REVIEW ARTICLE

Radiofrequency Ablation of Liver Tumors

A Systematic Review

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Objectives: To systematically review radiofrequency ablation (RFA) for treating liver tumors.

Data Sources: Databases were searched in July 2003.

Study Selection: Studies comparing RFA with other therapies for hepatocellular carcinoma (HCC) and colorectal liver metastases (CLM) plus selected case series for CLM.

Data Extraction: One researcher used standardized data extraction tables developed before the study, and these were checked by a second researcher.

Data Synthesis: For HCC, 13 comparative studies were included, 4 of which were randomized, controlled trials. For CLM, 13 studies were included, 2 of which were nonrandomized comparative studies and 11 that were case series. There did not seem to be any distinct differences in the complication rates between RFA and any of the other procedures for treatment of HCC. The local recurrence rate at 2 years showed a statistically significant benefit for RFA over percutaneous ethanol injection for treatment of HCC (6% vs 26%, 1 randomized, controlled trial). Local recurrence was reported to be more common after RFA than after laser-induced thermotherapy, and a higher recurrence rate and a shorter time to recurrence were associated with RFA compared with surgical resection (1 nonrandomized study each). For CLM, the postoperative complication rate ranged from 0% to 33% (3 case series). Survival after diagnosis was shorter in the CLM group treated with RFA than in the surgical resection group (1 nonrandomized study). The CLM local recurrence rate after RFA ranged from 4% to 55% (6 case series).

Conclusions: Radiofrequency ablation may be more effective than other treatments in terms of less recurrence of HCC and may be as safe, although the evidence is scant. There was not enough evidence to determine the safety or efficacy of RFA for treatment of CLM.

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HEPATOCELLULAR CARCINOMA (HCC) and colorectal liver metastases (CLM) are the 2 most common malignant liver tumors. While surgical resection remains the gold standard of therapy, only a few patients are suitable candidates for curative surgical resection because of the presence of liver malignancy in unresectable locations, the number and anatomic distribution of tumor lesions, or the presence of extrahepatic disease or poor liver function.[1,2] Several alternative treatments to control and potentially cure liver disease have been developed for use in patients with malignant liver tumors, whether primary or metastatic, who are not candidates for surgical resection. Some of these techniques are described as follows.

Hepatic arterial infusion chemotherapy, also referred to as "regional chemotherapy," involves the delivery of chemotherapeutic agents to the liver through a catheter surgically inserted in the hepatic artery, the main pathway through which liver tumors receive their blood supply.[3] Transarterial chemoembolization (TACE) involves the surgical insertion of a catheter into the hepatic artery and the periodic injection of chemotherapeutic agents mixed with embolic material into selected branches of the hepatic artery feeding the liver tumor.[4,5] Hepatic artery embolization using gelatin or other agents, which are usually mixed with a cytostatic product emulsified in ethiodized oil (Lipiodol, Laboratories Guerbet, Aulnay-sous-Bois, France), blocks the feeding artery of the tumor, inducing necrosis of the tumor without damaging the noncancerous areas.[6]

Percutaneous ethanol injection (PEI) involves a needle being introduced into a liver tumor and absolute or 95% ethanol slowly injected into the lesion.[2] As the ethanol diffuses into the cells, it induces nonselective protein degradation and cellular dehydration resulting in local areas of coagulation necrosis within and around the tumor.[7] In cryoablation, also known as "cryosurgical ablation,"[8] a specially designed probe delivers liquid nitrogen to the tissue under ultrasound guidance.[9] During the rapid freezing process, ice crystals form and multiple freeze-thaw cycles destroy normal cellular structures.[10]

Microwave coagulation therapy (MCT), also known as "percutaneous microwave co-

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Table 1. Included HCC Comparative Studies (13 Studies)

Source	Sample Size (Comparison)	Level of Evidence
Kurokohchi et al,[15] 2002	39 (20 RFA, 19 RFA-PEI)	II
Lencioni et al,[16] 2003, includes Olschewski et al,[28] 2001	102 (52 RFA, 50 PEI)	II
Shibata et al,[17] 2002	72 (36 RFA, 36 MCT)	II
Shiina et al,[18] 2000	60 (31 RFA, 29 PEI)	II
Livraghi et al,[19] 1999, includes Livraghi et al,[29] 1998	86 (42 RFA, 44 PEI)	III-1
Gasparini et al,[20] 2001	34 (10 RFA, 24 RFA-TACE)	III-2
Ikeda et al,[21] 2001	119 (23 RFA, 96 PEI)	III-2
Catalano et al,[22] 2000, includes Catalano et al,[30] 1999	102 (32 RFA, 56 multiple-session PEI, 14 single-session PEI, 14 LITT)	III-3
Catalano et al,[23] 2001	61 (16 RFA, 40 multiple-session PEI, 5 single-session PEI, 6 LITT)	III-3
Izumi et al,[24] 2001	84 (16 RFA, 68 MCT)	III-3
Kouyama et al,[25] 2000	40 (20 RFA, 20 MCT)	III-3
Livraghi et al,[26] 2001	20 (10 RFA, 10 TACE)	III-3
Yu et al,[27] 2002	145 (57 RFA, 88 surgical resection)	III-3

