Long-term results of radiofrequency ablation for unresectable colorectal liver metastases: a potentially curative intervention

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Objective: The long-term results and prognostic factors of radiofrequency ablation (RFA) for unresectable colorectal liver metastases (CRLM) in a single centre with >10 years of experience were retrospectively analysed.

Methods: A total of 100 patients with unresectable colorectal liver metastases (CRLM) (size 0.2–8.3 cm; mean 2.4 cm) underwent a total of 126 RFA sessions (237 lesions). The mean follow-up time was 29 months (range 6–93 months). Lesion characteristics (size, number and location), procedure characteristics (percutaneous or intra-operative approach) and major and minor complications were carefully noted. Local control, mean survival time and recurrence-free and overall survival were statistically analysed.

Results: No direct procedure-related deaths were observed. Major complications were present in eight patients. Local RFA site recurrence was 12.7% ($n=30/237$); for tumour diameters of <3 cm, 3–5 cm and >5 cm, recurrence was 5.6% ($n=8/143$), 19.5% ($n=15/77$) and 41.2% ($n=7/17$), respectively. Centrally located lesions recurred more often than peripheral ones, at 21.4% ($n=21/98$) vs 6.5% ($n=9/139$), respectively, $p=0.009$. Including additional treatments for recurring lesions when feasible, lesion-based local control reached 93%. The mean survival time from RFA was 56 (95% confidence interval (CI) 45–67) months. Overall 1-, 3-, 5- and 8-year survival from RFA was 93%, 77%, 36% and 24%, respectively.

Conclusions: RFA for unresectable CRLM is a safe, effective and potentially curative treatment option; the long-term results are comparable with those of previous investigations employing surgical resection. Factors determining success are lesion size, the number of lesions and location.

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Colorectal carcinoma is one of the most common malignancies in Western countries. In 20–25% of patients with colorectal carcinoma (synchronous) liver metastases are present at the time of diagnosis of the primary tumour [1–3]. Another 20–30% of patients develop (metachronous) liver metastases, which usually arise within 3 years of initial treatment of the primary tumour [1, 3]. In Europe and the USA, colorectal liver metastases (CRLM) are the most frequent cause of malignant hepatic tumours [4]. The prognosis of patients with untreated CRLM (receiving only symptomatic therapy) is poor, with a median survival rate of 4.5–12 months, depending on the extent of metastatic disease at the time of diagnosis [5]. Chemotherapeutics, using oxaliplatin and fluorouracil (5FU), can prolong survival in a palliative setting with a median survival of approximately 18 months [6–8]. More recent results show a median survival of 21.7 months for patients treated with

capecitabine, irinotecan and oxaliplatin [9]. Surgical resection is still considered the only method for definite treatment of malignant liver tumours by many [10–17]. Resection of liver metastases with curative intent results in a 5 year overall survival rate of 24–58% and a 10 year survival rate of 28% [11–19]. It is not uncommon, particularly in patients with primary colorectal carcinoma, for the liver to be the only site of metastatic disease [19]. Unfortunately, approximately 70–80% of patients with metastases confined to the liver are not suitable candidates for resection, owing to tumour anatomy (number, size and/or locations), extended extrahepatic disease and/or impaired general health status [20–22]. Therefore, several other local treatment methods such as tumour ablation, originally considered palliative procedures, have been investigated. Radiofrequency ablation (RFA) has shown promising results in the recent literature. It is a procedure with a relatively low complication rate (<10%, mostly minor complications that are often unnecessary to treat) and a very small risk of death (<1%), notably when compared with resection [20, 23]. The aim of this study was to retrospectively describe the long-term results and predictive factors of RFA for unresectable CRLM.

