

Colorectal Hepatic Metastases: Role of Radiofrequency Ablation

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Abstract

Introduction: Radiofrequency ablation (RFA) is a new minimally invasive treatment that has been increasingly used in the treatment of liver metastases. This review aims to outline the principles governing the use of RFA and to examine its role when applied to the management of colorectal liver metastases. **Methods:** A Medline search of experimental and clinical studies relating to the use of RFA in the management of colorectal hepatic metastasis was carried out. **Results:** RFA is currently used as an alternative to surgery in patients with unresectable disease, and sometimes as its companion, allowing patients hitherto considered unsuitable for resection to become surgical candidates. RFA has been shown to be safe and well tolerated, with few major complications and minimal patient discomfort. Although its use is unlikely to achieve cure in such patients, it has a definite role in palliation and relief of symptoms. Long-term data, when these become available, may also show improved survival. However, because RFA is a local ablative therapy, it does not address the progressive and systemic nature of colorectal carcinoma. **Conclusions:** RFA is an important alternative/complimentary tool in the management of colorectal hepatic metastases. Combining RFA with surgery or chemotherapy may reduce the incidence of local and systemic relapse.

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Introduction

Colorectal cancer is the second most common cancer in Singapore, accounting for 15.9% of all cancers registered with the Singapore Cancer Registry in the years between 1993 and 1997.¹ Despite recent advances in surgery, radiotherapy and chemotherapy, more than half of those afflicted will die from their cancer.

At the time of initial presentation, 15% to 25% of patients will already have liver metastases. Another 20% will develop hepatic metastases, despite treatment of the colorectal primary.² Left untreated, the median survival after detection of liver metastases is approximately 7.5 months.³ Successful surgical resection of these metastases has, however, produced 5-year survival rates of 28% to 40%.⁴⁻⁶ Unfortunately, fewer than 20% of patients with metastases confined to the liver are eligible for curative resection.⁷ Diffuse bilobar disease, metastatic deposits in close proximity to major blood vessels and biliary structures or inadequate hepatic reserve preclude surgery. Furthermore, even after an adequate resection, at least 50% of patients will develop recurrent disease.

In this group of patients with unresectable colorectal liver metastases, chemotherapy and local ablative therapies are available. Chemotherapy, either systemic or regional, has, however, proven disappointing. Despite multiple trials and different drug regimes, improvements in survival are

at best marginal.^{8,9} Over the years, a whole gamut of local ablative therapies have also been applied to this problem too. These include percutaneous ethanol injection, focused ultrasound, cryoablation, microwave tumour coagulation, laser photocoagulation and radiofrequency ablation (RFA). It is hoped that by decreasing the volume of viable tumour, a survival advantage or even cure can be achieved in some patients. There are also potential benefits of percutaneous destruction of tumour, including decreased cost, morbidity and the possibility of performing these procedures in outpatients. This review will discuss the role of RFA in the treatment of hepatic metastases from colorectal cancer. A MEDLINE search using the terms “radiofrequency ablation”, “colon carcinoma” and “hepatic metastases” was performed. To date, in the English literature, there is only 1 large clinical series focusing solely on the use of RFA in colorectal hepatic metastases.

Most of the other published reports have often involved multiple different treatment modalities or have included patients with both primary and secondary hepatic tumours or metastases from multiple primary tumours. In our review of published results, we therefore also considered selected reports satisfying the following criteria: (i) it included more than 10 patients with hepatic metastases of which a significant proportion arose from colorectal carcinoma, (ii) we could reliably determine the results directly attributable

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to the use of RFA in our sub-group of patients, or (iii) it was significant in the evolution of the technique of RFA.

Background

The use of alternating radiofrequency (RF) current to generate heat in living tissues, without causing pain or muscular contractions, was first described by the French physicist—d'Arsonval—in 1891. Since then, RF energy has been widely used in the operating theatres for electrocautery, in cardiovascular laboratories to ablate aberrant conduction pathways for the treatment of arrhythmias and in endoscopic techniques.

RF thermal ablation works by converting the energy of an electromagnetic wave into heat. A high frequency alternating current (around 500 kHz) passes from an active needle electrode placed within the tumour, to the passive electrode in the form of a dispersive pad applied to the skin. As a result of the “to and fro” agitation of tissue electrolytes surrounding the needle electrode in response to the change in direction of the alternating current, frictional heat is produced. Heat is not generated within the electrode itself, but rather in the surrounding tissues.

