Radiofrequency Ablation of Liver Tumours

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Assessment report

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee with the assistance of Leanne Sutherland, Philippa Middleton and Bronni Simpson from ASERNIP-S. The report was endorsed by the Commonwealth Minister for Health and Ageing on 8 August 2003.

Publication approval number: 3376

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Radiofrequency ablation (RFA) is a recently developed thermoablative technique that induces temperature changes by applying high-frequency alternating current via electrodes placed within the tissue to generate ionic agitation (Bilchik *et al* 2000). As the ions attempt to change direction and follow the alternating current, localised frictional heat is created in the areas surrounding the electrode tip, which generates areas of coagulative necrosis and tissue desiccation (Bilchik *et al* 2001). The radiofrequency energy radiates from the individual electrodes into the adjacent tissue (Bilchik *et al* 2000). The energy level and thus the heating effect dissipate rapidly at an increasing distance from the electrodes so that the highest temperature will always be at the points nearest to the electrodes (Curley *et al* 2001). RFA can be applied percutaneously (usually performed by radiologists), laparoscopically or intraoperatively. The open route is thought to be the most effective method of delivery as it allows surgeons to detect the lesions and target the RFA (Strasberg, unpublished).

RFA is used to treat primary hepatocellular carcinoma (HCC) or metastatic liver tumours in patients who are unsuitable for curative surgical resection due to the presence of liver malignancy in unresectable locations, the number and anatomical distribution of tumour lesions, and/or the presence of extrahepatic disease or poor liver function (Orloff *et al* 1981; Hemming and Gallinger, 2001).

Medical Services Advisory Committee — role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from ASERNIP-S was engaged to conduct a systematic review of literature on radiofrequency ablation of liver tumours. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of radiofrequency ablation of liver tumours

Clinical need

The purpose of RFA (in this review) is to treat non-resectable primary HCC or metastatic colorectal liver metastases (CLM) or neuroendocrine liver metastases (NLM). It is estimated that

about 200 HCC, 700 CLM and a few NLM patients a year in Australia would be suitable for RFA and expert opinion states that RFA is not widely practised in Australia.

Hepatocellular carcinoma (HCC)

Safety

RFA compared with PEI (percutaneous ethanol injection)

In one randomised control trial (RCT), no complications (apart from fever) were reported after either RFA or PEI treatment. However, another RCT of 102 patients stated that serious side effects or complications were found in 44% of patients treated with RFA and 34% of patients treated with PEI (not a statistically significant difference).

One quasi-RCT with 86 patients reported a 2% major and 8% minor complication rate for patients treated with RFA but did not state the complication rates for PEI. For one other RCT it was reported that patients treated with PEI had no major complications but it was not stated whether any RFA patients suffered major complications.

RFA compared with TACE (transarterial chemoembolisation)

The only comparative study was non-randomised and it reported that RFA was associated with fewer complications than TACE (0% compared with 20%, not statistically significant).

RFA compared with surgical resection

The only comparative study was non-randomised and did not report any safety outcomes, so conclusions about the safety of RFA compared with surgical resection cannot be made.

Effectiveness

RFA compared with PEI

While two year mortality did not show a statistically significant difference between RFA and PEI, local recurrence free survival (and local recurrence rate) at one and two years did show a statistically significant benefit for RFA in one RCT. In two other RCTs, local recurrence rates were lower for RFA than for PEI, but this result was not statistically significant in either study.

When the results of two RCTs and one quasi-RCT were pooled, the ablative response was statistically significantly better for RFA than for PEI, although none of the studies reached statistical significance on their own. However ablative response is a surrogate measure and was reported by tumour rather than by patient so this result should be interpreted cautiously.

RFA compared with TACE

In the only comparative study, which was non-randomised, 50% of RFA patients but only 30% of TACE patients showed a complete response (not statistically significant), although a statistically significant difference in mortality between the two treatment groups (0% for RFA patients compared with 40% for TACE patients) was seen.

RFA compared with surgical resection

The only comparative study was non-randomised and it indicated that RFA was associated with a higher rate of recurrence and a shorter time interval to recurrence compared with the surgical resection group. However, since surgical resection and RFA are usually performed on different groups of patients, it is difficult to compare the two treatment groups.

Cost effectiveness

RFA is more expensive than PEI across all the various assumptions (such as number of sessions and method of access for RFA). However the range of incremental cost effectiveness ratios (ICER) is large. The ICER per local recurrence-free survival in the base case (one session of percutaneous RFA compared with one session of PEI; 14% benefit of RFA) was $10,714 to $17,857; ranging from a low of $6,000 to $10,000 (high (25%) benefit of RFA) to a high of $215,000 to $248,333 (low (3%) benefit of RFA) in the sensitivity analyses (both one session of percutaneous RFA compared to one session of PEI).

Metastatic colorectal liver tumours (CLM)

Safety

The safety of RFA for treating CLM is based solely on case series as the only comparative study did not report any safety outcomes. Patients with more tumours (and therefore more RFA sessions) may have a higher complication rate.

Effectiveness

While most of the case series reported high levels of ablation with RFA (90% and above), this surrogate outcome may not reflect long-term effectiveness. Local recurrence rates varied from 4% to 55% and may depend on the method of access used for RFA. The only comparative study suggested that survival from the time of diagnosis was shorter for patients treated with RFA than surgical resection.

Metastatic neuroendocrine liver tumours (NLM)

Safety

The safety of RFA for treating NLM is based solely on case series as the only comparative study did not report any safety outcomes. In five of these case series the complication rates varied from 0% to 11%.

Effectiveness

The only comparative study (RFA, one patient; PEI, one patient) was inconclusive as both patients had incomplete tumour ablation (at two months), and local recurrence (at 18 months). In five case series, local recurrence varied from 0% to 20%.

Although cryotherapy was not compared with RFA in this review, other review work shows that none of the available studies of cryotherapy would have met the inclusion criteria.

Recommendation

MSAC recommended that, on the strength of evidence pertaining to radiofrequency ablation (RFA), public funding should be supported for the percutaneous treatment of non-resectable hepatocellular carcinoma not being considered for surgical resection.

MSAC recommended that, as there is not yet enough evidence on the use of RFA for colorectal metastases (CLM), public funding should not be supported at this time for RFA treatment of CLM.

Since there is currently insufficient evidence pertaining to RFA for neuroendocrine liver metastases (NLM), MSAC recommended that public funding should not be supported at this time for RFA treatment of NLM.

– The Minister for Health and Ageing accepted this recommendation on 8 August 2003.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of radiofrequency ablation, which is a therapeutic technology for treating liver tumours. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are in Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for radiofrequency ablation of liver tumours.

Background

Radiofrequency ablation of liver tumours

This evaluation was undertaken in response to an application for assessment of radiofrequency ablation of liver tumours, a treatment that is not currently reimbursed under the Australian Medicare Benefits Scheme (Commonwealth Department of Health and Ageing 2002).

The procedure

Radiofrequency ablation (RFA) is a recently developed thermoablative technique that increases the temperature in tissue near electrodes that receive high-frequency alternating current and generate ionic agitation (Bilchik *et al* 2000). As the ions try to change direction and follow the alternating current, localised frictional heat is created in the areas surrounding the electrode tip, which generates areas of coagulative necrosis and tissue desiccation (Bilchik *et al* 2001). The radiofrequency energy radiates from the individual electrodes into the adjacent tissue (Bilchik *et al* 2000). The energy level and thus the heating effect dissipate rapidly at an increasing distance from the electrodes so that the highest temperature will always be at the points nearest to the electrodes (Curley *et al* 2001). RFA can be applied percutaneously (usually performed by radiologists), laparoscopically or intraoperatively. The open route is thought to be the most effective as it allows surgeons to detect the lesions and apply the RFA more precisely (Strasberg, unpublished).

RFA is used to treat primary hepatocellular carcinoma (HCC) or metastatic liver tumours in patients who are unsuitable for curative surgical resection due to the presence of liver malignancy in unresectable locations, the number and anatomical distribution of tumour lesions, and/or the presence of extrahepatic disease or poor liver function (Orloff *et al* 1981; Hemming and Gallinger 2001).

Purpose

The purpose of RFA (in this review) is to treat non-resectable primary HCC or colorectal liver metastases (CLM) or neuroendocrine liver metastases (NLM). RFA has been used to treat metastatic liver tumours of other origins, however, these indications will not be assessed in this review.

Liver tumours

Primary liver tumours arise from malignant cells within the liver and HCC represents the most common form of primary liver cancer (Lau 2000; Michel *et al* 2002). Metastatic liver disease is more common than primary liver disease and develops when malignant cells migrate from other organs to the liver (McCarter and Fong, 2000; Bilchik *et al* 2001). The liver is second only to the lymph nodes as a common site of metastasis from other solid tumours (Weiss *et al* 1986). More than half of the patients with metastatic

liver disease will die from metastatic complications and, for many patients, the progressive involvement of the liver will be the major or sole determinant of their survival (Wood *et al* 1976; Markovic *et al* 1998).

Hepatocellular carcinoma (HCC)

HCC is one of the most common primary solid cancers in the world (Grasso *et al* 2000; Geoghegan and Scheele 2002). HCC is usually associated with liver cirrhosis, either arising from infection (chronic hepatitis B or C), toxic factors (alcohol), immunologic factors (biliary dysfunction) or genetic factors (haemochromatosis) (Carithers, 2000). HCC is generally diagnosed at an advanced stage at which the prognosis depends on tumour stage, anatomical distribution of tumour lesions and degree of liver function, all of which will determine the tolerance to invasive treatments (Markovic *et al* 1998; Grasso *et al* 2000).

Metastatic colorectal liver tumours (CLM)

Metastatic liver disease is often associated with colorectal carcinoma (Fong 1999) and about 50% of colorectal cancer patients will develop hepatic metastases within five years of initial diagnosis.

Metastatic neuroendocrine liver tumours (NLM)

Neuroendocrine tumours are derived from cells that release hormones in response to a signal from the nervous system. These relatively uncommon tumours secrete hormones in an uncontrolled way, and symptoms vary with tumour type and hormone released. Some examples of neuroendocrine tumours are carcinoid tumours, glucagonoma, pheochromocytoma, and medullary thyroid carcinoma. The rate of liver metastasis can vary with tumour type, from fewer than 5% of patients with a carcinoid tumour to 70–75% with glucagonoma. The five-year survival of patients with neuroendocrine tumours and liver metastases is 11–40% (Siperstein and Berber, 2001).

Clinical need / burden of disease

Hepatocellular carcinoma (HCC)

HCC is a relatively rare form of cancer in Australia, being more common in countries such as Africa and Asia (Australian Department of Veterans' Affairs 2003). One study has described the trend of HCC in Australia (Law *et al* 2000). Age-standardised incidence rates increased in men and women (from 2.06 and 0.57 per 100,000 respectively in 1983–85 to 3.97 and 0.99 per 100,000 respectively in 1995–96). Age-standardised death rates increased in Australian-born and overseas-born men and overseas-born women (from 1.43, 2.35 and 0.62 per 100,000 respectively in 1978–82 to 2.50, 4.41 and 1.36 per 100,000 respectively in 1993–97). However, death rates in Australian-born women did not increase dramatically (0.58 per 100,000 in 1978–82 to 0.63 per 100,000 in 1993–97) (Law *et al* 2000). The application cited an incidence of HCC in Australia of 2–4 per 100,000 which is in line with these figures. The applicants also estimated that 25% of people with HCC would be suitable for RFA, equating to about 200 people a year in Australia.

Metastatic colorectal liver tumours (CLM)

Australia has one of the highest incidence rates for colorectal cancer in the world, along with North America, and New Zealand (Australian Gastroenterology Institute 2001). After non-malignant skin cancer, it is the next most common cancer in Australia affecting both men and women. In 1998, there were 6,131 new cases of colorectal cancer diagnosed in males and 5,158 new cases in females; 2,533 males and 2,179 females died from colorectal cancer in 2002. About one in 17 men and one in 26 women will develop colorectal cancer before the age of 75 years (Australian Institute of Health and Welfare, 2002).

It is estimated that about 50% of patients with colorectal cancer will develop liver metastases within five years. (NHMRC Clinical Practice Guidelines, 1999a).

The applicants estimated that 10% of patients with CLM will be suitable for resection, and 10% would be suitable for ablative therapies. This equates to about 700 CLM patients a year in Australia who would be suitable for RFA.

Metastatic neuroendocrine liver tumours (NLM)

There was no available information on the incidence of primary neuroendocrine cancer or NLM, but these are known to be rare.

Expert opinion states that RFA is not widely practised in Australia.

Existing procedures

Surgical resection

Surgical resection of primary and metastatic liver tumours remains the gold standard of therapy. Several technical and surgical advances have dramatically increased resectability rates. It is generally accepted that resection is the only treatment that offers a complete cure, with five-year survival rates after resection of up to 40% (Scheele *et al* 1995). The number of lesions is no longer considered as important a predictor of long-term survival as once thought. The complete excision of all demonstrable tumour with clear resection margins of 1 cm or more has proven to be of much greater importance (Geoghegan and Scheele 2002). If this can be achieved, the survival rates of excision of up to eight lesions approach that of a solitary lesion. If complete excision cannot be achieved, surgical resection does not affect the natural history of the disease (Geoghegan and Scheele 2002).

Unfortunately, few patients are suitable for curative surgical resection due to the presence of liver malignancy in unresectable locations, the number and anatomical distribution of tumour lesions, and/or the presence of extrahepatic disease or poor liver function (Berry and Maddern 2000; McGahan and Dodd 2001). Thus, for the majority of patients with malignant liver tumours (whether primary or metastatic) who are not candidates for surgical resection, alternative treatments to control and potentially cure the liver disease are needed.

Percutaneous ethanol injection (PEI)

PEI is administered by introducing a needle percutaneously into a liver tumour and slowly injecting absolute or 95% ethanol into the lesion (Berry and Maddern 2000). The ethanol is first injected at the deepest aspect of the lesion and the needle withdrawn at small increments to allow uniform diffusion of ethanol within the tumour (Livraghi *et al* 2001). Both the needle insertion and injection of ethanol are monitored by ultrasound, or occasionally by computed tomography (Berry and Maddern 2000; Siperstein and Berber 2001).

As the ethanol diffuses into the cells it induces non-selective protein degradation and cellular dehydration resulting in local areas of coagulation necrosis within and around the tumour (Berry and Maddern, 2000). Fibrosis and vascular thrombosis may also contribute to the destruction of the tumour cells (Livraghi *et al* 2001). PEI is usually performed in several sessions (Berry and Maddern 2000). It has been suggested that the number of sessions required to ablate the tumour is about twice that of the tumour diameter in centimetres (Siperstein and Berber 2001).

Transarterial chemoembolisation (TACE)

TACE is the surgical insertion of a catheter into the hepatic artery, the main pathway through which liver tumours receive their blood supply, and the periodic injection of chemotherapeutic agents mixed with embolic material into selected branches of the hepatic artery feeding the liver tumour (Dodd *et al* 2000; Hemming and Gallinger, 2001). Embolisation of the hepatic artery selectively induces ischaemic necrosis in tumours while the arterial delivery of chemotherapy delivers drugs at a higher concentration directly to the liver tumour and therefore potentially decreases systemic side effects caused by traditional chemotherapy (Hemming and Gallinger, 2001). Another benefit is that embolisation lengthens the dwell time of the chemotherapeutic agents, thus prolonging drug exposure (Dodd *et al* 2000).

Hepatic arterial infusion chemotherapy (HAIC)

HAIC, also referred to as regional chemotherapy, is the delivery of chemotherapeutic agents to the liver through a catheter surgically inserted in the hepatic artery (Hemming and Gallinger 2001). By delivering chemotherapy directly to the tumour, HAIC therapy allows for a greater concentration of drug to reach the tumour. This potentially decreases the systemic side effects caused by traditional chemotherapy, due to lower drug exposure to extrahepatic tissues (DeSanctis *et al* 1997).

Hepatic artery embolisation (HAE)

HAE using gelatin or other agents, usually mixed with lipiodol, is a therapeutic technique that blocks the feeding artery of the tumour, thereby inducing necrosis of the tumour without damaging the non-cancerous areas (Yumoto *et al* 1991).

Comparators

The Supporting Committee decided on the following comparators for this review:

For hepatocellular carcinoma (HCC)

Surgical resection

Percutaneous ethanol injection (PEI)

Transarterial chemoembolisation (TACE)

For metastatic colorectal liver tumours (CLM)

Surgical resection

Hepatic arterial infusion chemotherapy (HAIC)

For metastatic neuroendocrine liver tumours (NLM)

Primarily, hepatic artery embolisation (HAE) with separate octreotide but other comparators were considered.

For the economic evaluation

Hepatocellular carcinoma (HCC)

PEI

NOTE: Although cryotherapy was not compared with RFA in this review, other review work (Sutherland *et al* 2002) and the evaluators' reply to the applicant response shows that none of the available studies of cryotherapy would have met the inclusion criteria.

Marketing status of the device / technology

There are three primary types of electrode used for RFA in Australia. A brief description of the product design and mechanisms of action are provided below.

RITA Medical Systems

One system uses retractable needle electrodes (Model70 and 90 Starburst XL Needles, RITA Medical Systems, Mountain View, CA, USA) (Rita Medical Systems, 2002. http://www.ritamedical.com/products). They consist of an insulated outer needle that houses either seven or nine retractable curved electrodes. Four of the electrodes are hollow and are used to measure the temperature of the adjacent tissue.

Grounding pads are placed on the patient's thigh, and the tip of the needle with the electrodes retracted is placed in the liver tissue to be treated. The electrodes are partially extended and the alternating current applied with gradually increasing wattage. The temperature at the needle tip is monitored via the electrodes until the temperature reaches between 95°C and 105°C and the electrodes are fully extended. As the tissue begins to desiccate, tissue resistance increases and conversely the wattage decreases. Once the ablation cycle is finished, a temperature reading greater than 50°C from the extended electrodes for one minute is indicative of satisfactory ablation.

Radiotherapeutics

This type of ablation device also has an insulated needle but houses up to 12 solid curved retractable electrodes (LeVeen Needle Electrodes and Radiofrequency Ablation System, Radiotherapeutics, Sunnyvale, CA, USA (now Boston Scientific) (Radiotherapeutics, 2002. http://www.bostonscientific.com/med_specialty/deviceDetail.jhtml?task=tskBasicDevice.jhtml&sectionId=4&relId=4,178,179,180&deviceId=13005). The tip of the radiofrequency needle is applied to the target tissue. The array of electrodes is fully extended into the tissue such that the electrodes move through the tissue in a constant radius curve from the tip of the needle (generating an umbrella-shaped configuration). An alternating electric current is increased every minute until peak power is attained. The device is designed to respond to changes in tissue impedance during the ablation process rather than tissue temperature. A rise in tissue impedance indicates successful tissue coagulation and ablation.

Radionics

This ablation system employs an insulated hollow needle electrode with an exposed uninsulated needle tip (Cool-Tip™ Radiofrequency Electrode and RF Ablation System, Radionics, Burlington, MA, USA) (Radionics, 2002 http://www.radionics.com/products/ablation/cooltip.shtml). The tip of the single needle or cluster needle electrode (that consists of three of the needles in a parallel triangular cluster) is closed and is able to record the temperature of the adjacent tissue. The shaft of the needle contains two internal channels to allow the needle to be perfused with cool sterile water or saline. The circulating internal water/saline cools the tissue adjacent to the tip of the electrode thus preventing charring of the tissue around the electrode tip which allows a greater volume of tissue to be treated (before tissue resistance prevents further current flow). The alternating electric current is delivered in a pulsed and cyclic manner and successful ablations usually increase the temperature of the tissue to 60–80°C.

Current reimbursement arrangement

RFA is not currently reimbursed, so there is no Medicare Benefits Schedule item number for this procedure.

Approach to assessment

Introduction

In undertaking this assessment, the literature available on radiofrequency ablation (RFA) and its comparators was reviewed, and a supporting committee convened to provide expect advice and evaluate the evidence on efficacy of RFA.

Criteria for selecting studies

Participants

Patients may have had additional disease treated at the same time, and may or may not have been previously treated for liver disease.

Indications

Individuals with either primary hepatocellular carcinoma (HCC) or metastatic colorectal (CLM) or neuroendocrine (NLM) liver carcinoma.

Intervention/comparisons

New intervention

The new intervention is defined as: radiofrequency ablation (RFA) of liver tumours conducted with any of the commercially available radiofrequency needle designs, and by any access method.

Comparative interventions

- Surgical resection
- Percutaneous ethanol injection (PEI)
- Transarterial chemoembolisation (TACE)
- Hepatic arterial infusion chemotherapy (HAIC)
- Hepatic artery embolisation (HAE) with octreotide separately

The comparative procedures were defined by the nature of the tumour type. For HCC the comparative interventions were: surgical resection, PEI, or TACE. For CLM the comparative interventions were surgical resection or HAIC. For NLM the comparator was primarily HAE with octreotide separately.

Outcomes

Comparative studies

The included comparative articles (assessing HCC, CLM, or NLM) must have contained information on at least one of the following outcomes:

1. Perioperative and postoperative mortality of patients
2. Perioperative and postoperative morbidity of patients included which may include, but not be limited to:
   - infection
   - bleeding
   - bile leaks
   - injury to other structures
   - discomfort and/or pain
3. Perioperative and postoperative factors for patients which may include, but not be limited to:
   - operative time
   - re-operation/re-intervention
   - treatment site (local) recurrence and/or new nodule formation
   - rate of 'new disease' not confined to the liver
   - completion of ablation and/or resection
4. Convalescence of patients which may include, but not be limited to:
   - length of hospital stay
   - time until resumption of usual activities (including work)
   - quality of life measures
   - postoperative care requirements
5. Costs and resource use

In addition to these outcomes the following will also be noted if reported:

- method of diagnosis

– method of preoperative and postoperative evaluation (computed tomography, magnetic resonance imaging, ultrasound)

– method of delivery (open, percutaneous, laparoscopic)

– location, size and number of lesions

– adjunctive chemotherapy or radiotherapy

– time to recurrence

– other concurrent treatment

Metastatic colorectal liver tumours (CLM) case series

The included case series assessing RFA for the treatment of CLM must have contained information on at least one of the following:

– follow-up period of at least one year (mean or median)

– a report on local recurrence by patient (not lesion/nodule)

Metastatic neuroendocrine liver tumours (NLM) studies

Any outcome in an article of any study type (comparative or case series) assessing RFA for the treatment of NLM was also included.

