Radio-frequency Ablation in the Treatment of Hepatic Malignancies*

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ABSTRACT

Tumour ablation using radio-frequency energy is attracting increasing attention as an effective minimally invasive ablative technique in the treatment of primary and secondary hepatic tumours. It has been shown to be safe and relatively well tolerated by patients, with few major complications and minimal patient discomfort, and is increasingly being used as an alternative to surgery in patients with unresectable disease.

Keywords: hepatic malignancies, minimally invasive therapy, radio-frequency ablation

INTRODUCTION

Radio-frequency (RF) ablation of tumours is a new minimally invasive technique that has recently been introduced for the treatment of both primary and secondary hepatic malignancies. Its use in the treatment of liver tumours was first reported by two independent groups of investigators (McGahan *et al* and Rossi *et al*) who experimented with RF equipment and published their initial studies in separate reports in 1990.[1,2] These studies involved the insertion of needle electrodes deep in the liver to create areas of focal thermal injuries surrounding the non-insulated tip of the needle electrodes. These initial studies were followed by extensive experiments in animal models in an attempt to increase the size of the thermal injury, and hence the volume of tissues that could be ablated using these needle electrodes.[3-7] Subsequent to these initial studies, Rossi *et al*, in 1993, reported their first experience in treating 13 patients with small hepatocellular carcinomas (HCC) using ultrasound (US)-guided percutaneous RF electrocautery.[8] Since then, this technique has created a great deal of interest worldwide as a viable treatment option for unresectable primary and metastatic hepatic neoplasms, and has been an area of increasing research and practice in recent years.

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MECHANISM OF ACTION

RF ablation is a local ablative technique that involves the use of a needle electrode which is electrically insulated along its entire length except for its distal 1 to 3cm tip (which comprises the exposed part of the needle). This exposed portion of the electrode is advanced into and positioned within the tumour lesion with the assistance of real-time imaging guidance (usually US and/or combined with computed tomography (CT)). A high frequency alternating current, operating in the radio-frequency range (460 to 500kHz), is then conducted to the exposed electrode tip to produce local ionic agitation ("to-and-fro" agitation) in the surrounding/adjacent tissues, resulting in frictional heat and hence a rise in temperature in the tissues. Temperatures exceeding 50°C will result in irreversible cellular damage leading to tissue coagulative necrosis.[6] Following each ablation, there will be an approximately spherical area of thermal injury produced around the exposed tip of the needle. Studies have documented the extent of thermal injury in normal liver tissue in vivo to be approximately 2.4 ± 0.2cm in diameter and in clinical practice to range from 1.8 to 3.6cm in diameter.[9]

EQUIPMENT

The basic components utilised in RF ablation include an RF electrical generator, needle electrode and grounding pads. The RF generator operates at frequencies of 460 to 500 kHz with power settings between 50 to 200 W. The grounding pads act as large dispersive electrodes for the current emitted from the active needle electrode, and are usually placed at the back of patient's thighs. As for needle electrodes, different manufacturers have pursued various designs – Radionics (Burlington, MA, USA) uses a 17-gauge internally cooled, straight single needle or 3-needle cluster; Rita Medical Systems (Mountain View, CA, USA) has a 15-gauge insulated outer needle with 4 to 8 curved retractable prongs (electrodes) of varying lengths; Radiotherapeutics (Mountain View, CA, USA) has produced a 14-gauge insulated outer needle with 10 curved retractable prongs; which when fully deployed, take up the configuration of an umbrella. Each ablation cycle is approximately of 12 to 15 minutes duration. Currently, no studies have been carried out to confirm a significant advantage of one needle design over another.

INDICATIONS AND LIMITATIONS

In order to minimise and exclude local tumour recurrence, RF ablation should aim to destroy not just the target tumour lesion completely, but should also include a 5 to 10mm cuff of normal liver tissue surrounding the lesion. To achieve complete and adequate ablation, the precise placement of the needle electrode within the tumour lesion is of utmost importance and extremely critical.

