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Review Article

# Recent technical advances in radiofrequency ablations for hepatocellular carcinoma

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A B S T R A C T

Radiofrequency ablation (RFA) has regarded as a curative treatment method for early stage hepatocellular carcinoma (HCC), providing comparable overall survival to surgical resection. However, lack of ideal guiding modality for RFA procedure and higher rate of local tumor progression (LTP) after treatment than surgical resection have been important limitations. To overcome the current limitations of RFA, the fusion imaging between real-time ultrasound and reference computed tomography/magnetic resonance images has been introduced. The fusion imaging could improve the feasibility of RFA for HCC by helping the accurate identification of target HCC, especially for invisible small HCC. In addition, RFA using multiple electrodes with multi-channel generator and various energy delivery modes could improve the therapeutic efficacy, by creating larger ablation volume than RFA using a single electrode. RFA using multiple electrodes can allow no touch ablation technique, which might have a potential to reduce LTP. In this review, these recently introduced ablation techniques will be discussed with the results of both animal and clinical studies.



Keywords: Hepatocellular carcinoma; Multimodal imaging; Radiofrequency ablation

## Introduction

Radiofrequency ablation (RFA) has been regarded as a curative treatment modality for hepatocellular carcinoma (HCC), together with surgical resection, particularly for small tumor less than 3 cm in size.[1] Although microwave has emerged as another energy source of local ablation for HCC, and replaced RFA due to the better physical properties compared to RFA, especially in Europe and North America, RFA provided comparable therapeutic efficacy for HCC to microwave ablation in recently published randomized controlled trials,[2,3] and still has an important role for HCC management. Regarding the treatment outcome, previous studies reported that RFA could provide about 60% of overall survival rate at 5-year after treatment for early stage HCC, which was similar to that after surgical resection.[4–7] It has been well known that the major complication rate of RFA is usually less than 5%, and significantly lower than that of surgical resection.[4–7] According to the result of meta-analysis and cost-effectiveness analysis done by Cucchetti et al,[8] RFA was more cost-effective than surgical resection for patients having very early stage HCC defined as single nodular HCC less than 2 cm and patients with two or three HCCs all less than 3 cm, probably owing to the less invasiveness of RFA compared to surgical resection. Based on the evidence provided by aforementioned previous studies, a practice guideline for HCC management proposed by the European Association for the Study of the Liver recommends RFA as the first line treatment modality for very early stage HCC, along with surgical resection.[9]

However, RFA has several drawbacks compared to surgical resection. One of the most important limitation of RFA is the higher rate of local tumor progression (LTP) than surgical resection owing to the incomplete ablation or insufficient ablation margin at the tumor periphery.[10] The reported 5-year cumulative incidence of LTP after RFA for HCC has ranged from 15% to 30%,[4,6,7] and was significantly higher than 3% to 5% of surgical resection. Regarding the risk factor for development of LTP after RFA for HCC, tumor size and insufficient ablation margin are well-known risk factors. Therefore, the creation of larger ablation volume enabling achievement of complete tumor destruction with sufficient ablation margin more than 5-mm would need to improve the local control rate of RFA for HCC. Another limitation of percutaneous RFA is the lack of ideal method to guide and monitor the procedure. Currently, real-time ultrasound (US) is widely used for the

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guidance of electrode placement within the target tumor and for the monitoring of RFA procedures. However, US has an intrinsic weakness in the visualization of target tumor located in the liver dome, the tip of the left lateral segment and below the ribs where the penetration of US beam is limited. In addition, small HCC around 1 cm in size would not be identified on B-mode US, making the accurate RF electrode placement within the target tumor difficult.