Abbreviations: HCC, hepatocellular carcinoma; LITT, laser-induced thermotherapy; MCT, microwave coagulation therapy; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

agulation," involves ultrasound-guided placement of an electrode into the lesion, followed by microwave treatment.[1] Coagulation necrosis and hemostasis result, destroying tissue in the treated area. Laser-induced thermotherapy (LITT), also referred to as "interstitial laser thermal ablative therapy" induces tissue damage and necrosis via heat photocoagulation.[11] The procedure, under either ultrasound or magnetic resonance control, is performed with an Nd:YAG laser.[12]

Radiofrequency ablation (RFA), also known as "radiofrequency thermal ablation," is a recently developed thermoablative technique. It induces temperature changes by using high-frequency alternating current applied via electrodes placed within the tissue to generate areas of coagulative necrosis and tissue desiccation.[13,14] Radiofrequency ablation can be applied percutaneously, laparoscopically, or at open surgery.

METHODS

This review is an update and summary of information obtained during 2 assessments, one for the Australian Safety and Efficacy Register of New Interventional Procedures–Surgical (ASERNIP-S) and the other for the Medical Services Advisory Committee (MSAC) of Australia. ASERNIP-S assesses the current safety and efficacy of new surgical techniques and technologies, and MSAC advises the Australian government on health technology reimbursement.

INCLUSION CRITERIA

Randomized controlled trials (RCTs), quasi-RCTs, and nonrandomized comparative studies assessing HCC or CLM treated with RFA or one or more other comparative inventions were considered for review. Case series assessing RFA for the treatment of CLM were included if the studies included consecutive patients, follow-up was at least 12 months (mean or median), and treatment site recurrence was reported per patient rather than per nodule. Studies containing mixed indications were considered for review if the results for each indication could be extracted separately. The comparative procedures were specified as surgical resection, hepatic arterial infusion chemotherapy, TACE, PEI, cryoablation, MCT, and LITT for the treatment of HCC or CLM.

SEARCH STRATEGY

Studies were identified by searching MEDLINE, PREMEDLINE, EMBASE, Current Contents, Cochrane Library, and the Science Citation Index in July 2003. The Clinical Trials Database, National Institutes of Health, and CancerLit (all in the United States), the National Health Service Centre for Research and Dissemination, the Health Technology Assessment, and the National Research Register (all in the United Kingdom), and the European Organization for Research and Treatment of Cancer Protocols Database were searched in July 2003. This was supplemented by hand searching recent conference proceedings and searching the Internet. Additional articles were identified through the reference sections of the studies retrieved.

DATA COLLECTION AND ANALYSIS

Articles were retrieved when they were judged to possibly meet the inclusion criteria. Two reviewers (one of which was L.M.S.) then independently applied the inclusion criteria, as defined in the protocol, to these retrieved articles. Any differences were resolved by discussion. Each included study was critically appraised for its study quality (based on the criteria used by the Cochrane Collaboration) and level of evidence according to the Hierarchy of Evidence developed by the National Health and Medical Research Council of Australia. The ASERNIP-S reviewer (L.M.S.) extracted information on data extraction sheets and a second reviewer checked them. Where 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, Oxford, England). Relative risks (RRs; for dichotomous outcome measures) and weighted mean differences (for continuous outcome measures) with 95% confidence intervals (CIs) were calculated for some of the outcomes in individual RCTs when it was thought that this would aid in the interpretation of results. The CIs represent the range within which the true value of an effect size is expected to lie, with a given degree of certainty (eg, 95%).

DESCRIPTION OF STUDIES

Hepatocellular Carcinoma

Thirteen comparative studies were included for review: 4 RCTs, level II evidence[15-18]; 1 quasi-RCT, level III-1 evidence[19]; and 8 nonrandomized comparative studies, level III-2 to III-3 evidence[20-27]

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Table 2. Included CLM Studies (2 Comparative Studies, 11 Case Series)

Source	Sample Size (Comparison)	Level of Evidence
Gillams and Lees,[31] 2001	46 (16 Surgical resection, 30 RFA)	III-2
Lees and Gillams,[32] 1999	Not stated (296 nodules, LITT; 125 nodules, RFA)	III-3
Bleicher et al,[33] 2000	54	IV
Chung et al,[34] 2001	6	IV
Cuschieri et al,[35] 1999	8	IV
Hoffman et al,[36] 2002	3	IV
Kosari et al,[37] 2002	18	IV
Kuvshinoff and Ota,[38] 2002	15	IV
Machi et al,[39] 2000	9	IV
Oshowo et al,[40] 2003	16	IV
Pearson et al,[9] 1999	46	IV
Rossi et al,[41] 1996	6	IV
Solbiati et al,[42] 2001, includes Solbiati et al,[43-45]*	158	IV

Abbreviations: CLM, colorectal liver metastases; LITT, laser-induced thermotherapy; RFA, radiofrequency ablation.
*Three articles were published in 2001[42-44] and 1 in 1999.[45]

(**Table 1**). Six studies compared RFA and PEI, 1 study compared RFA and RFA-PEI, 1 study compared RFA and TACE, 1 study compared RFA and RFA-TACE, 3 studies compared RFA and MCT, 2 studies compared RFA and LITT, and 1 study compared RFA and surgical resection (some studies contained more than 1 comparator).

