100 patients between 1999 and 2005.

Recurrence

Recurrence developed in 449 patients. Local tumour progression alone was found in 61 patients, local tumour progression with distant recurrence in 44 and distant recurrence alone in 344. Of these 344 patients, eight had recurrence in extrahepatic sites: five had lymph node metastasis, one had lung metastasis, one had bone metastasis and the remainder had both lymph node and lung metastasis. Of the 449 patients, the first recurrence was treated by iterative ethanol injection in

Table 2. Survival of patients undergoing ethanol injection, based on tumour number, tumour size and Child–Pugh class

Grading	<i>n</i>	Survival (%)					Median (years)	<i>P</i> value
		3-Year	5-Year	10-Year	15-Year	20-Year		
Overall survival	685	67.6	49.0	17.9	8.6	7.2	4.9	–
Tumour number								
Solitary	367	72.0	56.5	24.6	12.1	9.7	5.8	0.0001
2–3	232	71.5	46.3	12.9	5.9	–	4.7	
≥ 4	86	37.6	23.8	2.5	1.3	–	2.6	
Tumour size								
≤ 2.0 cm	240	83.6	63.8	27.6	12.3	6.1	6.9	0.0001
2.1–3.0 cm	221	68.0	47.9	15.0	10.7	10.7	4.8	
>3.0 cm	224	50.2	34.4	10.1	3.5	3.5	3.1	
Child–Pugh class								
A	425	77.3	58.7	24.4	12.5	10.4	6.2	0.0001
B	228	53.9	35.5	8.1	3.0	–	3.5	
C	32	37.5	18.8	3.1	–	–	1.9	
Combination of tumour number, tumour size, and Child–Pugh class								
Solitary, ≤ 3 cm	275	77.5	62.2	28.8	14.5	10.8	6.8	–
Solitary, ≤ 3 cm, Child–Pugh A	185	84.9	69.2	36.7	20.2	15.1	7.6	–
1–3 tumours, ≤ 3 cm	419	78.6	58.0	23.5	12.2	9.1	6.1	–
1–3 tumours, ≤ 3 cm, Child–Pugh A/B	402	80.5	59.5	24.3	12.8	9.6	6.2	–
Satisfied the indication criteria of surgical resection proposed in the BCLC protocol*	121	86.3	72.8	31.1	14.8	–	7.2	–

*Child–Pugh class A with a normal level of bilirubin, no significant portal hypertension and a single HCC.

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma.

Table 3. Multivariate analysis of variables relevant to survival, local tumour progression and distant recurrence

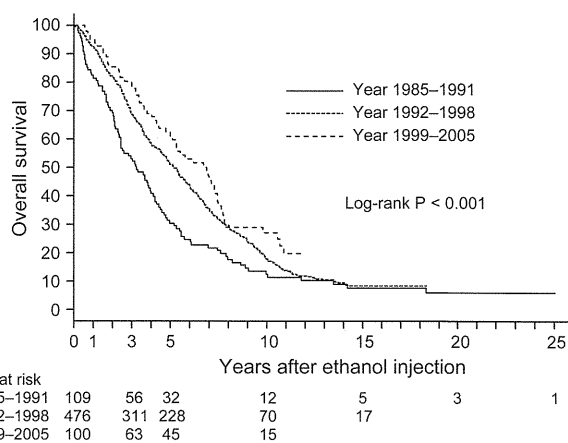
Variable	Multivariate analysis Hazard ratio (95% CI)	P value
Survival		
Age (per year)	1.03 (1.02–1.04)	<0.0001
Anti-HCV-positive	0.81 (0.69–0.94)	0.006
Child–Pugh class		
A	1	
B	2.01 (1.66–2.44)	<0.0001
C	3.11 (2.08–4.65)	<0.0001
Tumour size (cm)		
≤2.0	1	
2.1–3.0	1.26 (1.00–1.58)	0.051
3.1–5.0	1.51 (1.18–1.93)	0.001
>5.0	2.31 (1.61–3.31)	<0.0001
Tumour number		
solitary	1	
2–3	1.10 (0.90–1.35)	0.34
≥4	2.11 (1.59–2.78)	<0.0001
Serum AFP (ng/dl)		
≤100	1	
101–400	1.47 (1.14–1.90)	0.003
>400	2.16 (1.57–2.97)	<0.0001
Local tumour progression		
Tumour size (cm)		
≤2.0	1	
2.1–3.0	1.47 (1.15–1.88)	0.002
3.1–5.0 vs. ≤2.0	1.30 (0.97–1.75)	0.08
>5.0 vs. ≤2.0	2.81 (1.64–4.82)	0.0002
Distant recurrence		
Tumour size (cm)		
≤2.0	1	
2.1–3.0	1.42 (1.11–1.82)	0.006
3.1–5.0	1.28 (0.95–1.72)	0.10
>5.0	2.48 (1.43–4.28)	0.001
Tumour number		
solitary	1	
2–3	1.47 (1.16–1.85)	0.001
≥4	2.12 (1.36–3.28)	0.0008

