Radiofrequency ablation of unresectable liver tumours

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Unresectable liver tumours have a dismal prognosis. Treatment with systemic or regional chemotherapy rarely results in a durable complete response. Radiofrequency ablation is a novel technique to achieve local destruction, which can be repeated and has been shown to be safe and effective.

Surgery remains the only potentially curative treatment option for patients with primary or secondary liver cancer. Hepatocellular carcinoma (HCC) and metastatic colorectal cancer account for the majority of primary and secondary malignant tumours encountered in the liver. However, owing to constraints such as size, location, extent of tumour and it's impact on functional reserve, the presence of cirrhosis (in patients with primary tumours) or poor general health, only 5–15% of patients with liver tumours are suitable for curative procedures (including resection or liver transplantation for early HCC).

The 5-year survival rate for patients undergoing resection of HCC still remains disappointing, ranging from 15 to 35% depending on the size and grade of the tumour and underlying liver function. The outcome from surgery for colorectal metastasis is more encouraging, with some centres now consistently reporting 5-year survival rates of 45%. Patients who are not suitable for surgical resection or transplantation have a dismal prognosis and most of them die from local tumour load causing liver failure.

Treatment options currently available for patients with unresectable liver tumour include:

- Systemic or regional chemotherapy and hepatic artery embolization
- Ablative therapies, including: chemical ablation (ethanol injection), cryotherapy, the application of microwave or laser probes, high intensity focused ultrasound and radiofrequency ablation (RFA).

RFA is now the most commonly used ablative therapy for treatment of liver tumours.

EQUIPMENT

Radiofrequency generators produce a high-frequency (200–1200 kHz) alternating low voltage current at the treatment electrode. The electrical circuit consists of a needle electrode probe placed within the target lesion, and a 'ground pad' placed around the patient's thigh with the patient functioning as the resistance. When current is applied, ions in the tissue move towards or away from the electrode depending on their charge. As the current alternates, the ions rapidly change direction producing ionic agitation, resulting in frictional heating of the tissue.

A single electrode can produce a thermal lesion of up to 1.6 cm. To increase the size of the 'burn', modern RFA probes have either multiple prongs (umbrella-like), or are cooled during the ablation process by an infusion of the saline through the needle. This reduces charring and achieves a larger area of necrosis by facilitating heat dissipation, which allows for thermal lesions of up to 7 cm to be produced. In order to achieve adequate tumour destruction, a temperature of >100°C must be maintained for a period of time depending on the size of the tumour. Living mammalian cells die when exposed to temperatures of between 42 and 45°C for prolonged periods of time. To ensure 'supra-lethal' thermal injury in all target tissues, RFA techniques must achieve temperatures exceeding 50°C through out the lesion for at least 6 minutes. The authors currently expose tumours to 105°C for 10–15 minutes to ensure uniform supra-lethal killing.

INDICATIONS FOR RADIOFREQUENCY ABLATION

RFA is used to treat patients with primary or metastatic liver tumours which are not suitable for resection but with disease that is localized to the liver. Early reports suggested that RFA should be limited to patients with up to four

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lesions with each lesion being less than or equal to 4 cm in size. More recently, the number and size of lesions being treated has increased. Currently, most centres will limit the use of RFA to patients who have tumours of 5 cm or less in diameter and/or have a maximum number of seven lesions.

RFA can also be used in combination with liver resection to increase the number of potentially curable patients. This applies to patients with bilobar disease, who previously would have been deemed inoperable because of inadequate liver volume post resection. These patients can now be considered for resection of one lobe (the side with a larger volume of disease) and ablation of small volume disease in the remaining lobe. An emerging role for RFA is in controlling tumour progression in patients with early HCC who are awaiting liver transplantation. In addition, Elias et al (2002) have suggested that RFA should be the preferred mode of treatment for patients with recurrent disease after previous resection.

TECHNIQUE

In principle, one should always try to achieve total ablation in one session. The ultimate goal is to ablate the tumour plus a circumferential zone of normal tissue around the lesion. This is achieved by producing 'ablated bands' of tissue in a stepwise fashion across the lesion. With the systems that use deployable 'talons' these fine needles are deployed into viable tumour first. Once an area of ablation has been achieved, the talons and the needle (if necessary) are further deployed in ever-increasing bands until the entire lesion has been destroyed.

RFA of liver tumours can be carried out by one of three routes:

1. Percutaneous (ultrasound (US) or computed tomography (CT) guided). This is usually performed under local anaesthetic and sedation, the advantage being that it can be carried out as a day-case procedure. For this procedure the lesion needs to be in a position that can be accessed safely, away from adjacent organs and is easily visible.
2. Laparoscopic (intraoperative ultrasound (IOUS) guided).
3. Open (IOUS guided). This is for lesions that are close to major blood vessels, the diaphragm or bowel, or if the lesion can not be targeted under radiological guidance. This is carried out during laparotomy. IOUS is used to target the lesion and monitor ablation. Tumours situated close to blood vessels are difficult to treat by RFA as heat from the tissue is dissipated by flowing blood (heat sink effect). Occlusion of the hepatic inflow (portal vein and hepatic artery) – the Pringle manoeuvre – decreases the heat sink effect.

MONITORING THE ABLATION PROCEDURE

Once the probe is deployed in the tumour the ablation process is monitored using ultrasound. Greyscale sonographic findings observed during the thermal ablation includes a progressively increasing hyperechoic focus often seen surrounding the distal portion of the applicator. This is caused by microbubbles of gas that form in the heated tissue. Although contrast-enhanced CT is better to visualize the ablation progress, in view of the complexity of this procedure most centres carry out ablation under ultrasound guidance.

