Transarterial infusion chemotherapy using cisplatin-lipiodol suspension with or without embolization for unresectable hepatocellular carcinoma

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Short title: TACE with CDDP/LPD for HCC

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Abstract

Purpose

We evaluate the long-term prognosis and prognostic factors in patients treated with transarterial infusion chemotherapy using cisplatin-lipiodol (CDDP-LPD) suspension with or without embolization for unresectable hepatocellular carcinoma (HCC).

Patients and methods

The study subjects were 107 patients with HCC treated with repeated transarterial infusion chemotherapy alone using CDDP/LPD. The median number of transarterial infusion procedures was 2 (range, 1-9), the mean dose of CDDP per transarterial infusion chemotherapy session was 30 mg (range, 5.0-67.5), and the median total dose of transarterial infusion chemotherapy per patient was 60 mg (range, 10-390).

Results

Survival rates were 86% at 1 year, 40% at 3 years, 20% at 5 years, and 16% at 7 years. For patients with >90% LPD accumulation after the first transarterial infusion chemotherapy, rates were 98% at 1 year, 60% at 3 years, and 22% at 5 years. Multivariate analysis identified >90% LPD accumulation after the first transarterial infusion chemotherapy (P=0.001), absence of portal vein tumor thrombosis (PVTT) (P<0.001) and Child-Pugh class A (P=0.012) as independent determinants of survival. Anaphylactic shock was observed in 2 patients, at the 5th transarterial infusion chemotherapy session in one and the 9th in the other.

Conclusions

Transarterial infusion chemotherapy with CDDP/LPD appears to be a useful treatment option for patients with unresectable HCC without PVTT and in Child-Pugh class A.

LPD accumulation after the first transarterial infusion chemotherapy is an important prognostic factor. Careful consideration should be given on repeat infusion with CDDP/LPD to the possibility of anaphylactic shock.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide [1-4]. Recent advances in imaging and treatment modalities have resulted in a number of improvements in the prognosis of patients with HCC. Patients with small-size HCC, for example, are commonly treated by surgical resection and locoregional therapy such as percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT), laser photocoagulation and radiofrequency (RF) ablation, and the these treatments is often associated with satisfactory long-term prognosis [5-9]. However, these locoregional therapies are not suitable in all patients, mainly due to the presence of large tumor size, multiple HCC tumors, or a serious underlying chronic liver disorder.

Since the development of transcatheter arterial embolization for HCC [10-12], intraarterial treatments have been widely used for patients with unresectable HCC. Among these, transcatheter arterial chemoembolization (TACE) using anticancer drugs mixed with lipiodol (LPD) (Lipiodol Ultrafluide, Laboratoire Guerbet, Aulnay-Sous-Bois, France), which remains selectively in tumor tissue for extended periods of time, has now become one of the most effective treatment modalities for patients with unresectable HCC [13-27]. Randomized controlled trials recently confirmed the survival benefits of TACE in such patients [28,29].

Various anticancer drugs have been used as TACE agents in the treatment of HCC, including doxorubicin hydrochloride (ADM) [13-16], epirubicin hydrochloride [17], mitomycin C (MMC) [13,16], zinostatin stimalamer (SMANCS) [27] and cisplatin (cis-diaminedichloroplatinum; CDDP) [30-33]. However, the most effective of these anticancer drugs and protocols against HCC has yet to be identified. In particular, little or no information is available on the effects of TACE-CDDP/LPD on prognosis, or on the factor(s) predictive of a response.

Here, we conducted a retrospective study to determine the long-term prognosis of patients who received transarterial infusion chemotherapy with CDDP/LPD for unresectable HCC and identified factor(s) predictive of long-term prognosis.