AFP, α -fetoprotein; CI, confidence interval; HCV, hepatitis C virus.

399 (88.8%), chemoembolization in 44 (9.8%), systemic chemotherapy in three (0.7%) and best supportive care in three (0.7%).

The 1-, 3-, 5-, 10-, 15- and 20-year rates of local tumour progression with or without distant recurrence were 7.9% (95% CI = 5.7–10.0%), 15.6% (95% CI = 12.6–18.6%), 18.2% (95% CI = 15.0–21.4%), 18.4% (95% CI = 15.2–21.6%), 18.4% (95% CI = 15.2–21.6%) and 18.4% (95% CI = 15.2–21.6%) respectively (Fig. 4). Univariate analysis demonstrated that three variables were relevant to local tumour progression, whereas multivariate analysis indicated that only tumour size was significantly related to local tumour progression (Table 3).

The 1-, 3-, 5-, 10-, 15- and 20-year rates of distant recurrence without local tumour progression were 17.1% (95% CI = 14.0–20.1%), 42.6% (95%

**Fig. 3.** Survival according to the time period in which the first ethanol injection was performed (1985–1991 vs. 1992–1998 vs. 1999–2005)

CI = 38.6–46.7%), 53.5% (95% CI = 49.4–57.7%), 60.4% (95% CI = 56.3–64.5%), 60.8% (95% CI = 56.7–64.9%) and 60.8% (95% CI = 56.7–64.9%) respectively. Univariate analysis demonstrated that five variables were relevant to distant recurrence, whereas multivariate analysis indicated that tumour size and tumour number were significantly related to distant recurrence without local recurrence (Table 3).

Complications

Table 4 shows complications encountered. The incidence rates per treatment and per procedure were 2.1% (45 of 2147) and 0.33% (45 of 13 526) respectively. A patient died of multiple organ dysfunction syndrome caused by procedure-related hemoperitoneum. The tumour was not on the surface but inside the liver. The patient did not have marked bleeding tendency. The other developed myocardial infarction, resulting in death during the procedure. The treatment mortality rate was 0.06%.

Discussion

This study describes a 20-year experience with ethanol injection at a high-volume centre. We performed 2147 ethanol injection treatments on the 685 primary HCC patients, showing that ethanol injection has a high antitumour effect. Tumours were judged to have been completely ablated by final CT imaging in 98.2% of the treatments. The complete response rate may be higher in this study than others (17, 18), probably because we did not predefine the number of procedures in a treatment. We generally repeated the procedure until CT demonstrated complete tumour necrosis. Many other studies limited the procedure number of ethanol injection. Complete tumour ablation has been reported to relate to improved survival (19).

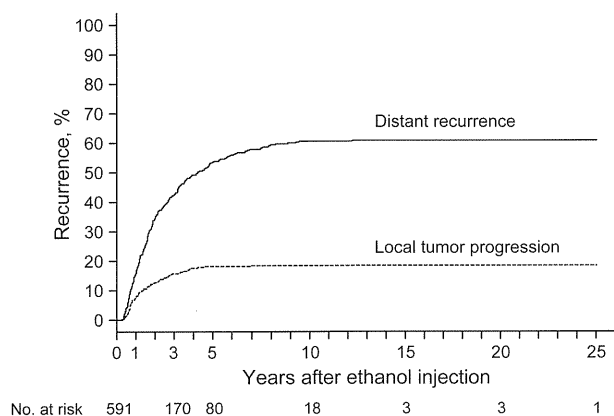


Fig. 4. Local tumour progression or distant recurrence in patients who underwent ethanol injection.