Types of studies

Randomised controlled trials (RCTs) and non-randomised comparative studies assessing patients with HCC or metastatic colorectal (CLM) or neuroendocrine (NLM) liver carcinoma treated with RFA or either one or more other comparative intervention/s were considered for review. If the studies contain mixed indications, they were considered for review if the results for each indication could be extracted separately.

Additionally, case series assessing RFA for the treatment of CLM were included if the studies had consecutive patients, a follow-up of at least 12 months (mean or median) and treatment site recurrence reported per patient, not just per nodule, and for which the results for metastatic liver carcinoma could be extracted separately.

Any study type (case series or comparative) assessing RFA for the treatment of NLM was considered for inclusion in the review.

Additional relevant published material in the form of case series and case reports, letters, conference material, editorials and abstracts were included as background information.

Publication status

Published, unpublished and grey literature (eg non-peer-reviewed conference abstracts) were considered for review.

Language restriction

Searches were considered without language restriction.

Review of literature

The medical literature was searched to identify relevant studies and reviews.

Literature search strategies

The following databases were searched until January 2003 (Table 1).

Table 1 Databases searched

Database	Platform	Edition
MEDLINE	Ovid	1966 to week 3 2003
	NLM gateway	Searched from week 16 2002 to week 3 2003
PREMEDLINE	Ovid	Searched from week 16 2002 to week 3 2003
PREMEDLINE and MEDLINE	Ovid	1966 to week 3 2003
EMBASE	Ovid	1980 to week 3 2003
Current Contents	Ovid	1993 to week 3 2003
Cochrane Library		Issue 4, 2002
Science Citation Index	Web of Science	Searched January 16 2003
Clinical Trials Database (US)	http://www.clinicaltrials.gov/	Searched January 16 2003
NHS Centre for Research and Dissemination (UK)	http://144.32.228.3/scripts/WEBC.EXE/nhscrd/newsearch	Searched January 16 2003
NHS Health Technology Assessment (UK)	http://www.ncchta.org/	Searched January 16 2003
National Research Register (UK)	http://www.doh.gov.uk/research/nrr.htm	Issue 4, 2001
EORTC Protocols Database	http://www.eortc.be/protoc/	Searched January 16 2003
National of Institute Health (US)	http://www.nih.gov/	Searched January 16 2003
CancerLit (US)	http://cancer.gov/clinical_trials/	Searched January 16 2003

Abbreviations: NHS, National Health Service; UK, United Kingdom; US, United States

Search terms

The search terms shown in Table 2 were used to identify articles in MEDLINE (Ovid and Ovid Pre-MEDLINE), EMBASE and Current Contents.

Table 2 Search terms

1.	resection OR surgery
2.	chemoembol*
3.	hepatic artery
4.	arterial drug administration
5.	catheter ablation
6.	artificial embol*
7.	ethanol injection OR alcohol injection
8.	radiofrequency OR radio frequency OR radio-frequency
9.	liver carcinoma OR liver cancer OR hepatocellular carcinoma OR liver cell carcinoma OR metastatic colorectal OR metastatic neuroendocrine
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
11.	8 AND 9
12.	10 AND 11

Search terms used for MEDLINE (NLM Gateway), Science Citation Index, Clinical Trials Database, NHS CRD; NHS HTA and National Research Register were:

> liver carcinoma OR liver cancer OR hepatocellular carcinoma AND (radiofrequency OR radio frequency OR radio-frequency) AND (ethanol OR surgery OR laser OR arterial OR cryo* OR hepatic artery)

A different, broad strategy for The Cochrane Library database was used as restricted searches turned up very few references. The simple search term was:

> radiofrequency OR radio frequency OR radio-frequency

Note: * is a truncation character that retrieves all possible suffix variations of the root word eg surg* retrieves surgery, surgical, surgeon, etc. In Cochrane the truncation character is *; in Current Contents, EMBASE and MEDLINE (Ovid) it is $. # is a wildcard symbol that substitutes for one required character in Current Contents, EMBASE and MEDLINE (Ovid).

Additionally, the reference list of each article included in the database as a result of the electronic search was hand searched to find other articles not otherwise identified in the electronic searches.

The applicant's submission was also reviewed to ensue that all the relevant literature was included. Additional published and unpublished data provided by the applicant in their submission has been referred to at various times throughout the process of review.

Methods of review

Articles were retrieved when they were judged to possibly meet the selection criteria. Two reviewers then independently applied the selection criteria to these retrieved papers (or abstracts). Any differences were resolved by discussion.

Duplicate publications were identified whenever possible, and the results of the most complete (usually latest) article used. However, double-counting of results from reporting of overlapping study periods from the same study may have occurred.

One reviewer assessed the eligible studies for quality and extracted the data onto data extraction sheets designed for this review and a second reviewer checked the data extraction.

Data were only extracted if reported in the text, tables, graphs or figures of the article, or when it could be accurately extrapolated from the data presented. Conversely, if a particular complication was not reported, it was assumed to be unreported rather than not having occurred. For example, if the re-operation rate was not reported in a study, no value was tabulated. This was done to avoid the bias caused by incorrectly assigning a value of zero to an outcome measurement on the basis of an unverified assumption.

When outcomes from RCTs could be sensibly combined (outcomes measured in comparable ways and no apparent heterogeneity), effect measures were calculated (using RevMan 4.1, Update Software). Relative risks (for dichotomous outcome measures) and weighted mean differences (for continuous outcome measures) with 95% confidence intervals were calculated for some of the outcomes in individual RCTs when it was thought this would help in interpreting results. The confidence intervals represent the range within which the 'true' value of an effect size is expected to lie, with a given degree of certainty eg 95%.

A detailed description of each included study is given in Appendix C Tables 11.1–11.5. Critical appraisals of the included comparative studies are presented in Appendix C Tables 12.1, 12.2 and 12.3.

The results from each study are given by outcome in Appendix E Tables 14–18.

Description and methodological quality of included studies

The evidence presented in the included studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC, 2000).

These dimensions (Table 3) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

Table 3 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
level	The study design used, as an indicator of the degree to which bias has been eliminated by design*
quality	The methods used by investigators to minimise bias within a study design
statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

*See Table 4

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 4.

Table 4 Designations of levels of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from NHMRC, 1999.

Included studies

Comparative studies

Hepatocellular carcinoma (HCC)

Ten comparative studies were included for review (Table 5). See Appendix C Table 11.1 for the study profiles.

Table 5 HCC comparative studies

Authors	Comparison	Level of evidence	HCC sample size (n)
Lencioni *et al* 1999 (includes Lencioni *et al* 1998a)	RFA compared with PEI	II	n = 80 (40 PEI, 40 RFA)
Shiina *et al* 2000	RFA compared with PEI	II	n = 60 (29 PEI, 31 RFA)
Olschewski *et al* 2001	RFA compared with PEI	II	n = 102 (50 PEI, 52 RFA)
Kurokohchi *et al* 2002	RFA compared with PEI/RFA	II	n = 39 (19 PEI/RFA, 20 RFA)
Livraghi *et al* 1999 (includes Livraghi *et al* 1998)	RFA compared with PEI	III-1	n = 86 (44 PEI, 42 RFA)
Ikeda *et al* 2001	RFA compared with PEI	III-2	n = 119 (96 PEI, 23 RFA)
Catalano *et al* 2000 (includes Catalano *et al* 1999)	RFA compared with multiple-session PEI (MS-PEI) or single-session PEI (SS-PEI)	III-3	n = 102 (56 MS-PEI, 14 SS-PEI, 32 RFA)
Catalano *et al* 2001	RFA compared with MS-PEI or SS-PEI	III-3	n = 61 (40 MS-PEI, 5 SS-PEI, 16 RFA)
Livraghi *et al* 2000	RFA compared with TACE	III-3	n = 20 (10 TACE, 10 RFA)
Yu *et al* 2002	RFA compared with surgical resection	III-3	n = 145 (88 surgical resection, 57 RFA)

Metastatic colorectal liver tumours (CLM)

One comparative study was included for review (Table 6). See Appendix C Table 11.2 for the study profile.

Table 6 CLM comparative studies

Authors	Comparison	Level of evidence	CLM sample size (n)
Gillams and Lees, 2001	RFA compared with surgical resection	III-2	n = 46 (16 surgical resection, 30 RFA)

Metastatic neuroendocrine liver tumours (NLM)

One comparative study was included for review (Table7). See Appendix C Table 11.4 for the study profile.

Table 7 NLM comparative studies

Authors	Comparison	Level of evidence	NLM sample size (n)
Mazziotti *et al* 1998	**RFA compared with PEI/RFA**	III-2	n = 2 (1 PEI/RFA, 1 RFA)

Randomised controlled trials (level II evidence) were examined for the adequacy of allocation concealment, handling of losses to follow-up, suitability of outcome measures, and any other aspect of the study design or execution that may have introduced bias. Non-randomised comparative studies (level III-2 and III-3 evidence) were evaluated for the method of patient selection, comparability of the patient groups, suitability of outcome measures, completeness of follow-up, and any other feature of the study design or execution that may have introduced bias (Appendix C, Tables 11.1, 11.2 and 11.3).

Case series

Metastatic colorectal liver tumours (CLM)

Nine case series were included for review (Table 8). See Appendix C Table 11.3 for the study profiles.

Table 8 CLM RFA case series

Authors	Level of evidence	CLM sample size (n)
Bleicher *et al* 2002	IV	n = 54
*Chung *et al* 2001a	IV	n = 6
Cuschieri *et al* 1999	IV	n = 8
*Kosari *et al* 2002	IV	n =18
*Kuvshinoff and Ota, 2002	IV	n = 15
Machi *et al* 2000	IV	n = 9
Pearson *et al* 1999	IV	n = 46
Rossi *et al* 1996	IV	n = 6
Solbiati *et al* 2001a, b (includes 2001c, 1999)	IV	n = 158

*Also NLM case series

Metastatic neuroendocrine liver tumours (NLM)

Eight case series were included for review (Table 9). See Appendix C Table 11.5 for the study profiles.

Table 9 NLM RFA case series

Authors	Level of evidence	NLM sample size (n)
Berber *et al* 2002	IV	n = 34
Buscarini *et al* 2001	IV	n = 1
*Chung *et al* 2001a	IV	n = 3
*Kosari *et al* 2002	IV	n = 7
*Kuvshinoff and Ota, 2002	IV	n = 6
Quellet *et al* 2002	IV	n = 2
Siperstein *et al* 2001 (includes 2000b and 1997)	IV	n = 18
Wessels *et al* 2001	IV	n = 3

*Also CLM case series

The case series were not assessed for methodological quality on an individual basis.

Excluded studies

See Appendix D Tables 13.1–13.4 for the studies excluded from review.

Expert advice

A supporting committee with expertise in liver cancer was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided in Appendix B.

Results of assessment

Description and methodological quality of included studies

Hepatocellular carcinoma (HCC)

The evidence for the safety and effectiveness of radiofrequency ablation (RFA) for the treatment of hepatocellular carcinoma (HCC) is based on 10 comparative studies; four RCTs, level II evidence (Lencioni *et al* 1999; Shiina *et al* 2000; Olschewski *et al* 2001; Kurokohchi *et al* 2002), one quasi-RCT (Livraghi *et al* 1999) and five non-randomised comparative studies, level III-1 to III-3 evidence (Catalano *et al* 2000; Livraghi *et al* 2000; Catalano *et al* 2001; Ikeda *et al* 2001; Yu *et al* 2002). Eight of these studies compare percutaneous ethanol injection (PEI) and RFA (Lencioni *et al* 1999; Livraghi *et al*,. 1999; Catalano *et al* 2000; Shiina *et al* 2000; Catalano *et al* 2001; Ikeda *et al* 2001; Olschewski *et al* 2001; Kurokohchi *et al* 2002). Two other studies compared surgical resection and RFA (Yu *et al* 2002) or transarterial chemoembolisation (TACE) with RFA (Livraghi *et al* 2000). The five non-randomised comparative studies were likely to have been retrospective comparisons of RFA with previous standard care.

Two retrospective comparisons by Catalano *et al* (2000; 2001) reviewed patient computed tomography (CT) scans for tumour recurrence and nodular changes after treatment with either RFA, multi-session PEI (MS-PEI), or single-session (one-shot) PEI (SS-PEI) for HCC. It is unclear whether the later article (Catalano *et al* 2001) is a partial subgroup analysis including some of the patients from the study population of the earlier report (Catalano *et al* 2000).

Evaluation of follow-up therapeutic response was performed via dynamic CT imaging (Olschewski *et al* 2001) or dual phase (arterial phase and portal venous phase) spiral CT imaging (Lencioni *et al* 1999; Shiina *et al* 2000). In one study, all patients were evaluated by unenhanced CT and additionally by either dual phase spiral CT, triple phase spiral CT or dual phase plus targeted delay spiral CT (Catalano *et al* 2000). Combined assessment by unenhanced CT and dual phase spiral CT was reported in another study (Catalano *et al* 2001). Contrast-enhanced CT was used in two studies (Ikeda *et al* 2001; Kurokohchi *et al* 2002). Two studies did not comment on the type of imaging that was used for follow-up evaluation (Livraghi *et al* 2000; Yu *et al* 2002).

Participants were not blinded to the procedure they were undergoing in any of the included studies and assessor blinding was either not stated or did not occur (Lencioni *et al* 1999; Livraghi *et al* 1999; Catalano *et al* 2000; Livraghi *et al* 2000; Shiina *et al* 2000; Catalano *et al* 2001; Ikeda *et al* 2001; Olschewski *et al* 2001; Kurokohchi *et al* 2002; Yu *et al* 2002). Follow-up time was rarely stated, with the longest clinical follow-up time being 44 months postoperatively (Catalano *et al* 2000). The basis of patient selection was stated in five of the 10 studies (Catalano *et al* 2000; Catalano *et al* 2001; Ikeda *et al* 2001; Olschewski *et al* 2001; Kurokohchi *et al* 2002). Eighty seven patients were excluded from review in one study due to the presence of residual viable tumour detected during post-treatment examination (Catalano *et al* 2000). Two studies investigated consecutive

patients. In one study there were 116 consecutive patients (102 included in this review) (Catalano *et al* 2001), while the other had 119 consecutive ones (Ikeda *et al* 2001). In another study, 122 patients were not included for review, although a reason for this was not stated (Yu *et al* 2002). Loss to follow-up was stated in one study in which eight patients died during the observation period (Catalano *et al* 2000).

In two RCTs, allocation to either treatment was not stated (Livraghi *et al* 2000; Shiina *et al* 2000). The quasi-RCT allocated patients into either treatment group according to their proximity to the hospital (Livraghi *et al* 1999). This form of allocation, although not concealed, is not based on patients' request or health status and may reduce the chance of selection bias on the part of the investigators and patients.

Most of the included studies concentrated on reporting effectiveness outcomes such as completeness of tumour ablation and number of sessions, rather than reporting on complications and other safety outcomes. One study reported using more than one type of electrode in their studies (Livraghi *et al* 1999). The postoperative outcomes from this study did not distinguish between the different electrodes so that it was unclear whether there were differences in patient outcomes for the different electrode types.

It was generally not considered appropriate to pool results across studies. Relative risks (RR) or weighted mean differences (WMD) and the 95% confidence intervals (CI) were calculated individually for the same outcomes in three RCTs (Lencioni *et al* 1999; Shiina *et al* 2000; Olschewski *et al* 2001) and the one quasi-RCT (Livraghi *et al* 1999). It was not considered appropriate to calculate WMD and CIs for the fourth RCT as the comparative treatment arm in this study was PEI combined with RFA (Kurokohchi *et al* 2002). Results were interpreted such that RFA was better than the comparative intervention when the upper limit of the 95% CI of the RR was <1 (except for 'positive' outcomes such as therapeutic effect) and for WMD <0. The RRs, WMDs and 95% CIs were calculated with RevMan 4.1 (Update Software Ltd. 2000).

RFA compared with PEI

Eight studies compared percutaneous ethanol injection (PEI) and RFA (Lencioni *et al* 1999; Livraghi *et al*,. 1999; Catalano *et al* 2000; Shiina *et al* 2000; Catalano *et al* 2001; Ikeda *et al* 2001; Olschewski *et al* 2001; Kurokohchi *et al* 2002).

The level II evidence (Lencioni *et al* 1999; Shiina *et al* 2000; Olschewski *et al* 2001; Kurokohchi *et al* 2002) was limited by small sample size, short follow-up period and lack of blinding of study participants or outcome assessors. In the quasi-RCT, one application of RFA was used for each lesion (one treatment cycle) while PEI was delivered as multiple sessions (MS-PEI) per lesion (one treatment cycle) (Livraghi *et al* 1999). One RCT stated that one application of RFA was used for each lesion but did not state how many sessions of PEI were performed per lesion (sessions per one treatment cycle) (Olschewski *et al* 2001). Two other RCTs did not indicate the number of RFA applications per lesion or how many sessions of PEI were performed per lesion (sessions per one treatment cycle) (Lencioni *et al* 1999; Shiina *et al* 2000). In the fourth RCT, RFA was performed alone or immediately after PEI but there was no mention of the number of sessions of RFA performed per lesion (Kurokohchi *et al* 2002).

The two retrospective comparisons (level III-3 evidence) were observational and retrospective in nature and reviewed patient CT scans for tumour recurrence and nodular changes after treatment with either RFA, MS-PEI or SS-PEI for HCC (Catalano *et al* 2000; Catalano *et al* 2001).).

RFA compared with TACE

One level III-3 conference abstract compared TACE and RFA. This non-randomised comparative study may have had a historical control group. The treatment groups were comparable as regards patient numbers and number of nodules treated per procedure. The nodules that were treated were also comparable in size (Livraghi *et al* 2000).

RFA compared with surgical resection

One conference abstract (level III-3) compared RFA with surgical resection. This study retrospectively reviewed patient data to evaluate the rates of recurrence in each group (Yu *et al* 2002).

Metastatic colorectal liver tumours (CLM)

The evidence for the safety and effectiveness of RFA for treating colorectal liver metastases (CLM) is based on one non-randomised comparative study (level III-2 evidence) (Gillams and Lees, 2001) and nine case series (level IV evidence) (Chung *et al* 2001a; Cuschieri *et al* 1999; Kosari *et al* 2002; Kuvshinoff and Ota 2002; Machi *et al* 2000; Pearson *et al* 1999; Rossi *et al* 1996; Solbiati *et al* 2001a, b; Bleicher *et al* 2002). Three of these studies were also included as case series of the evaluation of RFA for the treatment of neuroendocrine liver metastases (NLM) (Chung *et al* 2001a; Kosari *et al* 2002; Kuvshinoff and Ota 2002). The only non-randomised comparative study compared surgical resection and RFA (Gillams and Lees, 2001).

The non-randomised comparative study did not blind participants to the procedure and assessor blinding was either not stated or did not occur (Gillams and Lees, 2001). The basis of patient selection was not stated. The method of allocation to RFA was based on tumour location, previous hepatic resection, concomitant ill health, known extrahepatic disease, or patient preference (Gillams and Lees, 2001).

Of the nine case series, one was a conference abstract (Bleicher *et al* 2002). The longest follow-up period was a median of 19.5 months (Kosari *et al* 2002) and largest sample size was 158 patients (Bleicher *et al* 2002).

Metastatic neuroendocrine liver tumours (NLM)

The evidence for the safety and effectiveness of RFA for the treatment of NLM is based on one non-randomised comparative study (level III-2 evidence) (Mazziotti *et al* 1998) and eight case series (level IV evidence) (Berber *et al* 2002; Buscarini *et al* 2001; Chung *et al* 2001a; Kosari *et al* 2002; Kuvshinoff and Ota 2002; Quellet *et al* 2002; Siperstein *et al*

2001; Wessels *et al* 2001). The only non-randomised comparative study compared PEI and RFA (Mazziotti *et al* 1998).

The non-randomised comparative study did not blind participants to the procedure and assessor blinding was either not stated or did not occur (Mazziotti *et al* 1998). The basis of patient selection was not stated and the method of allocation to RFA was not stated.

Of the eight case series, one was a conference abstract (Buscarini *et al* 2001). The longest follow-up period was a median of 18 months (Berber *et al* 2002) and largest sample size was 34 patients (Berber *et al* 2002).

Continuing and unpublished clinical trials

There are several clinical trials currently being conducted on RFA. The results of these have not yet been published and could not be included for review. A list of these continuing, or as yet unpublished, studies is given in Appendix F Table 19.

Units of analysis

The units of measurement for the reported outcomes varied between the studies. Ideally, studies referred to the proportion of patients with a particular outcome; this was reported mainly for pain, analgesic requirements or complication rates. However, some outcomes were reported as the proportion of nodules treated in each group or the number of treatment sessions in each group, and therefore these results cannot be compared with outcomes reported on a per patient basis.

Hepatocellular carcinoma (HCC)

Is RFA safe?

Comparative studies

RFA compared with PEI

In one RCT, high fever for three or more days was reported in 28% of the RFA sessions and 10% of the PEI sessions performed (RR 2.80, 95% CI 1.59–4.92) (Shiina *et al* 2000). No other complications were reported in any of the patients (Lencioni *et al* 1999; Shiina *et al* 2000).

In another RCT, 44% of RFA-treated patients and 34% of PEI-treated patients had either serious side-effects or complications (RR 0.76, 95% CI 0.54–1.06) (Olschewski *et al* 2001).

In the quasi-RCT, 2% (1/42 patients) of RFA patients developed major complications within 24 hours of treatment (1 haemothorax) and 8% (3/42 patients) developed minor complications (intraperitoneal bleeding, haemobilia, pleural effusion, mild cholecystitis)

(Livraghi *et al* 1999). Transaminase levels were also two to four times higher than the baseline measurements in all RFA patients. The complication rates or transaminase levels for PEI patients were not given.

