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BRIEF ARTICLE

Evaluation of transarterial chemoembolization combined with percutaneous ethanol ablation for large hepatocellular carcinoma

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Abstract

AIM: To assess the effects of combined transcatheter arterial chemoembolization (TACE) and percutaneous ethanol ablation (PEA) in patients with large hepatocellular carcinoma (HCC).

METHODS: A total of 63 patients with unresectable large HCC were treated with TACE followed by PEA. The largest dimension of the tumors ranged from 5.3 cm to 17.8 cm. The survival rates, acute effects, toxicity and prognostic factors were analyzed.

RESULTS: The cumulative survival rates at 1, 3 and 5 years were 59.4%, 28.4% and 15.8%, respectively (a median survival of 27.7 mo). Tumor area was reduced by more than 50% in 30 (47.6%) cases. In 56 cases with increased α-fetoprotein (AFP) values, AFP level was declined by more than 75%. The combined therapy was generally well tolerated. Only two patients died from variceal bleeding associated with the therapy. The Cox proportional hazards model showed that the number of tumors, the tumor margin and the ethanol dose were independent prognostic factors.

CONCLUSION: The combined TACE and PEA therapy is a promising approach for unresectable large HCC.

Key words: Hepatocellular carcinoma; Chemoembolization; Ethanol ablation; Combination therapy

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world, responsible for an estimated one million deaths annually. It has a poor prognosis due to its rapid infiltrating growth and complicating liver cirrhosis. Surgery is the only potential cure, but the resection rate for HCC is only 10%-30%. The remaining patients are subjected to various modes of non-surgical therapy. Transcatheter arterial chemoembolization (TACE) has become one of the most popular approaches of non-surgical treatment, being effective in reducing tumor size in HCC and improving survival[1-4]. However, tumor cells remain viable in and

around the capsule, which is supplied by both arterial and portal blood, and these cells are often responsible for later recurrence and spread[5-10]. Further treatment is needed to eradicate residual tumor cells. We used TACE combined with percutaneous ethanol ablation (PEA) to treat 63 patients with large HCC and retrospectively evaluated the effects of this combined therapy and the prognostic factors.

MATERIALS AND METHODS

Ethics

This study was approved ethically by the Sun Yat-Sen University Cancer Center. All patients provided informed written consent. This work was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association.

Patients

From November 2001 to January 2009, 63 consecutive patients with large unresectable HCC were enrolled to this study. In all the patients, the diagnosis of HCC was made based on the histologic or angiographic findings combined with serum α-fetoprotein (AFP) levels. In 41 (65.1%) patients, the diagnosis of HCC was confirmed by histologic examination. The remaining 22 patients were diagnosed according to the findings on ultrasound, CT and angiography, and serum AFP levels. The enrolling criteria were as follows: (1) lesions detectable on ultrasound and CT; (2) tumor/liver volume ratio not above 0.7:1; (3) serum transaminase level under 80 IU/L; and (4) no evidence of extrahepatic metastasis or ascites. Patients who had ascites, extrahepatic metastasis, severe cirrhosis (class C according to Child's classification), or Karnofsky performance score < 70 were excluded. The baseline characteristics of patients are shown in Table 1.

Table 1 Baseline data of the patients

Variables	Values
Mean age (yr)	57.2
Cases of HBV-related liver disease	61.0
Cases of HCV-related liver disease	0.0
Mean AST (U/L)	43.4
Mean ALT (U/L)	49.5
Mean total bilirubin (μmol/L)	26.2
Mean AFP (ng/mL)	963.9
Mean tumor size (cm)	8.3

HBV: Hepatitis B virus; HCV: Hepatitis C virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; AFP: α-fetoprotein.

Methods

TACE was performed in the following processes: a 5.0 French catheter (Terumo, Tokyo, Japan) was inserted into the femoral artery by the Seldinger's method. Celiac angiography and selective hepatic arterial angiography were routinely performed to observe the tumorous blood supply, distribution of hepatic arteries and collateral circulation routes. The tip of the catheter was placed at the feeding artery of the tumor, and embolization was performed using emulsionized mixture of lipiodol ultra-fluid (Guerbet, France), Perarubicin (50 mg/m^2) and DDP (80 mg/m^2). The maximum dose for the embolization depended on the size of the tumor, blood supply and hepatic function of the patient. When the tumor was filled well with emulsifier, the embolization ended.

