REVIEW

Ablative therapy for liver tumours

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Established ablative therapies for the treatment of primary and secondary liver tumours, including percutaneous ethanol injection, cryotherapy, and radiofrequency ablation, are discussed. Newer techniques such as magnetic resonance imaging guided laser interstitial thermal therapy of liver tumours has produced a median survival rate of 40.8 months after treatment. The merits of this newly emerging technique are discussed, together with future developments, such as focused ultrasound therapy, which holds the promise of non-invasive thermoablation treatment on an outpatient basis.

SUMMARY

The roles of established ablative therapies for the treatment of primary and secondary liver tumours, including percutaneous ethanol injection (PEI), cryotherapy, and radiofrequency ablation (RFA), are discussed. PEI is effective for single small hepatocellular carcinomas (HCCs) with an equivalent survival to surgery of 70–80% at three years. PEI is relatively ineffective in the treatment of hepatic metastases. Cryotherapy of primary and secondary liver tumours has been shown to produce an overall survival of 46–89% in patients followed up for at least 20 months. RFA produces necrosis of 90% in HCCs measuring less than 3 cm in diameter but is less successful in larger tumours. However, magnetic resonance imaging (MRI) guided laser interstitial thermal therapy (LITT) of liver tumours has produced a median survival rate of 40.8 months after treatment. The merits of this newly emerging technique are detailed, along with future developments, such as focused ultrasound therapy, which holds the promise of completely non-invasive thermoablation treatment on an outpatient basis.

INTRODUCTION

Both primary and secondary liver tumours are a common problem. There are 25 000 new cases of colorectal carcinoma (CRC) metastases per annum in the UK alone.¹ Two thirds of patients with CRC have liver metastases by the time of their death.² For CRC hepatic metastases, survival is determined by the number and extent of metastases. Median survival with CRC liver metastases is 4.5–15 months. HCC, although not a common problem in the UK, is increasing in incidence worldwide due to the prevalence of hepatitis B virus (HBV) and, more particularly, hepatitis C virus (HCV) infection, both of which are major

causes of cirrhosis and the subsequent development of HCC.³ HCC is a tumour with rapid progression and a poor prognosis.⁴

RESECTION AND TRANSPLANTATION

Only 5–10% of all patients with CRC liver metastases are deemed suitable for resection. Of those who are resected, five year survival improves from 16% to 40% but there is an operative mortality of between 2.6% and 4.5% in large studies and a significant perioperative morbidity of 7–16%.^{5–7} Only 20–30% of patients undergoing potentially curative liver resection will remain free from tumour recurrence.⁸ In patients with a single small HCC and well preserved liver function, surgical resection provides a five year survival ranging from 47.1% to 60.5%. However, most HCCs (approximately 90%) are unresectable owing to underlying poor liver function or tumour multifocality.³

Transplantation for HCC is effective for small unresectable tumours (a single tumour <5 cm in diameter or three tumours all <3 cm in diameter) with a 6% perioperative mortality and an 83% recurrence free survival rate at four years.⁹

Tumours not suitable for resection or transplantation need minimally invasive treatment which provides good palliation or cure, and which is potentially repeatable with little morbidity. Various focal treatment options have been attempted to achieve these aims, including intra-arterial chemotherapy (for which little overall benefit has been demonstrated),¹⁰ PEI, and thermal ablation.

PERCUTANEOUS ETHANOL INJECTION

PEI has been shown to be effective for small HCCs but is not as effective in CRC metastases.⁷ PEI, administered under ultrasound (US) guidance, has been compared with surgical resection of the liver for single small HCCs (<5 cm). The technique has been shown to have equivalent survival to surgery with a three year survival of 79% for resection and 71% for PEI.^{11 12}

“PEI is relatively ineffective for CRC liver metastases”

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Abbreviations: RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; LITT, laser interstitial thermal therapy; HCC, hepatocellular carcinoma; CRC, colorectal carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; FUS, focused ultrasound; Nd:YAG, neodymium yttrium aluminium garnet.

