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ARTICLE

New horizons in MR-controlled and monitored radiofrequency ablation of liver tumours

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Abstract

There is a sustained interest in using magnetic resonance (MR) thermometry to monitor the radiofrequency ablation of liver tumours as a means of visualizing the progress of the thermal coagulation and deciding the optimal end-point. Despite numerous technical challenges, important progress has been made and demonstrated in animal studies. In addition to MR thermometry, MR can now be used for the guidance of the tumour targeting with 'fluoroscopic' rapid image acquisition, and it can provide several contrast mechanisms for post-procedural assessment of the extent of the thermal coagulation zone. Challenges of in vivo simultaneous MR thermometry implementation and the current limitations of the thermal dose model for the estimation of the extent of the thermal coagulation zone are discussed. MR imaging could enhance the success of RF ablation of liver tumours due to its potential to provide accurate targeting, monitoring, and post-procedural evaluation.

Keywords: *Radiofrequency ablation; monitoring; tumour targeting; MR thermometry; thermal dose.*

Introduction

Image-guided tumour ablation is one of the exciting and promising developments in radiology[1]. Radiofrequency ablation (RFA) is used in many centres to treat hepato-cellular carcinoma (HCC) and hepatic metastases as a complementary method to liver resection. There is interest in using magnetic resonance (MR) imaging to guide the tumour targeting and to perform a post-procedural imaging evaluation based on the different MR contrast mechanisms. Most importantly, MRI is the only imaging modality that can provide quantitative and high spatial resolution real time monitoring of the temperature changes (and hence thermal dose) evolution in the heated area. The value of temperature and thermal dose maps as a means of determining the cut-off point (or endpoint) for the application of power has not yet been demonstrated clinically, even though there is a sustained interest in this method.

The interest in MR thermometry stems from the hypothesis that real-time monitoring of RFA via MR thermometry should enable the operator to actually follow the evolution of the thermal coagulation necrosis. This would represent a significant improvement over relying on empirical settings for the electrical power and duration for the RFA procedure. As opposed to global measures such as impedance measures, the temperature and associated thermal dose maps should provide a local description of the temperature and the state of thermal coagulation of the tissue. Unlike thermocouples inserted in the electrode tip that can measure the temperature at a few points only, MR thermometry can calculate the temperature changes at each pixel. The derived thermal dose at every pixel could thus be monitored by the operator in real-time, and should provide reliable criteria for deciding when the entire tumour plus a safety margin of 10 mm have been completely necrosed via thermal coagulation (the endpoint of RFA). Damage to adjacent structures

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such as hepatic veins and bile ducts can also be prevented.

One of the main challenges of RF thermal ablation of liver tumours remains the incomplete ablation typically observed in the vicinity of large vessels which act as important heat sinks due to convection. The proximity to a large vessel can locally prevent the onset of thermal coagulation, as demonstrated via histology in both animal[2] and patient[3] studies. In such situations, local temperature and thermal dose real-time information should help the operator decide whether to continue the application of power, add more electrodes (when multi-polar configurations are possible), or reposition one or more of the existing electrodes.

Some of the earlier MR monitoring of RFA was performed under open-bore low-field MR systems with the T1 temperature measurement method. However, T1 exhibits not only temperature dependence but also a dependence on structural tissue changes, such as coagulation and tissue drying.[4] Thus, T1 monitoring is only a qualitative indication that 'something is happening' in the heating zone, and empirical recipes need to be used to be able to draw conclusions about the state of the tissue during the monitoring. The advent of closed-bore larger diameter high-field (1.5 T) interventional MR systems has made it possible to perform RFA inside 1.5 T systems and thus implement the proton resonance frequency (PRF) MR thermometry method.[5] PRF at 1.5 T has superior sensitivity to the T1 method[6] and depends only on temperature and not on tissue structural changes (tissue structural changes may only reflect on a loss of SNR in the heated region which leads to a loss of temperature accuracy). The PRF method at 1.5 T is promising, and provided that the susceptibility map remains constant, fat saturation is robust, and respiratory motion is accounted for, can give a real quantitative measure of the temperature increments at each pixel with high spatial and temporal resolution.