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Methods and materials

Patient selection, demographics and follow-up

A total of 100 patients (59 male; 41 female) with CRLM who were treated with RFA alone or in combination with resection between January 1999 and June 2009 during a total of 126 sessions (237 lesions) were retrospectively included. Mean age at the time of RFA was 63 years (range 35–83 years). Patients with a follow-up period of <6 months after the RFA procedure were excluded. To retrospectively assess the pre-procedural lesion characteristics (size, number and location of the lesions) and procedural characteristics (open or percutaneous approach), and to document all major and minor complications, treatment responses and recurrences elsewhere, the medical history (including the pre-procedural and follow-up scans and the intra-operative ultrasound report) of all patients was carefully evaluated using our electronic database (dismissal, referral and other medical letters, operation and radiology reports). Each new oncological event (local recurrence, new metastases (intra- or extrahepatic) and death) was recorded into the database. Missing data were obtained by contacting general physicians. Major complications were defined as complications that, if untreated, might threaten the patient's life, lead to substantial morbidity and disability, result in hospital admission or substantially lengthen hospital stay, as described by the International Working Group of Image-Guided Tumour Ablation [24]. Minor complications included typical post-ablation syndrome symptoms (fever, pain, nausea and vomiting) if present >4 days after the RFA procedure. Complications were further divided into two causal categories: those secondary to RF electrode placement (pneumothorax, infection and bleeding) and those secondary to thermal injury (damage to adjacent organs and grounding pad burns) [25]. Lesion location was classified as either central or peripheral. Central lesions included lesions in direct contact with or abutting a large vessel measuring at least 4 mm.

All patients were considered suitable for resection, intra-operative ultrasound (IOUS)-guided RFA or percutaneous ultrasound- and/or CT-guided RFA according to a multidisciplinary team including medical oncologists, nuclear physicians, surgical oncologists and both abdominal and interventional radiologists. All ablated lesions were considered unresectable according to guidelines proposed by the HEPATICA trial, in which we are actively involved. This active trial is a randomised two-arm Phase III study in patients post radical resection of liver metastasis of colorectal cancer to investigate bevacizumab in combination with capecitabine plus oxaliplatin (CAPOX) as adjuvant chemotherapy *vs* CAPOX alone as adjuvant treatment. Another reason to consider RFA above resection is the fact that some patients previously had surgical resection(s) or even hemihepatectomies for other CRLM. Furthermore, patients with a maximum number of five CRLM, solitary unresectable lesions ≤ 7 cm or 2 to 5 lesions <5 cm were generally considered suitable for local ablation of the liver disease. Nevertheless, in some cases the inclusion criteria to perform RFA were

broadened during surgery. For example, if hepatic disease appeared more extensive based on surgical exploration and IOUS (with the patient under general anaesthesia and the subcostal incision already performed), ablation was performed for lesions up to 8.5 cm in diameter and for a maximum number of eight lesions in selected cases. In general, a percutaneous approach was preferred for hepatic tumour recurrences, for a limited number of smaller and superficially located lesions and if the patient was elderly or significant comorbidities were present. The relatively low number of percutaneous approaches in our study is a consequence of the fact that we only started performing these procedures in late 2005. Pre-procedural imaging included at least a contrast-enhanced CT or MRI scan performed a maximum of 6 weeks before the procedure and an 18-fluoro-2-deoxyglucose positron emission tomography (^{18}F -FDG-PET) scan performed a maximum of 2 months before the procedure. Lesions were considered to represent CRLM based upon either pre-procedural PET avidity and/or typical CT and IOUS characteristics. For atypical lesions histology was obtained. For open procedures the definite decision to perform RFA was based on surgical exploration and IOUS. The follow-up imaging protocol consisted of 3, 6, 9, 12, 18 and 24 month follow-up CT scans and 6, 12 and 24 month follow-up ^{18}F -FDG-PET scans followed by annual PET and CT scans if no recurrence was present (Figure 1). The procedures carried out on humans were in accordance with the ethical standards of the World Medical Association (Declaration of Helsinki). For this retrospective study with anonymised patients, approval from the institutional ethical committee was waived.

Primary tumour treatment

In patients with liver metastases from colonic carcinoma, the primary tumour was resected before treatment of the liver metastases. Patients with rectal carcinomas received neo-adjuvant radiotherapy of the rectal cancer, followed by treatment of the liver disease and subsequent resection of the primary tumour.