Colorectal Liver Metastases

Thirteen studies were included for review: 2 nonrandomized comparative studies, level III-2 and III-3 evidence[31,32]; and 11 case series, level IV evidence[9,33-42] (**Table 2**). The nonrandomized comparative studies compared RFA and either surgical resection or LITT.

RESULTS

HEPATOCELLULAR CARCINOMA

Safety

The safety outcomes for treatment of HCC are listed in **Table 3** (RCTs and quasi-RCTs) and **Table 4** (nonrandomized comparative studies).

RFA Compared With PEI. Two of 3 RCTs comparing PEI and RFA reported complication rates. One study reported no complications in either group except for fever, which was significantly higher for RFA (RR, 2.80; 95% CI, 1.59-4.92)[18] and the other study found no difference (RR, 1.92; 95% CI, 0.71-5.32). In the RCT comparing PEI-RFA with RFA, none of the 19 patients receiving PEI-RFA had complications, but the complication rate for RFA alone was not stated.[15] In the quasi-RCTs, within 24 hours of treatment, 1 (2%) of 42 patients in the RFA group experienced a major complication (hemothorax) and 3 (8%) of 42 patients had minor complications (intraperitoneal bleeding, hemobilia, pleural effusion, and/or mild cholecystitis).[19] In the nonrandomized study by Catalano et al,[22] complications were more common in the single-session PEI treatment group than in the RFA or multiple-session PEI groups, in which individual complication rates generally occurred in less than 10% of patients.

RFA Compared With TACE. Major complications developed in 2 patients treated with TACE ($P=.07$), and 1 of these patients died 4 months after the procedure.[26] No complications were reported in patients treated with RFA.

RFA Compared With MCT. In the single RCT to report safety data, no life-threatening complications were reported for either treatment group and there were no significant statistical differences in the rate of major complications between RFA and MCT ($P=.67$, per-session analysis; $P=.36$, per-patient analysis).[17]

RFA Compared With LITT. One study comparing RFA and LITT reported safety data.[22] Complications such as arterioportal fistula, hepatic infarction, local atrophy, subcapsular fluid collection, and perihepatic effusion were more prevalent in the LITT group than in the RFA group. Portal vein damage occurred in 2 patients in the RFA group but was unreported in the LITT group. The other complications seemed to occur infrequently (<10% of patients) in both treatment groups.

RFA Compared With Surgical Resection. No safety data were reported for RFA compared with surgical resection.[27]

Efficacy

The efficacy outcomes for treatment of HCC are summarized in **Table 5** (RCTs and quasi-RCTs) and **Table 6** and **Table 7** (nonrandomized comparative studies).

RFA Compared With PEI. *RCTs and Quasi-RCTs.*

SURVIVAL/MORTALITY. One RCT reported no procedure-related deaths in patients treated with either RFA or PEI.[16] The 2-year survival rate was 98% (51 of 52 patients) after treatment with RFA compared with 88% (44 of 50 patients) after treatment with PEI (RR, 1.11; 95%

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Table 3. HCC Safety Outcomes: RCTs and Quasi-RCTs

Safety Outcomes	Kurokohchi et al,[15] 2002 (Level II Evidence)		Lencioni et al,[16] 2003 (Level II Evidence)		Shibata et al,[17] 2002 (Level II Evidence)		Shiina et al,[18] 2000 (Level II Evidence)		Livraghi et al,[19] 1999 (Level III-1 Evidence)	
	PEI-RFA (N = 19)	RFA (N = 20)	PEI (73 Lesions) (N = 50)	RFA (69 Lesions) (N = 52)	MCT (46 Nodules) (N = 36)	RFA (48 Nodules) (N = 36)	PEI (212 Sessions) (N = 29)	RFA (65 Sessions) (N = 31)	PEI (60 Nodules) (N = 44)	RFA (52 Nodules) (N = 44)
Complications, % (No. of patients)										
Major	0	NS	34 (17)	44 (23)	11 (4)*	3 (1)†‡	0	0	NS	2 (1), first 24 h
Minor									NS	8 (4), first 24 h
Pleural effusion§ (lesions)			NS	8 (4)						
Arteriovenous shunts§			NS	6 (3)						
Portal venous thrombosis (chemically induced)§			2 (1)	NA						
Postoperative fever (temperature ≥37.5°C, ≥3 d)			10 (5)	19 (1)			10% of sessions (21 sessions)	28% of sessions (28 sessions)‖		

Abbreviations: HCC, hepatocellular carcinoma; MCT, microwave coagulation therapy; NA, not applicable; NS, not stated; PEI, percutaneous ethanol injection; RCT, randomized, controlled trial; RFA, radiofrequency ablation.