This study showed that ethanol injection could achieve long-term survival over 20 years. Ninety-seven patients survived for more than 10 years and three for more than 20 years. Both tumour factors and liver function were relevant to survival. In addition, age was among the prognostic factors. In this study, 19.9% were older than 75 years, which may have resulted in the higher percentage (14.9%) of liver-unrelated deaths compared with other studies. Ant-HCV positivity was a good prognostic factor in this study.

Survival in ethanol injection appears to have improved with times. This is probably because of advances in imaging techniques, such as ultrasound and CT, more refined skills and greater experience in ablation and innovations in the treatment of underlying liver diseases.

Hepatocellular carcinoma frequently recurred after ethanol injection. Most recurrences were, however, not local tumour progression but distant recurrence. Frequent recurrence is not specific to ethanol injection. After hepatic resection, the tumour recurrence rate exceeds 70% at 5 years (20, 21). In this study, periodic follow-up detected most recurrence at limited stage. Ethanol injection was performed again for first recurrence in 88.8% of the cases. In hepatic resection, the rate of repeat resection for first recurrence has been reported to range from 10.4 to 30.6% (21, 22). As ethanol injection is less invasive than hepatic resection, iterative ethanol injection can be performed for recurrence more easily.

Ethanol injection was a safe procedure, although many patients in this study were at risk for surgical treatment because of advanced cirrhosis or other comorbidities. Only 121 (17.7%) of the 685 patients satisfied the indication criteria of surgical resection proposed in the BCLC (Barcelona Clinic Liver Cancer) protocol (23) and were, thus, considered good candidates for surgical resection. Other investigators also reported low complication rates of 0–3.2% (6–8, 24).

Table 4. Complications in 2147 treatments of ethanol injection for hepatocellular carcinoma

Complication	Number
Neoplastic seeding	9
Hemoperitoneum	9
Hemobilia	6
Liver abscess	6
Symptomatic pleural effusion	3
Massive hepatic infarction	3
Biliary cast	2
Hemothorax	2
Abnormal decrease in blood coagulation factor VIII	2
Biloma	1
Biliary bronchial fistula	1
Myocardial infarction	1

For hepatic resection, morbidity rates have been reported to be 38–47% even in recent studies (25–27).

Radiofrequency ablation has steadily replaced ethanol injection (11). At our institution, radiofrequency ablation is currently the first option for percutaneous ablation (28). Several randomized controlled trials including ours (12, 18, 29, 30) demonstrated more reliable local antitumour effect and higher survival. Our 10-year outcome of radiofrequency ablation (28) appears superior to this 20-year outcome of ethanol injection. In addition, radiofrequency ablation requires fewer treatment sessions and shorter hospitalization.

A meta-analysis showed, however, that ethanol injection did not differ from radiofrequency ablation for tumours ≤ 2 cm in diameter (31). A recent randomized controlled trial also demonstrated similar 5-year survival between the two ablations (32). Ethanol injection is at least more feasible and cheaper than radiofrequency ablation.

Surgical resection has been considered the treatment of first choice for HCC. Our first option for resectable tumours was also surgery. However, most patients who came to our department declined surgical resection. Thus, some patients in this study underwent ethanol injection not because of unresectable tumour but because of refusal of surgery. Those who preferred surgery would have gone directly to the surgical department, which has extensive experience in hepatic resection (27).

It is not easy to compare outcomes between ethanol injection and surgical resection. Indications are different between the two treatments. Furthermore, indications for each treatment are different from institution to institution. Thus, a case adjudged to be treatable by ethanol injection or surgical resection at an institution may not be given the same treatment at another. The best-known indication criteria may be those proposed in the BCLC protocol (23), which states that surgical resection should be restricted to patients with performance status 0, Child–Pugh class A, single HCC, normal portal pressure and normal serum bilirubin level. In patients satisfying

those criteria, the 5-year survival rate is expected to be >70% (20). In this study, 5-year survival rate of the patients satisfied the criteria was 72.8%, which appears satisfactory when compared with outcomes following surgical resection. Furthermore, in patients with solitary HCC, ≤ 3 cm in diameter, and Child–Pugh A, 5- and 10-year survival rates were 69.2% and 36.7% respectively. In patients treated by surgical resection, 5- and 10-year survival rates were 34.4–70.0% and 10.5–52.0% respectively (22, 33–39). Although this is an observational study with no control, survivals following ethanol injection appear comparable to those reported following surgical resection.