Pre- or post-procedural chemotherapy

Patients with synchronous CRLM suitable for resection and/or RFA received adjuvant chemotherapy schemes (regimens have changed several times during the past decade) after the procedure. Patients with metachronous CRLM were not uniformly treated with adjuvant chemotherapy. Adjuvant chemotherapy with 5FU and leucovorin, combined with irinotecan and/or oxaliplatin, is currently the standard treatment following RFA for CRLM. Patients with initially advanced liver disease received palliative chemotherapy. If partial response was present and the liver disease was down-staged sufficiently to enable resection and/or ablation with curative intent, patients were considered suitable for either intra-operative treatment (resection and/or ablation) or percutaneous RFA.

Figure 1. (a) Pre-procedural and (b–d) post radiofrequency ablation (RFA) follow-up portal-venous phase CT images of a patient with a solitary segment VIII colorectal liver metastases. 6 months after the initial procedure, a marginal avid lesion on (e) 18-fluoro-2-deoxyglucose positron emission tomography (^{18}F -FDG-PET) was histologically confirmed to represent RFA site recurrence. The recurrence was re-treated with RFA. (f–j) Follow-up CT scans after the secondary procedure show a continuously decreasing ablation zone without signs for recurrence. The patient is currently alive and disease-free.

Extrahepatic disease

Limited extrahepatic metastatic disease was not considered a contra-indication if all metastases could still be resected, ablated or irradiated with curative intent.

Intra-operative RFA

All patients were admitted to our centre at least 1 day before surgery. A subcostal incision laparotomy was performed for optimal liver exposure. The abdominal cavity was explored in order to exclude extrahepatic tumour manifestations. IIOUS (Prosound Alpha10, 10.0 MHz linear intra-operative probe and 5.0/1.25 MHz convex probe; Aloka, Tokyo, Japan) was performed by an interventional radiologist who carefully noted the exact size (maximum diameter), number and location of all CRLM. On the basis of the size of the lesion and on the proximity of adjacent vital structures within 2.0–5.0 cm, expandable-needle electrodes (LeVein, Boston Scientific, Natick, MA) were manually placed using ultrasound guidance. The procedure was carried out by interventional radiologists in close collaboration with surgical oncologists to avoid damage to surrounding organs and structures. Since 2008 we have used a novel bipolar RFA unit for lesions >3.5 cm (InCircle, RFMedical, Fremont, CA) in eight selected patients. All electrodes were connected to a commercially available RF generator (RF3000, Boston Scientific). Ablations were performed according to the protocols provided by the manufacturer. Primary end points for a technically successful ablation were at least two increases in tissue impedance (roll-off) with an interablation delay of 30 s and a fully hyperechoic ablation zone including a tumour-free margin of at least 1 cm on IIOUS. If necessary, the needle electrodes were repositioned for one or more overlapping ablations. Since early 2007, we have used contrast-enhanced intra-operative

ultrasound (CE-IIOUS) in selected cases (especially large or centrally located lesions) as secondary end point; CE-IIOUS was employed several minutes after ablation to detect residual vital tumour tissue. If deemed necessary, owing to the proximity of a large portal vein or hepatic artery, a so-called Pringle manoeuvre was performed (*i.e.* a large haemostat was placed so as to temporarily interrupt the flow of blood through both the hepatic artery and the portal vein). Needle track ablation was performed to avoid needle track haemorrhage and possible seeding of tumour cells.

Percutaneous CT and/or ultrasound-guided RFA

All procedures were performed under general anaesthesia. Patients were positioned either in a supine or prone position based upon the optimal percutaneous approach of the tumour. The procedure was planned on at least an unenhanced CT obtained just before the procedure. If the lesions were invisible on these unenhanced images, either a contrast-enhanced CT scan and/or ultrasound was chosen for image guidance. The RFA needles were carefully positioned using CT fluoroscopy aiming at a tumour-free ablation zone of at least 1 cm. Again, needle track ablation was performed to avoid needle track haemorrhage and possible seeding of tumour cells. For tumours with *a priori* high probability of needle track haemorrhage (centrally located tumours or impaired haemostasis), we used co-axial needle systems (CoAccess, LeVein, Boston Scientific) and manually placed a number of small haemostatic foam plugs (Willospoon, Will-Pharma, Zwabenburg, the Netherlands) in the needle track while retracting the co-axial needle. Primary end points for a technically successful ablation were at least two increases in tissue impedance (roll-off) with an interablation delay of 30 s. For lesions >3 cm, a contrast-enhanced CT scan directly after the procedure

was used as secondary end point. The ablation zone was defined as the non-enhancing hypodense region 70 s after the start of the contrast injection. When considered necessary, additional overlapping ablations were performed after electrode repositioning.