As temperature increases to between 60°C and 100°C, there is induction of irreversible cellular damage, culminating in coagulation necrosis.¹⁰ Because the amount of energy deposited varies inversely with the square of the distance from the electrode tip, the area of necrosis does not exceed 1.6 cm in diameter when using single monopolar RF techniques. Charring of tissue surrounding the needle tip increases impedance, which limits the propagation of heat. This was the main factor limiting the clinical use of RFA in the past. Most tumours are larger than 1.6 cm by the time they are detected. Successful treatment of these lesions would have meant the use of either multiple needle insertions, multiple treatment sessions or both. The “holy grail” of RFA research had been the development of a technique that can achieve safe and reliable large volume tissue destruction of tumour in a single treatment session.

Various techniques were proposed to overcome this limitation including the use of bipolar¹¹ and multipolar electrodes¹² and the instillation of saline through the needle electrode.¹³ Although these manoeuvres did actually succeed in obtaining larger areas of necrosis, often these were irregular and unreliable, which made their use unsatisfactory.

More recent RF technological developments have revolved around 2 different systems. The first (Radiotherapeutics, Sunnyvale, CA and RITA Medical Systems, Mountain View, CA) involves a 15G to 17G hollow needle which, when positioned within the lesion, deploys between 4 and 10 retractable curved electrodes, much like the spokes of an umbrella (Fig. 1). This technique

is able to produce a reliable area of ablation – 3 to 4 cm in diameter.¹⁴ The second system utilises an “internally cooled” electrode (Radionics, Burlington, MA, USA) (Fig. 2). Cold saline is circulated coaxially through 2 internal lumens within a 14G electrode. By cooling the electrode tip during the RF application, it is possible to increase generator output as well as prevent charring of tissue immediately adjacent to the needle tip. The technique can achieve a reproducible area of necrosis of 2.4 cm in diameter using a single cooled electrode.¹⁵ When 3 such electrodes are clustered about 0.5 to 1 cm apart, a spherical focus of coagulation necrosis is obtained which approaches 4.5 cm in diameter.¹⁶

The delivery of RF energy in pulses, rather than in a continuous manner, has also led to some improvements in the size of ablation.¹⁷ Furthermore, it was found that occlusion of tumour arterial supply, either mechanically or pharmacologically, could also increase the diameter of necrosis.¹⁸

Technique

Imaging Guidance

The needle probes are usually first positioned at the deep margin of the tumour and subsequently pulled back to cover the more superficial portion of the lesion. Ultrasound (US) is the imaging modality that is most commonly utilised for guidance in percutaneous RF ablation, either alone or in combination with computed tomography (CT) (Figs. 3 & 4). Advantages of US over CT and magnetic resonance imaging (MRI) include its real-time capability, vascular visualisation (with colour Doppler imaging), wide availability, speed and its relative low cost. Although US is extremely useful in guiding placement of the RF needle electrode, it has limited ability in assessing the effectiveness and extent of RFA. This is because RFA produces a dense echogenic area on US imaging, the size of which is only a rough approximation of the area ablated. In addition, the echogenic area obscures the margins of the tumour that is being treated, especially its posterior extent. A study in animals concluded that US overestimates the size of necrosis when compared with histopathology in 23%.¹⁹ Contrast-enhanced CT has, however, been accurate to within 2 mm of actual lesion size.²⁰

Approaches

RFA can be applied with either a percutaneous, open surgical or laparoscopic approach. Each of these techniques has its advantages and limitations. The percutaneous approach is minimally invasive and can be performed with conscious sedation. It would therefore be ideal for poor surgical-risk patients. The concern about a percutaneous approach has been the inability to control haemorrhagic complications. Fortunately, in our experience, haemorrhage is very uncommon.

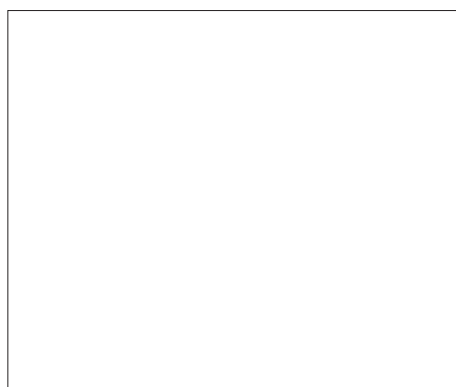


Fig. 1. LeVeen multiple array needle electrode showing with the tines retracted (left) and fully deployed (right) from the needle tip.



