Multivariate Analysis of the Predictors of Survival for Patients with Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization: Focusing on Superselective Chemoembolization

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Objective: While the prognostic factors of survival for patients with hepatocellular carcinoma (HCC) who underwent transarterial chemoembolization (TACE) are well known, the clinical significance of performing selective TACE for HCC patients has not been clearly documented. We tried to analyze the potential factors of disease-free survival for these patients, including the performance of selective TACE.

Materials and Methods: A total of 151 patients with HCC who underwent TACE were retrospectively analyzed for their disease-free survival (a median follow-up of 23 months, range: 1-88 months). Univariate and multivariate analyses were performed for 20 potential factors by using the Cox proportional hazard model, including 19 baseline factors and one procedure-related factor (conventional versus selective TACE). The parameters that proved to be significant on the univariate analysis were subsequently tested with the multivariate model.

Results: Conventional or selective TACE was performed for 40 and 111 patients, respectively. Univariate and multivariate analyses revealed that tumor multiplicity, venous tumor thrombosis and selective TACE were the only three independent significant prognostic factors of disease-free survival (p = 0.002, 0.015 and 0.019, respectively).

Conclusion: In our study, selective TACE was a favorable prognostic factor for the disease-free survival of patients with HCC who underwent TACE.

Index terms:
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Surgical resection or transplantation has been considered as the gold standard for the treatment of hepatocellular carcinoma (HCC) in those patients who are good surgical candidates (1, 2). However, the surgical indications are usually very limited, and consequently transarterial chemoembolization (TACE) has been widely practiced for the treatments of patients with unresectable HCC (3–8). The additional survival benefit of TACE over conservative managements has been analyzed in many previous randomized studies (8–14). Furthermore, the potential prognostic factors affecting the survival of patients with HCC who undergo TACE have been analyzed in many previous studies (15–18). Since the 1990's selective TACE such as segmental or subsegmental TACE has been performed to achieve favorable clinical results with regards to local tumor progression and overall survival (19–24). However, as far as we know, the survival benefit of selective TACE compared to conventional TACE has not been clearly reported in the literature.

In this study, we evaluated potential prognostic factors of disease-free survival for

patients with HCC who underwent TACE, while we focused on the role of selective TACE.

MATERIALS AND METHODS

Patients Selection

The requirements for patients to enter the study were as follows: (a) adult patients with hepatic cirrhosis and HCC (b) a prothrombin time ratio (*i.e.*, the normal time divided by the patient's time) greater than 40%, (c) a platelet count higher than 40,000 per cubic millimeter (40×10^9 /L), (d) newly diagnosed patients with no previous treatment for the HCC, (e) the patient was ineligible for surgical resection or transplantation, (f) the patient agreed to undergo TACE.

From August 1, 1998 to July 15, 2006, a total of 151 consecutive patients with HCC who underwent TACE in our hospital met the inclusion criteria, and the medical records of the patients were retrospectively reviewed. All of the 151 patients were monitored from the time of diagnosis to the date of death or to the time of study closure, if they were still alive. The study was censored on July 15, 2007. All of the patients had a known 1-year or longer survival status. The median follow-up period was 23 months (range: 1–88 months). All but seven patients were male. Their age ranged from 44 to 82 years (mean ± SD [standard deviation]: 64.2 ± 8.5 years). The other characteristics are shown in Table 1. The Institutional Review Board (IRB) of our hospital approved this study.

The diagnosis of HCC was verified histologically by performing a percutaneous needle biopsy for 12 patients (7.9%). For the other patients, a diagnosis was established based on the characteristic radiological features on at least two imaging examinations. These examinations included ultrasound, contrast-enhanced dynamic computed tomography (CT), magnetic resonance imaging (MRI) and hepatic angiography (for the hypervascular tumors seen on two or more imaging modalities), or the use of a single imaging technique with positive findings for HCC and an associated serum α-fetoprotein level > 400 ng/mL (25). In the majority of patients, the etiology of the cirrhosis was chronic viral hepatitis B or hepatitis C (Table 1).

