NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of Radiofrequency ablation for the treatment of liver tumours

Introduction

This overview has been prepared to assist members of IPAC advise on the safety and efficacy of an interventional procedure previously reviewed by SERNIP. It is based on a rapid survey of published literature, review of the procedure by one or more specialist advisor(s) and review of the content of the SERNIP file. It should not be regarded as a definitive assessment of the procedure.

Procedure name

Radiofrequency ablation (RFA); also known as radiofrequency thermal ablation (RFTA)

SERNIP procedure number

127

Specialty society

Radiology

Indication(s)

Hepatocellular carcinoma (HCC) and metastasis from colorectal carcinoma are the two most common malignant tumours to affect the liver. The annual incidence of HCC is estimated to be at least one per million.[1] Untreated HCC has a median survival of four to six months from the time of diagnosis.[2] Metastatic liver disease is frequently associated with primary colorectal carcinoma.[3] Approximately 50% of colorectal cancer patients will develop recurrence within five years of initial diagnosis with the liver being the most common site for metastatic disease.[4] For many patients the progressive involvement of the liver is the primary determinant of long-term survival. Without treatment the median survival is 6 months.[5,6]

Summary of procedure

RFA is a recently developed thermoablative technique that induces temperature changes by utilising high-frequency alternating current applied via an electrode(s) placed within the tissue to generate ionic agitation.[7] The ionic agitation is generated in the areas surrounding the electrode tip as the ions attempt to change directions and follow the alternating current, thereby creating localised friction heat. The resultant frictional heating of tissue surrounding the electrode generates localised areas of coagulative necrosis and tissue desiccation.[8] The radiofrequency energy radiates from the individual electrodes into the adjacent tissue.[9] The energy level and thus the heating effect dissipates rapidly at an increasing distance form the electrodes so that the highest temperature will always be at the points nearest to the electrodes.[8] RFA can be applied percutaneously, laparoscopically or intra-operatively.

The majority of malignant liver tumours remain inoperable due to their number, distribution and/or the presence of residual disease. Therefore, a number of alternative therapies have been developed including hepatic artery infusion chemotherapy (HAIC), as well as non-resectional chemotherapy, percutaneous ethanol injection (PEI), cryoablation, microwave coagulation therapy (MCT), laser-induced thermotherapy, and radiofrequency ablation. The theoretical disadvantages of these methods are that they may produce adverse side effects, and none have yet demonstrated a long-term survival advantage. The theoretical advantages of RFA include larger areas of tissue ablation and higher survival rates when compared with other ablative techniques.

Literature review

A systematic search of MEDLINE, PREMEDLINE, EMBASE, Current Contents, PubMed, Cochrane Library and Science Citation Index using Boolean search terms was conducted, from the inception of the databases until October 2002. The York Centre for Reviews and Dissemination, Clinicaltrials.gov, National Research Register, SIGLE, Grey Literature Reports (2002), relevant online journals and the Internet were also searched in October 2002. Searches were conducted without language restriction.

Articles were obtained on the basis of the abstract containing safety and efficacy data on radiofrequency ablation of the liver in the form of randomised controlled trials (RCTs), other controlled or comparative studies, case series and case reports. Conference abstracts and manufacturer’s information were included if they contained relevant safety and efficacy data. Foreign language papers were included if they contained safety and efficacy data and were considered to add substantively to the English language evidence base. In the case of duplicate publications, only the latest, most complete study, was included.

There were two systematic reviews containing all of the most recently available data.[10,11] The systematic review by Sutherland *et al.*[10] incorporated the findings of the other systematic review by Galandi and Antes,[11] and so only the Sutherland *et al.* review was included. In addition, safety data was extracted from 4 comparative studies which were excluded from the Sutherland *et al.* review due to narrower selection criteria than in the present overview. These studies have been included on the rationale that safety data may be associated with the technique, whereas the efficacy data are confounded by separate results not presented for each indication.

