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# Radiofrequency ablation of liver tumors: Actual limitations and potential solutions in the future

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## Abstract

Over the past decade, radiofrequency ablation (RFA) has evolved into an important therapeutical tool for the treatment of non resectable primary and secondary liver tumors. The clinical benefit of RFA is represented in several clinical studies. They underline the safety and feasibility of this new and modern concept in treating liver tumors. RFA has proven its clinical impact not only in hepatocellular carcinoma (HCC) but also in metastatic disease such as colorectal cancer (CRC). Due to the increasing number of HCC and CRC, RFA might play an even more important role in the future. Therefore, the refinement of RFA technology is as important as the evaluation of data of prospective randomized trials that will help define guidelines for good clinical practice in RFA application in the future. The combination of hepatic resection and RFA extends the feasibility of open surgical procedures in patients with extensive tumors. Adverse effects of RFA such as biliary tract damage, liver failure and local recurrence remain an important task today but overall the long term results of RFA application in treating liver tumors are promising. Incomplete ablation of liver tumors due to insufficient technology of ablation needles, tissue cooling by the neighbouring blood vessels, large tumor masses and ablation of tumors in close vicinity to heat sensitive organs remain difficult tasks for RFA. Future solutions to overcome these limitations of RFA will include refinement of ultrasonographic guidance (accuracy of probe placement), improvements in needle technology (e.g. needles preventing charring) and intraductal cooling techniques.



**Key words:** Radiofrequency ablation; Hepatocellular carcinoma; Thermoablation; Colorectal cancer; Liver metastases

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## INTRODUCTION

Although surgical resection still remains the treatment of choice for primary and secondary hepatic tumors[1], several local ablative therapeutic modalities have emerged as reliable alternatives to resection[2-5] or as adjuncts in oncological treatment. Throughout the past two decades, the importance of radiofrequency ablation (RFA) has continuously increased in the treatment of localized primary or secondary cancers in the liver[6-10]. Whereas the initial indication and clinical application of RFA in visceral surgery

included the treatment of small circumscript liver lesions, the indication has gradually expanded to more complex disease[8,11] and combination of other techniques such as transarterial chemoembolization (TACE) or microwave ablation (MWA)[12]. RFA represents an effective therapeutical tool for destruction of non-resectable primary and metastatic liver tumors of variable size and location and has proven to be successfully performed transcutaneously or by laparotomy or laparoscopy using sonographic or computer tomographic guidance[13]. Different approaches have been continuously evaluated and RFA has been combined with other invasive techniques, e.g. thermal ablation and/or MWA, to engage liver tumors with different therapeutical methods[14]. RFA has become widely accepted as an approach against primary liver tumors because of its ease and safety of use, lower level of invasiveness and high level of effectiveness. RFA has been repeatedly compared to open surgical procedures in different stages of liver tumor disease and the rate of complications within the RFA treated patients has displayed a lower frequency of severe complications; thus the efficacy of RFA is comparable to open surgery[4].

## ADVERSE EFFECTS OF RFA

Severe adverse effects of RFA of liver tumors have been critically investigated and the mortality in a comprehensive monocentric series of 143 RFA procedures in 122 patients resulted in a 1.4% fatal outcome[15]. Furthermore, major complications including biliary tract damage (4.9%), liver failure (2.8%), hepatic abscess formation (2.1%), peritoneal infection (1.4%), intrahepatic haematoma and pulmonary embolism occurred in less than 1% of cases[15]. The procedure specific complication rate was about 10% and the overall complication rate around 20%. In long term analysis, biliary stricture, hepatic failure, vascular damage and hepatic abscess formation were the most common major complications of RFA, reported in several studies[15,16]. Another prospective randomized trial indicated the long term survival after RFA of colorectal liver metastases in a 10 year experience[17]. They described an actuarial survival of 24 mo, with an actual 3 and 5 year survival of 20.2% and 18.4% respectively[17].

## NUMBER OF LIVER LESIONS ARE LIMITING RFA OUTCOME

The number of liver lesions was critical and median survival of patients with less or equal three hepatic lesions was significantly better than that of patients with more than three metastatic hepatic lesions[17]. Furthermore, it has been concluded that not only the number and dominant size of hepatic lesions but also the preoperative serum level of carcinoembryonic antigen (CEA) value were strong predictors of survival[17]. Interestingly, extrahepatic disease did not adversely affect survival in this large study, an overview of a total of 292 RFA procedures[17].