Chemoembolization Techniques

All patients had enhanced dynamic CT performed within four weeks prior to TACE. Informed consent was obtained for all of the patients before the procedure. All the TACE procedures were performed by two interventional radiologists with ten and six years of experience, respectively. Hepatic angiography was performed using 5 Fr angiographic catheters, followed by superselection of arterial feeders using a microcatheter (mainly Progreat™α; Terumo; Tokyo, Japan).

We administered an iodized oil-doxorubicin hydrochloride (Adriamycin; Kyowa Hakko Kogyo, Tokyo, Japan) emulsion into the feeders. The volume of the iodized oil ranged from 3 to 10 ml, and the amount of doxorubin ranged from 20 to 70 mg. Once the flow became sluggish, gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, MI) that were mixed with mitomycin-C (Kyowa Hakko Kogyo, Tokyo, Japan) and the contrast material were additionally administered into the feeders.

For selective TACE, chemoembolization was performed selectively as possible in the distal arteries that fed the

Table 1. Patient and Tumor Characteristics at Baseline

Characteristics		No.	%
Age	< 66 years	70	46.4%
	≥66 years	81	53.6%
Underlying causes	Hepatitis B	73	48.3%
	Hepatitis C	44	29.1%
	Hepatitis B and C	2	1.3%
	Others	32	21.2%
Performance score	0	89	58.9%
	1–2	62	41.1%
Platelet count ($\times 10^9$/L)	≥ 100,000	81	53.6%
	< 100,000	70	46.4%
Portal hypertension	No	84	55.6%
	Yes	67	44.4%
Presence of ascites	No	122	80.8%
	Yes	29	19.2%
Child-Pugh class	A	109	72.2%
	B	39	25.8%
	C	3	2.0%
Serum α–fetoprotein level	≤ 50 ng/mL	75	49.7%
	> 50 ng/mL	76	50.3%
Tumor number	Single	77	51.0%
	2–3	56	37.1%
	≥4	18	11.9%
Tumor maximal diameter	≤3 cm	78	51.7%
	3–5 cm	44	29.1%
	> 5 cm	29	19.2%
Tumor distribution	Unilobar	118	78.8%
	Bilobar	33	21.6%
Portal or hepatic vein thrombosis	No	138	91.4%
	Yes	13	8.6%
AJCC TNM staging	I	69	45.7%
	II	56	37.1%
	III / IV	26	17.2%

tumor (24). While performing selective TACE, attempts were made to completely occlude the arterial feeders. A small amount of saline solution was then injected slowly to confirm the complete occlusion of the segmental or subsegmental arterial feeder. If the retained contrast media was partially washed out after the saline injection, then additional gelatin sponge particles were infused until complete stasis of flow was achieved.

Conventional TACE was defined as TACE at the level of the right or left lobar hepatic artery or the proper hepatic artery. When catheterization of a segmental tumor feeder failed, then TACE was performed through the right or left hepatic arteries. Conventional TACE was performed more frequently when the tumors were supplied by multiple segmental arterial feeders.

For bilobar disease, we tried to treat all the tumors by selective TACE, if possible. If the patient's liver function was as poor as Child-Pugh class B or C, then only the larger tumors were selectively treated to preserve the liver function. When performing conventional TACE, occlusion of the arterial feeders was not intended, and only stasis of flow was obtained at the end of the procedure. This was done to minimize possible damage to the liver parenchyma.

Imaging Interpretation and Follow-up

The CT examinations were performed with an 8-slice multidetector CT scanner (Lightspeed; GE Medical Systems, Milwaukee, WI) with 5-mm collimation and 17.5 mm/sec table speed, or with a single-detector helical scanner (Prospeed Advantage; GE Medical Systems, Milwaukee, WI) with 10-mm collimation and a 10-mm/sec table speed. All the patients underwent both non-enhanced and contrast-enhanced three-phase helical CT one-month after their TACE. Two radiologists with twelve and seven years of experience, respectively, interpreted the CT and angiographic images independently, and the final decisions were reached by consensus.