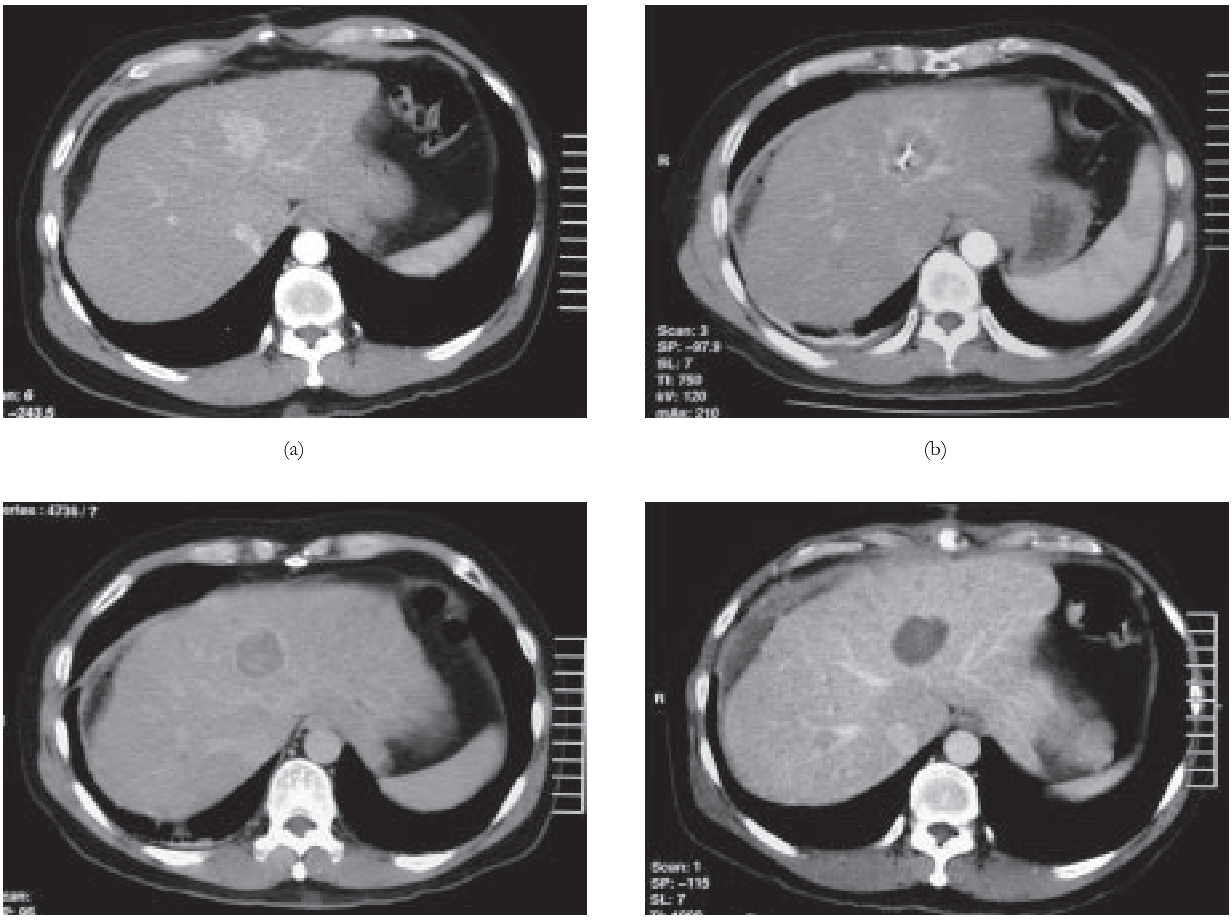
Based on experiments, a tumour measuring less than 2cm can be adequately treated with 1 or 2 ablations, which create a spherical thermal injury of about 3cm in diameter. Lesions of 2 to 4cm will require multiple electrode insertions and overlapping ablations in order to achieve complete and adequate ablation. Lesions measuring larger than 4cm have a higher risk of incomplete ablation. Hence, most investigators are limiting RF ablation treatment of liver malignancies to patients with no evidence of extra-hepatic disease, with 4 or fewer hepatic lesions, all of which must be 5cm or smaller in diameter. The ideal tumour therefore, would be a lesion measuring 3cm or smaller in diameter, located 1cm or more deep to the liver capsule, completely surrounded by liver parenchyma and 2cm or more away from large hepatic or portal veins.[10]

