Review Article

Local ablation therapy for hepatocellular carcinoma

From ethanol injection to radiofrequency ablation

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ABSTRACT

This article reviews the current status of local ablation therapy for hepatocellular carcinoma (HCC). In the treatment of HCC, non-surgical treatments play important roles since only 20-30% of patients are candidates for surgery. Still worse, even after curative surgical resection, 80% of patients develop recurrence within 5 years. Among non-surgical treatments, image-guided local ablation therapies have been widely used for cases of small-number and small-size lesions, because they are potentially curative, minimally invasive, and easily repeatable. Although percutaneous ethanol injection has long been a standard therapy, there has been a drastic shift from ethanol injection to radiofrequency ablation in recent years. Randomized controlled trials proved that radiofrequency ablation is superior to ethanol injection in the treatment of HCC from the viewpoint of not only treatment response but also long-term survival. Radiofrequency ablation will play more important roles in the treatment of HCC.

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The incidence of hepatocellular carcinoma (HCC) has been rising worldwide.[1-3] Unlike other solid tumors, surgery plays a limited role in the treatment of HCC.[4-6] Only 20-30% of patients can be candidates for hepatectomy, because of underlying cirrhosis, or multiple lesions. Still worse, even after apparently curative resection, 80% of patients develop recurrence within 5 years[7] because of latent metastasis or metachronous multicentric carcinogenesis. Liver transplantation may be effective in some cases,[8] but its feasibility is restricted by shortage of organ donors. Consequently, various non-surgical therapies have developed for HCC. Among them, image-guided local ablation therapies, such as percutaneous ethanol injection,[9-11] microwave coagulation,[12] and radiofrequency ablation[13-15] have been playing important roles, because they are potentially curative, minimally invasive, and easily repeatable. At our institute, we have treated 90% of previously untreated patients with HCC by local ablation therapies. We have performed ethanol injection on the total number of 2,000 since 1985, microwave coagulation on the total number of 200 since 1995, with satisfactory long-term results. However, since the introduction of radiofrequency ablation into clinical practice in 1999, there has been a drastic shift from ethanol injection and microwave coagulation to radiofrequency ablation (**Figure 1**).[15] Recent randomized controlled trials proved that radiofrequency ablation is superior to ethanol injection in the treatment of HCC.[16-18] In this article, we will first describe ethanol injection and microwave coagulation briefly, then radiofrequency ablation in more detail.

Percutaneous ethanol injection. In percutaneous ethanol injection, absolute ethanol is injected directly into lesions through 21-22 gauge needles which are inserted under ultrasound-guidance.[19] It can destroy a considerably large volume of tissue in one ablation. Ethanol injection was introduced into clinical practice in the early 1980's.[9-11] It has enabled us to treat HCC potentially curatively by non-surgical measures. Ethanol injection has been widely performed as a standard therapy for small HCC, such as those ≤3 cm in diameter.[19-20] Histopathological examinations after the therapy have revealed that ethanol injection can destroy the tumor completely when it is performed properly.[25] Some investigators have reported that its long-term survival may be similar to that of surgery.[19-24] According to the report of the 16th nationwide follow-up survey of the Liver

Cancer Study Group of Japan, the 1-, 2-, 3-, 4-, 5-, 7-, and 10-year survival rates of all 15,579 patients treated by ethanol injection were 92.4%, 79.3%, 65.5%, 52.8%, 42.2%, 27.2%, and 14.3%.[25] At our institute, the cumulative survival rates of 524 patients treated by ethanol injection were 89.8%, 79.0%, 65.9%, 55.5%, 47.7%, 32.4% and 17.3% at 1, 2, 3, 4, 5, 7 and 10 years.[26] A recent randomized controlled trial showed that there is no statistical significance for recurrence and survival between ethanol injection and surgical resection.[27] Its efficacy is not very reliable, however, because spread of injected ethanol is largely restricted by the capsule or septa of the lesion (**Figure 2**).[28] Thus, the number of patients treated by ethanol injection has sharply decreased since the recent introduction of radiofrequency ablation.[15] Randomized controlled trials showed that radiofrequency ablation is superior to ethanol injection for small HCC from the viewpoint of not only treatment response but also recurrence and survival.[16-18] Nowadays, ethanol injection is a treatment of choice only if radiofrequency ablation cannot be performed safely, such as those in which enteric-biliary reflux is observed so that radiofrequency ablation may develop liver abscess, or those in which adhesion exists between the lesion and the gastrointestinal tract so that radiofrequency ablation may cause gastrointestinal tract perforation or penetration even after artificial ascites technique.

