Local ablative therapies for colorectal liver metastases and the immune system

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Chapter 7

Adverse effects of radiofrequency ablation of liver tumours

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Introduction

Surgical excision offers the best chance of cure for both primary and secondary liver tumours[1-3]. Unfortunately, only a small number of patients that present with liver tumours are eligible for resection, as multifocal intrahepatic disease, extrahepatic disease, inadequate functional hepatic reserve or involvement of major liver vessels often preclude adequate surgical resection[4,5].

In light of these surgical limitations, local ablative therapies have emerged as alternative therapies for unresectable liver tumours. Radiofrequency ablation (RFA) is a promising treatment in selected cases of unresectable liver metastases and hepatocellular carcinoma (HCC)[6,7]. RFA offers a good alternative for cryoablation[8], percutaneous ethanol injection[9], interstitial laser coagulation[10-12] and microwave therapy[13]. The choice of one of these local ablative therapies is often a matter of local preference, institutional experience and availability. One important advantage of all types of local ablation compared to partial liver resection is its possible application as minimally invasive therapy, which can be repeated easily when recurrences are observed.

The effectiveness of RFA in achieving local disease control in the treatment of malignant tumours has been shown in a large number of patients[14,15]. RFA can be applied percutaneously[16], during laparoscopy[17,18] or at laparotomy[19,20], enabling simultaneous partial hepatic resection[21]. According to literature, RFA is considered a low risk procedure, with mortality rates varying from 0 to 1.6%[22-24] and complication rates between 2.4 and 9.5%[25-28]. These data illustrate that although RFA is considered safe, RFA may give rise to serious complications and even mortality. For decision making and patient information one should be aware of the morbidity and mortality rate related to this therapy. Further optimisation of patient care after RFA can be attained when recognition of RFA related complications is improved. The aim of this study is to describe both the immediate and delayed complications following RFA, permitting insight in the possibly eventful clinical course after RFA.

Patients and methods

Patients

For this study all patients with primary or secondary liver tumours that were treated with RFA from June 1999 through November 2003 in 8 medical centres in the Netherlands were prospectively registered. Curative resection was the treatment of choice in all patients. When resection was not feasible, patients were considered for RFA treatment alone or RFA treatment combined with resection. For all patients, a baseline

history and physical examination were performed. Hepatic function was evaluated before and immediately after RFA through laboratory indicators of synthetic function and in case of hepatocellular carcinoma (HCC), the Child Pugh classification was determined. For staging purposes, all patients underwent extensive pre-treatment diagnostic work-up including hepatic ultrasound (US) examination and computed tomography (CT) scanning of chest and abdomen. Medical records were reviewed for demographics and comorbidity, tumour histology, number, size and location of tumours, RFA procedure, type of RFA-electrode, procedure approach, number of applications, operative blood loss, application of vascular inflow occlusion (Pringle's manoeuvre), length of hospital stay and blood transfusion requirements.

Complication registration

Complications were registered by reviewing medical records and radiological images and by direct communication with surgeons. For description of RFA application and classification of complications, the recommendations of standardization as proposed by a subcommittee of The Working Group on Image-Guided Tumor Ablation[29] were used. All intra-operative and post-operative complications as detected by clinical examination or imaging techniques were classified as major or minor and included for analysis. Major complications were those that were either life threatening when left untreated or would lead to substantial morbidity and disability, hospital admission or substantially lengthened hospital stay. All other complications were considered minor. When patients only suffered from mild pain, elevated temperature or nausea during the first week after RFA, these events were not included in the complication analysis.

One or more complications may occur in one RFA procedure. Complications were considered RFA-related or not RFA-related when associated with concomitant partial liver resection or the type of approach. In addition, complications were classified as immediate complications or periprocedural complications (in the first 30 days after RFA) and delayed complications (> 30 days after RFA).

As RFA induces the release of liver enzymes during ablation and a necrotic mass incorporating both ablated tumour mass and surrounding liver parenchyma remains in situ after RFA we assessed the post-RFA grade of liver damage. The National Cancer Institute Common Toxicity Criteria (NCICTC) were used as described by the Southwest Oncology Group in cooperation with the National Cancer Institute[30]. Damage grade of the liver was divided in toxicity grade I to IV (table 1) and assessed after determination of aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyltransferase (γ-GT), alkaline phosphatase (AP) and bilirubin levels.