Fig. 2. A triple cluster RF electrode with a 2.5-cm exposed tip (above) and a single internally cooled RF electrode with a 3-cm exposed tip (below).

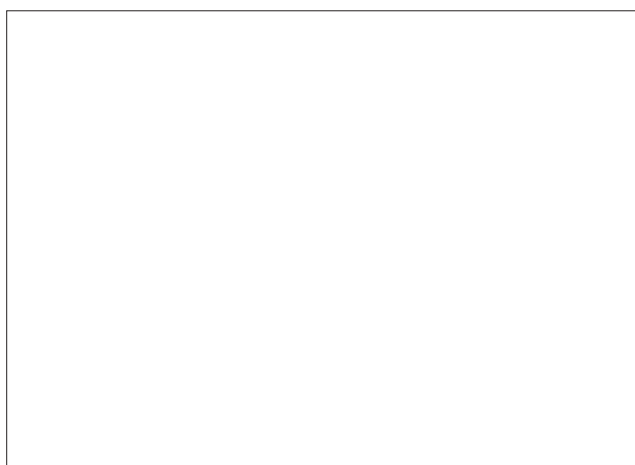


Fig. 3. Oblique intercostal US image obtained during RFA with an internally cooled electrode showing the needle tip and track (white arrows).

A laparoscopic approach is often used in conjunction with laparoscopic ultrasound to help determine the site and number of liver metastases and aid in placement of the probe. Laparoscopy also provides the opportunity for assessment of extra-hepatic disease. However, certain areas of the liver might be technically inaccessible to the laparoscope.

Open laparotomy is the most invasive approach and

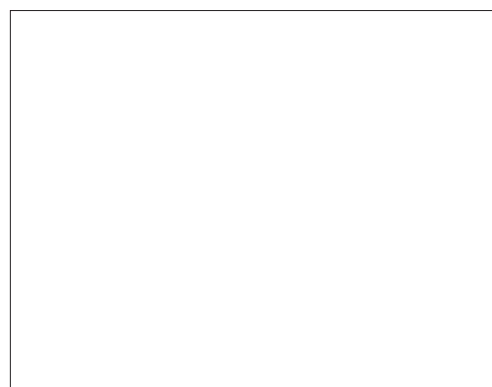


Fig. 4. Axial CT image during insertion of a needle electrode into the liver. Medial to this needle is intra-lesional haemorrhage and air (arrowhead) arising from prior ablation of an adjacent tumour.

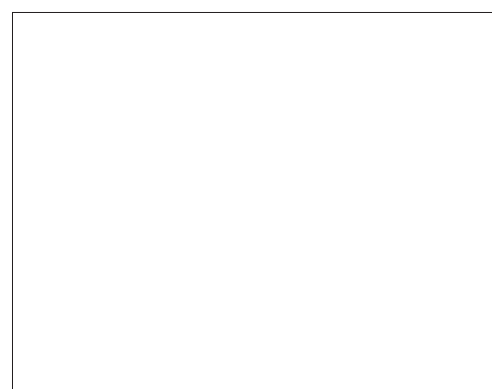


Fig. 5a. Axial contrast enhanced CT scan shows a hypodense lesion with rim enhancement in Couinaud segment 3 (arrow).

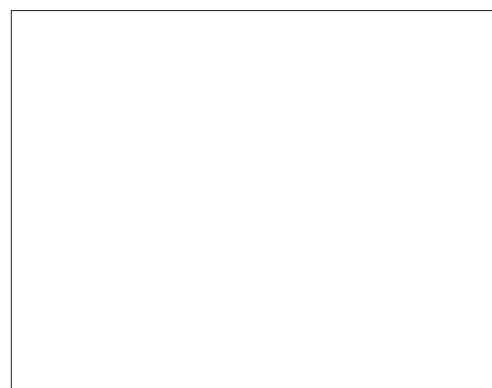


Fig. 5b. Contrast-enhanced axial CT scans obtained 3 months after treatment show uniform hypo-attenuation of the segment 3 lesion and absence of contrast enhancement.