Although the principles of real time monitoring of RFA of liver tissue with the PRF MR thermometry method at 1.5 T are well established and have been demonstrated in the liver ex-vivo[7,8] and in animal studies[9,10], very few clinical results have been published[11]. This is due to several technical challenges, such as RF interferences that degrade the MR images, continuous respiratory motion of the liver leading to intra-scan artifacts, large temperature errors in the presence of inter-scan motion (unless corrected by image registration algorithms), and large susceptibility artifacts of the RF electrodes which block the useful information around the active zone of the electrode[12]. The various types of electrodes used for RFA are described in the proposal for updating the terminology for RFA electrodes by Mulier *et al.*[13] The susceptibility artifacts are a persistent problem for RF electrodes, regardless of the manufacturer.[12]

Despite the lack of results for an integral MR-monitored patient RFA procedure, progress has been made on several aspects of MR thermometry with PRF at 1.5 T, as well as on targeting and post-evaluation imaging with MR. The goal of this review is to discuss some of the recent confirmations of the role of MRI in the targeting, intra-procedural monitoring, and post-procedural evaluation of RFA of liver tumours with MRI, and give some indication of potential future trends. In order to understand the challenges of RF ablation with MR guidance and MR monitoring, several subsequent steps of the procedures must be distinguished, namely targeting, monitoring and controlling, and post-procedural assessment. These distinct steps are discussed below.

Targeting with MRI

The targeting of the tumour refers to electrode placement under radiographic guidance. The targeting of the tumours has been performed under ultrasound (US) or computed tomography (CT) guidance, but MR-guided electrode placement may provide advantages and may be, in some cases, the only clinical option as some liver tumours are not visible under US or CT. The feasibility of RF electrode placement with sequential T1 images (not real-time) was demonstrated for both open-bore 0.23 T systems[14] and closed-bore 1.5 T systems[10,15]. The major drawback of MR-guided targeting has so far been the long procedure time. The advent of real-time 'fluoroscopic' pulse sequences and in-room MR-compatible screens has significantly decreased the electrode placement time. For MR targeting, the conspicuity of lesions may be enhanced occasionally by the administration of hepato-specific contrast materials such as mangafodipir-trisodium (Mn-DPDP; Teslascan, GE Healthcare)[16].

Initial clinical results at our institution at 1.5 T (Magnetom Espree, Siemens Medical Solutions, Erlangen, Germany) with a radial interleaved real-time acquisition with the ability to adjust the imaging plane interactively during the scan indicate that MR may supersede all other modalities for image-guided targeting (ultrasound, CT) thanks to: multi-planar double oblique targeting associated with high spatial resolution, speed, reliability, and lack of ionizing radiation. Patient consent was obtained prior to the procedure. The first four images in Fig. 1 show selected frames from the advancement of an MR-compatible RF electrode (Celon AG, Teltow, Germany) in the liver of a patient placed under general anaesthesia, 20 min after the administration of Mn-DPDP. The update rate provided by the balanced steady state free precession (b-SSFP or TrueFISP) radial k-space interactive pulse sequence (IRTTT, Siemens Medical Solutions, Erlangen, Germany) is of the order of 300 ms, and spatial resolution of $1.6 \times 1.6\,mm^2$. The targeting time per electrode was approximately 10 min. The targeting was immediately

Figure 1 **Liver metastases targeting under MRI real-time guidance. This procedure necessitated two parallel electrodes placed close to the outer boundary of the tumour on both sides of the tumour (the electrical current was circulating between the active zones on the two electrode tips). Therefore, the target was not the centre of the tumour, but the region just outside its boundary. Four different stages of the advancement of the first electrode are shown from left to right (a–d). The target tumour is a hepatic metastasis indicated by the white arrow. The targeting was assessed with a high-resolution VIBE T1-weighted image (e) which confirmed the correct final position of the two RF electrodes. Note that whereas the actual diameter of each MR-compatible bipolar RF electrode is 2 mm, the width of the susceptibility artifact is of the order of 8–12 mm (depending on the sequence TE and on the orientation of the needle with respect to B_0).**

followed by a high resolution T1-weighted volume interpolated breath hold examination (VIBE) MR control (Fig. 1) to confirm the accuracy of the needle placement before applying the RF power and thus starting the tissue thermal coagulation.