A residual viable tumor was judged to be present when an enhanced portion was seen within or around the original tumor on a one-month follow-up CT scan. If no definite evidence of residual tumor was noted on this one-month follow-up CT, then 3-phase contrast-enhanced CT was performed at a 3- or 4-month interval thereafter. Local tumor progression was judged to be present when eccentric focal disappearance of the iodized oil from the lesion was seen, or an enhanced portion was seen within or at the margin of the original mass on the next follow-up CT scans after the first one-month follow-up CT scan (26, 27). Radiofrequency ablation was first considered for the recurred small tumor that was $\leq$ 3 cm in the maximal diameter, if the tumor was not located in a difficult location. Additional TACE procedures were performed for other tumors. Repeated procedures were based on the tumor response and the patient's tolerance, and were not performed at a fixed time interval.

Analysis of the Prognostic Factors for Disease-Free Survival and the Image Interpretation

Disease-free survival was calculated by considering any death or recurrence as an event (28). All the patients were followed up with a standard protocol of surveillance that included performing a contrast-enhanced dynamic CT scan at one month after TACE, followed by a liver function test, a test for the serum α-fetoprotein level, a dynamic CT scan and chest radiography every three months or when the serum α-fetoprotein level was significantly increased (29). When recurrence was indicated by any of these examinations, the patients underwent hepatic angiography.

The disease-free survival was the only end point of this study, and this was analyzed for 20 potential prognostic factors, including 14 baseline patient factors (the patient's age and gender, hepatitis B infection, hepatitis C infection, the presence of ascites, the serum aspartate aminotransferase [AST] level, the serum alanine aminotransferase [ALT] level, the serum albumin level, the total bilirubin level, the platelet count, the prothrombin time [INR ratio], the Child-Pugh class, the presence of portal hypertension and the performance status score), five baseline tumor factors (the serum α-fetoprotein level, the tumor location that was either unilobar or bilobar, multiplicity of the tumors, the maximal tumor diameter and portal or hepatic vein tumor thrombosis), and finally one procedure-related factor (conventional versus selective chemoembolization).

Portal hypertension was defined by the presence of either esophageal varices or splenomegaly with a platelet count < 100,000/ml (30). The performance status assessment followed the guidelines of the Eastern Cooperative Oncology Group (ECOG) (31). The number of tumors was determined from the pre-embolization CT. Tumor size was determined as the maximal diameter of the nodule that was measured on the pre-embolization CT. Vascular invasion was assessed by dynamic CT and hepatic angiography. Lymph node invasion and distant metastases were assessed via a routine screening study such as ultrasonography, dynamic CT and chest X-ray. Bone scintigraphy or a brain CT was performed if suggestive symptoms were present. Abdominal lymph nodes with the shortest diameter being 10 mm or greater were regarded as metastatic nodes.

Statistical Analysis

For the 20 potential prognostic factors of disease-free survival, univariate and multivariate analyses were performed by using the Cox proportional hazard regression model, respectively. The main focus of analysis was on the role of selective TACE. The parameters that proved to be significant on the univariate analysis were subsequently tested with the multivariate model. The backward stepwise selection (likelihood ratio) technique was used for the multivariate test. For the survival analysis, multivariate analysis was performed twice, with and without inclusion of the procedure-related factors. If any independently significant baseline prognostic factor was not dropped by the addition of a procedure-related factor, then the confounding between the baseline and procedure-related factors was regarded as insignificant. The existence of variance inflation was also checked. For continuous variables, the cut-off was set at the median values on the univariate and multivariate analyses, while giving consideration to the clinical context.

P-values less than 0.05 were considered statistically significant. The SPSS software package (version 10.0; SPSS Inc., Chicago, IL) was used for the statistical analysis.