After 1-2 times of TACE, PEA was performed using an ethanol solution (99% concentration, mixed with lipiodol, 9:1 volume ratio) slowly injected into the tumor through a 15-cm 21 gauge Chiba needle (Cook, Bloomington, IN) guided by CT scan. The size of needle, the amount of ethanol injected per procedure and the number of procedures for the entire treatment, were planned depending on the volume of the tumor and the extent of the transient high-density zones induced by ethanol diffusion on CT scans. The procedure was completed when the entire targeted tumor appeared with a high density. PEA was performed 2-5 times for each tumor. The amount of ethanol injected per procedure and per tumor was 3-20 mL (mean ± SD, 8.2 ± 3.4 mL) and per patient 5-40 mL (mean ± SD, 30.5 ± 6.6 mL).

The follow-up protocol after the initial combined therapy was planned according to the volume of the tumor, tumor blood supply and the extent of the high-density zones on CT scans. The standard TACE for a 8.0-10.0 cm HCC needs two steps (3 wk for each step) when a good tumor blood supply was displayed on enhanced CT scan, and the standard PEA protocol for a 5.0-6.0 cm HCC needs three steps (1.5 wk for each step) when tumor blood supply was obviously decreased on enhanced CT scan. The ethanol treatment was ended when the entire targeted tumor appeared with a high density.

The therapeutic efficacy was evaluated by CT scan two mo after the combined treatment.

Prognostic factors

Factors thought to influence survival were selected and classified to obtain survival rates using the Kaplan-Meier method. The significance of the differences was evaluated by the log-rank test with univariate analysis. The following prognostic factors were investigated: sex, age, number of lesions, tumor size, tumor extension, tumor margin (the tumor margin is the edge of the tumor, and the boundary between the tumor tissues and normal tissues was determined based on hepatobiliary phase images), AFP, portal thrombosis, ascites, Child grade, Okuda stage, times of TACE and PEA and the total ethanol dose. Variables with possible prognostic significance were selected, and each variable was divided into 2-4 classes (Table 2). Factors related to the survival rate were used as variables, and stepwise multivariate analysis was performed. Multiple regression analysis was performed using the Cox proportional-hazard model to calculate the relative-risk ratio between each factor and the survival rate.

RESULTS

Recent results, survival and prognostic factors

Tumor area was reduced by more than 50% in 30 (47.6%) cases. In 56 cases with increased AFP, AFP level was declined by more than 75%.

