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Total Amount of Energy by Radiofrequency Ablation may Predict Local Recurrence of Hepatocellular Carcinoma

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Abstract

Background/Aims: Local recurrence of hepatocellular carcinoma after radiofrequency ablation (RFA) remains an important limitation. However, predictors for local recurrence by therapeutic procedures with RFA have not been investigated sufficiently. In current study, we evaluated factors associated with local recurrence after RFA using Cool-tip RF system with a single needle electrode.

Methods: Between January 2010 and April 2013, RFA was performed in 89 hypervascular hepatocellular carcinoma nodules ≤20 mm in diameter using Cool-tip RF system. Factors associated with local recurrence were analyzed for nodules with sufficient ablative margin after RFA. Treatment-associated factors evaluated included RFA maximum output, final temperature, frequency of breaks, and total amount of energy used; background factors included alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP), total bilirubin, albumin and prothrombin activity (PT) levels.

Results: Univariate analysis showed that RFA maximum output and total amount of energy as treatment-associated factors and DCP levels as a background factor were associated with local recurrence. Multivariate analysis revealed that only total amount of energy was the significantly correlated with local recurrence.

Conclusion: This study indicates that RFA using Cool-tip RF system may decrease local recurrence in hypervascular hepatocellular carcinoma ≤ 20 mm by achieving total amount of energy.

Keywords: Radiofrequency ablation; Local recurrence; Total amount of energy

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide [1,2]. Currently, radiofrequency ablation (RFA) is a first-line treatment of the major local ablative techniques for the treatment of HCC, preferably smaller than 3 cm and ineligible for resection or transplantation [3, 4].

However, local tumor recurrence remains an important limitation of RFA [5,6]. Many factors are associated with local recurrence following RFA. However, factors associated with the treatment procedure itself have not been fully evaluated yet among them. We have been performing RFA using the Cool-tip RF system in which the impedance control mode is used to increase the power output uniformly in a stepwise fashion at regular time intervals. In the present study, we investigated factors associated with local recurrence including those related to therapeutic procedures when using the Cool-tip RF system.

Methodology

Patients and Methods

Between January 2010 and April 2013, eighty-nine nodules of hypervascular HCC ≤ 20 mm were subjected to RFA at our institution. Diagnosis was based on imaging findings, clinical data and treatment course and it was confirmed by dynamic computed tomography (CT).

After local anesthesia, a 17-gauge cooled-tip electrode with a 3-cm exposed tip (Covidien, Boulder, CO) was attached to a radiofrequency generator and then inserted under ultrasonography guidance.

The ablation protocol included percutaneous puncture and 12-minute ablation in a stepwise fashion under impedance control mode.

Table 1: Patients' baseline clinical characteristics.

Gender (male/female)	56/33
Age (years)	70.92 ± 10.67
Etiology (HCV/HBV/Non B Non C)	54/15/20
Total Bilirubin(mg/dL)	0.72 ± 0.37
Albumin (g/dL)	3.48 ± 0.42
Platelet count (x10^4/μL)	11.43 ± 4.19
AFP (ng/mL)	22.31 ± 42.56
DCP (mAU/mL)	38.74 ± 46.28
Prothrombin time (%)	83.96 ± 11.51
Tumor size (mm	17.73 ± 2.12
Tumor location (left/right)	15/74

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; AFP: Alpha-Fetoprotein; DCP: des-gammacarboxy prothrombin.

The stepwise deployment technique refers to an ablation method in which the initial RF output is set depending on the length of the non insulated exposed active tip of the electrode, and increasing the power output in a stepwise fashion at regular time intervals. The RFA generator output automatically stops (here inafter called "break") when the impedance increases by 30 ohm compared with the initial level as the system ablates nodules. Then, after a 15-second hold of ablation and cooling, the 12-minute ablation is repeated with an output lower than that at the break.

The specific protocol was as follows: radiofrequency energy was applied in a step-wise fashion starting at 60 watts and progressing by 10 Watts (W) per minute. When a break occurred, ablation was stopped and then restarted with an output by 20 watts lower than that at the break.

During RFA, a personal computer with Real-Time Graphics (software) (RTG) installed was connected to the generator through an RS232C device to monitor radiofrequency (RF) output (W), RF current (mA), tip-electrode temperature (°C), and tissue impedance (ohm) on the display at the same time during the procedure. Based on the monitoring data, total amount of energy used was calculated by multiplying wattage by ablation time.

Triphasic or portal venous phase contrast-enhanced CT was performed within 7 days of the procedure and used to evaluate response to treatment. Lack of enhancement of the ablated tumor was considered as evidence of complete and technically successful ablation. Irregular peripheral or nodular enhancement within 1 cm of the ablated area, especially in the portal venous phase, was considered residual tumor and a technical failure [6]. Thereafter, radiologic follow-up was conducted at 3-month intervals for at least 1 year and was used to help evaluate local tumor recurrence. Evidence of irregular or nodular enhancement within 1 cm of the previously treated tumor was considered to be local tumor recurrence.