Tumours that are located adjacent to vital structures need to be assessed carefully before RF ablation is performed. Lesions in a subcapsular location or adjacent to the diaphragm can be treated, but there is usually greater intra- as well as post-procedural pain associated with the treatment. Treatment of subcapsular tumours abutting other abdominal viscera also carries the additional risk of damage to these organs, especially adjacent loops of bowel.[11,12] Complete ablation of tumours located adjacent to large blood vessels (for example, at the bifurcation of the right and left portal veins or adjacent to the main portal vein) is more difficult to achieve because the presence of blood flow within these vessels results in cooling of the adjacent tumour (the so-called "heat-sink" effect of flowing blood), and hence limiting the extent of coagulation necrosis.[9] Ablation of tumours located adjacent to the larger portal triads is associated with biliary ductal injury. Similarly, ablation of lesions abutting the wall of the gallbladder may be complicated by subsequent cholecystitis, with symptoms persisting as long as 2 to 3 weeks. Contra-indications to RF ablation include sepsis/active infection, severe debilitation or uncorrectable coagulopathies.

TECHNIQUE

RF ablation can be performed either percutaneously or intra-operatively. Some investigators have performed percutaneous ablation on an outpatient basis using only conscious sedation. At Singapore General Hospital, we usually perform the procedure percutaneously, using conscious sedation whenever possible, but only on in-patients. Patients are admitted the day prior to the procedure and the necessary patient preparations are carried out. After the procedure, the patient is observed overnight before discharge from hospital the following day. There are several advantages to a percutaneous approach as compared with an intra-operative procedure. It is less invasive, associated with minimal morbidity, relatively inexpensive, can be repeated as necessary to treat recurrent/residual tumour, and, as mentioned earlier, can be performed on an outpatient basis using conscious sedation.[13] However, there are some patients who may not be able to tolerate percutaneous RF ablation with only conscious sedation. General anaesthesia may be preferred in these patients and also when the procedure is anticipated to be difficult or protracted.

There are some advantages to an intra-operative approach, either laparoscopically or via open surgery. Intra-operative ultrasound examination allows the detection (and treatment) of small tumours not demonstrated by other imaging.[14] With open surgical treatment, technically difficult lesions located adjacent to diaphragm, bowel or gallbladder can be more easily treated by displacing them away from the mobilised liver. Intra-operative RF ablation, however, is associated with higher morbidity and mortality with longer hospital stays, requires general anaesthesia and



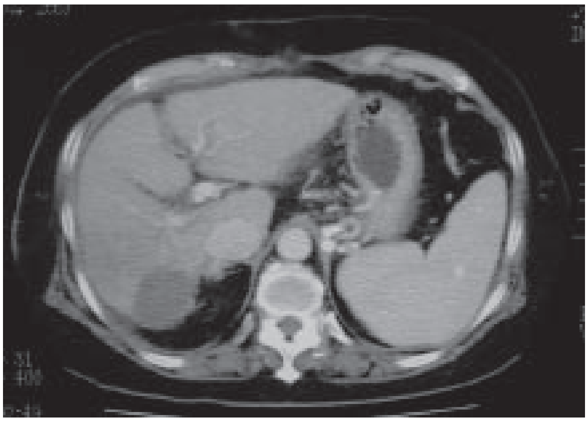
(a) (b) (c) (d)

Fig. 1. Radio-frequency ablation of hepatoma in segment 4A of the liver: changes in appearance on CT scan. Solitary and discrete hypervascular nodule in segment 4A of the liver which is consistent with hepatoma (Fig. 1a.). RF ablation of the nodule with the tip of RF needle electrode (identified by the focal hyperdensity) having been advanced into the tumour nodule using CT fluoroscopic guidance. Ablation was carried out for a duration of 12 minutes (Fig. 1b). Day 1 post-RF ablation: Tumour lesion has become hypodense with ill-defined hyperdensity within it (due to haemorrhage from the procedure) and some peri-tumoral hyperdensity as a result of reactive hyperaemia induced by the ablation procedure (Fig. 1c). One month post-RF ablation: the tumour lesion has become completely and homogeneously hypodense (equivalent to fluid density) with no evidence of peripheral nor focal enhancement to suspect residual / recurrent tumour (Fig. 1d).