Percutaneous microwave coagulation. In percutaneous microwave coagulation, the cancer tissue is ablated by heat produced by microwave energy emitted from the inserted electrode (16 gauge).[12] Heat may be conducted considerably homogeneously in all directions; the capsule or septa of the lesion may not prevent the conduction very much. It can surely destroy a certain amount of tissue, although its necrotic area is smaller (2 cm in diameter and 2.5 cm in length) compared with ethanol injection. Microwave coagulation became popular in Japan in the late 1990's. However, since the spread of radiofrequency ablation, microwave coagulation has rarely been performed.[15] According to the report of the 15th nationwide follow-up survey of the Liver Cancer Study Group of Japan, the 1-, 2-, 3-, 4-, and 5-year survival rates of all 828 patients treated by microwave coagulation were 93.8%, 85.6%, 77.1%, 67.3%, and 57.2%.[29]

Radiofrequency ablation. In percutaneous radiofrequency ablation, the electrode is inserted into the tumor under image guidance. Then radiofrequency energy is emitted from the exposed portion of the electrode, which is converted into heat and causes necrosis of the tumor. Radiofrequency ablation can ablate a tissue of up to 3 cm in diameter or more as expected. Thus, this therapy has an advantage of ethanol injection in that it can ablate a large volume of tissue in one ablation, and that of microwave

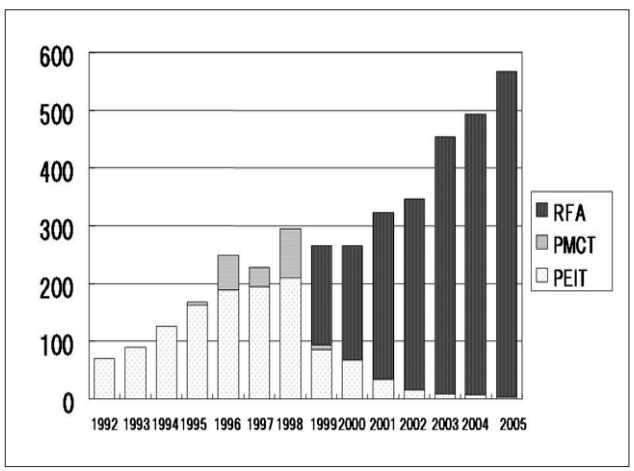

Figure 1 - Transition of local ablation therapies for liver tumors at the Department of Gastroenterology, University of Tokyo. At our institute, 90% of previously untreated patients with hepatocellular carcinoma have been treated by local ablation therapies. Since the introduction of radiofrequency ablation into clinical practice in 1999, there has been a drastic shift from ethanol injection and microwave coagulation to radiofrequency ablation. In 2005, we performed radiofrequency ablation on a total of 564 patients with liver tumors while we did ethanol injection on 7. PEIT - percutaneous ethanol injection therapy, PMCT - percutaneous microwave coagulation therapy, RFA - radiofrequency ablation.

