Local ablative therapies for colorectal liver metastases and the immune system

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Chapter 8

Local success rate of radiofrequency ablation of liver metastases

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Introduction

Colorectal cancer is one of the most common malignancies in the Western world, with 500,000 new cases presenting each year. In 25% of patients liver metastases are present at time of diagnosis[1] and eventually over 70% of patients will develop liver metastases[2,3]. Without treatment, the occurrence of liver metastases is associated with a poor prognosis of 5–9 months[4–6]. At present, the only curative treatment of liver metastases is resection, with a median survival of 46 months and 5 year survival of up to 37%[7]. Unfortunately, only 20% of patients are eligible for resection and a large group of patients remains for whom the development of new treatments is of utmost importance[8]. These patients may benefit from local ablative techniques such as radiofrequency ablation (RFA). Needle electrodes are inserted directly into the tumour and deliver a high frequency (200 kHz to 20 mHz) alternating current to the tissue, causing hyperthermia of the tissue and thus coagulative necrosis.

In recent years, RFA has emerged as a promising treatment option for colorectal liver metastases, although its exact role in the treatment of nonresectable liver metastases needs to be established. Initially, reports about its efficacy were mainly positive and no large studies into the complications of RFA were conducted. Several studies have proven RFA to be feasible and relatively safe, with tumour response rates of 52–95% and median survival of 30–37 months[9–15]. With increased follow-up time and the availability of larger patient groups however, it became evident that although RFA may be very useful, there are also less favourable considerations to be taken into account[16]. Complications do not occur very often (7.1 to 9.5%)[17–20] but when encountered, may be of a serious nature and may require surgical intervention, thus limiting the applicability of RFA to more specialized centres. Also, studies with longer follow-up showed that renewed local tumour growth at RFA treated site is considerable, with rates as high as 39% being reported (table 1)[15,21].

The occurrence of serious complications and the high number of local RFA failures emphasize the need of a more precise identification of risk factors for both the occurrence of complications and local tumour growth after RFA treatment. In current literature, the identification of these risk factors for local RFA failure is mostly limited and often not statistically validated (table 2). The purpose of this study therefore is to identify independent, validated risk factors for local tumour progression following RFA using multivariate adjusted statistic analysis and propose exclusion criteria for RFA treatment of colorectal liver metastases.

author	year	n	procedure	tumour diameter	median FUP (months)	RFA failure
Solbiati	1997	22	percutaneous	-	10.3	34%
Curley	1999	61	percutaneous/open	3.4	15	3.3%
Wood	2000	37	percutaneous/open	3.0	9	18%
Machi	2001	25	percutaneous/open	3.4	20.5	9.2%
Solbiati	2001	117	percutaneous	2.8	-	39.1%
Choy	2002	9	percutaneous/open	2.5	12	20%
Pawlik	2003	124	RFA plus liver resection	-	21.3	2.3%
de Baere	2003	155	percutaneous	2.5	18	9.6%
Oshowo	2003	16	open	-		33%
Livraghi	2003	88	percutaneous	2.1	28	40%

Table 1. RFA studies with colorectal cancer (CRC) patients in which rate of local tumour growth at RFA site is identified

author	year	statistics	size	number	location	adjacent vessels	approach
Solbiati	1999	unknown	yes ($p<0.05$)	-	yes	yes	-
Curley	1999	no	yes	-	no	yes	-
Wood	2000	two tailed t-test	yes	no	-	-	no
Machi	2001	no	yes	-	-	yes	-
Solbiati	2001	Wilcoxon / log-rank	yes ($p<0.001$)	-	-	-	-
Pawlik	2003	no	yes	-	-	-	-
Oshowo	2003	no	yes	-	-	-	-

Table 2. Factors determining local failure of RFA identified in various studies, with or without statistical analysis

Patients and methods

Patient inclusion
Between June 1999 and December 2003, 87 patients undergoing 104 RFA treatments of a total of 199 colorectal liver metastases were prospectively included in this analysis. Participating Dutch centres were Leiden University Medical Center in Leiden (n=23), Academic Medical Center in Amsterdam (n=1), University Medical Center Utrecht (n=15), Amphia Hospital Breda (n=16), The Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital in Amsterdam (n=6), VU Medical Center in Amsterdam (n=12), Maxima Medical Center in Veldhoven (n=8) and Medisch Spectrum Twente in Enschede (n=6).
Mean age of patients was 62 years and distribution among sexes was 57 males / 30 females. Further patient characteristics are listed in Table 3. Patients were not eligible for hepatic resection of metastases, due to location, number or size of lesions, or poor medical condition. Preoperative imaging consisted of CT scan of the abdomen and of the lungs. Postoperatively, CT scans were made at 1, 3 and 6 months and then after every 6 months.

