

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of radiofrequency ablation for colorectal liver metastases

Colorectal cancer is a type of cancer that develops in the colon (bowel) or rectum (back passage). Cancer cells can spread from where they start (the 'primary tumour') to other parts of the body to form one or more 'secondary tumours'. These secondary tumours are known as 'metastases' and for bowel cancer, they most commonly occur in the liver.

Radiofrequency ablation uses heat to destroy cancer cells in the liver. It involves placing one or more electrodes into the tumour. The electrodes are used to heat the tumour with the aim of destroying it. Radiofrequency ablation can be applied through the skin or during surgery.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in May 2009.

Procedure name

- Radiofrequency ablation for colorectal liver metastases

Specialty societies

- Association of Upper GI Surgeons (AUGIS)
- British Society of Interventional Radiologists
- Association of Laparoscopic Surgeons.

Description

Indications and current treatment

Colorectal cancer arises in the colon or rectum. It is the second most common cancer in women and the third most common cancer in men in the UK. Cancer will recur in around 50% of colorectal cancer patients within 5 years of initial diagnosis, with the liver being the most common site for metastatic disease.

The treatment of patients with liver metastases from colorectal cancer is usually palliative. However for a minority of patients, surgical resection with curative intent may be possible. Fitness for surgery and the number, location and size of the metastases may dictate the use of alternative treatment options. These include systemic chemotherapy, radiotherapy, thermal ablation, chemo-embolisation and selective internal radiation therapy.

Radiofrequency (RF) ablation may be indicated as the primary treatment for liver metastases where the patient is unfit for surgery or in the treatment of post-resection recurrence.

What the procedure involves

Radiofrequency ablation is a thermoablative technique that produces tumour destruction by heating cancer cells to temperatures exceeding 60°C.

Radiofrequency ablation induces temperature changes using high-frequency alternating current applied via an electrode or electrodes placed within the tissue to generate ionic agitation. The resulting frictional heating of tissue surrounding the electrode generates localised areas of coagulative necrosis and tissue destruction.

Different types of radiofrequency needle electrodes are available. The electrodes are inserted into the target tumour area (or areas) using imaging guidance during surgery (open or laparoscopic), or percutaneously.

List of studies included in the overview

This overview is based on 1570 patients from one systematic review¹, two non-randomised controlled trials^{2,3}, three case series^{4,5,6}, and two case reports^{7,8}.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Efficacy

A systematic review reported the outcome of one non-randomised controlled trial of 46 patients, which reported that median survival from diagnosis was

44 months in patients treated with RF ablation and 54 months in patients treated by surgical resection (measurement of significance not reported)¹. In the same systematic review, seven case series reported that cancer-related mortality ranged from 0% to 50% at 6- to 10-month follow-up, and six case series reported that survival ranged from one out of six patients at 11-month follow-up to seven out of eight patients at 2-to 6-month follow-up.

A non-randomised controlled trial of 418 patients reported that patients treated by surgical resection had 3-year overall survival of 73%, 4-year survival of 65%, and 5-year survival of 58%, which was significantly better than patients treated by RF ablation alone, or RF ablation plus resection (figures not reported) ($p < 0.0001$)². The difference in survival between patients treated by RF ablation alone and RF ablation plus surgical resection was not statistically significant ($p = 0.36$). Recurrence at any site occurred more often in the RF ablation group (84%) than in the surgical resection group (52%) at median 21-month follow-up ($p < 0.001$).

A non-randomised controlled trial of 258 patients reported that 3-year disease-free survival was significantly greater in patients treated with surgical resection alone (39.8% than in those treated with RF ablation plus resection (34.1%) (absolute figures not reported) ($p = 0.01$)³. Recurrence at any site at 1-year follow-up was significantly lower in the resection group (24.4%) than in the RF ablation plus resection group (60.5%) or the RF ablation alone group (65.9%) ($p < 0.001$).

A case series of 309 patients treated with percutaneous RF ablation reported 5-year survival of 24% for 123 patients with five or less metastases of 5 cm or less maximum diameter and 33% for 69 patients with three or less tumours below 3.5 cm in diameter⁴.

A case series of 161 patients treated with laparoscopic RF ablation reported that local recurrence occurred in 37% (124/335) of patients at 17-month follow-up⁵. A case series of 243 patients with unresectable disease (defined as a poor response to chemotherapy or comorbidity limiting surgical excision), reported 20.2% survival at 3-year follow-up, and 18.4% at 5-year follow-up⁶.

Safety

Four studies did not report on safety outcomes^{2,3,5,6}.

A systematic review described three cases series that reported postoperative complication rates of between 0% and 33%. The complications included bowel perforation, peritoneal seeding (such as peritoneal metastasis), bile duct stricture, wound infection, and postoperative bleeding¹.

A case series of 309 patients reported haemorrhage requiring transfusion in 1% (7/617) of treatment sessions, abscess in 1% (6/617), jaundice in < 1% (4/617) and visceral thermal injuries in < 1% (4/617) of treatment sessions⁴.

A case series of 122 patients reported infected biloma development (requiring percutaneous drainage) in 1% (1/122) of patients, and biliary dilation and

cholangitis, leading to biliobronchial fistula in 1% (1/122) of patients⁷. Minor complications (not requiring intervention) included small haemoperitoneum development in 2% (3/122), biliary dilation in 3% (4/122), and persistent pain (site not reported) in 2% (3/122).

A case report describes a patient (previously treated with surgical resection and also cryoablation), treated with percutaneous RF ablation for a colorectal liver metastasis⁸. At 3-week follow-up, a fistula to the gastric antrum (not otherwise described) was identified. It was treated conservatively without antibiotics but with an ileostomy bag. At 6-month follow-up there were no remaining signs of the fistula.

A second case report describes a patient who reported pain and fever (40°C) at 5-day follow-up. Abdominal ultrasound revealed an intrahepatic abscess, which was drained by ultrasound guided insertion of an 18F tube. The patient recovered uneventfully⁹.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to radiofrequency ablation for the treatment of colorectal liver metastases. Searches were conducted of the following databases, covering the period from their commencement to 20 January 2009 and updated to 03 August 2009: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy).