The systematic review by Sutherland *et al.*[10] included the following studies:

Study Type	Comparator	Number of studies	Tumour
• RCTs	PEI	3[12-14]	HCC
	MCT	1[15]	HCC
• Quasi-randomised	PEI	1[16]	HCC
• Non-RCT comparative	MCT	2[17,18]	HCC
	LITT	1[19]	metastatic
	HAIC	1[20]	HCC
	PEI or LITT	2[21,22]	HCC
	surgical resection	1[23]	HCC

Summary of key efficacy and safety findings

See following tables;
Please note that since the results of the studies included in the systematic review could not be statistically pooled, no quantitative results have been shown. The detailed results can be found in the full systematic review, a copy of which has been supplied.

Abbreviations

CSA	cryosurgical ablation
CT	computed tomography
HAIC	hepatic artery infusion chemotherapy
HCC	hepatocellular carcinoma
LITT	laser-induced thermotherapy
MCT	microwave coagulation therapy
PEI	percutaneous ethanol injection
RCT	randomised controlled trial
RFA	radiofrequency ablation

Comparator	Key efficacy findings	Key safety findings	Appraisal/Comments
Systematic Review[10]			
Percutaneous ethanol injection (PEI)	RFA results in: • fewer sessions required to achieve complete tumour ablation • lower rates of local recurrence at follow-up • no difference in therapeutic response • operative times and hospital stay shorter	RFA results in: • more fever, pain, and analgesic requirement	• small sample sizes • short follow-up periods • lack of patient blinding
Microwave coagulation therapy (MCT)	RFA results in: • fewer sessions required to achieve complete tumour ablation • longer operative times • more complete ablative effect with less nodules at follow-up	RFA results in: • lower incidence of minor complications • no difference in rate of major complications	• small sample sizes • short follow-up periods • lack of patient blinding • unbalanced treatment group in comparative study
Laser induced thermotherapy (LITT)	RFA results in: • residual tumour present in lower proportion of nodules • shorter treatment times	RFA results in: • fewer complications (such as arterioportal fistula, hepatic infarction, local atrophy, subcapsular fluid collection, perihepatic effusion	
Hepatic artery infusion chemotherapy (HAIC)	RFA results in: • non significant difference in complete control of tumour growth (RFA-50% vs HAIC 30%)	RFA results in: • fewer complications • lower mortality	• very limited data
Surgical resection	RFA results in: • higher rate of recurrence and shorter time interval to recurrence • less success in controlling tumour growth	No safety data reported	• surgical resection and RFA indicated for different patient groups therefore, comparison difficult
SUMMARY:	• RFA results in larger and more complete areas of ablation • RFA may be associated with higher survival rates	• No conclusions about safety could be reached	• evidence limited by small sample size, short follow-up times, lack of comparability between outcome measures

<table>
<tr><th>Authors, date, location, number of patients, length of follow-up, selection criteria</th><th>Key safety findings</th><th>Comments</th></tr>
<tr><td colspan="3">Comparative Studies for Safety Data</td></tr>
<tr><td>Elias et al.[24] 2000, FRANCE

N = 21

Median follow-up: 17.3 months (no loss to follow-up)

Selection criteria: feasible R0 resection with the assistance of RF, liver tumour visible with ultrasound, target lesions ≥ 1cm from main right or left biliary pedicles</td><td>post-operative mortality – 0%
• no RFA related complications
• hepatic complications – 4/21 (19%)
o transient liver failure – 3 (14%)
o biliary leakage – 1(5%)
o general complications – 6 (29%)
(treatment modality not defined)</td><td>RFA + hepatectomy - 17 patients
RFA + excision of extrahepatic lesions (liver metastases) – 2 patients
RFA alone – 2 patients</td></tr>
<tr><td>Hoshida et al.[25] 2002, JAPAN

N = 149
RFA - 45
PEI - 63
MCT - 18
PEI+MCT - 23

Follow-up: after treatment

Selection criteria: HCC, platelet count ≥ $40x10^3$μ/L, prothrombin activity ≥ 40%, less than 6 HCC lesions</td><td>• adverse events requiring additional medical treatment
o 4/45 (9%) RFA
o 10/63 (16%) PEI
o 3/23 (13%) PEI+MCT</td><td>series of 149 patients treated with either RFA, PEI, MCT, combination PEI/MCT (45 received RFA)</td></tr>
<tr><td>Bilchik et al.[26] 2000, USA

N = 199
RFA - 40
CSA - 159

Median follow-up: 16 months (range 1-77)