Fig. 5. Pre- and post-RFA of a colorectal hepatic metastasis.

associated with increased length of hospital stay and morbidity, but it does have several advantages. At surgery, one is able to displace adjacent structures such as the gall bladder or colon from the liver, preventing inadvertent thermal injuries to these organs when treating peripheral lesions. In addition, the surgical approach allows the opportunity to interrupt portal venous flow by the Pringle manoeuvre during RFA. This manoeuvre decreases the

TABLE I: ELIGIBILITY CRITERIA FOR RADIOFREQUENCY ABLATION OF HEPATIC METASTASES

I.	Prior resection of the primary tumour with no evidence of residual disease.
II.	Biopsy proven or strong clinical suspicion for colorectal metastases based on raised carcinoembryonic antigen (CEA) and correlative imaging.
III.	Surgically non-resectable hepatic metastases, either because patient is a poor surgical candidate, technically inaccessible or inadequate functional reserve.
IV.	All hepatic lesions are deemed potentially treatable by RFA alone or in combination with other treatment. If tumour involves major biliary ducts or major vessels, it might not be possible to perform RFA.
V.	No evidence of extrahepatic disease.
VI.	If percutaneous approach considered, patient must not have uncorrectable coagulopathy. Generally, patients should have a platelet count of more than 80,000 mL and prothrombin time/activated partial thromboplastin time of less than 3 sec above normal.

cooling effect of blood flow to any given area, thus optimising the size of coagulation necrosis and even allowing tumour adjacent to major vascular structures to be treated.

Follow-Up

Although there are some investigators who report the utility of contrast-enhanced ultrasound using micro-bubbles to help detect residual tumour, most institutions use CT or MRI for follow-up of these patients. In the immediate post-ablation scan, the aim is to assess the extent of ablation and to detect any potential complications. 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. This makes it difficult to distinguish it from residual tumour, limiting the accuracy of the immediate CT scan in assessing the completeness of ablation. Fortunately, this phenomenon is only transient and has been shown to disappear progressively in subsequent follow-up studies. Intra-lesional haemorrhage and air may also be seen in the immediate post-ablation scan (Fig. 4). These are associated with the introduction of the probe and also resolve over the course of time.

Multi-phase helical CT or gadolinium enhanced MR imaging is mainly used in subsequent follow-up of patients, often in combination with CEA tumour markers, if previously raised. These are usually carried out 1 month post-ablation and thereafter every 3 to 6 monthly. The main aim in these follow-up scans is to look for evidence of residual or recurrent tumour, either locally at the previous site of ablation or distant new hepatic lesions. Lesions that have been completely ablated will appear entirely and homogeneously hypodense on a CT scan with no focus of contrast enhancement (Figs. 5a & 5b). On T2W MR imaging, these are seen as low intensity areas without evidence of enhancement with gadolinium. If there is

evidence of tumour recurrence limited to the liver, repeat ablation is required and may be effective. One of the significant advantages of percutaneous RFA is that it can be repeated as often as is necessary to treat intra-hepatic recurrence.

Eligibility Criteria

In general, RFA should only be considered in patients who satisfy the criteria listed in Table I. At the present, there is no clear consensus with regards to the size and number of lesions that can be treated with RFA. Although there are and will be case reports of the procedure being successfully carried out in patients with 10 to 15 lesions, most would only perform RFA in patient with not more than 5 lesions. Similarly, some investigators have attempted ablation of lesions as large as 15 cm using multiple passes. It is, however, felt that 5-cm tumours are at the upper limit of its current ability, although we have no doubt that this will increase with future technological developments.

Rationale and Role of RFA

RFA, in the context of colorectal metastases, is unlikely to be curative. Like all other local ablative therapies, it does not address the progressive and systemic nature of the disease. Even if there should be no local recurrence in ablated lesions, many will subsequently develop other hepatic and/or extra-hepatic lesions as a result of co-existent micro-metastatic deposits. It is for this reason that the primary tumour must be treated along with or before RFA of the hepatic metastases.

At present, surgical resection of colorectal metastases in the liver remains the treatment of choice and should be recommended to the patient whenever possible. However, if surgery is refused or not appropriate because of bilobar disease, proximity of tumour to key vascular or biliary structures that preclude a clear tumour margin, or inadequate functional hepatic reserves as a result of coexistent cirrhosis, RFA can be offered to the patient, either alone or in combination with other therapies.

If RFA is used alone, ideally it should be able to deliver benefits approximating that of surgical resection in terms of local recurrence rates, long-term survival advantage as well as size of lesions that can be treated. The crucial factor in RFA, which impact all of the above end points, is the size of ablation it can reliably produce. Although there has been much development in this area over the past 7 years, more needs to be done before RFA can achieve this goal. Till then, operators need to be aware of its limitations and the necessity for careful patient selection.

