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Which patients will benefit from percutaneous radiofrequency ablation of colorectal liver metastases? Critically appraised topic

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Abstract

In clinical radiology, there are numerous examples of new techniques that were initially enthusiastically promoted and then subsequently abandoned when early promise was not realized in routine patient care. Appropriateness of new or established interventional radiology techniques to specific clinical conditions must be determined from clinical experience, from communication with experts in the field and/or careful review of available medical literature, and on an individual patient basis by means of review of clinical notes and diagnostic imaging studies. For patients with liver neoplasms, regional techniques such as radiofrequency ablation (RFA) have been developed and are now the subject of ongoing research. This article decribes the utilization of Evidence-Based Practice (EBP) techniques as a means of deciding the appropriateness of percutaneous RFA in treating colorectal liver metastases (CLM).

Key words: Liver neoplasms/secondary—Catheter ablation—Surgery—Interventional radiology—Evidence based medicine

Step 1: Ask: ''Which patients benefit from percutaneous radiofrequency ablation of colorectal liver metastases?''

For patients with resectable colorectal liver metastases (CLM), 5-year survival rates of 24–38% have been reported, although better patient selection for curative resection with more thorough pre-operative imaging has lead to reports of improved survival rates of 58% at 5 years [1].

Radiofrequency ablation (RFA) is being increasingly used in clinical practice, alone or in combination with other treatments such as surgery and/or local or systemic chemotherapy [1, 2].

At our institution we wondered about the current role of RFA and how RFA compared to surgical resection for treatment of colorectal liver metastases (CLM).

- Prior to the application of EBP techniques to this question, our opinion was that the indications for RFA in treating patients with CLM, were widening but that surgical resection, when indicated and feasible, was still the treatment of choice.
- To address the question using EBP techniques a focused clinical question or PICO question was designed, as previously described by Staunton et al. [3], which in written text, reads as follows In patients with colorectal liver metastases how does percutaneous radiofrequency ablation compare with surgical resection or other ablative techniques for annual recurrence and mortality rates ? (Fig. 1).

Step 2: Search

The search strategy followed an EBP approach, which is easily applicable to a range of scenarios in radiology [3–5].

- The initial step was to identify key words which were sensitive to all relevant articles and sufficiently specific so as to avoid yielding a large number of irrelevant articles.
- For the current question, the following MeSH terms—[''liver neoplasms'' OR ''liver neoplasms/secondary''] linked by the Boolean operator AND

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Patients	Intervention	Comparison	Outcomes
"liver neoplasms" **AND** OR "Liver neoplasms/secondary"	"catheter ablation"	AND "liver neoplasms /surgery"	Complications OR Efficacy OR Recuurence OR Mortality

Fig. 1. Outline of literature search strategy following PICO format.

["catheter ablation"] AND ["liver neoplasms/surgery"]—were chosen (Fig. 1).

- All searches, described below, were completed on 5 April 2007 by MMM and SMcG.
- To expedite the search, we initially entered the chosen MeSH terms into the "Find Systematic Reviews" option listed under the Clinical Queries link on the PubMed services sidebar.
- Next, the MesH terms were used to search the PubMed database with the following limits applied: *Humans, English*, 10 *years*.
- The Embase, NICE, Clinical Evidence and Cochrane Library databases were also searched, using "liver", "metastases", "radiofrequency" and "ablation" as search terms. These headings were used in preference to the MeSH terms chosen for the Medline searches, because of a very low yield from the above databases when the MeSH terms were used.