MATERIALS AND METHODS

Patients

From June 2000 to December 2007, 526 patients with naïve HCC were admitted to our hospital. Of these, 323 patients were treated with transarterial infusion chemotherapy, 68 with surgical resection, 5 with living-donor liver transplantation (LDLT), 54 with RF ablation, 13 with PEI, 4 with RF ablation and PEI, 32 with hepatic arterial infusion chemotherapy (HAIC), 3 with systemic chemotherapy, and 24 with conservative therapy. Of the 323 patients treated with transarterial infusion chemotherapy, 91 were later treated with surgical resection, 41 with RF ablation, 35 with transarterial infusion chemotherapy combined with PEI, 7 with LDLT, 7 with radiotherapy, 32 with HAIC, and 3 with a combination of systemic chemotherapy, leaving 107 patients treated with transarterial infusion chemotherapy alone for enrollment in this retrospective cohort study. The study group consisted of 75 men and 32 women ranging in age from 42 to 92 years (median, 73 years). Tests were positive for hepatitis C virus in 82 patients (78.8%) and for hepatitis B virus in 7 patients (6.7%). Seventy-five patients were classified with Child-Pugh class A (72.1%) disease and 29 with Child class B disease (27.9%). Median total bilirubin level was 1.0 mg/dL, and median serum albumin was 3.6 g/dL. Tumor staging was defined based on the tumor-node-metastasis staging system of the Liver Cancer Study Group of Japan (LCSGJ): stage I (fulfilling three intrahepatic conditions: solitary, <2 cm, no vessel invasion, n=9 (9%)), stage II (two of the three intrahepatic conditions, n=41 (38%)), stage III (one of the three intrahepatic conditions, n=53 (50%)), stage IVa (none of the three intrahepatic conditions, with no distant metastases or any intrahepatic conditions with lymph node metastases), and stage IVb (any intrahepatic condition with distant metastases) (stage IV, n=4 (3%)) [34]. The median value of the maximum diameter of the main tumor was 30 mm (range, 6-130). Forty-three (40%) patients had a solitary tumor, 35 (33%) had 2-3 tumors and 29 (27%) had ≥ 4 tumors. The clinical characteristics of the study group are summarized in **Table 1**. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the ethics committee of our hospital, and written informed consent was obtained from all participating patients.

Preparation of chemotherapeutic agents

LPD was mixed at 1 ml per 10 mg CDDP powder. Because CDDP powder was not available for clinical use in Japan from June 2000 to December 2004, we prepared CDDP powder from a commercially available CDDP solution (Randa; Nippon Kayaku, Tokyo, Japan) as described in our previous study [35]. After it became available from December 2004 to December 2007, we mixed CDDP powder with LPD (IA-call; Nippon Kayaku).

The particle size of CDDP powder is 28.5µm.

Imaging and confirmation of diagnosis

Pretreatment imaging studies included abdominal ultrasonography (US), contrast-enhanced dynamic CT, dynamic magnetic resonance (MR) imaging, digital subtraction angiography (DSA), angiography combined with CT during arterial portography (CTAP) and hepatic arteriography (CTHA). All tumors were diagnosed by distinctive findings on US, dynamic CT and/or dynamic MR imaging, DSA, CTAP and CTHA. Diagnosis was confirmed by early enhancement in the arterial phase and hypoattenuation in the portal venous or equilibrium phase on contrast-enhanced dynamic CT or dynamic MR images, or by hypoattenuation on CTAP and hyperattenuation on CTHA. In addition, changes in serum tumor markers (α -fetoprotein [AFP] or des- γ -carboxy prothrombin) were used to support the imaging-based diagnosis.

Transarterial infusion chemotherapy with or without embolization

Transarterial infusion chemotherapy was performed through the femoral artery under local anesthesia using the technique of Seldinger. An angiographic catheter was inserted into the hepatic feeding artery of the segment or subsegments containing the target tumor under CT scan during hepatic arteriography and arterial portography. We used CDDP/LPD suspension as an anticancer drug. The tumor vessels were evaluated by CTHA scans during hepatic arteriography. Dosage was based on tumor size, and injection was discontinued based on the full accumulation of iodized oil in the tumor vessels and the degree of visualization of the portal vein during injection on fluoroscopy**.** The accumulation of iodized oil in the tumor were evaluated by CTHA scan; if accumulation in the tumor was poor, other vessels were tested, and when a vessel was identified as a feeding vessel, CDDP/LPD was add to the infusion. CDDP/LPD was not injected on the right hepatic artery, left hepatic artery or proper hepatic artery.

Gelatin sponge was used for embolization (Gelpart; Nippon Kayaku, Tokyo, Japan), cut into 1- or 2-mm^3 cubes depending on vascular diameter. Gelatin sponge was used after arterial infusion chemotherapy in patients who had a membrane-covered lesion and a segmental lesion in the periphery. Most patients were treated by arterial infusion chemotherapy in principle, but gelatin sponge was not used in all patients, particularly those with chronic liver failure. Gelatin sponge was not conducted on the right hepatic artery, left hepatic artery or proper hepatic artery. Angiographic endpoint of gelatin sponge embolization was very mild embolization. Extrahepatic collateral arteries which supplied tumors were also embolized.