At the end of this study, 11 patients remained alive,

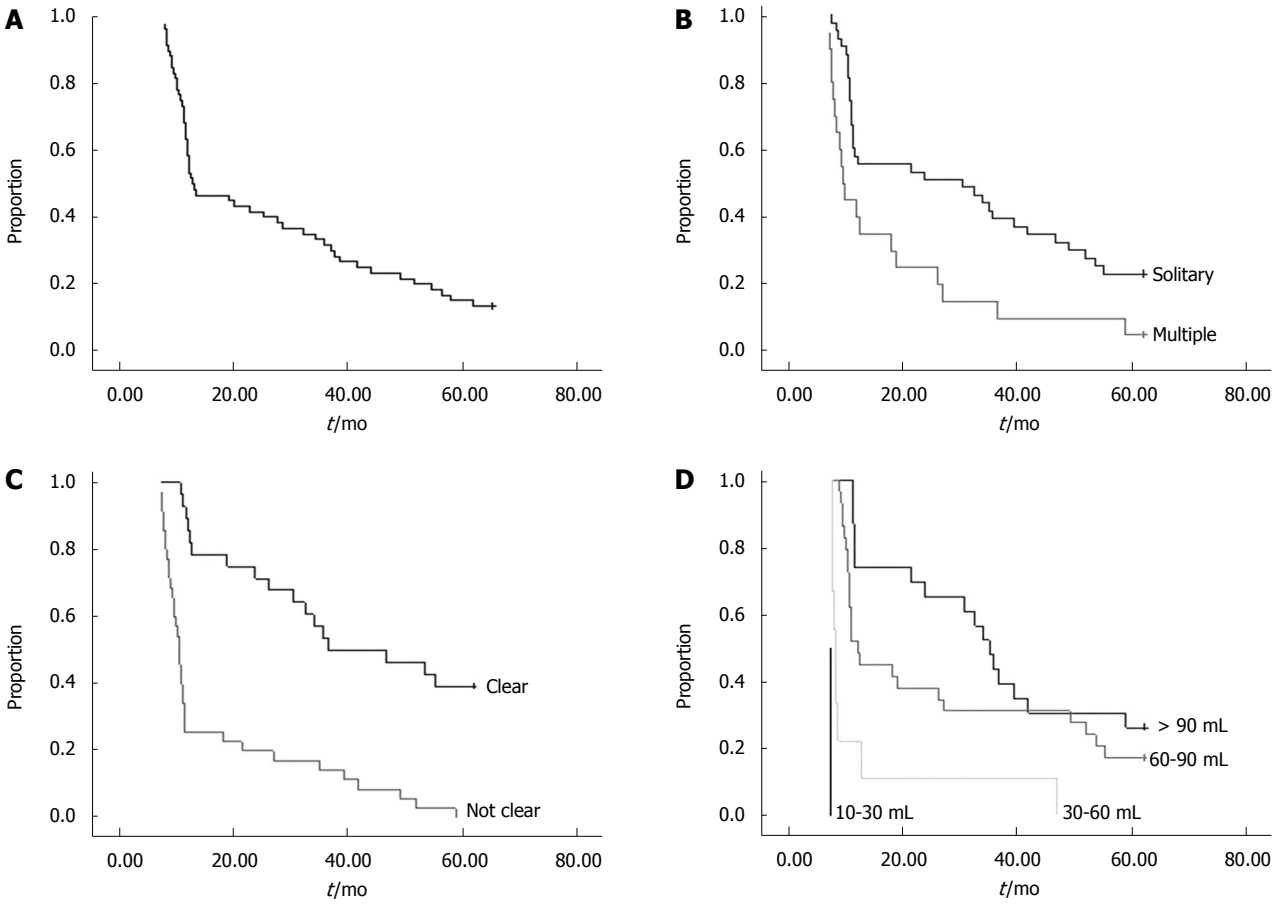

Figure 1 Overall cumulative survival curve and cumulative survival curves in patients based on the number of lesions, tumor margin and percutaneous ethanol ablation dose. A: Overall cumulative survival curve in 63 hepatocellular carcinoma (HCC) patients receiving combined therapy of transcatheter arterial chemoembolization (TACE) and percutaneous ethanol ablation (PEA); B: Cumulative survival curves in patients based on the number of lesions; C: Cumulative survival curves in patients based on the tumor margin; D: Cumulative survival curves in patients based on PEA dose.

Table 2 Variables and classes by univariate and multivariate analyses

Variables	Classes			
	A	B	C	D
Sex	M (52)	F (11)		
Age (yr)	< 55 (36)	> 55 (27)		
No. of lesions	Solitary (43)	Multiple (20)		
Tumor size (cm)	5-10 (41)	> 10 (22)		
Tumor extension	1 lobe (46)	2 lobe (17)		
Tumor margin	Clear (28)	Not clear (35)		
AFP	< 400 (22)	> 400 (41)		
Portal thrombosis	Absent (51)	Present (12)		
Ascites	Absent (56)	Present (7)		
Child grade	A (38)	B (25)		
Okuda stage	Ⅰ (29)	Ⅱ (34)		
TACE (number of times)	1 (11)	2 (26)	3 (20)	4 (6)
PEA (number of times)	1 (3)	2 (6)	3 (31)	> 4 (23)
Total ethanol dose	10-30 (2)	- 60 (9)	- 90 (29)	> 90 (23)

In the parenthesis are numbers of patients. AFP: α-fetoprotein; TACE: Transcatheter arterial chemoembolization; PEA: Percutaneous ethanol ablation.

and 52 patients had succumbed. The survival curve is shown in Figure 1A. Overall survival rates at one, three, and five years were 54.0%, 31.7% and 17.5%, respectively (median survival 27.7 mo).