	Grade			
	1	2	3	4
bilirubin		< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
AST/ALT	1 - 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
AP	1 - 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
γ-GT	1 - 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N

N= normal value

Table 1. Toxicity criteria

RFA-procedure

RFA was performed using three different commercially available RFA systems. In all cases the RFA electrode was ideally positioned in the centre of the tumour, inducing complete necrosis of all tumour tissue with a circumferential necrotic rim of 0.5 to 1.0 cm of liver parenchyma. Vascular inflow occlusion was used to increase the effectiveness of RFA by preventing heat-loss due to the 'heat-sink' effect. Specific RFA protocols, designed by each of the three manufacturers, were used for each system according to manufacturer recommendations.

The **Radionics RF system** (Radionics, Burlington, MA) consisted of a 500 kHz RF generator (series three Radionics) attached to a single or cluster cooled-tip electrode. For small tumours a single electrode with 3.0 or 4.0 cm of exposed metallic tip was used. For larger tumours, a triple electrode cluster was used consisting of three electrodes with an active tip length of 2.5 cm that are triangularly configured spaced 5 mm apart. A peristaltic pump infuses normal saline solution into the lumen of the electrode(s) to increase energy deposition. After each RFA application (lasting 8-12 minutes), local temperature was recorded by an embedded thermocouple, to ascertain therapeutic effectiveness. When local temperature was 65 °C or less, the ablation was continued for an additional 3 minutes.

The **Radiotherapeutics RF system** (Radiotherapeutics, Sunnyvale, CA) used in this study included a RF 2000 or 3000 generator system. The generator is connected to a deployable Leveen™ monopolar array electrode (4.0 cm maximum array diameter). After deployment in the centre of the tumour initial power was set at low level and increased with increments of 10 W, according to the algorithm provided by the manufacturer, until a major increase in impedance, so called 'roll off' was achieved.

The **RITA RF system** (RITA Medical Systems, Mountain View, CA) consisted of the RITA RF model 1500 connected to a 14-G Starbust XL deployable electrode of 2, 3, 4 or 5 cm with thermocoupling. The electrode

was flushed before puncture by injecting saline through the lateral hub. Initial power was set at 50 W and prongs were deployed at 2 -cm length. With increasing temperature prongs were gradually deployed to their maximum with a temperature of 110 °C and power set to 110 W. After switch off, tissue temperature was 70 °C for at least 30 seconds, to ensure complete technical ablation.

Statistical analysis

Univariate and multivariate analysis was performed to identify significant prognostic parameters associated with treatment morbidity after RFA. Analysis of statistical significance of qualitative comparison between groups was performed with Pearson's chi-square univariate analysis. Student's t test was used to test for qualitative comparison between groups with $p < 0.05$ representing a statistically significant difference between groups. Parameters that were analysed included: age, gender, tumour histology (metastatic lesion vs. HCC), previous liver therapy (local or systemic), number of tumours treated, RFA approach (percutaneous vs. laparotomy), type of laparotomy (RFA alone or RFA and concomitant liver resection), type of RFA needle (mononeedle vs. triple needle vs. deployable needle) and tumour location central (1, 4, 5 and 8) versus peripheral tumour location (2, 3, 6 and 7) and concomitantly performed major or minor partial liver resection.

Results

Patient and tumour characteristics

From June 1999 through November 2003, 122 patients (80 male, 42 female) with primary or secondary liver tumours were treated with RFA. Median age was 63 ± 9 years (range 39-83). Forty-seven patients had comorbidity (table 2). Patients were considered not eligible for surgical resection due to close proximity of tumours to large vascular structures (28%), previous partial liver resection or RFA (28%), impaired liver function (15%), bilobar disease (17%), extrahepatic disease (7%), insufficient remnant liver volume (4%) or refusal to undergo liver surgery (1%).

Thirteen patients (10.7%) had primary hepatocellular carcinoma (HCC) while 109 (89.3%) patients had liver metastases from colorectal carcinoma (n=87) or other primary tumours (n=22). Liver metastases had been detected synchronously with the primary tumour in 44 patients and metachronously in 65 patients. A total of 275 tumours were treated and the mean number of lesions per patient was 1.9 ± 1.3 (range 1-6). The average diameter of the tumour was 2.9 ± 1.6 cm (range 0.8- 11.0 cm) and an average of 1.6 ± 0.9 (range 1-5) RFA applications were needed to treat each lesion.

