Radiofrequency Ablation of Colorectal Liver Metastases: Mid-term Results in 68 Patients

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Abstract. The aim of this retrospective study was to evaluate the efficacy and medium-term survival, after percutaneous radiofrequency ablation (RFA), in patients suffering from hepatic metastases of colorectal cancer. Patients and Methods: Between 2000 and 2004, 68 patients (42 men, 26 women; mean age 63 years, range: 38-87 years), with non-resectable liver metastases from colorectal cancer, were treated by RFA subsequently or parallel to chemotherapy. The procedures were mainly performed under conscious sedation and local anesthesia using computed tomography fluoroscopy guidance. The number of lesions, the primary success rate, complications, follow-up time and disease-free survival, as well as the local recurrence rate, were evaluated. Results: One-hundred and eighty-three metastases with a mean diameter of 22.8 mm (5-50 mm) in 68 patients (2.7 +/- 1.1 lesions / patient) were successfully treated using RFA. No major complications and only 4 minor complications were noted. Over an average follow-up period of 21.4 +/- 10.6 months (range, 8 to 38 months), Kaplan-Meier analysis demonstrated a probability of 82% of remaining locally disease-free and a probability of 68% of surviving the first 38 months after treatment. Conclusion: For patients with non-resectable hepatic metastases of colorectal cancer, RFA is a safe option in a multimodal treatment concept and may lead to an improvement in survival.

Colorectal cancer (CRC) is one of the most common malignancies worldwide and 50% to 70% of the patients suffering from CRC develop hepatic metastases during the course of their disease. Hepatic metastatic spread significantly contributes to the morbidity and mortality in these patients. For an appropriately selected subgroup of patients, surgical resection of liver metastases is the accepted treatment option with curative intention (1). Without resection and further adjuvant therapies, patients with hepatic metastases from CRC are reported to have a median survival of less than 1 year (2-4). Systemic chemotherapy, radiation therapy and other treatment options, such as percutaneous ethanol injection (PEI), offer little or no benefit to these patients in terms of survival or quality of life.

In various surgical trials, authors have reported 5-year survival rates after hepatic resection of 25% - 40% when proper patient selection and optimal techniques were maintained (2, 3, 5-8). However, a surgical procedure, such as hepatic resection, is still associated with a substantial morbidity and a risk of mortality of approximately 5% (5, 9-12). Furthermore, surgical resection is mainly performed only once, since repetitive resection yields a higher complication rate and is limited by the hepatic functional reserve (11, 13-15). Therefore, only a minority (10%-20%) of patients may meet the essential criteria for surgical treatment (8, 10, 16). For patients not suitable for resection of liver metastases, systemic chemotherapy is the accepted treatment option. Recently published articles have described a median survival after chemotherapy with Oxaliplatin or Irinotecan of 19 and 17 months, respectively (17, 18). Even if systemic chemotherapy does not always improve patient survival first-hand, it is capable of reducing the overall tumor volume so that patients, who did initially present with non-resectable tumors, may become eligible for surgical resection.

The successful application of hepatic resection in patients with colorectal liver metastases has raised the assumption that an effective, minimally-invasive, percutaneous ablation therapy, such as radiofrequency-ablation (RFA), might achieve similar results and increase life expectancy with less morbidity, mortality and
procedure-related costs in comparison to surgery (19, 20). Therefore, percutaneous RFA for the treatment of focal liver malignancies is a procedure which is becoming more widely accepted as a treatment modality for patients with inoperable tumors (21).

Percutaneous, image-guided, tumor ablation with a thermal energy source (e.g. radiofrequency) permits the destruction of tumors without necessitating their removal. Needle electrodes are positioned within tumors and deliver alternating current, resulting in tissue heating and cell death (22, 23).

In this paper, we report our results for 68 patients who underwent RFA for liver metastases from colorectal cancer.

Patients and Methods

Patient selection. The decision to perform RF ablation was made by a multidisciplinary tumor board consisting of the treating physician, oncologists, surgeons and interventional radiologists in all cases. Informed patient consent was obtained after extensive information had been provided. For correct assessment of the number and size of the liver metastases, a contrast enhanced high resolution computed tomography (CT) scan and/or a magnetic resonance imaging (MRI) scan with gadolinium and/or superparamagnetic iron oxide (SPIO) contrast agents was performed. After installation of a combined positron emission tomography (PET) / CT in 2002, the patients received an additional F-18 fluorodeoxyglucose PET-CT for staging.