Univariate analysis indicated that 11 factors significantly influence the survival. Sex, age and TACE times were not significant ($P > 0.05$), (Table 3).

The Cox proportional hazards model showed that only the number of tumors, tumor margin and the total ethanol dose were independent factors predicting survival (Table 4).

The overall survival rates at one, three and five years in the 43 patients with a solitary lesion were 58.1%, 39.5% and 23.3%, respectively, and were 45.0%, 15.0% and 5.0%, respectively in the 20 patients with multiple lesions. The mean survival of patients with a solitary lesion was significantly longer ($P = 0.0145$) than that of patients with multiple lesions (Figure 1B). In the patients with clear tumor margin ($n = 28$), the 1, 3, and 5-year survival rates were 89.3%, 53.6% and 39.3%, respectively, and these figures were significantly higher ($P = 0.0052$) than in the patients without clear tumor margin ($n = 35$), who had survival rates of 25.7% at one year, 14.3% at three years, and 0 at five years (Figure 1C). The mean 1-, 3- and 5-year survival rates were estimated to be 0%, 0% and 0%, respectively, in the 2 patients who received 10-30 mL total ethanol dose; 33.3%, 16.7% and 0% in the 9 patients who received 30-60 mL total ethanol dose; 51.7%, 31.0% and 16.1% in the 29 patients who received 60-90 mL total ethanol dose; and 73.9%, 43.5%, and 26.1% in the 23 patients who received

Table 3 Factors affecting survival by univariate analysis *n* (%)

Variables	Class	Survival			*P* value
		1 yr	3 yr	5 yr	
Sex	A	27 (51.9)	16 (30.8)	9 (17.3)	
	B	7 (63.6)	4 (36.4)	2 (18.2)	0.924[1]
Age (yr)	A	21 (58.3)	11 (30.6)	5 (13.9)	
	B	13 (48.1)	9 (33.3)	6 (22.2)	0.223[1]
No. of lesions	A	25 (58.1)	17 (39.5)	10 (23.3)	
	B	9 (45.0)	3 (15.0)	1 (5.0)	0.0145[1]
Tumor size	A	28 (68.3)	18 (43.9)	11 (26.8)	
	B	6 (27.3)	2 (9.1)	0 (0)	0.0041[1]
Tumor extension	A	29 (63.0)	18 (39.1)	11 (23.9)	
	B	5 (29.4)	2 (11.8)	0 (0)	0.0054[1]
Tumor margin	A	25 (89.3)	15 (53.6)	11 (39.3)	
	B	9 (25.7)	5 (14.3)	0 (0)	0.0052[1]
AFP	A	16 (72.7)	10 (45.5)	9 (40.9)	
	B	18 (43.9)	10 (24.4)	2 (4.9)	0.0030[1]
Portal thrombosis	A	31 (60.8)	18 (35.3)	11 (21.6)	
	B	3 (25.0)	2 (16.7)	0 (0)	0.0111[1]
Ascites	A	32 (57.1)	19 (33.9)	11 (19.6)	
	B	2 (28.6)	1 (14.3)	0 (0)	0.0115[1]
Child grade	A	28 (73.7)	17 (44.7)	11 (28.9)	
	B	6 (24.0)	3 (12.0)	0 (0)	0.0132[1]
Okuda stage	A	22 (75.9)	14 (48.3)	10 (34.5)	
	B	12 (35.3)	6 (17.6)	1 (2.9)	0.0150[1]
TACE (No. of times)	A	3 (27.2)	2 (18.2)	1 (9.1)	
	B	13 (50.0)	7 (26.9)	3 (11.5)	
	C	13 (65.0)	8 (40.0)	5 (25.0)	
	D	5 (83.3)	3 (50.0)	2 (33.3)	0.1719[2]
PEA (No. of times)	A	1 (33.3)	0 (0)	0 (0)	
	B	2 (33.3)	1 (16.7)	0 (0)	
	C	16 (48.5)	10 (32.3)	5 (16.1)	
	D	15 (65.2)	9 (39.1)	6 (26.1)	< 0.0001[2]
Total ethanol dose	A	0 (0)	0 (0)	0 (0)	
	B	2 (33.3)	1 (16.7)	0 (0)	
	C	15 (51.7)	9 (31.0)	5 (16.1)	
	D	17 (73.9)	10 (43.5)	6 (26.1)	< 0.0001[2]