Total number of patients	122
Gender	
males	80
females	42
Mean age ± SD (years)	63 ± 9
Comorbidity	
none	76
liver cirrhosis	16
diabetes mellitus	8
COPD	3
cardial (hypertension e.g.)	19
Total number of tumours	275
Mean lesion diameter ± SD (mm)	29 ± 16
No of RFA procedures	143
No of tumours treated with RFA	
1	75
2-3	46
>3	22

Table 2. Patient and tumour characteristics

RFA procedure

One hundred twenty two patients were treated with 143 RFA procedures (table 3). Three different RFA electrodes were used; cooled tip single electrodes, cluster cooled-tip electrodes and deployable umbrella shaped electrodes. Thirty-five procedures were performed percutaneously (24%), while all other procedures were performed during laparotomy (76%). In 37 procedures (26%) RFA was performed concomitantly with partial liver resection.

Median total operation time was 3 ± 1.5 hours (range 1-10 hours), with a median blood loss of 600 ± 800 cc (4500 cc maximum blood loss). Vascular inflow occlusion was applied in 15 open RFA procedures (14% of open procedures). Mean hospital stay after RFA was 8 ± 4 days (range 4-25), which was significantly longer after open RFA than after percutaneous RFA (9 vs. 5 days, $p < 0.05$).

Total number of tumours	275
Total number of RFA procedures	143
open RFA	108
percutaneous RFA	35
Concomitant liver resection	37
hemihepatectomy	3
segment resection	26
metastastectomy	8
Mean RF application per tumour ± SD	1.6 ± 0.9
Pringle manoeuvre	15
Duration of operation ± SD (hours)	3 ±1.5
Hospital stay ± SD (days)	8 ± 4

Table 3. Procedure characteristics

Blood biochemistry

Compared to pre-RFA levels, bilirubin levels were elevated at 1 day after RFA to 18.50 ± 17.94 µmol/L. Three to five days after RFA, only 37% still had elevated bilirubin levels of 12.00 ± 16.70 µmol/L. Alkaline phosphatase at 1 day after RFA was elevated compared to pre-RFA values in only 2.7% of patients (52.20 ± 2.12 U/L) and 3-5 days after RFA, only 1 patient still had elevated AP of 59 U/L. Liver enzymes were more frequently increased, as AST was elevated in 69% of patients to a mean of 695 ± 716 U/L and ALT was elevated in 68% to 512 ± 483 U/L. At 3-5 days after RFA, levels remained elevated in 54% and 51% of patients for AST and ALT respectively, but mean values had decreased to 178 ± 361 U/L for AST and 314 ± 561 U/L for ALT. Maximum increase in γ-GT levels was not seen immediately after RFA but at 3-5 days after treatment, with 22% of patients showing elevated levels compared to pre-RFA γ-GT values to a mean of 183 ± 209 U/L.

As is illustrated in figure 1 overall liver toxicity one day after RFA was grade 1 in 2% of the patients, grade 2 in 18% of the patients, grade 3 in 57% of the patients and grade 4 in 23% of the patients. At 3 to 5 days after RFA, toxicity decreased to 14% grade 1 toxicity, 36% grade 2 toxicity, 40% grade 3 toxicity and 10% grade 4 toxicity.