Factors associated with local recurrence were analyzed for the nodules with a sufficient ablative margin after RFA.

Contributing factors associated with local recurrence included the following 15 parameters: age (≥ 65 years *vs.* <65 years), tumor location (left lobe *vs.* right lobe), gender (male *vs.* female), frequency of breaks (≥ 2 *vs.* < 2), maximum output (unit: by 10 watts), final temperature (°C) (≥ 60°C *vs.* <60°C), total amount of energy used (≥60 KJ or <60 KJ), tumor size (mm), platelet count, cause of chronic hepatic disease (HBV *vs.* HCV *vs.* non-HBV, non-HCV), total bilirubin, and albumin (≥3.8g/dL *vs.* <3.8g/dL)and pre-treatment alpha-fetoprotein (AFP) levels (≥100 ng/mL *vs.* <100 ng/mL**),** and pre-treatment des-gamma-carboxy prothrombin (DCP) levels (≥40 mAU/mL *vs.* <40 mAU/mL)and prothrombin activity (PT)(≥70% *vs.* <70%).

Ethics statement

All patients gave their informed consent after being fully informed on this study. Written informed consent was obtained from all participants. The study was approved by the Ethical Committee of our hospital and was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed using JMP® ver. 11.0 software

Table 2: Comparison of patients characteristics based on therapeutic effect.

	Non-Recurrence Group n=71	Recurrence Group n=18	*p*-value
Gender (male/female)	43/28	13/5	0.4231
Age (years)	71.6 ± 10.8	68.2 ± 10.1	0.2220
Tumor location (left/right)	13/58	2/16	0.7263
Pulse (<2/>=2times)	23/48	3/15	0.2522
Maximum Power (Watt)	120.1 ± 19.8	104.9 ± 19.4	0.0044
Temparature (°C)	76.6 ± 8.3	75.7 ± 6.6	0.6761
Total Jules (Joule)	60811.7 ±10199.5	49821.6 ±8267.4	<.0001
Tumer size (mm)	17.7 ± 2.2	18.2 ± 2.5	0.4886
Etilogy (HCV/HBV/NonBNonC)	44/11/16	10/4/4	0.7851
Total Bilirubin(mg/dL)	0.69 ± 0.31	0.84 ± 0.53	0.1285
Albumin (g/dL)	3.48 ± 0.42	3.49 ± 0.43	0.9586
Platelet (x10^4/μL)	11.36 ± 3.99	11.67 ± 5.01	0.7864
AFP (ng/mL)	24.0 ± 46.3	15.7 ± 22.2	0.4603
DCP (mAU/mL)	31.5 ± 24.7	67.4 ± 86.5	0.0027
Prothrombin time (%)	84.0 ± 11.7	84.0 ± 11.0	0.9843

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; AFP: Alpha-Fetoprotein; DCP: des-gammacarboxyprothrombin.

Table 3: Univariate and multivariate analyses of local recurrence in hepatocellular carcinoma patients.

	Univariate HR (95% CI)	*P* Value	Multivariate HR (95% CI)	*P* Value
Gender (male)	0.71(0.23-1.88)	0.502		
Age (>65years)	0.42(0.16-1.07)	0.069	0.43(0.15-1.25)	0.116
Tumor location (right)	0.58(0.09-2.03)	0.431		
Pulse(>=2times)	2.17(0.72-9.38)	0.183		
Maximum Power (by 10 Watt)	0.71(0.55-0.9)	0.004		
Temparature (<61)	1.46E-08	0.351		
Total Jules (>=60,000Joule)	0.09(0-0.42)	0.001	0.06(0-0.33)	<.0001
Tumer size (by 1mm)	1.1(0.89-1.44)	0.398		
Etilogy (HCV/HBV/NonBNonC)	0.96(0.57-1.72)	0.889		
T.Bil (>=1.2 mg/dL)	3.06(0.87-8.53)	0.078	3.64(0.89-13.4)	0.071
Alb (<3.8 g/dL)	0.83(0.32-2.38)	0.706		
Plt (<15 x10^4/µL)	1.62(0.53-7)	0.422		
AFP (>=100 ng/mL)	5.14E-09	0.164		
DCP (>40 mAU/mL)	3.6(1.4-9.24)	0.009	5.31(1.89-15.93)	0.002
Prothrombin time (<70%)	0.92(0.15-3.23)	0.910		

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; AFP: Alpha-Fetoprotein; DCP: Des-gammacarboxyprothrombin.

(SAS Institute Inc., Cary, NC). Cumulative local recurrence rates were calculated using the Kaplan–Meier method and compared using a log rank test for each parameter. Then, univariate analysis was conducted. Multivariate analysis was performed using Cox proportional hazards model. For all analyses, a P value of <0.05 was considered statistically significant.