## EFFECTS OF RFA IN BRIDGING FOR LIVER TRANSPLANTATION

RFA has also been propagated as a loco regional therapy for bridging HCC prior to liver transplantation. In a retrospective analysis of 123 patients, the impact of transcatheter arterial chemoembolization (TACE), yttrium-90 ($^{90}$Y) and RFA prior to OLT was investigated[18]. Interestingly, survival did not statistically change in the treatment groups compared to the non-treatment groups. Twelve patients were successfully down-staged but did not have a significant advantage in survival compared to patients that were transplanted without therapy. The authors concluded that loco-regional therapy is a safe method for patients on the transplant list that can downstage selected patients awaiting liver transplantation (OLT) but does not have an impact on survival of HCC[18].

## RFA AND THE OUTCOME IN PATIENTS WITH LIVER CIRRHOSIS

Another important topic of RFA is addressed in a study investigating the ablation of small hepatocellular carcinomas (HCC) in patients with liver cirrhosis. Mazzaferro *et al*[19] investigated RFA in 60 HCC in patients who underwent (OLT) (according to the Milan criteria). Single session RFA was performed and histological response was determined on the explanted livers. The post-RFA complete response rate was 55% rising to 63% for HCC with a diameter $\leqslant$ 3 cm[19]. Tumor satellites or new formations of HCC lesions were unaffected by RFA and significantly correlated with HCC > 3 cm in diameter. Radiological response rates were around 70% and not significantly different from histology. Major post-RFA morbidity was described with 8% and no mortality occurred[19]. Nevertheless, hepatic failure occurred in 2% and deterioration of Child-Pugh status was described[19].

## INDICATIONS AND LIMITATIONS IN THE USE OF RFA

Even though RFA has become a standard technique of ablation of liver tumors, it is of great importance to evaluate the right indications for the best possible benefit for patients. Current indications for RFA consist of limited but inoperable liver tumors, extent of distribution that permits ablation but not resection, non-operable liver tumors due to co-morbidity and non-operable due to inadequate residual functionality of liver tissue[20,21]. To further dissect the question '*who benefits most of RFA*', a study by McGrane *et al*[20] approached the question while highlighting the efficacy, the local recurrence rate and the safety of RFA application in the treatment of colorectal liver metastases. They found that RFA is not currently considered the method of choice for resectable colorectal metastases because surgical resection is, according to the reviewed literature, still superior to RFA[22]. Nevertheless,

RFA appeared safe and highly effective in tumor destruction depending on tumor size[23]. Importantly, the recurrence rate of 21.6% for tumors ≤ 2.5 cm, 52.8% for tumors 2.6 - 4.0 cm in size and 68.8% for tumors larger than 4.1 cm have been reported[24], indicating a strong argument for RFA application in smaller tumors. The reviewed data today are not sufficient to judge whether RFA prolongs survival in patients with advanced colorectal liver metastases[23]. A prospective trial by our group[25] has shown an overall survival rate at 1, 2 and 3 years of 88%, 80% and 57% respectively. An overall recurrence rate occurred in 8.8% and in lesions smaller than 3 cm in diameter was 1.6%[25]. In the conclusion of this study, the minimal local recurrence rate of colorectal liver metastases of less than 3 cm may competitively challenge the results of open surgery[25]. Despite promising single centre results, there is a strong body of opinion that does not recommend extensive RFA application today[21]. Future multi-centric studies will hopefully address this important question. In conclusion, there is an existing consensus that RFA indications can be proposed for colorectal liver lesions from 1 to 4, maximum 5 cm in diameter and that diameter and location of colorectal metastases are still the most limiting factors that challenge the use of RFA.