total n patients	*87*	
male	57	
female	30	
mean age (range)	*62*	*(39-78)*
total n RFA treatments	*104*	
percutaneous	31	
laparotomy	73	
occurrence of metastases	*104*	
synchronous	39	
metachronous	65	
total n lesions	*199*	
n lesions / patient	1,95	(1-6)
lesion diameter (cm)	2,9	(0,5-11,0)
n applications/lesion	1,5	(1-5)

Table 3. Patient and treatment characteristics

Radiofrequency ablation

RFA treatment was performed either percutaneously or during laparotomy, under ultrasound and/or CT guidance. RFA treatment is defined as the RFA procedure during which target lesions are treated with tumour ablation. Three different commercially available RF generators and three types of electrode systems were used: a single electrode with deployable tines (RITA Medical Systems, Mountain View, CA or Radiotherapeutics, Sunnyvale, CA) a linear monopolar electrode (Radionics, Burlington, MA) or triple electrodes cluster consisting of three triangularly configured electrodes (Radionics, Burlington, MA). Specific RFA protocols, designed by each of the three manufacturers, were used for each system according to manufacturer recommendations.

Registration of anti tumour efficacy and risk factors

Both local radiologists and an independent observer reviewed all CT scans separately. Two researchers monitored all RFA data by reviewing patient charts and laboratory and radiology reports. In accordance with the criteria and definitions as proposed by the Working Group on Image-Guided Tumour Ablation[22], we defined local tumour growth following RFA as the appearance of viable tumour tissue at the site of treatment. When vital tumour tissue was seen on follow-up CT scans within 30 days after initial RFA and a repeat RFA procedure was performed to ablate the remaining tumour tissue within 90 days after initial RFA, the initial RFA treatment was excluded from analysis and only results of the technical successful RFA procedure were analysed.

For the purpose of this analysis, various parameters were registered that may possibly influence local tumour control rate: patient age, gender, occurrence of metastases (synchronous vs. metachronous), number of treated tumours, size of treated tumours, tumour location (central vs. peripheral), procedure approach (percutaneous vs. laparotomy), type of laparotomy (with or without concomitant liver resection), RFA generator, type of electrode, number of electrode applications per lesion (during one procedure) and number of applied RFA procedures per patient.

Statistics

Univariate analysis using a Cox proportional hazards model was performed on all parameters, for all treated tumours. The variance of the estimated coefficients was adjusted using a "sandwich" estimator[23], accounting for possible correlation of event times of lesions and RFA procedures within patients. A p-value of < 0.05 was considered statistically significant. All statistically significant parameters were then analysed again using

a multivariate Cox model, also with robust estimates of standard errors. Here again a p-value of < 0.05 was considered statistically significant.

Results

A total of 199 colorectal liver metastases were ablated by 104 RFA treatments, either via percutaneous approach (31 treatments) or by laparotomy (73 treatments). In 73 patients, single RFA treatment was performed. Two RFA treatments were necessary in 11 patients, and 3 patients underwent 3 RFA procedures. The average diameter of the ablated metastases was 2.9 cm (0.5–11.0 cm), with 63% of lesions located in the right liver lobe and 37% located in the left liver lobe. Most lesions were ablated with deployable electrodes, either using the RF system by Radiotherapeutics (47.0%) or by RITA Medical Systems (29.3%). The remaining lesions were treated with Radionics electrodes, either with the linear monopolar electrode (17.7%) or with the cluster electrode (6.1%).

Adequate follow-up was obtained for 158 lesions (79.4%). The remaining 41 lesions occurred in deceased patients, in patients that were lost to follow-up or in patients without available CT or MRI scans in follow-up. At end of follow-up, local control was achieved in 85 lesions (53.8%), while 73 lesions showed local disease progression, resulting in an overall failure percentage of 46.2%. Mean follow-up of successfully treated lesions was 10,8 months (0,7-27,0 months). Mean time to local disease progression was 6,5 months (range 0,7-34,2 months). Treatment and tumour characteristics of both groups are listed in table 3. Univariate analysis indicated that age and gender of patients did not influence local tumour control rate (table 4). RFA treatment by laparotomy was associated with a lower local failure rate than treatment by percutaneous RFA (43.2% vs. 52.4%) but this difference was not significant ($p = 0.32$). Repeated RFA treatment seemed to influence local failure rates (72.2% after second RFA vs. 43.1% after first RFA treatment), but this difference was not statistically significant ($p = 0.085$). It should however be noted that the number of lesions that were treated a second (n=18) or a third (n=3) time compares unfavourably with the 137 lesions that were treated with primary RFA, hampering statistical significance. Neither the number of lesions that were treated in one RFA procedure nor the number of electrode applications per lesion correlated with increased local failure rates.