For treatment of large tumours (diameter >3 cm) or tumours close to major blood vessels, placement of multiple RF electrodes may be necessary, and this is possible when a multi-polar RF generator mode is available[17]. The new interactive imaging capabilities of interventional MR systems should enable the placement of three electrodes within a reasonable time (of the order of 30 min). MR-compatible ultrasound systems may have a complementary role for the initial insertion of the electrode especially when the space for needle placement inside the closed bore is limited. In the future, the RF electrode placement may be routinely performed under this type of MR 'fluoroscopic' interactive imaging.

Monitoring and controlling

MR thermometry

Monitoring and controlling refer to the continuous (or sequential) viewing of temperature and thermal effects occurring in the ablation zone during application of power and to the intra-procedural use of image-based feedback to modify the procedure (i.e. change electrode position or adapt energy delivery algorithm). The determination of the optimal endpoint from temperature and thermal dose maps represents the main goal of monitoring.

When RF ablation and MR thermometry are performed simultaneously, the MR images show severe RF interference due to the harmonics of the RF generator (operating at a nominal frequency of the order of 500 kHz) that fall within the reception window of the MR receive chain (centred around the 63.7 MHz carrier). In the past, intermittent power application and MR imaging was proposed for RFA[18], but this leads to implementation problems, lengthens the procedure, and may render it more inefficient. The use of hardware filtering inserted in the transmission line from the generator to the RF electrode to eliminate interfering harmonics and thus restore acceptable image SNR, permitting simultaneous RFA and MR thermometry, was demonstrated for 0.5 T[19] and 1.5 T[10] animal studies. At our institution, we were also able to restore the SNR of the MR images by introducing hardware filtering in the transmission line from the RF generator to the RF electrode and thus perform truly simultaneous RFA and MR thermometry at 1.5 T.

T1, diffusion, and spectroscopy-based MR thermometry methods are theoretically possible but have problems for real-time temperature monitoring[20,21]. The T1 method is not appropriate as it combines effects of temperature and tissue structural changes. The method of choice at 1.5 T remains PRF, as it provides linearity with temperature and tissue-independence[5].With the PRF method, a time series of phase images are acquired during the heating using spoiled gradient-echo based acquisitions. For such sequences, the temperature sensitivity can be optimized by setting the echo time TE equal to the T2* of the liver tissue. The dynamic (time) series of phase images acquired during the RF ablation procedure can be used to calculate the increments in temperature by subtracting the phase of the initial (reference) phase image from each phase image in the dynamic series, according to Eq. (1):

$$\Delta T(x) = \frac{\Delta \Phi(x)}{\alpha \cdot \gamma \cdot TE \cdot B_0} \tag{1}$$

where $\alpha = -0.01$ ppm/°C is the temperature-dependent water chemical shift, γ is the gyromagnetic ratio and B_0 is the field strength. Phase unwrapping is necessary to ensure the continuity of the resulting temperature values. The thermal maps resulting from this type of post-processing are usually displayed superimposed on the magnitude images. Recently, it has been shown that multi-acquisition and multi-echo balanced steady