[1]*P* value: B *vs* A; [2]*P* value: D *vs* A. AFP: α-fetoprotein; TACE: Transcatheter arterial chemoembolization; PEA: Percutaneous ethanol ablation.

Table 4 Significant factors predicting survival found using Cox proportional hazards model

Variables	Hazard ratio	*P* value
No. of lesions		
Multiple *vs* single solitary lesions	2.626	0.001
Tumor margin		
Not clear *vs* clear	2.439	0.000
Total ethanol dose		
30-60 mL *vs* 10-30 mL	0.386	0.000
60-90 mL *vs* 10-30 mL	0.202	0.000
> 90 mL *vs* 10-30 mL	0.116	0.000

over 90 mL total ethanol dose. Statistically significant difference was found between the high-dose group and low-dose group ($P < 0.0001$), (Figure 1D).

Side effects

Fever, abdominal pain, nausea and vomiting occurred in most of the patients after TACE and PEA. These symptoms were self-limiting in almost all the patients, lasting less than one week. A slight increase in serum bilirubin (37 cases), elevated serum transaminase level (59 cases), ascites (6 cases), leucopenia (15 cases) and thrombocytopenia (11 cases) were associated with the combined therapy. These side effects were transitory or easily controlled with medication in most of the patients. Two patients died of variceal bleeding because of the increased portal vein pressure caused by deterioration of liver cirrhosis after repeated TACE-PEA, which had an impact on liver function.

DISCUSSION

The rationale for combined therapy of TACE and PEA relies on the fact that after TACE, tumor blood supply is markedly decreased and intratumoral septa are usually destroyed as a result of the necrosis induced by the procedure. These histopathologic changes make subsequent PEA treatment easier as they can provide enhanced ethanol diffusion within the tumor. Consequently, treatment with PEA is facilitated by the TACE-derived fibrous wall around the lesion, which favors a better retention of the injected ethanol within the tumor[11-15]. Tanaka *et al*[14] first reported the effectiveness of TACE combined with PEA for large (> 3.0 cm in diameter) primary HCC compared with that of TACE alone. His study found that a partial

response of the tumor was seen in only 10% of the patients, and the 1-, 2-, and 3-year survival rates were 68%, 37% and 0%, respectively with TACE alone, and histologic examinations showed that TACE alone caused complete necrosis in only 20% of the tumors. In contrast, PEA combined with TACE significantly increased the partial response rate (45%), prolonged the 1-, 2-, and 3-year survival rates (100%, 85% and 85%), and achieved complete histologic necrosis in 83% of the tumors. Dohmen *et al*[15] proved that the combined TACE and PEA treatment had a lower incidence of local recurrence than TACE alone which resulted in an increased survival of the patients with unresectable large HCC.

Ethanol in PEA diffused within the cells, causing immediate dehydration of cytoplasmic proteins with consequent coagulation necrosis followed by fibrosis, and entered the circulation, inducing necrosis of endothelial cells and platelet aggregation with consequent thrombosis of small vessels followed by ischemia of the neoplastic tissues. Advantages of PEA were[16-18]: no remarkable damage to the remaining parenchyma, being safe, easy to be repeated when new lesions appear, low in cost, easy to operate, and possessing good long-term results. PEA can be carried out either in patients with HCC who have a poor liver function or in elderly patients (age $\geqslant$ 70 years)[19,20]. Our results proved that higher doses of ethanol can be injected, which can achieve complete and homogeneous perfusion even in large lesions.

