



Review Article

Radiofrequency ablation for hepatocellular carcinoma



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A B S T R A C T

Radiofrequency ablation (RFA) has changed the treatment strategy of hepatocellular carcinoma. Although RFA is usually applied for the treatment of small (≤ 3 cm) hepatocellular carcinomas, the combination with hepatic arterial chemoembolization has expanded the use of RFA to larger tumors. Refinements have lessened complications, leading to better prognosis even in the longer term.

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Introduction

Radiofrequency ablation (RFA) has been applied to clinical practice since the early 1990s and rapidly disseminated to become the first-choice locoregional treatment. Less than a decade after its introduction, RFA was resulting in a higher rate of complete necrosis and required fewer treatment sessions than percutaneous ethanol injection (PEI) in small (≤ 3 cm) hepatocellular carcinoma (HCC) lesions.¹ However, at about the same time, the diminishing effectiveness of RFA in achieving tumor necrosis with increasing tumor size was apparent.² In addition to tumor size, blood flow and tumor location affect the antitumor effect.^{3,4}

Attempts have been made to overcome these limitations and increase the antitumor effect.^{5–13} Furthermore, some measures have been developed to avoid RFA-related complications, resulting in marked improvement in the safety of liver RFA.^{14,15} These efforts have led to improved therapeutic outcomes, and 10-year survival rates have been reported recently.^{16,17}

The current status of liver RFA is reviewed in this manuscript.

Indication for liver RFA

The need for liver RFA is generally determined by taking into account patients' performance status, liver function, and tumor background. Based on the Barcelona Clinic Liver Cancer staging system, RFA is applied for the treatment of patients having very early (Stage 0) and early stage (Stage A) HCC. Patients with performance status of 0, Child-Pugh class A or B liver profile, and three or fewer HCC nodules ≤ 3 cm are indicated for RFA.¹⁸ However, these indication criteria also point out the limitation of RFA. Small ablation zone size obtained in a single treatment session limits the

indication of RFA. RFA is applied in <30 – 40% of HCC patients in Europe and the USA, and 30.6% in Japan.^{18,19} According to the report from the Liver Cancer Study Group of Japan, HCCs were found at a maximum size of ≤ 3 cm and 3.1 – 5 cm in 57.5% and 21.5% of HCC patients, respectively.¹⁹ If the indication for RFA is expanded to include a maximum size up to 5 cm, more HCC patients can benefit from RFA.

Exclusion criteria were determined by taking into account complications. Hemorrhage is one of the most frequent severe complications. Patients with abnormal coagulability, even after its correction, are usually excluded. In general, platelet counts <40 – $50 \times 10^9/L$ and/or international normalized ratio exceeding 1.5 are benchmarks of abnormal coagulability.

When the targeting tumor is adjacent to the critical organs, such as the gastrointestinal (GI) tract, the risk of collateral damage is high. The risk of liver abscess also becomes higher when there is a past history of biliary surgery.²⁰

Local therapeutic effect

Local tumor control is important in HCC patients because it is significantly linked with survival.²¹ Local tumor progression is usually evaluated by contrast-enhanced computed tomography or magnetic resonance imaging. Livraghi et al evaluated the initial therapeutic effect of RFA on HCC based on tumor size by evaluating the disappearance of tumor enhancement following RFA.^{1,2} The anticancer effect was stronger as the tumor size became smaller. Tumor enhancement completely disappeared in 90% of small HCCs (≤ 3 cm), 60% of medium-sized HCCs (3.1 – 5 cm), and 24% of large HCCs (> 5 cm; [Table 1](#)).^{1,2} The local tumor progression rate has been reported to be 2.4 – 19.5% at 3 years when the maximum tumor size

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Table 1 Therapeutic Response and Survival Rate after Radiofrequency Ablation