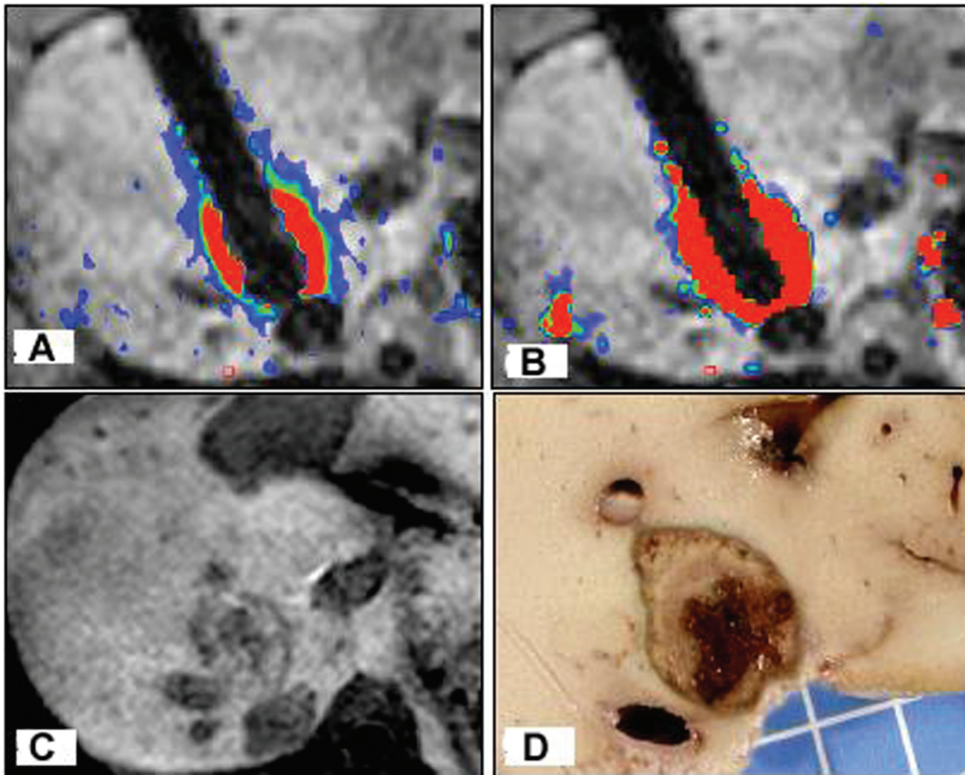

Figure 2 **MR thermometry during in vivo RFA ablation in a pig liver. (A) Representative thermal map calculated and displayed in real-time superimposed on the magnitude MR images: blue, +5°C; green, +10°C; red, +15°C and above. (B) Final thermal dose map (red indicates pixels where at least one lethal thermal dose has been reached). A base temperature of 37°C was assumed. Note the cooling effect of the proximity to the inferior vena cava. (C) Gd-EOB-enhanced T1-weighted image showing the thermal coagulation zone immediately after the RF ablation. (D) Histological aspect of the ablation zone also shows the cooling effect of the inferior vena cava.**

state free precession sequences could also be used to perform PRF MR thermometry, with a potential for increased temperature sensitivity[22].

With PRF, in immobile tissue at 1.5 T, the typical performance of single MR thermometry is less than 1°C temperature standard deviation (i.e. temperature noise), the temporal resolution is less than 1 s, and spatial resolution is about 2×2 mm[21]. Lipid signal suppression is necessary as the temperature-dependent chemical shift of lipid hydrogen atoms is nearly zero, and it is usually achieved by water-selective slice excitation[23] with binomial pulses. For RF ablation, as the electrode is fixed with respect to the imaged tissue, the susceptibility field map remains unchanged throughout the experiment and therefore susceptibility map corrections are not needed. However, the hardware-related global phase drift during the procedure needs to be eliminated. Finally, as the method is based on subtracting a reference phase image from the current phase image, robust respiratory triggering for the acquisition and residual motion image post-processing corrections are needed to achieve correct temperature measurements. Respiratory triggering will evidently reduce the temporal resolution of thermometry to one temperature update per respiratory cycle period at each slice.

Preliminary animal study results at our institution also indicate that in-vivo MR thermometry with the PRF method at 1.5 T during simultaneous RFA is feasible. Fig. 2 shows representative results obtained during MR-monitored of RFA in pig liver. Power was applied via a bipolar MR-compatible cooled electrode, and the imaging was performed with a gradient-echo-echo planar hybrid sequence with respiratory triggering. The phase images were used to calculate the temperature increments according to the PRF method, and the thermal dose was also calculated.

Thermal dose calculation and tissue coagulation prediction

The classical thermal dose calculation is based on an empirical model proposed by Sapareto *et al.*[24] In this model, which results by applying a few simplifications to the Arrhenius equation for tissue damage, a thermal dose equivalent at 43°C is calculated as follows:

$$t_{43} = \sum_{t=0}^{t=\text{final}} C^{(43-T)} \Delta T \qquad (2)$$

where t_{43} is the thermal dose in equivalent minutes at 43°C, T the average temperature during Δt and C is a constant resulting from the Arrhenius model and approximated to 0.5 above 43°C and 0.25 below 43°C. At 43°C, empirical studies show that it will take 240 min to cause cell necrosis via protein denaturizing and thermal coagulation. The thermal dose concept enables us to compare the effect of an arbitrary temperature–time evolution to the equivalent effect of hypothetically exposing the same tissue to a constant temperature of 43°C for a certain duration t_{43}. Eq. (2) allows t_{43} to be calculated precisely.