RESULTS

Among the 20 potential prognostic factors affecting disease-free survival, univariate analysis revealed that the presence of ascites, a higher serum α-fetoprotein level (> 40 ng/mL), a bilobar tumor distribution, tumor multiplicity, the tumor size and venous tumor thrombosis were the only significant baseline prognostic factors (p = 0.046, 0.016, 0.006, 0.000, 0.022 and 0.001, respectively). In addition, selective TACE was a significant procedure-related factor on the univariate analysis (p = 0.000) (Table 2).

Multivariate analysis for the prognostic factors that affected disease-free survival on the univariate analysis revealed that tumor multiplicity, venous tumor thrombosis and selective chemoembolization were the only three independently significant prognostic factors of disease-free survival (p = 0.002, 0.015 and 0.019, respectively) (Table 3). The two independently significant baseline factors were the same irrespective of including selective TACE in the multivariate analysis, except for minute numerical changes. The variance inflation was also minimal for the three significant factors after the addition of selective TACE in the multivariate analysis.

Conventional or superelective TACE was performed in 40 and 111 patients, respectively. Superselective TACE could not be performed because of the tumor extent (28 patients) or the vascular anatomy (12 patients). Among the 40 patients who underwent conventional TACE, the 1-, 2-, 3-, 4- and 5-year overall survival rates were 79%, 50%,

Table 2. Univariate Analysis of Prognostic Factors Affecting Disease-Free Survival of Patients with Hepatocellular Carcinoma who Underwent Transarterial Chemoembolization

	Regression Coefficient	Standard Error	Odds Ratio (95% CI)	*P* value
Age (< 66 vs. ≥ 66 years)	0.187	0.172	1.205 (0.860–1.690)	0.279
Gender (female/male)	0.176	0.457	1.192 (0.486–2.922)	0.701
Performance status score (0/1-2)	0.347	0.179	1.415 (0.996–2.010)	0.052
Hepatitis B infection (no/yes)	0.052	0.173	1.053 (0.751–1.477)	0.763
Hepatitis C infection (no/yes)	–0.139	0.194	0.870 (0.596–1.271)	0.472
Serum AST level (≤40 vs. > 40 units/L)	0.223	0.178	1.250 (0.882–1.771)	0.210
Serum ALT level (≤40 vs. > 40 units/L)	0.076	0.173	1.079 (0.769–1.513)	0.661
Presence of ascites	0.373	0.187	1.453 (1.005–2.097)	0.046*
Serum albumin level (≥3.5 vs. < 3.5 g/dL)	0.325	0.178	1.384 (0.976–1.962)	0.068
Total bilirubin (≤1.0 vs. > 1.0 mg/dL)	0.063	0.174	1.065 (0.757–1.500)	0.717
Platelet count (≥100 vs. < 100 [$\times 10^9$/L])	–0.043	0.173	0.958 (0.682–1.344)	0.803
Portal hypertension (no/yes)	0.310	0.176	1.363 (0.966–1.925)	0.078
Prothrombin time ratio (INR ≤1.15 vs. > 1.15)	–0.031	0.175	0.970 (0.688–1.366)	0.861
Child-Pugh class (A/B/C)	0.267	0.175	1.306 (0.926–1.842)	0.128
Serum α-fetoprotein level (≤40 vs. > 40 ng/mL)	0.421	0.174	1.523 (1.083–2.142)	0.016*
Tumor location (unilobar/bilobar)	0.574	0.209	1.775 (1.177–2.675)	0.006*
Tumor multiplicity (single/multiple)	0.686	0.179	1.985 (1.397–2.820)	0.000*
Tumor size (≤ 3 cm vs. > 3 cm)	0.398	0.174	1.488 (1.059–2.093)	0.022*
Venous tumor invasion (no/yes)	1.104	0.312	3.016 (1.637–5.555)	0.000*
Selective chemoembolization (no/yes)	–0.698	0.197	0.498 (0.338–0.732)	0.000*