The fluid replacement volume was 3000 ml/day on the day of treatment and 1000 ml/day for the next two days.

Criteria for evaluation of the therapeutic effect of transarterial infusion chemotherapy with or without embolization

The efficacy of transarterial infusion chemotherapy was evaluated by CT at 3 months after treatment, as follows: when LPD was seen in >90% of the tumor, efficacy was considered Grade I; in 50%to 90% of the tumor, Grade II; and in <50% of the tumor, Grade III [35]. Grading for lipiodol retention was based on quantitative measurement of tumor diameter in all tumors, based on the assumption that the tumor portion with retained LPD was necrotic tissue. The percentage of LPD accumulation in the target tumor was graded by two radiologists blinded to clinical status. Discrepancies between the two observers were resolved by adopting the lowest grade of assessment.

Follow-up Protocol

Concentrations of serum tumor markers, including AFP and des- γ -carboxy prothrombin, were measured once a month after transarterial infusion chemotherapy; follow-up US was performed every 3 months; and CT or MR imaging was performed every 6 months. Patients showing an increase in tumor markers, diminution of LPD accumulation, or new nodules remote from the treated nodules were readmitted for an additional round of transarterial infusion chemotherapy using the same procedure. On follow-up, patients treated with transarterial infusion chemotherapy who did not show complete uptake of LPD (i.e., those classified as Grade I), but did show the presence of a viable tumor, namely by arterial phase enhancement on CT/MR, were retreated with transarterial infusion chemotherapy within 3-6 months of the first treatment. Patients with tumor progression, appearance of PVTT and liver failure were excluded from TACE.

Complications

Major complications were defined in accordance with the definitions established by the Society of Interventional Radiology as hemorrhage requiring transfusion, liver abscess requiring percutaneous drainage, bile duct injury requiring biliary drainage, pleural effusion requiring thoracocentesis, hepatic failure, and death, (36). In all patients, the following laboratory tests were conducted before treatment and 1, 3, and 7 days, and 1 month after treatment: serum transaminases, bilirubin, alkaline phosphatase, albumin, creatinine, and complete blood cell count. Adverse reactions were assessed with the National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 3.0) [37].

Statistical Analysis

Data were collected and calculated at the end of the study and statistically analyzed on April 1, 2008. Cumulative survival rate was calculated from the initial date of transarterial infusion chemotherapy therapy and assessed by the Kaplan-Meier life-table method, with differences evaluated by the log rank test. Univariate analysis of predictors of survival was assessed by the Kaplan-Meier life-table method, and differences were evaluated by the log rank test. Multivariate analysis of predictors of survival was assessed by the Cox proportional hazards model. Statistical significance was defined as a *P* value less than 0.05. We also calculated hazard ratios and 95% confidence intervals (95%CI). All *P* values less than 0.05 on two-tailed tests were considered significant. Variables that achieved statistical (P <0.05) or marginal significance (P <0.10) on univariate analysis were entered into a multiple Cox proportional hazards model to identify significant independent factors. Parameters used for the prediction of survival were LPD accumulation, tumor number, PVTT (present or absence), Child-Pugh class, AFP, age, gender, etiology, transcatheter arterial embolization (TAE) (with or without) and tumor size. All analyses were performed with SPSS software (version 16, SPSS, Chicago, IL).

RESULTS

Therapeutic effects of transarterial infusion chemotherapy-CDDP/LPD

The median number of transarterial infusion chemotherapy procedures per patient was 2 (range, 1-9). The mean dose of CDDP per single session of transarterial infusion chemotherapy was 30 mg (range, 5.0-67.5), and the median total dose of CDDP per patient was 60 mg (range, 10-390). LPD accumulation was evaluated after first transarterial infusion chemotherapy: Grade I was recorded in 58 patients (55%), Grade II in 36 (33%), and Grade III in 13 (12%) (Table 2).