A randomized controlled trial showed no significant difference in survival between ethanol injection and surgical resection (40). Several non-randomized controlled trials also reported similar overall survival between the two treatments (5–7, 40–43), whereas others reported higher survival with resection (44). Further studies are necessary to resolve this issue of comparing ablation with resection.

We made strenuous efforts to standardize the procedure of ethanol injection because many physicians performed ethanol injection at our institution. In addition to proficient practice of ethanol injection, detailed preoperative planning, cautious postoperative evaluation of therapeutic effect and careful follow-up are vital to achieve satisfactory outcomes.

Source population in this study may represent selection bias, as we performed ethanol injection on most patients who were hospitalized at our department; however, many patients with unfavourable tumour conditions for ethanol injection might not have been referred to us. Therefore, caution is required when extrapolating our findings to the general population of HCC patients.

A second limitation is that study population cannot be clearly defined. This study was based on daily clinical practice over a 20-year period. Indication criteria of ethanol injection changed over time, mainly because of the introduction of the other ablations: microwave ablation and radiofrequency ablation. Furthermore, various treatments besides percutaneous ablations were available for HCC, such as surgical resection and chemoembolization, with frequently overlapping indications.

One further limitation is the fact that this was a single-centre study. To extrapolate the findings in this study to patients at other institutions, consideration should be given to differences in the indications, methods, expertise, performance of available ultrasound and CT equipment and others. Treatment outcome may be influenced by the physicians' expertise and the institution's volume of care. We performed over 2000 ethanol injection treatments, which may represent a much greater number of treatments than those in most other institutions.

In conclusion, our 20-year experience shows that ethanol injection was potentially curative, resulting in

long-term survival over 20 years. Findings in this study may suggest that other ablation therapies, such as radiofrequency ablation, will achieve similar or even better long-term results in HCC.

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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

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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

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, $\geq 3000/\mu\text{L}$; hemoglobin, ≥ 8.5 g/dL; platelet count $> 30000/\mu\text{L}$; and prothrombin time international normalized ratio, ≤ 2.3), adequate hepatic function (albumin, ≥ 2.8 g/dL; total bilirubin, ≤ 3 mg/dL; and alanine aminotransferase [ALT] and aspartate aminotransferase [AST], ≤ 5 times the upper limit of the normal range), and adequate renal function (serum creatinine, ≤ 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^2 tests, 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, <i>n</i> (%)	
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 /μl) ^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, <i>n</i> (%)	
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

