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Combination of radiofrequency ablation and transcatheter arterial chemoembolization to treat hepatocellular carcinoma: measurement of distance from needle tip to nodule for assessment of local tumor progression

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Abstract

Objective: This study was performed to determine the relationship between the minimum distance from the radiofrequency ablation (RFA) needle tip to the tumor and local tumor progression (LTP) of hepatocellular carcinoma (HCC) nodules and identify prognostic factors for LTP.
Methods: We reviewed 197 patients (197 nodules) who underwent RFA after transcatheter arterial chemoembolization for HCC from January 2010 to January 2015. Three-dimensional registration of images was used to calculate the minimum distance from the tip to the tumor. We then divided the minimum distance into two groups: <2 and ≥ 2 mm. Contrast-enhanced computed tomography was performed after treatment. The LTP rate was calculated 1 and 3 years after RFA. We performed multivariate analysis to identify independent prognostic factors for LTP.
Results: The cumulative 1-year LTP rates in the <2- and ≥ 2-mm groups were 82.7% and 4.3%, respectively, and the cumulative 3-year LTP rates in the two groups were 94.8% and 10.8%, respectively. The minimum distance from the needle tip to the tumor was an independent prognostic factor for LTP.

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Conclusions: A minimum distance of 2 mm from the needle tip to the tumor should be completely ablated along with the tumor.

Keywords
Transcatheter arterial chemoembolization, radiofrequency ablation, margin, hepatocellular carcinoma, local tumor progression, prognostic factor

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Introduction

The incidence of hepatocellular carcinoma (HCC) has been increasing during the past 20 years.[1] Liver transplantation, hepatic resection, and ablation are curative treatments for Barcelona Clinic Liver Cancer stage A HCC.[2,3] Although liver transplantation and hepatic resection are curative treatments, they are not feasible choices for many patients because of the donor shortage.[4]

Radiofrequency ablation (RFA) is a minimally invasive treatment for HCC that achieves a high complete ablation rate. Good survival and local control rates were shown in several studies, especially for nodules of <3 cm.[5,6] The RFA procedure is successful when the ablation zone includes both the tumor and an adequate margin. However, local tumor progression (LTP) is often observed after successful RFA.[7,8] The risk factors for LTP include an insufficient ablative margin,[8] the presence of vessels around the HCC,[9] a tumor size of ≥3,[9] and tumors in special locations.[10]

Several studies have demonstrated the relationship between the ablative margin and recurrence of HCC. Ablation of adequate margins beyond the nodule is necessary to achieve complete tumor ablation, and the tumor along with a surrounding margin of ≥5 mm should be completely ablated.[11,12] The RFA system used in our center is a Model 1500X radiofrequency generator manufactured by RITA Medical Systems (Fremont, CA, USA). The radiofrequency needle is a StarBurst open type (AngioDynamics, Latham, NY, USA). All RFA procedures are performed after TACE in our center. The ablation margin depends on the distance from the needle tips to the nodules when using this cluster needle system. However, no prior studies have shown how the minimal distance from the needle tips to the nodules is related to LTP. Therefore, in this study, we examined the relationship between the distance from the needle tips to the tumor and LTP in patients with HCC. We also analyzed the relevant prognostic factors for LTP.

Materials and methods

Patient selection

We reviewed patients who underwent TACE plus RFA for HCC from January 2010 to January 2015. The inclusion criteria were nodules of 1.0 to 5.0 cm in diameter, no previous treatment for the target nodules, and regular follow-up in our center. HCC was diagnosed according to the criteria of the American Association for the Study of Liver Disease.[13] Written informed consent for treatment was obtained from all patients before surgery. This study was approved by the Ethics Committee of Peking University First Hospital.

TACE procedure

A 5-French catheter was inserted into the trunk of the celiac artery, and angiography was performed to evaluate the arterial blood supply of the tumors. Microcatheters (Asahi Intecc Co., Ltd., Japan) were then superselectively introduced into the tumor's feeding arteries. TACE was performed using 20 to 60 mg of epirubicin mixed with 2 to 8 mL Lipiodol (Guerbet, Villepinte, Seine-Saint-Denis, France), and further embolization was performed with a 150- to 350-μm or 350- to 560-μm gelatin sponge (Hangzhou Alicon Pharmaceutical Technology Co., Ltd. Hangzhou, China).

