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Recent Progress in Radiofrequency Ablation Therapy for Hepatocellular Carcinoma

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Key Words

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Abstract

In order to attain better ablation and more effective management of hepatocellular carcinoma (HCC), new approaches and devices in radiofrequency ablation (RFA) therapy were presented and discussed in a workshop at the 50th Annual Meeting of the Liver Cancer Study Group of Japan. A novel bipolar RFA apparatus was introduced in Japan in January 2013. Hundreds of subjects with HCC were treated with multipolar RFA with varied devices and plans. Among these, no-touch ablation was one of the most useful procedures in the treatment of HCC with the apparatus. In RFA therapy, a few assisting devices and techniques were applied for convenience and improvement of the thermal ablation procedure. Contrast-enhanced ultrasonography and three-dimensional fusion imaging technique using volume data of CT or MRI could improve exact targeting and shorten the treatment time for RFA procedures under ultrasonographic guidance. A more complicated method using a workstation was also reported as being helpful in planning the ablated shape and volume in multineedle RFA. The effective use of sedatives and antianalgesics as well as a novel microwave apparatus with a cooled-tip electrode was also discussed.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide, with an annual incidence of one million new cases [1]. In about 90% of the patients, HCC is a late complication of cirrhosis. The 5-year incidence of HCC in patients with cirrhosis is 15–20%. The risk of developing HCC has been reported to be 0.5% per year for hepatitis B and 5% per year for hepatitis C patients. Consequently, HCC is now emerging as a major health concern for the next decades. Most patients develop few symptoms when the tumor is small and often present with multifocal disease only at a late stage. The natural course of HCC includes progressive tumor growth compromising the hepatic function, intrahepatic metastases and spread to distant sites. In general, HCC has a poor prognosis, with a median survival of 3–6 months after the onset of symptoms. Nowadays, an increasing number of HCCs is discovered at an early stage because of an increasing awareness and screening of asymptomatic patients with cirrhosis [2]. During the last decade, percutaneous locoregional therapy has become the predominant treatment for a small HCC associated with cirrhosis because of poor liver function reserve and a high recurrence rate after surgical resection.

Radiofrequency ablation (RFA) therapy [3] became available in 1999 in Japan, and turned into an indispensable procedure for the management of small-sized HCC. RFA therapy is especially useful for patients with recurrent tumors, bilobar tumors and tumors located deep in the liver. It is also effective in elderly patients and in patients with other concomitant diseases and cardiac, renal, lung or neurological complications. In the last 15 years, many devices and studies have been described in order to better manage the early stages of HCC.

At the 50th Annual Meeting of the Liver Cancer Study Group of Japan (congress president: Prof. Masatoshi Kudo), a workshop was conducted regarding the recent progress in RFA, which was presented and discussed by 11 hepatology experts (for a summary, see below).

Current Status of RFA

A complete tumor ablation rate of over 90% was achieved with RFA, and the remainder can usually be ablated with additional RFA therapy. Although the tumor recurrence rate or the residual tumor rate is significantly higher after RFA compared with surgical resection, overall survival is generally regarded as not significantly different between RFA and surgery.

Sunakozaka and colleagues compared the prognosis after surgical resection [4, 5] (n = 157) with that after RFA (n = 363) using propensity scores with the inverse probability of treatment weighting method. After selection bias regarding the treatment type (RFA or resection) was adjusted for to some extent, the survival rates between patients with RFA and resection were not different retrospectively. The odds ratio for survival of the propensity score was 1.15 (favoring surgical resection, 95% CI 0.56–2.28). These experts found that the survival period seemed prolonged when patients with decreased liver function received RFA therapy instead of surgery. A multicenter prospective randomized controlled trial (the SURF study) will show the real efficiency of RFA in recurrence-free survival and overall survival in the Japanese clinical setting.