*Includes liver abscess, cholangitis with intrahepatic bile dilatation, subcutaneous abscess with skin burn, or subscapular hematoma.

†Hepatic infarction.

‡$P = .36$ for difference according to patient, Fisher exact probability test.

§Intraoperative or perioperative.

‖$P = .08$.

Table 4. HCC Safety Outcomes: Nonrandomized Comparative Studies

Safety Outcomes	Ikeda et al,[21] 2001 (Level III-2 Evidence)		Catalano et al,[22] 2000 (Level III-3 Evidence)				Livraghi et al,[26] 2001 (Level III-3 Evidence)	
	PEI (N = 96)	RFA (N = 23)	Multiple-Session PEI (98 Nodules) (N = 56)	Single-Session PEI (31 Nodules) (N = 14)	RFA (48 Nodules) (N = 32)	LITT (25 Nodules) (N = 14)	TACE (N = 10)	RFA (N = 10)
Complications, % (No. of patients)							20 (2)	0*
Arterioportal fistula			1.8	14.3	3.1	14.3		
Hepatic infarction			1.8	14.3	NS	14.3		
Portal thrombosis			5.4	14.3	6.2	NS		
Caval thrombosis			1.8	NS	NS	7.1		
Biliary duct dilation			7.1	21.4	6.2	7.1		
Local atrophy			1.8	28.6	9.4	14.3		
Subcapsular collection			1.8	14.3	6.2	14.3		
Perihepatic fluid			5.4	28.6	9.4	28.6		
Pleural fluid			3.6	14.3	6.2	7.1		
Acute cholangitis requiring drainage	1 (1)	0						
Hemothorax	0	0						
Intraperitoneal bleeding	0	0						
Hemobilia	0	0						

Abbreviations: HCC, hepatocellular carcinoma; LITT, laser-induced thermotherapy; NS, not stated; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

*$P = .07$.

CI, 1.00-1.24). The local recurrence-free survival rate after 2 years was 96% (50/52) in the RFA group compared with 62% (31/50) in the PEI group (RR, 1.55; 95% CI, 1.24-1.94, in favor of RFA). Event-free survival at 2 years also tended to favor RFA, although this result did not reach statistical significance.

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Table 5. HCC Efficacy Outcomes: RCTs and Quasi-RCTs

	Lencioni et al,[16] 2003 (Level II Evidence)		Shibata et al,[17] 2002 (Level II Evidence)		Shiina et al,[18] 2000 (Level II Evidence)		Livraghi et al,[19] 1999 (Level III-1 Evidence)	
Efficacy Outcomes	PEI (73 Lesions) (N = 50)	RFA (69 Lesions) (N = 52)	MCT (46 Nodules) (N = 36)	RFA (48 Nodules) (N = 36)	PEI (212 Sessions) (N = 29)	RFA (65 Sessions) (N = 31)	PEI (60 Nodules) (N = 44)	RFA (52 Nodules) (N = 42)
Procedure-related death (patients), %	0	0						
Complete ablative response (nodules), %	82	91*	89	96†			80	90‡
Follow-up, mean duration (SD), mo	22.4 (8.6)	22.9 (9.4)			4			
Local recurrence, %	26	6			3.5	0§		
Residual foci of untreated disease, %			17	8				
Showing incomplete effect (nodules), %			50	NS				
New lesions, %	22	25			14	10		
Distant metastasis, %	0	0						
Local recurrence-free survival, %								
1 y Postoperative	84	98						
2 y Postoperative	62	96						
Survival, %								
1 y Postoperative	96	100						
2 y Postoperative	88	98						

Abbreviations: HCC, hepatocellular carcinoma; MCT, microwave coagulation therapy; NS, not stated; PEI, percutaneous ethanol injection; RCT, randomized, controlled trial; RFA, radiofrequency ablation.
*$P = .11$.
†$P = .26$, Fisher exact probability test.
‡$P = .18$.
§Treatment lesions.