RFA procedure

RFA was performed 1 or 2 weeks after TACE. All RFA procedures were performed under ultrasound guidance, and computed tomography (CT) or cone-beam CT (CBCT) were then used to verify the location of the needle tip. Cone-beam CT was only used when the tumors were completely deposited with Lipiodol and showed a clear boundary. Some tumors were not completely deposited with Lipiodol. The HCC nodules usually showed low density on a plain CT scan, and we were able to verify the tip and tumor margin in such cases. In a few cases, we determined the tumor boundary by adjusting the CT window width and window level and thus ensured the success of the operation. Upon completion of ablation, the needle was withdrawn and track ablation was simultaneously performed to prevent bleeding and tumor seeding. Electrocardiographic monitoring was performed for 12 hours after RFA. The endpoint of RFA was the observation of low-density tumors containing bubbles on plain CT or strong echoes in the tumor areas under ultrasonography. Technical success was defined as the successful completion of TACE and RFA.

Calculation of distance from needle tips to HCC nodules

The radiofrequency needle was a StarBurst open type (AngioDynamics), and the cluster needle contained nine electrodes. To obtain three-dimensional registration of images, CT scans using 1-mm slices were performed when performing RFA. Three-dimensional registration of images was used to calculate the distance from the tip of every needle to the tumor (Figure 1). The minimum distance from the needle tip to the tumor was recorded. If the locations of the needle tips were adjusted during treatment, the minimum distance was recalculated.

Groups

We divided the minimum distance into two groups: <2 and ≥ 2 mm. LTP was defined as the development of a new tumor around the ablation zone.

Follow-up

Contrast-enhanced CT was performed 1, 3, 6, 9, and 12 months after the treatment and within 3 months after the 1-year follow-up.

Statistical analysis

The rate of LTP was calculated by the Kaplan–Meier method and compared using the log-rank test. Risk factors for LTP were evaluated by univariate analyses, and we performed multivariate analysis using Cox regression to identify independent prognostic factors for LTP. A significant difference was considered to be present when $P \leq 0.05$. All statistical analyses were

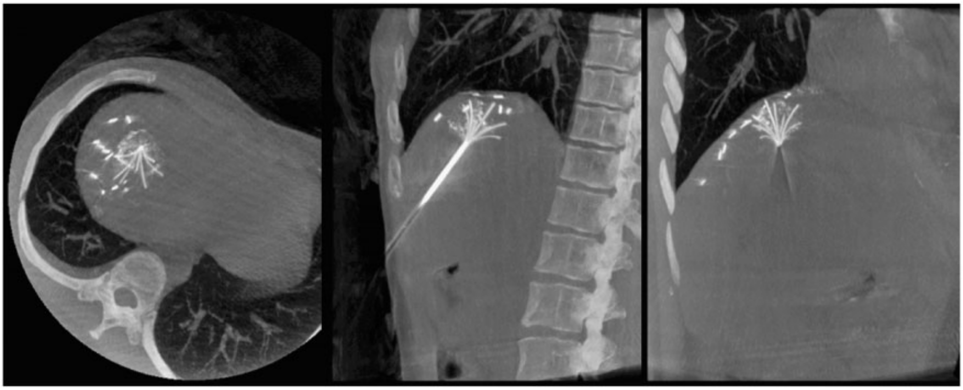

Figure 1. Three-dimensional registration of images.

performed using IBM SPSS, Version 20.0 (IBM Corp., Armonk, NY, USA).

Results

In total, 197 patients (147 male, 50 female) with 197 nodules were enrolled in our study. The patients' general conditions are shown in Table 1. The mean tumor size was 2.6 ± 1.5 cm, and the mean follow-up period was 36.4 ± 24.1 months. Technical success was achieved in all patients. No patient had severe complications after RFA.

Forty-eight of the 58 patients in the <2-mm group developed tumor progression within 1 year, and 55 patients developed tumor progression within 3 years. When the minimum distance was >2 mm, the number of patients with tumor progression decreased significantly. Of the 139 patients, only 6 patients developed tumor progression within 1 year, and only 15 patients developed tumor progression within 3 years. The cumulative 1-year LTP rates in the two groups were 82.7% and 4.3%, respectively ($P \leq 0.001$). The cumulative 3-year LTP rates in the two groups were 94.8% and 10.8%, respectively ($P \leq 0.001$) (Figure 2, Table 2).