RFA can also be used in combination with surgery or chemotherapy. When used in conjunction with surgery, it allows surgeons to extend the therapeutic envelope and offer treatment to a wider cohort of patients, including

those who were previously considered unresectable. Conceptually, combining RFA and systemic or regional chemotherapy is very attractive. RFA can destroy larger visible tumours, whilst chemotherapy is used to kill remnant tumour cells and occult metastases. It is hoped that this would translate into greater survival advantage for the patient.

Results of RFA

Despite the recent slew of reports on the use of RFA on liver cancers, these results must all be viewed as preliminary – principally as assessments of safety and short term efficacy – because long-term follow-up has only recently been available.

RFA Alone

Rossi et al²¹ in 1996 were amongst the first to report their experience of RF ablation of hepatic tumours. They initially experimented with simple monopolar and bipolar needles in a mix of primary and secondary liver cancers. They struggled to achieve complete necrosis of tumour, requiring multiple RFA sessions for tumour nodules with a mean diameter of 2.2 cm. Their subsequent results with expandable multi-prong electrodes¹⁴ were more encouraging. This study involved 37 patients, of whom 14 had a total of 19 hepatic metastases. There were no mortality or major complications encountered. On average, treatment was completed in 1.3 sessions and with 1.7 electrode insertions. Of the 14 patients, 3 underwent surgical resection after RFA. Histological examination of these 3 specimens showed complete tumour necrosis. Of the 11 remaining patients with 16 metastatic nodules at a mean follow-up of 12 months, 1 (9%) had local recurrence, 8 (73%) had other hepatic or systemic disease and 2 patients (18%) were tumour-free. Rossi's efforts showed that RFA was safe and effective in controlling local recurrence of hepatic disease, but fails to address the systemic nature of the disease.

Another group involving Solbiati et al²² and Livraghi et al¹³ in 1997 reported their results on small groups of patients with hepatic metastases highlighting the utility of concomitant intra-parenchymal injection of saline to improve the zone of destruction. Although they were successful in increasing the area of ablation, necrosis was found to be incomplete in almost half of the lesions treated, causing the investigators to abandon this approach in favour of internally cooled electrodes.²³

Solbiati et al,²⁴ in a recent review of their data, published their results of 117 patients with 179 metachronous colorectal hepatic metastases, which ranged in size from 0.9 cm to 9.6 cm. Percutaneously inserted single or clustered internally cooled electrodes were used in all patients. The estimated median survival was 36 months (95% CI: 28, 52 months). The 1-, 2- and 3-year survival rates were 93%,

69% and 46%, respectively. In 77 (66%) of the 117 patients, new metastases were observed at follow-up. Estimated median time until new metastases was 12 months (95% CI: 10, 18 months). Survival and time to new metastases were not significantly related to number or size of metastases treated. Seventy (39%) of 179 lesions developed local recurrence after treatment. Of these, 54 were reported within 6 months and 67 at 1 year. No local recurrence was seen after 18 months. The frequency and time to local recurrence were related to lesion size. Patients with local recurrence were retreated whenever possible. This study documents the relative safety of RFA in treatment of colorectal metastases, with results that compare favourably with recent surgical series, despite the fact that most of the patients were considered not good surgical candidates.

The French study reported by De Baere et al,²⁵ on 68 patients with 121 hepatic metastases that were mainly colorectal in origin, combined both percutaneous (in 47 patients and 88 metastases) and intraoperative approaches (21 patients with 33 lesions). The latter was performed during partial hepatectomy to destroy unresectable metastases. Local control was achieved in 91% of the lesions (84% of patients). At a mean follow-up of 13.7 months (range, 4 to 23 months), 81% of patients were alive including 50% who did not have evidence of any hepatic disease. However, only 31% of patients were actually tumour-free, emphasising the excellent local control afforded by RFA, but a lack of effect on tumour-free survival in most patients due to the natural history of a metastasizing tumour.

Bowles et al²⁶ treated 76 patients with advanced, unresectable liver tumours with RFA. Fifty-one of his patients had metastatic liver disease, of which 39 were colorectal in origin. A total of 328 tumours were ablated in 99 treatment sessions. At a mean follow-up of 15 months, local recurrence for all tumour types was 9% per lesion (30/328). The surgical recurrence rate for colorectal metastases was 31% per procedure. Size, vascular invasion and total volume ablated were predictors of local recurrence but the number of tumours were not.