Table 6. HCC Efficacy Outcomes: Nonrandomized Comparative Studies

	Gasparini et al,[20] 2001 (Level III-2 Evidence)		Ikeda et al,[21] 2001 (Level III-2 Evidence)		Catalano et al,[23] 2001 (Level III-3 Evidence)				Catalano et al,[22] 2000 (Level III-3 Evidence)			
Efficacy Outcomes	RFA-TACE (N = 24)	RFA (N = 10)	PEI (N = 96)	RFA (N = 23)	Multiple-Session PEI (73 Nodules) (N = 40)	Single-Session PEI (11 Nodules) (N = 5)	RFA (25 Nodules) (N = 16)	LITT (11 Nodules) (N = 6)	Multiple-Session PEI (98 Nodules) (N = 56)	Single-Session PEI (31 Nodules) (N = 14)	RFA (48 Nodules) (N = 32)	LITT (25 Nodules) (N = 14)
Complete tumor necrosis (within 7 d after treatment), % (No. of patients)	Incomplete data	100 (10)										
Complete tumor necrosis (1 mo), % (No. of patients)			94 (90)	100 (23)†								
Local recurrence at 1 y, % (No. of patients)			14 (13)*	17‡ (4)†								
Local recurrence (3-22 mo), %					14	9	16	9				
No. of new nonlocal nodules (3-22 mo)					62	14	23	14				
Residual tumor, % of nodules									54.1	67.7	35.4	76.0

Abbreviations: HCC, hepatocellular carcinoma; LITT, laser-induced thermotherapy; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.
*$P > .10$.
†Owing to discrepancies in the text, values quoted may be overestimated.
‡Includes a total of 48 patients for surgical resection group over the same 38-month RFA study period.

RECURRENCE. In 1 study, the local recurrence rate at 2 years was 6% (3 of 52 patients) for RFA and 26% (13 of 50 patients) for PEI (RR, 0.22; 95% CI, 0.07-0.73, in favor of RFA).[16] No local recurrence of tumors was reported by Shiina et al[18] in the RFA group, compared with 1 recurrence in the PEI group (RR, 0.31; 95% CI, 0.01-7.38). New lesions were reported in 10% of RFA-treated patients and 14% of PEI-treated patients (RR, 0.70; 95% CI, 0.17-2.87).[18]

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Table 7. HCC Efficacy Outcomes: Nonrandomized Comparative Studies All at Level III-3 Evidence

	Izumi et al,[24] 2001		Kouyama et al,[25] 2000		Livraghi et al,[26] 2001		Yu et al,[27] 2002	
Efficacy Outcomes	MCT (N = 68)	RFA (N = 16)	MCT (20 Nodules) (N = 20)	RFA (20 Nodules) (N = 20)	TACE (N = 10)	RFA (N = 10)	Surgical Resection (N = 48)*	RFA (N = 57)
Patients without recurrence, %	70	87.5†						
Volume of necrosis, mL†			5.1 (1.7)‡	11.8 (4.2)‡§				
Patients with complete control of tumor growth, %					30	50†		
Recurrence rate, %	30	12.5					19	39
Interval between treatment and recurrence, d							392.3 (269)†‡	160.1 (105)†‡
Deaths, % (No. of patients)					40 (4)	0‖		

Abbreviations: HCC, hepatocellular carcinoma; MCT, microwave coagulation therapy; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.
*Includes a total of 48 patients for surgical resection group over the same 38-month RFA study period.
†$P>.10$ compared with comparative intervention.
‡Numbers in parentheses indicate that the unit of measurement was not defined.
§$P<.01$ compared with comparative intervention.
‖$P>.05$ compared with comparative intervention.

THERAPEUTIC RESPONSE AND LONG-TERM TUMOR CONTROL. In the quasi-RCT,[19] no statistically significant differences were noted in therapeutic response between RFA and PEI as measured by the percentage of nodules showing complete necrosis. In 1 RCT, there were no statistically significant differences in the number of nodules with complete tumor ablation after treatment with a single RFA session (91% of RFA-treated nodules) compared with 1 cycle of PEI (82% of PEI-treated nodules).[16] When results for this outcome were combined across both studies, RFA showed a statistically significant better response compared with PEI (RR, 1.12; 95% CI, 1.00-1.25). However, per-lesion analysis rather than per-patient analysis may artificially inflate the result, and ablative response may not result in tumor control.

Nonrandomized Comparisons. In 1 study, residual viable tumor tissue was present in 35% (17/48) of RFA-treated nodules, 54% (53/98) of multiple-session PEI-treated nodules, and 68% (21/31) of single-session PEI-treated nodules.[22] In another study,[23] which may have had some patients in common with the study by Catalano et al,[22] local recurrence was associated more often with nodules treated with either RFA (16% [4/25]) or multiple-session PEI (14% [10/73]) than with single-session PEI (9% [1/11]). New nonlocal nodule formation was more common after multiple-session PEI (62 nodules) or RFA (23 nodules) than after single-session PEI (14 nodules). Because of difficulties in interpreting the reported data, it was impossible to associate new nonlocal nodule formation with the number of nodules with local recurrence. In addition, the study did not report in which patients new nodules developed, only reporting on a per-nodule basis.

In Ikeda et al,[21] complete tumor necrosis (1-month follow-up) was evident in all 23 patients (100%) after treatment with RFA, compared with 90 (94%) of 96 patients treated with PEI ($P>.10$). However, local recurrence was evident in 15% (4/17) of patients after RFA and in 13% (13/96) of patients after PEI ($P>.10$).