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with colorectal liver metastases
Intervention/test	Radiofrequency ablation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

Existing assessments of this procedure

There were no published assessments from other organisations, other than those included in table 2, identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Microwave ablation for the treatment of metastases in the liver. NICE interventional procedures guidance 220 (2007). Available from www.nice.org.uk/IPG220
- Selective internal radiation therapy for colorectal metastases in the liver. NICE interventional procedures guidance 093 (2004). Available from www.nice.org.uk/IPG93
- Radiofrequency ablation for the treatment of colorectal metastases in the liver. NICE interventional procedures guidance 92 (2004). Available from www.nice.org.uk/IPG92 (current guidance).

Table 2 Summary of key efficacy and safety findings on radiofrequency ablation for colorectal liver metastases

Abbreviations used: CEA, carcinoembryonic antigen; CT, computed tomography; IQR, interquartile range; RF, radiofrequency; US, ultrasound;			
Study details	Key efficacy findings	Key safety findings	Comments
Sutherland (2003)¹ Systematic review Patients with colorectal liver metastases. 1 non-randomised controlled study 46 patients (16 surgical resection and 30 RFA) 9 case-series studies Bleicher et al 2000: 54 patients Chung et al 2001: 6 patients Cuschieri et al 1999: 8 patients Kosarie et al 2002: 18 patients Kuvshinoff and Ota 2002: 15 patients Machi et al 2000: 9 patients Pearson et al 1999: 46 patients Rossi et al : 6 patients Solbiati et al (4 studies): 158 patients Inclusion criteria: Criteria for resectability in each individual study are not reported. Follow up: not reported – varied across included studies	Non-randomised controlled study Median survival from diagnosis of liver metastases RFA: 44 months Surgical resection: 54 months 5-year survival RFA: 40% Surgical resection: 53% Case series Local recurrence (6 studies): ranged from 4% at a median 15-month follow-up to 55% at a median 18-month follow-up in another study. New recurrence (5 studies): ranged from 2% to 56%. Therapeutic response (2 studies): complete ablation ranged from 74% to 84%. Mortality (7 studies): Cancer-related mortality rates ranged from 0–50% at 6–10-month follow-up. Survival (6 studies): ranged from 17% (1/6) at 11 months to 88% (7/8) at 2–6 months.	Non randomised controlled study No safety data reported Uncontrolled evidence 6/9 studies reported complication rates. Postoperative complications rates ranged from 0% to 33% (3 studies – small number of patients given the patient numbers). These complications included: - wound infection - bile duct stricture - bowel perforation - peritoneal seeding (not otherwise defined) - postoperative bleeding.	Inclusion criteria for the review included case series assessing RFA for the treatment of colorectal metastases were included if the studies had: consecutive patients; a follow up of at least 12 months, treatment site recurrence reported per patient, not just nodule, results from metastatic liver carcinoma could be extracted separately. Studies included open, laparoscopic and percutaneous approaches. Considered two comparators for patients with metastatic colorectal liver tumours: surgical resection (operable) and hepatic arterial infusion chemotherapy (inoperable)

Abbreviations used: CEA, carcinoembryonic antigen; CT, computed tomography; IQR, interquartile range; RF, radiofrequency; US, ultrasound;			
Study details	Key efficacy findings	Key safety findings	Comments
Abdalla E K (2004)² Non randomised controlled study USA Study period: 1992 to 2002 Study population: patients with pathologic confirmation of colorectal liver metastases. Age: 60 years, (mean), Sex: 61% male. n = 418 (n = 57 RF, n = 101 RF + resection). Inclusion criteria: no previous hepatic resection or RF ablation. RF ablation was not performed adjacent to major biliary structures. Patients included in the RF arms of the study were selected as having 1) potentially curative treatment and 2) complete resection was not possible. Based on imaging or preoperative findings. Technique: open laparotomy, US guided RF ablation with needle repositioning for tumours >2.5 cm and repeat treatment, or resection, or combination with RF ablation versus chemotherapy. Follow-up: 21 months median. Conflict of interest: not reported	Overall survival Patients treated with resection had a 73% overall survival at 3 years, 65% at 4 years and 58% at 5 years, which was significantly better than that following RF ablation alone, or RF ablation and resection (figures not reported) ($p < 0.0001$). Multivariate analysis including other risk factors (tumour stage and number of tumours) showed that patients treated with RF ablation plus resection had worse survival than those treated with resection alone (hazard ratio 2.15, 95% confidence interval [CI] 1.28 to 3.59) ($p = 0.004$). Similarly, patients treated with RF ablation alone had worse survival than those treated with resection alone, hazard ratio 2.79 (95% CI 1.68 to 4.62) ($p < 0.0001$). The difference in survival between RF ablation alone and RF ablation plus resection was not statistically significant ($p = 0.36$). In patients whose cancer was considered 'unresectable' there was a statistically significant difference (improved) in survival for patients treated with RF ablation and resection compared to a control group treated with chemotherapy alone ($p = 0.003$), and in patients treated with RF ablation alone compared with chemotherapy ($p = 0.005$). Recurrence Recurrence at any site occurred more often in patient treated by RF ablation only (84%) than with resection only (52%) ($p < 0.001$).	Safety outcomes were not reported on.	Retrospective study 70 patients found to have disease too extensive for curative therapy based on disease distribution or extent were treated by chemotherapy. Concomitant procedures were undertaken in patients in the RF group, the resection group and the resection plus RF ablation group, which included contralateral hepatic resection, and/or intra-arterial pump placement. Patients not randomised to study groups, but selected depending on clinical criteria. Authors state that a proposal for a randomised controlled trial comparing RF ablation versus resection for <i>potentially resectable</i> (author's italicisation) colorectal liver metastases may be inappropriate at this time.