The RFA of liver metastases was performed in patients not eligible for surgery. RFA was indicated when the maximum diameter of the lesions did not exceed 5 cm and the number was limited to 5 metastases. Thromboses of the portal vein, as well as severe coagulopathy or septicemia, were contraindications for RFA. In our study, patients with active extra-hepatic tumor spread were excluded from RFA. However, the presence of a few, asymptomatic, e.g., pulmonary, metastases with no evidence of further extrahepatic tumor manifestation was not considered to be an absolute contraindication for RFA.

Patients were referred to RFA if their liver metastases did not respond to chemotherapy or if residual active tumor was detectable after the completion of systemic treatment. Eleven patients (16%) had undergone liver resection prior to RFA and in 4 patients (6%) RFA was performed on non-resectable metastases, while the remaining tumor manifestations were resected surgically.

Technical details. All RFA were performed using multitined expandable electrodes (RITA Starburst XL, RITA Medical Systems, Mountain View, CA, USA) that were placed under CT-fluoroscopy-guidance. With this needle design, an array of multiple, stiff, curved wires was deployed from a single 14-gauge cannula in the metastasis and, during ablation, progressively distended to its maximum diameter of 5 cm. After attachment to the high-power RF-generator (e.g., RITA Generator Model 1500X, RITA Medical Systems), the RF current is emitted from the active, non-insulated curved electrodes. Most devices used currently are monopolar in that there is a single "active" electrode, with current dissipated at a return grounding pad. Bipolar devices have two "active" electrode applicators, which are usually placed in proximity to achieve contiguous coagulation between the two electrodes. The RF current was applied to the non-insulated curved electrodes until the target temperature of 95-100°C was reached in the tumor. To control the ablation result instantaneously after completing the procedure, a post-procedural contrast-enhanced CT scan, with the needle still in place, was performed to depict incomplete ablation with the option of an immediate additional session of ablation, as well as to detect potential peri-procedural complications. For metastases less than 3 cm in size, a single session of ablation, with a maximum needle diameter of 5 cm, was used to provide a sufficient safety margin. In lesions up to 5 cm in size, the needle was repositioned in several sessions to achieve a volume large enough to cover the entire lesion, including a safety margin of at least 5 mm around the tumor. To provide an energy deposit of at least 100 kJ, ablation times of 30 to 45 minutes, depending on the delivered power, were necessary. To avoid puncture-related bleeding, needle track ablation after completion of the procedure was performed at a lower power level (ca. 25 watts).

RFA procedure. Our standard approach for RFA was to perform the procedure under conscious sedation and local anesthesia. The majority of ablations were performed with administration of a combination of midazolam maleate, parecoxib-sodium and piritramid, however, other medications are equally effective. The blood pressure, respiration, heart rate, oxygen saturation and electrocardiogram were monitored continuously. In patients who presented low pain tolerance, or lesions unusually large and/or difficult to target, the procedure was performed with general anesthesia. Each RF procedure was conducted with the patient in a supine position, local anesthesia of the puncture site and conscious sedation. After performing a contrast-enhanced CT scan, the optimal approach for the lesion was determined. The exact positioning of the needle, as well as the complete coverage of the lesion with the hooks fully distended, was warranted by CT-fluoroscopy guidance. Peri-interventional antibiotics were applied to each patient. In critical localizations, e.g., a metastasis adjacent to the falciforme ligament, additional local anesthesia was administered. After the RF procedure, a contrast-enhanced CT scan was acquired with the needle kept in place to rule out complications and to ensure the complete ablation of the target lesion (Figure 1). The needle was retracted using track ablation of the puncture canal.

Post-procedure monitoring and follow-up. A CT scan was obtained 24 h after treatment prior to discharge in order to provide a baseline scan for follow-up studies (Figure 2). Patients were usually discharged from the hospital the day after the procedure if no complications occurred and were rescheduled for a contrast-enhanced CT scan 6 weeks after treatment. The standard scanning protocol for follow-up after RFA was a portal-venous phase acquisition following 120 cc of contrast medium injection with a flow rate of 3 cc/sec and a concentration of 300 mg iodine/cc. The injection was followed by a saline chaser (50 cc) using the same flow-rate. The scanning parameters were set to 120 kV and 165 mAs. The collimation was 16x0.75 mm. If the blood examination was indicative of new or recurrent tumor growth, not confirmed by CT, an F-18 fluorodeoxyglucose PET-CT scan was indicated.
The follow-up data were obtained from oncologists or primary care physicians and the imaging data were acquired in our department (Figure 3). The descriptive data in terms of mean, median and standard deviation were calculated for tumor size and number, RFA time, disease-free survival and local recurrence. The survival expectancy was calculated by Kaplan-Meier analysis and is represented by the respective curves.

