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CT-guided radiofrequency ablation after with transarterial chemoembolization in treating unresectable hepatocellular carcinoma with long overall survival improvement

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ABSTRACT

Purpose: To assess the time to disease progression (TTP), long-term survival benefit and safety of patients with unresectable hepatocellular carcinoma (HCC) treated with computed tomography (CT)-guided radiofrequency ablation (RFA) with transarterial chemoembolization chemoembolization (TACE).

Methods: This study was approved by the institutional review board. We reviewed the records of patients with intermediate and advanced HCC treated with CT-guided RFA with TACE between January 2000 and December 2009. Median TTP, overall survival (OS) and hepatic function were analyzed with the Kaplan–Meier method and log-rank tests.

Results: One hundred and twenty-two patients (112 men and 10 women, mean age 53 years, range 18–86 years) were included in the study. The median follow-up time was 42 months (range 6–89 months), TTP was 6.8 months, the median OS was 31 months, and the 1-, 3-, and 5-year OS were 88.5%, 41.0%, and 10.7%. The results of the univariate analysis revealed that intrahepatic lesion, AJCC stage, and Child-Pugh stage were predictors of OS ($P < 0.01$). In the multivariate analysis, the AJCC stage system showed a statistically significant difference for prognosis. Procedure-related death was 0.21% (1/470) within 1 month, and a statistical difference was found between the TACE and RFA of liver decompensation and Child-Pugh stage ($P < 0.05$).

Conclusions: The survival probabilities of OS increased with CT-guided RFA with TACE, as observed in randomized studies from Europe and Asia. The longest TTP was observed for the intermediate stage HCC. The procedures were well tolerated with acceptable minor and major complications in unresectable HCC patients.

Hepatocellular carcinoma (HCC) ranks fifth for men and eighth for women as a source of malignant tumors worldwide [1]. The limited hepatic reserve, presence of multifocal tumors, and hepatic vessel invasion or distant metastasis indicate that 70–85% of patients with intermediate or advanced HCC are precluded for curative surgery resection at the time of diagnosis [2]. In the past 30 years, transarterial chemoembolization (TACE) has become the major palliative treatment option for otherwise unresectable HCC in patients who have reasonably preserved hepatic function and an acceptable performance status [3]. Unfortunately, the response rates for TACE remain unacceptably low; the 5-year survival rates stratified by TNM stage (III and IV) were 20% and 10%, respectively [4]. Opportunities to improve the clinical benefit of first-line treatment for patients with unresectable HCC are critical for improving patient outcomes.

Radiofrequency ablation (RFA), a thermal *in situ* destruction technique, has provided survival rates similar to those of resection and has been used as a substitute for surgical resection in eligible early-stage HCC patients [3,5]. However, the efficacy of RFA treatment is markedly hindered by its inability to effectively treat tumors greater than 3–5 cm in diameter and tumors in

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difficult-to-treat locations. RFA treatment is further hindered because of heat dispersion by the bloodstream [5].

Data from recent studies suggest that RFA increases necrosis and promotes longer survival by dose-intense delivery with a chemo-agent and a reduction in arterial inflow into the tumor by TACE [6]. However, during the ablation of large tumors by guided ultrasound, artifacts may be produced from the interference of gas release during the RFA procedure, which can limit the ability to visualize coagulated tissue in real time [7].

TACE with ultrasound guided RFA has been used widely, with reported success in prospective and retrospective studies in HCC [5–7]. CT-guided intraprocedural RFA with anatomical detail and overlapping large lesion has not been well documented in the treatment of HCC. Furthermore, whether TACE-RFA can attain adequate destruction of tissue volume with the desired synergetic result and safe threshold value in unresectable HCC has not been determined [7,8].

Because TACE was also used in the treatment of advanced stage HCC [8,9], we performed this study with TACE and CT-guided RFA in the treatment of selected intermediate and advanced HCC, in order to investigate the feasibility and survival benefits and determine whether this method should warrant further study.

1. Materials and methods

1.1. Patient population

This study was approved by the Sun Yat-Sen University Cancer Center review board. Newly diagnosed patients with intermediate or advanced HCC treated between January 1, 2000, and December 31, 2009, were eligible from a database of consecutive medical records at the Minimally Invasive Interventional Division, Medical Imaging Center.