In the non-randomised study by Catalano *et al* (2000), an inflammatory granulation rim representing non-viable tumour (necrotic) tissue was seen mainly after RFA or MS-PEI. This rim was detected as a margin of slightly hyperattenuating tissue on arterial, portal or delayed CT phase. Complications were most common in the SS-PEI treatment group (eg biliary duct damage in 21%, local atrophy of the liver surface in 29%, and perihepatic effusion in 29% of SS-PEI-treated patients) than in the RFA or MS-PEI groups, for which individual complication rates generally occurred in less than 10% of patients (Catalano *et al* 2000). No safety outcomes were reported in the second Catalano study (Catalano *et al* 2001).

In the third non-randomised study, one complication was reported in the PEI treatment group (acute cholangitis that required drainage) while none was reported for the RFA treatment group (Ikeda *et al* 2001).

RFA compared with TACE

No complications were reported for RFA, but two patients treated with TACE developed major complications (p = 0.07), with one patient dying four months after the procedure (Livraghi *et al* 2000).

RFA compared with surgical resection

No safety data were reported (Yu *et al* 2002).

Is it effective?

Comparative studies

RFA compared with PEI

RCTs and quasi-RCTs

Survival/Mortality

In one RCT, two year mortality was 1/52 (2%) after treatment with RFA compared with (6/50) 12% in the PEI-treated group (RR 0.16, 95% CI 0.02–1.28) (Olschewski *et al* 2001).

In the same RCT, local recurrence-free survival after two years was 50/52 (96%) in the RFA group compared with 31/50 (62%) in the PEI group. This represents a relative 'risk' of 1.55 (95% CI 1.24–1.94) in favour of RFA. Event-free survival at two years also tended to favour RFA, although this result did not quite reach statistical significance.

Recurrence

This translates to a local recurrence rate at two years of 1/52 (2%) for RFA and 13/50 (26%) for PEI; relative risk 0.07 95% CI 0.01–0.54 in favour of RFA (Olschewski *et al* 2001).

In another RCT there was a trend to less local tumour recurrence (after a median of 15 months) for RFA-treated tumours (2/49 tumours, 4%) than for PEI-treated tumours (9/52, 17%) – in those 88% of tumours considered to have undergone complete ablative responses. This did not quite reach statistical significance when measured as a relative risk (RR 0.24, 95% CI 0.05–1.04; p = 0.06) but was given as p<0.05 in the paper (Lencioni *et al* 1999).

In one RCT no local recurrence of tumours 0/31 (0%) was reported for the RFA group at four months follow-up, compared with 1/29 (3.5%) for the PEI group (RR 0.31, 95% CI 0.01–7.38) (Shiina *et al* 2000).

New lesions were reported to have formed in 10% of RFA-treated patients and in 14% of PEI-treated patients (RR 0.70 95% CI 0.17–2.87) (Shiina *et al* 2000).

Therapeutic response (defined by CT at four months) and long-term tumour control

In one RCT (Lencioni *et al* 1999) and in the quasi-RCT (Livraghi *et al* 2000), no statistically significant differences were seen in therapeutic response between RFA and PEI, as measured by the percentage of nodules showing complete necrosis. In another RCT, there were no statistically significant differences in the number of nodules with complete tumour ablation (detected by dynamic CT imaging) after treatment with a single RFA session (91% of RFA-treated nodules) compared with one cycle of PEI treatment (82% of PEI-treated nodules) (Olschewski *et al* 2001). However, when results for this outcome are combined across all three studies, RFA shows a statistically significantly better response than PEI (RR 1.10 95% CI 1.02–1.19). It should be noted that this is on a per lesion, rather than per patient, basis which may artificially inflate the result. In addition ablative response may be a surrogate outcome.

In one RCT, the area of necrosis was smaller and the tumour volume lower for nodules treated with RFA than for ones treated with PEI/RFA (Kurokohchi *et al* 2002).

Sessions required

In one RCT fewer sessions were needed for complete tumour ablation in the RFA group than in the PEI-treatment group (p<0.01) although it was unclear if this was per patient or per nodule treated (Lencioni *et al* 1999).

In another RCT the RFA group also needed fewer sessions (p<0.0001), although it was unclear whether sessions were achieving complete ablation (Shiina *et al* 2000). In the quasi-RCT fewer treatment sessions were required per nodule when patients received RFA rather than PEI (Livraghi *et al* 2000).

Operating time and length of hospital stay

In the quasi-RCT procedure time was shorter for PEI than for RFA (Livraghi *et al* 1999). In one RCT patients undergoing RFA spent fewer days in hospital than those undergoing PEI treatment (p<0.0001) (Shiina *et al* 2000).

Pain

In one RCT analgesia was needed more often with RFA treatment than with PEI (RR 3.13 95% CI 1.90–5.14) (Shiina *et al* 2000). In the quasi-RCT five patients undergoing RFA had their treatment interrupted due to severe pain (Livraghi *et al* 1999). However, it was not stated whether this was the case for any PEI patients. One patient in the PEI group needed post-treatment analgesia, while two patients in the RFA group were in pain for three to four days after surgery and required analgesics.

Non-randomised comparisons

In one study more nodules increased in diameter after being treated with either RFA (58%) or SS-PEI (71%) than ones treated with MS-PEI (29%) (Catalano *et al* 2000). Nodules also appeared to be more round or oblong in shape when treated by either RFA or SS-PEI than those treated by MS-PEI (Catalano *et al* 2000). Residual viable tumour tissue (which tended to correlate with irregular nodule borders) was present in 35% of RFA-treated nodules, 54% of MS-PEI-treated nodules and 68% of SS-PEI-treated nodules (Catalano *et al* 2000).

In the second retrospective study (Catalano *et al* 2001), which may have had some patients in common with Catalano *et al* (2000), patients who did not show residual viable tumour on the first post-treatment CT scan but developed tumour recurrence (either local or non-local) on follow-up CT scan (3–22 months after the last treatment session) were evaluated with imaging. Nodules with local recurrence (viable tumour tissue within or around the nodule edge but in continuity with the edge of the treated nodule) were associated more often with either RFA (16%) or MS-PEI (14%) treatment than SS-PEI (9%) treated nodules (Catalano *et al* 2001). New non-local nodule formation (either within the same or within different liver segments from the treated nodule) was more common after MS-PEI (62 nodules) or RFA (23 nodules) treatment than after SS-PEI (14 nodules) treatment (Catalano *et al* 2001). Because it was hard to interpret the reported data, it was not possible to associate new non-local nodule formation with the number of nodules with local recurrence. In addition, the study did not report which patients developed new nodules, but reported on a per nodule basis only.

In the third study, fewer sessions, fewer days in hospital, and less analgesia were needed after treatment with RFA than with PEI, although these differences were not statistically significant (Ikeda *et al* 2001). In the same study, complete tumour necrosis (one month follow-up) was evident in all patients (100%) after treatment with RFA compared with 94% of patients treated with PEI (p >0.1). However, local recurrence was evident in 15% and 13% of patients after RFA and PEI respectively (p >0.1).

RFA compared with TACE

Four patients died after TACE treatment while no deaths were reported for the RFA group (follow-up period not stated, p<0.05) (Livraghi *et al* 2000).

Complete control of tumour growth was achieved in 50% (5/10) patients of the tumours treated with RFA compared with 30% (3/10) patients treated with TACE, which was not statistically significant (no p value stated) (Livraghi *et al* 2000).

RFA compared with surgical resection

The two treatment groups were first compared over two study periods (RFA, March 1999–May 2001; surgical resection, October 1990–February 2001) that overlapped by 38 months (Yu *et al* 2002). In the RFA treatment group 39% of patients showed recurrence compared with 24% of patients treated by surgical resection. The mean interval between the time of treatment and recurrence was shorter for the RFA treatment group (160.1 days {104.8}) than for the surgical resection group (634.9 days {169.4}). There were no reported differences in the intra-hepatic and extra-hepatic patterns of recurrence between the two treatment groups (Yu *et al* 2002). Note: {} indicates unit of measurement not defined.

Comparing the treatment groups over the same 38-month period (March 1999–May 2001), the recurrence rate in the RFA treatment group remained the same (39%) whereas recurrence rates in the surgical resection treatment group were lower (19%). The mean time interval between treatment and recurrence for the surgical resection treatment group during this particular period was longer (292 days {269.1}) than that reported for the RFA treatment group (160.1 days {104.8}) (Yu *et al* 2002).

Recurrence rates were also examined, taking into account the tumour size. When the tumour size was greater than 3.5 cm in diameter, the rate of recurrence was 38% in the RFA treatment group compared with 23% for the surgical resection treatment group (Yu *et al* 2002). In patients with a tumour diameter smaller than 3.5 cm, the rate of recurrence was 39% in the RFA treatment group and 14% in the surgical resection group ($p = 0.045$) (Yu *et al* 2002).

What are the economic considerations?

Since effectiveness could not be established for CLM, only the cost-effectiveness of RFA for treating HCC was assessed. The comparator used for RFA was PEI, since there was so little information available from the other two comparators used to evaluate effectiveness. In particular the only level II (RCT) evidence was from comparisons of RFA with PEI for treating HCC. The outcome measure used in the economic analysis for effectiveness was local recurrence-free survival.

No studies comparing the costs of RFA with PEI for treating HCC could be located. Thus the economic evaluation contains several assumptions sourced from the findings of this review (where applicable), and costings from the literature, the original application, manufacturers and hospital data.

An incremental cost-effectiveness approach has been used, where only the costs that are likely to differ between RFA and PEI are included.

Effectiveness assumptions

In one RCT, the relative 'risk' of local recurrence-free survival (LRFS) at one year was 1.17 (95% CI 1.03–1.33) in favour of RFA (Olschewski *et al* 2001). This comparison was based on a single session of RFA (via percutaneous access) which resulted in 51/52 (98%) LRFS, versus a single session of PEI which resulted in 42/50 (84%) LRFS. This equates to a 14% risk difference between RFA and PEI, with a 95% CI of 3–25%. The risk difference of 14% is presented as the base case and sensitivity analyses are given for the lower and upper confidence intervals of 3% and 25% respectively. (Note that a trial based on the effectiveness of a single PEI session may underestimate the effectiveness of PEI.)

Number of sessions

In the studies included in the review, RFA was applied usually in one, but sometimes two, sessions. In contrast, PEI was usually applied in multiple sessions. The economic evaluation contains separate cost comparisons for one RFA session versus one PEI session, one RFA session versus three PEI sessions, and two RFA sessions versus three PEI sessions.

Access methods

Although the effectiveness measure is based on RFA via a percutaneous approach, the literature records that all three access methods are used. Therefore, the economic evaluation contains a separate cost comparison for each of the three RFA access methods: percutaneous, laparoscopic and open. It also assumed that separate sessions for both multi-session RFA and PEI will be done on different days, meaning multiple sets of disposable items and multiple hospital admissions (when appropriate).

Cost of disposable equipment

The cost of disposable equipment (needles) ranges from $1700 to $2700 for each session of RFA (source: application and manufacturers) and is $200 for PEI (needles) per session. Therefore the base case for RFA disposable equipment (one session) was assumed to be $1700–2700.

Theatre banding

Although neither RFA or PEI have been allocated a Medicare Benefits item number, laparoscopic RFA is assumed to fall under into theatre band 3 ($550) and open RFA is assumed to fall under theatre band 4 ($750) (source: DHA). Therefore the base cases for theatre banding are assumed to be:

- percutaneous nil
- laparoscopic $550
- open $750

Hospital stay

Percutaneous RFA and PEI are assumed to be same-day procedures, laparoscopic RFA to require a one-day hospital stay and open RFA a seven-day hospital stay. Hospital stay is costed at $600 per day (source: Farmer *et al* 2002). Therefore the base cases for hospital stay are assumed to be:

- percutaneous nil
- laparoscopic $600
- open $4200

Capital costs

The capital costs for the RFA generator were $40,000–65,000 (source: manufacturers). These costs are not included in the unit-cost economic evaluation.

Recurrent equipment costs

The cost of recurrent equipment costs (service, maintenance) varies between $640 and $6,500 per unit per year (source: application and manufacturers). These costs are not included in the unit cost economic evaluation. All costs are in Australian dollars.

Incidence of HCC

About 200 new cases of HCC that would be suitable for RFA are estimated to occur in Australia each year (source: AIHW, application).

RFA unit costs

	BASE CASE	
	RFA (1 session)	**RFA (2 sessions)**
PERCUTANEOUS		
— consumables	1700–2700	3400–5400
Subtotal	**$1700–2700**	**$3400–5400**
LAPAROSCOPIC		
— consumables	1700–2700	3400–5400
— theatre band	550	1100
— hospital stay	1 day = 600	2x1 day = 1200
Subtotal	**$2850–3850**	**$5700–7700**
OPEN		
— consumables	1700–2700	NA
— theatre band	750	NA
— hospital stay	7 days = 4200	NA
subtotal	**$6650–7650**	**NA**

The only comparative cost element for PEI is the cost of the needles ($200 per session).

Incremental cost-effectiveness ratios (ICER)

The incremental cost-effectiveness ratio has been calculated per procedure.

BASE CASE: cost per incremental recurrence-free survival at one year
1. Single session RFA versus single session PEI

1.1	**14% LRFS benefit for RFA**		**ICER per LRFS**
	1.1.1	percutaneous RFA	$10,714–17,857
	1.1.2	laparoscopic RFA	$18,929–26,071
	1.1.3	open RFA	$46,071–53,214

SENSITIVITY ANALYSES
2. Single session RFA versus three sessions of PEI

2.1	**14% LRFS benefit for RFA**		**ICER per LRFS**
	2.1.1	percutaneous RFA	$7,857–15,000
	2.1.2	laparoscopic RFA	$16,071–23,214
	2.1.3	open RFA	$43,214–50,357

PEI is usually delivered in multiple sessions, so sensitivity analyses are presented for one session of RFA versus three sessions of PEI. This analysis is based only on the decrease in the cost difference between the two methods when multiple PEI sessions are used. There were no data on the relative difference in effectiveness between the two methods using this clinical regimen and the risk difference of 14% is used. Since multiple PEI sessions are likely to be more effective than single sessions, the incremental effectiveness of RFA is likely to be less than in the base-case analysis and therefore the incremental cost-effectiveness ratio is likely to be underestimated in this sensitivity analysis.

3. Two sessions of RFA versus three sessions of PEI

3.1	**14% LRFS benefit for RFA**		**ICER per LRFS**
	3.1.1	percutaneous RFA	$20,000–34,286
	3.1.2	laparoscopic RFA	$36,429–50,714
	open RFA		NA

RFA may also be applied in more than one session (percutaneous and laparoscopic access). No figures are available on any additional effectiveness from multiple RFA sessions, although it might be anticipated to be more effective, and thus the effectiveness of RFA may be underestimated in this sensitivity analysis.

4. Single session RFA versus single session PEI (low (3%) benefit of RFA)

4.1	**3% LRFS benefit for RFA**		**ICER per LRFS**
	4.1.1	percutaneous RFA	$50,000–83,333
	4.1.2	laparoscopic RFA	$88,333–121,667
	4.1.3	open RFA	$215,000–248,333

5. Single session RFA versus single session PEI (high (25%) benefit of RFA)

5.1	**25% LRFS benefit for RFA**		**ICER per LRFS**
	4.1.1	percutaneous RFA	$6,000–10,000
	4.1.2	laparoscopic RFA	$10,600–14,600
	4.1.3	open RFA	$25,800–29,800

Metastatic colorectal liver tumours (CLM)

Is it safe?

Comparative studies

RFA compared with surgical resection

No safety data were reported in the single included comparative study (Gillams and Lees 2001).

Case series

Complications

Complication rates were reported in six of the nine included CLM studies (Chung *et al* 2001a; Cuschieri *et al* 1999; Kosari *et al* 2002; Machi *et al* 2000; Pearson *et al* 1999; Solbiati *et al* 2001a, b).

Intraoperative complications did not occur in any patient in one study (Machi *et al* 2000) and either did not occur or were unreported for the other eight studies (Chung *et al* 2001a; Cuschieri *et al* 1999; Kuvshinoff and Ota 2002; Machi *et al* 2000; Pearson *et al* 1999; Rossi *et al* 1996; Solbiati *et al* 2001a, b; Bleicher *et al* 2002).

Postoperative complication rates ranged from 0% (Cuschieri *et al* 1999; Pearson *et al* 1999) to 33% (early 22%, late 11%) (Machi *et al* 2000). Some patients in the Machi *et al* 2000 study underwent repeat RFA operations (one to three times) for recurrent tumours which may have contributed to the higher complication rate in this study.

Is it effective?

Comparative studies

RFA compared with surgical resection

The median survival from diagnosis of liver metastases was 44 months for patients treated with RFA (Gillams and Lees 2001). The mean survival from diagnosis of liver metastases was 54 months for patients treated with surgical resection. Five-year survival rates were lower (40%) for patients treated with RFA than that for patients treated with surgical resection (53%) (Gillams and Lees 2001). It should be noted that these survival figures are from the time of diagnosis, and not treatment, of liver metastases.

Case series

Recurrence

Seven case series reported recurrence after RFA (Bleicher *et al* 2002; Cuschieri *et al* 1999; Kosari *et al* 2002; Kuvshinoff and Ota 2002; Machi *et al* 2000l; Pearson *et al* 1999; Solbiati *et al* 2001a, b).

Local recurrence (patients)

Six studies reported local recurrence (Bleicher *et al* 2002; Kosari *et al* 2002; Kuvshinoff and Ota 2002; Machi *et al* 2000l; Pearson *et al* 1999; Solbiati *et al* 2001a, b;) (see below, Table 10). The local recurrence rate ranged from 4% at a median 15 months follow-up in one study (Pearson *et al* 1999) to 55% at a median 18 months follow-up in another study (Solbiati *et al* 2001a, b).

The large variation in recurrence rates may be related to the method of access as Pearson *et al* 1999 performed RFA surgically during an open operative procedure, whereas Solbiati *et al* (2001a, b) performed RFA percutaneously. In both studies, the patients were considered unsuitable for surgical resection, but no further details were provided on their condition, which could influence this result.

Table 10 Local recurrence (with at least one year follow-up) and method of access

Study	Local recurrence rate (per patient)	Method of access
Bleicher *et al* 2002	24% 13/54	Open/percutaneous/ laparoscopic
Kuvshinoff *et al* 2002	40% 6/15	Open/percutaneous/ laparoscopic
Machi *et al* 2000	22% 2/9	Open
Pearson *et al* 1999	4% 2/46	Open
Solbiati *et al* 2001a, b	55% 64/117	Percutaneous

New recurrence (patients)

Five studies reported the rate of new liver metastases (Cuschieri *et al* 1999; Kosari *et al* 2002; Machi *et al* 2000; Pearson *et al* 1999; Solbiati *et al* 2001a, b). The rate of new liver metastases ranged from 2% in one study (Pearson *et al* 1999) to 56% in another study (Solbiati *et al* 2001a, b).

Therapeutic response

The completeness of tumour ablation after RFA was reported in two studies (Cuschieri *et al* 1999; Solbiati *et al* 2001a, b). In one study, the percentage of nodules showing complete ablation on ultrasound (with a minimum 0.5 cm margin) was 84% (Cuschieri *et al* 1999). The time period to ultrasound was not stated.

In the other study 74% of nodules showed complete ablation on helical computed CT (time period to CT not stated) (Solbiati *et al* 2001a, b). This study also reported the completeness of tumour ablation according to tumour size. For tumours smaller than 3 cm in diameter, 82% of tumours demonstrated complete tumour ablation. For tumours greater than 3 cm in diameter, 48% of tumours demonstrated complete tumour ablation (Solbiati *et al* 2001a, b).

Mortality

Seven studies reported mortality rates (Chung *et al* 2001a; Cuschieri *et al* 1999; Kosari *et al* 2002; Machi *et al* 2000; Pearson *et al* 1999; Rossi *et al* 1996; Solbiati *et al* 2001a, b).

Treatment-related mortality

Treatment-related mortality was reported as 0% in two studies (Chung *et al* 2001a; Solbiati *et al* 2001a, b).

Cancer-related mortality

Seven studies reported cancer-related mortality rates (Chung *et al* 2001a; Cuschieri *et al* 1999; Kosari *et al* 2002; Machi *et al* 2000; Pearson *et al* 1999; Rossi *et al* 1996; Solbiati *et al*

2001a, b). Mortality rates ranged from 0% (follow-up period not stated) (Pearson *et al* 1999) to 50% at 6–10 months follow-up (Chung *et al* 2001a). It was not stated whether mortality was related to the disease being treated.

Survival

Six studies reported on survival (Chung *et al* 2001a; Cuschieri *et al* 1999; Machi *et al* 2000; Pearson *et al* 1999; Rossi *et al* 1996; Solbiati *et al* 2001a, b). Survival rates ranged from 17% at 11 months (Chung *et al* 2001a) to 88% at 2–6 months follow-up (Cuschieri *et al* 1999). Estimated median survival time after treatment with RFA was 33 months (Solbiati *et al* 2001a, b).

Identification of tumours

One study reported on the effectiveness of pre-operative imaging studies for the identification of CLM tumours (Machi *et al* 2000). In this study, 23 nodules were identified before surgery by imaging studies (including CT scan). Additionally eight nodules in four patients (44%) were identified at surgery by inspection and palpation. All of these 31 tumours were subsequently identified by intraoperative ultrasound, which also helped identify another six nodules in five patients (56%) that were pre-operatively unrecognised by imaging (including CT scan) and nonpalpable (Machi *et al* 2000). All additional nodules were treated with RFA as resection was not possible (due to location of tumours or presence of extrahepatic disease).

Metastatic neuroendocrine liver tumours (NLM)

Is it safe?

Comparative studies

RFA compared with PEI

No safety data were reported (Mazziotti *et al* 2001).

Case series

Complications

The complication rate was reported in five of the included eight NLM studies (Berber *et al* 2002; Chung *et al* 2001a; Kosari *et al* 2002; Siperstein *et al* 2001; Wessels *et al* 2001).