## MODERN ULTRASOUND POTENTIATES THE OUTCOME OF RFA

The role of ultrasound guidance is increasing in the application of RFA and became an optimal method for accurate targeting of liver tumors. Ultrasound guidance for RFA is advantageous to the CT or MRT guidance because it is more mobile, practical, readily available as well as rapid and cost-effective[26]. Advances in non-linear imaging modes and the development of 3-dimensional (3D) ultrasound probes have led to a significant improvement in the real-time contrast enhanced volumetric imaging. This progress impacts the detection, the planning and the targeting strategy of RFA needles. Although general limitations of RFA such as treatment of perihilar hepatic lesions due to the risk of biliary damage and consecutive fistula still are an issue, the technical progress is not to stop. Intraoperative ultrasound (IOUS) has been proven to gain significant new information not identified in preoperative radiological imaging. Therefore, IOUS has become the gold standard for the final evaluation of respectability of liver tumors[27]. Contrast-enhanced ultrasound (CE-US) has been shown to be highly accurate in detecting the extent and distribution of liver tumors[27]. Some recent studies have shown that new CE-US applications are of comparable sensitivity and accuracy as CT and MR scans[28,29]. A further advantage of CE-US is the possibility to restage the actual situation directly before the therapeutical intervention. The application of advanced 3 dimensional CE-US (CE-3DUS) offers new possibilities to detect liver tumors more comprehensively. The CE-3DUS data set may be transferred and computed online by a sonologist. Furthermore, dealing with larger liver tumors and recurrent liver disease, the CE-3DUS can define active tumor tissue more clearly[26]. Another important topic in targeting tumors is the selection of RFA needle electrodes. That highly depends on the tumor size to be ablated. For smaller tumors (2 to 3 cm in diameter) the geometry of tumors is usually spherical. However, larger tumors (> 3 cm) may become more ellipsoid. Local advanced disease often manifests with satellite metastases, indicating a more lobular growing tumor mass[26]. Therefore, the 3D-ultrasonographic assessment of the tumor geometry and determination of the lesion's long axis is required to plan the RFA intervention. Accurate delineation of the active tumor margins in 3 dimensions is critical to determine the actual size of the liver lesion. In an analogy to surgical liver resection, a safety margin of 0.5 to 1.0 cm should be reached in any circumstance. Especially during the ablation process, the 3D ultrasonographic technique is vastly superior to standard ultrasound[26]. The importance of the true delineation and geometry of liver tumors is also largely related to the limited ablative capability of RFA needle electrodes available today. In CE-3DUS the exact volume and rim of the liver mass can be calculated automatically, depending on the software, giving another important tool for planning RFA. The placement of RFA needle electrodes can be performed with reference to the probe position with the aid of a needle-guide or free-hand control[26]. The more specified and computed information provided by CE-3DUS enables a more aggressive approach to the ablation of large liver lesions. The combination of several RFA needle electrodes and/or electrodes with multiple antennas create coagulation necrosis beyond 7 cm[26]. Importantly, the number of electrodes should be minimized to prevent tumor cell spill and further complications.

Another important part of the RFA treatment is to monitor the response. To assess the initial response to RFA treatment, CE-3DUS can be performed around 10 min after the RFA treatment. The absence of any intralesional enhancement or moving microbubbles is consistent with the complete coagulation necrosis of affected liver tissues. The security of total coagulation necrosis is detectable in highly vascularized tumors[26].

## WHAT ARE THE LIMITATIONS OF ULTRA-SONOGRAPHIC TECHNIQUES?

The limitations of this new ultra-sonographic technique consist of limited spatial resolution of the current 3D probes. The volumetric measurement may be distorted as a result of motion when using the mechanical probe. Furthermore, the presence of gas production during the ablative process may cause a shadowing artefact that may lead to inaccurate assessment of treatment response and calculation of ablation zone dimensions. A significant learning curve in the adoption of the new technique is further discussed[26]. This aspect of highly advanced 3D

ultra-sonographic application in combination with RFA shows how future therapeutical tools may have significant impact in treatment of metastatic liver disease and how a combination of two of more medical modalities can enlarge our therapeutical capacity to defeat malignant disease of the liver.