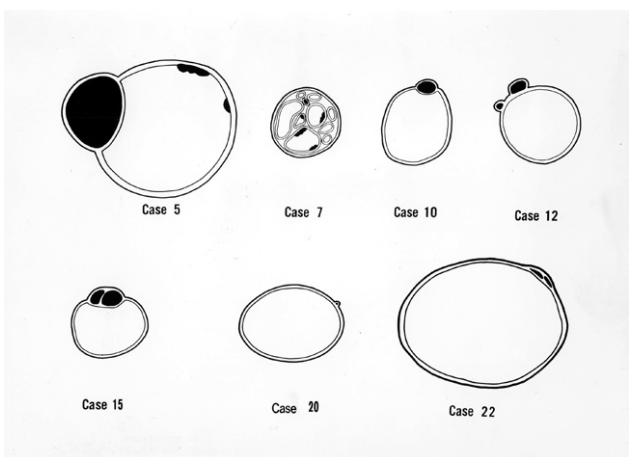

Figure 2 - Scheme of cases of incomplete necrosis treated by ethanol injection. In an early period of our study, we histopathologically examined 24 lesions of hepatocellular carcinoma treated by ethanol injection and found that the lesion was completely necrotic in 17 lesions, 90% necrotic in 6 lesions, and 70% necrotic in the remaining lesion Viable cancer tissue remains in small nodules around the main lesion, along the edge of the lesion, or in portions isolated by septa. This is because spread of injected ethanol is largely restricted by the capsule or septa of the lesion, which results in less reliable efficacy in ethanol injection than thermal ablation.

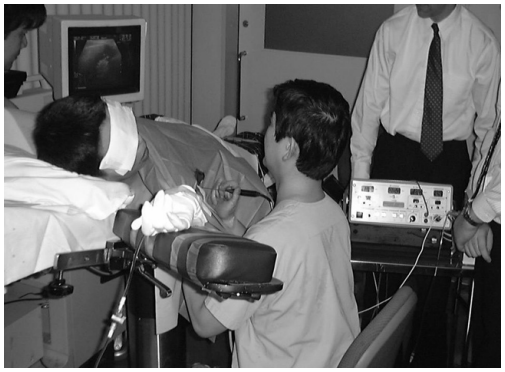

Figure 3 - A view of radiofrequency ablation. An electrode is inserted percutaneously into the lesion under ultrasound-guidance.

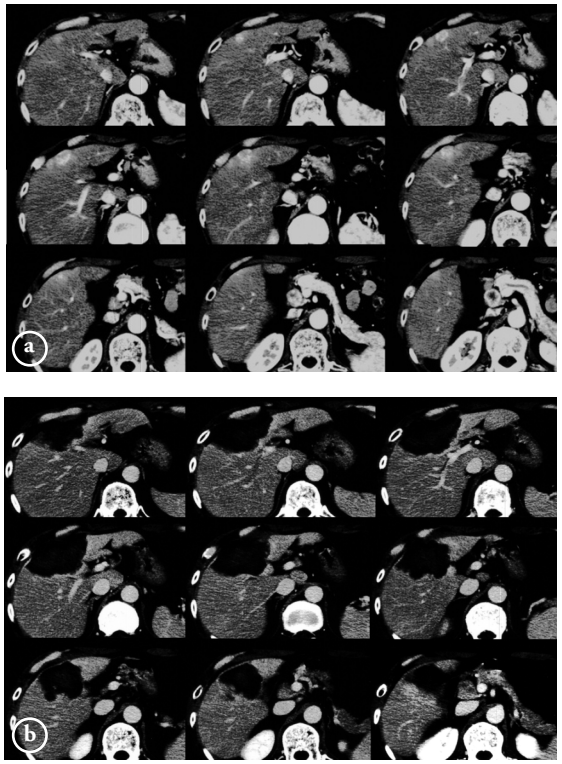

Figure 4 - Computerized tomography scan taken before radiofrequency ablation. **a)** A 62-year old man had confluent multinodular-type hepatocellular carcinoma of 4 cm on the surface in S4. **b)** After the second session of radiofrequency ablation. Not only the lesion but also some amount of surrounding tissue became non-enhanced area. When we see cases like this, we can understand that radiofrequency ablation can surely be a curative treatment of liver tumors.