Abbreviations used: CEA, carcinoembryonic antigen; CT, computed tomography; IQR, interquartile range; RF, radiofrequency; US, ultrasound;																			
Study details	Key efficacy findings	Key safety findings	Comments																
Gleisner A L(2008)³ Non randomised controlled study USA Study period: Jan 1991 to Aug 2006. Study population: patients with colorectal liver metastases treated with curative intent. Age: 61 years, (median), Sex: 66% male. Tumour stage T1/T2 = 14%, T3/T4 = 86. Median size of largest lesion 3.0 cm. n = 258 (n = 11 RF, n = 55 RF + resection). Inclusion criteria: patients without prior 'liver directed' therapy, patients treated with percutaneous or laparoscopic RF ablation were excluded. Patients in the RF arms were selected when at least one hepatic tumour was considered unresectable because of location of disease, inadequate liver remnant, proximity to major vessels, or medical comorbidity Technique: Open laparotomy, US guided RF ablation alone or in combination with resection, Vs resection alone. Follow-up: not reported. Conflict of interest: none	Survival (Unadjusted actuarial analysis) 3-year disease-free survival was significantly greater in patients treated with resection alone (39.8%) than in those treated with RF ablation plus resection (34.1%) (p = 0.01). There was no significant difference in survival between the RF plus resection group (34.1%) and the RF ablation alone group (7.4%) (p = 0.20). 3 year overall survival was significantly greater in patients treated with resection (74.1%) than in those treated with RF plus resection (44.9%) (p < 0.01). There was no significant difference in survival between the resection group (74.1%) and the RF ablation alone group (72.7 %) (p = 0.20). On multivariate analysis only baseline CEA level > 100ng/ml (hazard ratio 1.99, 95% CI 1.09 to 3.65) (p < 0.05), and treatment with RF ablation plus resection (hazard ration 2.09, 95% CI 1.28 to 3.42) (p < 0.05) were independent predictors of worse disease-free survival. Recurrence Any site recurrence at 1-year follow-up. p value resection versus RF alone or RF plus resection. <table> <tr> <td>Resection</td><td>RF plus resection</td><td>RF alone</td><td>p =</td></tr> <tr> <td>24.4%</td><td>60.5%</td><td>65.9%</td><td>< 0.001</td></tr> </table> Liver only recurrence at 1-year follow-up. p value resection versus RF alone or RF plus resection. <table> <tr> <td>Resection</td><td>RF plus resection</td><td>RF alone</td><td>p =</td></tr> <tr> <td>2.0%</td><td>10.3%</td><td>41.3%</td><td>< 0.001</td></tr> </table>	Resection	RF plus resection	RF alone	p =	24.4%	60.5%	65.9%	< 0.001	Resection	RF plus resection	RF alone	p =	2.0%	10.3%	41.3%	< 0.001	Safety outcomes were not reported on.	Prospective data collection. Chemotherapy regimen varied between patients. Patients treated with resection had larger tumours (3.5 cm IQR 2.0 to 5.0) than those treated with RF ablation plus resection (2.5 cm IQR 1.9 to 4.0) (p = 0.02). Patients treated with resection had fewer tumours (1 metastasis IQR 1 to 2) than those treated with RF ablation plus resection (5 metastases IQR 3 to 6) (p < 0.001). 5 of the 11 patients who underwent RF ablation alone were treated for a lesion immediately adjacent to the hepatic veins.
Resection	RF plus resection	RF alone	p =																
24.4%	60.5%	65.9%	< 0.001																
Resection	RF plus resection	RF alone	p =																
2.0%	10.3%	41.3%	< 0.001																

Abbreviations used: CEA, carcinoembryonic antigen; CT, computed tomography; IQR, interquartile range; RF, radiofrequency; US, ultrasound;			
Study details	Key efficacy findings	Key safety findings	Comments
Gillams AR (2009)⁴ Case series UK Study period: 1997–2007 Study population: patients with colorectal liver metastases Sex: 64% male. Mean age = 64 years n = 309 (617 treatment sessions) Inclusion criteria: patients deemed to be inoperable by multidisciplinary team; 5 or fewer tumours ≤ 5 cm in diameter or as many as 9 tumours but with maximum diameter of 4 or 4.5 cm or a solitary tumour < 7 cm in diameter. Technique: percutaneous RFA under combined US and CT guidance/monitoring. Follow-up: 5 years Conflict of interest: none stated	For 123 patients with ≤ 5 tumours of ≤ 5 cm maximum diameter and no extrahepatic disease, median survival was 46 months from liver metastasis diagnosis and 36 months from ablation. Five-year survival after diagnosis was 34% and 24% after ablation. For 69 patients with ≤ 3 tumours below 3.5 cm in diameter, 5-year survival was 40% after diagnosis and 33% after ablation. On multivariate analysis, significant survival factors were the presence of extrahepatic disease ($p < 0.001$) and liver tumour volume ($p = 0.001$).	‘There was no procedure related mortality’. Major complications (requiring intervention of hospital stay beyond 72 h) = 4.7% (29/617): • systemic complications = 0.8% (5/617) • visceral thermal injuries = 0.6% (4/617) • abscess = 1.0% (6/617) • jaundice = 0.6% (4/617) • haemorrhagic complications requiring transfusion = 1.1% (7/617) • anaesthetic complication = 0.2% (1/617) • pneumothorax = 0.2% (1/617) • asymptomatic pseudoaneurysm = 0.2% (1/617)	Prospective study Losses to follow-up were not described. Some patients progressed between referral for ablation and treatment and so were treated for more extensive disease than intended. Kaplan-Meier survival analysis.