Results from computer search engines

- The initial Clinical Queries search retrieved twenty-two systematic reviews (SR's).
- The abstracts of the 22 SR's were analysed and three were excluded because of foreign language [6–8], and 12 additional SR's were excluded because they either addressed RFA in hepatocellular cancer exclusively or management of recurrent disease [9–20]. One further SR was excluded as it was published in *Investigative Radiology*, a journal to which we did not have access [21]. This left six relevant, accessible SRs published between 2003 and 2006 [1, 22–26].
- The PubMed search retrieved 857 abstracts, which were reviewed on Medline, when available. No randomized trials were retrieved; however, five non-randomized comparative studies, which compared RFA to surgical resection for CLM were identified. Of these five non-randomized comparative studies, only one compared image-guided percutaneous RFA to surgical resection [27]; the other four studies compared surgical resection to RFA performed at laparoscopy or laparotomy, or contained hetererogenous groups, in which the majority of RFA was performed at laparoscopy/laparotomy with a few additional percutaneous cases. Since the current review was designed to study the role of percutaneous RFA in CLM, these four comparative studies were excluded. One additional SR published in 2002 was discovered, leaving a total of seven SRs, which on initial review appeared to address the focussed clinical question [28].
- The search of the Cochrane Library database of SRs, yielded two protocols for future SRs out of a total of 4,655 records but no additional completed SR were reviewed.
- Searching the EMBASE database retrieved 346 abstracts, 74 of these pertaining to the radioablative and/or surgical treatment of CLM and a single SR [2] not retrieved by PubMed on the day of the search. On the day following the search (6 April 2007), a notification from *my NCBI* to SMcG informed us of its publication on Medline [2].
- Search of the Clinical Evidence database of the British Medical Journal Publishing Group (http://www.clinicalevidence.com) yielded no relevant retrievals.
- Search of the National Institute of Clinical Excellence (NICE) website retrieved the institution's Guidlines (Radiofrequency Ablation for the treatment of colorectal metastases in the liver) [29].
- During the course of the search, there were numerous references to the CLOCC trial (EORTC protocol 40004—clocc) (Chemotherapy + Local ablation vs. Chemotherapy) [30]. Based on our search, this would appear to be the only ongoing randomized controlled trial involving RFA. This phase II study was activated on 16/4/2002 and compares RFA and chemotherapy to chemotherapy alone in patients with unresectable colorectal liver metastases [30].

Step 3: Appraise

- The retrieved literature was then critically appraised by the two authors (MMM and SMcG) using EBP techniques [5, 31, 32].

EBP appraisal of an SR

- The eight SR's were published between 2002 and 2007, The most recent SR, which was published in January 2007 [2], did not focus specifically on the use of RFA for CLM; rather it was an SR with a very broad scope which examined many aspects of the management of CLM, including imaging at diagnosis, imaging during follow-up, role of diagnostic laparoscopy and various treatments including surgery, chemotherapy and "experimental treatments" such as portal vein embo-

lization, ablative therapy (RFA, cryotherapy and percutaneous ethanol injection) and isolated hepatic perfusion [2]. This SR, however, was not deemed the SR which would best form the basis for the current SR because of its wide scope and resultant limited literature specific to RFA for CLM and also the absence of raw data, and the required indices needed to perform EBP analyses of study strength [2].