PEI has also been compared with laser interstitial thermal therapy (LITT) for CRC metastases⁷ using US to guide needle placement, but with follow up by dynamic contrast enhanced computed tomography (CT). No safety margin of normal hepatic tissue was coagulated. This study found complete necrosis in 52% of tumours treated by LITT but incomplete necrosis in all cases treated by PEI. The authors concluded that PEI is relatively ineffective for CRC liver metastases.

CRYOSURGERY

The principle of cryosurgery (in situ freezing) is destruction of tumour by means of ice crystal formation.¹³ The frozen tumour is left in situ to be resorbed.¹⁴ Conventionally, the procedure is performed using a Seldinger exchange technique (18 gauge needle). A vacuum insulated cryoprobe is placed into the tumour under US guidance, either percutaneously or usually intraoperatively. However, large tumours need multiple probes. Once the probe is in position, it is anchored in place by rapidly lowering the probe temperature to -100°C .¹⁵ Freezing is started by circulating liquid nitrogen at -196°C through the cryoprobe, with 1–3 cycles of 15 minutes each applied. Lethal temperatures in the tissues of below -20°C are achieved. The probe is then withdrawn and the track filled with gel foam.¹⁴ The effects of cryosurgery can be monitored intraoperatively with US. The anterior margin of the frozen perimeter of the ice ball that is produced is seen as an area of increased echogenicity. Although the entire ice ball may not be visualised, US correlates well with the actual size of freezing. MRI can clearly identify the ice ball as it expands as a sharply margined tear drop or ellipsoid shaped area of signal void on all sequences.¹⁶ However, the frozen periphery does not correlate precisely with necrotic margins.^{15–17} The post-procedure appearances of cryosurgically treated lesions can be followed up with CT or MRI as a low density area on CT, mimicking an infarct or abscess,¹⁸ or as an area of signal void on MRI.

Several studies have looked at intraoperative US guided cryotherapy in both primary and secondary liver tumours. Onik *et al* treated 18 patients with unresectable CRC metastases with intraoperative cryotherapy, resulting in complete remission in 22% and a mean survival time of 21.4 months.¹⁴ Lee and colleagues¹⁵ reviewed several studies of hepatic cryosurgery in primary and secondary tumours and found an overall survival of 46–89% in patients followed up for at least 20 months. Lesions most suitable for cryosurgery fell into the following categories: less than four lesions in multiple lobes, lesions near the portal vein which may not have a conventional surgical margin (an ice ball can form even when immediately adjacent to a vessel wall), and patients with a limited hepatic reserve who could not undergo resection of the liver.

Silverman *et al* performed MR guided percutaneous cryoablation of 15 hepatic tumours (14 metastases, one haemangioma) in 12 patients. This study was innovative in two main respects—firstly, cryoprobes were inserted percutaneously rather than intraoperatively (which was made possible because the cryoprobe diameter was 13–14 gauge, smaller than the usual intraoperative cryoprobe) and secondly, the procedure was performed in an open 0.5 T magnet enabling near real time monitoring of ice ball development.¹⁶ In this initial group, MR guided cryotherapy was both feasible and safe with no major complications. Gadolinium enhanced MRI performed 24 hours after the procedure demonstrated that 75% or more of the tumour was necrotic in eight of 12 patients.

In a study of 308 patients, Bilchik *et al* compared cryosurgery alone with RFA alone and cryosurgery combined with RFA in unresectable primary and secondary liver

tumours. Combining cryosurgery with RFA decreased the morbidity of the procedure compared with cryosurgery alone. Recurrence rates for small tumours (<3 cm) were similar for cryosurgery and RFA. However, RFA was less suitable for large tumours (>3 cm) with a local recurrence rate of 38% for RFA treated patients compared with 17% for cryosurgery treated patients.¹⁹

The advantages of cryotherapy over RFA or PEI are: (i) the interface of frozen/unfrozen liver can be seen intra-procedurally as an echogenic edge with posterior acoustic shadowing on US or as a sharply demarcated area of signal void on all MR sequences, and (ii) cryotherapy can be used near large vessels with very little risk of thrombosis. The same is true of thermal therapy.¹⁷

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The complications of cryotherapy include haemorrhage, pleural effusion, abscess formation (which can be difficult to assess due to the similar appearances to an ice ball on both US and CT), biliary strictures or perforation, small vessel ischaemia, arteriovenous malformation formation, myoglobinuria, platelet consumption, and splitting of the liver capsule.¹⁷ Patients who undergo large intraoperative procedures commonly spend up to two days in the ITU.