Survival rates

No significant difference in overall survival was seen between patients with and without embolization (P=0.20) (**Fig. 1**). Survival rate assessed as Grade I was 98% at 1 year, 60% at 3 years, and 22% at 5 years. Respective rates, in contrast, were 68%, 52%, and 22% in those assessed as Grade II, and 48%, 20%, and 0% in those assessed as Grade III (**Fig. 2**). The probability of survival correlated with the extent of LPD accumulation in Grades I and III ($P<0.05$). Representative examples of patients with grades I and II are shown in Figs. 3 and 4.

We then investigated the relationship between survival after the initiation of transarterial infusion chemotherapy and various clinicopathological variables by univariate analysis. Results showed that survival correlated significantly with Grade I ($P = 0.001$), absence of PVTT ($P <0.05$), and AFP <200 ng/mL ($P = 0.013$) (Table 3). Grade I, absence of PVTT, Child-Pugh class A, number of tumors =1 and AFP <200 ng/mL were then entered into the multiple Cox proportional hazard model, which identified Grade I (*P* = 0.001), absence of PVTT (*P* <0.001) and Child-Pugh class A as significant and independent determinants of survival (*P* = 0.012).

Adverse reactions and complications

The total number of transarterial infusion chemotherapy procedures was 274. The most common adverse reactions were fever, nausea, and loss of appetite. Among patients with various NCI-CTC.grade 2 adverse reactions, nausea and/or vomiting was the most common (96 patients, 35%), followed by grade 1 fever (71 patients, 26%), grade 3 thrombocytopenia (60, 22%), grade 2 abdominal pain (26, 9%), grade 2 liver dysfunction (26, 9%), grade 3 liver dysfunction (8, 3%), grade 3 renal dysfunction (2, 0.7%), grade 4 liver dysfunction (2, 0.7%), and anaphylactic shock (2, 0.7%). No intrahepatic biloma or liver abscess formation was seen. One patient received 9 courses of transarterial infusion chemotherapy, with a total dose of CDDP of 310 mg. On injection of 15 mg/1.5 ml of CDDP/LPD suspension into the catheter on the 9th transarterial infusion chemotherapy, the patient experienced a decrease in systolic blood pressure from 110 to 78 mmHg, and shortness of breath. He was successfully treated with oxygen and intravenous epinephrine and corticosteroid and was moved to the intensive care unit, but improved after 24 hours and was transferred back to the general ward. Another patient received 5 TACEs, with a total dose of CDDP of 95 mg. Injection of 20 mg/2 ml of CDDP/LPD suspension into the catheter on the 5th transarterial infusion chemotherapy resulted in anaphylactic shock, but this patient also subsequently improved within 24 hours.

Causes of death

Forty-five of the 107 patients died during the study period. Causes of death were HCC-related (rupture of HCC) in 23 (51%), hepatic failure in 8 (18%), rupture of esophageal varices in 3 (7%) and other diseases in 11 (24%). No immediate or procedure-related death was seen within 30 days of infusion.

DISCUSSION

The prognosis of patients with small HCC has improved markedly in recent years following the introduction of locoregional therapies. However, these therapies are not indicated in many patients due to large tumor size, multiple tumors and poor underlying liver status. TACE has been widely used for these patients. Although various anticancer agents have been used as TACE agents for unresectable HCC, including ADM, epirubicin hydrochloride, MMC, SMANCS and CDDP, the most effective anticancer drug for HCC remains to be defined. *In vitro* testing has indicated the efficacy of CDDP as suitable for TACE [38], but only a few reports have described the determinants of survival after initiation of TACE with CDDP/LPD suspension [39]. The purpose of the present study was to investigate the long-term prognosis of patients undergoing transarterial infusion chemotherapy with CDDP/LPD suspension for unresectable HCC and factors predictive of prognosis.

Overall survival rates in the 107 enrolled patients were 86% at 1 year, 40% at 3 years, 20% at 5 years, and 16% at 7 years. Ono et al [39] reported that survival rates of patients with unresectable HCC of 30% at 3 years with CDDP/LPD compared with 14% at 3 years with ADM. In other studies, survival rates at 3 years for unresectable HCC were 56% with ADM [40] and 32% with epirubicin hydrochloride [41]. Thus, the survival rate at 3 years achieved in the present study is closely similar to those reported for ADM and epirubicin hydrochloride. The determinants of survival in the present study were Grade I (>90% LPD accumulation in the first transarterial infusion chemotherapy), Child-Pugh grade A and the absence of PVTT; indeed, for patients with unresectable HCC free of PVTT who are rated as Child-Pugh grade A, comparatively excellent long-term prognosis is expected for those who show >90% LPD accumulation after the first transarterial infusion chemotherapy.