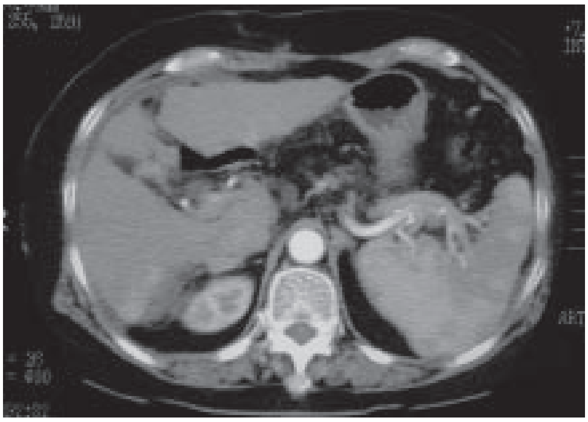
its attendant risks, is more expensive and may not be feasible to repeat, particularly with open surgical technique.[13]

Prophylactic antibiotics are routinely administered in some institutions, sometimes both pre- and post-procedure, although no trials to validate their use have been carried out. We routinely prescribe a single dose of a cephalosporin and Flagyl.

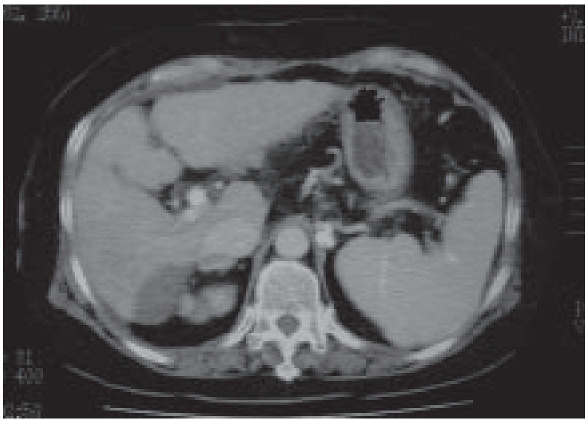
US is the imaging modality that is most commonly utilised for guidance in percutaneous RF ablation. We use US for imaging guidance either alone or in combination with CT fluoroscopy, the latter being more commonly practised (Figs. 1a and b). There are several advantages of US over CT and magnetic resonance imaging (MRI); these include its real-time capability, vascular visualisation (particularly on colour Doppler imaging), widespread availability, speed and its relatively low cost. Although US is extremely useful in guiding the initial placement of the RF needle electrode, its usefulness in assessing the effectiveness and extent of RF ablation is somewhat limited. This is because on US imaging, RF ablation produces an extremely dense, bright and echogenic area, the size of which is only a rough approximation of the area ablated.[15] Further limiting the usefulness of US imaging is the observation that this echogenic area produced during ablation obscures the margins of the tumour that is being treated, especially its posterior extent; it has been concluded in a study in animals with histopathological correlation that US overestimates the size of necrosis in 23% when compared to



(a)



(b)



(c)

Fig. 2. Three months post-RF ablation of a segment 6 hepatoma in another patient. The ablated tumour is identified by the hypoattenuated area (Fig. 2a). However, slightly inferior to this image, there are areas of contrast enhancement seen both on the lateral aspect (Fig. 2b) and medial aspect (Fig. 2c) of the ablated tumour lesion which would be indicative of residual/recurrent tumour.

histopathology.[16] CT and MRI are reported to be more accurate in assessing the extent of RF ablation, with contrast-enhanced CT having been reported to be accurate to within 2mm of actual lesion size.[15,17,18]

CT scan of the liver is performed in most institutions within a few hours post-ablation to assess the extent of ablation and to detect any potential complications.[17] We routinely perform a CT scan on our patients 24 hours after the ablation procedure mainly to look for complications (Fig. 1c). Immediately post-ablation, CT scan may demonstrate a rim of contrast-enhancement, which is attributable to reactive hyperaemia around the margins of the ablated lesion (Fig. 1c). This makes it difficult to distinguish it from residual tumour, and hence limiting the accuracy of the immediate CT scan in assessing the completeness of ablation. However, this phenomenon is only transient and has been demonstrated to disappear progressively in subsequent follow-up studies.

