RESEARCH ARTICLE

Transarterial Chemoembolization Monotherapy in Combination with Radiofrequency Ablation or Percutaneous Ethanol Injection for Hepatocellular Carcinoma

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Abstract

Purpose: To evaluate whether combined transarterial chemoembolization (TACE) with radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI) for hepatocellular carcinoma (HCC) have superior efficacy to transarterial chemoembolization (TACE) alone a retrospective review was conducted. Methods: During January 2009 to March 2013, 108 patients with hepatocellular carcinoma underwent TACE or combined therapies (TACE+RFA or TACE+PEI). The long-term survival rates were evaluated in those patients by various statistical analyses. Results: The cumulative survival rates in the combined TACE+RFA/PEI group were significantly superior to those in the TACE alone group. When the comparison among the groups was restricted to patients with two or three tumors fulfilling the Milan criteria, significantly greater prolongation of survival was observed in the combined TACE+ RFA/PEI group than in the RFA/PEI alone group. Conclusions: In terms of the effect on the survival period, combined TACE+ RFA/PEI therapy was more effective than TACE monotherapy, and also more effective than PEI or RFA monotherapy in cases with multiple tumors.

Keywords: HCC - radiofrequenc ablation - percutaneous ethanol injection - transarterial chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third most common cause of cancer-related death (Benson et al., 2009). Hepatic resection is still to get the possibility of cure for patients with HCC, but majority of patients diagnosed with HCC have loose surgery opportunity (Hsu et al., 2011). Radiofrequency ablation (RFA), percutaneous ethanol injection (PEI) and transarterial chemoembolization (TACE) have been considered to be effective treatment modalities for most patients of HCC (Golfieri et al., 2013; Xu et al., 2014a; 2014b; 2104c; 2014d; 2015a; 2015b; 2015c). Ultrasound guided RFA and PEI have been shown to be highly HCCs and multiple HCCs exceeding the Milan criteria (MC) have been widely treated by TACE, using chemotherapeutic agents such as cisplatin or epirubicin mixed with lipiodol and emboli cagents such as gelatin-spongeparticles.

In this paper, we report results of our retrospective review conducted to evaluate the superiority, in terms of the survival rate and survival prolongation, of combined TACE+ RFA/PEI over TACE alone in the treatment of HCC.

Materials and Methods

Patients

The study include 108 consecutive patients diagnosed with HCC, based on the pathological or typical imaging findings, between 2009 and 2013. The following eligibility criteria were employed: (1) previously untreated patients, and (2) no history of previous surgical treatments such as hepatic resection or liver transplantation. Patients were not included if they fulfilled one or more of the following criteria: poor hepatic function (Child-Pugh class C, especially presence of poorly controlled hepatic encephalopathy or ascites); presence of extra-hepatic metastasis; vascular contraindications to chemoembolization (hepatic artery thrombosis, main portal vein thrombosis, arteriovenous shunting); poor performance status. In patients with multiple nodules (not more than three) having a diameter of less than 3cm each, we performed ultrasound (US) examination. If we

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Table 1. Patient Characteristics according to the Therapeutic Group

	TACE	RFA/PEI	Combined therapy
Patients	41	29	38
Age	67.3±7.6	65.3±9.3	66.3±8.2
Sex			
Male/Female	23/18	15/14	21/17
Albumin(g/L)	37.3±0.6	35.4±0.5	36.1±0.5
Total bilirubin(g/L)	11.3±0.7	9.3±0.9	10.1±1.1
AST(U/l)	72±31	67±29	78±39
ALT(U/l)	61±37	59±26	64±33
Child-Pugh(n)			
A/B	21/20	13/16	17/21
Number of tumor (s)(n)			
Solitary/2 or 3/>3	15/19/7	16/11/2	18/16/4
Clinical stage(n)			
I/II/III/IVA	13/14/11/3	10/14/5/0	13/14/5/4

Table 2. Causes of Death in This Study

N	Total	TACE	RFA/PEI	Combined therapy
Cancer death	46	21	13	7
hepatic failure	19	9	6	4
rupture of esophageal-gastric varices	5	3	2	0
bacterial infection	3	2	1	0
extra-hepaticmetastasis	8	3	2	3
other disease	6	2	3	1

could detect all the lesions by US, we performed RFA or PEI alone. If not, or in patients with more than three nodules, we performed TACE alone. Combined therapy was administered in the following patients: (1) patients with nodules fulfilling the MC, but in whom some of the HCC lesions could not be detected by US; (2) patients with a single lesion measuring more than 3cm in diameter; 3) patients with a large main lesion with small intra-hepatic metastasis and more than three lesions. Out of the 108 patients, 41were treated by TACE alone, 29 were treated by PEI or RFA alone (RFA/PEI group), and the remaining 38 received both TACE and PEI or RFA (combined TACE+ RFA/PEI group). All patients provided written, informed consent for the procedure, and our institutional review board approved the retrospective review of the patients' medical and imaging records.