CDDP is a potent anticancer drug against HCC *in vitro*. Using the 3-(4,5-dimethyithiazol-2-yl)-2, 5-diphenyl-2H-tetrazolium bromide (MMT) assay, Furukawa et al [38] reported the *in vitro* chemosensitivity of HCC to seven anticancer drugs as follows: ADM 30%, CDDP 20%, MMC 17.5%, 5-fluorouracil 12.5%, methotrexate 5.4%, etoposide 0%, and CPT-11 0%, indicating that ADM and CDDP are the most effective anticancer drugs for HCC *in vitro*. In their study, however, Kamada et al [35] reported that survival rate for the CDDP/LPD group was significantly better than for the ADM/LPD group. Comparison of the effects and long-term prognosis for these anticancer drugs when used as TACE agents in randomized control trial studies is required.

Greater than 90% LPD accumulation after the first transarterial infusion chemotherapy was an independent determinant of survival. The proportion of patients who achieving this after the first transarterial infusion chemotherapy (55%) in the present study was higher than the 15% reported in our previous study [35]. This difference might be due to our present use of angiography combined with CT during arterial portography and hepatic arteriography, which provides better evaluation of drug accumulation in real time, and hence allows the addition of an additional dose or drug when needed. In addition to, CDDP/LPD was not injected on the right hepatic artery, left hepatic artery or proper hepatic artery.

It seems that grading LPD uptake serves instead to represent a method to assess underlying tumor biology. Favorable tumor biology manifests with tumor necrosis and a high degree of LPD uptake, such as the case shown in Figure 3 while unfavorable tumor biology results in lesser degrees of tumor necrosis and secondarily lower LPD uptake. It is doubtless that the effects of TACE mainly are affected by embolization with LPD and gelatin sponge. However, no significant difference in overall survival was seen between patients with and without embolization in our study.

Ikeda et al also reported that although TAE had a stronger antitumor effect than TAI, it did not significantly improve survival (42). In contrast, Yamamoto et al. reported that complete embolization after injection of cisplatin-lipiodol suspension resulted in higher survival than incomplete embolization [32]. We consider that gelatin sponge embolization was locally effective in the tumor, but because survival rates were also related to liver function, gelatin sponge embolization was not a significant prognostic factor in this study.

Although we used CDDP-lipiodol suspension in the present study, Takaki et al. recently reported that lipiodol retention was better with the emulsion than with the suspension (43). Evaluation of the best mixing method of cisplatin and lipiodol requires long-term investigation.

Analysis of adverse reactions and complications with transarterial infusion chemotherapy -CDDP/LPD showed minimal renal or liver dysfunction. This favorable finding may be due to selective infusion of the drug under CTAP and CTHA: because the injected area can be viewed directly under CTHA, the amount of injected drug that can cause damage to non-cancer tissue is minimal (44), and the mean dose of CDDP per single session of transarterial infusion chemotherapy was a relatively low 30 mg. Nevertheless, anaphylactic shock was observed in 2 (0.7%) patients. A recent review study reported five patients with gynecological malignancies who experienced anaphylaxis to CDDP after receiving previously uncomplicated courses of this agent, with the hypersensitivity reaction following a median of seven courses [45,46]. In our study, two patients experienced hypersensitivity at the 5th and 9th courses, respectively, suggesting the need for caution when administering platinum agents to patients previously treated with the agent. Monitoring during CDDP/LPD injection is therefore warranted, and injection should be stopped at the first sign of symptoms.

In conclusion, Transarterial infusion chemotherapy with CDDP/LPD appears to be a useful treatment option for patients with unresectable HCC without PVTT and in Child-Pugh class A. LPD accumulation after the first transarterial infusion chemotherapy is an important prognostic factor. Careful consideration should be given on repeat infusion with CDDP/LPD to the possibility of anaphylactic shock.

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Table 1. Characteristics of 107 patients who underwent repeated transarterial infusion chemotherapy using CDDP/LPD suspension for unresectable HCC.