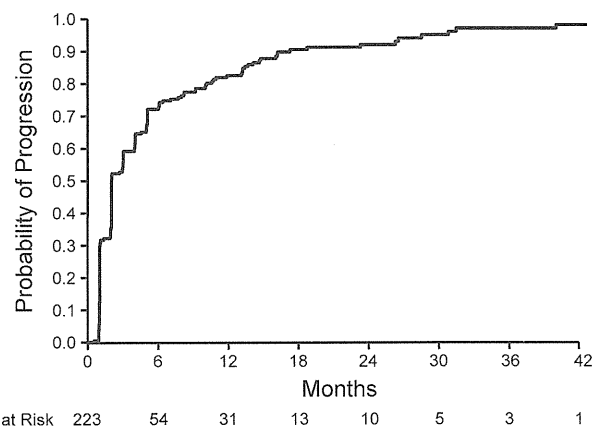


Fig. 1 Kaplan–Meier analysis of time to progression

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

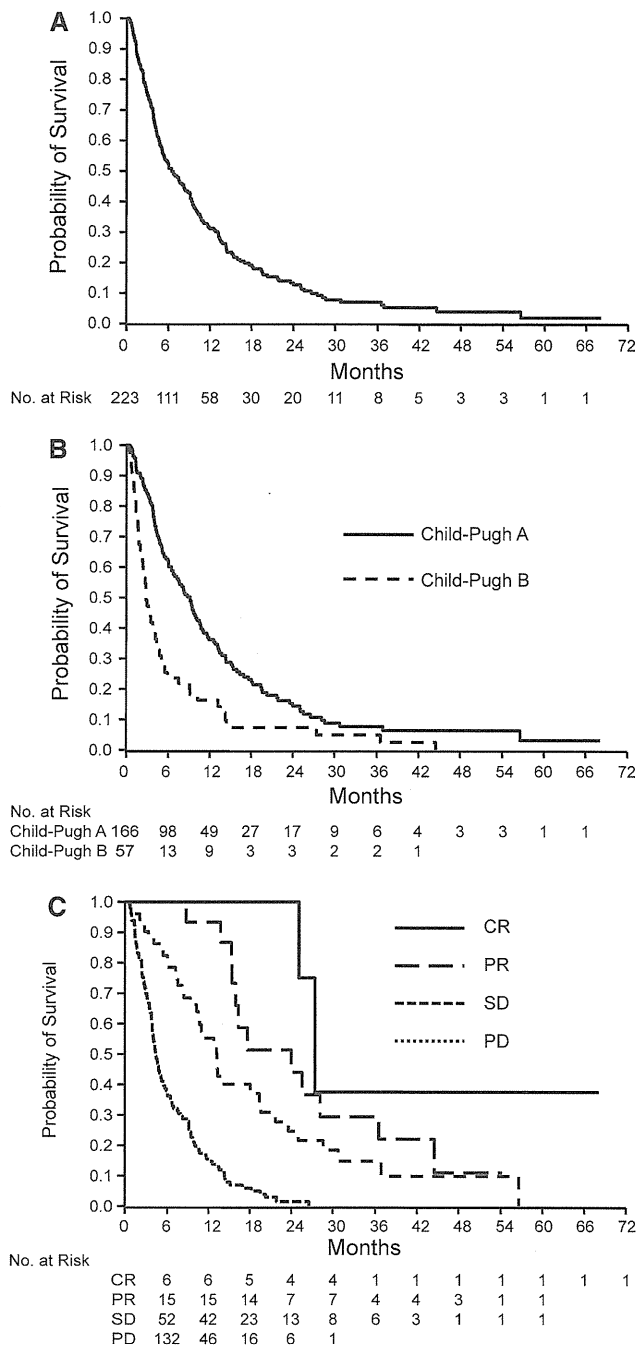


Fig. 2 Kaplan–Meier analysis of overall survival (a); stratified based on Child–Pugh classification (b) and response to treatment (c). CR complete response, PR partial response, SD stable disease, PD progressive disease

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

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/ μ L	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)

showed that all of these factors were also independent prognostic factors (Table 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 leukopenia (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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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 partial 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 (<i>n</i> = 54,145)	Hepatectomy (<i>n</i> = 5,270)	RFA (<i>n</i> = 11,688)	TAE (<i>n</i> = 37,187)	<i>p</i> value
Sex, <i>n</i> (%)					<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), <i>n</i> (%)					<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, <i>n</i> (%)					
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		
	<i>n/N</i>	% (95 % CI)	<i>P</i>	<i>n/N</i>	% (95 % CI)	<i>P</i>	<i>n/N</i>	% (95 % CI)	<i>P</i>
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