Some surgeons have reported that recurrent or residual tumor tissue after RFA might have malignant characteristics in the pathology of resected HCCs. Saito and colleagues analyzed the clinicopathological features of 10 HCC patients who showed local recurrence after RFA therapy. They selected retrospective patient data as well as searched at the surgical department for biased data and compared them with data of 78 HCC patients without previous RFA intervention. The incidence of poorly differentiated histology (4/10 vs. 72/78, $p < 0.01$) and portal vein invasion (8/10 vs. 13/78, $p < 0.01$) was significantly higher in the HCC patients with previous RFA therapy than in the treatment-naïve HCC patients. The survival rate was significantly lower ($p = 0.03$) and the disease-free survival rate lower ($p = 0.01$) in the patients undergoing RFA therapy. The investigators also noticed a high incidence of extrahepatic metastases (3/10 vs. 6/78, $p < 0.05$) after surgical resection of recurrent HCC after RFA therapy. They analyzed angiogenesis markers (HIF-1, VEGF), cancer stem cell markers (EpCAM, CD44) [6, 7] and epithelial-mesenchymal transition (EMT) markers (TGF-β, twist, snail-1, vimentin) in RT-PCR of the patient serum and in immunohistochemistry of the resected specimen. Since almost all angiogenesis markers, stem cell markers and EMT markers increased to some extent in HCC with previous RFA therapy, the investigators supposed that insufficient thermal ablation led to a malignant transformation with EMT. Since treatment-naïve and treatment-resistant HCCs after the other modalities of therapy sometimes also show these malignant characteristics to some

extent, the analysis of the limited number of selected patients in the surgical department should be carefully interpreted considering the presence of significant data bias.

Monopolar and Bipolar Ablation

In Japan, monopolar RFA treatment (cooled-tip, LeVeen or RITA system) became available in 1999 and bipolar RFA treatment (CelonPOWER) in 2013. More than 50 institutions and hospitals currently use the bipolar system.

Kawamura and colleagues presented various advantages of the bipolar RFA system, especially the no-touch ablation procedure. Treatment benefit is mostly obtained in subcapsular tumors [8], tumor nodules just behind major vascular structure, potentially poorly differentiated tumors, and irregularly shaped nodules. Since other types of HCC nodules also showed a decreased dissemination risk with the treatment, 44 of 130 nodules (34%) were treated with no-touch ablation.

Joko and colleagues reported on 174 patients undergoing bipolar RFA. More than 70% of the treatments were performed using 3 electrodes, and more than half of the nodules were treated with no-touch ablation. These experts revealed that current bipolar apparatus could treat tumors as large as 3.5 cm in diameter with the no-touch system using 3 needles (6 electrodes) around the nodules. They proposed to extend the indication for RFA to cases where multipolar ablation is performed appropriately, except for small-sized HCC.

On the contrary, Nasu and colleagues studied the ideal use of single-needle ablation with the bipolar RFA system. They tried to obtain a small and round ablative area for a small HCC nodule using a single 20-mm applicator (T20) and compared two types of radiofrequency output programs: a conventional protocol with constant 20-Watt output to 10 kJ energy (n = 9) and a step-up protocol with increasing power from 10 W to 3 kJ, from 15 W to 6 kJ and from 20 W to 10 kJ (n = 6). The longitudinal length of the ablated area was the same in the two protocols; however, the transverse length was significantly longer in the step-up protocol ($p = 0.0015$). Although the step-up protocol required a longer treatment time, the revised manner of output control generated a more round and larger necrotic area. Nasu and colleagues therefore recommended the step-up control of output for a small-sized HCC using a 20-mm applicator.

Nakanishi and colleagues reported the usefulness of bipolar RFA in a patient with a cardiac pacemaker comparing monopolar and bipolar ablation. The patient showed a significant decrease in blood pressure with monopolar ablation but did not show any blood pressure change with the bipolar RFA procedure.

Application and Assisting Devices

When RFA is performed under ultrasonographic guidance, there are several reasons for the difficulty in targeting and inserting a needle to an exact point of an HCC nodule, e.g. a small lesion of less than 1 cm, invisible or vague nodules, concomitant confusing or misleading nodular lesions around the tumor and local tumor progression of a previously ablated lesion. When a small nodular lesion is detected on CT or MRI during the follow-up period after ablation therapy or surgical resection, ultrasonography sometimes cannot demarcate the lesion.

Uchino and colleagues studied patients with HCC tumors that are hard to visualize on B-mode ultrasonography. Sonazoid-enhanced ultrasonography was performed in 107 patients with 140 lesions that were vague and invisible on ordinary ultrasound. A total of 140 sessions of RFA therapy were performed under contrast-enhanced ultrasound, and an electrode was inserted in the Kupffer phase in 109 sessions (77.9%), in the arterial phase in 14 sessions (10.0%), and in the ordinary B-mode in the remaining 17 sessions (12.1%). In 114 cases (88.4%), an effective enhancement was achieved at the first session of RFA, and in these complete ablation was attained in 97.4%. Sonazoid-enhanced ultrasonography was useful in small-sized lesions, subcapsular lesions, lesions neighboring previous ablated areas and lesions requiring an additional ablation. On the contrary, sonazoid enhancement was often ineffective in obese patients and patients with a shrunk liver.