In typical RFA thermal dose real-time monitoring software tools[8,10], if t_{43} is superior to 240 for a given pixel, the pixel becomes red on the thermal dose map and it is assumed to correspond to necrosed tissue (this is also illustrated in our preliminary in vivo animal study in Fig. 2B). For liver tissue, the correlation between the prediction of thermal coagulation region size by thermal dose (assuming a lethal value of $t_{43} = 240$) and by histology was performed ex-vivo[8], and in-vivo in animal studies[10], but this type of correlation will remain difficult for patients, with few cases undergoing resection of a liver lobe containing a previously ablated lesion. Also, we should note that the Sapareto model and the lethal t_{43} value of 240 were developed for hyperthermia treatments with temperatures around 43°C, whereas the tissue heating with RFA is much more rapid and can reach very high temperatures. We note that whenever temperatures of about 57°C are reached the Sapareto model predicts essentially instantaneous coagulation. Thus, binary threshold methods based exclusively on temperature isotherms are not in contradiction with the thermal dose model, but they may be only partially correct as they only take into account pixels that have reached temperatures above 57°C (or some other fixed threshold) for the zone of thermal coagulation. However, depending on the temperature–time evolution, tissue regions that have seen varying temperatures between 43°C and 57°C (for the typical procedure durations between 10 and 30 min) may also accumulate enough thermal dose to become thermally coagulated. For such regions temperature isotherms recorded at a fixed time instant may not be sufficient by themselves to predict thermal coagulation.

It appears that the value of 240 equivalent minutes at 43°C as lethal thermal dose has some predictive value, but it needs further validation for use as a complete ablation criterion for RFA of liver tumours. The predictive value for complete coagulation for both thermal dose and binary threshold methods is difficult to evaluate in-vivo in patient studies due to the errors in the identification of the actual boundary of the coagulation zone from T1- and T2-weighted post-procedural imaging. A bovine liver study relying on MR imaging only for the identification of the ablated zone found the lethal t_{43} to be 340 (and not the typical 240) equivalent minutes at 43°C, but with large error bounds[25]. Ideally, the thermal dose map predictive value and the post-procedural MR imaging predictive value need to be established by comparisons against histology. The histological study resulting from patient RFA followed within 6 weeks by resection of malignant liver tumours indicated that the boundary between viable and non-viable cells is sharply delimited[3]. Generally, the number of RFA patients undergoing a subsequent resection of the ablated zone is limited, and thus such validation data may also be limited. Animal studies are important in confirming the predictive value of the lethal thermal dose by using histology as the reference. A study of RFA ablation in rabbit liver has indicated that the thermal dose maps have an average predictive precision of about 1 mm through a comparison with histological measurements performed after 8 days[10]. However, the same validation needs to be performed for RFA of tumour tissue. The lethal thermal dose may not be the same for cells of different types of tissue and thus it may exhibit a dependence on the tumour type. Another source of error for patient studies is the unknown base temperature of the liver, typically assumed to be equal to 37°C.

Post-procedural assessment with MRI

The ultimate goal of the MR monitoring with thermal dose maps is to confirm complete tumour ablation (including the 10 mm safety margin) and thus the endpoint of the procedure. However, the reliability of the thermal dose as a predictor of complete ablation still needs to be validated in patient studies. Thus, at the present time, post-procedural imaging remains necessary for the confirmation of complete tumour coverage, and is often achieved in clinical routine via a CT scan.

Another possibility is to perform a robust MR-image based protocol for the evaluation of the RFA procedure success immediately after the RFA procedure, while the patient is still inside the MR system. T1, T2, perfusion and diffusion imaging may all play a role as they all reflect the tissue thermal coagulation as a change of contrast[26]. First, the shape and size of the resulting coagulation volume needs to be characterized. A standardized description terminology for the size and geometry of the thermal coagulation volumes has been proposed, including description of the index tumour, the ablation zone, and the ablation margin[27]. Second, and more importantly, the post-procedural MR imaging should be sufficient to indicate the success of the procedure in terms of complete tumour coverage.