Therapeutic Procedures

TACE was performed by selectively introducing a catheter into the hepatic artery. An emulsion consisting 2–10mL of iodized oil and 0.5mg/kg body weight of epirubicin was injected slowly underfluo-roscopic monitoring. Embolization was performed with gelatin-sponge particles.

RFA was performed under real-time US guidance. After local anesthesia, the active electrode needle tip was introduced into the tumor center, and thermal ablation of the tumor was conducted at 100°C for at least 5 min.

PEI was performed under real-time US guidance. After local anesthesia, a 21 gauge needle was inserted into the lesion. The entire amount of absolute ethanol was injected through the needle. The PEI was repeated twice a month for 2–6 sessions, until the tumor was replaced by an avascular area on dynamic computed tomography (CT).

Combined TACE+ RFA/PEI consisted of additional RFA or PEI performed 7-10 days after TACE. The cases with multiple HCCs, we underwent RFA or PEI for their three main tumors.

Table 3. Comparison of the Survival Rate Following Group 1 and Group 2

	Patients	Survival rate(%)			*P* value
	1 year	2 years	5 years		
Group 1					
TACE alone	41	80.5	26.8	2.4	0.0035
Combined therapy	38	86.8	55.3	15.4	
Group 2					
RFA/PEI alone	29	86.2	48.3	8.2	0.734
Combined therapy	38	86.8	55.3	15.4	

Statistical Analysis

Statistical analysis was conducted using the Stata 10.0. Group comparison was performed by the chi-square test for independent variables or Fisher's exact test for comparison of more than two independent groups. The survival rate and survival duration from the time of diagnosis of HCC to the time of death in each group was assessed by the Kaplan–Meier method and log-rank test. *P* values<0.05 were considered to denote significance in all the significance tests.

Results

108 patients enrolled in this retrospective study were classified into three groups; TACE alone group (n=41), RFA or PEI alone group (n=29), and combined therapy group (TACE+RFA/PEI; n=38), according to the primary therapy employed. The patient characteristics in relation to the HCC were more favorable in the RFA/PEI alone group than in the other groups (Table1). By the end of the analysis period (median follow-up time, 24.6 months [range, 1–58months]), 87 patients had died of the cancer (46 patients, 52.9%), hepatic failure (19 patients, 19.5%), rupture of esophageal-gastric varices (5 patients, 5.7%), bacterial infection (3 patients, 3.4%), extra-hepaticmetastasis (8 patients, 9.2%), or other disease (6 patients, 6.9%) (Table2).

Survival

TACE alone vs. combined therapy: The presence of a tumor not exceeding 5cm in diameter in patients with a single HCC tumor, or the presence of no more than three tumor nodules, none exceeding 3cm in diameter in patients with multiple tumors. The TACE alone group included 41 patients and the combined therapy group included 38 patients who exceeded MC. Combined therapy was significantly superior to TACE alone for this group in terms of both the MST (32.8 months [range, 3-58 months] vs. 21.3months [range, 2-43months]; *P*=0.0035) and the cumulative survival rate (97.3%, 86.8%, 55.3% and 15.4%

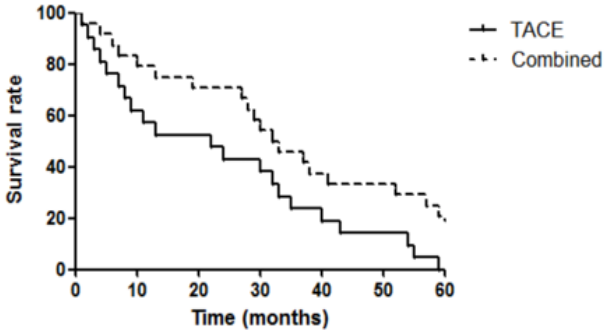

Figure 1. Survival Curves for Transarterial Chemoembolization (TACE) Alone vs. Combined Therapy

vs. 95.1%, 80.5%, 26.8% and 2.4% at 6months, 1year, 2years and 5years, respectively; *P*=0.0035; Table 3).

RFA/PEI alone vs. combined therapy: There was no significant difference, overall, in the MST between the combined therapy group (32.8 months [range, 3-58months]) and the RFA/PEI alone group (29.1 months [range, 2-52 months]; *P*=0.081). Further, there were no significant differences in the cumulative survival rates, overall, between the combine dgroup and the RFA/PEI alone group (97.3%, 86.8%, 55.3% and 15.4% in the combined therapy group vs.100%, 86.2%, 48.3% and 8.2% in the PEI/RFA alone group at 6 months, 1year, 2 years and 5 years, respectively; *P*=0.734; Table 3).