RADIOFREQUENCY ABLATION

RFA is becoming a widely used ablative technique for primary and secondary liver tumours. A 14 to 21 gauge perfusion electrode needle with a cooled exposed tip, chilled to -5°C by internal water irrigation, is placed in the tumour under US or CT image guidance.^{20–23} The advantage of this arrangement is that the duration of the ablation, and therefore both the energy delivered and lesion size obtained, is increased because no tissue charring occurs around the cooled needle tip.²⁴ Alternating electric current in the range of radiofrequency (RF) waves (460 kHz) is applied from an RF generator.²⁵ This agitates ions in tissues surrounding the electrodes, causing localised heating and therefore thermal coagulative necrosis. The aim is to kill the entire tumour and, additionally, a cuff of surrounding normal tissue.

The RFA probe may be placed under US guidance with the RFA being performed blind (without real time imaging), such as in a study of HCCs by Francica *et al* where complete necrosis was seen on follow up CT in 75% of cases after a single session.²³ Alternatively, US can be used to visualise an echogenic area that develops around the probe. This method has been noted to be limited, with very poor correlation between the lesion size seen on US and the actual lesion size observed at histological examination.²⁶

Treatment of hepatic tumours by RFA was assessed with radiological-pathological follow up by Goldberg and colleagues.²² Twenty three tumours (all <8 cm, both CRC metastases and HCCs) were treated with RFA. Needle insertion was performed using CT or US guidance, percutaneously or intraoperatively. Those patients where the needles were inserted ultrasonographically were imaged throughout the procedure. All patients were imaged within four hours of RFA and again with CT or MR within five days of the procedure. All treated tumours were then resected for pathological analysis. Goldberg *et al* noted that the area of hyperechogenicity seen on US did not correlate well with the area of coagulation but that both CT and MR showed good correlation, within 2 mm, for the zone of ablation compared with histological findings.²⁷

Two papers by Livraghi *et al* provide further information on RFA in HCCs.^{28–29} For small HCCs (<3 cm diameter), RFA produced a higher number of lesions with complete necrosis than

PEI (90% compared with 80%). These authors also noted advantages of RFA over PEI. RFA only needed an average of 1.2 sessions whereas PEI required 4.8 sessions for tumour ablation, on average. They described an “oven” effect, where the size and shape of the necrotic area corresponded to the size and shape of the tumour, and suggested that this may be because surrounding cirrhotic liver acts like a thermal insulator.³⁰

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In the subsequent paper, these authors looked at RFA of medium (3.1–5 cm) and large (5.1–9.5 cm) HCCs.²⁹ RFA was applied until real time US showed that the whole tumour was hyperechoic. Follow up was with CT. Complete absence of enhancement and low density of the lesion was judged to represent complete necrosis. Medium and non-infiltrating tumours were treated significantly more often than large tumours. In this series there were only two major complications in 126 treatments. The complication rate of RFA was higher than for PEI in patients with HCC, with major complications in 2% and minor complications in 8%. The complications of the technique are similar to cryosurgery and include pleural effusions, and bleeding into the peritoneal and pleural cavities and into the biliary tree.²⁸

More recently, the same authors surveyed all 39 Italian centres performing internally cooled RFA of liver malignancies and found that a complete response was only achieved in 70% of all tumours (72% of HCCs and 68% of metastases) (Solbiati L, *et al.* Presented at the Radiological Society of North America Meeting, November/December, 2000).