- Three other recent SR's [1, 22, 24] were were based on extensive literature searches. There were notable, strong components to each of these SR's, which were considered important to our analysis. Garden's [22] and Sutherland's [24] SR's followed EBP strategy throughout, whereas McKay's SR did not [1]. Garden's SR [22], suffered the same problem as the 2007 SR [2], in that it did not provide us with raw data in which strength of SR could be independently assessed by calculation of EBP indices using available spreadsheets [33–35].
- Although not solely focused on RFA of CLM, the review by Sutherland et al. was considered the most valid and best current evidence and the best SR on which to complete our analysis and therefore this was appraised in detail [24]. The objective of the SR was to systematically review RFA for treating liver tumors; however, its search and appraisal of the literature was performed separately for hepatocellular carcinoma and CLM [24]. Thus the lack of sole focus on CLM was not a disadvantage.
- Thoroughness of SR's search strategy: Descriptions of the methodology for this SR indicates that a very thorough, complete and exhaustive search of both the primary and secondary evidence, supplemented by hand-searching of recent conference proceedings and Internet searches (suggesting that a thorough search of the "gray literature") was performed, thus reducing the potential for publication bias [24].
- One of the problems, with the Sutherland SR was that, although published in 2006, the search was completed in July 2003, with no mention of updated searches being performed during the period when the peer-review process was underway [24]. The search period, thus, did not include the only non-randomized comparative study, retrieved during our search, which compared percutaneous image-guided RFA to surgical resection [27]. This non-randomized study therefore currently represents the best current evidence comparing RFA to surgical resection for patients with CLM [27].
- In comparison to Sutherland's SR [24], the McKay [1] review, and the Garden [22] and Bipat SR's [2], search period concluded in January 2006, October 2003 (not specifically stated), and 2005, respectively. Because of concerns regarding the completion of the Sutherland [24] search in July 2003, the bibliographies of the McKay [1], Garden [22] and Bipat [2] reviews were thoroughly analysed for important additional case series or comparative studies. Also, a thorough review of Medline subsequent to January 2006 (conclusion of search of McKay review) was performed in an attempt to identify publications of importance to the current PICO question, which were published subsequent to search period of the most recent SR [2].
- Methodological quality of SR: Thirteeen studies were included in the Sutherland review [24]. The studies retrieved by the authors included two available non-randomized comparative studies (level III-2 and III-3 evidence) and eleven case series (level IV evidence). There were no randomized controlled trials and no SR's included in the SR. Therefore the methodological quality of the primary studies was weak and the level of evidence is weak [24].
- The best comparative study comparing RFA to surgical resection for CLM was published outside the search period of the Sutherland [24] review but was included in the McKay [1] and Garden [22] reviews. The comparative studies retrieved and appraised in the Sutherland [24] SR did not include any safety data for resection and thus the safety of RFA vs. surgical resection could not be compared. We, therefore, performed a detailed appraisal of the Oshowo [27] comparative study as the comparison of percutaneous RFA and surgical resection was a major component of this critical appraisal.

Findings following appraisal

RFA compared with surgical resection (SAFETY)

- The Sutherland SR [24], retrieved no comparative studies, which reported safety data. Oshowo [27] reported a non-randomized comparison (level III) of 45 consecutive patients with solitary CLM treated with RFA (25 patients) or surgical resection (20 patients).
- The patients treated with RFA (25 patients) were not candidates for surgical resection due to proximity of tumor to major vascular structures (nine patients), medical co-morbidity (nine patients) and extra-hepatic disease (seven patients) [27]. Excluding the important differences in tumor proximity to major vasculature, co-existence of medical co-morbidity and extra-hepatic disease, the RFA and surgical resection groups were similar for male:female ratio, mean age (57 vs. 63 years) and tumor size (3 vs. 4 cm) [29]. However, the non-randomized nature of this study is a serious limitation, as the study groups are not comparable for a number of important reasons—proximity to vascular structures (9/25 patients {36%}) and extent of extra-hepatic disease (7/25 {28%}) [27]. It is important to note that proximity to vascular structures not only limits feasability of surgical resection but also potentially negatively impacts the ability of RFA to achieve

tumor necrosis due to the " heat-sink" effect.
- The median hospital stay appeared shorter for RFA (1 vs. 8 days) [27]. There was no death reported in the RFA group, whereas, one peri-operative death was reported in the surgical resection group [27]. Complication rates were very low in both the RFA and surgical resection groups, pleural effusion (one patient) in the RFA group vs. chest infection (one patient) in the surgical resection group [27]. There was no need for post-procedural blood transfusion in either group [27]. In Sutherland's SR [24], treatment-related mortality for RFA in CLM was reported in three case-studies as being 0%. In this SR, a review of selected case-series of patients post-RFA suggested complication rates of 0%–33% (early 22%, late 11%) [24].