The tumour size however was the most important factor influencing local failure rates, with a p-value of < 0.00005. Also of significance was the location of the tumour. RFA treatment of lesions located in central liver parenchyma (segment 1-4-5) resulted in 58.7% local failure, whereas peripheral lesions showed a lower failure rate of 38.7% ($p = 0.0052$). These differences remained significant after multivariate analysis.

parameter	total n lesions	local control		local progression		p-value
gender						0.4
age						0.098
occurrence of metastases						*0.0335*
synchronous	56	36	(64.3%)	20	(35.7%)	
metachronous	97	47	(48.5%)	50	(51.5%)	
unknown	5					
lesion location						*0.0052*
central	63	26	(41.3%)	30	(58.7%)	
peripheral	93	57	(61.3%)	43	(38.7%)	
unknown	2					
RFA approach						*0.32*
percutaneous	42	20	(47.6%)	22	(52.4%)	
laparotomy	111	63	(56.8%)	48	(43.2%)	
unknown	5					
RFA electrode						*0.011*
Radionics monopolar	21	12	(57.1%)	9	(42.9%)	
Radionics cluster	8	2	(25,0%)	6	(75.0%)	
Radiotherapeutics	63	25	(39.7%)	38	(60.3%)	
RITA	41	30	(73.2%)	11	(26.8%)	
unknown	25					
repeat RFA treatment						*0.085*
first treatment	137	78	(56.9%)	59	(43.1%)	
second treatment	18	5	(27.8%)	13	(72.2%)	
third treatment	3	2	(66.7%)	1	(33.3%)	
n treated lesions						*0.24*
lesion diameter						*< 0.0001*
applications/lesion						*0.53*

Table 2. Results of univariate analysis, adjusting for within-patient correlation

Regarding RFA treatment, we found that the different electrodes were of considerable importance. The average diameter of lesions treated with Radionics clustered triple electrode was 4.4 cm, with a local failure rate after RFA of 75.0%. We feel that this high percentage can be attributed largely to the high average tumour size. RITA deployable electrodes were used to treat lesions with a smaller average diameter of 2.7 cm and resulted in a local failure rate of only 26.8% ($p=0.0062$). The RITA electrode also compared significantly favourably with the Radiotherapeutics electrode (60.3% local failure rate, $p=0.0062$) that was used to treated lesions with a similar average diameter (2.8 cm). The difference in local failure rate with the Radionics monopolar electrode (42.9%), treating lesions of 3.0 cm average diameter, however was not significant. The overall p-value comparing the four different RFA systems was 0.011 and remained significant after secondary multivariate analysis.

Discussion

Several studies report on the rate of local failure after RFA treatment. There is remarkable variation in these reported failure rates, ranging from 2.3 to 40%. One of the reasons for these variations may be the definition and assessment of local tumour growth following RFA. Explicitly, we use the term local tumour growth rather than local recurrence, according to the proposed terms by the Working Group on Image-Guided Tumour Ablation[22]. Tumour reappearing at the site of previous RFA mostly is not the actual new growth of tumour at that site but is the outgrowth of remaining tumour cells after incomplete RFA and should therefore be distinguished from local recurrence. Different studies, especially those performed in the early days of RFA treatment for liver metastases, do not necessarily use the same definitions and diagnostic methods. For instance, one could consider either every tumour in the liver segments containing the treated RFA lesions a local failure or only those at the exact site of earlier RFA treatment. Also, the interval between RFA treatment and local tumour growth may be of importance, as one could argue that local tumour growth after an interval of > 12 months may not be due to outgrowth of remaining tumour cells after inadequate RFA treatment but is in fact the growth of new tumour cells, i.e. local recurrence. Regarding diagnostic methods, it should be noted that local tumour progression following RFA usually occurs at the rim of the ablated lesion and that this progress can be difficult to visualize on ultrasound or even CT scan, especially in the first months after treatment (figure 1).

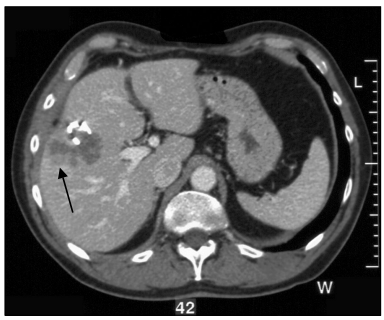

Figure 1. Lesion treated with RFA, with residual tumour tissue at the rim of necrotic tissue following RFA

The use of positron emission tomography (PET) scanning in detection of residual tumour tissue following RFA may become more widespread in the near future, as several studies showed a higher sensitivity of this diagnostic method when compared to CT scanning[24,25]. However, the small number of patients included in these studies and the limited clinical availability of PET scans will hamper this development. By using the standardised terms as proposed by the aforementioned Working Group, these differences may be prevented, enabling a more reliable comparison of study outcomes.