RFA in Combination with Other Therapy

Elias et al²⁷ combined hepatic resection and intraoperative RFA in the management of 33 metastatic lesions in 21 patients, who were thought not to be amenable to surgical resection alone. No operative mortality or RFA-related complications was encountered. Clear resection margins were achieved in 18 patients (86%). Other than the patient in whom it was not possible to destroy all metastatic lesions intraoperatively, only 1 local recurrence (3% of lesions) was reported after a mean follow-up of 17.3 months. The 2-year overall and disease-free survivals were

94.7% and 22%, respectively. This study shows that RFA can be used in combination with surgery to allow surgeons to extend potentially curative resection to patients who were otherwise not considered surgical candidates.

Similarly, Jiao et al²⁸ reported on 35 patients with primary and secondary liver cancer who were deemed not suitable for curative resection alone, including 17 patients with colorectal metastases. Of these 17, 16 had multiple/bilateral lesions and the remaining 1 had poor hepatic function. A combination of RFA (either percutaneous or intraoperative) and liver resection or metastectomy was employed in 9 of these patients, while the other 8 were treated with intraoperative RFA alone. Of these 17 patients, 10 patients (59%) had stable disease with a mean follow-up of 7.6 months, 4 had died and 3 had developed local or systemic recurrence.

In Japan, Kainuma et al²⁹ investigated the efficacy of combining RFA with hepatic arterial infusion (HAI) of chemotherapeutic agents in 9 patients with bilobar colorectal liver metastases. RFA was applied either percutaneously or intraoperatively using a multi-prong electrode followed by 5-fluorouracil with or without doxorubicin and cisplatin administered weekly via a HAI pump. A total of 64 lesions were treated over 20 sessions, with nodules varying in size from 0.5 to 4.8 cm. Each patient had a mean of 6 deposits, ranging from 2 to 13. During the mean follow-up of 15.2 months, local recurrence was observed in 5 patients (55%), new lesions in 4 (44%) and extrahepatic disease in 5 (55%). Six (67%) of the 9 patients were alive at 1 year and 3 (33%) for more than 2 years. Kainuma's study suggests that RFA may be safely combined with chemotherapy with possible survival advantage. It is conceivable that the superior results of local ablative treatment of liver metastases may be due to patient selection, especially since patients selected for local ablative therapy often only have a limited number of metastatic deposits, while patients given chemotherapy often show widespread liver involvement. A European Organization for Research and Treatment of Cancer (EORTC) study is currently in progress comparing RFA plus chemotherapy versus chemotherapy alone for unresectable colorectal liver metastases.

RFA versus Other Local Ablative Therapy

Many other modalities of local ablation have been applied to the treatment of hepatic metastatic disease with varying degrees of success. These include percutaneous ethanol injection (PEI), cryosurgical ablation (CSA) and other forms of thermal ablation (laser, microwave, focused ultrasound). Although there have been no prospective randomised controlled trials comparing RFA with these other forms of local therapy, historical data provide some perspective on this issue.

Since the initial reports on the use of laser to ablate liver metastases in the early 1990s, developments in laser technology have enabled increased power deposition and internal cooling of laser probes, achieving increased volume of necrosis. In a comparison of the effectiveness between cooled tip radiofrequency and interstitial laser photocoagulation, Lees et al³⁰ found it easier and quicker to achieve larger ablation volumes with RFA, particularly when including a margin of normal liver around tumours. It was postulated that this would be reflected in a difference in rates of local recurrence with these 2 modalities of therapy.

During CSA, tumours are frozen with the aid of liquid nitrogen circulating through a probe placed within the tumour. Tumour destruction arises from a freeze-thaw process, resulting in cell death and microvascular thrombosis. Local tumour control can be obtained for metastatic lesions up to 8 to 9 cm in size.^{31,32} However, the complication rate after CSA is much higher, between 10% and 20%, including some serious ones such as haemorrhage and cryo-shock. Pearson et al³³ compared the complications and early recurrence rate with either CSA or RFA in patients with unresectable malignant liver tumours. A total of 146 patients were entered into 2 consecutive, prospective, non-randomised trials of whom 90 had colorectal adenocarcinoma. Of these, 46 patients underwent intraoperative RFA and the other 44 had CSA performed. The median diameters of all lesions treated with CSA and RFA were not significantly different (3.6 cm versus 3.8 cm). In the CSA group, there was 1 mortality and an overall complication rate of 41%. In contrast, no treatment-related death was recorded with RFA and complications were seen in only 3 patients (3.3%). With a median follow-up of 15 months, tumour had recurred in 13.6% of lesions treated with CSA compared with 2.2% in the RFA group. Although this was not a prospective randomised trial, this study suggests that RFA has fewer complications and local recurrences when compared with CSA.