Abbreviations used: CEA, carcinoembryonic antigen; CT, computed tomography; IQR, interquartile range; RF, radiofrequency; US, ultrasound;			
Study details	Key efficacy findings	Key safety findings	Comments
Berber E (2008) ⁵ Case series USA Study period: Nov 1999 to Aug 2005 Study population: patients with two or more colorectal liver metastases treated with curative intent. Age: not reported, Sex: not reported. Median size of largest lesion 2.6 cm (all lesions not only colorectal metastases). n = 161 (480 metastases) Inclusion criteria: Patients with unresectable tumours involving < 20% of the liver volume, enlarging liver lesions, worsening symptoms, or failure to respond to other treatment modalities. 80% of patients with colorectal metastases had progression of their metastases before RF ablation. Technique: General anaesthesia. Laparoscopic, US guided RF ablation. Follow-up: 17 months (range 3 to 36). Conflict of interest: not reported	Recurrence Overall (in all tumour types) local recurrence was identified on CT evaluation in 21.7% (231/1032 of tumours) and 37% (124/335) of patients. Of all tumour types treated, local recurrence was highest for colorectal liver metastases (34% 161/480) and 46% of patients (absolute numbers not reported). 83% of recurrences were evident at 1 year, and 97% by 2-year follow-up. 28% (45/161) of tumours which had local recurrence were amenable to repeat RF ablation, of which 40 were treated. Multivariate analysis identified that colorectal metastasis tumour type was a significant predictor of local recurrence (hazard ratio 2.6, 95% CI 1.94 to 3.44) ($p > 0.0001$). Other significant predictors of local recurrence were tumour size, ablation margin, and blood vessel proximity.	Safety outcomes were not reported on.	Study reports on a total of 335 patients with 1032 unresectable liver tumours, but describes results from patients with colorectal liver metastases separately. Mean follow-up period reported is for all liver tumours in the study not specifically for colorectal metastases. Patients with unresectable tumours due to technical factors, comorbidity, extrahepatic disease, or patient choice. Efficacy outcomes are reported per tumour and per patient. Not clear whether efficacy outcomes include patients who were amenable to repeat RF ablation and underwent a second treatment.

Abbreviations used: CEA, carcinoembryonic antigen; CT, computed tomography; IQR, interquartile range; RF, radiofrequency; US, ultrasound;			
Study details	Key efficacy findings	Key safety findings	Comments
Siperstein A E (2007) ⁶ Case series USA Study period: May 1997 to Dec 2006 Study population: patients with colorectal metastases, Sex: 63% Male, Age: 62 years (mean). Mean size of largest lesion = 3.9 cm, mean number of tumour s= 2.8, Stage T3/T4 = 87%. Median period from diagnosis to treatment = 8 months. n = 243 (292 treatments) Inclusion criteria: Patients referred for RF ablation by a multidisciplinary team. Patients with unresectable disease (defined as a poor response to chemotherapy or comorbidity limiting surgical excision). 80% of patients with colorectal metastases had progression of their metastases before RF ablation. Technique: Laparoscopic, US guided RF ablation. Patients discharged on first postoperative day. Follow-up: 24 months (median) (range 1 to 94 months) Conflict of interest: Supported by manufacturer	Survival Median overall actuarial survival was 24 months. Actual survival was 20.2% at 3 years, and 18.4% at 5 years (absolute figures not reported). Patients with <3 lesions at baseline had a statistically significant longer survival (mean 27 months), than those with >3 lesions (mean 17 months) (p = 0.0018). No factor was found to be predictive of overall survival in multivariate analysis. Excluding patients found to have extrahepatic disease at baseline, median actuarial time to progression was 6 months. Median survival was not related to sex (p = 0.34), nor stage of tumour (p = 0.35).	Safety outcomes were not reported on.	Prospective study. Consecutive patient cohort. The majority of patients received chemotherapy at some point in their treatment. Baseline chemotherapy regimens changed during the course of the study.

Abbreviations used: CEA, carcinoembryonic antigen; CT, computed tomography; IQR, interquartile range; RF, radiofrequency; US, ultrasound;						
Study details		Key efficacy findings		Key safety findings		Comments
Veltri A (2008) ⁷		Surgical parameters		Complications		Decision to perform RF ablation made jointly by surgeon and interventional radiologist.
Case series		The RF ablation procedure was technically feasible in all patients. Complete and sustained ablation was obtained in 55% (102 /186) lesions treated.		There were no perioperative or postoperative deaths related to complications or morbidity.		
Italy		Recurrence		Overall 11% (13/115) of patients had an adverse event		RF ablation system used varied during the study period.
Study period: Mar 1996 to Jan 2005		26% (49/186) of lesions initially considered completely ablated at imaging showed local recurrence at a mean of 10.7 months follow up				
Study population: patients with colorectal metastases, Sex: 61% Male. Age: 65 years (mean). Mean size of largest lesion = 2.9 cm, mean number of tumour s= 1.6.		Survival		ComplicationRate		The denominator number of patients used in calculating overall adverse events is less than the total number of patients treated.
n = 122 (199 tumours)		Overall actual survival (absolute numbers not reported)		Major		
Inclusion criteria: Patients not candidates for surgical resection due to contraindications to general anaesthesia, extrahepatic metastases, recurrence after resection, disease progression despite chemotherapy, or lesions in sites judged unresectable.		1 year2 years3 years5 years		Infected biloma (requiring percutaneous drainage)		Number of patients available for analysis at each follow up time point is not reported.
Technique: General anaesthesia. Laparoscopic or percutaneous, US guided RF ablation. n = 21 patients treated with a 'combined' procedure with ischaemia-inducing manoeuvres.		From diagnosis		Biliary dilation, cholangitis, leading to biliobronchial fistula		
Follow-up: 24 months (mean) (range 1 to 86 months)		From RF ablation		Minor (no intervention required)		More than 75% of patients underwent subsequent treatment after ablation which might have affected outcome.
Conflict of interest: Supported by charity		Of the 69 patients who died during follow-up 13% (9/69) were from intercurrent diseases, 6% (4/69) were from hepatic progression, 7% (5/69) from extrahepatic progression, and 74% (51/69) because of both local and systemic progression.		Small haemoperitoneum		
		In patients with tumour <3cm in diameter median survival was 36.2 months (95% CI 27.5 to 50.9), which was significantly longer than in patients with tumour >3cm in diameter (23.2 months. 95% CI 14.6 to 31.6)(p = 0.006).		Biliary dilation		
				Persistent pain		
				Hyperthermia		
				Subcapsular fluid collection		