Complications

We investigated the side effects of each therapy and the influence of each on deterioration of the hepatic function. Hemoperitoneum and seeding of the needle tract were found as the major complications in the RFA/PEI group. Acute cholecystitis and hepatic failure due to obstruction of the proper hepatic artery were observed in each patient of the TACE alone group. Biloma, hemoperitoneum and hepatic failure were brought about each one patient in combined therapy.

Discussion

Hepatic resection or liver transplantation can only be offered to a minor proportion of patients because of the poorly liver function and limited availability of living donors (Chinnet al., 2001). Therefore, various treatments have been developed in an attempt to destroy unresectable HCCs in situ, such as TACE, RFA and PEI (Yang et al., 2012). We believe that all of these treatments have some adverse effects on the liver function. Thus, we conducted this study to evaluate the usefulness of these treatments in HCC patients (Cho et al., 2010). This study was not a randomized controlled study, but the characteristics of the patients were similar to those in such a study. TACE is one of the most commonly employed therapies in patients with unresectable HCC.

We considered that it would be important clearly delineate the usefulness of TACE, RFA or PEI used alone or incombination. In regard to TACE, it is often difficult to achieve complete necrosis of the target tumor by TACE alone, because HCC often shows intracapsular or extracapsular invasion and viable tumor cells remain after TACE (Germani et al., 2010). Therefore, TACE needs to be repeated to achieve better result, however, the modality still does not yield sufficient control of the growth of HCC when it is used alone. This perhaps explains why the main cause of death in the TACE alone group was the cancer itself, just as that in the palliative treatment group in our study. On the other hand, while the causes of death were similar in the RFA/PEI alone group and the combined therapy group, the number of cancer deaths were smaller in these groups as compared with that in the TACE alone group (Llovetet al., 1999).

Recently, RFA and PEI have been shown to be highly effective in patients with small HCC tumors (Yau et al., 2014). RFA, thermal ablation mainly causes coagulation necrosis inside and also a little in the surrounding region of the tumor. In PEI, the injection of absolute alcohol into the tumor causes cellular dehydration, coagulation necrosis, and vascular thrombosis within the HCC (Bruix et al., 2001). While complete necrosis of the target HCC can be obtained in most patients with small HCC tumors treated by RFA or PEI alone, a similar result can be obtained in only about 40% of the patients treated by TACE alone (Riaz et al., 2010). However, several factors limit the effect of both RFA and PEI, such as tumor consistency, tumor vascul arization, and tumor size. Therefore, RFA and PEI are generally indicated for tumors fulfilling the MC, defined as the presence of a tumor not exceeding 5 cm in diameter in patients with a single HCC or presence of not more than three tumor nodules, with none exceeding 3cm in diameter. Recently, some studies have revealed significantly superior survival in patients receiving combined therapy with more than one interventional modality than in patients treated by one modality alone (Burrelet al., 2012; Liapi et al., 2011).

The purpose applying several modalities in combination is to achieve improved outcomes in patients with HCC. The rationale for combining TACE with PEI lies in the fact that after TACE, the tumor consistency is markedly softened and the intra-tumoral septa are usually disrupted, allowing enhanced ethanol diffusion within or easier thermal ablation of the tumor (Wilson et al., 2012). Therefore, combined TACE+RFA/PEI have

been expected to improve the survival rates in patients with advanced HCC. In our study, we compared RFA/PEI alone and combined TACE+RFA/PEI therapy, and

found no significant difference in the overall survival, especially in the cases with single lesion fulfilling the MC. On the other hand, in the cases with 2-3 lesions

fulfilling the MC, the MST in the combined therapy was significantly superior to that in the RFA/PEI alone group. Moreover, several prospectiver andomized trials have also shown improved survival in patients treated by TACE+PEI as compared with that in patients receiving TACE alone (Yau et al., 2014).

In ours tudy, the MST in the combined therapy group was significantly more prolonged than that in the RFA/PEI alone group without serious deterioration of hepatic function. Our study supported this result and several other groups have also reported that combined therapy was superior to monotherapy for the treatment of HCC.

On the other hand, one study group reported that in their randomized control study, the local recurrence rate was not significantly different between the combined TACE+RFA and RFA alone groups in patients with solitary HCC (Reig M et al., 2013). This result needs to be investigated further.