RFA Compared With TACE. Complete tumor necrosis (within 7 days after treatment) was found in all (10/10) patients treated with RFA but was incompletely reported for patients treated with RFA-TACE.[20] Four patients died after TACE treatment, whereas no deaths were reported in the RFA group (follow-up period not stated, $P<.05$).[27] Complete control of tumor growth was achieved in 5 (50%) of 10 patients treated with RFA compared with 3 (30%) of 10 of patients treated with TACE (no *P* value stated).[26]

RFA Compared With MCT. In the RCT, complete therapeutic effect was seen in 96% (46/48) of RFA-treated nodules and 89% (41/46) of MCT-treated nodules (RR, 1.08; 95% CI, 0.96-1.21).[17] In 1 nonrandomized comparative study, the volume of necrosis was larger in RFA-treated nodules than in MCT-treated nodules ($P<.01$).[25] In the other nonrandomized comparative study, 88% (14/16) of RFA-treated patients and 70% (48/68) of MCT-treated patients had no new HCC nodules elsewhere in the liver at a median follow-up of 18 months (range, 7-39 months), a non–statistically significant difference.[24]

RFA Compared With LITT. Residual viable tumor tissue was present in 76% (19/25) of LITT-treated nodules and 35% (17/48) of RFA-treated nodules.[22] Catalano et al[23] reported that local recurrence was associated more often with RFA (16% [4/25]) than with LITT (9% [1/11]). New nonlocal nodule formation was more common after RFA (23 nodules) than after LITT (14 nodules). Difficulties in interpreting the reported data meant it was impossible to associate new nonlocal nodule formation with the number of nodules with local recurrence or to relate new tumor development to individual patients.

RFA Compared With Surgical Resection. Comparing the treatment groups during the same 38-month follow-up, the recurrence rate in the RFA group was 39% (22/57) and in the surgical resection group was 19% (9/48).[27] The mean time between treatment and recurrence in the surgical resection group was 392 days (269 [the unit of mea-

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sure was not defined]) compared with 160 days (105 [the unit of measure was not defined]) in the RFA group.[27]

COLORECTAL LIVER METASTASES

Safety

RFA Compared With Surgical Resection and LITT. In the comparative studies, no safety data were reported for either surgical resection[31] or LITT.[32]

Case Series. The case series safety outcomes for CLM are summarized in **Table 8**. Complication rates were reported in 7 of 11 included CLM studies.[9,34,35,37,39,40,42] Intraoperative complications did not occur in any patient in 1 study.[39] In Oshowo et al,[40] 2 complications (focal grounding-pad burn and chest infection) were reported in 1 (6%) of 16 patients. It was not stated whether this patient received RFA alone (n=6) or RFA–surgical resection (n=10). Postoperative complication rates ranged from 0%[36,41] to 33% (early, 22%; late, 11%).[39] Some patients in the Machi et al[39] study underwent 1 to 3 repeat RFAs because of recurrent tumors, which may have contributed to the higher complication rate in this study.

Efficacy

Efficacy outcomes for CLM comparative studies are presented in Table 8.

RFA Compared With Surgical Resection. Survival after diagnosis of liver metastases was 44 months (median) in patients treated with RFA and 54 months (mean) in patients treated with surgical resection.[31] Five-year survival rates from the time of diagnosis were lower (40%) with RFA than with surgical resection (53%), but no *P* value was given.[31]

RFA Compared With LITT. Complete ablation was achieved in 92% (45/49) of nodules treated with single-electrode RFA, but no figures were reported for the percentage of complete ablation in nodules treated with either triple-cluster RFA or LITT. Treatment with LITT generated the largest mean volume of necrosis (105 mL), RFA with the triple-cluster electrode generated 74 mL of necrosis, and RFA with a single electrode generated the smallest volume of necrosis (27 mL).[32]

Case Series. Efficacy outcomes for CLM case series are given in **Table 9**.

Local Recurrence. Six studies reported local recurrence.[9,33,37-39,42] Local recurrence rates ranged from 4% (2/46) at a median 15 months of follow-up in 1 study[9] to 55% (64/157) at a median 18 months of follow-up in another study.[42] The large variation in recurrence rates may be related to the method of access: Pearson et al[9] performed RFA surgically during an open operative procedure, whereas Solbiati et al[42] performed RFA percutaneously. In both studies, the patients were considered unsuitable candidates for surgical resection, but no further details were provided on the condition of these patients, which also could have influenced this result.

New Recurrence. Five studies reported the rate of new liver metastases,[9,35,37,39,42] ranging from 2% (1/46) in 1 study[9] to 56% (89/158) in another study.[42]

Therapeutic Response. The completeness of tumor ablation after RFA was reported in 3 studies.[35,40,42] In Oshowo et al,[40] complete ablation was noted in 4 (67%) of 6 patients treated with RFA alone but was not stated for the 10 patients treated with RFA–surgical resection. The percentage of nodules showing complete ablation was 84% (27/32) in 1 study[35] and 74% in another[42] (follow-up period for neither study was stated). The latter study also reported the completeness of tumor ablation according to tumor size. Eighty-two percent of tumors smaller than 3 cm in diameter demonstrated complete tumor ablation compared with 48% of tumors larger than 3 cm in diameter.[42]

Mortality. The treatment-related mortality rate was reported as 0% in 3 studies.[34,40,42] Eight studies reported cancer-related mortality rates,[34,35,37,39-42] which ranged from 0% (follow-up period not stated)[9] to 50% (3/6) at 6 to 10 months of follow-up.[34] It was not stated whether deaths were related to the disease being treated.