coagulation in that it can surely destroy a certain size of tissue. Radiofrequency ablation is mainly performed percutaneously under ultrasound guidance, while it can also be used under laparotomy,[30] laparoscopy,[31] or thoracoscopy.[32] Several types of radiofrequency ablation systems are commercially available.[33] In the RITA (Mountain View, CA, USA) and Boston Scientific (Natick, MA, USA) systems, expandable-type electrodes are used; multiple thin curved monopolar electrodes extend from the central cannula (18-14 gauge) of the electrode. Radiofrequency emanates from each of these hooks resulting in increased coagulation. In the Valley Lab (Boulder, CO, USA) system, cooled-tip electrodes (17 gauge) are used. These electrodes have 2 hollow lumens that permit continuous internal cooling of the tip with a chilled perfusate. As a result, heating of tissues nearest to the electrode is reduced, which allows for greater current deposition without tissue charring or impedance rises. We use the cooled-tip electrodes in our institute because some lesions can be ablated with these electrodes but not with the expandable-type ones. In Japan, more than 1400 institutes have introduced radiofrequency ablation in the treatment of liver tumors and the system with the cooled-tip electrodes has an 80% share of the market while in other countries, the systems with expandable type electrodes are more widely used.

Patient selection. The general requirements for radiofrequency ablation are as follows: 1. histopathologically confirmed HCC or characteristic imaging features of HCC, 2. unresectable lesions or refusal of surgery, 3. absence of apparent vascular or biliary invasion, 4. absence of refractory ascites, 5. absence of marked bleeding tendency (prothrombin times should be 50% or more, and platelet count should be 50,000/mm^3 or more), 6. serum bilirubin level of less than 3.0 mg/dl, 7. lesions located in portions where the electrode can be inserted and held safely, 8. informed consent. With regard to the size of the lesions, radiofrequency ablation is usually performed for small lesions up to 3 cm in diameter, since the size of necrosis achieved by each radiofrequency ablation process is limited. Larger tumors can be treated by radiofrequency ablation, however, with overlapping of ablated areas. A combination of transcatheter arterial chemoembolization and radiofrequency ablation is often useful for large tumors. With regard to the number of the lesions, most investigators have performed radiofrequency ablation on patients with 3 or fewer lesions. It is impractical to treat very many lesions with radiofrequency ablation because of the number of necessary treatment sessions. In addition, it is very likely that there are also small undetectable metastases in cases of many lesions, and therefore, even if all detected lesions are treated by radiofrequency ablation, complete cure cannot be expected in those

cases. In cases of more than 3 lesions, in which complete cure cannot be expected, radiofrequency ablation may still be performed with a combination of transcatheter arterial chemoembolization. Chemoembolization is first performed to treat all lesions, and then radiofrequency ablation may be performed against main lesions.

Anatomical locations of the tumor may have potential influence on the efficacy and complication of radiofrequency ablation, although we have put no restrictions on lesion location, and we have successfully performed radiofrequency ablation on more than 99% of patients at our institute.[34] It is risky to perform ablation for lesions adjacent to the Glisson's capsule. It frequently causes biliary injury, which results in biliary stricture or biloma. It may also damage the hepatic artery and the portal vein, which results in hepatic infarction. "Heat-sink" effect due to the blood flow may cause incomplete necrosis of lesions contiguous with large vessels. It is also risky to carry out ablation near other organs, such as the gallbladder and the heart. Lesions near the gastrointestinal tract may be treated safely if the artificial ascites technique can separate the lesion from the tract.[35] Subcapsular lesions are reported to be a high risk of malignant cell seeding,[36] and thus, if possible, the lesion should be punctured through the nontumorous liver. Lesions beneath the diaphragm can be ablated successfully if you have the artificial pleural effusion technique.[37] Radiofrequency ablation can be used even in cases in which complete cure cannot be expected, since it is not very invasive, and it definitely reduces the tumor mass. In those cases, only main lesions may be treated by radiofrequency ablation to reduce the tumor burden, and some lesions may be treated by other therapies.