Complications occurred in 5% of the procedures performed in one study (Berber *et al* 2002). No intraoperative complications were reported in another study (Wessels *et al* 2001). It was reported that no patients developed complications in two studies (Chung *et al* 2001a; Kosari *et al* 2002) but that 11% did in another study (Siperstein *et al* 2001).

Is it effective?

Non-randomised comparative

RFA compared with PEI

Local recurrence (patients)

Local recurrence was detected by CT scan and confirmed by examination of the surgical specimen in one patient (100%) after treatment with RFA (2 months) and in another one patient (100%) after treatment with PEI (18 months) (Mazziotti *et al* 2001). (Note: there were only two NLM patients in the study.)

Therapeutic response

Incomplete tumour ablation was found to have occurred in both patients (one treated with RFA and the other treated with PEI). The single nodule treated with RFA was 50% ablated whereas the single nodule treated with PEI was less than 20% ablated upon examination of surgical specimen (Mazziotti *et al* 2001).

Mortality

Mortality was 0% at five months for the patient treated with RFA and 0% at eight months for the patient treated with PEI (Mazziotti *et al* 2001).

Case series

Recurrence

Local recurrence (patients)

Five studies reported on local recurrence after RFA (Berber *et al* 2002; Buscarini *et al* 2001; Kosari *et al* 2002; Quellet *et al* 2002; Siperstein *et al* 2001). The local recurrence rate ranged from 0% (mean 10.1 months; at 6 months) (Buscarini *et al* 2001; Quellet *et al* 2002) to 20% at mean 12.1 months (Siperstein *et al* 2001).

New recurrence (patients)

Three studies reported on new liver metastases (Berber *et al* 2002; Kosari *et al* 2002; Siperstein *et al* 2001). The rate of new liver metastases ranged from 17% at 15 months (Siperstein *et al* 2001) to 57% (follow-up period not stated) (Kosari *et al* 2002).

Therapeutic response

The ablative response was reported in two studies (Buscarini *et al* 2001; Siperstein *et al* 2001). Complete ablation was achieved in all patients at one week in one study (Siperstein *et al* 2001) and in the single patient reported in the other study (follow-up period not stated) (Buscarini *et al* 2001).

Mortality

Six studies reported on mortality (Berber *et al* 2002; Chung *et al* 2001a; Kosari *et al* 2002; Quellet *et al* 2002; Siperstein *et al* 2001; Wessels *et al* 2001).

Treatment-related mortality

Two studies reported on treatment-related mortality (Berber *et al* 2002; Chung *et al* 2001a). In both studies, a 0% mortality rate was reported.

Cancer-related mortality

Six studies reported on cancer-related mortality (Berber *et al* 2002; Chung *et al* 2001a; Kosari *et al* 2002; Quellet *et al* 2002; Siperstein *et al* 2001; Wessels *et al* 2001). Mortality rates ranged from 0% in two studies (follow-up periods not stated) (Chung *et al* 2001a; Quellet *et al* 2002) to 33% at 6 months follow-up (Wessels *et al* 2001). It was not stated if mortality was related to the disease being treated.

Survival

Survival periods were reported in one study (Berber *et al* 2002). Mean survival after diagnosis of primary neuroendocrine cancer was 5.5 years. Mean survival after detection of liver metastases was three years while the mean survival after treatment of NLM with RFA was 1.6 years (Berber *et al* 2002).

Identification of tumours

One study reported on the effectiveness of preoperative CT scan compared to laparoscopic ultrasound for identifying NLM tumours (Berber *et al* 2002). In this study, 20 lesions out of 234 (9%) in 11 out of 42 ablations (26%) that were not seen on preoperative CT scans were visualised by laparoscopic ultrasound.

Conclusions

The small number of studies with comparable interventions and outcome measures made it difficult to objectively assess and compare outcomes. This was further compounded by variability in the units of measurement (eg by patient or by lesion) making comparisons between the studies difficult.

The case-series data were also difficult to interpret, due to different patient groups and interventions that could not be easily compared.

Nonetheless, some conclusions could be drawn, particularly about the effectiveness of RFA for HCC. Very few studies reported safety data in any detail and it was impossible to determine if RFA was safer or less safe than its comparators. The structure of this review meant several large case series of RFA had to be excluded as they did not report outcomes for each indication separately. In one multicentre study of over 1,000 patients, the major complication rate was 2.43% (Rhim *et al* 2003). In a review of 82 studies of RFA involving 3670 patients, the overall complication rate was 8.9% (Mulier *et al* 2002). These findings are broadly in line with the safety outcomes reported in the studies included in this review.

Hepatocellular carcinoma (HCC)

Safety

RFA compared with PEI (percutaneous ethanol injection)

In one RCT, no complications (apart from fever) were reported after either RFA or PEI treatment. However, another RCT of 102 patients stated that serious side effects or complications were found in 44% of patients treated with RFA and 34% of patients treated with PEI (not a statistically significant difference).

One quasi-RCT with 86 patients reported a 2% major and 8% minor complication rate for patients treated with RFA but did not state the complication rates for PEI. One other RCT reported that patients treated with PEI did not have any major complications but did not state if any RFA patients suffered major complications.

RFA compared with TACE (transarterial chemoembolisation)

The only non-randomised comparative study reported that RFA was associated with fewer complications than TACE (0% compared with 20%, not statistically significant).

RFA compared with surgical resection

The only non-randomised comparative study did not report any safety outcomes so conclusions about the safety of RFA compared to surgical resection cannot be made.

Effectiveness

RFA compared with PEI

While two-year mortality did not show a statistically significant difference between RFA and PEI, local recurrence-free survival (and local recurrence rate) at one and two years did show a statistically significant benefit for RFA in one RCT. In two other RCTs, local recurrence rates were lower for RFA than for PEI, but this result was not statistically significant in either study.

When the results of two RCTs and one quasi-RCT were pooled, the ablative response was statistically significantly better for RFA than for PEI, although none of the studies reached statistical significance on their own. However, ablative response is a surrogate measure and was reported by tumour rather than by patient so this result should be interpreted cautiously.

RFA compared with TACE

The only comparative study was non-randomised and it found that 50% of RFA patients compared with 30% of TACE patients showed a complete response (not statistically significant), although a statistically significant difference in mortality between the two treatment groups (0% for RFA patients compared with 40% for TACE patients) was seen.

RFA compared with surgical resection

The only comparative study was non-randomised and indicated that there was a higher rate of recurrence and a shorter time interval to recurrence in the RFA group than in the surgical resection group. However, since surgical resection and RFA are usually performed on different groups of patients, it is difficult to compare the two treatment groups.

Cost-effectiveness

RFA is more expensive than PEI across all the various assumptions (such as number of sessions and method of access for RFA). However the range of incremental cost effectiveness ratios is large. The ICER per local recurrence-free survival in the base case (one session of percutaneous RFA compared to one session of PEI; 14% benefit of RFA) was $10,714–17,857; ranging from a low of $6,000–10,000 (high (25%) benefit of RFA) to a high of $215,000–248,333 (low (3%) benefit of RFA) in the sensitivity analyses (both one session of percutaneous RFA compared with one session of PEI).

Metastatic colorectal liver tumours (CLM)

Safety

The safety of RFA for treating CLM is based solely on case series as the only comparative study did not report any safety outcomes. Patients with more tumours (and therefore more RFA sessions) may have a higher complication rate.

Effectiveness

While most of the case series reported high levels of ablation with RFA (90% and above), this surrogate outcome may not reflect long-term effectiveness. Local recurrence rates varied from 4% to 55% and may depend on the method of access used for RFA. The only comparative study suggested that survival from the time of diagnosis was shorter for patients treated with RFA than surgical resection.

Metastatic neuroendocrine liver tumours (NLM)

Safety

The safety of RFA for treating NLM is based solely on case series as the only comparative study did not report any safety outcomes. In five of these case series the complication rates varied from 0% to 11%.

Effectiveness

The only comparative study (RFA, one patient; PEI, one patient) was inconclusive as both patients had incomplete tumour ablation (at two months), and local recurrence (at 18 months). In five case series, local recurrence varied from 0% to 20%.

Recommendations

MSAC recommended that on the strength of evidence pertaining to radiofrequency ablation (RFA) public funding should be supported for the percutaneous treatment of non-resectable hepatocellular carcinoma not being considered for surgical resection.

MSAC recommended that as there is currently insufficient evidence pertaining to RFA for colorectal metastases (CLM) public funding should not be supported at this time for this procedure for treating CLM.

Since there is currently insufficient evidence pertaining to RFA for neuroendocrine liver metastases (NLM), MSAC recommended that public funding should not be supported at this time for this procedure for treating NLM.

– The Minister for Health and Ageing accepted this recommendation on 8 August 2003.

Appendix A MSAC terms of reference and membership

The MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or Affiliation**
Dr Stephen Blamey (Chair)	general surgery
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Paul Craft	clinical epidemiology and oncology
Professor Jane Hall	health economics
Dr Terri Jackson	health economics
Ms Rebecca James	consumer health issues
Professor Brendon Kearney	health administration and planning
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Mr Lou McCallum	consumer health issues
Dr Ewa Piejko	general practice
Professor John Simes	clinical epidemiology and clinical trials
Mr Chris Sheedy	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing
Professor Richard Smallwood	Chief Medical Officer, Commonwealth Department of Health and Ageing
Dr Robert Stable	Australian Health Ministers' Advisory Council representative
Professor Bryant Stokes	neurological surgery
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Supporting committee

Supporting committee for MSAC application 1052

Radiofrequency ablation of liver tumours

Associate Professor Richard King (Chair) Consultant Physician and Gastroenterology	Member of MSAC
Associate Professor Ken Thomson Radiology	Member of MSAC
Professor Bryant Stokes Neurological surgery	Member of MSAC
Ms Rebecca James Consumer Representative	Member of MSAC
Professor Peter Angus Director, Dept of Gastroenterology and Hepatology, Austin and Repatriation Medical Centre	Nominated by the Gastroenterological Society of Australia
Professor Rob Gibson Department of Radiology, Royal Melbourne Hospital	Co-opted Member
Dr Matthew Links Cancer Centre, St George Hospital	Nominated by the Royal Australasian College of Physicians
Dr Samuel Ngan Division of Radiation Oncology, Peter McCallum Cancer Centre	Nominated by the Royal Australasian College of Radiologists
Dr Robert Padbury Divisional Director, Surgical and Specialty Services, Flinders Medical Centre	Nominated by the Royal Australasian College of Surgeons

Appendix C Studies included in the review

Table 11.1 Study profile and quality assessment of HCC RFA comparative studies

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Lencioni *et al* (1999) (includes 1998) *Location*: Pisa, Italy	**1) Percutaneous ethanol injection (PEI)** PEI was used with 22 G multiple-side-hole needles **2) Radiofrequency ablation (RFA)** Percutaneous RFA was used with either 17 G cooled-tip electrode needles or 14 G expandable electrode needles with four retractable lateral exit jack-hooks on the tip Therapeutic response was assessed by dual-phase spiral CT at 4-month intervals Local recurrence is defined as recurrence within or around a tumour considered to have undergone a complete response	Randomised controlled trial (abstract) Method of allocation concealment not stated *Level of evidence*: ii *Intention-to-treat analysis:* Not stated *Basis of patient selection:* Not stated *Eligibility rate:* Not stated *Follow-up:* Range 9–24 months (mean 16.3 [5.1] months, median 14 months) *Lost to follow-up:* Not stated *Study period:* December 1996–November 1999 *Operator details:* Not stated	*Sample size*: 80 patients (114 nodules) **1)** n = 40 (61 nodules) **2)** n = 40 (54 nodules) *Patient diagnosis:* HCC *Mean diameter:* 2.2 [0.6] cm (1–3 cm) *Mean age:* Not stated *Gender mix:* Not stated *Patient co-morbidities:* All patients had either Child-Pugh class A or B liver cirrhosis	*Inclusion criteria:* Either single or multiple (up to three) nodular-type HCC lesions Lesions 3 cm or smaller

Table 11.1 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Shiina *et al* (2000) *Location*: Department of Gastroenterology, University of Tokyo, Japan	Each treatment was repeated until dual-phase helical CT scan confirmed that not only the lesions but the surrounding tissue became nonenhancing **1)** Percutaneous ethanol injection (PEI) **2)** Radiofrequency ablation (RFA) Percutaneous cool-tip electrodes (Radionics, Burlington, Massachusetts, USA)	Randomised controlled trial (abstract) Method of allocation concealment not stated *Level of evidence: ii* *Intention-to-treat analysis:* Not stated *Basis of patient selection:* Not stated *Eligibility rate:* Not stated *Follow-up:* Four months after treatment *Lost to follow-up:* Not stated *Study period:* Not stated *Operator details:* Not stated	*Sample size:* 60 patients (277 sessions) **1)** n = 29 (212 sessions) **2)** n = 31 (65 sessions) There were no significant differences in age, sex, number of lesions, diameter of the largest lesion, and liver function between the two groups *Patient diagnosis:* HCC *Mean age:* Not stated *Gender mix:* Not stated *Patient co-morbidities:* Liver cirrhosis child a or child b	*Inclusion criteria*: Patients ≤3 HCC lesions of ≤3 cm in diameter

Table 11.1 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Olschewski *et al* (2001) *Location:* University Hospital Freiburg, Germany, and University of Pisa, Pisa, Italy	**1)** Percutaneous ethanol injection (PEI) **2)** Radiofrequency ablation (RFA) Percutaneous ultrasound-guided	Randomised controlled trial (abstract) Method of allocation concealment not stated *Level of evidence: II* *Intention-to-treat Analysis:* Not stated *Basis of patient Selection:* Not stated *Eligibility rate:* Not stated *Follow-up:* 1) 22.4{8.6} months 2) 22.9 {9.4} months *Lost to follow-up:* Not Stated *Study period:* Not Stated *Operator details:* Not stated	*Sample size*: 102 patients (142 nodules) **1)** n = 50 (73 nodules) **2)** n = 52 (69 nodules) *Patient diagnosis:* HCC *Mean diameter:* Not stated *Mean age:* Not stated *Gender mix:* Not stated *Patient co-morbidities:* Not stated	*Inclusion criteria:* HCC nodules not exceeding 5 cm in diameter

Note: {} indicates unit of measurement not defined

Table 11.1 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Kurokohchi *et al* (2002) *Location*: Third Department of Internal Medicine, Kagawa Medical University, Kagawa, Japan	Patients were treated with either PEI combined with RFA or RFA alone RFA in this phase was performed using RITA-500PA system (RITA Medical Systems, Mountain View, CA USA). Patients were randomised to either treatment group **1)** Percutaneous ethanol injection (PEI) combined with percutaneous radiofrequency ablation (RFA) Mean ethanol injected (mL) 6 (range 2–15) **2)** Percutaneous RFA PEI combined with RFA or RFA alone was performed under real-time ultrasonography guidance. For combined PEI and RFA treatment, a 15-gauge RFA needle was inserted into the centre of the tumour and 99.5% ethanol injected slowly into the lesion through the side hole of the handpiece. Amounts of ethanol injected into the tumours were determined according to the size of the tumours and were always kept below the estimated double volume of the tumours. Ethanol injection was ceased if resistance to the injection was felt. RFA was performed immediately after ethanol injection for 10 min once the electrodes were deployed by applying the maximum allowable output power of 50 W (temperature control mode and control power delivery fixed to the 'L' mode). The needle electrodes were retracted and the needle rotated 45° and RFA was performed again for more than 10 min Five to seven days after RFA, dynamic contrast-enhanced computed tomograph (CT) was performed	Randomised controlled trial Patients were divided randomly in one of the two treatment groups *Level of evidence: II* Intention-to-treat Analysis: Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated Follow-up: 6–27 months (mean 18 months) *Lost to follow-up:* Not stated Study period: Not stated *Operator details:* Not stated	*Sample size*: 39 **1)** n = 19 **2)** n = 20 *Patient diagnosis:* Biopsy proven HCC *Mean size:* **1)** 2.6 cm (range 1–5) **2)** 1.9 cm (range 1–3) *Mean age:* **1)** 66 years (range 51–80) **2)** 68 years (range 54–80) *Gender mix:* **1)** M/F = 14 (74%)/5 (26%) **2)** M/F = 13 (65%)/7 (35%) *Patient co-morbidities:* Liver Cirrhosis Classification *Child-Pugh class A* **1)** 14 (74%) **2)** 14 (70%) *Child-Pugh class B* **1)** 5 (26%) **2)** 6 (30%)	Not stated

Table 11.1 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Livraghi *et al* (1999) (includes 1998) *Location*: Department of Radiology, Ospedale Civile, Via C. Battisti Vimercate, Italy; Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; Department of Internal Medicine, Ospedale San Biagio, Clusone, Italy; and Department of Radiology, Ospedale Generale, Busto Arsizio, Italy *Continued*	Pre-treatment US and unenhanced and dual-phase spiral CT was performed with injection of 140 mL of iopamidol at a rate of 3 mL/second. The entire liver was scanned twice In 68 patients (36 PEI; 32 RFA) HCC was confirmed with US-guided needle biopsy. Biopsy was not performed on patients in whom US and CT findings consistently indicated HCC and an α-fetoprotein level >200 μ/L or abnormal des-γ-carboxy-prothrombin levels Procedures performed under US guidance Note: The two patient groups were comparable for age, sex, type of cirrhosis, Child-Pugh class, number of lesions, lesion diameter, type of HCC (nodular, contiguous multinodular, or infiltrating), α-fetoprotein level, and des-γ-carboxy-prothrombin (DCP) level (p >0.05) **1)** Percutaneous ethanol injection (PEI) Patients who lived within two hours from the hospital No sedative or local analgesia was administered A 20 cm long, 21 gauge needle with a closed conical tip and three terminal side holes (PEIT needle; Hakko, Tokyo, Japan) was used to inject 1–4 Ml ethanol per session. Ethanol diffusion was monitored by real-time US. The needle was held in place 20–30 seconds after completion of the injection to prevent reflux of ethanol and then withdrawn. Treatment ended when perfusion was considered to be total. Two to six sessions per lesion (1 treatment cycle) were performed according to lesion size. Treatments were performed two times per week and after treatment patients were observed for 1–2 hours	Multicentre-randomised controlled trial Patients were allocated into treatment groups 1 or 2 according to their proximity to the hospital *Level of evidence: III-1* *Intention-to-treat Analysis:* Not stated *Basis of patient selection:* Not stated *Eligibility rate:* Not stated *Follow-up:* 4–28 months (mean 10 months). 39/86 patients have undergone CT eight months or later *Lost to follow-up:* Not stated *Study period:* July 1995–July 1997 *Operator details:* PEI performed by one radiologist and one nurse RFA performed by two radiologists. CT scans were interpreted, by means of consensus, by two radiologists who also performed the treatments and were not blinded	*Sample size*: 86 patients (112 nodules) **1)** n = 44 (60 nodules); **2)** n = 42 (52 nodules) *Patient diagnosis:* Biopsy proven HCC *Mean diameter:* **1)** 2.5 cm (range 1.1 – 3). **2)** 2.3 cm (range 1.2 – 3) *Mean age: **1)** 68.9 years **2)** 67.8 years* *Gender mix:* **1)** M/F = 33 (75%)/11 (25%) **2)** M/F = 31 (74%)/11 (26%) *Patient co-morbidities:* *Aetiology of underlying liver disease* Hepatitis C virus positive PEI 34 patients RFA 33 patients Hepatitis B surface antigen positive PEI 6 patients RFA 5 patients Alcoholic PEI 3 patients RFA 3 patients Note: One patient in each group had cirrhosis of unknown origin *Liver cirrhosis classification* Child-Pugh class A PEI 38 patients RFA 39 patients Child-Pugh class B PEI 6 patients RFA 3 patients	*Inclusion criteria:* Patients with lesions $\leq$3 cm *Exclusion criteria:* Patients with a platelet count <40 x 10^9/L or less than 40% thrombin activity.