Survival. Seven studies reported survival rates, which ranged from 17% (1/6) at 11 months of follow-up[34] to 88% (7/8) at 2 to 6 months of follow-up.[35] In 1 study, estimated median survival time after treatment with RFA was 33 months.[42] In Oshowo et al,[40] 11 (69%) of 16 patients were alive at 2 years and 7 (64%) of 11 survivors had no evidence of residual or recurrent liver disease.

COMMENT

STUDY LIMITATIONS

The few 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 because of different patient groups and interventions that could not be easily compared.

Nevertheless, some patterns of results were evident, particularly for the efficacy of RFA for treatment of HCC. Few studies reported safety data in any detail, and it was impossible to determine whether RFA was safer or less safe than its comparators. The structure of this review meant that several large case series of RFA had to be excluded because they did not report outcomes for each indication separately. In one multicenter study of more than 1000 patients, the major complication rate was 2.4%.[46] In a review of 82 studies of RFA involving 3670 patients, the overall complication rate was 8.9%.[47] These findings are broadly in line with the safety outcomes reported in the studies included in this review.

SAFETY AND EFFICACY OF RFA FOR TREATMENT OF HCC

In terms of the safety of RFA for treatment of HCC, there did not seem to be any distinct differences in the complication rates between RFA and any of the other

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Table 8. CLM Combined Efficacy and Safety Outcomes: Case Series*

Source	Recurrence Rate		Complete Ablation	Deaths	Survival, No. of Cases/ Total No. of Cases (%)	Complications/ Other
	Local	New				
Bleicher et al,[33] 2000	13/54 (24) patients					
Chung et al,[34] 2001				Treatment related, 0/6; cancer related, 3/6 (50); 6-10 mo	1/6 (17); 11 mo with disease	No evidence of disease, 2/6 (7 and 18 mo) Postoperative bleeding, 1/6 (17)
Cuschieri et al,[35] 1999		1/8 (13); 4 mo	27/32 (84) treated tumors, minimum 0.5-cm margin	1/8 (13); 6 wk	7/8 (88); 6-20 mo	0/8
Hoffman et al,[36] 2002						Pulmonary metastases, 1/3 (33) patients; 3-20 mo
Kosari et al,[37] 2002	5/76 (7); lesions; 2 patients also underwent liver resection	New hepatic disease: 8/18 (44)		New hepatic and systemic disease: 1/18 (6) patients; 2.5 y		New systemic disease, 6/18 (33) Complications, 1/18 (6); RFA–surgical resection
Kuvshinoff and Ota,[38] 2002 Median 4-mo follow-up	6/15 (40)				Recurrence free, 9/15 (60)	Any recurrence, 13/15 (87)
Machi et al,[39] 2000 12.6-mo follow-up (range, 4-21 mo)	2/9 (22) 2/37 (5) lesions, 1 lesion/ patient	New liver metastases, 3/9 (33)		3/9 (22)	6/9 (66), and free of disease	Intraoperative, 0/9 Early, 2/9 (22) Late, 1/9 (11) Extrahepatic recurrence, 4/9 (44); 2/4 (50) also had new liver metastases
Oshowo et al,[40] 2003 2-y follow-up			4/6 (67), RFA alone; not stated for 10 patients who underwent RFA–surgical resection	Procedure related, 0% Follow-up, 5/16 (31)	11/16 (69) 7/11 (64) with no residual or recurrent liver disease	2 in 1 patient Note: N = 16 (6 RFA alone, 10 RFA–surgical resection)
Pearson et al,[9] 1999 median 15-mo follow-up	2/46 (4)	1/46 (2) also had local recurrence		0/46		0/46
Rossi et al,[41] 1996				Surgery, 1/2 (50) 35 mo No surgery, 0/4	Surgery, 1/2 (50); 24 mo No surgery, 4/4 (2 local and 1 distant recurrence)	6 patients; 2 underwent hepatic resection within 35 d of RFA, and 4 did not undergo surgery
Solbiati et al,[42] 2001	64/117 (55) patients, median 18 mo	89/158 (56) patients, Kaplan-Meier estimated 44%; 18 mo (n = 117)	204/276 (74) lesions according to tumor size: <3 cm, 173/211 (82); >3 cm, 31/65 (48)	Treatment related, 0/223 sessions; cancer related, 55/158 (35) patients; mean follow-up, 20 mo	Kaplan-Meier estimated survival (n = 158), median 33 mo	Major, 3/223 (1) treatment sessions Minor (not requiring therapy), 12/223 (5) sessions

Abbreviations: CLM, colorectal liver metastases; RFA, radiofrequency ablation.
*Values are given as the number in sample/total number (percentage) of the population unless otherwise indicated.