Conclusion

RFA has been busy carving a niche for itself in the treatment not only of colorectal metastases, but also of other primary and secondary liver cancers, as well as at other sites such as the lung, breast, kidney and bone. It is currently used as an alternative to surgery in patients with unresectable disease and sometimes as its companion, allowing patients hitherto considered unsuitable for resection to become surgical candidates. RFA has been shown to be safe and well tolerated, with few major complications and minimal patient discomfort. Although its use is unlikely to achieve cure in such patients, it has a definite role in palliation and relief of symptoms. Long-term data, when these become available, may also show

improved survival.

It is obvious the successful use of RFA can only be achieved with a clear understanding of its limitations, coupled with knowledge of the natural history and biologic features of colorectal cancer. After all, RFA, like all other local ablative therapies, is unable to address the systemic nature of cancer spread. It is likely that the best results will be obtained with combination therapy. We wait with eager anticipation the results of on-going trials involving both RFA and regional or systemic chemotherapy. Faced with the many possibilities in treatment options for colorectal metastases, a collaborative effort between medical oncologists, oncologic surgeons and interventional radiologists is essential to ensure the best outcome for these patients.

REFERENCES

- Chia K S, Seow A, Lee H P, Shanmugaratnam K. Cancer incidence in Singapore 1993-1997. Singapore: Singapore Cancer Registry, 2000. Report No 5.
- Ruers T, Bleichrodt R P. Treatment of liver metastases, an update on the possibilities and results. *Eur J Cancer* 2002; 38:1023-33.
- Stangl R, Altendorf-Hofmann A, Charnley R M, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994; 343:1405-10.
- Nordlinger B, Guiguet M, Vaillant J C, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. *Cancer* 1996; 77:1254-62.
- Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg* 1995; 19:59-71.
- Fong Y, Cohen A M, Fortner J G, Enker W E, Turnbull A D, Coit D G, et al. Liver resection for colorectal metastases. *J Clin Oncol* 1997; 15:938-46.
- Nakamura S, Suzuki S, Baba S. Resection of liver metastases of colorectal carcinoma. *World J Surg* 1997; 21:741-7.
- Rougier P, Laplanche A, Huguier M, Hay J M, Ollivier J M, Escat J, et al. Hepatic arterial infusion of floxuridine in patients with liver metastases from colorectal carcinoma: long term results of a prospective randomized trial. *J Clin Oncol* 1992; 10:1112-8.
- Kemeny N, Seiter K, Conti J A, Cohen A, Bertino J R, Sigurdson E R, et al. Hepatic arterial floxuridine and leucovorin for unresectable liver metastases from colorectal carcinoma. New dose schedules and survival update. *Cancer* 1994; 73:1134-42.
- Goldberg S N, Gazelle G S, Mueller P R. Thermal ablation therapy for focal malignancy: a unified approach to underlying principles, techniques and diagnostic imaging guidance. *AJR Am J Roentgenol* 2000; 174:323-31.
- McGahan J P, Wei-Zhong G, Brock J M, Tesluk H, Jones C D. Hepatic ablation using bipolar radiofrequency electrocautery. *Acad Radiol* 1996; 3:418-22.
- Goldberg S N, Gazelle G S, Dawson S L, Rittman W J, Mueller P R, Rosenthal D L. Tissue ablation with radiofrequency using multiprobe arrays. *Acad Radiol* 1995; 2:670-4.
- Livraghi T, Goldberg S N, Monti F, Bizzini A, Lazzaroni S, Meloni F, et al. Saline enhanced radio-frequency tissue ablation in the treatment of liver metastases. *Radiol* 1997; 202:205-10.
- Rossi S, Buscarini E, Garbagnati F, Di Stasi M, Quaretti P, Rago M, et al. Percutaneous treatment of small hepatic tumours by an expandable RF needle electrode. *AJR Am J Roentgenol* 1998; 170:1015-22.