Statistical analysis

Local control, mean survival time and 1, 3, 5 and 8 year overall survivals were statistically analysed. Kaplan–Meier plots of survival were acquired using standard statistical analysis software SPSS (SPSS for windows version 11.5, Chicago, IL). Factors determining local success, progression-free and overall survival were compared using log rank analysis; $p < 0.05$ was considered significant. Variables investigated were the number, position and size of CRLM, percutaneous *vs* intra-operative approach, operator experience, the presence of extrahepatic disease and a history of liver resection and/or pre- or post-procedural chemotherapy.

Results

Patient and lesion characteristics are summarised in Tables 1 and 2. A total of 100 patients with 237 unresectable histologically proven CRLM underwent a total of 126 RFA sessions. The mean number of treated CRLM in a single session was 1.9 (range 1–8). The mean size of ablated CRLM was 2.4 cm (range 0.2–8.3 cm). The mean follow-up time was 29 months (range 6–93 months).

Of the 237 RFA procedures, 221 were performed during open laparotomy and 16 were approached

Table 2. Summary of lesion characteristics

Characteristic	
Number of lesions (n)	237
Lesion size (cm)	
Average size	2.4
Min–max	0.2–8.3
Location	
Central (n)	98
Peripheral (n)	139

percutaneously. An intra-operative Pringle manoeuvre was performed during RFA in five patients. RFA was considered technically successful in all cases. Procedure characteristics are summarised in Table 3.

There were no direct procedure-related mortalities. One 80-year-old male patient with a history of coronary artery disease died 3 days after RFA owing to an autopsy-proven massive myocardial infarction. Obduction revealed a fully ablated CRLM. Major complications were present in 8 patients and minor complications in 18 (Table 4).

After a median follow-up of 29 months (range 6–93 months), 68 patients (68%) had a recurrence either at the RFA site or elsewhere (Figures 2 and 3). Including additional treatments (re-RFA, surgical resections and/or radiotherapy) for recurring lesions when feasible, 54% (54/100) of all patients were disease-free after a follow-up period of at least 6 months.

The first oncological tumour-recurring event consisted of 30 patients with local recurrence at the RFA site: 9 isolated at the RFA site, 8 at the RFA site in combination with limited (locally treatable) disease elsewhere and 13 at the RFA site in combination with extended disease elsewhere. In seven patients a limited number of new liver metastases were treated with either resection and/or RFA. In six patients, limited recurrence (re-treatment possible) was found outside the liver (four in the lung, one in lymph node and one in the adrenal gland). In 38 patients, recurrence was judged as extended disease, unsuitable for local treatment. The percentage of patients with recurring disease not at the RFA site was 50.0% (28/56) for initially solitary CRLM and 70.5% (31/44) for initially multiple CRLM (>1); $p = 0.04$.

Local RFA site recurrence was 12.7% ($n = 30/237$); for tumour diameters <3 cm, 3–5 cm and >5 cm, recurrence was 5.6% ($n = 8/143$), 19.5% ($n = 15/77$) and 41.2% ($n =$

Table 1. Summary of patient characteristics

Characteristic	
Number of patients (n)	100
Average age (years)	63
Age range (years)	35–83
Gender	
Male (n)	59
Female (n)	41
Primary tumour	
Colon (n)	71
Rectum (n)	29
Diagnosis metastasis	
Synchronous (n)	34
Metachronous (n)	66
Chemotherapy	
None (n)	49
Pre-RFA (n)	43
Post RFA (n)	5
Pre- and post RFA (n)	3
Surgical resections ^a	
Pre-RFA (n)	8
In same session with RFA (n)	37
Post RFA (n)	8
Extrahepatic disease ^b	
Lung metastases (n)	4
Lymphadenopathy (n)	2
Intraperitoneal deposition (n)	1

^aOf other colorectal liver metastases. ^bLimited extrahepatic disease diagnosed at the same time as, or before, the detection of liver disease.