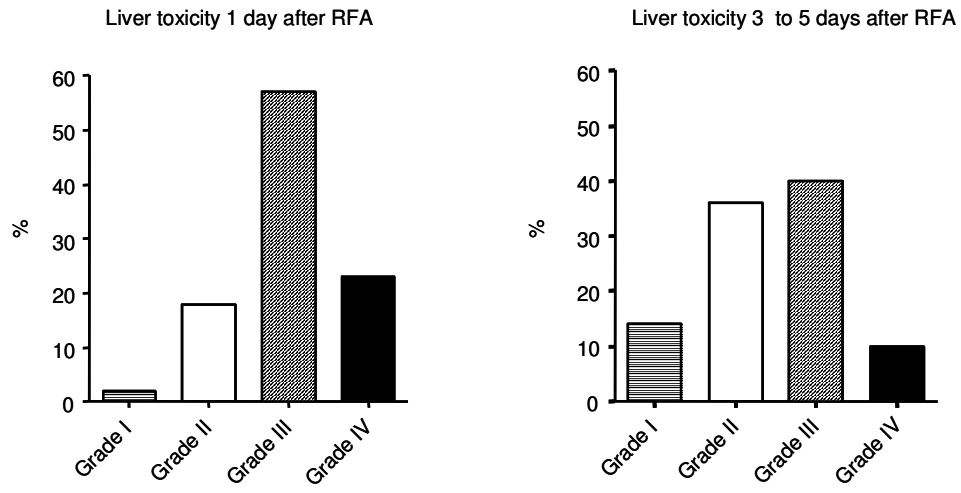

Figure 1. Liver toxicity following RFA, 24 hours post-RFA and 3-5 days post-RFA

Mortality

Two patients (1.4%) died within 30 days after RFA after two RFA procedures, both of whom were treated during an open procedure and concomitant partial liver resection.

A 64-year-old female (patient 1) with a Child Pugh A cirrhosis and HCC died on day 25 after combined RFA and local excision. Postoperatively she developed an intrahepatic haematoma resulting in hypovolemic shock and liver failure. In spite of maximum supportive therapy she eventually died from liver failure.
The second patient, a 67-year old male (patient 2) with colorectal liver metastases died on day 26 after combined RFA and right hemihepatectomy. He was diagnosed with a liver abscess, liver failure and abdominal peritonitis. During relaparotomy a paracolic infected haematoma (*Staphylococcal Aureus* and *Streptococcus*) was removed. Unfortunately, he succumbed to septic shock secondary to a necrotising pancreatitis and a hepatic vein thrombosis, as discovered during autopsy. Mortality was only partially related to RFA in this last patient, as it mainly resulted of a surgical complication.

After percutaneous RFA, mortality was 0%, but this was not significantly different from that of open RFA procedure ($p = 0.42$).

Morbidity

A total of 43 complications were reported after 29 RFA procedures. Of these 43 complications, 8 were attributed to the two patients who died within one month after RFA. Total postoperative complication rate was 21.5%. Nineteen complications were graded as major and occurred after 10 RFA procedures (major complication rate: 6.9%). Eleven out of 19 major complications were considered to be RFA related and occurred after 9 RFA procedures (RFA related major complication rate: 6.3%). Twenty-four minor complications occurred after 21 RFA procedures (minor complication rate: 14.7%). Five of these were considered RFA related and developed after 5 RFA procedures (RFA related minor complication rate: 3.5%). Overall, 16 RFA related complications developed after 14 RFA procedures (RFA related overall complication rate: 9.8%).

Thirty-three complications developed immediately or periprocedurally after 25 RFA procedures (immediate or periprocedural complication rate: 17.5%), while 10 complications developed delayed after 7 RFA procedures (delayed complication rate: 4.9%). Immediate or periprocedural complications were mainly not RFA-related (23 out of 33 complications) while a majority of delayed complications were RFA related (6 out of 10 complications). Delayed complications were mainly major and consisted of biliary stricture (n=4), bilioma (n=1), hepatic abscess (n=3) or hepatic vascular damage (n=2).

Analysis of variance of RFA parameters influencing complication rate

To identify prognostic parameters associated with increased morbidity rate univariate analysis was performed. Eleven possible prognostic parameters were evaluated but no parameters could be identified with an increased risk of morbidity (table 4) although a trend could be observed when concomitant liver resection was applied ($p = 0.070$).

	morbidity	p-value
Gender		0.292
male	16.9%	
female	24.1%	
Age		
< 50	12.5%	0.773
50-70	19.6%	
>70	20.7%	
Comorbidity		0.410
yes	16.4%	
no	20.7%	

Table 4a. Patient related factors

	morbidity	p-value
Tumour histology		0.465
hepatocellular carcinoma	26.7%	
liver metastases	18.8%	
Previous therapy		0.500
yes	16.0%	
no	20.7%	
Tumour diameter		0.347
<3 cm	17.1%	
3-5 cm	21.4%	
> 5 cm	20.0%	
Location of tumours		0.683
central	18.0%	
peripheral		
Number of treated lesions		0.308
1-3	20.0%	
>3	15.6%	