We also follow-up the patients routinely with repeat CT scans of the liver at 1 month post-ablation, and thereafter every 3 months as in most other institutions. This detects any evidence of residual or recurrent tumour, either at/adjacent to the previously ablated site (Figs. 2b and c) or distant new lesions. To enable early detection of tumour recurrence, a triphasic CT scan of the liver is mandatory as most early hepatocellular carcinoma recurrences are demonstrated only in the arterial phase. Lesions that have been completely ablated will appear entirely and homogeneously hypodense (fluid density) on a CT scan with no focus of contrast enhancement (Figs. 1d and 2a). If there is evidence of tumour recurrence limited to the liver (Figs. 2b and c), repeat ablation is required and may be effective. One of the significant advantages of percutaneous RF ablation is that it can be repeated as often as is necessary to treat intra-hepatic recurrence. Additional monitoring of the patient with repeated alpha-fetoprotein levels (usually at 3-month intervals) is also performed routinely.

PATIENT OUTCOME

Percutaneous RF ablation is usually well tolerated with few serious complications. Minor complications that we have commonly encountered in the majority of patients include intra- and/or post-procedural pain (usually mild to moderate), right hypochondrium discomfort, post-procedural fever, right pleural effusion (usually small and asymptomatic) and transient elevation of liver function tests. Low incidence of major complications reported in the literature include intra-peritoneal and intra-tumoral haemorrhage, sepsis, hydropneumothorax, damage to adjacent structures such as diaphragm, bile ducts/gallbladder and bowel, needle tract tumour seeding and skin burns around the grounding pads.[13,24] Hence, it is important to ensure that grounding pads are placed properly on the patient's thighs before commencement of ablation to avoid complication of skin burns.

RF ablation in the treatment of hepatic malignancies is a fairly new technique, and hence only minimal data on long-term results are available. The early studies focused mainly on the completeness of tumour ablation with only limited follow-up. Rossi *et al* treated 39 patients with small (≤ 3cm diameter) HCC nodules using a conventional needle electrode with a mean follow-up of 23 months.[19] Rossi *et al* published a subsequent study involving 23 patients using an expandable umbrella-type electrode with a mean follow-up of 12 months.[20] Livraghi *et al* performed RF ablation on 42 patients with small (≤3cm) HCCs with a mean follow-up of 10 months.[21] Francica *et al* treated 15 patients with HCCs with a mean follow-up of 15 months.[22] These studies were for tumour lesions no greater than 3cm in diameter. In all these studies, complete necrosis of tumour nodules was achieved in at least 90% of the treated lesions at 6 months. To emphasise the importance of size criteria on the completeness of RF ablation achieved, Livraghi *et al* ablated HCCs measuring > 3cm in diameter (size of tumour lesions ranging between 3.1 to 9.5cm; mean diameter 5.4cm) in 114 patients, achieving complete necrosis in only 47.6 to 71% for non-infiltrating tumours 3.1 to 5.0cm but only 25% for non-infiltrating tumours > 5.0cm in size.[23] Disease-free survival of 71% at 12 months and 64% at 23 months was achieved by Rossi *et al*, with patient survival of 94%, 68% and 40% at 1, 3 and 5 years respectively post-RF ablation.[19,20]

OTHER LOCAL ABLATIVE TECHNIQUES

Several local ablative techniques have been used in the treatment of hepatic malignancies apart from RF ablation. These include transarterial chemoembolisation (TACE), percutaneous ethanol injection therapy (PEIT), percutaneous injection of Yttrium-90 microspheres. microwave coagulation therapy, percutaneous interstitial laser photocoagulation (ILP) and percutaneous cryoablation.

TACE of hepatic tumours has been studied and reported extensively and is often reserved for unresectable hepatic tumours, although ongoing research into the most effective combination of existing or new drugs continues. The normal liver receives 75% of its blood supply from the portal vein and 25% from the hepatic artery, whereas 95% of the blood supply to hepatic malignancies is from hepatic artery; hence, selective embolisation of the hepatic artery induces tumour ischaemic necrosis while normal liver tissues survive off the portal vein.[10] Reported response rates for primary and most metastatic hepatic malignancies in the literature range between 60 to 80%, with average duration of one year. A meta-analysis of HCC patients treated with TACE shows patient survival rates of 70%, 40% and 10% at 1, 3 and 5 years respectively, but there was wide variation owing to influence of various prognostic factors such as tumour burden, tumour staging and underlying cirrhosis.[25]