The diagnosis of intermediate and advanced HCC was based mainly on the established practice published by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) [10].

Intermediate stage HCC is characterized by multinodular tumors larger than 3 cm, with ECOG PS 0, whereas advanced stage HCC includes symptomatic tumors with ECOG PS 1–2 or an invasive tumor pattern (portal vein invasion, N1, M1) [3]. Hepatic tumors were evaluated by contrast-enhanced CT/MRI and divided into three gross pathologic types: a nodular type consisting of one or more nodes with a diameter between 3 and 5 cm; a massive type consisting of single or multiple tumors with a diameter between 5 and 10 cm; and a gigantic type with a diameter greater than 10 cm, regardless of the presence of daughter lesions [11].

The inclusion criteria were as follows: intermediate stage HCC with Child-Pugh class A or B liver function, no history of hepatic encephalopathy or ascites refractory to diuretics, and financial ability to afford to complete the protocol without interruption (Table 1).

In consideration of the previous research in advanced HCC with the TACE procedure [8,9], some of the exclusion criteria should not be considered absolute contraindications. The selection should be based on the extent of the disease. Thus, lesions or multiple lesions with ECOG PS scores 1–2 are the presence of a single-branch portal vein tumor thrombosis or extrahepatic metastases (in the lung, bone, or hilar region of the lymph nodes with less than three lesions and the diameter less than 3–5 cm) that could be treated by local control (RFA, radiotherapy, etc.) were not grounds for exclusion.

The excluded criteria included primary diffuse HCC, extensive intrahepatic metastases and main portal vein tumor thrombosis due to a liver tumor, Child-Pugh C liver profile, ECOG PS scores more than 2, or uncorrectable coagulopathy [12].

Table 1
Demographic and clinical characteristics of 122 patients with intermediate or advanced stage hepatocellular carcinoma treated with CT-guided RFA after with ATCE.

Characteristic	Number of the cases	Ratio (%)
Sex		
Male	112	92
Female	10	8
Age, years		
>75	16	13
55–75	67	55
30–54	31	25
<30	8	7
Gross pathological type (mean, standard deviation of tumor)		
Gigantic (12.3, 0.50 cm)	55	45
Massive (6.3, 0.50 cm)	36	30
Nodular (3.8, 0.50 cm)	31	25
Lesion counts		
1	54	44
2	34	28
≥3	34	28
Child-Pugh class		
A	96	79
B	26	21
Alpha-fetoprotein level, ng/mL		
≤100	19	16
101–200	42	34
201–400	25	20
>400	36	
Hepatitis		
B	90	74
C	4	3
Neither	28	23
Stages of HCC		
Intermediate HCC	72	59
Advanced HCC	50	41
AJCC stages		
IIIA	60	49
IIIB	7	57
IIIC	22	18
IV	33	27
Characteristics of advanced stage HCC (n = 50), PS1-2		
Portal vein tumor thrombosis	17	34
Extrahepatic metastasis	28	56
Portal vein tumor thrombosis and extrahepatic metastasis	5	10
Contraindications for surgery		
Insufficient hepatic reserve	60	49
Difficult hepatectomy	29	24
Extrahepatic metastases	33	27

The demographic data of these patients are shown in Table 1. TACE with RFA was used in 131 patients. Of these patients, 9 patients were absent for the follow up. The inclusion criteria were met by 122 patients (112 men, 10 women). The mean (range) age was 53 years (18–86 years).

All of the patients referred to our institution with HCC complicating liver cirrhosis were primarily screened for liver transplantation or resective surgery. The patients provided written informed consent to undergo the TACE with additional CT-guided RFA. Patients made their decision on the basis of the attending physician's recommendation with their own preference. At the time of enrollment, the patients understood that additional CT-guided RFA treatment may be not better than TACE alone to alter their disease progression.

1.2. Tumor diagnosis and staging

1.2.1. Treatment procedures

Pretreatment evaluation included a complete history, physical examination, chest radiography, and laboratory studies, including complete blood cell count, prothrombin time, total bilirubin,