It is necessary to analyze prognostic factors in a large number of patients in sufficient detail and to evaluate the result of each method of treatment between groups with similar prognostic factors. Our study showed that only the number of tumors, tumor margin and the total ethanol dose were independent factors predicting survival. Although various prognostic factors have been reported[21-23], no conclusion has been drawn as to which factor is significant. In this study, the significant factors for better prognosis included the number of tumors, tumor margin and the total ethanol dose. The prognostic factors identified in this study suggested that, therapeutic results in patients with solitary tumors and clear tumor margin treated at a higher total ethanol dose should be better than those in patients with multiple tumors, without clear tumor margin treated at a lower total ethanol dose. It is worth noting the tumor margin is one of the important prognostic factors. It is determined based on hepatobiliary phase images and represents the growth pattern of tumor to some extent. The tumor margin imaging can predict microscopic portal vein invasion, intrahepatic metastasis and early recurrence after hepatectomy in HCC patients[24].

Ebara *et al*[25] and Vilana *et al*[26] proposed tumors < 30 mm in size and < 3 in number as indications for PEA, mainly because of technical limitation such as the inability to inject an effective volume of ethanol into the whole area of the tumor. Our results suggested that some tumors > 50 mm in size could be treated by PEA because the therapeutic results of PEA were also good for large HCC patients with solitary tumors and clear tumor margin at a higher total ethanol dose after TACE.

Long-term survival rates of PEA-treated patients are similar to those obtained in matched patients undergoing partial hepatectomy[27,28]. However, the long-term prognosis remains disappointing because of the high recurrence rate among patients with HCC after PEA, especially in those with multiple lesions, cirrhosis and a high level of AFP and those without a clear tumor margin and peritumoral capsule[29,30]. In fact, histological examination of HCC after PEA reveals that residual tumor tissues remain in portions isolated by septa or with extracapsular or intracapsular invasion. It has been demonstrated that the high vascularity of HCC promotes an early wash-out of injected ethanol, so that PEA for patients with hypervascular tumors may be less effective than for patients with hypovascular tumors[31,32].

COMMENTS

Background

The incidence of large hepatocellular carcinoma (HCC) is increasing in China and HCC has a poor prognosis due to its rapid infiltration and complicating liver cirrhosis. The results in this study indicated that combined transcatheter arterial chemoembolization (TACE) with percutaneous ethanol ablation (PEA) is a promising therapeutic approach for large unresectable HCC.

Research frontiers

The authors analyzed the prognostic factors in a large number of patients in detail and evaluated the result of each method of treatment between groups with similar prognostic factors. This study showed that the number of tumors, tumor margin and the total ethanol dose were independent factors predicting survival.

Innovations and breakthroughs

This is the first study to report that the number of tumors, tumor margin and the total ethanol dose were independent factors predicting survival of large HCC. The combined TACE and PEA therapy is a promising approach for large unresectable HCC.

Applications

By understanding the independent prognostic factors, this study may represent a future strategy in the treatment of patients with large unresectable HCC.

Terminology

TACE has become one of the most popular approaches of non-surgical treatment, with good results in reducing the tumor size of HCC and improving the survival of the patients. PEA is facilitated by the TACE-derived fibrous wall around the lesion, which favors a better retention of the injected ethanol within the tumor.

Peer review

This is a constructive study to report that the number of tumors, tumor margin and the total ethanol dose were independent factors predicting survival of large HCC, which is expected to improve the therapeutic effects for large unresectable HCC.

REFERENCES

1 **Yamada R**, Kishi K, Sato M, Sonomura T, Nishida N, Tanaka K, Shioyama Y, Terada M, Kimura M. Transcatheter arterial chemoembolization (TACE) in the treatment of unresectable liver cancer. *World J Surg* 1995; **19**: 795-800

2 **Mondazzi L**, Bottelli R, Brambilla G, Rampoldi A, Rezakovic I, Zavaglia C, Alberti A, Ideo G. Transarterial oily chemoembolization for the treatment of hepatocellular carcinoma: a multivariate analysis of prognostic factors. *Hepatology* 1994; **19**: 1115-1123

3 **Hatanaka Y**, Yamashita Y, Takahashi M, Koga Y, Saito R, Nakashima K, Urata J, Miyao M. Unresectable hepatocellular carcinoma: analysis of prognostic factors in transcatheter management. *Radiology* 1995; **195**: 747-752