Abbreviations used: CEA, carcinoembryonic antigen; CT, computed tomography; IQR, interquartile range; RF, radiofrequency; US, ultrasound;			
Study details	Key efficacy findings	Key safety findings	Comments
Frich L (2005)⁸ Case report Norway Study period: not reported Study population: patients with colorectal metastases, Sex: 100% Male, Age: 67 years (at diagnosis). Size of lesion = 1.5 cm, period from diagnosis to treatment = 28 months. n = 1 Inclusion criteria: Patient with colorectal liver metastases. Technique: General anesthesia, percutaneous, US guided RF ablation. Follow-up: 6 months Conflict of interest: not reported	Patient underwent primary surgery on the sigmoid colon in 2001 and at the time biopsy-proven liver metastases in both liver lobes were present. 15 months later right hepatectomy performed, removing four lesions with free resection margins. A further 3 months later 1 metastasis was treated with MRI guided percutaneous cryoablation. CT examination at a further 10-month follow-up found a 1.5 cm diameter tumour in segment III of the left liver lobe, close to the wall of the gastric antrum. At 2-day follow-up post RF ablation, repeat US scan found that an area without contrast enhancement with a 5 cm diameter was still present and a vascular structure could be seen traversing the left anterior part of the thermal lesion. The postoperative course was uneventful. At 3-day follow-up, the patient was assessed with CT scan per protocol and discharged. At 3-week follow-up the patient noted local tenderness and a skin rash at the site of electrode placement. An abscess was diagnosed and incised at the local hospital. A further 2 days later, the patient observed gastric content in the wound. Perforation of the gastrointestinal tract was suspected and the patient admitted. Fistulography showed passage of contrast material from the abdominal skin wound through a fistula to the gastric antrum. There was no abscess cavity, and the internal opening of the fistula could not be identified by gastroscopy. Secretion from the fistula tested positive for <i>streptococcus milleri</i>. The patient was treated conservatively without antibiotics; an ileostomy bag was fitted. At 1 week after discharge secretion was 40 ml/four, but ceased within 3 weeks. At 6-month follow-up there were no signs of either the fistula or abscess. CT of the abdomen did not show any new liver tumours or recurrence at the site of RF ablation.		Operator experience of this technique not reported. 'Denominator' of patients treated at the institution not reported. This patient was included in an ongoing trial of RF ablation. Considerable history of liver interventions.

Abbreviations used: CEA, carcinoembryonic antigen; CT, computed tomography; IQR, interquartile range; RF, radiofrequency; US, ultrasound;			
Study details	Key efficacy findings	Key safety findings	Comments
Pende V (2007)⁹ Case report Italy Study period: not reported Study population: patient with colorectal metastases, Sex: 100% Female, Age: 61 years (at diagnosis). Period from diagnosis to treatment = 20 months. n = 1 Inclusion criteria: Patient with colorectal liver metastases. Technique: Percutaneous, US guided RF ablation. Follow-up: 10 months Conflict of interest: none	Patient underwent left colectomy and liver resection as primary procedure. 20 months later percutaneous RF ablation was performed on liver segments V to VII because of a new periportal metastasis. Postoperatively the patient had hyperpyrexia (38.5°C), cough, and dyspnoea. X ray showed a right pleural effusion, and thoracocentesis found bile stained fluid. A drainage tube was inserted. CT scan showed a right subdiaphragmatic fluid collection. Endoscopic retrograde cholangiopancreatography showed a biliopleural fistula originating from the anteromedian duct. A 6F nasobiliary drain was positioned over the fistula. Bilious fluid leak from the chest tube slowed and had stopped at 2-day follow-up, and the pleural tube removed. At 5-day follow-up, the patient reported abdominal pain and fever (40°C). Abdominal US showed an intrahepatic abscess on segments V to VII and a 18F tube was inserted to drain the purulent biloma. Percutaneous cholangiopathy demonstrated an irregular cavity not communicating with the biliary tree. A repeat endoscopic retrograde cholangiopancreatography showed 'opacization' of the liver cavity through a biliary duct from the residual segment VIII. A 15 cm plastic biliary endoprosthesis was placed after drain removal. A further 7 days later abdominal US confirmed regression of the abscess. The percutaneous tube was removed, leaving the biliary stent in place. The patient recovered uneventfully, but died at 10-month follow-up due to disease progression.		'Denominator' of patients treated at the institution not reported. Previous liver resection surgery undertaken. Concomitant chemotherapy regimen (if any) not reported.

Validity and generalisability of the studies

- There is considerable variation both within and between studies, in terms of patient inclusion criteria, with respect to how 'surgical resectability' is defined (judged), both in technical (surgical) and patient comorbidity terms. Therefore it is difficult to interpret efficacy outcomes reported in different patient groups in different studies.
- Some patients had multiple lesions ablated.
- No randomised controlled trials are available. In non-randomised controlled trials, patients selected for surgical resection may have had a different clinical profile than those who received RF ablation.
- Comparison of risk factors was not always formally reported, although sometimes considered within multivariate regression analysis.
- Many patients received concomitant chemotherapy. It is difficult to disaggregate the effect on outcomes of each treatment modality.
- Survival outcomes have been analysed either from time of diagnosis or from time of RF ablation procedure.

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Dr M Callaway (Royal College of Radiologists), Prof. I Taylor (Royal College of Surgeons), Mr G Poston (British Association of Surgical Oncology), Mr D Alcorn (British Society of Interventional Radiology)

- Three Specialist advisers who responded considered the procedure to be established and no longer new.
- The main comparator treatments are chemotherapy or surgical resection.
- The key efficacy outcomes for this procedure are overall survival and local recurrence rates.
- Anecdotal adverse events following this procedure include damage to biliary tree, persistent pleural effusion, post-ablation syndrome, bradycardia, bleeding, infection, pain and abscess.
- Additional theoretical adverse events may include injury to the bowel or diaphragm, damage to the pleura or lungs and seeding of the tumour.

- There is controversy over the indication for this procedure; most operators will no longer consider lesion > 4 cm in diameter for treatment.
- The role of this procedure among other treatment strategies is still not clear. Chemotherapy regimens are changing rapidly so evidence on the use of RFA with chemotherapy is limited.
- The perception is that this procedure does not offer the curative potential of surgical resection.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme were unable to obtain patient commentary for this procedure.

Issues for consideration by IPAC

- Non English language studies are not included in this overview.
- Studies with patients with mixed liver tumour pathology (either hepatocellular carcinoma and metastatic tumours; or metastatic tumours from colorectal cancer as well as a range of primary sites) where outcomes of patients with colorectal liver metastases were not reported separately were not selected for this overview.