Table 4b. Tumour related factors

	morbidity	p-value
RFA approach		0.070
percutaneous	8.6 %	
laparotomy	22.4%	
Concomitant liver resection		
yes	32.4%	
no	17.1%	
Type of electrode		0.643
single cooled electrode	9.5 %	
triple cooled electrode	21.5%	
deployable (Radiotherapeutics)	22.2%	
deployable (RITA med)	20.6%	

Table 4c. RFA related factors

Intrahepatic haematoma

One patient developed an intrahepatic haematoma immediately after RFA with partial hepatectomy due to a tear in the liver parenchyma. This complication was considered RFA-related since the intrahepatic haematoma was located around the ablated lesion as seen on post-RFA US and CT-scan. Initially, treatment was conservative but as bleeding persisted, a laparotomy was performed at 3 weeks after RFA and the bleeding liver segment could be resected. The effect of this intervention is difficult to determine as this patient died soon after this surgical intervention due to liver failure (as described earlier, patient 1).

Hepatic abscess

Four patients who were all treated with RFA and hepatic resection developed a total of 6 hepatic abscesses. Hepatic abscesses were located at the site of ablation in two patients and therefore considered RFA-related. In the other two patients, occurrence of the abscesses was not related to RFA as they developed in the contralateral, partially resected liver lobe. All patients initially showed full recovery after RFA but returned to the hospital with complaints of fever. In all cases, hepatic abscesses were detected on CT scan. Treatment

consisted of percutaneous drainage (n=1) or drainage during one or more laparotomies (n=2). One patient with only a small subphrenic abscess was treated with intravenous antibiotics alone. One patient died after surgical intervention as a consequence of septic shock (as described earlier, patient 2). One patient was diagnosed with hepatic abscess 2 weeks after RFA, while in the other patients abscesses were detected between 1 and 4 months after RFA and can therefore be considered periprocedural or delayed complications.

Wound infection/miscellaneous
Two patients who underwent RFA during laparotomy presented with fever at 10 and 14 days after RFA respectively, without presence of abdominal abscesses on CT-imaging. In both patients a subfascial wound abscess was detected and surgical drainage was performed, after which patients recovered fully.

Peritoneal infection
One patient developed infected ascites (*Staphylococcal* and *Difteroids)* (as described earlier, patient 1) and one other patient developed an infected paracolic haematoma (as described earlier, patient 2) at 21 days and 11 days after RFA respectively. Both patients underwent surgical intervention but eventually died, as described earlier.

Biliary tract damage
Nine patients developed biliary tract damage after RFA. Biliary strictures were reported in 6 patients at one week to 4 months after RFA procedures. All 6 patients developed jaundice with peak bilirubin levels ranging from 74 to 940 µmol/L. One patient was treated with partial sphincterotomy while the other patients underwent one or more ERCPs (endoscopic retrograde cholangiopancreaticography) for stenting of the choledochal bile duct. Multiple stent changes (2 to 4) were necessary in 5 patients. Nevertheless, two patients with biliary strictures eventually developed a biliopleural fistula (n=1) and a bilioma (n=1) respectively, originating from the biliary stricture. These were successfully treated with surgical closure and percutaneous drainage.

A bilioma without biliary stricture was seen in one patient at three months after RFA. Although the bilioma was percutaneously drained, a bilicutaneous fistula developed, which resolved with conservative treatment. One patient developed fever 5 days after RFA that was most likely caused by cholangitis and was treated with intravenous antibiotics. A thermal lesion of the gallbladder during RFA of a tumour close to the gallbladder was encountered in one patient. Cholecystectomy was performed immediately after intra-operative diagnosis. In total, biliary tract damage was related directly to RFA in 6 of the 9 patients. In two

patients biliary damage was due to concomitant metastasectomy and hemihepatectomy and in one patient it could not be differentiated whether biliary damage was caused by RFA or partial hepatectomy. Biliary tract damage was an immediate complication in one patient, a periprocedural complication in 2 patients and a delayed complication in 6 patients.

Liver failure

Four patients suffered from liver decompensation after RFA, two of whom died due to liver failure. The first of two fatal liver failures developed in a patient with Child Pugh A liver cirrhosis and HCC immediately after RFA and metastasectomy. The second patient underwent RFA in the left lateral lobe and a right hemihepatectomy (as described earlier, patient 2).