Age (years)*	73 (42-92)
Gender (male/female)	75/32
Etiology (HCV/HBV /others)	82/7/18
Child-Pugh class (A/B/C)	75/29/3
T-bilirubin (mg/dl) *	1.0 (0.2-5.4)
Albumin (g/dl) *	3.6 (2.4-4.7)
Tumor stage (T1/2/3/4) [a]	9/41/53/4
Tumor size (mm) *	30 (6-130)
Tumor number 1/2-3/ >3	43/ 35/ 29
Tumor portal vein thrombus (present/absence)	3/104
α -Fetoprotein (ng/mL)*	32.2 (5-35 610)
Des- γ -carboxy prothrombin (mAU/mL)*	167 (10-1160 000)
TAE (with/without)	62/45
Period of follow-up (months) *	13 (1-92)

*Data are median and (range)

TAE: transcatheter arterial embolization

Table 2. Transarterial infusion chemotherapy with cisplatin lipiodol suspension.

Number of procedures*	2 (1-9)
Mean dose of CDDP per single session (mg) *	30 (5-67.5)
Total dose of CDDP per single case (mg) *	60 (10-390)
LPD accumulation of transarterial infusion chemotherapy (Grade I/II/III) (%)	55/33/12

*Data are median and (range)

Table 3. Univariate and multivariate analyses of predictors of survival.

	Univariate analysis (Log-rank test)	Multivariate analysis (Cox Proportional Hazard Model)		
Variable	P value	Hazard Ratio	95%CI	P value
Grade I	0.001	0.335	0.172-0.654	0.001
Absence of PVTT	0.050	0.052	0.012-0.218	<0.001
Child-Pugh class A	0.083	0.436	0.228-0.834	0.012
Number of tumors =1	0.095			
α-Fetoprotein <200	0.013			
Age <70	0.40			
Gender	0.80			
HBV/HCV/nonBnonC	0.33			
TAE (with/without)	0.20			
Tumor size <20mm	0.42			

PVTT: portal vein tumor thrombosis; TAE: transcatheter arterial embolization

FIGURE LEGENDS

Fig. 1. Cumulative survival curves of patients treated with TACE using CDDP/LPD suspension for unresectable HCC. Survival rates were 86% at 1 year, 40% at 3 years, 20% at 5 years, and 16% at 7 years.

Fig. 2. Cumulative survival curves according to the degree of LPD accumulation in the tumor. Survival rates of patients assessed as Grade I were 98% at 1 year, 60% at 3 years, and 22% at 5 years. By comparison, rates in patients assessed as Grade II were 68% at 1 year, 52% at 3 years, 22% at 5 years, and in those assessed as Grade III were 48% at 1 year, 20% at 3 years, and 0% at 5 years. Survival probability correlated with the degree of LPD accumulation between Grade I and Grade III ($P<0.05$).

Fig. 3. Imaging studies in an 88-year-old man treated for unresectable HCC with TACE conducted between April 2006 and April 2008. Gelatin sponge embolization was conducted. a) CTAP in April 2006. The HCC tumor (longest diameter 4 cm) in S7 showed hypoperfusion on CTAP. b) CTHA in April 2006 shows hyperenhancement of the same lesion. c) DSA in April 2006 showing the same lesion. d) CT taken 3 months after the first TACE. The lesion shows accumulation of LPD evaluated as Grade I. e) CT in April 2008 shows no recurrence 2 years later. Des-γ-carboxy prothrombin, a tumor marker, was decreased from 1100 to 0 mAU/mL. The patient remains alive and is cancer-free.