POST-PROCEDURE IMAGING

Several studies have assessed tumour necrosis with CT using complete lack of enhancement in the arterial or portal venous phase as an indicator of complete necrosis.^{23–31} When both MR and CT are used in follow up, a well demarcated non-enhancing area of coagulative necrosis is seen. CT and MR show good correlation for the zone of ablation (within 2 mm).²¹

Two animal studies, using MRI as follow up after RFA with radiological-pathological correlation, showed treated lesions were hypointense on all sequences with a hyperintense rim. T₂ weighted images showed best tumour-to-treated thermal lesion contrast. MR agreed with pathological findings to within a diameter of 2 mm.^{32–33}

Follow up assessment of the lesions that are created can also be performed with US using a microbubble contrast agent, such as in the study by Solbiati *et al* where contrast enhanced US and CT were performed pre- and post-RFA.³⁴ When comparing these modalities, US had a sensitivity of 50% in detecting residual lesions but a specificity of 100%. Thus at present contrast enhanced US does not have the sensitivity of CT or MR but newer contrast agents are being developed in conjunction with technical developments in US scanning.

While the ablation therapies discussed above are minimally invasive and have been shown to improve survival, they are not amenable to accurate real time image monitoring during a procedure. Such an option is highly desirable to optimise tumour ablation and to tailor requirements to the individual patient's needs. CT, MRI, or US are imaging modalities which may be adopted for this purpose with varying degrees of accuracy. MR guided laser interstitial thermal therapy (LITT) differs from other treatment options

because it can be performed with precisely reproducible monitoring of the thermal lesions at the time that they are being produced.

LASER INTERSTITIAL THERMAL THERAPY

LITT was first described by Bown in 1983 using bare infrared fibres.³⁵ Laser therapy is particularly suited to MRI because optical fibres are not affected by and do not affect the MR signal, unlike RFA.³⁶ LITT is performed with an infrared laser, such as neodymium yttrium aluminium garnet (Nd:YAG, wavelength 1064 nm) laser, delivered through a thin (400 µm diameter) quartz fibreoptic.^{37–42} Initially, bare laser fibres were used with multiple punctures with each fibre producing about 1 cm diameter destruction. These lesions were limited by tissue charring around the laser fibre tip, and to produce larger lesions many fibres had to be used. Such fibres have been superseded by larger interstitial fibres which diffuse the laser energy using a frosted/etched distal tip, producing greater tissue penetration by preventing local tissue charring (carbonisation).⁴³

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In addition, the temperature of the fibre tip may be reduced with a water cooling system to further reduce tissue charring and increase the penetration of heat into the tissue. Laser light is converted into heat in the target area causing coagulative necrosis and tumour shrinkage in an elliptical area around the needle tip as the temperature rises above 55°C, with minimal damage to surrounding structures.^{36–39} MR guided advancement of the needle between heating periods increases the transverse diameter of the lesion, as may placement of multiple needles within a single lesion.⁴⁴

LITT has been used with real time US as well as MRI. Masters *et al* used LITT to treat liver metastases from CRC, breast, and stomach primary carcinomas.⁴² Eighteen patients were treated on 31 occasions with a percutaneous approach. Evolving thermal changes were monitored with real time US. The procedure was well tolerated with no major adverse effects and at least partial necrosis was achieved in 44% of metastases. Small lesions (<3 cm) were more easily treated.⁴² The limitations of this study are that real time US only correlates poorly with the extent of thermal ablation.

Vogl *et al* have performed LITT on a much larger group of patients using CT to guide placement and MR to confirm position and monitor temperature changes. This technique produced local tumour control in 98.1% of patients three months after treatment (see later for further discussion).^{39–40}

“OPEN MAGNET” SYSTEMS AND NEEDLE TRACKING

MR is ideally suited for image guided fibre placement because of its multiplanar capacity, soft tissue discrimination, and thermal mapping capabilities.^{45–47} However, there is poor access to patients in conventional magnets and therefore lasers are usually placed under US or CT guidance with patients being transferred to the MR scanner for monitoring of laser therapy.³⁸ This may cause movement of laser fibres during transfer which can only be adjusted with substantial difficulty once the patient is in the bore of the magnet.