## WHAT ARE THE PROGNOSTIC PREDICTORS AFTER RFA?

In general, authors reported that the prognosis of patients with hepatocellular carcinoma (HCC) treated by RFA is highly dependent on tumor characteristics and liver function[30,31]. The usefulness of α-fetoprotein (AFP), *Lens culinaris agglutinin A-reactive fraction of AFP* (AFP-L3) and prothrombin induced by vitamin K absence of antagonist Ⅱ (PIVKA-Ⅱ) has been detailed in previous studies[32]. Depending on the Child-Pugh stage, PIVKA-Ⅱ was found to be the best prognostic predictor after curative RFA in Child-Pugh stage A liver disease[33]. PIVKA-Ⅱ levels above 100 mAU/ml prior to RFA therapy significantly predicted the recurrence and shortening of the period within the Milan criteria[33]. In the ablation of HCC, des-gamma-carboxy prothrombin (DCP) not only reflected the biological aggressiveness and progression of HCC tumors but DCP levels were significant predictors of survival[34]. Likewise, DCP levels were also significant predictors in recurrence free survival[34]. Another study investigated predictors of survival after RFA of colorectal cancer metastases in the liver. They concluded, after analyzing patients demographics and tumor characteristics, that the number and size of liver metastases and serum CEA are among the most significant factors to predict patient outcome after RFA treatment for colorectal cancer metastases[35].

## COST EFFECTIVENESS OF RFA

In times of financial restrictions where health insurance rates are increasing every year, the cost effectiveness of a new medical procedure needs to be addressed carefully. Today there is no doubt that RFA is a standardized and safe tool in experienced hands to treat patients with malignant liver disease where options of curative resection and cure are limited. Nevertheless, the cost analyzes has to be made critically. A prospective randomized trial has reported average costs of hospital stays with RFA at 1584 € for percutaneous RFA in an outpatient setting, 3824 € for percutaneous RFA in an inpatient setting, 8194 € for laparoscopic RFA and 12967 € for intraoperative RFA combined with surgical resection[36]. The economical impact of RFA complications was a longer duration of hospital stay (2-6 d on average and an added cost of 1660 €)[36]. These sober numbers only display the treatment budget without any emotional background, mandatory in an ethical concept to globally address the question of cost effectiveness between economical and social resources.

Cost benefits of RFA is an area that is difficult to assess simply because, although total costs of a medical procedure can be relatively easy assessed, the total economic costs are very difficult to measure as the earlier start of reintegration in the patient's normal life cannot be "financially" measured by simple figures.

## FUTURE CONCEPTS IN RFA

According to the American Association for the Study of Liver Diseases (AASLD) guidelines, RFA is a safe and effective method to treat patients with advanced liver tumors[37]. For hepatic tumors less than 3 cm in diameter, initial complete tumor response rates of ⩾ 90% and local tumor progression rates between 10% to 20% have been reported[37]. A three year local recurrence free interval has been reported in more than 95%. Although these are promising clinical outcomes, the complete tumor response rates for HCC following RFA in histopathological diagnostic criteria has reported to be less than 50% in certain reports[38,39]. Regarding conventional histopathological diagnostic criteria as the gold standard, RFA must be considered as only a palliative treatment modality due to the apparently poor histopathological tumor response rates[37]. This discrepancy between radiological and histopathological findings is a result of at least two main effects: conventional histological assessment based on H&E stained tissue specimens are sometimes inconclusive in determining tumor viability[40] and a thermal fixation effect following RFA. Thermal fixation can be considered as a different form of cell death in addition to coagulation necrosis[41]. Thermal fixation seems to result from the denaturation of the tissue's structural and enzymatic proteins. This inhomogeneity needs attention and could be addressed in future randomized trials. Therefore, not only clinical studies are mandatory.

Accurate probe placement using laparoscopic ultrasound guidance is required to achieve complete tumor ablation. Not only the probe placement but also the continuous linear heat release from the applied needle is critical. A recently published study showed an image-guided surgery system for laparoscopic RFA (LapAssistant)[42]. This technology is based on an electromagnetic tracking system that helped to navigate the laparoscopic ultrasound probe and a RFA needle[42].

The success of laparoscopic ultrasound guidance is highly dependent on the localisation of the liver tumors to access. Whereas tumors in the ventral part of the liver are relatively easy to access, tumors in the posterior area of the liver are often technically not ideal to reach.

Together with technical advances in RFA-needle design, heat application and heat diffusion in tissue have to be studied intensely to overcome incomplete ablation of tumors due to the effect of vessel cooling and other limitations of RFA. Together with more advanced intraoperative imaging, e.g. CE-3DUS and 3D-navigation in laparoscopic RFA, more advanced needle and RFA technology and more refined histopathological assessment, one can potentially target more complex liver tumors.