In conclusion, combined TACE+ RFA/PEI therapy was more useful than TACE alone for patients with a single tumor, regardless of whether the MC were fulfilled or exceeded. Combined TACE+ RFA/PEI also yielded superior survival as compared to RFA/PEI alone in HCC patients with multiple tumors fulfilling the MC.

References

Benson AB, Abrams TA, Ben JE, et al (2009). NCCN clinical practice guidelings in omcology: hepatobiliary cancers. *J Natl Compr Canc Netw*, **7**, 350-59.

Bruix J, Sherman M, Llovet JM, et al (2001). Clinical management of hepatocellular carcinoma: conclusions of the Barcelona-2000 EASL conference. European Association for the study of the Liver. *J Hepatol*, **35**, 421-30.

Burrel M, Reig M, Forner A, et al (2012). Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolization (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. *J Hepatol*, **56**, 1330-5.

Chinn SB, Lee FT, Kennedy, et al (2001). Effect of vascular occlusion on radfiofrequency ablation of the liver: Results in a porcine model. *AJR Am J Roentgenol*, **176**, 789-95.

Cho YK, Kim JK, Kim WT, at al (2010). Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: a Markov model analysis. *Hepatology*, **51**, 1284-90.

Germani G, Pleguezuelo M, Gurusamy, et al (2010). Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocellular: a meta-analysis. *J Hepatol*, **52**, 380-87.

Golfieri R, Renzulli M, Mosconi C et al (2013). Hepatocellular carcinoma responding to superselective transarterial chemoembolization: an issue of nodule dimension? *J Vasc Interv Radiol*, **24**, 509-17.

Hsu CY, Huang YH, Chiou YY, et al (2011). Comparision of radiofrequency ablation and transterial chemoembolization for hepatocellular carcinoma within the Milan criterial: a propensity score analysis. *Liver Transpl*, **17**, 556-66.

Liapi E and Geschwind JF (2011). Transcatheter arterial chemoembolization for liver cancer: is it time to distinguish conventional from drugeluting chemoembolization? *Cardiovasc Intervent Radiol*, **34**, 37-49.

Llovet JM, Bru C, Bruix J (1999). Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis*, **19**, 329-38.

Riaz A, Lewandowski RJ, Kulik L, et al (2010). Radiologic-pathologic correlation of hepatocellular carcinoma treated with chemoembolization. *Cardiovasc Intervent Radiol*, **33**, 1143-52.

Reig M, Rimola J, Torres F et al (2013). Postprogression survival of patients with advanced hepatocellular carcinoma: rational for second-line trial design. *Hepatology*, **58**, 2023-31

Wilson TR, Fridlyand J, Yan Y, et al (2012). Widespread potential for growth-factor-driven resistence to anticancer kinase inhibitors. *Nature*, **487**, 505-9.

Xu C, Lv PH, Huang XE, Wang SX, et al (2015a). Efficacy of transarterial chemoembolization combined with radiofrequency ablation in treatment of hepatocellular carcinoma. *Asian Pac J Cancer Prev,* **16**, 6159-62.

Xu C, Huang XE, Lv PH, et al (2015b). Radiofrequency ablation in treating colorectal cancer patients with liver metastases. *Asian Pac J Cancer Prev,* **16**, 8559-61.

Xu C, Lv PH, Huang XE, et al (2015c). Radiofrequency ablation for liver metastases after transarterial chemoembolization: a systemic analysis. *Asian Pac J Cancer Prev,* **16**, 5101-6.

Xu C, Lv PH, Huang XE, et al (2014a). Internal-external percutaneous transhepatic biliary drainage for patients with malignant obstructive jaundice. *Asian Pac J Cancer Prev,* **15**, 9391-4.

Xu C, Lv PH, Huang XE, et al (2014b). Analysis of different ways of drainage for obstructive jaundice caused by hilar cholangiocarcinoma. *Asian Pac J Cancer Prev,* **15**, 5617-20.

Xu C, Huang XE, Wang SX, et al (2014c). Drainage Alone or Combined with Anti-tumor Therapy for Treatment of Obstructive Jaundice Caused by Recurrence and Metastasis after Primary Tumor Resection. *Asian Pac J Cancer Prev,* **15**, 2681-4.

Xu C, Lv PH, Huang XE, et al (2014d). Safety and efficacy of sequential transcatheter arterial chemoembolization and portal vein embolization prior to major hepatectomy for patients with HCC. *Asian Pac J Cancer Prev,* **15**, 703-6.

Yang JD, Kim WR, Park KW, et al (2012). Model to estimate survival in ambulatory patients with hepatocellular carcinoma. *Hepatology*, **56**, 614-21.

Yau T, Tang VY, Yao TJ, at al (2014). Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology*, **146**, 1691-700.