Technique. Planning ultrasound should be performed carefully to select the optimal approach. In Japan, radiofrequency ablation is performed on an inpatient basis.[15] The patients should fast at least 4 hours before the treatment and should be given premedications for analgesia and sedation. In radiofrequency ablation, grounding is achieved by attaching 2 pads to the patient's thighs. An 17-gauge, cooled-tip electrode with a 2- or 3-cm exposed tip is attached to a radiofrequency generator (CC-1 Cosman Coagulator, Valley Lab). After local anesthesia, the electrode is inserted under ultrasound-guidance (**Figure 3**). During ablation, the temperature is measured with a thermocouple in the electrode. Tissue impedance is also monitored by circuitry incorporated into the generator. A peristaltic pump infused 0^0C saline into the electrode lumen to maintain the tip temperature below 20^0C. Radiofrequency energy is usually delivered for 6-12 minutes for each application as follows: after measurement of baseline impedance, generator output is gradually increased up to 1,400 mA. This level is maintained until the impedance increased over 10 Ohms from the baseline. Then the current is temporarily reduced until impedance becomes stabilized. Output is decreased and increased repeatedly for the remainder of the session to avoid tissue charring. Twelve-minute ablation using a 3-cm exposed-tip electrode produces a quasi-spherical necrotic volume 3 cm in diameter. For large lesions, the electrode is repeatedly inserted into different sites, so that the entire lesion can be enveloped by assumed necrotic volumes. Following the procedure, the patients should remain in bed until the next morning. If the entire lesion is assumed to have become necrotic, enhanced CT is performed (**Figure 4**). When any possible undestroyed portions remain, the therapy is repeated until CT demonstrates the entire tumor necrosis.

Local tumor progression and distant recurrence. Although many investigators reported that radiofrequency ablation could achieve complete tumor necrosis in most cases on CT, local tumor progression

Table 1 - Studies reporting long-term survival outcomes of radiofrequency ablation.

Authors and year	Conditions of the cases	Years	No. of cases	Survival rates	
				1-year	3-years
Rossi et al,[13] 1996	1-2 HCCs <3 cm	40	39	94	68
Buscarini et al,[42] 2001	Child A-B, 1-3 HCCs <3.5 cm	33	82	89	62
Lencioni et al,[43] 2005	Child A-B, 1 HCC <5 cm or ≤3 cm	48	187	97	71
Machi et al,[44] 2005	Unresectable or recurrent HCC	40	65	75	50
Tateishi et al, 2005	Naïve patients	54	319	95	78
	Non-native patients	38	345	92	62
Cabassa et al,[46] 2006	Child A-B, 1 HCC <5 cm or ≤3 cm	43	59	94	65

HCC - hepatocellular carcinoma, *not primary outcomes

is not infrequent; the local tumor progression rate at 3 years was reported to be 1.7-20.4%.[17,18,38,39] The most important factor associated with failure of the local tumor control is the tumor size.[38-40] It is not easy to obtain a certain amount of safety margin all around the large tumor in 3 dimensions. Although various new radiofrequency ablation devices to increase the ablation volume have been introduced, a large tumor of 3 cm or more still requires multiple overlapping ablations. While local tumor progression is related to incomplete tumor ablation, distant intra- and extra-hepatic recurrence is mainly determined by the biological characteristics and natural history of HCC. The incidence of distant intra- and extra-hepatic recurrence ranges from 41-73%.