Note.— * statistically significant (p value < 0.05), CI = confidence interval

Table 3. Independent Significant Prognostic Factors Affecting Disease-Free Survival as Determined by Multivariate Analysis

	Multivariate Analysis for Disease-Free Survival			
	Regression Coefficient	Standard Error	Hazard Ratio (95% CI)	*P* value
Multiplicity of tumor	0.567	0.183	1.764 (1.232–2.525)	0.002*
Portal or hepatic vein tumor thrombosis	0.779	0.320	2.179 (1.163–4.081)	0.015*
Selective chemoembolization	−0.484	0.206	0.617 (0.412–0.923)	0.019*

Note.— * statistically significant (p value < 0.05)

36%, 28% and 21%, respectively. The median survival was 24 months. The number of TACE sessions ranged from 1 to 12 (average: 2.3 sessions). The 1-, 2- and 3-year disease-free survival rates were 24%, 9% and 3%, respectively. The 1-, 2- and 3-year disease-free survival rates for patients who underwent selective TACE were 30%, 12% and 4%, respectively (the median disease-free survival: 6 months). The 1-, 2- and 3-year disease-free survival rates for patients who underwent conventional TACE were 8%, 3% and 0%, respectively (the median disease-free survival: 2 months).

The initial one-month follow-up CT revealed complete loss of contrast enhancement of the tumors in 98 patients (65%). Local tumor progression occurred in 87 patients. New foci of tumor occurred in 73 patients. For the residual or recurred HCC tumors, we performed additional TACE for 60 patients, local ablative therapies for six patients and combined therapy of TACE and ablative therapies for 11 patients. Conservative management was done for the other patients. At the end of the study, 110 patients had expired. Among them, 72 patients died with recurrent HCC. There was no procedure-related mortality.

DISCUSSION

The survival benefit of TACE over conservative management has been analyzed in many previous randomized studies and review articles (8–14). However, to the best of our knowledge, there have been no randomized trials or controlled studies for determining the survival benefit of selective TACE over conventional TACE. While considering the additional cost and procedural time of segmental or subsegmental TACE, it would be necessary to evaluate whether selective TACE can induce an additional overall or disease-free survival benefit so as to compensate for the additional cost and time of performing this procedure.

We think that improved disease-free survival status can be expected by the potential merits of selective TACE as follows: (1) damage to the liver parenchyma can be restricted to the specific liver segments, and (2) the tumoricidal effect can be potentiated because the chemoembolic agents are focused into specific liver segments (21, 22). Despite these potential merits, it was not clear whether selective TACE could enhance the disease-free survival status of patients, when compared to conventional TACE. The beneficial effect of initial selective TACE might have been weakened by the high rate of intra-hepatic tumor recurrence, especially for patients with viral hepatitis-originated HCC (32). However, this study showed that selective TACE could improve the disease-free survival status of patients with inoperable HCC.

In this study, the significant baseline prognostic factors for disease-free survival were similar to the factors for tumor recurrence, as were determined by the previous studies on TACE (19, 20, 22). Further more in our study, the most powerful adverse prognostic factor of survival was portal or hepatic venous thrombosis, and similar results were found by previous studies on patients who were treated with liver resection or transplantation (33–35).

The limitations of this study are as follows. First, this was a retrospective analysis and not a randomized controlled trial. However, we did not perform a randomized controlled study between selective and conventional TACE because of the anticipated potential advantages of selective TACE. Although we did not perform a controlled study, the impact of selective TACE on patient survival was adjusted by the multivariate analysis. Second, the number of patients who underwent conventional TACE was relatively small when compared to those patients who underwent selective TACE. Third, the intrahepatic or extrahepatic tumor recurrence might have been underestimated. However, the main focus of this study was not to evaluate the tumor recurrence rate itself, but to evaluate the prognostic impact of procedure-related factors on the disease-free survival.