There have been several efforts to overcome the current limitations of RFA. For example, the fusion imaging between real-time US and reference computed tomography (CT) or magnetic resonance (MR) imaging can help the accurate identification of target tumor and exact placement of electrode. Several recent studies reported that RFA using real-time US/CT or MR fusion imaging guidance could expand the feasibility of RFA for invisible small HCC and improve the therapeutic efficacy of RFA in local tumor control.[10–12] In addition, RFA using multiple electrodes and multi-channel generator with various switching system has a potential to create larger ablation volumes in a given time compared to the RFA using a single electrode which is a conventional manner. Both animal studies and clinical studies reported that RFA using multiple electrodes could provide larger ablation zone with lower rate of LTP than RFA using a single electrode.[13–16] The use of multiple electrodes for RFA procedure enables no-touch ablation technique which has a potential to reduce the LTP rate. In this review, we will briefly discuss the recent technical advances in RFA for HCC, focusing on the real-rime US/CT or MR fusion imaging guidance and use of multiple electrodes system with the results of published studies. The potential merit of no-touch RFA for HCC treatment will also be discussed.

## Fusion Imaging between Real-Time Ultrasound and the Reference Computed Tomography or Magnetic Resonance Images

US has several merits over other imaging modalities such as CT or MR including real-time imaging capability, no need of radiation exposure, wide accessibility and low cost.[17,18] Owing to these merits, US has been the most widely used guiding modality for interventional procedures of the liver including RFA for HCC. However, US also has several drawbacks for guidance of RFA procedures. First, the scan plane of US is different from that of CT or MR. US images are usually acquired in oblique axial or sagittal plane. In contrast, liver CT or MR images are usually obtained in orthogonal axial or coronal plane. Owing to the difference in scan plane between US and CT or MR, the operator should mentally register the reference CT or MR image to real-time B mode US image during the procedure.[10] Indeed, difference in scan plane between real-time US and reference CT or MR images might cause error during the mental registration, resulting in miss-targeting or incomplete ablation.[19] Limited sonic window is another drawback of US for guidance of interventional procedures. It has been well known that US might have several blind areas in the liver including liver dome, far lateral tip of liver left lateral segment and below the ribs, and the target tumor located in these blind areas might not be identified on B-mode US. To overcome the current limitations of B-mode US for guidance of interventional procedures, fusion imaging between real-time US and the reference CT/MR images has been developed and introduced during the past decade. Among the various tracking methods, electromagnetic tracking technique is the most commonly used tracking method for the fusion imaging of the liver.[20] There are three elements including magnetic field generator, position sensor, and position sensor unit in the electromagnetic tracking method for fusion imaging,[11] and currently, almost all major US vendors provide them. For the liver fusion imaging, either internal or external markers to align the real-time B mode US image to the reference CT/MR images can be used. However, owing to the need of obtaining the reference CT/MR images with the external fiducial markers attached to the patient body surface before procedures for the use of external markers, internal markers including anatomic landmarks of the patients such as bifurcation of portal or hepatic veins have been widely used in the current fusion imaging technique of the liver.[21]

Fusion imaging between real-time US and the reference CT/MR images using electromagnetic tracking method and internal markers usually consists of three steps. The first step is transferring the reference CT/MR images obtained before RFA procedures to the US machine. Then, the plane registration is performed to align the real-time B mode US images to the transferred reference CT/MR images at the same plane. For this step, any plane showing the anatomic landmarks including portal or hepatic vein clearly on both US and the reference CT/MR images can be chosen. After plane registration, point registration can be done as the third step to match between real-time US images and the reference CT/MR images more precisely by pointing out the same anatomic landmarks near the target tumor on both real-time US images and the reference CT/MR images. Even after initial fusion imaging precisely performed, some miss-registration between real-time US and the reference CT/MR images would occur during the procedures, mainly due to the patient respiratory motion. In that case, point registration can be repeatedly done to adjust fusion imaging and to match two imaging sets precisely again. After aforementioned three steps, the real-time US images and the reference CT/MR images display side-by-side showing the same plane or real-time US images are overlaid to the reference CT/MR images on the US monitor, and move synchronously during the procedures enabling accurate detection of target lesion and monitoring the procedures.[10] The time needed for the fusion imaging would depend on the operator's experience level and the involved fusion technique, but generally ranges from 1 to 5 minutes. This working time of the fusion imaging enables the clinical use of fusion imaging for interventional procedures. Although the fusion imaging could match the two image sets precisely, there would be some registration errors. Several *ex vivo* experimental studies reported that there would be an approximately 3 mm registration error between real-time US and the reference CT/MR images.[22,23]