Moderate liver failure due to right portal vein thrombosis after combined metastasectomy and RFA developed in one other patient and resolved following medical treatment. One patient with HCC and Child Pugh A cirrhosis, who was treated with RFA alone via laparotomy, developed transient liver decompensation (Child Pugh grade increased from 5 to 13) but responded well to supportive care. As no portal thrombosis could be detected by US and, due to small tumour size, RFA was performed with a single application of a RF single cooled-tip electrode, no evident cause could be defined for this failure. Liver failure can be considered a periprocedural complication in these patients, as liver failure developed during the first month after RFA in all four patients.

Hepatic vascular damage

Hepatic vascular damage was a periprocedural complication in three patients and delayed in two patients. Portal vein thrombosis occurred in two patients, at one week and four days after RFA, respectively, and was associated with ascites and oedema. In both patients, portal thrombosis was directly related to RFA as treated tumours were located in the centre of the liver. Pringle manoeuvre was applied during RFA in one patient. No damage of the adjacent biliary tract was incurred. Both patients were conservatively treated with antibiotics. Thrombosis of the right hepatic vein was discovered during autopsy in the patient who died due to multi organ failure (as described earlier, patient 2).

Two more patients with central tumours developed arterial vascular damage. In both patients RFA was performed without vascular occlusion and complications were directly related to RFA. Of these two patients, one presented with rectal blood loss one week after RFA and partial hepatectomy. The patient was transferred to the ICU and recovered after multiple blood transfusions. In the other patient hepatic arterial aneurysm was not discovered until a bleeding episode 6 months after percutaneous RFA of a central liver

tumour. After embolisation of the aneurysm, liver segmental infarction developed, which required surgical excision.

Pulmonary complications
Three patients reported shortness of breath acutely after RFA due to a pneumothorax (n=1) or symptomatic pleural effusion (n=2). Uneventful pleural effusion was not scored as a complication. Clinical symptoms disappeared without therapeutic intervention and hospital stay was not longer than the average hospital stay. Three other patients developed fever after RFA due to pneumonia and were all successfully treated with antibiotics. One patient developed a pulmonary embolus in the right pulmonal artery two weeks after RFA. He was artificially respirated and heparinised successfully.

Cardiac complications
Two cases of atrial fibrillation were noted within 1 week after RFA, none of which were fatal or required cardiac massage. Upon medical treatment, arrhythmia resolved and hospital stay was not longer than average hospital stay.

Miscellaneous minor complications
Postoperatively, one patient developed significant thrombocytopenia from unknown cause. Two other patients, both of whom had undergone RFA in an open procedure, developed a transient paralytic ileus postoperatively that was not considered RFA-related. One patient developed urinary tract infection, which was adequately treated with antibiotics. An upper gastrointestinal bleeding was reported once after RFA but resolved spontaneously. Other minor complications included brachial plexopathy after sudden withdrawal of the arm and abortion of percutaneous RFA due to excessive pain.

Discussion

This is the first study to our knowledge reporting on RFA complications including all recent published guidelines recommended by a subcommittee of The Working Group on Image-Guided Tumour Ablation[31]. In order to prevent heterogeneous study results and to create uniform comparative morbidity and mortality results, they suggest categorizing complications in major or minor, RFA related or not RFA related and according to the moment of diagnosis after RFA i.e. as immediate, periprocedural or delayed.
RFA is generally described in literature as a safe and effective therapy. Mortality is rare and in the three largest studies including more than 6,000 patients, ranges from 0.2% to 0.5%, while reported complication rates range from 7.1 to 9.5%[32,33]. Our study reports a considerably higher overall mortality (1.4%). Both of these patients underwent partial hepatectomy and RFA. A combination of RFA and partial liver resection is most often well tolerated, but it may lead to liver failure and death. This emphasizes the value of pre-operative evaluation of functional liver reserve. This is especially important when RFA is applied to patients with liver cirrhosis or when RFA is performed simultaneously with extended partial liver resection.
No mortality occurred in our study when RFA was applied during laparotomy without concomitant liver resection, suggesting RFA to be a safe and well tolerated technique when applied alone comparable to literature[34-36].