RFA, radiofrequency ablation.

Table 3. Summary of procedure characteristics

Procedure characteristic	n
Approach	
Intra-operatively ultrasound-guided	221
Percutaneously CT-guided	16
Electrode	
Monopolar 2.0 cm	85
Monopolar 3.0 cm	34
Monopolar 3.5 cm	22
Monopolar 4.0 cm	45
Monopolar 5.0 cm	38
Bipolar 4.0 cm	8
Bipolar 5.0 cm	5
Operator experience	
History ≤ 10 procedures	62
History > 10 procedures	175

Table 4. Summary of complications

	Cause	Complication	n
Mortality	Directly related to RFA		0
	Indirect	Myocardial infarction	1
Major complications	Related to electrode placement	Abscess	4
		Haemorrhage	1
	Related to thermotherapy	Grounding pads burning wounds	2
		Diaphragm perforation with pleural empyema requiring drain	1
Minor complications	Post-ablation symptoms >4 days after procedure	Pain	16
		Fever	8
		Nausea	6
		Vomiting	4
	Other	Benign cardiac arrhythmia	1

Classified according to the International Working Group of Image-Guided Tumour Ablation [24].

RFA, radiofrequency ablation.

7/17), respectively. Centrally located lesions recurred more often than peripheral ones: 21.4% ($n=21/98$) vs 6.5% ($n=9/139$); $p=0.009$. Including additional treatments for recurring lesions when feasible, lesion-based local control (percentage of locally controlled lesions) reached 93%.

The mean survival time from RFA was 56 (95% CI 45–67) months. Overall 1, 3, 5 and 8 year survival from RFA was 93%, 77%, 36% and 24%, respectively. The outcome was dependent on the maximum size of the largest CRLM and on the number of lesions (Figure 4). No significant difference could be inferred between the percutaneous and intra-operative approach because of insufficient numbers for any comparison to be made.

Discussion

In patients with liver metastases unsuitable for resection, an alternative treatment method such as RFA could be helpful in achieving local tumour control and even cure. However, drawing general conclusions about the impact of RFA on survival is difficult. Patients referred to our institution represent a selected population. Also, our group of patients is very heterogeneous with regards to tumour characteristics and treatment regimes. The different treatment strategies (*i.e.* pre-operative chemotherapy, previous resection and/or RFA, portal vein ligation during RFA procedure, resection following RFA and post-operative chemotherapy) possibly obscure the effect of RFA. Nevertheless, in our series, a 5 year overall survival of 36% remains promising, especially as we included all patients in whom RFA was performed (tumours up to 8.3 cm in diameter, a maximum number of 8 lesions treated in 1 session and chemotherapeutically downstaged patients with initially advanced disease). Because of the lack of randomised trials comparing RFA with another treatment modality (such as chemotherapy or surgical resection), the precise effect of RFA on survival is still ill-defined [26]. In general, patients treated with RFA, having unresectable liver metastases, could be considered as having more, larger and/or bilobar liver metastases than patients amenable for surgical resection. Therefore, it should be emphasised that patients treated with RFA have a poorer prognosis than patients treated with resection of their

metastases. Recent literature and our study provide intriguing information regarding the results of RFA. The limited available information on long-term outcomes suggests that RFA has a positive effect on overall survival [27, 28]. Reported overall median survival after RFA varies from 28.9 to 45.5 months [27–31]. This rate is even better for patients with fewer (<5) or smaller (<5 cm) tumours [27]. Some are even arguing comparable outcome after resection and RFA of low-volume liver disease [28, 31]. Although many still consider RFA to represent a palliative treatment option, in our institute the treatment is always performed with curative intent (*i.e.* only if the entire macroscopically visible tumour load can be ablated with or without additional resections). Our results and the results from other long-term follow-up studies show that full cure can be achieved in a reasonable percentage of patients [32]. The inclusion criteria for performing RFA are continuously broadening to cover larger lesions, lesions located in regions that are difficult to access, a larger number of lesions and shifting definitions of how limited extrahepatic disease is defined. Therefore, the overall results are mainly determined by the treatment limits that we set ourselves and should always be interpreted in the context of rigorous patient selection. Resection is the gold standard of management, but this still only applies to the minority of patients with liver metastases. As previously mentioned, the 5 year overall survival rate after surgical resection of colorectal metastases is 24–58%. The prognosis of patients following resection of solitary liver metastases is even better, with a recent report describing a survival rate exceeding 70%. Although in recent years more and more patients have been considered amenable for surgical resection, clear definitions on resectability are lacking [22].