Author	Patient number	Tumor number	Tumor size (cm)	Combination with TACE	Complete response rate (%)	Follow-up period (months)	Local recurrent rate (%)	Local tumor progression rate (%)			Survival rate (%)						
								1-year	3-year	5-year	10-year	1-year	3-year	5-year	10-year		
Livraghi et al 1999 ¹	42	52	≤3	No	90	NA	NA										
Livraghi et al 2000 ²	114	126	3.1–9.5	No	60 (3.1–5 cm) 24 (>5 cm)	NA	NA										
Lencioni et al 2005 ²³	187	240	≤5	No	92	24	5	10									
Tateishi et al 2005 ²⁴	664	2,140	0.8–9.7	No	100	19.1	NA	2.4									
Nakazawa et al 2007 ²⁵	85	85	≤3	No	NA	30.3	16.5	19.5									
Takaki et al 2007 ⁶	173	255	≤5	All patients	100	23	7	2 (≤3 cm) 12 (>3 cm)	8 (≤3 cm) 25 (>3 cm)	NA (≤3 cm) NA (>3 cm)	32	32	3.2	100	62	41	
Takaki et al 2009 ⁸	20	32	5.1–10	All patients	100	30	25	15	3.9 (≤3 cm) 1.1 (≤3 cm)	3.9 (≤3 cm) 2.9 (>3 cm)	3.2	3.2	3.2	95.5	81.4	60.2	27.3
Shina et al 2012 ¹⁶	1,170	2,106	≤5	325 patients (27.7%)	99.4	38.2	NA										
Fujimori et al 2013 ¹⁷	277	382	1.0–12.0	All patients	100	44.9	5.4	2.9 (>3 cm) 13.3 (>3 cm)	16.1 (>3 cm)								

TACE, transarterial chemoembolization.

is ≤ 3 cm (Table 1).^{6,17,22,23} Infiltrating tumor morphology, previous treatment history, subphrenic tumor location, vicinity to the vessels, and ablative margin may significantly worsen local tumor progression.^{6,22–25}

Some of these limitations can be overcome. When the tumor is in the liver dome, it is sometimes difficult to depict the whole tumor by ultrasonography, and almost half of the subphrenic tumors recur at 3 years after RFA.²⁶ The usefulness of artificial pleural effusion, artificial ascites, and real-time virtual sonography has been reported to depict tumors that are invisible by conventional ultrasonography.^{27–29} By contrast, there is no blind spot when using computed tomography as an image guide; in particular, iodized-oil accumulates in the tumor after chemoembolization (Fig. 1).³⁰ The local tumor progression rate is as low as 3% at 5 years after the combination therapy of RFA and chemoembolization.³⁰

The ablative zone is limited by blood flow (heat-sink effect), causing a small ablative margin.^{3–9,31} An ablative margin of at least 5 mm is required to avoid local tumor progression, because microsatellite lesions are frequently present surrounding the HCC nodule.²⁵ Sasaki et al measured the distance of microsatellites from the main HCC nodule in resected specimens.³² Most of the microsatellite lesions were present within 5 mm of the main tumor when the tumor size was ≤ 25 mm.³² The overall survival rate of patients with a microsatellite distance exceeding 5 mm was lower than that of patients with a microsatellite distance < 5 mm.³²

Overlapping insertions of RF electrodes sometimes fail to produce large ablation zones relative to the number of ablations.^{25,33} A decrease in blood flow in the liver causes expansion of the ablative zone size.^{5,31,34} Balloon occlusion of the hepatic artery, chemoembolization of the hepatic artery, portal venous embolization, and hepatic venous balloon occlusion have been combined with RFA in an attempt to expand the ablative zone size.^{5–9} RFA following chemoembolization is the most popular combination therapy among these options (Fig. 1).

Takaki et al performed RFA following chemoembolization and reported a 5-year local tumor progression rate of 8% in patients with small (≤ 3 cm) HCCs, 25% in those with HCCs measuring 3.1–5 cm, and 32% in those with HCCs measuring 5.1–10 cm maximum diameter.^{6,8} Morimoto et al compared the local tumor progression in HCC lesions measuring 3.1–5 cm between RFA alone and combination of RFA and chemoembolization.³⁵ The 3-year local tumor progression rate was significantly lower in combination therapy than RFA alone (6% vs. 39%, $P = 0.012$).

Recently, microwave ablation has emerged as a valuable alternative to RFA in the treatment of hepatic malignancies.³⁶ Microwave ablation is a promising heat-based thermal ablation modality that has particular applicability in treating hepatic malignancies; the ability to generate very high temperatures in a very short time can potentially improve treatment efficiency and larger ablation zones with less heat-sink effect.³⁶ Comparison of local tumor progression between RFA and microwave ablation is required.

Survival after RFA

Superiority of RFA to PEI in prolonging patient survival has been shown in a randomized controlled trial.³⁷ The 3-year survival rates were 48–67% following PEI and 63–81% following RFA. Chen et al performed a randomized control trial between RFA and hepatectomy in patients who had HCC ≤ 5 cm, and found the same overall and recurrence-free survival between the two patient groups.³⁸

Combination therapy of RFA and chemoembolization also provides HCC patients the same survival as surgical intervention does. Yamakado et al retrospectively compared overall and recurrence-free survivals between this combination therapy and hepatectomy in Child-Pugh grade-A patients who had HCC lesions within

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