Figure 1, Kawaoka T et al

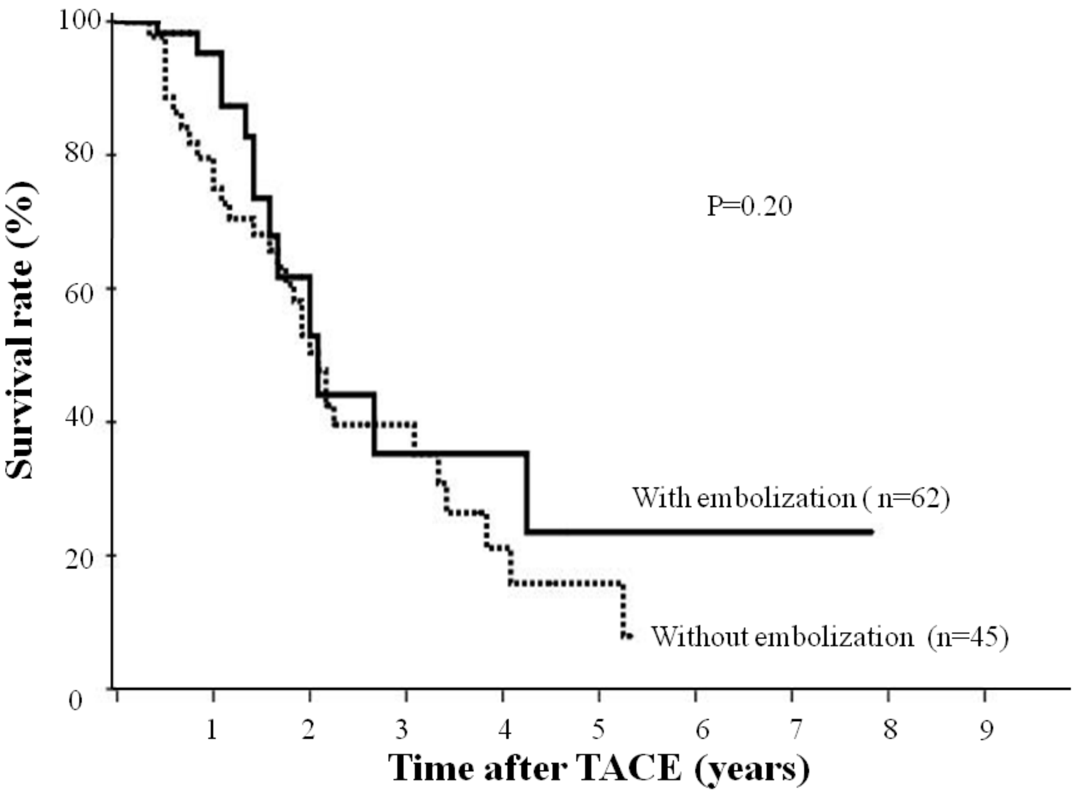
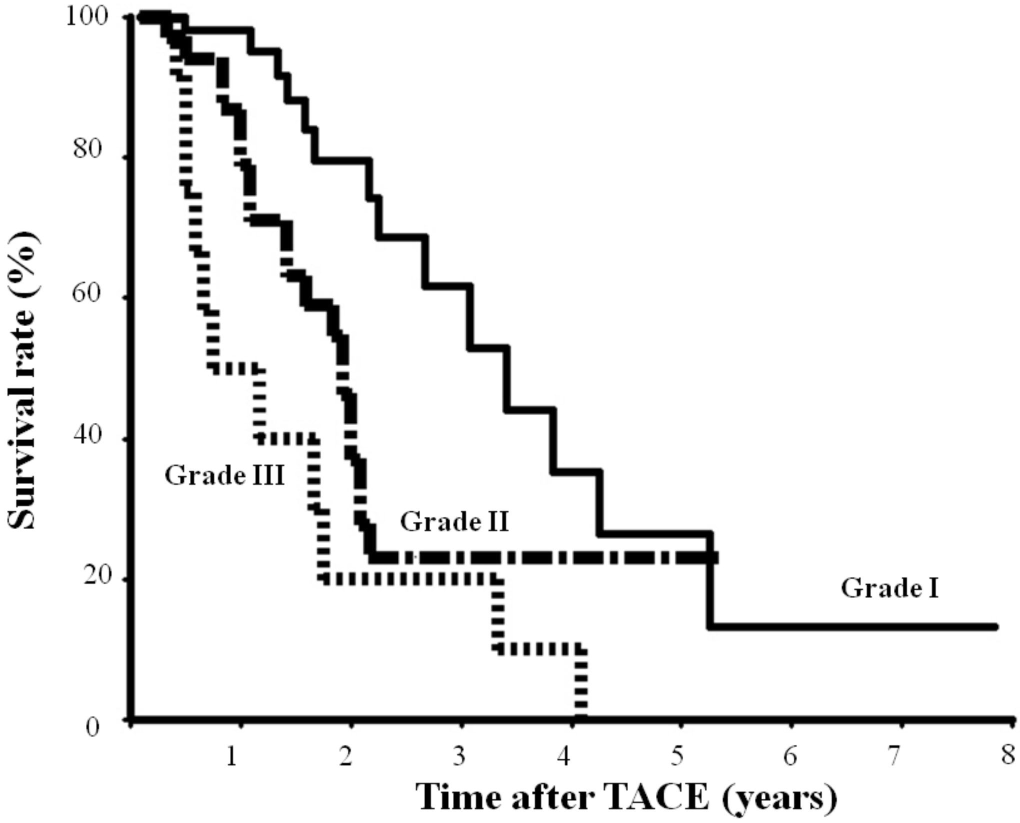