RFA compared with Surgical resection (Efficacy)

- As stated above, Oshowo et al. [27] in a non-randomized comparison study reported very similar survival (median survival and 3-year survival) for patients treated with RFA vs. patients treated with surgical resection. Median survival and 3 year survival was similar in both groups, an interesting finding considering the patients in the RFA group had extra-hepatic disease at the time of treatment [27].
- The Sutherland [24] SR, however, suggested reduced survival following treatment with RFA compared with surgical resection for CLM (44 vs. 54 months). Five-year survival rates for patients treated with RFA were lower than surgical resection for patients with CLM (40% vs. 53%) [24]. This data, however, was from a non-randomized study and the authors did not report statistical analysis of this data [24].
- Sutherland's [24] SR reported that eight studies reported cancer-related mortality rates following RFA, which ranged from 0% (follow-up period not stated) to 50% at 6–10 months of follow-up. In one study estimated median survival time after treatment with RFA was 33 months [26, 36]. In Oshowo et al. [27], 20/25 patients were alive at 20 months and 7/25 patients were alive at 40 months. The median survival was 37 months with a 3-year survival rate of 52.6%. McKay's [1] SR retrieved six studies which reported at least 3-year survival following RFA for unresectable CLM. McKay's [1] SR, similar to Sutherland's [24] found scant literature, comprising uncontrolled case series. McKay [1] reported 1-year survival data for CLM of 75%–99%, 2-year survival of 45%–75% and 3-year survival of 37%–58% including a single study reporting a 5-year survival of 30% in a subset of patients with fewer than five lesions that were all less than 5 cm in diameter. McKay [1] cautioned that although many reports suggested promising survival data following RFA in unresectable CLM, that patient selection is a concern when interpreting this data. In all studies, there is potential for heterogeneity in selection criteria for unresectable disease and also for publication bias. Also, patients in many series have had other treatments, such as previous surgery and/or chemotherapy which can impact outcome data.

RFA compared with LITT (Efficacy)

- Complete ablation was achieved in 92% (45/49) of nodules treated with single-electode RFA. No data was available for triple-cluster RFA or LITT, which are more commonly used in current everyday practice [24]. McKay et al. [1] reported varied rates of complete tumor necrosis for RFA ranging between 98% and 50%. However, McKay's [1] SR cautioned that this variability between reports may be explained by the subjective nature of the evaluation for necrosis and difference in imaging modalities for this evaluation (CT/PET vs. CT vs. MR Imaging) and the heterogeneity between series.
- With regard to volume of necrotic tumor, Sutherland's [24] SR reported greatest volume of necrotic tissue with LITT (105 mL) vs. RFA with triple-cluster (74 mL) and single electrode (27 mL). Sutherland's [24] review of case series suggested complete liver tumor necrosis rates of 84% and 74% in two studies. The latter study suggested that the rate of complete tumor necrosis was related to tumor size; with a smaller size being more favorable (82% total necrosis < 3 cm vs. 48% > 3 cm) [24].

RFA vs. surgical resection (local recurrence)

- Sutherland's [24] SR reported that local recurrence rates for patients with CLM treated with RFA ranged from 4% at a median of 15 months in one study to 55% at median of 8 months in another study. McKay et al. [1] also reported a wide range of local recurrence ranging from 5 to 39%.
- Sutherland [24] suggested that RFA performed surgically may have a lower recurrence (4%) compared with percutaneous RFA (55%) based on results of two non-comparative studies. Sutherland [24] suggested that method of access, i.e., percutaneous vs. surgical, may explain this discrepancy. The issue of percutaneous vs. surgical RFA, however, has not been studied in a scientifically well-designed study and there is little evidence in the literature to support Sutherland's suggestion.