We believe the higher overall complication rate in our study (21.5%) to be due to various reasons. First, RFA was performed with partial liver resection in 26% of procedures, which resulted in the registration of additional complications not directly related to RFA. Several studies report a higher mortality and complication rate when RFA is applied in combination with partial liver resection[37 38]. After excluding complications that were not RFA-related, the complication rate in our study decreased to 9.8%, which is comparable to the earlier mentioned studies in which complication rates ranged between 7.1-9.5%[39-41]. Second, the choice of approach for performing RFA partly depends upon the training of the responsible physician. In The Netherlands, RFA was introduced by surgeons and the great majority of RFA procedures in our study (75%) were performed during laparotomy, inflicting more surgical trauma. Livraghi *et al.* found that RFA is associated with more complications when performed in surgical centres, which was attributed to the more limited experience of surgeons with percutaneous image guided techniques[42]. According to recently published recommendations of experts in the field, RFA should only be performed during laparotomy when a percutaneous approach is not possible due to central location of the tumour, direct surrounding of vital organs such as bowel loops or inappropriate tumour imaging by US or CT[43].

A third explanation for the relatively high complication rate in our study is that multiple centres were involved rather than a single institution. Only one recent study evaluated the effect of operator experience on morbidity rate and demonstrated a 4-fold decline in morbidity between the first 50 (16%) and second 50 RFA procedures (4%, $p < 0.05$) within a single institution[44]. Our study included much of this learning curve of each participating investigator as the number of RFA procedures in each institute varied from only 5 to 25 RFA procedures. It is therefore likely that morbidity rate will be further reduced in the future.

In addition to following the recommendations of the subcommittee of The Working Group on Image-Guided Tumour Ablation to strive for uniform reports of complications after RFA, we describe complications in accordance with the subdivision that was used in a recent exhaustive review describing the range and incidence of complications after RFA[45]. Based on this subdivision, we conclude that the distribution of complications in our study mirrors the distribution reported in literature worldwide[46]. Abdominal bleeding, hepatic abscess, biliary tract damage and liver failure were the most common complications reported in this review. Prevalence of RFA-related biliary tract damage (4.9%) and hepatic vascular damage (2.8%) in our study was higher than in the two earlier mentioned studies (0.7% to 1.0% and 0% to 0.6%, respectively), whereas Stippel *et al.* described a higher biliary tract damage rate of 9.5% and related this high incidence to the fact that patients with tumours in close proximity to biliary tract damage were not excluded from RFA treatment[47-49]. Inclusion criteria differ from institute to institute and might influence overall rate of biliary tract complications and hepatic vascular damage. Since it is believed that large bile ducts and hepatic vessels are protected by the cooling effect of hepatic blood flow[50 51], application of vascular inflow occlusion could be associated with increased occurrence of biliary tract damage. In our study vascular inflow occlusion was performed only selectively (14% of open procedures) and we therefore do not believe this to be the reason for our increased biliary tract complication rate. In literature, two specific recommendations have been made to prevent biliary tract damage, i.e. intraductal cooling and prophylactic stentplacement [52,53]. Neither technique was used in our study.

Although RFA has found wide application, its exact role in the treatment of colorectal liver metastasis has not yet been firmly established. As properly conducted trials comparing RFA to resection of liver tumours have not yet been performed, RFA should at present only be used in patients who are not eligible for surgery. This study demonstrates that RFA is most often well tolerated and can be performed with acceptable overall complication rate. However, during its introduction phase in the Netherlands RFA was associated with slightly higher complication and mortality rates than previously reported in literature. We recommend that patients treated with RFA should be monitored closely for the development of complications. Further registration and assessment should reveal the influence of the learning curve on morbidity

rate. Special attention should be given to the possible development of biliary strictures, as it is one of the most common complications after RFA, especially when RFA is performed in or near the hilum of the liver. Although the initial clinical course might be uneventful, hospital readmission with a febrile episode should raise suspicion of a potential complication. In these cases, we recommend immediate imaging by ERCP or CT scan to prevent the development of secondary complications like abscesses or fistulas. Although RFA seems to be a straightforward technique, it is essential that RFA should only be performed in experienced hepato-biliary units with multidisciplinary teams consisting of a hepatobiliary surgeon, gastroenterologist and interventional radiologist.

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