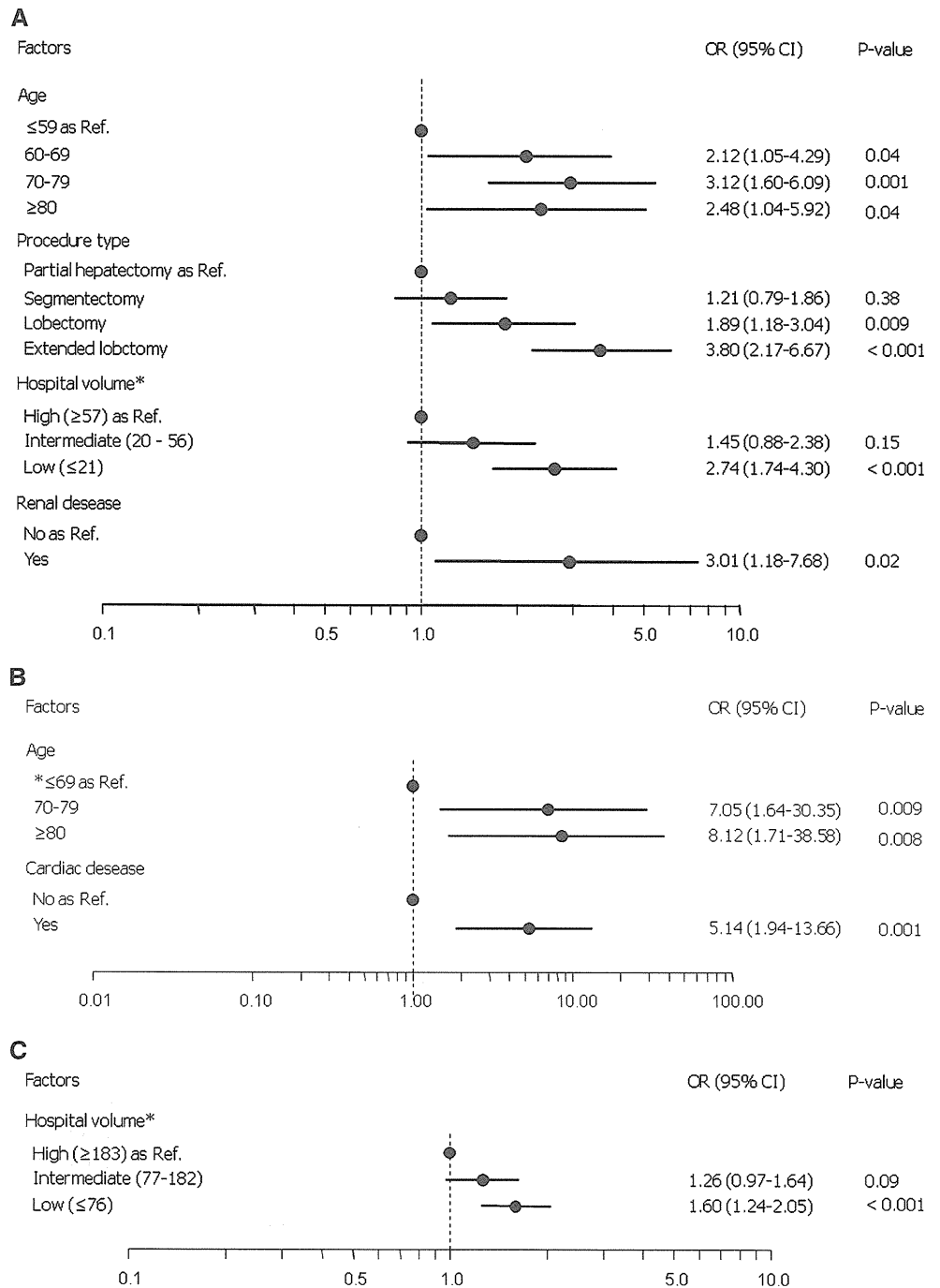
In-hospital complications occurred in 763 (14.48 %), 531 (4.54 %) and 1,668 (4.49 %) for hepatectomy, RFA, and TAE patients, respectively. The details of the complications are listed in Table 3. Postoperative hemorrhage was the commonest complication of hepatectomy and was seen in 361 (6.85 %) admissions. 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 transcatheter 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 (<i>n</i> = 5270)	RFA (<i>n</i> = 11688)	TAE (<i>n</i> = 37187)
Overall, <i>n</i> (%) ^a	763 (14.48)	531 (4.54)	1,668 (4.49)
Hemorrhage, <i>n</i> (%)	361 (6.85)	56 (0.48)	102 (0.27)
Bile duct stenosis, <i>n</i> (%)	59 (1.12)	152 (1.30)	657 (1.77)
Liver abscess, <i>n</i> (%)	19 (0.36)	36 (0.31)	201 (0.54)
Pneumothorax, <i>n</i> (%)	1 (0.02)	16 (0.14)	–
Perforation of gastrointestinal tract, <i>n</i> (%)	2 (0.04)	3 (0.03)	–
Peritonitis, <i>n</i> (%)	98 (1.86)	98 (0.84)	–
Heat burn, <i>n</i> (%)	–	7 (0.06)	–
Hepatic infarction, <i>n</i> (%)	–	7 (0.06)	3 (0.00)
Liver failure, <i>n</i> (%)	122 (2.31)	131 (1.12)	617 (1.66)
Cardiac complication, <i>n</i> (%)	35 (0.66)	15 (0.13)	37 (0.10)
Ruptured suture, <i>n</i> (%)	40 (0.76)	2 (0.02)	2 (0.00)
Renal failure, <i>n</i> (%)	26 (0.49)	2 (0.02)	35 (0.09)
Pulmonary embolism, <i>n</i> (%)	7 (0.13)	4 (0.03)	14 (0.04)
Wound infection, <i>n</i> (%)	12 (0.23)	11 (0.09)	11 (0.03)
Pneumonia, <i>n</i> (%)	57 (1.08)	30 (0.26)	117 (0.31)
Allergy to anesthetic agents, <i>n</i> (%)	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–