Compared to the conventional B-mode US images only, the fusion imaging can identify the target tumor more accurately. Owing to this merit of fusion imaging, the usefulness of fusion imaging for RFA of HCC has been evaluated just after the introduction of the fusion imaging in interventional procedure of the liver. According to the results of early studies, the fusion imaging could significantly improve the lesion conspicuity of target HCC[21] as well as the feasibility of RFA for HCC.[21,22,24] The number of RFA sessions for HCC would also be reduced with the aid of the fusion imaging compared to the use of B-mode US only guidance.[21,22,24] Indeed, the fusion imaging enabled RFA even for invisible HCC on conventional B-mode US since the fusion imaging can display reliable landmarks including hepatic vessels near the target HCC seen on the reference CT/MR images on real-time working US images, resulting in the operator confidence for performing RFA for invisible HCCs.[10,11] Regarding the therapeutic efficacy of RFA for invisible HCC on conventional B-mode US, Ahn et al[12] reported that the technical effectiveness of RFA using the fusion imaging for invisible HCC on conventional B-mode US was similar to that of RFA for visible HCC. Given that, the fusion imaging would be a preferred guiding modality for RFA of HCC, significantly increasing the target tumor conspicuity as well as technical feasibility especially for small invisible HCC on conventional B-mode US. Currently, the fusion imaging between real-time US and the reference CT/MR images is considered as one of the standard guiding methods for RFA of HCC.

Despite the clinical usefulness of the fusion imaging for RFA of HCC, there have also been several limitations in the current fusion imaging technique. Even after the repeated application of point registration, there might be some registration errors between real-time US images and the reference CT/MR images in the fusion imaging technique. The possible cause of registration error in the fusion imaging is the difference in acquisition status between real-time US images and the reference CT/MR images. The real-time US images are usually obtained during the free-breathing while the reference CT/MR images are usually scanned during the breathing holding. Therefore, the reference CT/MR images can be regarded as a static imaging whereas the real-time US images as a dynamic imaging. Since the liver moves three dimensionally during the different respiratory cycles changing the volume and shape among the different respiratory phases to some degree, the difference in respiratory status between real-time US images and the reference CT/MR images can cause some registration errors in the fusion imaging.[10] In addition, since most of the commercially available fusion imaging systems utilize the rigid registration algorithm, the potential difference in liver shape and volume between dynamic real-time US images and static reference CT/MR images would not be compensated.[25] Peripheral tumor location might be another limitation of the current fusion imaging for RFA of HCC. According to the result of study done by Lim et al,[26] the incidence of miss-targeting under the guidance of the fusion imaging is 1.3% (7/551) of patients with HCCs treated by RFA, and the majority of miss-targeting occurred in HCC less than 1.5 cm and located in the liver peripheral portion. Peripherally located HCC is more prone to registration error than centrally located HCC since the relatively long distance between anatomic landmarks and the target tumor can increase the registration error.[10] In addition, deformation of liver shape during the various respiratory cycles might be more pronounced in the liver peripheral portion than in the central portion.[26] Therefore, caution needs to reduce the miss-targeting for HCC located in the peripheral portion of the liver. In this regard, contrast-enhanced US combined with the fusion imaging can decrease the miss-targeting of HCC, particularly located in the peripheral portion of the liver.[11]