With 47%, local failure rate in our study is higher than reported in other studies. This high number may be partly explained by the specific focus of our study on this local treatment failure, with all treated lesions being evaluated separately on CT scan by the same, blinded observer. Possibly we should also take into account the learning curve of this developing technique, as it is only applied in specialized Dutch centres since 1999 and our study comprises all RFA applications since its introduction.

Nevertheless, our study clearly identifies factors that influence local failure rate. In accordance with earlier findings, we show that the size of the treated tumour is the most important factor in the efficacy of total tumour ablation using RFA[13,15,26-30], with local treatment failure rates correlating with increased tumour size. In our opinion this is due to the difficulty of placing adequate overlapping electrodes in large tumours. At present, real-time imaging of the induced necrosis is not available, so careful planning of electrode placement before commencing the procedure is essential. Upcoming developments in stereotactic three-dimensional imaging techniques may be very helpful to improve electrode placement but at the same time will further complicate the RFA procedure[31,32].

The other factors influencing the rate of local tumour growth after RFA are similarly associated with impaired ability to achieve adequate treatment margins. It is therefore not so much the size of the treated tumour itself that hinders adequate ablation, but the difficulties in achieving sufficient necrosis in all tumour areas. This is reflected in the high rate of local tumour growth after treating tumours located centrally in the liver, near its large vessels. The proximity of vessels restricts the placement of electrodes and often not all tumour tissue is ablated due to a heat-sink effect[33,34], even with the application of a Pringle manoeuvre, which consists of temporary occlusion of inflow via portal vein and hepatic artery. Similarly, when access is limited due to location of tumours high up in the liver, this may result in inadequate ablation.

In light of this theory, we expected local failure rate following percutaneous RFA to be higher than failure following an open procedure, as the latter allows for better electrode accessibility and visibility. This was indeed the case, as the incidence of local failure after percutaneous treatment was almost 10% higher than after laparotomy, but these findings were not significant. The relatively small number of patients who were treated with percutaneous RFA (31 patients vs. 73 patients with RFA by laparotomy) may partly explain these results, and more pronounced differences might be seen with increased number of treated patients. Hypothetically, the type of electrode used for RFA may also be of influence for local recurrence, as there are two types of electrodes in use: electrodes with expandable needles inducing spherical necrotic lesions with diameters ranging from 2 to 7 cm and single electrodes resulting in a cylindrical necrotic lesion with a diameter of up to 3 cm. Ablation of a large tumour that requires multiple electrode insertions can be more easily achieved with the expandable electrodes as overlapping margins can be more safely achieved. This is partly confirmed by the results of our study, as we did not explicitly find differences in local tumour control between expandable (Radiotherapeutics or RITA Medical Systems) and linear (Radionics) electrodes. We did however find significant differences between the electrode types, with the deployable RITA Medical Systems electrodes showing the lowest local failure rate of only 26.8%, as opposed to failure rates over 60% for the Radiotherapeutics deployable electrode and the Radionics clustered triple electrode. Of course, both the small number of lesions treated with the cluster electrode (n=8) as well as the fact that the triple electrode is specifically used for larger lesions should be taken into account when interpreting these results. Even though our analysis corrected for within-patient correlation, we should consider the fact that the use of varying RFA systems is institution related. Therefore, we cannot conclude without restrictions that certain electrode systems are more effective than others.

Considering the abovementioned pitfalls and problems when striving for local tumour control with RFA, we advise that application of RFA should not be lightly embarked on. It requires specialized experience and skills to insert all electrodes properly, especially in larger tumours or tumours located near large vessels or

adjacent organs. If tumour is not completely ablated, there will be no positive effect on overall or disease-free survival, depriving the procedure of its effectiveness. As placement of electrodes is essential, adequate treatment planning is of pivotal importance. CT scans and ultrasound may contribute in achieving this goal, and future three-dimensional stereotactic electrode placement may further improve RFA results. We would also recommend an extensive pre-treatment workup with abdominal and thoracic CT scan, preferably within two weeks before treatment. This will avoid non-beneficial treatment of patients with extrahepatic disease and its associated risk of complication of about 10%.

In summary, we suggest the following exclusion criteria for treatment of liver tumours with RFA: pre-existing extrahepatic disease, tumour size over 5 cm, tumour location near central vascular structures or tumours in difficult locations in patients who are not eligible for on open procedure. Possible differences in anti-tumour efficacy of the various available RFA electrode systems need to be further assessed in a randomised, prospective setting before any specific recommendations can be made regarding these systems.

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