Minami and colleagues retrospectively analyzed difficult-to-visualize tumors on B-mode ultrasonography. They compared fusion imaging assistance, enhanced ultrasonography assistance and both fusion imaging plus enhanced ultrasonography assistance in the treatment of RFA. Enhanced ultrasonography was additionally performed when fusion imaging was ineffective in demarcating a tumor, and vice versa. Since the number of required treatment sessions, local tumor progression rate and incidence of adverse events were not different among the three treatment groups, fusion imaging and contrast-

enhanced ultrasonography are regarded as mutually complementary and useful assisting devices in RFA therapy. In addition, Nakanishi and colleagues stated that fusion imaging and sonazoid-enhanced ultrasonography in RFA are helpful and improve the certainty of the ablation procedure.

Sano and colleagues proposed various devices to improve RFA therapy with the bipolar system. The ablation area and shape after treatment were evaluated three-dimensionally using workstation software, and simulation techniques seemed helpful in an appropriate bipolar ablation procedure even after treatment. The ultrasonography function of the Virtu-TRAX™ (GE Healthcare) can indicate the exact depth of multiple inserted needles and helps to perform a sufficient and safe ablation.

Analgesic Agents

In the treatment of RFA, most Japanese doctors use morphine, pethidine, pentazocine or fentanyl as antianalgesics and midazolam or diazepam as sedatives instead of general anesthesia. The administration of these conventional analgesics is sometimes associated with insufficient analgesic effects, and sedatives may cause serious or life-threatening breathing problems such as shallow, slowed or temporarily stopped breathing. Since benzodiazepine derivatives often induce a drowsy and unconscious state followed by significant difficulty in 'awake ablation', following the operators' instructions is mandatory.

Nagai and colleagues used dexmedetomidine, an alpha-2 adrenergic receptor agonist highly specific to the central nervous system. Its indication has recently been expanded to include nonintubated patients requiring sedation for surgery or short-term procedures. It is also useful as an adjunct for sedation and general anesthesia in certain operations and invasive medical procedures such as colonoscopy. The investigators performed monopolar or bipolar RFA therapy in 23 patients with HCC. The sedative ability of dexmedetomidine was evaluated with six grades using the Ramsay sedation score. During the median ablation period of 14 min, all patients were successfully treated with (n = 18) or without (n = 5) additional analgesic agents. Although Nagai and colleagues added pentazocine or pethidine in some patients, they emphasized that dexmedetomidine was very safe during and after the procedure for elderly patients, and that its administration was easy to control.

Novel Microwave Ablation

Noguchi and colleagues introduced a novel microwave device, the cooled microwave antenna (CMA), which is already available in Western countries. The CMA system has been reported to ablate larger volumes of tissues than previous microwave devices without a tip-cooling system. The investigators compared the ablation ability of the cooled-tip RFA system with that of the CMA device using ex vivo bovine liver. The median size of the ablation area was 46.2 × 34.0 mm after 12 min with the cooled-tip system (n = 5), whereas it was 56.0 × 35.8 mm after 5 min and 69.0 × 48.6 mm after10 min with the CMA system (n = 5). The CMA system thus ablated a larger area in a shorter time, because high ablative power seemed to be provided to a wide range of liver tissues without heating the tip of the electrode. The experts emphasized that the use of the CMA system can result in both a shorter treatment time and a larger ablation volume in the treatment of HCC.

Future Perspective of RFA

The recent development of RFA has expanded the range of treatments of HCC. The main characteristic of RFA therapy is the localized tumor destruction in situ with maximal preservation of the noncancerous part of the liver parenchyma, in contrast to the significant liver damage caused by other interventional therapies such as transcatheter arterial chemoembolization and intra-arterial chemotherapeutic infusion [9].

Future studies from the technical viewpoint should focus on (1) the development of optimal ablation techniques for bipolar and multipolar systems that can generate optimal volumes and shapes of tissue destroyed, (2) varied efforts for reducing side effects (most favorable analgesic therapy, avoidance of biliary tree complication, and so on), (3) various attempts of image assistance to attain more effective RFA procedure, and (4) the assessment of efficacy of multimodal and combined treatments.

Disclosure Statement

The authors declare that no financial or other conflicts of interest exist in relation to the content of this article.

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