## INTRADUCTAL COOLING AND TISSUE PROTECTION ARE KEY FOR SUCCESSFUL RFA

Liver tissue contains parenchymal cells, bile duct structures, vascular tissue and, to some extent, matrix related tissue structures that are more prominent in cirrhotic liver disease and only marginally apparent in normal liver tissue. However, liver tumors are inhomogeneous tissues with an imbalance of parenchymal, bile duct, vascular and matrix tissue components. This heterogeneity of tumor tissue also changes the physical density of tissues and sensitivity to thermal ablation. Bile ducts are especially prone to thermal injury during RFA and consecutive complications after RFA treatment[43]. Intraductal cooling during RFA[43,44] has become an important tool to better control the unwanted thermal collateral damage. In general, a tumor location within 10 mm of a central bile duct is frequently considered a contraindication to RFA[43,45,46]. It has been demonstrated that bile ducts within 6 mm of RFA are getting injured when not protected simultaneously with intraductal cooling[47]. In a porcine model, it has further been shown that abscess formation and biliary obstruction occur more likely when bile ducts are within the area of RFA induced necrosis[48]. In another porcine model it has been proven that the epithelial and bile duct damage became less prominent after intraductal cooling when analyzing histological tissue sections 48 h after RFA[49]. Stenosis of the bile duct normally occurs when the duct is within the range of the ablation zone. Clinically, bile duct stenosis due to RFA generally becomes evident after 3 to 4 wk[45,50]. The usage of cool-tip 10 mm RFA electrodes in order to increase the treatment potential of HCC lesions has suggested for hypovascular HCC lesions of less than 10 mm in diameter[44]. To further prevent skin burns, it has been further suggested to only treat lesions at least 16 mm below the liver capsule[44].

## HOW TO OVERCOME LIMITATIONS OF RFA

Thermal ablation techniques are subjected to a dilemma: the tumor tissues have to be completely destroyed but at a price that no viable normal liver parenchyma and bile duct structures are being damaged unnecessarily. Therefore, the amount of thermal energy applied to the tumor mass has to be exactly regulated. This important regulation is further complicated by the often inhomogeneous tissue architecture and composition of liver masses and the inconsistent distribution of blood vessels. We developed a novel needle perfusion technique that has shown to enhance the efficiency of RFA in treating liver tumors[51]. In this non randomized, retrospective study we studied the outcome of standard *vs* perfusion RFA needle technique in liver tumors of a median diameter of 2 cm. The group treated with the perfusion RFA needle displayed a significantly shorter RFA time of 8.0 min *vs* 18.9 min in the standard RFA protocol group[51]. The rates of incomplete ablations were comparable at around 3% in both groups whereas the local recurrence rate was 6.9% overall, 11.1% in the standard group compared to 4.8% in the perfusion group[51]. We concluded that the perfusion of an expandable RFA needle with saline solution significantly accelerates the ablation procedure of liver tumors with less complications and no disadvantage regarding the oncosurgical outcome[51]. The beneficial aspect of this needle perfusion technique may result from the better and more efficient thermal energy application without the regularly occurring charring effect. Saline-linked surface RFA has been described elsewhere and prevents charring and results in deeper coagulation of tumor lesions[52]. Reports in pig livers showed that tissue destruction to 20 mm can be safely achieved with novel saline-linked RFA[52]. A different bimodal electric tissue ablation-modified RFA technique has provided data that the modification of standard RFA technique with the addition of a direct electrical current (electric tissue ablation-modified RFA) helped to significantly enlarge the ablation radius in a liver pig model[53].

## CONCLUSION

Every new surgical technique faces hurdles, initial weaknesses and limitations. The development of refined instrumentation combined with a set of specific surgical skills has tremendously aided the implementation of RFA in clinical practice. Although the limitations and shortcomings of RFA are discussed and RFA is not considered a curative treatment in advanced hepatic tumors, it is a critical tool for patients awaiting liver transplantation (bridging therapy) as well as for patients with advanced central liver tumors where open surgery or other treatment modalities are of limited use. With the combination of potential future advances in imaging, diagnostic and modern treatment tools together with advanced probes and 3D-technology, we believe that RFA will extend its clinical position in the treatment of advanced end stage liver tumors in the near future.

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