- McKay [1] cautions that local recurrence should be differentiated from the development of new lesions, which can be as high as 57% in some patients, and as such, does not necessarily indicate failure of RFA. McKay [1] noted that there was a discrepancy between CLM patients treated with surgical resection and RFA in terms of the development of new liver lesions (11% vs. 35%). McKay [1] proposes that a possible explanation is that surgical resection reduces the remaining liver volume at risk for the development of new lesions, whereas RFA does not have such an effect.
- With regard to factors predisposing to local recurrence, Solbiati et al. [36] reported increasing local recurrence rate and decreasing time to development of local tumor recurrence with increasing tumor size. Local recurrence rates and estimated time to recurrence were 21.6% and 15.5 months for tumors ≤ 2.5 cm, 52.8% and 8.5 months for tumors 2.6–4.0 cm in size and 68.4% and 6.4 months for tumors ≥4.1 cm [36].

Extent of disease and RFA

- Gillams et al. [37] reported 30% survival at 5 years for patients with five or fewer CLM, less than 5 cm in diameter with no extraheptaic disease and 26% for patients with less than 10 metastases less than 4 cm in diameter.
- Solbiati et al. [38] investigated the use of RFA for treatment of CLM in patients in whom surgery was contraidicated and in whom there were 4 or less CLM less than 4 cm in size. Survival rates were 67% at 2 years and 33% at 3 years [38].
- The CLOCC trial is investigating the efficacy of chemotherapy plus ablation in patients who have fewer than 10 CLM that are smaller than 4 cm in diameter, who are not candidates for resection. The entry criteria in this trial therefore allows entry of CLM patients with very extensive disease.

Apply

The literature regarding RFA for CLM is sparse and although good quality SR's have been published, these are based on small studies with heterogenous patient selection techniques [1, 2, 22, 24]. However, data regarding patient survival is difficult to appraise.

- For resectable CLM, RFA is not currently considered equivalent to surgical resection and, where feasible, surgical resection should be performed [1].
- RFA appears safe and is highly effective in tumor destruction [2]. The effectiveness of RFA in achieving tumor destruction is dependent on tumor size. Local recurrence however is a significant problem and is dependent on the size of tumor ablated. As discussed previously, recurrence rates of 21.6% for tumors ≤ 2.5 cm, 52.8% for tumors 2.6–4.0 cm in size and 68.4% for tumors ≥4.1 cm have been reported [36].
- McKay et al. [1] suggest longer-term survival data are required before comparative trials comparing RFA to surgical resection can be considered.
- The best current evidence is not of sufficient strength to answer the question as to whether RFA prolongs survival in patients with extensive CLM [2]. If RFA is being considered in this clinical setting, the patient should be first reviewed at a tertiary hepatobiliary referal unit and such patients should be considered for entry into a clinical research protocol such as the CLOCC trial.
- There is a growing body of opinion, albeit amongst a subgoup of RFA proponents, which suggests that patients ineligible for the CLOCC trial could still be considered for palliative RFA, although current evidence does not show a definite survival benefit [22].
- The results of the CLOCC trials are awaited to answer many questions related to treatment of CLM with RFA, for which current best evidence cannot provide definitive answers [30].
- Gilliams et al. [39] recommended that extensive RFA should not be performed. Based on this review, and while we await the results of the CLOCC trial, a conservative approach to patient selection for RFA is advocated. The indications for RFA proposed by Gilliams et al. [39] (Table 1) would appear reasonable. With regard to extent of disease, for which RFA is feasible, survival data reported by Gilliams (1–5 CLM, 1–5 cm in diameter) and Solbiati (1–4 CLM, 1–4 cm in diameter) are encouraging and could be used to guide patient selection [37, 38].

Table 1. Current Indications for radiofrequency ablation

Limited but inoperable liver disease
Extent or distribution permits ablation but not resection
Non-operable due to co-morbidity
Nonoperable due to inadequate residual functioning normal liver

Note: Modified from Gilliams [39]. Indications listed in the above article, which were outside the scope of this review were excluded

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