An “open magnet” configuration allows access to the patient so that needle placement and adjustment can be easily performed. MR images can be obtained in multiple

Figure 1 Vertically orientated double magnet configuration (0.5 T) with a 56 cm gap for the operator to gain access to the patient. A liquid crystal monitor within the bore displays the current magnetic resonance image to the operator.

planes and complex non-orthogonal needle paths are easily tracked. There are a number of different open designs including a horizontally placed “sandwich” arrangement with magnets above and below the patient and access at the sides. Our group has used a superconducting 0.5 T (GE Medical Systems) magnet which comprises a vertically orientated double magnet configuration. For interventional procedures the patient lies through the central bore of both magnet rings. There is a 56 cm gap between the two rings for the operator to gain access to the patient (fig 1). Liquid crystal monitors within the bore display current MR images to the operator during procedures. Near real time imaging with the use of

single shot gradient recall sequences updates the image every 1.5 seconds.⁴⁷ Flexible transmit-receive surface coils are attached to the body area to be imaged, instead of fixed RF transmitting body coils used in conventional scanners.⁴⁷ All equipment, including anaesthetic equipment, is MR compatible. Image registration is performed in three dimensions to guide needle placement.⁴⁸ The advantage of MR over conventional CT axial imaging is that images can be generated in any oblique plane, including along the line of the potential needle track.⁴⁵ The needle itself is seen as a line of low signal. Before the needle enters the patient, the potential needle track can be seen using flash point or MR tracking, and the safest route planned.

MR THERMOMETRY

Temperature sensitive real time MR imaging can display both transient and permanent temperature elevations in tissue non-invasively, with high spatial and temporal resolution, as tissue is heated to beyond 57–60°C (the threshold for protein denaturation).⁴

MR thermometry exploits T_1 signal magnitude which varies inversely with temperature in the range 10–50°C. The rate of change depends on the tissue imaged. Signal intensity diminishes as heat is increased with signal loss in tissues appearing blacker on T_1 weighted images.^{49–51} Our group has used a software tool to produce colourised thermal maps of heated areas during heat application for real time temperature quantification (Sun Micro Systems Sparc 20). This is particularly useful for showing the very early thermal changes before irreversible necrosis has occurred. The grey scale loss in the T_1 signal is converted to a colour spectrum (fig 2) which ranges from blue (coolest area), through turquoise, green, and yellow to red (the hottest area).⁴ The images are updated every four seconds. At approximately 55°C, irreversible tissue necrosis occurs and a persistent green colour develops on the colour scale. The advantage of near

Figure 2 (Top left to bottom right) Near real time colour thermal map acquired during laser interstitial thermal therapy of colorectal carcinoma metastasis. Images are acquired in the sagittal plane and regularly updated as necrosis develops. The colour scale ranges from blue to green to yellow to red. Once a persistent green colour develops, irreversible necrosis has occurred.

Figure 3 Axial T₁ weighted gadolinium enhanced magnetic resonance imaging of the liver in a patient with colorectal carcinoma metastasis four weeks after (top row) the first thermal ablation and four weeks after (bottom row) a second thermal ablation. After the first ablation, low signal non-enhancement in the centre of the metastasis represents necrosis but some enhancing tumour remains around the periphery. After the second ablation no enhancement is seen, and there is uniform low signal representing complete necrosis of the metastasis.

real time imaging and thermal mapping is that not only can the LITT needle be accurately placed but the temperature effect on tissues can also be monitored dynamically and the position of the needle adjusted during the procedure to optimise the size and extent of the ablation. This allows optimisation of the energy that needs to be delivered to each individual tumour under treatment.⁴ This is particularly useful in lesions which are adjacent to large vessels which can conduct heat away from the area to be ablated (so-called "heat sink") or lesions surrounded by fat, which can quickly conduct heat to surrounding local tissues producing much larger areas of necrosis. With near real time thermal mapping the duration of heat and power applied can be altered for different patients to produce a reliable consistent result each time with maximum safety assured. Without real time imaging the extent of tissue necrosis can only be approximated.⁵²