Figure 2, Kawaoka T et al



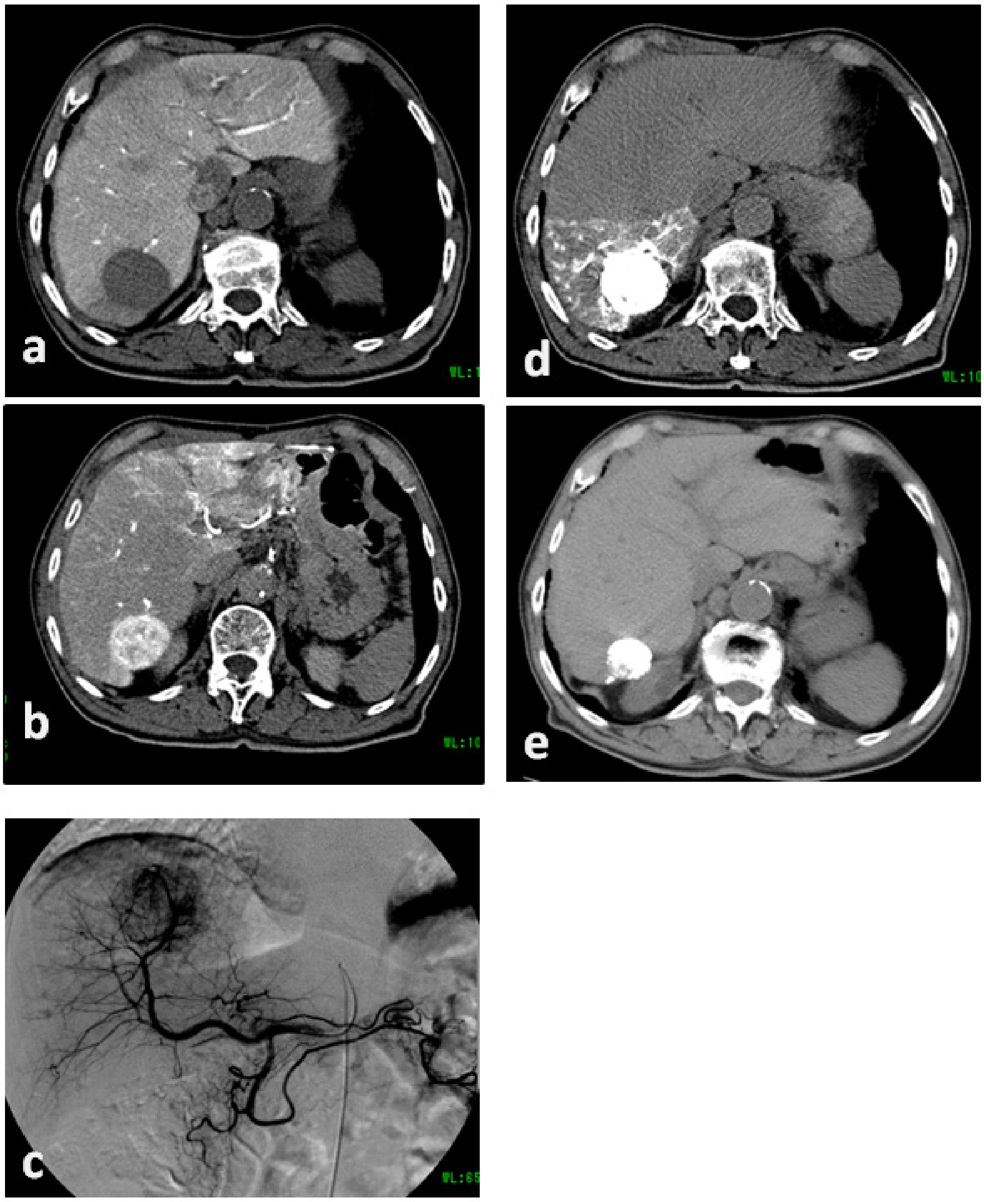


Figure 3, Kawaoka T et al