References

- 1 Sutherland LM. (2003) Radiofrequency Ablation of Tumours. MSAC report. MSAC application 1052:1–98.
- 2 Abdalla EK, Vauthey JN, Ellis LM et al. (2004) Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Annals of Surgery* 239:818–825.
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- 5 Berber E and Siperstein A. (2008) Local recurrence after laparoscopic radiofrequency ablation of liver tumors: an analysis of 1032 tumors. *Annals of Surgical Oncology* 15:2757–2764.
- 6 Siperstein AE, Berber E, Ballem N et al. (2007) Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. *Annals of Surgery* 246:559–565.
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- 8 Frich L, Edwin B, Brabrand K et al. (2005) Gastric perforation after percutaneous radiofrequency ablation of a colorectal liver metastasis in a patient with adhesions in the peritoneal cavity. *AJR American*:S120–S122.
- 9 Pende V, Marchese M, Mutignani M et al. (2007) Endoscopic management of biliopleural fistula and biloma after percutaneous radiofrequency ablation of liver metastasis. *Gastrointestinal Endoscopy* 66:616–618

Appendix A: Additional papers on radiofrequency ablation for colorectal liver metastases

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Abitabile, P., Hartl, U., Lange, J., and Maurer, C. A. (2007) Radiofrequency ablation permits an effective treatment for colorectal liver metastasis. <i>European Journal of Surgical Oncology</i> 33 (1) 67-71	Case series n = 47 FU = 33 months	Excellent local tumour control was achieved with radiofrequency ablation of small liver metastasis	Larger studies included in table 2
Aloia, T. A., Vauthey, J. N., Loyer, E. M., et al (2006) Solitary colorectal liver metastasis: resection determines outcome. <i>Archives of Surgery</i> 141 (5) 460-466.	NRCT n = 180 (30 RF) FU = 31 months	The survival rate following HR of solitary colorectal liver metastasis exceeds 70% at 5 years.	Larger studies included in table 2
Basdanis, G., Michalopoulos, A., Papadopoulos, V., et al (2004). Clinical short-term results of radiofrequency ablation in patients with liver metastases from colorectal cancer. <i>Techniques in Coloproctology</i> 8 Suppl-9	Case series n = 18 FU = 18 months	RFA is a safe, well tolerated procedure for the treatment of unresectable colorectal liver metastases	Larger studies included in table 2
Berber, E., Pelley, R., and Siperstein, A. E. (2005) Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study <i>Journal of Clinical Oncology</i> 23 (7) 1358-1364	Case series n = 135 FU = N/R	RFA is a useful adjunct to chemotherapy in those patients with liver-predominant disease	Larger studies included in table 2
Berber, E., Tsinberg, M., Tellioglu, G., et al (2008) Resection versus laparoscopic radiofrequency thermal ablation of solitary colorectal liver metastasis. <i>Journal of Gastrointestinal Surgery</i> 12 (11) 1967-1972	NRCT n = 158 (68 RF) FU = N/R	RFA still achieved long-term survival in patients who were otherwise not candidates for resection	Larger studies included in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Charalampopoulos, A., Macheras, A., Misiakos, E., et al (2007) Thoracoabdominal wall tumour seeding after percutaneous radiofrequency ablation for recurrent colorectal liver metastatic lesion: a case report with a brief literature review. <i>Acta Gastroenterologica Belgica</i> 70 (2) 239-242	Case report n = 1 FU = 18 months	A large size, bulky and superficial mass on the liver parenchyma adjacent to the thoracoabdominal wall as well as multiple RFA sessions, seem to represent risk factors for tumour dissemination through the needle electrode used during the RFA procedure in hepatic metastases of colorectal cancer	Larger studies included in table 2
Chen, M.-H., Dai, Y., Yan, K., et al (2005) Intraperitoneal hemorrhage during and after percutaneous radiofrequency ablation of hepatic tumors: Reasons and management. <i>Chinese Medical Journal</i> 118 (20) 1682-1687	Case series n = N/R FU = N/R	It is important to perform close monitoring during and after RF ablation in order to identify intraperitoneal haemorrhage in time	Number of patients with colorectal liver metastases was not determinable Safety outcome reported elsewhere
Cheng JGR. Laparoscopic radiofrequency ablation and hepatic artery infusion pump placement in the evolving treatment of colorectal hepatic metastases. <i>Surgical Endoscopy</i> 2003; 17(4):669	Case series n = 45 FU = 12 months	Mean survival LRFA 25.4 ± 3.4 months	Larger studies included in table 2
Chiou, Y.-Y., Chou, Y.-H., Chiang, J.-H., et al (2005) Percutaneous ultrasound-guided radiofrequency ablation of colorectal liver metastases. <i>Chinese Journal of Radiology</i> 30 (3) 153-158.	Case series n = 63 FU = 22 months	Further studies are necessary to determine the long-term efficacy of RFA in colorectal liver metastases	Larger studies included in table 2
Geyik, S., Akhan, O., Abbasoglu, O., et al (2006) Radiofrequency ablation of unresectable hepatic tumors. <i>Diagnostic & Interventional Radiology</i> 12 (4) 195-200	Case series n = 20 FU = N/R	RFA of primary and metastatic liver malignancies is a safe and effective tool for local control of disease in unresectable hepatic malignancies	Larger studies included in table 2
Evrard, S., Becouarn, Y., Fonck, M., et al (2004) Surgical treatment of liver metastases by radiofrequency ablation, resection, or in combination. <i>European Journal of Surgical Oncology</i> 30 (4) 399-406.	Case series n = 23 (colorectal) FU = 14 months	RFA increased resectability of liver metastases and reduced the morbidity.	Larger studies included in table 2
Hildebrand, P., Kleemann, M., Roblick, U., et al (2007) Laparoscopic radiofrequency ablation of unresectable hepatic malignancies: indication, limitation and results. <i>Hepato-</i>	Case series n = 14 FU = 23 months	Laparoscopic RFA is safe and provides a minimally invasive procedure with the option of simultaneous inflow-occlusion during	Larger studies included in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Gastroenterology 54 (79) 2069-2072		thermoablation	
Howard, J. H., Tzeng, C. W., Smith, J. K et al (2008), Radiofrequency ablation for unresectable tumors of the liver. American Surgeon 74 (7) 594-600	Case series n = 58 (colorectal) FU = 24 months	RFA is a safe and effective way for treating HCC and other unresectable tumours in the liver that are not eligible for hepatic resection	Larger studies included in table 2
Hur, H., Ko, Y. T., Min, B. S. et al (2009) Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. American Journal of Surgery 197 (6) 728-736	NRCT n=67 (35 RF) FU=N/R	HR had better outcomes than RFA for recurrence and survival after treatment of solitary colorectal liver metastases.	Larger studies included in table 2
Jakobs, T. F., Hoffmann, R. T., Trumm, et al (2006) Radiofrequency ablation of colorectal liver metastases: mid-term results in 68 patients. Anticancer Research 26 (1B) 671-680	Case series n = 68 FU = 21 months	For patients with non-resectable hepatic metastases of colorectal cancer, RFA is a safe option in a multimodal treatment concept and may lead to an improvement in survival	Larger studies included in table 2