Eleven variables with possible effects on LTP were analyzed. Univariate analysis showed that the tumor location, tumor size, local Lipidol deposition, and minimum distance from the needle tip to the tumor were significant predictive factors for LTP ($P < 0.001$ for all) (Table 3). Only the minimum distance from the needle tip to the tumor was an independent prognostic factor for LTP in the multivariate analysis ($P < 0.001$) (Table 4).

Discussion

A high LTP rate ranging from 2% to 53% is problematic during RFA procedures. Analysis of the ablative margins has been performed in several studies to achieve better local control of HCC by RFA. A study from Japan showed that an ablation zone with an ablative margin of ≥5 mm was the most important factor for local control of HCC.[8] A more recent study from China showed that for HCC tumors of >3.0 to ≤5.0 cm, an ablative margin of >1.0 cm could result in a lower risk of recurrence than an ablative margin of 0.5 to 1.0 cm, emphasizing the need for a more defensive strategy using ablative margins of >1.0 cm for ablating HCC tumors of 3.1 to 5.0 cm.[14] Consequently, a margin of

Table 1. Patients' baseline data.

Data	n
Sex	
Male	147
Female	50
Age, years	
<60	103
≥60	94
ECOG performance status	
0	193
1	3
2	1
Child–Pugh class	
A	192
B	5
AFP level	
<400 ng/mL	89
≥400 ng/mL	108
Hepatitis	
B	121
C	28
None	48
Capsule	
Yes	103
No	94
Tumor location	
Normal	140
Contiguous vessels	37
Contiguous organs	20
Tumor size	
<3 cm	117
≥3 cm	80
Local Lipiodol deposition	
<50%	78
≥50%	119
Shortest distance from needle tip to tumor	
<2 mm	58
≥2 mm	139

Data are presented as number of patients.
ECOG, Eastern Cooperative Oncology Group; AFP, alpha fetoprotein.

≥5 mm appeared to be associated with a lower rate of LTP after percutaneous RFA of HCC.

An adequate safety margin is necessary for RFA because daughter nodules that cannot be seen are still present around the HCC. In HCC, blood from the tumor drains into the surrounding hepatic sinusoids through the continuity between the tumor sinusoids and portal venules in the pseudocapsule or surrounding hepatic sinusoids. The drainage area is a high-risk area for intrahepatic metastasis, and daughter nodules are commonly seen there.[15] Therefore, the safe margin should exceed the tumor boundary.

Various RFA systems are available on the market. The RFA system used in our center is a Model 1500X radiofrequency generator manufactured by RITA Medical Systems, and the needle of this system is a StarBurst open type manufactured by AngioDynamics. When using this needle, the ablation range depends on the distance from the needle tip to the nodule. Therefore, we examined how the distance from the needle tip to the tumor is associated with LTP of HCC measuring 1 to 5 cm. We determined that when the minimum distance from the needle tip to the tumor was >2 mm, the 1- and 3-year LTP rate was clearly reduced.

In our study, all RFA procedures were performed after TACE. Performance of the procedures in this order has more advantages than performance of RFA alone. The decreased arterial blood flow to an HCC induced by TACE may reduce the heat sink effect of large vessels adjacent to the HCC, resulting in a considerable increase in the volume of the ablation zone by RFA.[16] The effect of chemotherapy and hypoxic injury induced by TACE on cancer cells is then enhanced by the high temperature during RFA, making it possible to extend the ablation zone.[17] In addition, the tumor boundaries can be better identified by deposition of Lipiodol in the tumor.

