Surgical treatment of liver and lung metastasis. New techniques and outcomes
Mutsaerts, E.L.A.R.
Initial experience with radiofrequency ablation for hepatic tumours in the Netherlands


European Journal of Surgical Oncology 2003; 29: 731-734
Introduction
Patients with primary or metastatic malignant hepatic tumours that are considered unresectable because of multifocal disease, postoperative inadequate functional hepatic reserve or location of the tumour near major vascular or biliary structures, may be considered for other local treatment options. Techniques for local ablation of tumours in the liver include ethanol injection, thermoablation with cryoprobes, interstitial laser coagulation and recently, radiofrequency ablation 1-4.
Radiofrequency ablation uses a high frequency alternating current from the uninsulated tip of a needle electrode, placed under image guidance into the tumour. Ionic agitation produces frictional heating 5. When tumour cells are heated above 45 to 50 °C, intracellular proteins are denatured and cell membranes are destroyed by dissolution and melting of lipid bilayers 6,7. Several studies have shown fewer complications following RFA than with cryoablation 8,9. Series from the USA and Italy showed complication rates of less than 3% after RFA treatment 1,10. RFA was introduced in The Netherlands in 1999 and has since then been used in several centres.
The aim of this study was to report the initial experience of several Dutch centres with RFA.

Patients and Methods
Between June 1999 and November 2001, 50 patients (35 men and 15 women) with a mean age of 59 years (range 21-81) were included in a multicentre, prospective study of RFA treatment. Table 1 lists the patient characteristics.
All patients underwent CT scan of the abdomen and a chest X-ray or CT. Patients were excluded if they were found to have extrahepatic disease at preoperative evaluation and also

Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (Male/Female)</td>
<td>35 / 15</td>
</tr>
<tr>
<td>Age at operation (years)*</td>
<td>59 (range 21-81)</td>
</tr>
<tr>
<td>Indication of RFA</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Colorectal metastases</td>
<td>39</td>
</tr>
<tr>
<td>Metastases of other origin</td>
<td>9</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>36</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>3</td>
</tr>
<tr>
<td>Serious steatosis hepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Liver abscess after chemotherapy</td>
<td>1</td>
</tr>
<tr>
<td>Cardio-pulmonary</td>
<td>6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
</tbody>
</table>

*Values are mean (range).
patients with poor hepatic function (Child’s C cirrhosis).
At the start of the study some patients with resectable tumours were treated by RFA to be
followed subsequently by resection to determine in vivo the effect of RFA on the tissue level.
After this experience only patients where complete resection of all hepatic tumours was not
feasible, were included. They underwent RFA as the only therapy or RFA as an adjuvant
therapy to resection in multifocal disease at open surgery.
Follow-up CT scans were made after 1, 3 and 6 months postoperatively, and every 6 months
thereafter, for 2 years.
We recorded the indication for surgery; co-morbidity; number and location of tumours;
feasibility of RFA, number of tumours treated with RFA; number of applications; resection
specifications; general or procedure related complications; histopathology reports of resected
tumours after RFA. In patients with non-resectable, RFA treated tumours, the site of liver
recurrence was recorded.
All patients entered into this study gave informed consent.

RFA-technique
All centres involved in this study used the RF 2000™ radiofrequency generator and the
LeVeen™ Needle Electrode (both RadioTherapeutics Corporation, Sunnyvale, CA). All
patients underwent RFA at laparotomy. Tumours were visualised by ultra-sonography (US).
Under US-guidance and assisted by direct palpation, a 3 or 3.5 cm (array diameter) LeVeen
Needle Electrode was inserted and deployed in the tumour. The needle electrode was
positioned in the centre of tumours smaller than 3 cm, and near the most posterior interface
in tumours larger than 3 cm in which treatments were repeated. RF energy was applied
(according to the standardized manufacturer’s algorithm ⁸) to the tissue with an initial power
setting of 50 W and subsequently increased with increments of 10 W each minute to a
maximum power of 90 W. The power setting was left at this point until power “roll-off”
occurred; tissue impedance (an increase in tissue resistance caused by decreased conductivity
of electrical current by protein denaturation and loss of intracellular fluids) rose to over 200
Ω at which time the power passively decreased to less then 10 W. After waiting 30-60 s, a
second phase was started at 75% of the last maximum power until a second roll-off
occurred.
If no roll-off occurred at each off these two phases, a total of 15 minutes per phase elapsed.
The two-phase procedure was repeated for larger tumours (>3 cm). In these cases, the needle
electrode was repositioned at 2.5 to 3.0 cm intervals within the tumour in order that an
overlap occurred with each application.

Histopathology
Histopathologic examination was performed of all resected tumours treated with RFA. Liver
specimens were fixed in 4% (w/v) formaldehyde, embedded in paraffin and processed for
routine hematoxylin and eosin staining (H and E) on sections (4 μm). Tumour biopsies were
frozen in liquid nitrogen for detection of activity of nicotinamide adenine dinucleotide
Table 2: Treatment combination of patient-group/number of complications

<table>
<thead>
<tr>
<th>(Multi-modality) therapy of liver tumours</th>
<th>Patients (n = 50)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFA followed by resection of ablated tumour</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>RFA alone</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>RFA and ethanol injection other tumour</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>RFA and resection of other tumours</td>
<td>13</td>
<td>4</td>
</tr>
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RFA: Radiofrequency Ablation

diaphorase (NADHd), which is used as a marker of mitochondrial viability. NADHd activity was demonstrated in cryostat sections (8 μm) using an incubation solution containing the substrate NADH (0.1 mg/mL; Sigma Diagnostics, St. Louis, Missouri, USA) and the indicator nitro blue tetrazolium (NBT; 1.0 mg/mL, Sigma Diagnostics). Cryostat sections were incubated with this solution for 30 minutes at room temperature. Sections were post-fixed with 4% (w/v) buffered formaldehyde, rinsed with distilled water and mounted in glycerol jelly.