Joosten, J., Jager, G., Oyen, W., et al (2005) Cryosurgery and radiofrequency ablation for unresectable colorectal liver metastases. European Journal of Surgical Oncology 31 (10) 1152-1159	NRCT n = 58 (28 RF) FU = 25 months	In patients with unresectable colorectal liver metastases, CSA and RFA can be used either alone or as an effective adjunct to resection in achieving complete tumour clearance of the liver	Larger studies included in table 2
Kanellos, I., Demetriades, H., Blouhos, K et al (2004) Radio-frequency ablation of hepatic metastases from colorectal cancer. Techniques in Coloproctology 8 Suppl-22	Case report n = 2 FU = 2 to 5 months	RF ablation emerges to be a promising method for the treatment of hepatic metastases from colorectal cancer	Larger studies included in table 2
Leblanc, F., Fonck, M., Brunet, R., et al (2008) Comparison of hepatic recurrences after resection or intraoperative radiofrequency ablation indicated by size and topographical characteristics of the metastases. European Journal of Surgical Oncology 34 (2) 185-190	NRCT n = 52 (22 RF) FU = 17 months	Assessing IRFA indications by size and the topographical characteristics of the liver metastases yields identical local recurrence rates to resection after 2 years of follow up	Larger studies included in table 2
Lee, W. S., Yun, S. H., Chun, H. K., et al (2008) Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal	NRCT n = 153 (37 RF)	Despite of higher local recurrence rate, RFA may be considered as a therapeutic option for patients whose tumours	Larger studies included in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
liver metastasis. Journal of Clinical Gastroenterology 42 (8) 945-949	FU = 38 months	are considered unsuitable for conventional surgical treatment	
Liu S, Yuk W, Lee KF et al. (2009) Needle track seeding: a real hazard after percutaneous radiofrequency ablation for colorectal liver metastasis. World Journal of Gastroenterology 15 (13) 1653-1655	Case report n=1 FU = 6 months	We believe that tumor seeding after percutaneous RFA in our patient was possibly related to its unfavorable subcapsular location and the use of an expansion-type needle.	Have peritoneal seeding reported elsewhere in overview
Liberale, G., Delhaye, M., Ansay, J., et al (2004) Biliary pleural fistula as a complication of radiofrequency ablation for liver metastasis. Acta Chirurgica Belgica 104 (4) 448-450	Case report n = 1 FU = 1 month	This description of a life-threatening complication emphasises the need for better knowledge of the contraindications of RFA, particularly for the treatment of large tumours at proximity of main bile ducts	Larger studies included in table 2 Safety outcome reported elsewhere.
Machi, J., Oishi, A. J., Sumida, K., et al (2006) Long-term outcome of radiofrequency ablation for unresectable liver metastases from colorectal cancer: evaluation of prognostic factors and effectiveness in first- and second-line management. Cancer Journal 12 (4) 318-326	Case series n = 100 FU = 25 months	Compared with historical survival, RFA appears to confer a survival benefit over systemic chemotherapy alone	Larger studies included in table 2
Ogata, S., Kianmanesh, R., Varma, D., et al (2005) Improvement of surgical margin with a coupled saline-radiofrequency device for multiple colorectal liver metastases. Journal of Hepato-Biliary-Pancreatic Surgery 12 (6) 498-501	Case report n = 1 FU = 14 months	Improving the surgical margin with a coupled saline-radiofrequency device is feasible and effective, avoiding small remnant liver even after multiple tumorectomies	Larger studies included in table 2
Oshowo A, Gillams AR, Harrison E, Lees WR, et al. (2003) Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. British Journal of Surgery 90:1240–3	NRCT n = 45 (25 RF) FU = N/R	Mean survival RFA: 37 months (range 9–67 months) Resection: 41 months (range 0–97 months)	Larger studies included in table 2
Oshowo A, Gillams AR, Lees WR, Taylor I. Radiofrequency ablation extends the scope of surgery in colorectal liver metastases. European Journal of Surgical Oncology 2003; 29(3):244–7.	Case series n = 16 FU = N/R	Patients were treated with a combination of liver resection and RF ablation.	Larger studies included in table 2
Park, I. J., Kim, H. C., Yu, C. S., et al (2008) Radiofrequency ablation for metachronous liver	NRCT	Compared with hepatic resection, RFA for metachronous hepatic	Larger studies included in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
metastasis from colorectal cancer after curative surgery. <i>Annals of Surgical Oncology</i> 15 (1) 227-232	n = 89 (30 RF) FU = N/R	metastases from colorectal cancer was associated with higher local recurrence and shorter recurrence-free and overall survival rates	
Ritz, J.-P., Lehmann, K. S., Reissfelder, C., (2006) Bipolar radiofrequency ablation of liver metastases during laparotomy. First clinical experiences with a new multipolar ablation concept. <i>International Journal of Colorectal Disease</i> 21 (1) 25-32	Case series n = 10 FU = 3 months	Bipolar radiofrequency using the novel multipolar ablation concept permits a safe and effective therapy for the induction of large volumes of coagulation in the local treatment of liver metastases	Larger studies included in table 2 Studies with longer follow up are included in table 2
Salemis, N. S. and Tsohataridis, E. (2008) Hepatic abscess after combined surgical resection and radiofrequency ablation of metastatic colon adenocarcinoma. <i>Infectious Diseases in Clinical Practice</i> 16 (1) 69-72	Case report n = 1 FU = 6 months	Patients with alterations of the biliary tree and immunocompromising conditions are at high risk of developing this major complication	Larger studies included in table 2 Safety outcome reported elsewhere.
Stang A, Fischbach R, Teichmann W et al. (2009) A systematic review on the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases. <i>European Journal of Cancer</i> 45 (10) 1748-1756	Systematic review n=? (21 studies) FU=N/R	Findings support that RFA prolongs time without toxicity and survival as an adjunct to hepatectomy and/or chemotherapy in well-selected patients, but not as an alternative to resection	Search date to Aug 2008, no additional studies not identified in overview and no meta analysis.
Suppiah, A., White, T. J., Roy-Choudhury, S. H., et al (2007) Long-term results of percutaneous radiofrequency ablation of unresectable colorectal hepatic metastases: final outcomes. <i>Digestive Surgery</i> 24 (5) 358-360	Case series n = 30 FU = 22 months	PcRFA is safe and associated with increased disease-free and overall survival in patients with unresectable colorectal hepatic metastases	May be the same patients as reported in White (2007)
van Duijnhoven, F. H., Jansen, M. C., Junggeburst, J. M., et al (2006) Factors influencing the local failure rate of radiofrequency ablation of colorectal liver metastases. <i>Annals of Surgical Oncology</i> 13 (5) 651-658	Case series n = 87 FU = 25 months	Lesions that are difficult to reach by electrodes should be approached by an open procedure	Larger studies included in table 2