In conclusion, selective TACE could prolong the disease-free survival period of patients with inoperable HCC, as was shown by the multivariate analysis. A future larger scale controlled study between conventional TACE and selective TACE will be helpful to further evaluate this subject.

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References

1. Colella G, Bottelli R, De Carlis L, Sansalone CV, Rondinara GF, Alberti A, et al. Hepatocellular carcinoma: comparison between liver transplantation, resective surgery, ethanol injection, and chemoembolization. *Transpl Int* 1998;11:S193-S196
2. Segawa T, Izawa K, Tsunoda T, Kanematsu T, Shima M, Matsunaga N, et al. Evaluation of hepatectomy in small hepatocellular carcinoma: comparison with transcatheter arterial embolization therapy. *Nippon Geka Gakkai Zasshi* 1992;93:1095-1099
3. Nakamura H, Hashimoto T, Oi H, Sawada S. Transcatheter oil chemoembolization of hepatocellular carcinoma. *Radiology* 1989;170:783-786
4. Bronowicki JP, Vetter D, Dumas F, Boudjema K, Bader R, Weiss AM, et al. Transcatheter oily chemoembolization for hepatocellular carcinoma. A 4-year study of 127 French patients. *Cancer* 1994;74:16-24
5. Uchida H, Ohishi H, Matsuo N, Nishimine K, Ohue S, Nishimura Y, et al. Transcatheter hepatic segmental arterial embolization using lipiodol mixed with an anticancer drug and Gelfoam particles for hepatocellular carcinoma. *Cardiovasc Interv Radiol* 1990;13:140-145
6. Takayasu K, Suzuki M, Uesaka K, Muramatsu Y, Moriyama N, Yoshida T, et al. Hepatic artery embolization for inoperable hepatocellular carcinoma: prognosis and risk factors. *Cancer Chemother Pharmacol* 1989;23:S123-S125
7. Yamada R, Kishi K, Sonomura T, Tsuda M, Nomura S, Satoh M. Transcatheter arterial embolization in unresectable hepatoellular carcinoma. *Cardiovasc Interv Radiol* 1990;13:135-139
8. Pelletier G, Roche A, Ink O, Anciaux ML, Derhy S, Rougier P, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. *J Hepatol* 1990;11:181-184
9. Madden MV, Krige JE, Bailey S, Beningfield SJ, Geddes C, Werner ID, et al. Randomised trial of targeted chemotherapy with lipiodol and 5-epidoxorubicin compared with symptomatic treatment for hepatoma. *Gut* 1993;34:1598-1600
10. Bruix J, Llovet JM, Castells A, Montana X, Bur C, Ayuso MC, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. *Hepatology* 1998;27:1578-1583
11. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med* 1995;332:1256-1261
12. Pelletier G, Ducreux M, Gay F, Luboinski M, Hagege H, Dao T, et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. *J Hepatol* 1998;29:129-134
13. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. *Lancet* 2002;359:1734-1739
14. Lo CM, Ngan H, Tso WK, Lin CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164-1171
15. Lee HS, Kim KM, Yoon JH, Lee TR, Suh KS, Lee KU, et al. Therapeutic efficacy of transcatheter arterial chemoembolization as compared with hepatic resection in hepatocellular carcinoma patients with compensated liver function in a hepatitis B virus-endemic area: a prospective cohort study. *J Clin Oncol* 2002;20:4459-4465
16. Liem MS, Poon RT, Lo CM, Tso WK, Fan ST. Outcome of transarterial chemoembolization in patients with inoperable hepatocellular carcinoma eligible for radiofrequency ablation. *Word J Gastroenterol* 2005;11:4465-4471
17. O'Suilleabhain CB, Poon RT, Yong JL, Ooi GC, Tso WK, Fan ST. Factors predictive of 5-year survival after transarterial chemoembolization for inoperable hepatocellular carcinoma. *Br J Surg* 2003;90:325-331
18. Stefanini GF, Amorati P, Biselli M, Mucci F, Celi A, Arienti V, et al. Efficacy of transarterial targeted treatments on survival of patients with hepatocellular carcinoma. An Italian experience. *Cancer* 1995;75:2427-2434
19. Takayasu K, Muramatsu Y, Maeda T, Iwata R, Furukawa H, Muramatsu Y, et al. Targeted transarterial oily chemoembolization for small foci of hepatocellular carcinoma using a unified helical CT and angiography system: analysis of factors affecting local recurrence and survival rates. *AJR Am J Roentgenol* 2001;176:681-688
20. Maeda S, Fujiyama S, Tanaka M, Ashihara H, Hirata R, Tomita K. Survival and local recurrence rates of hepatocellular carcinoma patients treated by transarterial chemolipiodolization with and without embolization. *Hepatol Res* 2002;23:202-210
21. Matsui O, Kadoya M, Yoshikawa J, Gabata T, Tkashima T, Demachi H. Subsegmental transcatheter arterial embolization for small hepatocellular carcinomas: local therapeutic effect and 5-year survival rate. *Cancer Chemother Pharmacol* 1994;33:S84-S88
22. Nishimine K, Uchida H, Matsuo N, Sakaguchi H, Hirohashi S, Nishimura Y, et al. Segmental transarterial chemoembolization with Lipiodol mixed with anticancer drugs for nonresectable hepatocellular carcinoma: follow-up CT and therapeutic results. *Cancer Chemother Pharmacol* 1994;33:S60-S68
23. Matsui O, Kadoja M, Yoshikawa J, Gabata T, Takashima T, Demachi H. Small hepaocellular carcinoma: treatment with subsegmental arterial embolization. Radiology 1993;88:78-93
24. Iwamoto S, Sanefuji H, Okuda K. Angiographic subsegmentectomy for the treatment of patients with small hepatocellular carcinoma. *Cancer* 2003;97:1051-1056
25. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona 2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001;35:421-430
26. Jang KM, Choi D, Lim HK, Lim JH, Lee JY, Lee WJ, et al. Depiction of viable tumor in hepatocellular carcinoma treated with transarterial chemoembolization: multiphasic helical CT with review of the previous serial CT images. *Korean J Radiol* 2005;6:153-160
27. Goldberg SN, Grassi CJ, Cardellar JF, Charboneau JW, Dodd