Table 11.1 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Livraghi *et al* (1999)	**2)** Radiofrequency ablation (RFA) Patients who lived more than two hours from the hospital One hour before being treated patients received an oral sedative and intravenous analgesia A 20 cm long, 18 gauge, cooled-tip electrode with a 2–3 cm-long exposed metallic tip (Radionics, Burlington, Massachusetts, USA) was attached to a 500-kHz generator (series 3; Radionics) capable of producing 140W. Local temperature and tissue impedance was measured. Saline (0°C) was infused into the cooled tip of the electrode to maintain a tip temperature of 20–25°C. For each treatment session, a single electrode was positioned at the centre of the tumour and one application was used for each tumour for 10–12 minutes (one treatment cycle) After treatment, patients were hospitalised for 48 hours and discharged if complication free Patient levels of transaminase, alkaline phosphatase, bilirubin, electrolytes, haemoglobin, fibrinogen, prothrombin activity, and complete blood cell count were measured before treatment, 24 hours, 48 hours, and one month after treatment		*Mean α-fetoprotein level (ng/mL)* PEI 63 RFA 94 *Mean DCP level (ng/mL)* PE I 3.7 RFA 4.9 *Type of HCC* Nodular PEI 46 patients RFA 41 patients Contiguous multinodular PEI 3 patients RFA 2 patients Infiltrating PEI 11 patients RFA 9 patients	

Table 11.1 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Ikeda *et al* (2001) *Location* Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, Tokyo, Japan	Before being treated all patients were examined by ultrasonography (US), computed tomography (CT) and angiography. Diagnosis of HCC was based on biopsy (82%) or CT and angiography (18%) **1)** Percutaneous ethanol injection (PEI) A 22-gauge needle (Top, Tokyo, Japan) was introduced percutaneously into the tumour and/or its marginal area under US guidance. 2–8 ml of absolute ethanol was injected each time, depending on ethanol diffusion, which was monitored by real-time US. Injection was repeated 1–2 times per week for 4–6 sessions with the number of session varying with tumour size **2)** Percutaneous radiofrequency ablation (RFA) RFA was delivered using the RITA 500PA system (RITA Medical Systems, Mountain View, CA, USA). 15-gauge expandable needle electrodes with thermometers on the tips were used RFA needles were introduced percutaneously under US guidance into the centre of the tumour and the hooks deployed. Temperature was maintained at ~ 100°C at the hook tips for 8 minutes. The hooks were then turned around the major axis at an angle of 45° and RFA performed again. At the end of the procedure, the hooks were retracted and the electrode was removed while coagulating the tract using 20W of power. The procedure was repeated once weekly. If residual tumour tissue was identified on contrast-enhanced CT 3–7 days after RFA, an additional session was performed Note: Before RFA was introduced all patients were treated with PEI. After RFA introduction, all patients except those with HCC nodules that were difficult to approach or located in unsafe areas for RFA, were treated with this technique	Comparative study with concurrent control Prior to February 1999, all patients were treated with PEI. After February 1999, all patients were treated with RFA except those with lesions that were difficult to approach or located in unsafe areas *Level of evidence: III-2* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* **1)** Median 30.8 months (range 5.2–69.8) **2)** Median 11.4 (range 1.4–20.7) p<0.01 *Lost to follow-up:* Not stated *Study period:* **1)** January 1995–January 2000 **2)** February 1999–January 2000 *Operator details:* Not stated	*Sample size*: 119 consecutive patients **1)** n = 96 **2)** n = 23 *Patient diagnosis:* HCC *Median size* **1)** 1.9 cm (range 1.0–3.0) **2)** 1.8 cm (range 1.4–2.9) p = 0.39 *Median age:* **1)** 66 years (range 23–81) **2)** 62 years (range 50–83) p = 0.46 *Gender mix:* **1)** M/F = 64 (67%)/32 (33%) **2)** M/F = 18 (78%)/5 (22%) p = 0.41 *Patient co-morbidities:* Not stated	*Inclusion criteria:* Solitary HCC <3 cm in diameter Patients who had not received any prior treatment other than hepatic resection (% of patients receiving prior hepatic resection not stated)

Table 11.1 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Catalano *et al* (2000) Includes 1999 *Location* Department of Radiology, S Maria della Grazie Hospital, via Domitiana Loc. La Schiana, Pozzuoli, and Department of Diagnostic Imaging, Psi Napoli, via Ciccarelli 1, Naples, Italy	One to five nodules per patient (mean = 1.9) with a diameter ranging from 1 to 8 cm (mean = 4.2 cm) All patients treated percutaneously for HCC **1)** Multiple session percutaneous ethanol injection (MS-PEI) **2)** Single session percutaneous ethanol injection (SS-PEI) **3)** Radiofrequency ablation (RFA) Cooled-tip electrode and expandable electrode Note: This study took place during a similar study period as in Catalano *et al* (2001)	Retrospective comparative review (historical control group and therefore non-randomised) *Level of evidence: III-3* *Intention-to-treat Analysis:* Not stated *Basis of patient Selection:* 116 consecutive patients *Eligibility rate:* Not stated *Follow-up:* CT performed 3–28 days after last session (mean = 18 days). The patients were followed for 12–44 months (median 22 months) *Lost to follow-up:* 8 patients died during the observation period *Study period:* December 1996–October 1999 *Operator details:* Not stated	*Sample size:* 102 patients (177 nodules) **1)** n = 56 (98 nodules) **2)** n = 14 (31 nodules) **3)** n = 32 (48 nodules) *Patient diagnosis:* HCC *Mean diameter:* **1)** 2.8 cm **2)** 4.6 cm **3)** 3.8 cm *Mean age:* 56 years (range 38–76) *Gender mix:* M/F = 68 (59%)/48 (41%) *Patient co-morbidities:* Not stated	Not stated

Table 11.1 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Catalano *et al* (2001) *Location* Department of Radiology, S Maria della Grazie Hospital, via Domitiana Loc. La Schiana, Pozzuoli, Naples, Italy	All patients underwent pre-treatment CT and post-treatment CT at 3–26 days after their final ablation session (mean = 17 days) **1)** Multiple session percutaneous ethanol injection (MS-PEI) **2)** Single session percutaneous ethanol injection (SS-PEI) **3)** Radiofrequency ablation (RFA) Cooled-tip electrode and expandable electrode Lesions still necrotic, those with local recurrence, and new heterotopic lesions were defined and classified in four different patterns (Couinaud's segmental anatomy) Solid tissue, enhancing at arterial phase acquisition, within the edge of a treated nodule Solid tissue, enhancing at arterial phase acquisition, around a necrotic treated nodules and in continuity with its border Solid tissue, enhancing at arterial phase acquisition, within the same segment of the necrotic treated nodule Solid tissue, enhancing at arterial phase acquisition, within different liver segments from the necrotic treated nodule Nodules showing pattern A or B were considered locally recurring and were counted as single sites of relapse. Cases with pattern C and D were counted as new nodules and each was noted a site of relapse. Nodules showing more than one feature were considered as having a mixed pattern	Retrospective comparative review (historical control group and therefore non-randomised) Level of evidence: III-3 *Intention-to-treat Analysis:* Not stated *Basis of patient Selection:* 67 were retrospectively selected out of 144 consecutive patients initially treated with ablative procedures for HCC *Eligibility rate:* Not stated *Follow-up:* 3–26 days after last ablation session (mean = 17 days) *Lost to follow-up:* Not Stated *Study period:* December 1996–November 1999 *Operator details:* Hardcopy images were retrospectively evaluated by two nonblinded radiologists who arrived at a consensus	*Sample size:* 61 patients (109 nodules) **1)** n = 40 (73 nodules) **2)** n = 5 (11 nodules) **3)** n = 16 (25 nodules) *Patient diagnosis:* Pathologically proven HCC *Nodules/patient:* **1)** one–four **2)** one–three **3)** one–three *Mean diameter:* **1)** 2.9 cm **2)** 4.8 cm **3)** 3.9 cm *Mean age:* M range 41–76yrs F mean 57yrs *Gender mix:* M/F = 44 (66%)/23 (34%) *Patient co-morbidities:* Liver cirrhosis	*Inclusion criteria:* Patients with pathologically proven HCC and with a final diagnosis of tumour recurrence who had undergone one or more helical computed tomography (CT) studies after last treatment session *Exclusion criteria:* Patients with one or more nodules showing residual viable tumour on post-treatment CT examination

Table 11.1 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Livraghi *et al* (2000) *Location* Vimercate, Italy	Study conducted at 2 centres 20 matched patients in regards to age, Child class, total number of tumours, mean tumour size, size of largest tumour treated, α-fetoprotein levels and bilobar location **1)** Transarterial chemoembolisation (TACE) **2)** Radiofrequency ablation (RFA) Tumours treated with internally-cooled electrodes (Radionics, Inc., Burlington, Massachusetts, USA) Access method not stated Note: patients were recruited over 3 years at 2 centres	Non-randomised retrospective comparative study (abstract) *Level of evidence: III-3* *Intention-to-treat analysis:* Not stated *Basis of patient selection:* Not stated *Eligibility rate:* Not stated *Follow-up:* 12–36 months *Lost to follow-up:* Not stated *Study period:* Over three years *Operator details:* Not stated	*Sample size:* 20 patients (77 nodules) **1)** n = 10 (40 nodules) **2)** n = 10 (37 nodules) *Patient diagnosis:* Multi-focal HCC *Mean size:* **1)** 2.4 cm **2)** 2.5 *largest tumour treated:* **1)** 4.8 cm **2)** 4.1 cm *Mean age:* **1)** 68.6 years **2)** 67.8 years *Gender mix:* Not stated *Patient co-morbidities:* Liver cirrhosis α-fetoprotein level >200 ng/mL TACE 3 patients RFA 2 patients *Patient details:* Bilobar location TACE 2 patients RFA 2 patients	*Inclusion criteria:* Child class A

Table 11.1 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Yu *et al* (2002) *Location* Department of Surgery, and Diagnostic Radiology, and Internal Medicine, Chonbuk National University Medical School, Korea	**1)** Surgical resection **2)** Radiofrequency ablation (RFA)	Multicentre cohort study (comparative study but may have a historical control group and therefore would be retrospective and non-randomised) (abstract) *Level of evidence:* III-3 *Intention-to-treat Analysis:* Not stated *Basis of patient Selection:* Not stated *Eligibility rate:* Not stated *Follow-up:* Not stated *Lost to follow-up:* Not stated *Study period:* **1)** October 1990–February 2001 **2)** March 1999–May 2001 (38 month RFA study period) *Operator details:* Not stated	*Sample size:* 145 patients **1)** n = 88 (over entire surgical resection study period) (n = 48 over 38 month RFA study period) **2)** n = 57 *Patient diagnosis:* HCC *Mean age:* Not stated *Gender mix:* Not stated *Patient co-morbidities:* Not stated	Not stated

Table 11.2 Study profile and quality assessment of CLM RFA comparative studies

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Gillams and Lees (2001) *Location* London, England	Patients received pre-therapeutic contrast enhanced computed tomography Exploratory laparotomy with a view to resection was performed in some patients Patients found to have more extensive disease a laparotomy were still included in the study 3 patients with tumours >10 cm received systemic chemotherapy (not indicated which treatment arm patients were assigned) **1)** Surgical resection **2)** Radiofrequency ablation (RFA)	Prospective non-randomised comparative Method of allocation to RFA based on tumour location, previous hepatic resection, concomitant ill health, known extrahepatic disease, or patient preference Only data from patients that underwent RFA or resection reported *Level of evidence: III-2* *Intention-to-treat Analysis:* Analysis was performed by intention to treat *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* 6–27 months (mean 18 months) *Lost to follow-up:* Not stated *Study period:* June 1998 and May 2001 *Operator details:* Not stated	*Sample size:* 45 **1)** 16 2) 30 *Patient diagnosis:* Solitary CLM *Number of nodules:* Not stated *Mean size:* Could not be separated from patients undergoing other forms of treatment *Mean age:* Could not be separated from patients undergoing other forms of treatment *Gender mix:* Could not be separated from patients undergoing other forms of treatment *Patient co-morbidities:* Not stated	Not stated

Table 11.3 Study profile and quality assessment of CLM RFA case series

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Bleicher *et al* (2002) *Location* Surgical Oncology, The John Wayne Cancer Institute, and Cancer Centre, Century City Hospital, California, USA	Open/percutaneous/laparoscopic radiofrequency ablation (RFA) Percutaneous RFA was performed under computed tomography (CT) guidance and intraoperative ultrasound was used for the laparoscopic and open approaches. Each lesion was ablated at a temperature of 100°C for 25 minutes and overlapping ablations were performed for lesions >3 cm in size	Case series Only data from patients with metastatic colorectal (CLM) liver carcinoma reported *Level of evidence:* IV *Intention-to-treat Analysis:* Not stated *Participation rate:* Not state d *Eligibility rate:* Not state *Follow-up:* Mean 13.7 month *Lost to follow-up:* Not state *Study period:* 1997 and 200 *Operator details:* Not state	Sample size: 54 *Patient diagnosis:* CLM *Number of nodules:* Could not be separated from other tumour types *Mean size:* Could not be separated from other tumour types *Age:* Could not be separated from other tumour types *Gender mix:* Could not be separated from other tumour types *Patient co-morbidities:* Not stated	*Inclusion criteria:* Patient with unresectable hepatic lesions

Table 11.3 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Chung *et al* (2001a) *Location* John Wayne Cancer Institute, Saint John's Health Center, Santa Monica, CA, USA	Laparoscopic radiofrequency ablation (RFA) All patients underwent complete history and physical examination, serum tests, chest radiography, and high resolution computed tomography (CT) scanning of the chest, abdomen, and pelvis with thin cuts through the liver. The livers of some patients were examined by fluorodeoxyglucose positron emission tomography (PET) scan and/or magnetic resonance imaging (MRI) Laparoscopy was used to evaluate all patients for extrahepatic disease All eight liver segments were also examined by Laparoscopic ultrasonographic For RFA a 15-gauge needle with retractable electrodes (RITA Medical Systems, Mountain View, California, USA) was used. The RFA needle was placed percutaneously in the abdomen and directed into the centre of the lesion under real-time ultrasound guidance. The electrodes were then deployed, and 50 W of alternating power delivered to achieve 100°C for 10 minutes. Lesions >3 cm were treated with overlapping ablations. During the second year of the study, larger lesions were treated using a Cool-Tip electrode (Radionics, Burlington, Massachusetts, USA) On completion of RFA, the probe tract was cauterised as the needle was removed Patients were followed up with CT scans all of which were reviewed by a single experienced radiologist	Prospective case series Only data from patients with metastatic colorectal (CLM) or neuroendocrine (NLM) liver carcinoma reported *Level of evidence: IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Mean 11.3 months *Lost to follow-up:* Not stated *Study period:* November 1997–November 1999 *Operator details:* Not stated	*Sample size:* 9 CLM 6 NLM 3 *Patient diagnosis:* metastatic liver carcinoma *Mean number of nodules:* CLM 2.3 (range 1–3) NLM 4.7 (range 2–7) *Mean size (of largest lesion):* CLM 2.5 cm (range 2–3) NLM 2.8 (2.5–3) *Mean age:* Could not be separated from total patients *Gender mix:* Could not be separated from total patients *Patient co-morbidities:* All patients had received some form of prior adjuvant therapy Some patients had undergone prior abdominal surgery	*Inclusion criteria:* Patients with unresectable primary or metastatic hepatic malignancies with no evidence of extrahepatic disease Patients over 18 years of age and with a life expectancy of at least four years Note: tumours were defined as unresectable on the basis of their number (>4 lesions), distribution (bilobar disease), proximity to major vascular and/or biliary structures, and attendant co-morbidities *Exclusion criteria:* Pregnancy, evidence of active infection, and recent (<30 days) chemotherapy/biotherapy/radiotherapy Patients who could not undergo laparoscopy or laparotomy Patients with hepatic tumours occupying more than 40% of the liver Patients who had received a hepatic arterial infusion pump

Table 11.3 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Cuschieri *et al* (1999) *Location* Department of Surgery, Ninewells Hospital and Medical School, University of Dundee, Scotland	**Laparoscopic radiofrequency ablation (RFA)** Pre-treatment imaging studies were real time US and helical CT. Non-enhanced CT and enhanced CT 30- and 120-seconds after injection of contrast material CLM confirmed in all patients by US-guided needle biopsy of solitary nodule or the largest nodule in patients with more than one nodule Laparoscopic ultrasound guided RFA was used with the Zomed 500 RF generator (460 kHz) with RITA electrosurgical needles (Zomed International, Mountain View, California, USA). The RFA needle was inserted percutaneously into the tumour under contact ultrasound guidance and the electrodes deployed. RFA was ideally performed so as to ablate a zone that exceeded the limits of the tumour by a minimum of 0.5 cm as detected by intraoperative ultrasound. The power delivery was set at 50W and all lesions were heated to a temperature >90°C for 10 minutes. Following RFA, the lesion was again scanned by contact ultrasound Nodules <2.5 cm — single insertion of RFA needle Nodules >2.5 cm two-site RFA performed by sequential needle insertion	Prospective case series Only data from patients with metastatic colorectal (CLM) liver carcinoma reported *Level of evidence: IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* 6–20 months *Lost to follow-up:* Not stated *Study period:* Not stated *Operator details:* Not stated	*Sample size: 8* *Patient diagnosis:* CLM *Number of nodules:* 32 lesions treated (46 in total) *Mean size:* Not stated *Mean age:* 40–71 years *Gender mix:* Not stated *Patient co-morbidities:* Four patients had undergone prior systemic infusion chemotherapy with high dose 5-FU/folinic acid All patients had bilateral disease	Not stated

Table 11.3 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Kosari *et al* (2001) *Location* Department of Surgery, Department of Radiology, Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota, USA	Open/percutaneous/laparoscopic radiofrequency ablation (RFA) The RITA (RITA Medical Systems, Mountain View, California, USA) model 70 was used until April 2000; The RITA Star Burst XL was used thereafter Percutaneous RFA was used for lesions that were not on the surface of the liver and not adjacent to a hollow viscus or the diaphragm/lung base — otherwise a laparoscopic RFA was used. If other intra-abdominal procedures were performed, an open approach was used The RFA electrode was inserted to the tumour under ultrasound (US) or computed tomography (CT) guidance and the needles deployed. Power was applied at 100–150W (350–500 MHz). Once a tissue temperature of 80–110°C was reached, RFA was performed, from 12 minutes (3 cm lesions) up to 20 minutes (5 cm lesions), while monitored by US or CT imaging. The needle tract was ablated by removal of the probe. For laparoscopic or open RFA, needle tract haemostasis was achieved with conventional electrocautery Concurrent procedures performed with open RFA included: liver resection, hepatic artery pump insertion, bowel resection, tumour resection	Case series Only data from patients with metastatic colorectal (CLM) or neuroendocrine (NLM) liver carcinoma reported *Level of evidence: IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Median 19.5 months (range 6–34). Unable to determine follow-up for CLM or NLM separately *Lost to follow-up:* Not stated *Study period:* November 1998–February 2001 *Operator details:* Not stated	*Sample size:* CLM 18 (5 patients had six or more lesions) NLM (carcinoid) 7 *Patient diagnosis:* CLM or NLM *Number of nodules:* CLM 76 NLM 29 *Mean size:* CLM 1.7 cm (range 0.38–4.5) NLM 2.2 cm *Mean age:* Could not be separated from other tumour types *Gender mix:* Could not be separated from other tumour types *Patient co-morbidities:* 3 CLM patients had medical contraindication to major surgery (not stated for NLM) 5 CLM patients had anatomical contraindication (not stated for NLM) 6 CLM patients with RFA in conjunction with another procedure (not stated for NLM)	*Exclusion criteria:* Patients with unresectable extrahepatic disease. Patients with technically resectable disease Inability to achieve an ablation margin of at least 0.5 cm All lesions >6 cm, for percutaneous therapy lesions >5 cm Tumours adjacent to a sectoral, or larger, bile duct

Table 11.3 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Kuvshinoff *et al* (2002) *Location* Division of Surgical Oncology, Ellis Fishel Cancer Center, University of Missouri, Columbia, Missouri, USA Note: Group is part of a phase II trials with RFA in conjunction with hepatic artery infusion chemotherapy.	Open/percutaneous/laparoscopic radiofrequency ablation (RFA) Patients underwent ultrasound (US) guided RFA either laparoscopically, percutaneously, or by open laparotomy. RFA was performed with the RITA system (RITA Medical Systems, Mountain View, California, USA). Tumour ablation was performed by heating to 100°C for eight–ten minutes using 50–150W of power. A cool-down period of 30 seconds was monitored to ensure that temperatures exceeded 65°C. Lesions required overlapping ablations. Ideally a 1 cm margin of normal parenchyma surrounding the lesion was achieved. During open laparotomy, hepatic vascular inflow occlusion (Pringle manoeuvre) was used when target temperatures could not be reached. Choice of laparoscopically, percutaneously, or open laparotomy. RFA was based on surgical considerations (location of liver lesions, need for hepatic or extrahepatic resection, and prior abdominal surgeries). 5 NLM patients had RFA combined with resection. Note: percutaneous access worse than open or laparoscopic for all tumour types.	Case series Only data from patients with metastatic colorectal (CLM) or neuroendocrine (NLM) liver carcinoma reported *Level of evidence: IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Follow up to 16 months *Lost to follow-up:* Not stated *Study period:* March 1999–April 2001 *Operator details:* Not stated	*Sample size:* 15 CLM 6 NLM *Patient diagnosis:* CLM *Number of nodules:* Could not be separated from other tumour types *Mean size:* Not stated *Mean age:* Could not be separated from other tumour types *Gender mix:* Could not be separated from other tumour types *Patient co-morbidities:* 3/15 patients had synchronous resection of extrahepatic disease All CLM patients had extensive preRFA chemotherapy	*Inclusion criteria:* Patients with hepatic malignancies not considered appropriate for resection (based on a combination of factors including the distribution of tumours, present or suspected extrahepatic disease, prohibitive co-morbidities or advanced age, liver transplant listing or severe underlying cirrhosis, or the need for a synchronous extrahepatic procedure)

Table 11.3 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Machi *et al* (2000) *Location* Department of Surgery, University of Hawaii at Manoa, Kuakini Medical Center and Queen's Medical Center, Hawaii, USA	Open Radiofrequency ablation (RFA) All patients underwent preoperative blood tests, imaging studies (including computed tomography) Laparotomy was performed through a midline abdominal incision under general anaesthesia. After surgical exploration, intraoperative ultrasound (US) was used. The number, size and location of the CLM tumours were recorded. One to two CLM tumours were biopsied Resection of the primary colorectal cancer was performed in a standard manner (lower anterior or anterior resection). 4 patients had RFA performed simultaneously with colorectal resection, 5 patients had RFA immediately after colorectal resection For RFA a 460 KHz alternating current generator with a 14- or 15-gauge needle was used (4, 7, or 9 electrodes) (RITA Medical Systems, Mountain View, California, USA). The needle was inserted into the tumour and the electrodes deployed under intraoperative US. The average target temperature at the electrode tips was set at 100–105°C Hepatic vascular inflow occlusion (Pringle manoeuvre) was used when target temperatures could not be reached. At the target temperature, the current was delivered for 6–25 minutes, depending on the ablation size of 3–5 cm. The RFA process was monitored by intraoperative US and continued to achieve an ablation margin of 1 cm or more. For larger tumours, multiple overlapping ablations were performed. At completion of procedure, the RFA needle tract within the liver parenchyma was cauterised during withdrawal of the needle Some patients underwent repeat RFA operations one to three times for recurrent tumours All patients received adjunctive systemic chemotherapy	Case series *Level of evidence:* IV *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Mean 12.6 months (range 4–21) *Lost to follow-up:* Not stated *Study period:* August 1997–March 2000 *Operator details:* Not stated	*Sample size:* 9 (37 nodules) *Patient diagnosis:* Biopsy proven colorectal liver metastases (CLM) *Number of nodules:* Mean 4.1 (range 1–9) *Mean size:* 3.6 cm (range 0.7–7) *Mean age:* 67.2 years *Gender mix:* M/F = 3/6 *Patient co-morbidities:* Preoperative tumour marker levels (CEA) were elevated in all patients (mean 267μg/L, range 5–1330) All patients had RFA performed in conjunction with resection of the primary colorectal cancer 2 patients had locally advanced cancers, which required pelvic exenteration and combined partial cystectomy. One patient had several peritoneal metastatic nodules, which were excised grossly	*Inclusion criteria:* Patients with synchronous CLM and non resected primary colorectal cancer