The tissue structural changes will reflect on the signal intensity for the different image contrasts. On T2-weighted images, the hyperintense region corresponding to the tumour on pre-procedural imaging is expected to become isointense with the parenchyma on post-procedural imaging after complete thermal coagulation. In reality,

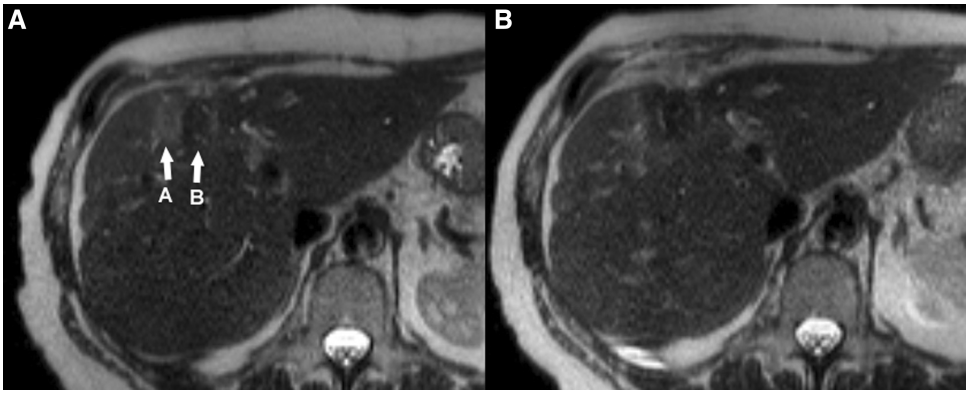

Figure 3 **Changes in signal in the ablation area. Left: pre-ablation respiratory-triggered T2-weighted HASTE images showing a 3-month-old hypointense necrosis from a previous RF ablation of a liver metastases (B) and a hyperintense local tumour recurrence to the left of the old ablation zone (A). Right: image acquired with the same sequence immediately after the RFA procedure showing hypointensity in region A as well. Note the hyperintense rim corresponding to haemorrhage.**

the necrosis zone is surrounded in the early phase after ablation by a zone in which phenomena such as oedema, haemorrhage and inflammation lead to signal hyperintensity on T2-weighted images. This makes it difficult to visually identify the exact location of the border between coagulation necrosis and viable cells from T2-weighted images with limited spatial resolution. Therefore, the T2-weighted imaging in the early phase is not sufficient by itself to confirm the success of the RF ablation procedure. Hepato-specific contrast materials may help differentiate peri-ablational enhancement in the haemorrhage zone from residual tumour. For the identification of residual (incompletely ablated) tumour, dynamic Gd enhancement may play a role, and in particular a double-contrast method where iron-oxide particles are administered to render the viable parenchyma hypo-intense prior to dynamic Gd-enhanced imaging has been proposed to identify incompletely ablated tumour regions[28]. Also, new experimental intravascular MR contrast agents are investigated as potential indicators of differences in blood vessel density between ablated and residual tumour areas[29]. Finally, diffusion imaging may play a role in characterizing the post-ablation region as the coagulated region will exhibit very low apparent diffusion coefficient (ADC) values, whereas the haemorrhage zone will exhibit higher ADC than the rest of the parenchyma. The most used criterion remains the T2-weighted evaluation, whereby pre-treatment hyperintense tumour regions are expected to become slightly hypointense or isointense with the liver tissue after the procedure[14]. Fig. 3 illustrates a case of pre- and post-procedural T2-weighted images at our institution.

Summary

MR imaging could enhance the success of RF ablation of liver tumours due to its potential to provide accurate targeting, monitoring, and post-procedural evaluation. For targeting, the feasibility of rapid and accurate electrode placement during real-time MR imaging has been demonstrated. For thermometry monitoring and control, the main remaining challenges are related to the motion of the liver due to respiration, the large electrode susceptibility artifacts, and the determination of a correct lethal thermal dose for *in-vivo* tumour and parenchyma cells. Even though the ability to perform simultaneous RF ablation and MR acquisition with appropriate RF filtering has already been demonstrated, further improvements in the filtering scheme and the generator design may be possible to minimize interference and increase the image SNR in all configurations. MR thermometry and thermal dose mapping in real time will remain essential for visualizing areas with incomplete coagulation due to perfusion heat sink effects. For post-treatment assessment, MR should be able to distinguish between the different regions of an ablation zone more accurately than other imaging modalities. The vision is to use exclusively MRI at all stages of the RF ablation procedure and move towards an integrated MR-guided and monitored RFA procedure. The advantage would be the ability to combine and superimpose the following information for quantification with an integrated clinical evaluation tool: pre-procedural tumour and neighbouring vessel segmentation with associated 3D rendering and volumetric measures; 3D thermal dose maps predicting the extent of thermal coagulation; and post-procedural 3D imaging with multiple contrast mechanisms.

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