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Table 9. CLM Efficacy Outcomes: Nonrandomized Comparative Studies

	Gillams and Lees[31] (Level III-2 Evidence)*		Lees and Gillams[33] (Level III-3 Evidence)*		
Efficacy Outcomes	Surgical Resection (N = 16)	RFA (N = 30)	LITT (296 Nodules) (N = NS)	RFA Single Electrode (49 Nodules) (N = NS)	RFA Triple-Cluster Electrode (76 Nodules) (N = NS)
Mean volume of necrosis, mL			105 (Range, 80-320)	27 (3.7-cm diameter)	74 (Range, 70-707)
Lesions with complete ablation, %			NS	92	NS
Median (mean) survival from diagnosis of liver metastases, mo	NS (54)	44 (NS)			
5-y Survival, %	53	40			
Median survival, <7-cm maximum diameter tumor and no extrahepatic disease, mo	NS	62			
Median survival, no vessel continuity and no extrahepatic disease (potentially candidates for surgery), mo	NS	68			

Abbreviations: CLM, colorectal liver metastases; LITT, laser-induced thermotherapy; NS, not significant; RFA, radiofrequency ablation.
*No safety outcomes reported.

comparative procedures reporting safety outcomes (PEI, TACE, MCT, and LITT), although many studies only reported complications for 1 of 2 treatment groups.

In terms of efficacy, a more complete ablative response was seen after RFA than after PEI (statistically significant for pooled studies). No clear differences were noted for the ablative effect between RFA and MCT or for complete treatment response when RFA was compared with TACE. There was no statistically significant difference between RFA and PEI for mortality, although there was a significant difference when RFA was compared with TACE. Local recurrence rates were less with RFA than with PEI in 2 RCTs (not statistically significant in either study). In another RCT, local recurrence-free survival (and local recurrence rate) at 2 years showed a statistically significant benefit for RFA over PEI. Local recurrence was reported to be more common after RFA than after LITT. A higher rate of recurrence and a shorter time to recurrence was associated with RFA compared with surgical resection. However, inasmuch as surgical resection and RFA are usually performed in different groups of patients, it is difficult to compare the 2 treatment groups.

SAFETY AND EFFICACY OF RFA FOR TREATMENT OF CLM

The safety of RFA for treating CLM is based solely on case series because the 2 comparative studies did not report safety outcomes. Complication rates were reported in 7 case series. The postoperative complication rate ranged from 0% to 33%. Patients who undergo more RFA sessions may have a higher complication rate.

In terms of efficacy, one comparative study suggested that survival from the time of diagnosis was shorter in patients treated with RFA than with surgical resection. The other comparative study suggested that the mean volume of necrosis was greater after LITT compared with RFA. In the case series, complete ablation was seen in 74% (204/276) and 84% (27/32) of treated tumors and in 67% (4/6) of treated patients, although this surrogate outcome may not reflect long-term effectiveness. In addition, the completeness of ablation may be related to tumor size because small tumors may be more easily destroyed by RFA than larger tumors. Local recurrence rates varied from 4% to 55% and may depend on the method of access used for RFA. No treatment-related deaths were reported in 3 case series.

CONSIDERATIONS FOR RFA

Technical considerations that may influence the success of ablative therapies include the size, location, and number of nodules in the liver. The method of delivery (although not able to be assessed in this review) may also influence the outcome of ablative therapies. Izumi et al[24] used both percutaneous and laparoscopic access, but the results from the 2 methods were combined within the individual treatment arms. Assessment of complete ablation according to method of delivery would be useful because an open procedure may enable better access and visualization of disease and monitoring of ablation than laparoscopic or percutaneous delivery. This may influence the rate of and time to recurrence. Surrounding structures or organs such as blood vessels, diaphragm, or bowel can also easily be damaged, which may be averted with better visualization during the procedure.

CONCLUSIONS

Despite the limitations of the data, RFA generally resulted in larger and more complete areas of ablation, and RFA may also be associated with higher survival rates than the other ablative techniques assessed in this review. Surgical resection was associated with a lower rate of recurrence and longer time to recurrence compared with RFA in treatment of HCC. However, these 2 procedures are usually performed in different patient groups, with RFA usually performed in patients who are unable to undergo surgical resection. Continued improvement in tech-

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nology and increasing clinical experience may also influence the success of RFA for treatment of liver tumors.

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Disclaimer: The ASERNIP-S review group recommended that surgeons performing RFA to treat HCC or CLM should participate in an audit of their outcomes of RFA, preferably at a national level. The MSAC recommended that, on the strength of evidence pertaining to RFA, public funding should be supported for percutaneous RFA for treating HCC but not for treating CLM, at this stage.
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