Ever since the widespread introduction and application of RFA as a local treatment method of liver metastases, the issue of recurrence has been of great importance. Distant recurrence (elsewhere in the liver or extrahepatic) rates vary from 28% to 84% [17, 20]. Reported local recurrence rates (at the RFA site) range widely, from 2% to 60% [19, 28, 31–34]. In our series 12% had local RFA site recurrence. As local recurrence often represents a small marginal focal spot, many recurrences can be re-treated with RFA relatively easily. Definite local control after additional ablations (93% in our study)

Figure 2. Flowchart showing the outcome of all patients after radiofrequency ablation (RFA). The final outcome after additional local treatments (RFA or other local treatments with curative intent) for recurrence is displayed in red. CRLM, colorectal liver metastases.

might therefore be a more important parameter. Furthermore, as several patients with local RFA site recurrence also had advanced recurrences elsewhere (making them unsuitable for re-ablation), the real percentage of lesions that could theoretically be locally controlled after secondary sessions is probably still underestimated. Factors predicting local RFA site recurrence were tumour size and centrally located lesions. The latter observation is probably caused by the so-called heat sink effect (*i.e.* the continuous cooling of tumour tissue by adjacent vessels), but could also be due to the use of less oversized needle electrodes to prevent damage to the main bile ducts. Our group has previously described moderately promising results for RFA of larger liver tumours using a novel bipolar unit [35]. Furthermore, there is increasing evidence that transarterial

chemo-embolisation (TACE) with irinotecan drug-eluting beads before or within 24 h of RFA can increase ablation sizes and improve local control in selected patients [36, 37].

Conclusion

RFA for unresectable CRLM is a safe and effective treatment option and can provide long-term survival benefit comparable with surgical resection. For the treatment of larger volume CRLMs, especially lesions ≥ 5.0 cm, one or more re-treatments are often necessary to reach local control in an acceptable number of patients. Other factors determining local success are the number of lesions and their location. The technique

Figure 3. Recurrence-free survival plots for (a) different numbers of colorectal liver metastases (CRLM) treated with radiofrequency ablation (RFA), (b) different sizes of the largest CRLM present in each patient, (c) patients who also had surgical resections for other CRLM before or within the same session as the RFA procedure vs "RFA alone" patients and (d) patients with vs those without (neo)adjuvant chemotherapy regimens, excluding patients who only received chemotherapy for tumour recurrence at a later time point.

can be considered at least as a valuable asset to surgical resection. To define the true place of RFA within the different treatment modalities for CRLM, further studies are needed. Such studies will probably be complicated by the evolving definitions of resectability, consequent expanding indications for hepatic resection of CRLM [38–40] and the use of modern, more effective cytotoxic agents such as oxaliplatin and irinotecan [41]. The management of colorectal liver metastases requires a

multimodality treatment approach. The prognosis of solitary and multiple liver metastases is improving and the search for the optimal treatment strategy for the individual patient is challenging. Thus, proper patient selection and multidisciplinary management of CRLM is crucial. Recurrence remains an ongoing concern in evaluating the management of patients with (colorectal) liver metastases. Overall, the results of our study are encouraging and suggest not only prolonged survival, but

Figure 4. Kaplan–Meier survival plots for (a) different numbers of colorectal liver metastases (CRLM) treated with radiofrequency ablation (RFA), (b) different sizes of the largest CRLM present in each patient, (c) patients who also had surgical resections for other CRLM before or within the same session as the RFA procedure vs “RFA alone” patients and (d) patients with vs those without (neo)adjuvant chemotherapy regimens, excluding patients who only received chemotherapy for tumour recurrence at a later time point.

also a considerable chance of achieving a cure in selected patients. Advantages of RFA include its relative safety and simplicity and the possibility of repeating the procedure. It is important to emphasise that the prognosis of CRLM is not as ominous as previously thought.

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