## Radiofrequency Ablation Using Multiple Electrodes with Various Switching Methods

Traditionally, RFA for HCC has been performed using a single electrode placing it in the central portion of the target tumor. Since a single internally cooled electrode can confidently create a ablation zone with 2.5–3 cm in size, complete tumor destruction with a sufficient ablation margin more than 5 mm could be achieved for HCC with 1.5–2 cm in diameter.[27] In contrast, for HCC larger than 2 cm, obtaining complete tumor destruction with a sufficient ablation margin with the use of a single electrode in a single ablation session would be quite difficult. Thus, multiple overlapping technique is frequently needed to obtain a sufficient margin around the target tumor.[28–31] However, multiple overlapping technique using a single electrode is quite challenging, especially under the US guidance, since an echo-cloud complex of micro-bubbles created during the first session of RFA can limit the sonic window, making the reposition of an electrode to the appropriate area difficult. Indeed, insufficient overlapping can increase the risk of incomplete tumor ablation as well as the development of LTP.[28,32]

One potential method to overcome the current limitation of RFA using a single electrode is the use of multiple electrodes for RFA procedures. To use multiple electrodes, the multi-channel generator is also needed, and multiple electrodes systems with multi-channel generators and various energy delivery modes have been developed and introduced in clinical practice.[10] Among the various energy delivery methods using multiple electrodes, switching monopolar RFA has been the most widely used technique. In switching monopolar mode using multiple electrodes, RF energy is delivered to a single electrode and then switched to another electrode (i.e., single switching monopolar mode) when the impendence around the first electrode increased after the RF energy application. Previous studies reported that RFA using multiple electrodes with switching monopolar mode could create an ablation zone up to 5 cm size in both animal[32] and human liver.[33] Therefore, RFA with multiple electrodes and switching monopolar mode can be used for the treatment of medium sized (2–4 cm) HCC. According to the result of prospective study done by Woo et al,[34] switching monopolar RFA with up to three multiple internally cooled electrodes provided 99.4% of technical effectiveness rate and 11% of 3-year cumulative incidence of LTP for small and medium sized HCC. Regarding the complication rate, there would be a possibility of increasing the rate of complication such as bleeding in RFA using multiple electrodes compared to the RFA using a single electrode, since RFA using multiple electrodes inevitably needs more electrode insertions than RFA using a single electrode. However, the major complication rate after RFA using multiple electrodes and switching monopolar mode ranged from 3% to 5%,[15,34,35] which seemed similar to that of RFA using a single electrode.

The use of more than three electrodes for RFA of HCC enables the dual switching monopolar (DSM) RFA. In contrast to the switching monopolar mode which deliver the RF energy to a single electrode and switch to another electrode (i.e., single switching monopolar mode), in DSM mode, RF energy is simultaneously applied to two electrodes and switched between the pair of electrodes.[36] Since the RF energy is applied to the two electrodes at the same time, RFA using DSM mode can improve the efficacy of RF energy delivery which would result in the creation of a larger ablation zone in a given time when compared to RFA using single switching monopolar mode.[37] DSM RFA using three electrodes created a significant larger volume of ablation zone compared to the RFA using single switching monopolar mode in both *ex vivo*[36] and *in vivo* animal models.[38] In addition, Choi et al[37] reported that DSM RFA could obtain a significantly larger ablation volume in a given time than RFA using single switching monopolar mode in their prospective study.

In contrast to the single/dual switching monopolar mode that RF currents flow between electrode and dispersive ground pad, in bipolar mode, RF currents flow between two electrodes.[13,31] Therefore, RFA using bipolar mode can concentrate the RF currents between tips of the electrodes, improving the RF energy delivery efficacy and hear production compared to the monopolar mode RFA. However, inherent possibility of overheating which can cause charring and rapid rise in impedance would be a potential limitation of RFA using bipolar mode. To overcome this potential limitation of bipolar mode, two methods have been introduced: 1) switching bipolar/multipolar mode; and 2) saline-perfused bipolar RFA using internally cooled wet electrodes with the instillation of saline into the target tissue during the RFA procedures.[10] In switching bipolar/multipolar mode, when impedance rise after the application of RF energy to one pair of electrodes, then RF energy delivery switches to another pair of electrodes, keeping the continuous RF energy delivery and avoiding the rapid rise of impedance and charring.[39,40] In saline perfused bipolar RFA, the infused saline into the intratumoral tissue could alter the tissue conductivity, allowing greater deposition of RF current to the target tissue.[13] In addition, a previous experimental study reported that bipolar mode RFA using two or three internally cooled wet electrodes with saline perfusion could create more spherical shape of ablation than RFA with switching monopolar mode.[41]