Results

In 50 patients, 102 tumours (1-8 tumours per patient) with a mean diameter of 2.5 cm (range 1-7 cm) were treated with RFA. Table 2 shows the treatment combinations performed in the patients. In 12/50 patients vascular inflow occlusion was applied during RFA. One patient, with extrahepatic disease at laparotomy, underwent trial RFA procedure of a single liver lesion to assess its local effect at follow up.

In seven patients, the radiofrequency ablated tumours (n=11) were resected and examined for NADHd-diaphorase staining to assess non-viable tumour. In all tumours, non-viability of the cells was confirmed.

Postoperative complications

Postoperative complications occurred in 14 of the 50 patients (28%). One patient with HCC in a Child’s class B cirrhosis died 26 days postoperatively from progressive liver failure. She underwent a central resection in segment four and two RF ablations in segment seven and eight.

Five patients developed (late) postoperative jaundice. One patient was treated for metastases located on both sides of the left hepatic duct and probably sustained collateral thermal duct injury due to the RFA procedure. Two patients also underwent a concomitant cholecystectomy and developed obstruction of the proximal hepatic duct about 4-6 weeks after surgery. The first of these two patients had undergone a cholecystectomy of a previously inflamed gall bladder and common bile duct that developed into an ischemic stenosis. The second patient with an obstruction of the proximal hepatic duct had undergone RFA just above the bile duct bifurcation but also had extirpation of a large tumour positive node.
behind the common bile duct. A fourth patient underwent a right extended hemihepatectomy after ablation of a tumour in that part of the liver. The fifth patient showed early recurrent metastatic disease with compression of the biliary system.

Other complications were fever (n=5), thrombocytopenia (n=1), melaena (n=1) (a possible diagnosis of haemobilia was suggested, although this was never confirmed) and paralytic ileus (n=1), which all eventually resolved.

**Follow-up**

One patient was lost to follow-up. A follow-up analysis with CT scans was performed in all patients. Median follow-up time of the 41 patients with non-resected RF ablated tumours was 11 months (range 1-24 months). Of these 41 patients, 26 patients developed recurrent disease. Only three patients developed a recurrence at the site of previous RFA after 6, 7 and 12 months; 13 patients had recurrent metastases elsewhere in the liver but no recurrence at the RFA site and 10 patients had extrahepatic metastatic disease. Of the 41 patients, five had died to date at the completion of the study, 21 are alive with disease and 15 are alive without demonstrable disease.

**Discussion**

Radiofrequency ablation is a therapeutic option for unresectable tumours located in the liver. The morbidity and mortality rate is comparable to surgical resection alone. Three complications were probably related to the RFA: progressive liver failure in the patient with Child B cirrhosis; stricture of the left hepatic duct; and postoperative thrombocytopenia. Hence, this study was not able to confirm the low complication rate of 3% reported after RFA in the USA and Italy. Firstly, this is possibly related to the multicentre nature of the study and the fact that the study describes the initial experience of each participating centre. Secondly, all patients were treated with RFA at laparotomy, 30% in combination with resection. In a review, Mulier et al. concluded that complication and mortality rates are related to the approach and the extent of the procedure.

A common, potentially fatal complication in cirrhotic liver resection is liver failure. Curley et al. treated 110 cirrhotic patients with radiofrequency ablation in the liver without treatment related deaths and a complication rate of 12.7%. In our study several complications were related to proximity of major biliary structures. The low flow in our damaged biliary ducts may explain for the enhanced thermal effects of RFA, in comparison to the (high flow) major blood vessels. Elias et al. have described a technique of intraductal cooling. One patient developed postoperative thrombocytopenia after ablation of three tumours with a size of 2.4 cm, 4.4 cm and 4.3 cm, respectively. This suggests that the thrombocytopenia may be related to the amount of hepatic tissue destroyed around the tumour.

All resected tumours treated with RFA showed complete destruction with NADH-
Initial experience with radiofrequency ablation

diaphorase staining $^{20,21}$, but three of 41 patients developed a local recurrence at the site of previous RFA within 12 months. Local recurrence may be explained by difficulties in achieving complete ablation by overlapping fields in larger tumours. This in turn may be due to hyperechoic blurring of the ultrasound image during the RFA procedure by air bubbles. Great care must be taken to position the needle electrode correctly in order that the thermal lesion encompasses all of the target tissue. Intra-procedural CT or MR guidance may improve this problem.

In other series, a local recurrence rate of 1.8%-18% has been reported $^{1,22-24}$. Local treatment of liver tumours does not appear to be a solution for a hematogenously disseminated disease. The high recurrence rate elsewhere in the liver and at extrahepatic sites therefore needs additional treatments.

In conclusion, RFA appears to be a valuable technique for the local treatment of selected hepatic tumours. The combination of partial resection of resectable liver tumours and RFA of locally unresectable lesions holds promise as a treatment with curative intent. Whether this combination improves survival, is yet to be proven. At this moment, a new study is launched by the EORTC (CLOC C trial) to evaluate the role of RFA instead of chemotherapy for non-resectable colorectal liver metastases. Location of hepatic tumours near major biliary structures is a relative contraindication for this procedure. Hence, although RFA may provide a simple method for local treatment of unresectable liver tumours, the results of this study show that introduction of this technique should not be underestimated and involves morbidity and even mortality.

References