PEIT was introduced by Sugiura *et al* in 1983 and has been extensively used for unresectable HCCs.[26] Ethanol causes dehydration and necrosis of the tumour cells accompanied by fibrosis and also small blood vessel thrombosis leading to tumour ischaemia. However, there is less homogeneous ethanol diffusion with larger tumour size especially at the periphery, thereby increasing risk of residual viable tumour at the margins of the lesion. Also, frequent need for several treatment sessions per lesion, coupled with limited injection volume tolerated in a single session, have resulted in a practical limitation on the number of lesions that can be treated. Consequently, many authors have restricted PEIT to lesions 3cm or less in diameter and three or fewer in number, although there have been reports of PEIT being used to treat larger and more numerous tumours.[27] One, 3- and 5-year survival rates of patients with multiple HCCs (maximum 3 nodules; maximum size 3cm) treated with PEIT were 94%, 68% and 36% respectively.[10] However, Livraghi *et al* reported higher rate of complete necrosis and fewer treatment sessions with small HCCs (measuring 3cm or less in diameter) using RF ablation versus PEIT and recommended RF ablation as the treatment of choice.[21]

Percutaneous injection of glass microspheres containing Yttrium-90 directly into the tumour lesion has been reported with more than 90% tumours showing reduction in size.[28] However, there are radiation hazard issues associated with this technique including hazard to the patient when there is extrahepatic leak of the Yttrium-90 microspheres as well as to medical personnel when surgical intervention is required if the procedure is complicated by haemoperitoneum after percutaneous puncture.[29]

Microwave ablation of liver tissues using a small diameter coaxial system with needle electrodes applied percutaneously was developed in 1986 by Tabuse *et al* and this technique was applied to treat liver tumours in the 1990s.[30] The underlying mechanism involves vibration and rotation of molecular dipoles resulting in generation of heat and hence thermal coagulation of lesion. Generally, this method is limited to patients with four or fewer lesions measuring 5cm or less in diameter.[10] Mean disease-free period of 24.2 months in a cohort of 60 patients with 69 HCCs following microwave ablation with one and 2-year overall survival rates of 83.1% and 68.7%, respectively, have been reported.[10]

The use of ILP in the treatment of hepatic tumours was reported by Steger *et al* in 1989 in the treatment of 2 patients with metastatic liver tumours via percutaneous approach under US guidance.[31] In ILP, thin laser fibres emit laser light at optical or near-infrared wavelengths from their tips to produce thermal coagulation effect. A single laser fibre with light energy of 2.0 to 2.5W will produce an approximate spherical volume of necrosis 2cm in diameter while multiple fibres may be used to create larger area of necrosis.[10] This treatment has been mainly used in unresectable liver metastatic tumours using the neodymium yttrium aluminium garnet (Nd-YAG) laser. Lesion size and number limitations are similar to those of other local ablative techniques, with most investigators limiting lesions to those measuring up to 4cm in diameter and 5 or fewer in number.[27] Median survival of 27 months and 5-year survival rate of 26% have been reported.[10]

Cryoablation involves destruction of tumours in situ using the freeze-thaw process. Subfreezing temperatures (below –20 to –30°C) are delivered through penetrating or surface cryoprobes within which a cryogen (such as liquid nitrogen) is circulated; cell death is caused by direct freezing, denaturation of cellular proteins with cell membrane rupture and tissue ischaemic hypoxia with cryolesions as large as 6 to 8cm achieved.[10] Treatment usually involves open surgical technique or laparoscopic technique with US being the predominant imaging guidance. Treatment indications are patients with unresectable primary or secondary liver tumours and the number of lesions are generally limited to four or fewer.[10] Median survival of 32 months post-cryoablation treatment of metastatic liver disease, disease-free survival of 35% and 7% at 1 and 2 years respectively, and overall survival rates of 76% and 61% at 1 and 2 years respectively have been reported in a recent study by Ruers *et al*.[32]

CONCLUSION

RF ablation has been shown to be a safe and promising new technique and provides a viable option for the treatment of unresectable HCCs as well as metastatic hepatic malignancies. It is well tolerated with few major complications and minor patient discomfort. At the present moment, tumour size seems to be the critical limiting factor. However, with technological advances in the design of needle electrodes and RF equipment with availability of more powerful RF generators in the near future, and investigation into combination therapies (such as combined transarterial chemoembolisation and RF ablation, or combined surgery, RF ablation and chemotherapy), larger volumes of tissue necrosis hopefully can be achieved and thereby enabling larger size tumours to be treated.

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