Appendix B: Related NICE guidance for radiofrequency ablation for colorectal liver metastases

Guidance	Recommendations
Interventional procedures	Microwave ablation for the treatment of metastases in the liver. NICE interventional procedures guidance 220 (2007). 1.1 Current evidence on the safety and efficacy of microwave ablation for the treatment of metastases in the liver does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to use microwave ablation for the treatment of metastases in the liver should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information, including about other treatment options. In addition, use of the Institute's information for patients ('Understanding NICE guidance') is recommended • Audit and review clinical outcomes of all patients having microwave ablation for the treatment of metastases in the liver (see section 3.1). 1.3 Patient selection should be carried out by a multidisciplinary team that includes a hepatobiliary surgeon. 1.4 The procedure should be performed under appropriate imaging guidance. 1.5 As a number of devices are available, and there is some uncertainty about the energy levels that should be used, any adverse events relating to this procedure should be reported to the Medicines and Healthcare products Regulatory Agency. 1.6 Further research on the procedure would be useful. The Institute may review the procedure upon publication of further evidence.

	Selective internal radiation therapy for colorectal metastases in the liver. NICE interventional procedures guidance 93 (2004). 1.1 Current evidence on the safety of selective internal radiation therapy (SIRT) for colorectal metastases in the liver appears adequate. With regard to efficacy, the procedure may reduce tumour bulk, but there is a lack of evidence of symptom relief or increased survival, and combination with other treatments makes interpretation of the published literature difficult. 1.2 Clinicians wishing to undertake selective internal radiation therapy for colorectal metastases in the liver should take the following actions. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. Use of the Institute's Information for the Public is recommended. • Audit and review clinical outcomes of all patients having selective internal radiation therapy for colorectal metastases in the liver. 1.3 Publication of research studies with outcome measures which include survival will be useful in reducing the current uncertainty about the efficacy of the procedure. The Institute may review the procedure upon publication of further evidence. Radiofrequency ablation for the treatment of colorectal metastases in the liver. NICE interventional procedures guidance 92 (2004). (Current guidance). 1.1 Current evidence on the safety of radiofrequency ablation of colorectal metastases in the liver appears adequate. However, the evidence of its effect on survival is not yet adequate to support the use of this procedure without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake radiofrequency ablation of colorectal metastases in the liver should take the following actions. • Ensure that patients offered it understand the uncertainty about the procedure's efficacy and provide them with clear
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	written information. Use of the Institute's Information for the Public is recommended. • Audit and review clinical outcomes of all patients having radiofrequency ablation for the treatment of colorectal metastases in the liver. 1.3 Publication of research studies with outcome measures which include survival will be useful in reducing the current uncertainty about the efficacy of the procedure. The Institute may review the procedure upon publication of further evidence.
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Appendix C: Literature search for radiofrequency ablation for colorectal liver metastases

Database	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	20/01/2009	Issue 4, 2008	9
Database of Abstracts of Reviews of Effects – DARE (CRD website)	20/01/2009	N/A	6
HTA database (CRD website)	20/01/2009	N/A	7
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	20/01/2009	Issue 4, 2008	7
MEDLINE (Ovid)	20/01/2009	1950 to January Week 1 2009	435
MEDLINE In-Process (Ovid)	20/01/2009	January 19, 2009	48
EMBASE (Ovid)	20/01/2009	1980 to 2009 Week 03	510
CINAHL (NLH Search 2.0)	20/01/2009	N/A	92
BLIC (Dialog DataStar)	20/01/2009	N/A	34
National Research Register (NRR) Archive	20/01/2009	N/A	None found
UK Clinical Research Network (UKCRN) Portfolio Database	20/01/2009	N/A	None found
Current Controlled Trials <i>meta</i> Register of Controlled Trials - <i>m</i> RCT	20/01/2009	N/A	
Clinicaltrials.gov	20/01/2009	N/A	

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	(liver* adj3 (cancer* or carcinoma* or tumour* or tumor* or malignan* or metastas*)).tw.
2	Colorectal Neoplasms/
3	1 or 2
4	RFA.tw.
5	(radio freq* adj3 ablat*).tw.
6	(radiofrequen* adj3 ablat*).tw.

7	or/4-6
8	3 and 7
9	limit 8 to yr="2004 - 2009"
10	animals/
11	humans/
12	10 not (10 and 11)
13	9 not 12
14	limit 13 to english language
15	from 14 keep 1-435