Table 11.3 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Pearson *et al* (1999) *Location* Department of Surgical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, Texas, and the Department of Surgical Oncology, Allegheny Hospital, Pittsburgh, Pennsylvania, USA, and Department of Surgical Oncology, G. Pascale National Caner Institute, Naples, Italy	Open radiofrequency ablation (RFA) All patients underwent baseline evaluation including a history and physical examination; serum laboratory tests including serum tumour markers; computed tomography (CT) or magnetic resonance imaging of the abdomen and pelvis; and a chest radiograph RFA was used surgically during an open operative procedure (RF 200 generator system, 100W, Radiotherapeutics, Mountain View, California, USA). The 15-gauge needle was placed into the tumour under ultrasound guidance. The electrodes were deployed and RFA and power initially applied at 50W and then increased in 10W increments at 1, 2, 3, and 4 minutes to a maximum power of 90W. Power and tissue impedance was monitored during the procedure and continued at maximum power until tissue impedance increased to the point when power output fell rapidly (roll-off). After a 20 second pause, power was reapplied at 75% of maximum power until roll-off occurred again. Ablation was performed to achieve a 1 cm margin necrosis surrounding the tumour. For lesions ≥3 cm multiple ablations were performed Some patients did undergo resection of disease in one lobe and RFA of tumour in the remaining lobe	*Case series* Only data from patients with metastatic colorectal (CLM) liver carcinoma reported *Level of evidence: IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Median 15 months *Lost to follow-up:* Not stated *Study period:* January 1992. Completion date unclear *Operator details:* Not stated	*Sample size:* 46 *Patient diagnosis:* Histologically confirmed CLM *Number of nodules:* Could not be separated from other tumour types *Mean size:* Could not be separated from other tumour types *Mean age:* Could not be separated from other tumour types *Gender mix:* Could not be separated from other tumour types *Patient co-morbidities:* Not stated	*Inclusion criteria:* Patients with CLM not considered appropriate for resection based on the number or bilobar location of tumours, tumour proximity to major vascular structures, and/or presence of cirrhosis with functional hepatic reserve that was inadequate to tolerate major hepatic resection Patients must have had a life expectance of at least 3 months and may have failed all other therapeutic modalities or have had tumour abutting a major portal or hepatic vein branch or the inferior vena cava but must not have received chemotherapy or radiation therapy for at least 4 weeks prior to RFA, clinical or radiographic evidence of extrahepatic disease, a history of hepatic encephalopathy, no altered mental status, minimal or ascites, no active infection *Exclusion criteria:* Patient were excluded tumour involved the main right or left bile duct (or both)

Table 11.3 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Rossi *et al* (1996) *Location* Department of Gastroenterology, Department of Radiology, Department of Pathology, Hospital of Piacenza, Piacenza, and Department of Radiology, Department of National Cancer Institute, Milano, and Department of Biostatistics, Verona, Italy, and ZoMed International, California, USA	**Percutaneous radiofrequency ablation (RFA)** All patients underwent sonography and dynamic computed tomography RFA was used with a 480 kHz generator system (Radionics, Burlington, Massachusetts; ZoMed International, Mountain View, California, USA). A monopolar electrode was inserted into the tumour under sonographic guidance (maximum 6 insertions per session). The temperature at the electrode tip was maintained at 90°C for 120 seconds. If a bipolar electrode was used, the two electrodes were held in parallel and inserted 2 cm apart in the tumour under sonographic guidance (maximum 2 insertions per session). A temperature of 90°C was maintained at the needle tips for 20 minutes Once RFA was complete, the generator was turned off and the electrodes removed. If multiple sessions were required, they were performed once or twice a week. For tumours <3 cm, an ablation area of approximately twice the tumour volume was planned. For tumours >3 cm, the number of treatment was determined by imaging findings	*Case series* Only data from patients with metastatic colorectal (CLM) liver carcinoma reported *Level of evidence: IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Mean 17.5 months *Lost to follow-up:* Not stated *Study period:* March 1991–July 1995 *Operator details:* Not stated	*Sample size:* 6 *Patient diagnosis:* Histologically confirmed CLM *Number of nodules:* Could not be separated from other tumour types *Mean size:* Could not be separated from other tumour types *Age:* Range 57–66 years *Gender mix:* Could not be separated from other tumour types *Patient co-morbidities:* 2 patients had delayed surgery due to temporary high risk and, within 35 days of RFA, underwent surgery	*Inclusion criteria:* Presence of a single tumour not >3.5 cm in diameter or not more than three nodules, none of which exceeded 3 cm in diameter Patients must not have had extrahepatic disease

Table 11.3 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Solbiati *et al* (2001a, b) Includes Solbiati *et al* 2001c (n = 109) and 1999 (n = 98) *Location* Department of Radiology, Ospedale Generale, Busto Arsizio, and Department of Radiology, Ospedale Civile, Vimercate, Italy, and Beth Israel Deaconess Medical Center, Boston, Massachusetts, and Decision Analysis and Technology Assessment Group, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts, Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts, USA	**Percutaneous radiofrequency ablation (RFA)** Either single-electrode or triple-clustered cool-tip electrodes (Radionics, Burlington, Massachusetts, USA) were used. Treatments lasted no more than 45 minutes each Repeat treatments were performed when partial necrosis was achieved or when local recurrence or new metastases were observed (total 223 sessions). Multiple lesions were often treated in a single session Note: Solbiati *et al* (2001b) (n = 117) is a subset of Solbiati *et al* (2001a) (n = 158)	*Case series* Only data from patients with metastatic colorectal (CLM) liver carcinoma reported *Level of evidence: IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Mean 20 months (up to 61 months) *Lost to follow-up:* Not stated *Study period:* Started July 1995 Completion date not stated *Operator details:* Not stated	*Sample size:* 158 *Patient diagnosis:* CLM *Number of nodules:* 276 *Mean size:* 2.8 cm (range 0.5–9) *Mean age:* 64.5 (range 34–86) *Gender mix:* Not stated *Patient co-morbidities:* Patients had previously resected colorectal malignancies Previous metastasectomy 13% Co-morbidity and/or extensive disease 87%	*Inclusion criteria:* Patients with CLM not considered appropriate for resection

Table 11.4 Study profile and quality assessment of NLM RFA comparative studies

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Mazziotti *et al* (2001) *Location* Clinica Chirurgica 2, Policlinico S. Orsola, University of Bologna, Italy	**1)** Percutaneous ethanol injection (PEI) combined with percutaneous radiofrequency ablation (RFA) The number of treatment sessions ranged from two to 21 cycles **2)** Percutaneous RFA RFA was administered percutaneously. The number of treatment session ranged from two to three cycles All patients underwent chest and abdominal computed tomography (CT) scan. The primary tumour had previously been removed in all patients 2 NLM patients, 1 underwent RFA and 1 underwent PEI/RFA 1 patient received systemic chemotherapy (not indicated which treatment arm patients were assigned) Both patients underwent surgery after RFA, or RFA/PEI	Prospective non-randomised comparative Method of allocation to either PEI/RFA or RFA not stated Only data from patients with metastatic neuroendocrine (NLM) liver carcinoma reported *Level of evidence: III-2* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Not stated *Lost to follow-up:* Not stated *Study period:* 1982 and August 1997 *Operator details:* Not stated	*Sample size:* 2 *Patient diagnosis:* NLM *Number of nodules:* NLM 3 *Mean size:* Could not be separated from patients undergoing other forms of treatment *Mean age:* Could not be separated from patients undergoing other forms of treatment *Gender mix:* Could not be separated from patients undergoing other forms of treatment *Patient co-morbidities:* Not stated	*Exclusion criteria:* Patients with extrahepatic, pulmonary, or lymph node diffusion of the tumour

Table 11.5 Study profile and quality assessment of NLM RFA case series

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Berber *et al* (2002) *Location* Department of General Surgery, The Cleveland Clinic Foundation, Ohio, USA	Percutaneous radiofrequency ablation (RFA) (laparoscopically-guided) Diagnostic laparoscopy was performed with biopsy of any suspicious extrahepatic lesions, followed by laparoscopic ultrasound of the liver to map out all metastatic lesions From January 1996 to January 2001 percutaneous RFA was applied with the RITA model 500 generator and the model 30 (four electrodes) or model 70 (seven electrode) needles (RITA Medical Systems, Mountain View, California, USA). The RFA generator was run in the temperature-controlled mode with an average target temperature of 105°C and a maximum power of 50W (generating a 3.5–4 cm spherical ablation site). Each cycle of RFA was maintained for 5 minutes (total time 7–10 minutes). For lesions <3 cm, a single RFA session was used. For lesions >3 cm, multiple overlapping ablations were performed. At the completion of RFA, the temperature was monitored for another 1–2 minutes After January 2001 percutaneous RFA was used with the Starburst XL 14-gauge needle (9 electrodes) and the model 1500 generator (RITA Medical Systems, Mountain View, California, USA). The generator was run in the average-temperature mode with a target temperature of 150°C. Various algorithms were used. Lesions <3 cm were ablated with a single 3 cm ablation. Lesions between 3–4 cm were ablated with a single 4 cm ablation. Lesions <5 cm, were ablated with a single 5 cm ablation. Lesions >5 cm required 2–4 ablations. One patient was treated with the Starburst XLI needle RFA was used with palliative intent in 28 patients (82%) and with curative intent in six (18%) After RFA, 11 patients (32%) received some form of adjuvant therapy	Case Series *Level of evidence: IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Mean 1.6 years [1.2] (range 1–5) *Lost to follow-up:* Not stated *Study period:* January 1996–August 2001 *Operator details:* Not stated	*Sample size: 34* *Patient diagnosis:* NLM Carcinoid 18 Medullary thyroid 7 Secreting islet 5 Non-secreting islet 4 *Number of nodules:* 234 (mean per patient 5.6, range 1–16) *Mean size:* 2.3 cm [0.6] (range 0.5–10) *Mean age:* 52 years [11.7] *Gender mix:* M/F = 25/9 *Patient co-morbidities:* Extrahepatic disease 15/34 patients (44%) Surgery for treatment of primary cancer 25/34 (74%) Failed other treatment modalities (44%)	*Inclusion criteria:* Liver metastases for neuroendocrine tumours Enlarging of the liver, worsening of symptoms, or failure to respond to other treatment modalities. Patients with minor extrahepatic disease were not excluded from the study

Abbreviation: SEM, standard error of the mean

Table 11.5 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Buscarini *et al* (2001) *Location* Piacenza, Italy	Radiofrequency ablation (RFA) RFA was used with ultrasound guidance using a 14-gauge needle with four expandable electrodes (RITA Medical Systems, Mountain View, California, USA) within three days of transarterial chemoembolisation (TACE). Temperatures at the electrodes were 95°C and 120°C for 16–32 minutes For TACE Gelfoam particles were injected into feeding tumoural arteries	Case series *Level of evidence: IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* 6 months *Lost to follow-up:* Not stated *Study period:* 1994–2000 *Operator details:* Not stated	*Sample size: 1* *Patient diagnosis:* NLM (carcinoid) *Number of nodules:* Not stated *Mean size:* 5.2 cm (range 4–6.7) *Mean age:* 61 years *Gender mix:* M *Patient co-morbidities:* Not stated	*Inclusion criteria:* Patients with refractory symptoms (worsening of symptoms and increased octreotide requirements) of malignant carcinoid syndrome and unresectable hepatic metastases

Table 11.5 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Chung *et al* (2001a) *Location* John Wayne Cancer Institute, Saint John's Health Center, Santa Monica, CA, USA	Laparoscopic radiofrequency ablation (RFA) All patients underwent complete history and physical examination, serum tests, chest radiography, and high resolution computed tomography (CT) scanning of the chest, abdomen, and pelvis with thin cuts through the liver. The livers of some patients were examined by fluorodeoxyglucose positron emission tomography (PET) scan and/or magnetic resonance imaging (MRI) of the liver Laparoscopy was used to evaluate all patients for extrahepatic disease All eight liver segments were also examined by laparoscopic ultrasonography For RFA a 15-gauge needle with retractable electrodes (RITA Medical Systems, Mountain View, California, USA) was used. The RFA needle was placed percutaneously in the abdomen and directed into the centre of the lesion under real-time ultrasound guidance. The electrodes were then deployed, and 50 W of alternating power delivered to achieve 100°C for 10 minutes. Lesions >3 cm were treated with overlapping ablations. During the second year of the study, larger lesions were treated using Cool-Tip electrode (Radionics, Burlington, Massachusetts, USA) On completion of RFA, the probe tract was cauterised as the needle was removed Patients were followed up with CT scans all of which were reviewed by a single experienced radiologist	Prospective case series Only data from patients with metastatic colorectal (CLM) or neuroendocrine (NLM) liver carcinoma reported *Level of evidence: IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Mean 11.3 months *Lost to follow-up:* Not stated *Study period:* November 1997–November 1999 *Operator details:* Not stated	*Sample size: 9* CLM 6 NLM 3 *Patient diagnosis:* metastatic liver carcinoma *Mean number of nodules:* CLM 2.3 (range 1–3) NLM 4.7 (range 2–7) *Mean size (of largest lesion):* CLM 2.5 cm (range 2–3) NLM 2.8 (2.5–3) *Mean age:* Could not be separated from total patients *Gender mix:* Could not be separated from total patients *Patient co-morbidities:* All patients had received some form of prior adjuvant therapy Some patients had undergone prior abdominal surgery	*Inclusion criteria:* Patients with unresectable primary or metastatic hepatic malignancies with no evidence of extrahepatic disease Patients over 18 years of age and with a life expectancy of at least four years Note: tumours were defined as unresectable on the basis of their number (>4 lesions), distribution (bilobar disease), proximity to major vascular and/or biliary structures, and attendant co-morbidities *Exclusion criteria:* Pregnancy, evidence of active infection, and recent (<30 days) chemotherapy/biotherapy/radiotherapy Patients who could not undergo laparoscopy or laparotomy Patients with hepatic tumours occupying more than 40% of the liver Patients who had received a hepatic arterial infusion pump

Table 11.5 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Kosari *et al* (2001) *Location* Department of Surgery, Department of Radiology, Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota, USA	Open/percutaneous/laparoscopic radiofrequency ablation (RFA) The RITA (RITA Medical Systems, Mountain View, California, USA) model 70 was used until April 2000; The RITA Star Burst XL was used thereafter Percutaneous RFA was used for lesions that were not on the surface of the liver and not adjacent to a hollow viscus or the diaphragm/lung base. Otherwise, a laparoscopic RFA was used. For other intra-abdominal procedures an open approach was used The RFA electrode was inserted to the tumour under ultrasound (US) or computed tomography (CT) guidance and the needles deployed. Power was applied at 100–150W (350–500 MHz). Once a tissue temperature of 80–110°C was reached, RFA was performed, from 12 minutes (3 cm lesions) up to 20 minutes (5 cm lesions), while monitored by US or CT imaging. The needle tract was ablated by removal of the probe. For laparoscopic or open RFA, needle tract haemostasis was achieved with conventional electrocautery Concurrent procedures with open RFA included: liver resection, hepatic artery pump insertion, bowel resection, tumour resection	Case series Only data from patients with metastatic colorectal (CLM) or neuroendocrine (NLM) liver carcinoma reported Level of evidence: IV *Intention-to-treat analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Median 19.5 months (range 6–34). Unable to determine follow-up for CLM or NLM separately *Lost to follow-up:* Not stated *Study period:* November 1998–February 2001 *Operator details:* Not stated	*Sample size:* CLM 18 (5 patients had six or more lesions) NLM (carcinoid) 7 *Patient diagnosis:* CLM or NLM *Number of nodules:* CLM 76 NLM 29 *Mean size:* CLM 1.7 cm (range 0.38–4.5) NLM 2.2 cm *Mean age:* Could not be separated from other tumour types *Gender mix:* Could not be separated from other tumour types *Patient co-morbidities:* 3 CLM patients had medical contraindication to major surgery (not stated for NLM) 5 CLM patients had anatomical contraindication (not stated for NLM) 6 CLM patients with RFA in conjunction with another procedure (not stated for NLM)	*Exclusion criteria:* Patients with unresectable extrahepatic disease Patients with technically resectable disease Inability to achieve an ablation margin of at least 0.5 cm All lesions >6 cm, for percutaneous therapy lesions >5 cm Tumours adjacent to a sectoral, or larger, bile duct

Table 11.5 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Kuvshinoff *et al* (2002) *Location* Division of Surgical Oncology, Ellis Fishel Cancer Center, University of Missouri, Columbia, Missouri, USA Note: Group is part of a phase II trials with RFA in conjunction with hepatic artery infusion chemotherapy	Open/percutaneous/laparoscopic radiofrequency ablation (RFA) Patients underwent ultrasound (US) guided RFA either laparoscopically, percutaneously, or by open laparotomy. RFA was performed with the RITA system (RITA Medical Systems, Mountain View, California, USA). Tumour ablation was performed by heating to 100°C for eight–ten minutes using 50–150W of power. A cool-down period of 30 seconds was monitored to ensure that temperatures exceeded 65°C. Lesions required overlapping ablations. Ideally, a 1 cm margin of normal parenchyma surrounding the lesion was achieved. During open laparotomy, hepatic vascular inflow occlusion (Pringle manoeuvre) was used when target temperatures could not be reached Choice of laparoscopically, percutaneously, or open laparotomy. RFA was based on surgical considerations (location of liver lesions, need for hepatic or extrahepatic resection, and prior abdominal surgeries) Five NLM patients had RFA combined with resection Note: percutaneous access was found to be worse than open or laparoscopic for all tumour types	Case series Only data from patients with metastatic colorectal (CLM) or neuroendocrine (NLM) liver carcinoma reported Level of evidence: *IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Follow up to 16 months *Lost to follow-up:* Not stated *Study period:* March 1999–April 2001 *Operator details:* Not stated	*Sample size:* 15 CLM 6 NLM *Patient diagnosis:* CLM *Number of nodules:* Could not be separated from other tumour types *Mean size:* Not stated *Mean age:* Could not be separated from other tumour types *Gender mix:* Could not be separated from other tumour types *Patient co-morbidities:* 3/15 patients had synchronous resection of extrahepatic disease All CLM patients had extensive preRFA chemotherapy	*Inclusion criteria:* Patients with hepatic malignancies not considered appropriate for resection (based on a combination of factors including the distribution of tumours, present or suspected extrahepatic disease, prohibitive co-morbidities or advanced age, liver transplant listing or severe underlying cirrhosis, or the need for a synchronous extrahepatic procedure)

Table 11.5 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Quellet *et al* (2002) *Location* Department of Oncologic Surgery, Institut Gustave Roussy, Cedex, France	Radiofrequency ablation (RFA) Treatment consisted of right hepatectomy combined with RFA of lesions in the remaining left liver. For each patient, RFA of two lesions lying precisely in the future resection plane was performed, followed immediately by right hepatectomy in which the surgical plane passed through the necrotic zone created during RFA	Case report Only data from patients neuroendocrine liver carcinoma (NLM) were reported Level of evidence: *IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Not stated *Lost to follow-up:* Not stated *Study period:* May 2000 and December 2001 *Operator details:* Not stated	Sample size: 2 *Patient diagnosis:* NLM (multiple bilateral) *Number of nodules:* Not stated *Mean size*: Not stated) *Mean age:* Not stated *Gender mix:* Not stated *Patient co-morbidities:* Not stated	Not stated

Table 11.5 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Siperstein *et al* (2001) Includes 1997 and 2000b *Location* Department of general Surgery, Cleveland Clinic Foundation, Ohio, USA University of California, California, USA	Radiofrequency ablation (RFA) Laparoscopic ultrasound guided RFA was used with a 15-gague needle with four electrodes (one patient treated with a needle with three electrodes) (RITA Medical Systems, Mountain View, California, USA). At completion of RFA, the tissue temperature was measured during a cooling down period of two minutes, and temperatures above 60°C were considered as successful ablation. Lesions >4 cm were treated with overlapping ablations	Prospective non-randomised comparative Only data from patients neuroendocrine liver carcinoma (NLM) were reported Level of evidence: *IV* *Intention-to-treat Analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* Mean 12.1 months (range 3–35) *Lost to follow-up:* 17% *Study period:* January 1996–February 1999 *Operator details:* Not stated	Sample size: 18 *Patient diagnosis:* Histologically confirmed NLM Carcinoid 8 nonfunctional islet cell 2 gastrinoma 1 Medullary thyroid 6 Insulinoma 1 *Number of nodules:* 115 (mean 6 per patient) *Mean size:* 3.2 cm [1.9] (range 1.3–10) *Mean age:* 52 years *Gender mix:* 14M/4F *Patient co-morbidities:* Not stated	*Inclusion criteria:* Patients without extensive hepatic replacement or extrahepatic disease

Table 11.5 continued

Authors	Intervention	Study design	Study population	Inclusion/exclusion criteria
Wessels *et al* (2001) *Location* Department of Surgery, and Department of Molecular Genetics and Microbiology, University of Florida College of Medicine, Florida, USA	Patients had prior treatment with transarterial hepatic chemoembolisation (TACE) but had developed refractory symptoms (worsening of symptoms and increased octreotide (somatostatin analogue) requirements) of malignant carcinoid syndrome. Computed tomography (CT) confirmed the presence of new hepatic metastases, or metastases that were refractory to TACE therapy Radiofrequency ablation (RFA) Before RFA patients had to be treated with the octreotide to manage malignant carcinoid syndrome All patients underwent surgical exploration and intraoperative ultrasonography. The presumed refractory metastases were localised using preoperative CT, and confirmed by intraoperative ultrasound and ultrasound-guided biopsy. RFA was applied using a 3.5 cm Le-Veen-type needle and an RF2000 generator (Radiotherapeutics, Palo Alto, California, USA). Each lesion was treated with at least two cycles of RFA. The first cycle was continued until maximal tissue impedance was achieved or until a total of 15 minutes of treatment was obtained. After a two minute cool-down period, a second cycle of RFA was used with the same impedance and time criteria Patients were interviewed before and after treatment, and symptom severity score assigned by a physician who was not a member of the surgical team Symptom severity score: 1 No Symptoms 2 Mild Symptoms 3 Symptoms impact on daily living 4 Severe symptoms 5 Disabling symptoms	Case series Level of evidence: *IV* *Intention-to-treat analysis:* Not stated *Participation rate:* Not stated *Eligibility rate:* Not stated *Follow-up:* 6 months *Lost to follow-up:* Not stated *Study period:* 1994–2000 *Operator details:* Not stated	Sample size: 3 *Patient diagnosis:* Biochemically confirmed NLM (carcinoid) *Number of nodules:* 7 *Mean size:* 2.8 cm *Mean age:* 39.6 years *Gender mix:* M/F = 1/2 *Patient co-morbidities:*	*Inclusion criteria:* Patients with refractory symptoms (worsening of symptoms and increased octreotide requirements) of malignant carcinoid syndrome and unresectable hepatic metastases