Results

Patients background

Table 1 summarizes the clinical background characteristics of all patients. There were 56 men and 33 women with a mean age of 70.92 ± 10.67 years old. The mean tumor diameter was 17.73 ± 2.12 mm. The cause of chronic hepatic disease was hepatitis B virus (HBV) in 15 patients, hepatitis C virus (HCV) in 54, and non-HBV, non-HCV in 20 patients. Pretreatment serum AFP and DCP levels were 22.31 ± 42.56 ng/mL and 38.74 ± 46.28 mAU/mL, respectively.

Factors associated with local recurrence

Local recurrence occurred in 18 out of 89 nodules. The overall observation period was 445 ± 291 days. The mean time to local recurrence was 274 ± 298 days in the group in which local recurrence occurred, while the mean observation period was 489 ± 298 days in the group with no local recurrence. There was a significant difference in maximum output, total amount of energy used and DCP level between the recurrent group and the non-recurrent group (Table 2). The mean pre-treatment AFP level was 15.7 ± 22.2 ng/mL in the recurrent group, while it was 24.0 ± 46.3 ng/mL in the non-recurrent group with no significant difference. The mean pre-treatment DCP level was 67.4 ± 86.5 mAU/mL in the recurrent group, while it was 31.5 ± 24.7 mAU/mL in the non-recurrent group.

Analysis of factors associated with local recurrence (Table 3)

Univariate analysis revealed that among the above 15 parameters, maximum output, total amount of energy use and DCP levels had a significant difference as a factor associated with local recurrence. Univariate analysis showed that RFA maximum output (p= 0.004) and total amount of energy used ≥ 60 KJ or < 60 KJ(p= 0.0010) as treatment-associated factors, and DCP level (p= 0.009) as background factor, were associated with local recurrence, while multivariate analysis revealed that the hazard ratio was 0.066 for total amount of energy used ≥ 60 KJ versus that < 60 KJ, which indicated that total amount of energy used was a significant independent factor contributing to local recurrence.

Discussion

Radiofrequency ablation (RFA) was first described by Rossi et al., and is a local thermal ablation therapy for HCC [7]. In this study, the 1-, 3-, and 5-year survival rates were reported to be 95%, 67%, and 45%, respectively [8]. RFA, a palliative modality for HCC, causes coagulative necrosis and results in cell death [9]. The procedure attracted much attention because it was safer than percutaneous microwave coagulation therapy and its ability to necrotize tumors was equivalent to the coagulation therapy [10].

Although RFA is superior in local control to the conventional percutaneous ethanol injection therapy (PEIT) or percutaneous microwave coagulation therapy (PMCT) [11-14], local recurrence was generally found to be more frequent after RFA than after hepatic resection. Local recurrence after RFA may be attributable to insufficient ablation of the primary tumor and/or the presence of tumor venous invasion in the adjacent liver. Surgical resection could remove the primary tumor [15]. Thus, it is important for RFA to evaluate factors associated with local recurrence. However, no factors associated with treatment procedures were not fully mentioned yet. Radiofrequency ablation with a percutaneously inserted electrode ablates tumors more completely than other locoregional treatments, reducing the rate of local recurrence [13,16].

To further improve local disease control and outcome, several studies have been conducted to analyze risk factors and patterns of local recurrence after radiofrequency ablation of HCC.

To the best of our knowledge there have been few reports regarding the relationship between local recurrence and treatment associated factors of RFA.

Therefore, in the present study, we aimed to examine the relationship between local recurrence and treatment associated factors of RFA.

The importance of imaging modalities for the diagnosis of local recurrence has been reported. As a cause of local recurrence, there is a possibility of incomplete tumor ablation which cannot be captured by imaging following treatment. We attached importance to the role of histological diagnosis to assess the presence of residual tumor, and reported that presence of viable cells in the needle was a predictor of local recurrence when using RITA Star-burst needle [17]. The RFA device is used to destroy tumor tissue through which the radiofrequency energy passes to the human body and joule heat is generated. With a high frequency of 480 kHz, it enables a wider area of tumor tissue ablation. RFA devices are broadly divided into those with a deployment needle and those with a single needle.

The Cool-tip RF system employing a single needle is designed to prevent an impedance increase caused by carbonization of the tissue surrounding the electrode by circulating cold water inside the electrode, leading to a favorable dispersion of radiofrequency. Typically, we perform RFA using the impedance control mode, which allows the RF generator to detect impedance changes automatically, and according to which the break occurs. In this study, we analyzed treatment factors associated with local recurrence using the single-needle Cool-tip RF system.

We identified the total amount of energy used only as a factor contributing to local recurrence in this study. It has so far been presumed that there is a possible relationship between frequency of breaks or the final temperature and local recurrence. However, this study did not reveal that these 2 factors were significantly associated with local recurrence.

As this study showed that there was a significant difference in local recurrence rate when the total amount of energy used was ≥ 60 KJ, it may be an important treatment goal to achieve at least a total amount of energy of ≥ 60 KJ.

In conclusion, multivariate analysis showed that the total amount of energy used was the most important treatment factor influencing cumulative local recurrence. To evaluate the response to RFA, it is necessary to secure at least a visible ablation margin. Furthermore, it is preferable to achieve a total amount of energy of ≥ 60 KJ for better local control.

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