## No Touch Radiofrequency Ablation

Using multiple electrodes for RFA procedures enables the "no-touch" ablation technique which could be another merit of using multiple electrodes, in addition to the creation of larger ablation volume. Traditionally, RFA for HCC has been performed by placing a single electrode into the central portion of target tumor for optimal thermal energy delivery. Therefore, target HCC itself is directly punctured during the electrode placement for RFA procedures. The violation of HCC itself during the treatment would have a potential risk of tumor cell dissemination to the adjacent peritumoral liver parenchyma, which might result in the development of LTP. Direct tumor puncture RFA could also have a potential of tract seeding, although the incidence of tract seeding seemed quite low ranging from 0.3% to 2.8%.[42–44] In addition, when the electrode is not accurately inserted into the central portion of HCC (i.e., off-center electrode insertion to the target HCC), some portion of the HCC far from the electrode might not sufficiently reach a lethal temperature, which would potentially result in the development of LTP after RFA for HCC.

Contrast to the conventional direct tumor puncture RFA, multiple electrodes are inserted into the outside of target HCC boundary, not violating tumor itself in touch RFA (Fig. 1). Therefore, theoretically, there would be no risk of tract seeding after no touch RFA since tumor itself is not punctured during the RFA procedure. Also, since multiple electrodes are inserted into the peritumoral parenchyma outside the target HCC, no touch RFA can create a larger ablation volume compared to the RFA using a single electrode with tumor puncture method, potentially reducing the incidence of LTP.[39,45] In addition, blood supply to the target HCC could be blocked in the early period of no touch RFA since tumor feeders are usually located in the tumor periphery where the area initially ablated in no touch RFA. Another potential merit of no touch RFA over direct tumor puncture RFA would be the less number of tumor cells in systemic circulation after treatment because peripherally located draining vein of HCC could also be obliterated in early phase of treatment. However, there would be some limitations in no touch RFA compare to the direct tumor puncture RFA. First, since multiple electrodes should be inserted into the outside of target tumor boundary, no touch RFA is technically more challenging. In addition, when the distance between electrodes is not ideal, the shape of ablation zone could be irregular and unpredictable. Owing to the use of multiple electrode and larger ablation zone, the possibility of complication such as bleeding requiring angiographic embolization, parenchymal and vascular damage would increase. Regarding the therapeutic efficacy of no touch RFA for HCC, Seror et al[45] reported the long-term results of no touch RFA using multipolar mode for the treatment of HCCs within Milan criteria, showing the estimated 5-year cumulative incidence of LTP of 6%, which seemed better than 15% to 30% of conventional tumor puncture RFA. In addition, Kim et al[46] reported that no touch RFA significantly reduced the rate of peritoneal tumor dissemination compared to direct tumor puncture RFA in their rabbit liver tumor model. No touch RFA could provide significantly lower rate of LTP and better local tumor control than conventional tumor puncture RFA in both multicenter retrospective study[39] and a prospective randomized controlled trial.[47] According to the result of a recently published multicenter prospective study done by Lee et al,[48] the cumulative incidence of LTP after no touch RFA for single HCC equal to or less than 2.5 cm in size was 1.6% at 2-year, which seemed better