4 **Nishimine K**, Uchida H, Matsuo N, Sakaguchi H, Hirohashi S, Nishimura Y, Guo Q, Ohishi H, Nagano N, Yoshioka T. Segmental transarterial chemoembolization with Lipiodol mixed with anticancer drugs for nonresectable hepatocellular carcinoma: follow-up CT and therapeutic results. *Cancer Chemother Pharmacol* 1994; **33** Suppl: S60-S68
5 **Sakurai M**, Okamura J, Kuroda C. Transcatheter chemoembolization effective for treating hepatocellular carcinoma. A histopathologic study. *Cancer* 1984; **54**: 387-392
6 **Yu YQ**, Xu DB, Zhou XD, Lu JZ, Tang ZY, Mack P. Experience with liver resection after hepatic arterial chemoembolization for hepatocellular carcinoma. *Cancer* 1993; **71**: 62-65
7 **Nosaka T**. The relationship between hepatoma and portal vein. *Nippon Geka Gakkai Zasshi* 1994; **95**: 807-813
8 **Choi SH**, Chung JW, Lee HS. Hepatocellular carcinoma supplied by portal flow after repeated transcatheter arterial chemoembolization. *AJR Am J Roentgenol* 2003; **181**: 889-890
9 **Lee KH**, Sung KB, Lee DY, Park SJ, Kim KW, Yu JS. Transcatheter arterial chemoembolization for hepatocellular carcinoma: anatomic and hemodynamic considerations in the hepatic artery and portal vein. *Radiographics* 2002; **22**: 1077-1091
10 **Honda H**, Tajima T, Kajiyama K, Kuroiwa T, Yoshimitsu K, Irie H, Aibe H, Shimada M, Masuda K. Vascular changes in hepatocellular carcinoma: correlation of radiologic and pathologic findings. *AJR Am J Roentgenol* 1999; **173**: 1213-1217
11 **Dimitrakopoulou-Strauss A**, Strauss LG, Gutzler F, Irngartinger G, Kontaxakis G, Kim DK, Oberdorfer F, van Kaick G. Pharmacokinetic imaging of 11C ethanol with PET in eight patients with hepatocellular carcinomas who were scheduled for treatment with percutaneous ethanol injection. *Radiology* 1999; **211**: 681-686
12 **Kirchhoff T**, Chavan A, Galanski M. Transarterial chemoembolization and percutaneous ethanol injection therapy in patients with hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 1998; **10**: 907-909
13 **Lencioni R**, Cioni D, Donati F, Bartolozzi C. Combination of interventional therapies in hepatocellular carcinoma. *Hepatogastroenterology* 2001; **48**: 8-14
14 **Tanaka K**, Nakamura S, Numata K, Okazaki H, Endo O, Inoue S, Takamura Y, Sugiyama M, Ohaki Y. Hepatocellular carcinoma: treatment with percutaneous ethanol injection and transcatheter arterial embolization. *Radiology* 1992; **185**: 457-460
15 **Dohmen K**, Shirahama M, Shigematsu H, Miyamoto Y, Torii Y, Irie K, Ishibashi H. Transcatheter arterial chemoembolization therapy combined with percutaneous ethanol injection for unresectable large hepatocellular carcinoma: an evaluation of the local therapeutic effect and survival rate. *Hepatogastroenterology* 2001; **48**: 1409-1415
16 **Livraghi T**. Role of percutaneous ethanol injection in the treatment of hepatocellular carcinoma. *Dig Dis* 2001; **19**: 292-300
17 **Livraghi T**. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis. *Hepatogastroenterology* 2001; **48**: 20-24
18 **Allgaier HP**, Deibert P, Olschewski M, Spamer C, Blum U, Gerok W, Blum HE. Survival benefit of patients with inoperable hepatocellular carcinoma treated by a combination of transarterial chemoembolization and percutaneous ethanol injection-a single-center analysis including 132 patients. *Int J Cancer* 1998; **79**: 601-605
19 **Koda M**, Murawaki Y, Mitsuda A, Ohyama K, Horie Y, Suou T, Kawasaki H, Ikawa S. Predictive factors for intrahepatic recurrence after percutaneous ethanol injection therapy for small hepatocellular carcinoma. *Cancer* 2000; **88**: 529-537