- Goldberg S N, Gazelle G S, Solbiati L, Rittman W J, Mueller P R. Radiofrequency tissue ablation: increased lesion diameter with a perfusion electrode. *Acad Radiol* 1996; 3:636-44.
- Goldberg S N, Solbiati L, Hahn P F, Cosman E, Conrad J E, Fogle R, et al. Large-volume tissue ablation with radiofrequency by using a clustered, internally cooled electrode technique: laboratory and clinical experience in liver metastases. *Radiology* 1998; 209:371-9.
- Goldberg S N, Stein M C, Gazelle G S, Sheiman R G, Kruskal J B, Clouse M E. Percutaneous radiofrequency tissue ablation: optimization of pulsed-radiofrequency technique to increase coagulation necrosis. *J Vasc Interv Radiol* 1999; 10:907-16.
- Rossi S, Garbagnati F, Lencioni R, Allgaier H P, Marchiano A, Fornari F, et al. Percutaneous radio-frequency thermal ablation of nonresectable hepatocellular carcinoma after occlusion of tumour blood supply. *Radiology* 2000; 217:119-26.
- Hansen P D, Rogers S, Corless C L, Swannstrom L L, Siperstien A E. Radiofrequency ablation lesions in a pig liver model. *J Surg Res* 1999; 87:114-21.
- Goldberg S N, Gazelle G S, Comptom C C, Mueller P R, Tanabe K K. Treatment of intrahepatic malignancy with radiofrequency ablation: radiologic-pathologic correlation. *Cancer* 2000; 88:2452-63.
- Rossi S, Di Stasi M, Buscarini E, Quaretti P, Garbagnati F, Squassante L, et al. Percutaneous RF interstitial thermal ablation in the treatment of hepatic cancer. *AJR Am J Roentgenol* 1996; 167:759-68.
- Solbiati L, Ierace T, Goldberg S N, Sironi S, Livraghi T, Fiocca R, et al. Percutaneous US-guided radio-frequency tissue ablation of liver metastases: treatment and follow up in 16 patients. *Radiology* 1997; 202:195-203.
- Solbiati L, Goldberg S N, Ierace T, Livraghi T, Meloni F, Dellanoce M, et al. Hepatic metastases: percutaneous radio-frequency ablation with cooled-tip electrodes. *Radiology* 1997; 205:367-73.
- Solbiati L, Livraghi T, Goldberg S N, Ierace T, Meloni F, Dellanoce M, et al. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long term results in 117 patients. *Radiology* 2001; 221:159-66.
- De Baere T, Elias D, Dromain C, El Din M G, Kuoch V, Ducreux M, et al. Radiofrequency ablation of 100 hepatic metastases with a mean follow up of more than 1 year. *AJR Am J Roentgenol* 2000; 175:1619-25.
- Bowles B J, Machi J, Limm W M L, Severino R, Oishi A J, Furumoto N L, et al. Safety and efficacy of radiofrequency thermal ablation in advanced liver tumours. *Arch Surg* 2001; 136:864-9.
- Elias D, Goharin A, El Otmány A, Taieb J, Duvillard P, Lasser P, et al. Usefulness of intraoperative radiofrequency thermoablation of liver tumours associated or not with hepatectomy. *Eur J Surg Oncol* 2000; 26:763-9.
- Jiao L R, Hansen P O, Havlik R, Mitry R R, Pignatelli M, Habib N. Clinical short-term results of radiofrequency ablation in primary and secondary liver tumours. *Am J Surg* 1999; 177:303-6.
- Kainuma O, Asano T, Aoyama H, Takayama W, Nakagohri T, Kenmochi T, et al. Combined therapy with radiofrequency thermal ablation and intra-arterial infusion chemotherapy for hepatic metastases from colorectal cancer. *Hepatogastroenterology* 1999; 46:1071-7.
- Lees W R, Gillams A. Comparison of the effectiveness of cooled tip radiofrequency and interstitial laser photocoagulation in liver tumour ablation. *Radiology* 1999; 213(P):123.
- Seifert J K, Morris D L. Prognostic factors after cryotherapy for hepatic metastases from colorectal cancer. *Ann Surg* 1998; 228:201-8.
- Ruers T J M, Jager G J, Wobbes T. Cryosurgery for the treatment of colorectal liver metastases: long term results. *Br J Surg* 2001; 88:844-9.
- Pearson A S, Izzo F, Fleming R Y, Ellis L M, Delrio P, Roh M S, et al. Intraoperative radiofrequency ablation or cryoablation for hepatic malignancies. *Am J Surg* 1999; 178:592-9.