Table 12.1 Critical appraisals of HCC RFA comparative studies

	Kurokochi *et al* (2002) (Level II)	**Lencioni *et al* (1999) (Level II)**
Quality of reporting		
Study details	Limited detail on patient groups Outcomes expressed as size and volume of tumour necrosis RFA and PEI therapies	Limited detail on patient groups and on the reporting of surgical methods Outcomes expressed as the number of nodules RFA and PEI therapies. No detail reported on the mean size (diameter) of the nodules to be treated or the number of lesions in each size category
Baseline equality	Similar patient numbers in each treatment group Patients in each treatment group of similar mean age and gender mix	The same number of patients in each group but slightly different numbers of lesions Patients in each treatment group of similar mean age
Study methodology and rigour		
Potential for bias	Blinding of patients not stated *Selection bias* — patients were divided randomly in one of the two treatment groups, method of allocation concealment not stated *Operator (performance) bias* — no details reported *Assessor (detector) bias* — not stated whether outcome assessors were blinded	Blinding of patients not stated *Selection bias* — no details reported, method of allocation concealment not stated *Operator (performance) bias* — no details reported *Assessor (detector) bias* — not stated whether outcome assessors were blinded
Confounding factors	Number of nodules treated in each treatment group not stated	Treatment groups differed slightly in the number of nodules to be treated
Chance variation	Small sample size	Small sample size
Internal validity	Losses to follow-up not stated	Method of randomisation not stated; losses to follow-up not stated
External validity	Study included patients with biopsy-proven HCC lesions 1–5 cm in diameter	Study included patients with HCC lesions 1–3 cm in diameter
Adjustment for prognostic factors	No details reported	No details reported
Attempt made to compensate for limitations in study design	No details reported	No details reported
Study outcomes analysis		
Followed intention-to-treat principle	Not stated	Not stated
Objective or subjective outcomes	Mixed	Objective
Defined and/or standardised outcome criteria	Outcomes defined	Outcomes defined

Table 12.1 continued

	Olschewski *et al* (2001) (Level II)	Shiina *et al* (2000) (Level II)
Quality of reporting		
Study details	Good. Surgical methods well reported Outcomes expressed as the number of patients or number of nodules RFA and PEI therapies	Limited detail on patient groups and on the reporting of surgical methods Outcomes expressed as the number of sessions performed PEI and RFA therapies
Baseline equality	Similar number of patients and lesions in each treatment group Age and gender mix not stated	Similar patient numbers in each treatment group and no statistically significant difference between the patient groups however the statistical method used to determine this was not stated and complete study population details absent. Gender mix and age not mentioned
Study methodology and rigour		
Potential for bias	Blinding of patients not stated *Selection bias* — No details reported, method of allocation concealment not stated *Operator (performance) bias* — No details reported *Assessor (detector) bias* — Not stated whether outcome assessors were blinded	Blinding of patients not stated *Selection bias* — no details reported, method of allocation concealment not stated *Operator (performance) bias* — no details reported *Assessor (detector) bias* — not stated whether outcome assessors were blinded
Confounding factors	Treatment groups differed in the number of patients, the number of nodules to be treated, and the mean size (diameter) of the nodules to be treated	Number of nodules treated, the size (diameter) the nodules to be treated, or the number of lesions in each size category not stated
Chance variation	Small sample size	Statistical comparison of outcomes was made but the statistical method that was used was not stated. Small sample size meant that chance variation could be a factor in statistically significant results
Internal validity	Method of randomisation not stated; losses to follow-up not stated	Method of randomisation not stated; losses to follow-up not stated
External validity	Study included patients with lesions smaller than 5 cm in diameter	Study included patients with small lesions and with liver disease classified as Child-Pugh A or Child-Pugh B
Adjustment for prognostic factors	No details reported	No details reported
Attempt made to compensate for limitations in study design	Yes, multivariate analysis adjusting for major prognostic factors	No details reported
Study outcomes analysis		
Followed intention-to-treat principle	Not stated	Not stated
Objective or subjective outcomes	Mixed	Objective
Defined and/or standardised outcome criteria	Outcomes defined	Defined

Table 12.1 continued

	Livraghi *et al* (1999) (Level III-1)	**Ikeda *et al* (2001) (Level III-2)**
Quality of reporting		
Study details	Good. Surgical methods well reported Outcomes expressed as the number of tumours and patients PEI and RFA therapies	Good. Surgical methods well reported Outcomes expressed as the number of tumours and patients PEI and RFA therapies
Baseline equality	Patient groups were comparable (p>0.05) but the statistical method used to determine this was not stated. Gender mix skewed towards males but similar gender distribution ratio between the two treatment groups	Treatment groups differed in the number of patients and gender mix
Study methodology and rigour		
Potential for bias	Blinding of patients not stated *Selection bias* — patients assigned on the basis of location of residence relative to the hospital *Operator bias* — low. Two out of four possible operators performed PEI or RFA procedures *Assessor bias* — high. Two assessors (also operators) by means of consensus. The lack of blinding may potentially introduced bias from the outcome assessors who evaluated the scans	Blinding of patients not stated *Selection bias* — patients assigned on the basis of date of presentation to treating institution *Operator bias* — not stated *Assessor bias* — not stated
Confounding factors	No mention of the number of lesions in each size category	No mention of the number of lesions in each size category
Chance variation	Small sample size and statistical comparison of outcomes was not made	Statistical comparison made for some of the reported outcomes and method of analysis not stated
Internal validity	Poor randomisation method for determining treatment type and a lack of blinding. Losses to follow up not stated	Non-randomised. Losses to follow up not stated
External validity	Study included elderly patients (over 65 years of age) and with lesions	Study included patients with small solitary HCC with no previous treatment
Adjustment for prognostic factors	No details reported	No details reported
Attempt made to compensate for limitations in study design	No details reported	No details reported
Study outcomes analysis		
Followed intention-to-treat principle	Not stated	Not stated
Objective or subjective outcomes	Mixed	Objective
Defined and/or standardised outcome criteria	Defined	Defined

Table 12.1 continued

	Catalano *et al* (2000) (Level III-3)	Catalano *et al*(2001) (Level III-3)
Quality of reporting		
Study details	Adequate detail on patient groups but limited reporting of surgical methods Outcomes expressed as the number of tumours MS-PEI, SS-PEI, LITT and RFA therapies	Adequate detail on patient groups but limited reporting of surgical methods Outcomes expressed as the number of tumours MS-PEI, SS-PEI, LITT and RFA therapies
Baseline equality	Limited description of patient groups. Gender mix skewed toward males	Limited description of patient groups. Gender mix skewed toward males
Study methodology and rigour		
Potential for bias	Observational study *Selection bias* — not stated *Operator bias* — not stated *Assessor bias* — postoperative CT scans were evaluated retrospectively. The number of assessors and their qualifications not stated	Observational study. Lack of randomisation may result in uneven distribution of potential confounders between the two patient groups *Selection bias* — not stated *Operator bias* — not stated *Assessor bias* — postoperative CT scans were retrospectively evaluated by two nonblinded radiologists who arrived at consensus. The lack of blinding may potential introduced bias from the outcome assessors who evaluated the scans
Confounding factors	Treatment groups differed in the number of patients, the number of nodules to be treated, and the size (diameter) the nodules to be treated. No mention of the number of lesions in each size category. Lack of randomisation may result in uneven distribution of potential confounders between the two patient groups	Treatment groups differed in the number of patients, the number of nodules to be treated, and the mean size (diameter) of the nodules to be treated. Study population for review selected on the basis of post-treatment tumour recurrence as detected by helical CT scan
Chance variation	Small sample size and statistical comparison of outcomes was not made	Small sample size and statistical comparison of outcomes was not made
Internal validity	Non-randomised. Losses to follow up not stated	Non-randomised, small sample size, unbalanced groups. Losses to follow up not stated
External validity	Study included patients with multiple HCC nodules	Study included patients with HCC lesions
Adjustment for prognostic factors	No details reported	No details reported
Attempt made to compensate for limitations in study design	No details reported	No details reported
Study outcomes analysis		
Followed intention-to-treat principle	Not stated	Not applicable
Objective or subjective outcomes	Objective	Subjective
Defined and/or standardised outcome criteria	Defined	Defined

Table 12.1 continued

	Livraghi *et al* (2000) (Level III-3)	Yu *et al* (2002) (Level III-3)
Quality of reporting		
Study details	Limited detail on patient groups and on the reporting of surgical methods Outcomes expressed as the number of patients TACE and RFA therapies	Limited detail on patient groups and on the reporting of surgical methods Outcomes expressed as the number of patients Surgical resection and RFA therapies
Baseline equality	Same number of patients in each treatment group and patients of similar mean age. Patient groups were matched but details not stated	Treatment groups differed in patient numbers. No other details reported apart from diagnosis
Study methodology and rigour		
Potential for bias	*Selection bias* — no details reported *Operator bias* — no details reported *Assessor bias* — no details reported	*Selection bias* — no details reported *Operator bias* — no details reported *Assessor bias* — no details reported
Confounding factors	Treatment groups differed in the number of nodules to be treated and the mean size (diameter) of the nodules. No detail on the number of lesions in each size category. Blinding of patients, operators or postoperative outcome assessors not stated	No detail on the number of lesions in each size category. Blinding of patients, operators or postoperative outcome assessors not stated
Chance variation	Small sample size. The same number of patients in each group and statistical comparison of outcomes were made	Statistical comparison made for only one of the reported outcomes and method of analysis not stated
Internal validity	Non-randomised. Losses to follow up not stated	Non-randomised. Losses to follow up not stated
External validity	Study included patients with HCC lesions 1–3 cm in diameter	Study included patients with HCC
Adjustment for prognostic factors	No details reported	No details reported
Attempt made to compensate for limitations in study design	No details reported	No details reported
Study outcomes analysis		
Followed intention-to-treat principle	No details reported	No details reported
Objective or subjective outcomes	Objective	Objective
Defined and/or standardised outcome criteria	Defined	Defined

Table 12.2 Critical appraisals of CLM RFA comparative studies

	Gillams and Lees (2001) (Level III-2)
Quality of reporting	
Study details	Limited detail on patient groups and on the reporting of surgical methods Outcomes expressed as survival times Surgical resection and RFA therapies
Baseline equality	Not clear
Study methodology and rigour	
Potential for bias	Blinding of patients, operators or postoperative outcome assessors not stated *Selection bias* — patients assigned to treatments based on tumour location, previous hepatic resection, concomitant ill health, known extrahepatic disease, or patient preference *Operator bias* — no details reported *Assessor bias* — no details reported
Confounding factors	Treatment groups differed in the number of patients treated No detail on the number of lesions treated
Chance variation	Small sample size and statistical comparison of outcomes was not made
Internal validity	Non-randomised. Losses to follow up not stated
External validity	Study included patients with solitary CLM
Adjustment for prognostic factors	No details reported
Attempt made to compensate for limitations in study design	No details reported
Study outcomes analysis	
Followed intention-to-treat principle	Yes
Objective or subjective outcomes	Subjective
Defined and/or standardised outcome criteria	Defined

Table 12.3 Critical appraisals of NLM RFA comparative studies

	Mazziotti *et al* (2001) (Level III-2)
Quality of reporting	
Study details	Limited detail on patient groups and on the reporting of surgical methods Outcomes expressed as the number of patients PEI and RFA therapies
Baseline equality	Same number of patients in each treatment group and patients of similar mean age. Patient groups were matched but details not stated
Study methodology and rigour	
Potential for bias	Blinding of patients, operators or postoperative outcome assessors not stated *Selection bias* — allocation of percutaneous ablation therapy based on radiologist opinion (7 patients) and refusal to undergo surgery (1 patient). Method of allocation to either PEI and/or RFA not stated *Operator bias* — no details reported *Assessor bias* — no details reported
Confounding factors	Treatment groups differed in the number of nodules to be treated
Chance variation	Small sample size
Internal validity	Non-randomised. Losses to follow up not stated
External validity	Study included patients with NLM or CLM lesions
Adjustment for prognostic factors	No details reported
Attempt made to compensate for limitations in study design	No details reported
Study outcomes analysis	
Followed intention-to-treat principle	No details reported
Objective or subjective outcomes	Objective
Defined and/or standardised outcome criteria	Defined

Appendix D Studies excluded from the review

Table 13.1 HCC studies excluded from review

Study	Reason for exclusion
Buscarini *et al* 1999 (Includes 1998)	RFA combined with TACE
Buscarini *et al* 1998 (includes 1996)	RFA compared with PEI, combined results of two treatment groups
Christians *et al* (2001)	RFA compared with PEI, TACE or resection, combined results of the treatment groups
Hosida *et al* 2002	RFA compared with PEI, combined results of two treatment groups
Izumi *et al* 2001	RFA compared with MCT
Kouyama *et al* 2000	RFA compared with MCT
Lencioni *et al* 1999 Includes 1998b	RFA combined with segmental arterial embolisation
Pereira *et al* 2001	RFA combined with TACE
Shibata *et al* 2000	RFA compared with MCT
Yamakoda *et al* 2002 (Includes 2001)	RFA combined with TACE

Table 13.2 CLM studies excluded from review

Study	Reason for exclusion
Bleicher *et al* 2003	CLM case series, recurrence rate reported per lesion
Bloomston *et al* 2002	RFA compared with chemoembolisation
De Baere *et al* 2000	CLM and other LM, combined results of two treatment groups
Goldberg *et al* 2002	RFA compared with chemoembolisation
Goldberg *et al* 2000	Follow-up not stated
Ianitti *et al* 2002	No recurrence reported
Jiao *et al* 1999	Follow-up <12 months
Kainuma *et al* 1999	RFA compared with chemoembolisation
Machi *et al* 2001	Recurrence reported per lesion
Mazziotti *et al* 1998	CLM results not included in review, PEI not a comparator for CLM
Risse *et al* 2001	Unable to separate data for CLM and other LM
Rose *et al* 1999	Follow-up <12 months
Rossi *et al* 1998	Unable to separate data for CLM and other LM
Scudamore *et al* 1999	Follow-up <12 months
Solbiati *et al* 1997a	Unable to separate data for CLM and other LM
Solbiati *et al* 1997b	Unable to separate data for CLM and other LM

Table 13.3 NLM studies excluded from review

Study	Reason for exclusion
Chung *et al* 2001b	RFA with or without CSA, unable to separate data
Jaeck *et al* 2001	No RFA results

Table 13.4 Mixed indications studies excluded from review

Study	Reason for exclusion
Adam *et al* 2002	RFA reported separately (HCC and mixed metastatic disease) but unable to separate data for mixed metastatic disease
Arata *et al* 2001	HCC and CLM, unable to separate data
Beppu *et al* 2001	HCC and CLM, unable to separate data
Berber *et al* 2000	HCC, CLM and other LM, unable to separate data
Bilchik *et al* 2000	RFA and CSA, HCC, CLM and other LM, unable to separate data
Bowles *et al* 2001	HCC, CLM and other LM, unable to separate data
Curley *et al* 1999	HCC, CLM and other LM, unable to separate data
De Baere *et al* 2001	HCC, CLM and other LM, unable to separate data
De Baere *et al* 1999	HCC, CLM and other LM, unable to separate data
Dupuy *et al* 2000	HCC, CLM and other LM, unable to separate data
Elias *et al* 2002	HCC, CLM and other LM, RFA compared with resection, unable to separate data
Elias *et al* 2000	HCC, CLM and other LM, RFA compared with resection, unable to separate data
Gillams and Lees, 1999a	HCC, CLM and other LM, unable to separate data
Gillams and Lees, 1999b	HCC, CLM and other LM, unable to separate data
Lees and Gillams, 2000	LM, RFA compared with LITT, combined result of both treatment groups — unable to separate data
Lees and Gillams, 1999	LM, RFA and LITT
Machi *et al* 2002	HCC and CLM, unable to separate data
Maeta *et al* 1994	HCC and CLM, RFA with or without HAIC, unable to separate RFA alone data for mixed indications
Moffat *et al* 1983	HCC, CLM and other LM, RFA with or without HAIC, unable to separate RFA data for mixed indications
Moffat *et al* 1985	HCC, CLM and other LM, RFA with or without HAIC, unable to separate RFA alone data for mixed indications
Nagata *et al* 1997 Includes 1990	HCC, CLM and other LM, RFA alone or RFA combined with either TACE, radiotherapy, immunotherapy or chemotherapy, unable to separate data for mixed indications
Siperstein *et al* 2000a	HCC, CLM and other LM, unable to separate data
Tait *et al* 2002	HCC, CLM and other LM, RFA or cryotherapy, unable to separate RFA data for mixed indications
Urata *et al* 1995	HCC and LM, did not indicate type of LM
Wong *et al* 2001	HCC, CLM and other LM, unable to separate RFA data for mixed indications
Wood *et al* 1999	HCC, and LM, unable to separate RFA data for mixed indications

Abbreviations: CLM; metastatic colorectal liver carcinoma; CSA, cryoablation; HAIC, hepatic artery infusion chemotherapy; HCC, hepatocellular carcinoma; LITT, laser-induced thermotherapy; LM, liver metastases; MCT, microwave coagulation therapy; NLM, metastatic neuroendocrine liver carcinoma; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transcatheter chemoembolisation

Appendix E Results tables

Table 14.1 Safety outcomes for RFA for the treatment of HCC liver tumours — RCTs and quasi-RCTs

	Lencioni *et al* (1999) (Level II)		Shiina *et al* (2000) (Level II)		Olschewski *et al* (2001) (Level II)		Kurokohchi *et al* (2002) (Level II)		Livraghi *et al* (1999) (Level III-1)	
Safety outcomes	**PEI** n = 40 (61 nodules)	**RFA** n = 40 (54 nodules)	**PEI** n = 29 (212 sessions)	**RFA** n = 31 (65 sessions)	**PEI** n = 50 (73 nodules)	**RFA** n = 52 (69 nodules)	**PEI/RFA** n = 19	**RFA** n = 20	**PEI** n = 44 (60 nodules)	**RFA** n = 42 (52 nodules)
Patients with major complications within 24 hours									Not stated	2%
Patients with minor complications within 24 hours									Not stated	8%
Patients with major complications or change in vital signs							0/19 (0%)	Not stated		
Patients with serious side effects or complications					34% (33/50)	44% (29/52) pns				
Patients with complications			0%	0%						
Fever ≥ 37.5º C for ≥ 3 days			10% of sessions	28% of sessions****						
Transaminase levels 2–4 times over baseline at 24 hours post-treatment (% patients)									Not stated	100%

pns p = not significant; ****p = 0.0008

Table 14.2 Effectiveness outcomes for RFA for the treatment of HCC liver tumours — RCTs and quasi-RCTs

	Lencioni *et al* (1999) (Level II)		Shiina *et al* (2000) (Level II)		Olschewski *et al* (2001) (Level II)		Kurokohchi *et al* (2002) (Level II)		Livraghi *et al* (1999) (Level III-1)	
Effectiveness outcomes	**PEI** n = 40 (61 nodules)	**RFA** n = 40 (54 nodules)	**PEI** n = 29 (212 sessions)	**RFA** n = 31 (65 sessions)	**PEI** n = 50 (73 nodules)	**RFA** n = 52 (69 nodules)	**PEI/RFA** n = 19	**RFA** n = 20	**PEI** n = 44 (60 nodules)	**RFA** n = 42 (52 nodules)
Local recurrence-free survival										
1 year postoperative					83%	98%				
2 years postoperative					62%	96%				
Event-free survival										
1 year postoperative					77%	86%				
2 years postoperative					43%	64%				
Mortality										
1 year postoperative					2/50 (4%)	0/52 (0%) pns(a)				
2 years postoperative					6/50 (12%)	1/52 (2%) pns(b)				
Local recurrence										
2 years postoperative (by patient)					13/50 (26%)	1/52 (2%)				
in tumours considered to have been completely ablated — median 15 months (by lesion)	9/52 (17%)	2/49 (4%)*								
4 month follow-up by CT (by patient)			1/29 (3.5%)	0/31 (0%)						
Type of incomplete necrosis (lesions): *Infiltrating HCC* *Contiguous multinodular HCC* *Nodular HCC*									6 4 2	1 1 3
New lesions			4/29 (14%)	3/31 (10%)						
Therapeutic response										
Complete therapeutic tumour ablative response (% of total nodules), measured by CT	52/61 (85%)	49/54 (91%) pns(c)			60/73 (82%)	63/69 (91%) pns(d)			48/60 (80%)	47/52 (90%) pns(e)
Mean number of sessions to achieve tumour ablation	3.3{1.1}	1.3{0.5}**								

pns p = not significant; a) p = 0.3; b) p = 0.08; c) p >0.1; d) p = 0.11; e) p = 0.127; *p<0.05; **p =0.01; ***p =0.001; ****p =0.0001

Note: [] indicates standard deviation; {} indicates unit of measurement not defined