20 **Teratani T**, Ishikawa T, Shiratori Y, Shiina S, Yoshida H, Imamura M, Obi S, Sato S, Hamamura K, Omata M. Hepatocellular carcinoma in elderly patients: beneficial therapeutic efficacy using percutaneous ethanol injection therapy. *Cancer* 2002; **95**: 816-823
21 **Okuda K**, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, Nakajima Y, Ohnishi K. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985; **56**: 918-928
22 **Calvet X**, Bruix J, Gines P, Bru C, Sole M, Vilana R, Rodes J. Prognostic factors of hepatocellular carcinoma in the west: a multivariate analysis in 206 patients. *Hepatology* 1990; **12**: 753-760
23 **Rosellini SR**, Arienti V, Nanni O, Ugenti F, Tassinari M, Camporesi C, Boriani L, Versari G, Costa PL, Amadori D. Hepatocellular carcinoma. Prognostic factors and survival analysis in 135 Italian patients. *J Hepatol* 1992; **16**: 66-72
24 **Ariizumi SI**, Kitagawa K, Kotera Y, Takahashi Y, Katagiri S, Kuwatsuru R, Yamamoto M. A non-smooth tumor margin in the hepatobiliary phase of gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced magnetic resonance imaging predicts microscopic portal vein invasion, intrahepatic metastasis, and early recurrence after hepatectomy in patients with hepatocellular carcinoma. *J Hepatobiliary Pancreat Sci* 2011; Epub ahead of print
25 **Ebara M**, Ohto M, Sugiura N, Kita K, Yoshikawa M, Okuda K, Kondo F, Kondo Y. Percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. Study of 95 patients. *J Gastroenterol Hepatol* 1990; **5**: 616-626
26 **Vilana R**, Bruix J, Bru C, Asyuso C, Sole M, Rodes J. Tumor size determines the efficacy of percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. *Hepatology* 1992; **16**: 353-357
27 **Huo TI**, Huang YH, Wu JC, Lee PC, Chang FY, Lee SD. Survival benefit of cirrhotic patients with hepatocellular carcinoma treated by percutaneous ethanol injection as a salvage therapy. *Scand J Gastroenterol* 2002; **37**: 350-355
28 **Koda M**, Murawaki Y, Mitsuda A, Ohyama K, Horie Y, Suou T, Kawasaki H, Ikawa S. Predictive factors for intrahepatic recurrence after percutaneous ethanol injection therapy for small hepatocellular carcinoma. *Cancer* 2000; **88**: 529-537
29 **Ishii H**, Okada S, Nose H, Okusaka T, Yoshimori M, Takayama T, Kosuge T, Yamasaki S, Sakamoto M, Hirohashi S. Local recurrence of hepatocellular carcinoma after percutaneous ethanol injection. *Cancer* 1996; **77**: 1792-1796
30 **Teratani T**, Ishikawa T, Shiratori Y, Shiina S, Yoshida H, Imamura M, Obi S, Sato S, Hamamura K, Omata M. Hepatocellular carcinoma in elderly patients: beneficial therapeutic efficacy using percutaneous ethanol injection therapy. *Cancer* 2002; **95**: 816-823
31 **Dimitrakopoulou-Strauss A**, Strauss LG, Gutzler F, Irngartinger G, Kontaxakis G, Kim DK, Oberdorfer F, van Kaick G. Pharmacokinetic imaging of 11C ethanol with PET in eight patients with hepatocellular carcinomas who were scheduled for treatment with percutaneous ethanol injection. *Radiology* 1999; **211**: 681-686
32 **Tanaka K**, Nakamura S, Numata K, Kondo M, Morita K, Kitamura T, Saito S, Kiba T, Okazaki H, Sekihara H. The long term efficacy of combined transcatheter arterial embolization and percutaneous ethanol injection in the treatment of patients with large hepatocellular carcinoma and cirrhosis. *Cancer* 1998; **82**: 78-85

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