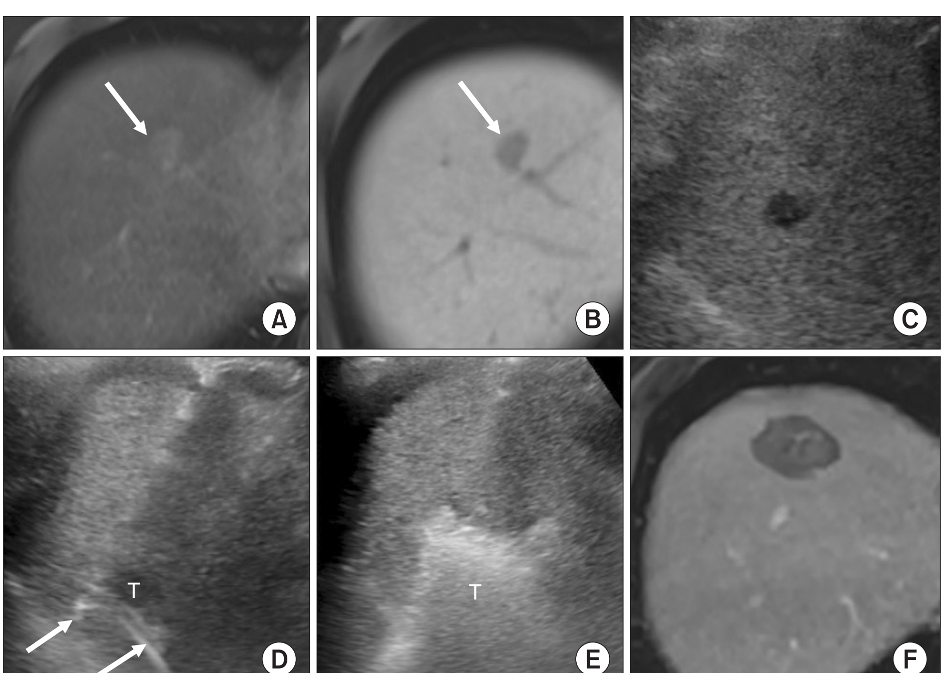


**Fig. 1.** Radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) using multiple electrodes and no-touch ablation technique. (A) Gadoxetic acid enhanced arterial phase axial magnetic resonance (MR) image shows a 1.5-cm sized enhancing nodular lesion in segment VIII dome of the liver (arrow). (B) This nodule shows low signal intensity on hepatobiliary phase (arrow) indicating HCC. (C) On B-mode ultrasound image, target tumor appears as low echoic nodular lesion. (D) Three electrodes are inserted into the outside of target tumor boundary, and two of them are shown (T, target tumor; and white arrow, electrode tip). (E) After the delivery of RF energy, the echo-cloud complex is created, completely encompassing the target tumor. (F) There is no local tumor progression on portal venous phase axial gadoxetic acid enhanced liver MR image obtained 3 years after no touch RFA.

than that after conventional tumor puncture RFA. Given that, no touch RFA might be a preferred treatment method to conventional tumor puncture RFA since it can provide significantly better local tumor control.

## Conclusion

RFA is a curative treatment modality for HCC, and plays a pivotal role for management of HCC patients. However, lack of ideal guiding modality and higher rate of LTP after treatment compared to surgical resection have been important limitations of the current RFA technique. To overcome the current limitations of RFA, the fusion imaging between real-time US and the reference CT/MR images has been developed and introduced in clinical practice. The fusion imaging can help the accurate identification of target tumor, resulting in significant improvement of RFA feasibility. In addition, the fusion imaging enables RFA for invisible HCC on conventional B-mode US images, providing similar therapeutic outcome after treatment to that for visible HCC. The use of multiple electrodes with multi-channel generator and various energy delivery modes for RFA procedure can provide significantly larger ablation volume in a given time than the use of a single electrode, and thus would improve the therapeutic efficacy of RFA for HCC. The use of multiple electrodes for RFA procedures enables no touch ablation technique. Since no touch RFA could provide significantly lower rate of LTP after treatment compared to the conventional tumor puncture RFA, no touch RFA might be a preferred ablation method. Given that, no touch RFA using multiple electrodes under the guidance of the fusion imaging between real-time US and the reference CT/MR image could synergistically improve the therapeutic efficacy of RFA, by improving the local tumor control. Therefore, to obtain the most optimal outcome of RFA for HCC, the operators should be familiar with these recently developed techniques.


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## Conflicts of Interest

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