MONITORING THE EFFECT OF ABLATION

Between 2 and 4 weeks post ablation a contrast enhanced CT scan is carried out to assess the degree of tumour destroyed. The ablated tumour will appear as an unenhanced area while enhancement of the lesion suggests viability. Repeated ablations can be carried out to achieve compete 'killing'. Each follow-up CT must be scrutinized for evidence of tumour recurrence both adjacent to the treated lesion and remote from the ablated site, as well as outside the liver. The presence of extra-hepatic disease is a contraindication to further ablation therapy.

RESULTS

The recurrence rate after RFA depends on the disease biology, size and number of the lesions being treated (Bleicher et al, 2003) as well as the response to other adjuvant therapies used.

Hepatocellular carcinoma

When using RFA for the treatment of HCC, complete necrosis of the tumour can be achieved in up to 90% of tumours when the lesions are less than 3 cm in size. This may be because the cirrhotic liver retains heat. In 1996, Rossi et al reported long term follow up after RFA (5 years with a median follow up of 2 years) – a median survival of 44 months was reported in cirrhotic patients with HCC of less than three lesions which are smaller than 3 cm in width, after complete RFA (Rossi et al, 1996). More recently it has been shown that, with the combination of RFA and transarterial chemoembolization (TACE), survival in patients with unresectable primary and secondary liver tumours is

improved (Bloomston et al, 2002). In the authors' institution TACE is used before ablation in all HCCs in an attempt to achieve complete necrosis, but its effect on long-term survival is unknown.

Secondary tumours

Ablating metastatic disease appears to be more complex than for primary liver cancer. The 'biology' of metastatic disease may be such that by the time there are visible tumours in the liver there are many more microscopic metastases. Heat dissipation in the non-cirrhotic liver makes the procedure less effective and the tumour margin is often more locally invasive, requiring a more aggressive approach to the ablation of metastatic tumours in order to minimize recurrence.

The effectiveness of RFA in prolongation of life in patients with unresectable liver tumours is difficult to judge as there are as yet no published randomized controlled trials. The literature remains dominated by single centre experiences and anecdotal reports of idiosyncratic practices.

COMPLICATIONS

Following RFA most patients will have transient pyrexia of up to 38°C. More troublesome complications including haemorrhage, injury to adjacent viscera such as the gall bladder and colon (especially during percutaneous placement), and infection of necrotic tumour (Mulier et al, 2002). The overall complication rate is about 10%. Tumour dissemination both in the bloodstream and along the needle tract have been reported but ablation of the needle tract as the probe is removed reduces the risk of tumour implantation. The overall mortality of the procedure is less than 1%.

FUTURE

RFA is a safe, effective and well-tolerated treatment for unresectable hepatic malignancies less than 6 cm in diameter (Curley and Izzo, 2002). With advances in technology better generators and probes will be able to produce larger lesions. Tissue harmonic imaging and contrast-enhanced US can make monitoring of the ablation and follow up more accurate.

Future strategies must be aimed at changing the tumour response to radiofrequency treatment; this will involve multimodality treatment including systemic and regional treatments along with RFA.

An important area of research relates to understanding of effect of ablation on cells at the periphery of ablated zone. The authors' data, as yet unpublished, suggests the presence of an unablated zone between the necrotic lesion and the healthy hepatic tissue which has been confirmed on vital staining – and which they have called the transition zone – with evidence of apoptosis. This suggests that any improvement in the effectiveness of the ablation process should be aimed at having an effect on this 'unstable' transition zone.

CONCLUSION

RFA of liver cancers has been an important advance for patients with unresectable disease or those with poor functional reserve. The short-term results are promising, but long-term data and randomized controlled trials are awaited. It can be carried out safely and all patients with unresectable liver tumours who fulfil reasonable criteria (< seven lesions, 3–5 cm in size) should now be considered for RFA as part of their multi-modality treatment plan. **HM**

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Bleicher RJ, Allegra DP, Nora DT, Wood TF, Foshag LJ, Bilchik AJ (2003) Radiofrequency ablation in 447 complex unresectable liver tumours: Lessons learned. *Ann Surg Oncol* **10:** 52–8

Bloomston M, Binitie O, Fraiji E et al (2002) Transcatheter arterial chemoembolization with or without radiofrequency ablation in the management of patients with advanced hepatic malignancy. *Am Surg* **68:** 827–31

Curley SA, Izzo F (2002) Radiofrequency ablation of primary and metastatic hepatic malignancies. *Int J Clin Oncol* **7:** 72–81

Elias D, De Baere T, Smayra T, Ouellet JF, Roche A, Lasser P (2002) Percutaneous radiofrequency thermoablation as an alternative to surgery for treatment of liver tumour recurrence after hepatectomy. *Br J Surg* **89**(6): 752–6

Mulier S, Mulier P, Ni Y et al (2002) Complications of radiofrequency coagulations of liver tumours. *Br J Surg* **89:** 1206–22

Rossi S, Di Stasi M, Buscarini E et al (1996) Percutaneous RF interstitial thermal ablation in the treatment of hepatic cancer. *AJR Am J Rontgenol* **167:** 759–68

KEY POINTS

- Unresectable liver tumours have a dismal prognosis.
- Radiofrequency ablation (RFA) is a novel technique which kills the tumour in situ by generating heat.
- RFA can be used percutaneously as a day-case procedure.
- RFA is safe and effective in achieving local tumour control.
- Randomized trial results are needed to understand the effects of RFA on long-term survival.