Survival. There have been only several studies which reported long-term follow-up of patients treated by radiofrequency ablation (**Table 1**). Survival rates range from 75-97% at one year, from 50-78% at 3 years, and from 33-54% at 5 years.[41-46] Survival depends on not only tumor factors but also liver function. There have been a few randomized controlled trials to compare radiofrequency ablation with ethanol injection. In a study by Lin et al,[17] 157 patients with 186 HCCs 4 cm or less were randomly assigned to radiofrequency ablation, conventional ethanol injection, and higher-dose ethanol injection. Radiofrequency ablation was superior to conventional ethanol injection and higher-dose ethanol injection from the viewpoint of the local tumor progression, overall survival, and cancer-free survival. In the other study by Lin et al,[47] 187 patients with HCC were assigned to radiofrequency ablation, ethanol injection, or acetic acid injection.[47] Radiofrequency ablation was superior to ethanol injection and acetic acid injection with respect to local recurrence, overall survival, and cancer free survival rates, but radiofrequency ablation also caused more major complications. In our study, 232 patients with HCC who had 3 or fewer lesions, each 3 cm or less in diameter, and liver function of Child-Pugh class A or B were entered onto a randomized controlled trial.[18] The primary endpoint was survival, and the secondary endpoints were overall recurrence and local tumor progression. Radiofrequency ablation had a 46% smaller risk of death, a 43% smaller risk of overall recurrence and an 88% smaller risk of local tumor progression than ethanol injection. The incidence of adverse events was not different between the 2 therapies. Recently, a randomized controlled trial to compare radiofrequency ablation with surgical resection reported that there was no difference between these 2 treatments from the viewpoints of overall survival and disease-free survival while post-treatment complications were more often and severe after surgery.[48]

Adverse effects and complications. Knowledge of the broad spectrum of adverse effects and complications and relevant management is mandatory to perform radiofrequency ablation safely, although its mortality and morbidity rates are much lower than those reported for surgery. Common adverse effects of radiofrequency ablation were pain, fever, nausea, and asymptomatic right pleural effusion. Mulier et al[49] reviewed 82 articles and reported that the mortality and morbidity rates of 3,670 patients treated by radiofrequency ablation were 0.5% and 8.9%. There were 20 deaths reported, as a result of sepsis (n=7), liver failure (n=7), cardiac complications (n=4), peritoneal hemorrhage (n=1), and bile duct stricture (n=1). Major complications were abdominal bleeding (1.6%), abdominal infection (1.1%), bile tract damage (1%), liver failure (0.8%), dispersive pad skin burn (0.6%), hepatic vascular damage (0.6%), visceral damage (0.5%), cardiac complications (0.4%), myoglobinemia or myoglobinuria (0.2%), tumor seeding (0.2%), coagulopathy (0.2%), and others. The complication rate was similar for the percutaneous (7.2%), laparoscopic (9.5%), and simple laparotomic (9.9%) approach while the laparotomic combined with cryotherapy, hepatic or extrahepatic resection had a morbidity rate of 31.8%. A multicenter study in Italy reported that 6 deaths (0.3%) were noted among 2,320 patients treated with the cooled-tip electrode, including multi organ failure following intestinal perforation (n=2), septic shock following *Staphylococcus aureus*-caused peritonitis (n=1), massive hemorrhage following tumor rupture (n=1), liver failure following stenosis of right bile duct (n=1), and sudden death of unknown cause 3 days after the procedure (n=1).[50] Fifty patients (2.2%) had additional major complications. Common complications were peritoneal hemorrhage (0.5%), neoplastic seeding (0.5%), intrahepatic abscess (0.3%), and intestinal perforation (0.2%). An increased number of treatment sessions were related to a higher rate of major complications. A multicenter survey in Korea revealed one procedure-related death (0.09%) due to peritoneal hemorrhage and 37 major complications (2.4%) among 1,139 patients in 11 centers. Reported complications were hepatic abscess (0.7%), peritoneal hemorrhage (0.5%), biloma (0.2%), ground pad burn (0.2%), pneumothorax (0.2%), vasovagal reflex (0.1%), and others.[51]

In conclusion, in the treatment of HCC, image-guided percutaneous local ablation therapies have been playing more and more important roles. Among various local ablation therapies, radiofrequency ablation has been replacing ethanol injection as a standard therapy for patients who have unresectable HCC or who do not want surgery. Randomized controlled trials of radiofrequency ablation with surgery from the viewpoint of survival would be mandatory in the near future.

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Statistics

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Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of *P* values, which fails to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the computer software used.