Selection criteria: no evidence of extrahepatic disease but not candidates for surgical resection due to size/location of lesions or hepatic dysfunction</td><td><table><tr><th></th><th>RFA</th><th>CSA</th></tr><tr><td>blood loss</td><td>40 [20] mL</td><td>800[200]mL</td></tr><tr><td>thrombocytopenia</td><td>0 (0%)</td><td>111/159 (70%)</td></tr><tr><td>pleural effusion</td><td>0 (0%)</td><td>127/159 (80%)</td></tr><tr><td>hepatic abscess</td><td>3/40 (7.5%)</td><td>11/159 (7%)</td></tr><tr><td>bile duct injury</td><td>1/40 (2.5%)</td><td>7/159 (4%)</td></tr><tr><td>mortality</td><td>1/40 (2.5%)</td><td>5/159 (3%)</td></tr></table></td><td>68 patients received RFA – 40 RFA alone, 14 RFA + resection, 9 RFA + cryosurgical ablation (CSA), 5 RFA+CSA+resection

240 patients received cryosurgical ablation (CSA) – 159 CFA alone, 81 CSA+ resection</td></tr>
</table>

Study details	Key safety findings	Comments
Ikeda *et al.*[27] 2001, JAPAN N = 119 RFA - 23 PEI - 98 *Median follow -up:* 11.4 (range 1.4-20.7) months *Selection criteria:* solitary HCC < 3cm diameter, no prior treatment other than hepatic resection	RFA & PEI: • haemothorax – 0 (0%) • intraperitoneal bleeding – 0 (0%) • haemobilia – 0 (0%) PEI: acute cholangitis - 1(1%)	119 patients with HCC – 23 RFA, 98 PEI

Specialist advisor's opinion / advisors' opinions
Specialist advice was sought from the Association of Upper Gastrointestinal Surgeons and the British Association of Surgical Oncology

Specialist Advisors stated that RFA is performed in 8 UK centres by experienced radiologists. They emphasised the need for appropriate selection of patients, preferably at a multidisciplinary team meeting, and adequate training of surgeons/specialists to perform the procedure. The procedure should be monitored by CT or ultrasound to ensure that the correct area of the liver is ablated. Accurate imaging guidance is important to ensure that the electrode is positioned away from structures which can be easily damaged. This in turn will ensure lower complication rates. Higher complication rates occur where there are increasing numbers of punctures, larger volumes of necrosis, more advanced liver disease, and lesions located close to the diaphragm, into the liver hilum, or close to vessels or viscera.

Issues for consideration by IPAC
None

References

1. Di Bisceglie A, Rustgi V, Hoofnagle J. NIH conference on hepatocellular carcinoma. *Ann Intern Med* 1988; 108:390-401.

2. Nagase N, Yuki H, Hamada T, Hirose S, Kawashima R, Inokuchi K. The natural history of hepatocellular carcinoma. A study of 100 untreated cases. *Cancer* 1984; 54 :1461-1465.

3. Fong Y. A promising technique for liver cancer? *Cancer Journal From Scientific American* 1999; 5(6):339-340.

4. Geoghegan JG, Scheele J. Treatment of colorectal metastases. *British Journal of Surgery* 2002; 86(2):148-169.

5. Wood CB, Gillis CR, Blumgart LH. A retrospective study of patients with liver metastases from colorectal cancer. *Clincial Oncology* 1976; 2:285-288.

6. August DA, Sugarbaker PH, Ottow RT. Hepatic resection of colorectal metastases. *Annals of Surgery* 1985; 201:210-218.

7. Bilchik AJ, Wood TF, Allegra D, Tsioulias GJ, Chung M, Rose DM, Ramming KP, Morton DL. Cryosurgical ablation and radiofrequency ablation for unresectable hepatic malignant neoplasms - A proposed algorithm. *Archives of Surgery* 2000; 135(6):657-662.

8. Bilchik A, Wood T, Allegra D. Radiofrequency ablation of unresectable hepatic malignancies: Lesions learned. *The Oncologist* 6, 24-33. 2001.

9. Curley SA. Radiofrequency ablation of malignant liver tumours. *The Oncologist* 2001; 6 (1):14-23.

10. Sutherland LM, A Systematic Review of Radiofrequency Ablation of Liver Tumours. ASERNIP-S Report No 28. Adelaide, South Australia: ASERNIP-S; October 2002.