Table 14.2 continued

	Lencioni *et al* (1999) (Level II)		Shiina *et al* (2000) (Level II)		Olschewski *et al* (2001) (Level II)		Kurokohchi *et al* (2002) (Level II)		Livraghi *et al* (1999)[58] (Level III-1)	
Effectiveness outcomes	**PEI n = 40 (61 nodules)**	**RFA n = 40 (54 nodules)**	**PEI n = 29 (212 sessions)**	**RFA n = 31 (65 sessions)**	**PEI n = 50 (73 nodules)**	**RFA n = 52 (69 nodules)**	**PEI/RFA n = 19**	**RFA n = 20**	**PEI n = 44 (60 nodules)**	**RFA n = 42 (52 nodules)**
Size of coagulated necrosis										
Longest diameter (cm) measured by CT scan							4.2 {1.1}	2.5 {0.7}***		
Shortest diameter (cm) measured by CT scan							3.7 {0.8}	2.2 {0.6}***		
Height (cm) measured by CT scan							4.2 {0.6}	2.5 {0.5}***		
Volume (cm^3)							34.9 {15.43}	8.4 {5.9}***		
Treatment details										
Mean number of sessions per patient			7.3	2.1****						
Single treatment cycle (by tumour)									44/60 (73%)	44/52 (85%)
Second treatment cycle (by tumour)									16/60 (27%)	8/52 (15%)
Mean number sessions/tumour (1^{st} & (when performed) 2^{nd} treatment cycle)									4.8	1.2
Mean procedure time required per session (minutes)									30	45
Hospital stay, mean (days)			30.3	12.7****						
Pain and analgesic requirements										
Intravenous administration of analgesia or pain killers required during or immediately after treatment			11%	35%****						
Treatment interrupted due to severe pain									not stated	5
Post-treatment analgesia required									1	not stated
Pain for 3–4 days — requiring analgesics									not stated	2

*p<0.05; **p =0.01; ***p =0.001; ****p =0.0001
Note: [] indicates standard deviation; {} indicates unit of measurement not defined

Table 14.3 Safety outcomes for RFA for the treatment of HCC liver tumours—non-randomised comparative studies

	Catalano *et al* (2001) (Level III-3)			Catalano *et al* (2000) (Level III-3)			Ikeda *et al* (2001) (Level III-2)	
Safety outcomes	**MS-PEI n = 40 (73 nodules)**	**SS-PEI n = 5 (11 nodules)**	**RFA n = 16 (25 nodules)**	**MS-PEI n = 56 (98 nodules)**	**SS-PEI n = 14 (31 nodules)**	**RFA n = 32 (48 nodules)**	**PEI n = 96**	**RFA n = 23**
Complications and parenchymal changes (helical CT scan assessed):								
Nodular granulation rim (% of nodules)				10.2%	25.8%	20.8%		
Peritumoural THAD (% of nodules)				14.3%	12.9%	33.3%		
Arterioportal fistula (% of patients)				1.8%	14.3%	3.1%		
Hepatic infarction (% of patients)				1.8%	14.3%	Not stated		
Portal thrombosis (% of patients)				5.4%	14.3%	6.2%		
Caval thrombosis (% of patients)				1.8%	Not stated	Not stated		
Biliary duct dilation (% of patients)				7.1%	21.4%	6.2%		
Local atrophy (% of patients)				1.8%	28.6%	9.4%		
Subcapsular collection (% of patients)				1.8%	14.3%	6.2%		
Perihepatic fluid (% of patients)				5.4%	28.6%	9.4%		
Pleural fluid (% of patients)				3.6%	14.3%	6.2%		
Acute cholangitis requiring drainage							1% (1/96)	0%
Haemothorax							0%	0%
Intraperitoneal bleeding							0%	0%
Haemobilia							0%	0%

Abbreviations: THAD, transient hyperattenuation difference

	Livraghi *et al* (2000) (Level III-3)	Yu *et al* (2002) (Level III-3)		
Safety outcomes	**TACE** n = 10	**RFA** n = 10	**Surgical resection** n = 88	**RFA n = 57**
Complications	20%	0% pns(a)		

[a]p = 0.07

Table 14.4 Effectiveness outcomes for RFA for the treatment of HCC liver tumours—non-randomised comparative studies

	Catalano *et al* (2001) (Level III-3)			**Catalano *et al* (2000) (Level III-3)**			**Ikeda *et al* (2001) (Level III-2)**	
Effectiveness outcomes	MS-PEI **n = 40 (73 nodules)**	SS-PEI **n = 5 (11 nodules)**	RFA **n = 16 (25 nodules)**	MS-PEI **n = 56 (98 nodules)**	SS-PEI **n = 14 (31 nodules)**	RFA **n = 32 (48 nodules)**	PEI **n = 96**	RFA **n = 23**
Treatment details:								
Mean treatment sessions							4.0 (range 4–6)	1.3 (range 1–2)[pns##]
Median hospital stay (days)							17 (range 12–72)	10 (range 4–16)[pns##]
Intrahepatic recurrence (spiral CT scan assessed):								
Local recurrence at 3–22 months post-treatment	14%	9%	16%					
Complete tumour necrosis (1 month after treatment)							94% (90/96)	100% (23/23)[pns¶]
Local recurrence at 1 year (progression in the treated tumour on follow-up CT)							14% (13/96)	17% [†] (4/17)[pns¶]
Number of new non-local nodules detected at 3–22 months post-treatment (within same segment or within different liver segments from the treated nodule)	62	14	23					
Nodular changes (spiral CT scan assessed):								
Nodular diameter (increased compared with pre-treatment CT scan) (%)				28.6%	71%	58.3%		
Nodular shape (changed compared with pre-treatment CT scan) (%)				21.4%	61.3%	79.2%		
Nodular borders (spiral CT scan assessed):								
Changed compared with pre-treatment CT scan (%)				53%	77.4%	81.3%		
Well defined (%)				61.2%	87%	85.4%		
Poorly defined (%)				38.8%	12.9%	14.6%		

[†]Note: due to discrepancies in the text, the values quoted may be an overestimation

Table 14.4 continued

	Catalano *et al* (2001) (Level III-3)			Catalano *et al* (2000) (Level III-3)			Ikeda *et al* (2001) (Level III-2)	
Effectiveness Outcomes	**MS-PEI n = 40 (73 nodules)**	**SS-PEI n = 5 (11 nodules)**	**RFA n = 16 (25 nodules)**	**MS-PEI n = 56 (98 nodules)**	**SS-PEI n = 14 (31 nodules)**	**RFA n = 32 (48 nodules)**	**PEI n = 96**	**RFA n = 23**
Residual tumour:								
100%				3%				
>75%				6.1%				
>50%				10.2%	3.2%			
>25%				11.2%	19.4%	12.5%		
<25%				23.5%	45.2%	22.9%		
Absent				45.9%	32.3%	64.6%		

Table 14.4 continued

	Livraghi *et al* (2000) (Level III-3)		Yu *et al* (2002) (Level III-3)	
Effectiveness outcomes	**TACE n = 10**	**RFA n = 10**	**Surgical resection n = 88**	**RFA n = 57**
Patients with complete control of tumour growth (%)	30%	50% pns##		
Recurrence rate (over entire study period)			24%	39%
Interval between the time of treatment and recurrence (days) (over entire study period)			634.9{169.4}	160.1{104.8}
Recurrence rate (over the same 38-month period)			19% (n = 48)	39%
Interval between the time of treatment and recurrence (days) (over the same 38-month period)			392.3{269.1} (n = 48)	160.1{104.8}
Recurrence rate (nodule diameter ≥ 3.5 cm) (over the same 38-month period)			22.7% (n = 48)	38.1%
Recurrence rate (nodule diameter ≤3.5 cm) (over the same 38-month period)			15.4% (n = 48)	38.1% ¦ ¦ ¦
Mortality	4	0¦		

¶p >0.1 compared with comparative intervention; ##p not stated, {} indicates unit of measurement not defined; ¦ ¦ ¦ p = 0.045 compared with comparative intervention¦ p<0.05 compared with comparative intervention
Abbreviations: NS, not stated

Table 15 Outcomes for RFA for the treatment of CLM — non-randomised comparative studies

	Gillams and Lees (2001) (Level III-2)	
Outcomes	**Surgical resection n = 16**	**RFA n = 30**
Median survival from diagnosis of liver metastases (months)	Not stated	44
Mean survival from diagnosis of liver metastases (months)	54	Not stated
5-year survival	53%	40%
Median survival <7 cm maximum diameter tumour and no extra-hepatic disease (months)	Not stated	62
Median survival no vessel continuity and no extra-hepatic disease (potentially operable patients) (months)	Not stated	68

Table 16 Outcomes for RFA for the treatment of CLM — case series

Study	Outcomes					
	Recurrence rate		Complete ablation	Mortality	Survival	Other
	Local	New				
Bleicher *et al* (2002)	*Patients* 13/54 (24%)					
Chung *et al* (2001a)				Treatment-related mortality 0/6 (0%) Cancer-related mortality 3/6 (50%) (6–10 months)	1/6 (17%) (11 months) with disease	No evidence of disease 2/6 (7 and 18 months) Postoperative bleeding 1/6 (17%) All patients discharged within 2 days (except bleeding patient)
Cuschieri *et al* (2001)		*Patients* 1/8 (13%) after 4 months (2 new lesions not at treatment site, patient underwent repeat RFA)	Complete ablation with min 0.5 cm margin (ultrasound detected) 27/32 (84%) treated tumours	1/8 (13%) (6 weeks, due to progressive disease)	7/8 (88%) (6–20 months) (6/7 patients had normal CT/MRI and liver function at follow-up)	Complications 0/8 (0%) patients Hospital stay 2–3 days Treatment abandoned 1/8 (reasons not stated)
Kosari *et al* (2001)	*Lesions* 5/76 (7%) (2 patients also had liver resection) NOT reported as patients	*Patients* 8/18 (44%) new hepatic disease		1/18 (6%) new hepatic and systemic disease, 2.5 years after initial treatment)		Mean size of locally recurrent lesion (cm) 3.1 (range 1–4) New systemic disease 6/18 (33%) patients Complications 1/18 (6%) (wound infection, RFA and liver resection combined)
Kuvshinoff *et al* (2002)	*Patients* 6/15 (40%) (Not indicated if this includes patients who are alive)				Recurrence-free survival 9/15 (60%) median 4 months	Any recurrence 13/15 (87%) median 4 months Unable to extrapolate overall disease-free survival at 8 months

Table 16 continued

Study	Outcomes					
	Recurrence rate		Complete ablation	Mortality	Survival	Other
	Local	New				
Machi *et al* (2000)	2/9 patients (22%) at 12.6 months (range 4–21) (1 lesion per patient, 2/37 lesions (5%)) 1 patient also had new liver metastases and extrahepatic recurrence (lung), the other had extrahepatic recurrence (peritoneal)	New liver metastases 3/9 (33%)		3/9 (22%) 1 patient at 13 months with local recurrence and new liver metastases with extrahepatic recurrence (lung) 1 patient at 10 months local recurrence and extrahepatic recurrence (peritoneal) 1 patient at 18 months had extrahepatic recurrence (peritoneal)	6/9 (66%) patients alive and free of disease (4/6 had no recurrence of any kind at 4–10 months follow-up, 2/6 had extrahepatic recurrence treated by percutaneous RFA)	Nodules identified prior to surgery by imaging studies (including computed tomography) 23 Additional nodules identified at surgery 8 in 4 patients (44%) (inspection and palpation) All tumours (31) identified by intraoperative US Additionally, intraoperative US identified 6 nodules in 5 patients (56%) preoperatively unrecognised and nonpalpable tumours Note: these additional nodules were treated with RFA as resection was possible (location of tumours or presence of extrahepatic disease) Mean ablation time (minutes) 100 (range 12–248) Mean length of hospital stay (days) 8.6 (range 5–15) Minimum blood loss during RFA Intraoperative complications (RFA and colorectal) 0/9 patients (0%) Early complications 2/9 (22%) (wound infection and thrombocytopenia in 1 patient, heart failure in 1 patient) Abdominal bleeding 0/9 (0%) Late complications 1/9 (11%) (bile duct stricture at 4 months, patient required biliary stent placement)

Continued

Table 16 continued

Study	Outcomes					
	Recurrence rate		Complete ablation	Mortality	Survival	Other
	Local	New				
Machi *et al* (2000) *Continued*						Postoperative tumour marker levels (CEA) decreased in all patients (mean 23μg/L, 8.7% of preoperative mean, mean reduction 91%) Extrahepatic recurrence 4/9 (44%) (2/4 also had new liver metastases)
Pearson *et al* (1999)	*Patients* 2/46 (4%) median 15 months 1 of the 2 patients also had new liver metastases diagnosed at the same time	*Patients* 1/46 (2%) patient also had local recurrence		0/46 (0%)		Complications Haemorrhage 0/46 (0%) Renal insufficiency 0/46 (0%) Symptomatic pleural effusion 0/46 (0%) Pneumothorax/injured diaphragm 0/46 (0%)
Rossi *et al* (1996)				*Surgery (2 patients)* 1/2 (50%) at 35 months for lung metastases *No surgery (4 patients)* 0/4 (0%)	*Surgery (2 patients)* 1/2 (50%) without tumour at 24 months *No surgery (4 patients)* 1/4 (25%) with local progression at RFA site and new liver metastases at 12 months 1/4 (25%) with local progression and new liver metastases at 12 months 1/4 (25%) without tumour at 12 months 1/4 (25%) with lung metastases at 10 months	6 patients — 2 underwent hepatic resection within 35 days of RFA and 4 did not have surgery

Table 16 continued

Study	Outcomes					
	Recurrence rate		Complete ablation	Mortality	Survival	Other
	Local	New				
Solbiati *et al* (2001a, b)	Patients 64/117 (55%) had at least 1 local recurrence at 18 months median follow-up (34/64 had retreatment of at least 1 of these lesions)	Patients 89/158 (56%) new metastases (helical CT) 44% estimated Kaplan-Meier local recurrence at 18 months (n = 117)	Complete tumour necrosis (helical CT) 204/276 lesions (74%) Complete tumour necrosis according to tumour size (helical CT) <3 cm 173/211 (82%) >3 cm 31/65 (48%)	Treatment-related mortality 0/223 sessions (0%) Cancer-related mortality 55/158 (35%) (mean 20 months follow-up)	Kaplan-Meier estimated survival (n = 158) 1 year 96% 3 years 43% 5 years 14% Estimated median survival 33 months	Major complications occurred 3/223 treatment sessions (1%) (1 jejunal (required surgery), 1 large bowel perforation(required surgery), 1 peritoneal seeding) Minor complications (not requiring therapy) 12/223 sessions (5%)

Table 17 Outcomes for RFA for the treatment of NLM — non-randomised comparative studies

	Mazziotti *et al* (2001) (Level III-2)	
Outcomes	**PEI n = 1**	**RFA n = 1**
Local recurrence (progression of disease at treatment site detected by CT scan so underwent surgical resection and examination of surgical specimen)	1/1 (100%) (18 months)	1/1 (100%) (2 months)
Incomplete tumour necrosis (detected by CT scan so underwent surgical resection and examination of surgical specimen)	1/1 (100%) >80% incomplete	1/1 (100%) 50% incomplete
Mortality	0/1 (0%) (8 months)	0/1 (0%) (5 months)

Table 18 Outcomes for RFA for the treatment of NLM — case series

	Outcomes					
Study	**Recurrence rate**		**Complete ablation**	**Mortality**	**Survival**	**Other**
	Local	**New**				
Berber *et al* (2002)	*Patients* During follow-up (Mean 1.6 [1.2] years) 4/32 (13%) *Lesions* 6/227 (3%) (between 6–12 months) mean size of recurrent lesion 4.2 cm [6.4]	*Patients* During follow-up (Mean 1.6 [1.2] years) New liver lesions 9/32 (28%)		Perioperative mortality 0/34 (0%) (treatment-related mortality) Mortality during follow-up (Mean 1.6 [1.2] years) 9/34 (27%) (6/34 (18%) due to progression of liver disease; 2/34 (6%) due to progression of extrahepatic disease; 1/34 (3%) unknown cause)	Mean survival after diagnosis of primary disease (years) 5.5 [4.7] Mean survival after detection of liver disease (years) 3 [1.7] Mean survival after RFA (years) 1.6 [1.2]	Patients with significant symptoms prior to RFA 19/34 (56%) Resolution of symptoms after RFA 12/19 (63%) Significant relief 3/19 (16%) Some relief 3 (16%) No change 1/16 (6%) Length of symptomatic response (months) mean 10.1 [8.7] (range 6–24) Mean hospital stay (days) 1.1 (range 1–2) Complications 2/42 procedures (5%) (1 perioperative transient atrial fibrillation, and postoperative hepatic abscess) 20 lesions in 11 ablations not detected on preoperative CT scan but visualised by laparoscopic ultrasonography Repeat ablations 8/7 patients Tumour markers decreased 65% of patients (3 months) Mortality 0% New liver disease 40% No decrease in tumour markers 35% of patients (3 months) Mortality 43% Hepatic or extrahepatic disease 86%

Continued

Table 18 continued

Study	Outcomes					
	Recurrence rate		Complete ablation	Mortality	Survival	Other
	Local	New				
Berber *et al* (2002) *continued*						New extrahepatic disease 8/32 (25%) Progression of disease 4/32 (13%) No progression of cancer 13/32 (41%)
Buscarini *et al* (2001)	No local recurrence (mean 10.1 months, could not be separated for other tumour types)		Complete tumour ablation (1/1 patient)			
Chung *et al* (2001a)				Treatment-related mortality 0/3 (0%) Cancer-related mortality 0/3 (0%)		No evidence of disease 1/3 (10 months) Alive with disease 2/3 (13 and 18 months) Postoperative bleeding 0/3 (0%) All patients discharged within 2 days
Kosari *et al* (2001)	*Lesions* 2/29 (7%) (in 1 patient, likely to be due to incomplete RFA because of tumour location)	*Patients* 4/7 (57%) new hepatic disease		1/7 (14%) (antecedent complications of uncontrolled carcinoid disease)		Mean size of locally recurrent lesion (cm) 3.5 (range 1–3.5) New systemic disease 2/7 (29%) patients Complications 0/7 (0%)
Kuvshinoff *et al* (2002)						5/6 patients had no measurable disease on CT scan (follow-up not stated)
Quellet *et al* (2002)	*Patients* 0/2 (0%) at 6 months (disease free)			0/2 (0%) (follow-up not stated)		

Table 18 continued

Study	Outcomes					
	Recurrence rate		Complete ablation	Mortality	Survival	Other
	Local	New				
Siperstein *et al* (2001)	*Patients* 3/15 patients (20%) mean 12.1 months (15/18 followed up) *Lesions* 6/100 (6%)	New lesions with liver 1/6 patients (17%)	Complete ablation 1 week 6/6 (100%) patients (13/13 lesions) 3 months 4/4 (100%) patients (11/11 lesions)	315 (20%) patients during follow-up (not indicated if these are the 3 patients lost to follow-up)		Complications 2/18 patients (11%) (1 perioperative transient atrial fibrillation, 1 upper gastrointestinal bleeding)
Wessels *et al* (2001)				Mortality 1/3 (33%) (died 6 months after RFA from systemic metastases)		Intraoperative complications 0/3 patients Initial necrosis and subsequent tumour regression (1, 4, and 12 weeks) 3/3 patients (100%) Symptom score change: Patient 1 2-1 Patient 2 4-2 Patient 3 4-2 Octreotide dose change (μg/day) Patient 1 900 – 600 (33% reduction) Patient 2 1157 – 714 (38% reduction) Patient 3 900 – 0 (100% reduction) (died 6 months) Tumour size change on CT following 3/3 (100%) patients

Appendix F Ongoing and unpublished clinical trials

Table 19 Ongoing and unpublished clinical trials

Trial	Study title	Study details	Project status
NRR (study 0084078348)	Percutaneous radiofrequency thermocoagulative ablation of colorectal disease metastatic to the liver	Not stated	End date: 30/06/2003
NRR (N0084096603)	A phase II trial of adjunctive combination chemotherapy for patients with low volume inoperable liver metastases from colon cancer treated with RFA (Radiofrequency Ablation)	30 patients Phase II trial	End date: 31/12/2002
NRR (N0264098280)	The role of radiofrequency ablation on the outcome of metastasis of the liver	Not stated	End date: 30/06/2002
NRR (N0084078194)	A Phase II study of combination primary chemotherapy (campto-5FU/FA) followed by radiofrequency ablation (RFA) for patients with low volume inoperable liver metastases from colon cancer	Phase II	End date: 01/06/2004
EORTC 40004	CLOCC trial (chemotherapy + local ablation versus chemotherapy)	Randomized phase III study of local treatment of liver metastases by radiofrequency combined with chemotherapy versus chemotherapy alone in patients with unresectable colorectal liver metastases	Still open
NCI-G01-2045	Surgery with or without radiofrequency ablation followed by irinotecan in treating patients with colorectal cancer that is metastatic to the liver	Phase II trial to determine the effectiveness of surgery with or without radiofrequency ablation followed by irinotecan in treating patients who have colorectal cancer that is metastatic to the liver	Currently recruiting patients — target 70
NCI-G00-1850	Magnetic-resonance-guided radiofrequency ablation in treating patients with primary kidney cancer, liver metastases, or other solid tumours	Not stated	Currently recruiting patients
NCI99-C-0025	The use of radiofrequency ablation to treat hepatic neoplasms	Noncomparative study of unresectable primary and secondary liver tumours	Not stated

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; NCI, National Cancer Institute; NRR, National Research Register; RFA, radiofrequency ablation.

Abbreviations

Measurement abbreviations

CI	confidence interval
RR	relative risk
[]	standard deviation
{}	unit of measurement not defined
WMD	weighted mean difference

General abbreviations

CLM	colorectal liver metastases
CT	computed tomography
HAE	hepatic artery embolisation
HAIC	hepatic artery infusion chemotherapy
HCC	hepatocellular carcinoma
LITT	laser-induced thermotherapy
MCT	microwave coagulation therapy
NLM	neuroendocrine liver metastases
MS-PEI	multiple-session percutaneous ethanol injection
PEI	percutaneous ethanol injection
RCT	randomised controlled trial
RFA	radiofrequency ablation
SS-PEI	single-session percutaneous ethanol injection
TACE	transcatheter chemoembolisation

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