We confirmed that a >2-mm minimum distance from the needle tip to the tumor should be completely ablated along with the tumor. We believe that this result has

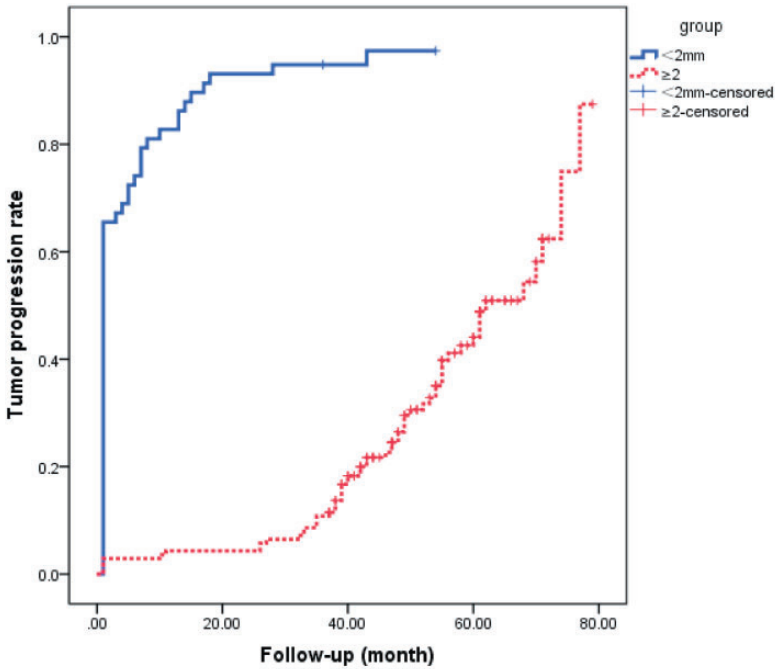

Figure 2. Calculation of local tumor progression (LTP) rate. The LTP rate was calculated between the <2- and ≥2-mm groups by the Kaplan–Meier method.

Table 2. LTP rates in the two study groups.

Minimum distance	Patients, n	LTP at 1 year, n	LTP rate at 1 year	LTP at 3 years, n	LTP rate at 3 years
<2 mm	58	48	82.7%	55	94.8%
≥2 mm	139	6	4.3%	15	10.8%

important clinical significance. Although the minimum distance is not equal to the safe margin, it may reflect the safe margin of RFA. Because of the thermal transmission effect, the ablative margin should exceed the tip of the needle, especially after TACE. Therefore, by determining the minimum distance from the needle tip to the tumor, we are able to determine whether the tumors can be completely eliminated. This could also provide a standard for clinical RFA. The radiofrequency needle tip must extend 2 mm beyond the tumor boundary.

The univariate analysis showed that the tumor location, tumor size, local Lipidol deposition, and minimum distance from the needle tip to the tumor were significant predictive factors for LTP. The multivariate analysis showed that the minimum distance from the needle tip to the tumor was a significant independent factor for LTP. An adequate ablative range is required because most recurrent lesions emerge from the

Table 3. Significant variables for local tumor progression in the univariate analysis.

Characteristics	n	P value	Exp(B)
Sex			
Male	147	0.254	0.486
Female	50		
Age, years			
<60	103	0.531	1.112
≥60	94		
ECOG 0			
Yes	193	0.922	14.267
No	4		
Child–Pugh A			
Yes	192	0.261	2.951
No	5		
AFP level, ng/mL			
<400	89	0.131	0.315
≥400	108		
Hepatitis			
Yes	149	0.810	0.986
No	48		
Capsule			
Yes	103	0.054	1.796
No	94		
Tumor location			
Normal	140	<0.001	0.288
Special	57		
Tumor size			
<3 cm	117	<0.001	0.107
≥3 cm	80		
Local Lipiodol deposition			
<50%	78	<0.001	0.221
≥50%	119		
Shortest distance from needle tip to tumor			
<2 mm	58	<0.001	0.172
≥2 mm	139		

ECOG, Eastern Cooperative Oncology Group; AFP, alpha fetoprotein.

Table 4. Cox regression analysis for local tumor progression.

Characteristics	P value	Hazard ratio	95% CI
Tumor location	0.368	0.778	0.451–1.344
Tumor size	0.314	0.732	0.399–1.344
Local Lipiodol deposition	0.823	1.075	0.572–2.018
Shortest distance from needle tip to tumor	<0.001	21.429	9.790–46.905

CI, confidence interval.

tumor border, the area most likely to contain viable tumor cells.

Conclusion

In conclusion, a minimum distance of 2 mm from the tumor should be completely ablated along with the tumor. This was the independent prognostic factor for LTP in the multivariate analysis.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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