11. Galandi D, Antes G. Radiofrequency thermal ablation versus other interventions of hepatocellular carcinoma. (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.

12. Lencioni R, Cioni D, Donati F, Crocetti L, Granai, G, Bartolozzi C. Percutaneous treatment of small hepatocellular carcinoma: radiofrequency ablation versus percutaneous ethanol injection: a prospective randomised trial (final report). *Radiology* 1999; 213:123.

13. Olschewski M, Lencioni R, Allgaier H-P, Cioni D, Deibert P, Frings H, Crocetti L, Laubenberger J. Zuber I, Paolicchi A, Blum HE, Bartollozzi C. A randomised comparison of radiofrequency thermal ablation and percutaneous ethano injection for the treatment of small hepatocellular carcinoma. *American Society of Clinical Oncology* 2001: 126A.

14. Shiina S, Teratani T, Obi S. Prospective randomised controlled trial comparing percutaneous radiofrequency ablation and percutaneous ethanol injection therapy for small hepatocellular carcinoma. *Gastroenterology* 2000; 118:959A.

15. Shibata T, Iiumuro, Yamamoto Y, Meatani Y, Amatani, F, Itoh K, Konishi. Small hepatocellular carcinoma: Comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. *Vascular and Interventional Radiology* 2002; 223: 331-337.

16. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: Treatment with radio-frequency ablation versus ethanol injection. *Radiology* 1999; 210(3):655-661.

17. Kouyama H, Kawanisi T, Gotou K. Comparison between radiofrequency ablation and percutaneous microwave coagulation therapy for hepatocellular carcinoma. *Gastroenterology* 2000; 118:912A.

18. Izumi N, Asahina Y, Noguchi O, Uchihara M, Kanazawa N, Itakura J, Himeno Y, Miyake S, Sakai, T, Enomoto N. Risk factors for distant recurrence of hepatocellular carcinoma in the liver after complete coagulation by microwave or radiofrequency ablation. *Cancer* 2001; 91(5):949-956.

19. Lees WR, Gillams AR. Complications of radiofrequency and laser ablation of liver metastasis: incidence and management *Radiology* 1999; 213: 122

20. Livraghi T, Meloni F, Corso R, Rampoldi A. Comparison between RF ablation and TACE in the treatment of multi-focal hepatocellular carcinoma: preliminary experience. *Radiology* 2000; 217;287

21. Catalano O, Esposito M, Nunziata A, Siani A. Multiphase helical CT findings after percutaneous ablation procedures for hepatocellular carcinoma. *Abdominal Imaging* 2000; 25(6):607-614.

22. Catalano O, Lobianco R, Esposito M, Siani A. Hepatocellular carcinoma recurrence after percutaneous ablation therapy: Helical CT patterns. *Abdominal Imaging* 2001; 26(4):375-383

23. Yu HC, Le J-M, Kim D-G, Cho BH. Recurrence pattern of the radiofrequency ablation for hepatocellular carcinoma. *Journal of Hepato-Biliary-Pancreatic Surgery* 2002 (9 Suppl 1):125 (F-231).

24. Elias D, Goharin A, El Otmany A, Taieb J, Duvillard P, Lasser P *et al.* Usefulness of intraoperative radiofrequency thermoablation of liver tumours associated or not with hepatectomy. *European Journal of Surgical Oncology* 2000; 26(8):763-769.

25. Hoshida Y, Shiratori Y, Koike Y, Obi S, Hamamura K, Teratani T, Shiina S, Omata M. Hepatic volumetry to predict adverse events in percutaneous ablation of hepatocellular carcinoma. *Hepato-Gastroenterology* 2002; 49:451-455.

26. Bilchik AJ, Wood TF, Allegra D, Tsioulias GJ, Chung M, Rose DM, Ramming KP, Morton DL. Cryosurgical ablation and radiofrequency ablation for unresectable hepatic malignant neoplasms - A proposed algorithm. *Archives of Surgery* 2000; 135(6):657-662,

27. Ikeda M, Okada S, Ueno H, Okusaka T, Kuriyama H. Radiofrequency ablation and percutaneous ethanol injection in patients with small hepatocellular carcinoma: A comparative study. *Japanese Journal of Clinical Oncology* 2001; 31(7):322-326.