GD 3rd, Dupuy DE, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria. *J Vasc Interv Radiol* 2005;16:765-778
28. Itamoto T, Nakahara H, Tashiro H, Ohdan H, Hino H, Ochi M, et al. Indications of partial hepatectomy for transplantable hepatocellular carcinoma with compensated cirrhosis. *Am J Surg* 2005;189:167-172
29. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg* 2002;235:373-382
30. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999;16:329-338
31. Sorensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An interobserver variability study. *Br J Cancer* 1993;67:773-775
32. Jang JW, Choi JY, Bae SH, Yoon SK, Woo HY, Chang UI, et al. The impact of hepatitis B viral load on recurrence after complete necrosis in patients with hepatocellular carcinoma who receive transarterial chemoembolization: implications for viral suppression to reduce the risk of cancer recurrence. *Cancer* 2007;110:1760-1767
33. Izumi R, Shimizu K, Ii T, Yagi M, Matsui O, Nonomura A, et al. Prognostic factors of hepatocellular carcinoma in patients undergoing hepatic resection. *Gastroenterology* 1994;106:720-727
34. Tsai TJ, Chau GY, Lui WY, Tsay SH, King KL, Loong CC, et al. Clinical significance of microscopic tumor venous invasion in patients with resectable hepatocellular carcinoma. *Surgery* 2000;127:603-608
35. Jonas S, Bechstein WO, Steinmüller T, Herrmann M, Radke C, Berg T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 2001;33:1080-1086