We have reported our early experience in 12 patients with both primary and secondary liver tumours.⁴ In total, 27 procedures were performed in this study (but to date 100 procedures have been performed). All patients were unsuitable for resection or transplantation and had no more than six lesions, none of which exceeded 8 cm in diameter. The lesions were punctured using real time multiplanar MR image guidance under local or general anaesthesia. A water cooled interstitial laser fibre and a Nd:YAG source were used to deliver thermoablation. The real time MR colour scale described above was used to determine when the lesion was completely ablated and therefore monitor the length of time for which thermal ablation was applied. Most patients were discharged the following day and monitored with follow up MRI. Thermal lesions with a mean diameter of 3 cm per laser fibre and a maximum diameter of 5 cm were produced. Follow up MR demonstrated low signal non-enhancing material replacing tumour for at least six months suggesting successful complete ablation. Two patients with lesions of less than 3 cm in diameter had complete tumour ablation after only one procedure. All other lesions remained unchanged in size or showed a small increase in size. A patient treated with laser ablation is shown in fig 3.

The largest series of liver LITT comes from Vogl and colleagues.³⁷⁻⁴¹ This group has performed 1822 laser

ablations on 733 liver tumours in 251 patients. The liver tumours include CRC metastases (the majority), HCCs, and metastases from breast and other primary sites. After evaluating lesions on a conventional MR scanner 2-5 days prior to LITT, CT was used to localise tumours and position the catheter. This group established the optimum position of the laser applicator with MRI. Real time MR thermometry was used to document ablation extent. Follow up MR was performed two days post-procedure and every three months thereafter. All patients tolerated the procedure well. Complications included subcapsular haematoma (1.2% of patients), pleural effusions (5.7%), and a liver abscess (0.29%). The overall survival rate for all liver tumours was 40.8 months (38 months for CRC metastases alone).³⁸⁻⁴⁰

FOCUSED ULTRASOUND

A further benefit should emerge with the arrival of MR guided focused US (FUS) tissue ablation which is completely non-invasive.⁵³ This method uses sharply focused high energy US transducers of different focal lengths to induce local temperature elevation during a short exposure time (1-20 seconds). Targeting is carried out using MR and as the FUS is applied, temperature sensitive phase difference sequences are used to provide instantaneous thermal maps of the target area. By moving the FUS probe, adjacent small lesions can be produced, amounting to a significant area of ablation. Movement of the transducer within the magnet is controlled by a hydraulic positioning device. Power monitoring circuitry is included for patient safety. The target volume to be ablated is outlined with cross sectional MR images. The US focus moves to ablate the defined volume.⁵⁴ After an initial low dose test heat pulse, without tissue damage, short high intensity pulses are applied to produce non-haemorrhagic sharply demarcated lesions.⁵⁴

"The advantages of FUS are that it is completely non-invasive, the site and shape of the lesion can be chosen, each sonication is delivered within a few seconds, and lesions are very sharply defined"

The advantages of FUS are that it is completely non-invasive, the site and shape of the lesion can be chosen, each sonication is delivered within a few seconds, and lesions are very sharply defined.³³ The main limitation of FUS is that, as for all US, it cannot penetrate bone or air and therefore is not useful for hollow organ gastrointestinal or pulmonary applications, for example.

SUMMARY

While PEI and RFA are both accepted techniques for ablation of liver tumours, RFA is superior to PEI for both HCCs and colorectal metastases. There are multiple potential benefits of percutaneous LITT in an "open magnet" system, with real time imaging of both fibre placement and lesion ablation. Placement of needles and the energy required to perform thermal ablation can be monitored continuously and optimised as required. The patient is easily accessible throughout the procedure, allowing both fibre adjustment and monitoring of sedation, analgesia, or anaesthesia. MR guided placement and ablation enables lesion size to be tailored to the individual patient, which could potentially result in an improvement in survival compared with unmonitored tumour ablation. MR guided LITT has been shown to be equivalent in percentage necrosis achieved when compared with RFA of HCCs (Rossi M, *et al.* Presented at the Radiological Society of North America Meeting, November/December 2000). A controlled trial of RFA and MR guided LITT in secondary liver tumours would be useful. However, all ablation techniques are invasive which may be hazardous in certain patients with decompensated chronic liver disease or with coagulopathies. For the future, focused US offers the promise of a completely non-invasive option which ultimately would allow ablation techniques to be performed safely on an outpatient basis.

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