**Results**

Between January 2000 and June 2004, 68 consecutive (42 male / 26 female; mean age 63±15 years) patients with liver metastases from CRC were prospectively treated with RFA. Overall, 183 liver metastases were ablated. The mean
The number of metastases at the time of the first ablative treatment was $2.7 \pm 1.1$. The mean maximum diameter was $22.8 \text{ mm}$ with a range from 5 to 50 mm. Eleven out of 68 patients (16%) presented with stable extra-hepatic disease under chemotherapy at the time of treatment. Of all the patients, 78% (53/68) had undergone RFA subsequently or parallel to chemotherapy, 12% (8/68) combined radiation-chemotherapy, 4% (3/68) radiation therapy, 3% (2/68) transarterial chemoperfusion and 3% (2/68) transarterial chemoembolisation.

The follow-up ranged from 6 to 38 months (mean $21.4 \pm 10.6$ month) and the mean number of metastases treated was $2.7$ (range 1-5) per patient. The mean size of the metastases was $22.8 \text{ mm}$ (range 5-50 mm). The patient status was determined 6 weeks after treatment, followed by re-evaluation every 3 months for the first year, extended to 6 months after 1-year follow-up, if neither evidence for tumor recurrence nor for new intra-hepatic tumor lesions were noted.

Survival and local recurrence. One-, 2- and 3-year survival rates were 96%, 71% and 68%, respectively, estimated from the survival curves (Figure 4). Nevertheless, the median survival time has not yet been reached.

Thirty-three (18%) of the 183 metastases had local recurrence observed after RFA (Figure 5). The median time until local recurrence cannot yet be determined with the Kaplan-Meier method due to the small number of local recurrences observed. However, this method estimated a local recurrence rate of 18% at a mean follow-up time of 21.4 months for all patients. Most local recurrences were observed in the first 8 months after RFA, presumably due to incomplete ablation. During the available follow-up, the rate of local recurrence has stabilized after 20 months at 18% to date. The frequency of local recurrence is related to the size of the metastasis treated (Figure 6).

Complications. In 68 patients no major and 4 minor complications occurred. Neither prolonged hospitalization nor further medical treatment were required. One patient with a liver metastasis in segment 8, just below the diaphragm, developed an asymptomatic pneumothorax. A plain chest
X-ray did not reveal progression of the pneumothorax 6 hours after ablation. Therefore, no placement of a chest tube was necessary. The most likely explanation for this complication was a puncture through a deep, caudally-reaching costophrenic recess that had not been detected.

In one patient, bleeding after removal of the device from the puncture site was observed. After 10 minutes of manual compression, the hemorrhage stopped. The control scans 24 hours after treatment revealed a chest wall-hematoma.

Figure 3. A 51-year-old male patient presenting with CRC and a metachronous liver metastasis. After hemi-hepatectomy, tumor recurrence at the resection margin was noted (a). RFA (b) parallel to systemic chemotherapy was performed. During a follow-up of 6 weeks (c), 3 (d), 9 (e) and 34 (f) months, a decrease in size of the ablated area was noted. Thirty-four months after the procedure, no evidence for local recurrence or for new intra-hepatic metastases was seen.
Figure 4. Time to death after RFA. Kaplan-Meier survival curve for all patients is illustrated. A probability of 68% for survival was found 38 months after treatment.

Figure 5. This graph illustrates the probability for local recurrence in all patients. The highest probability is noted in the first 8 months after RFA. After a plateau-like time-period, the probability for tumor recurrence increases again until 22 months after treatment. The overall probability for local tumor recurrence is 18% during follow-up.
Mild abdominal discomfort and heat sensations during the procedure were reported by most of the patients, without necessitating further pain medication. Transient, moderate-to-severe pain was reported by 11 patients (16%) during or immediately after RFA. However, in 1 patient the procedure was aborted due to severe pain, not controllable with conscious sedation. After 5 days, the procedure was resumed with general anesthesia. Eight patients (12%) had nausea during or after intervention. Two out of 68 patients suffered from a post-ablation syndrome with pain, fever and chills. However, these symptoms disappeared a few days after treatment with non-steroid anti-inflammatory drugs and the patients recovered rapidly.

Discussion

In the United States, approximately 147,000 new cases of CRC have been estimated for 2004, while approximately 57,000 individuals die from this disease per year. CRC is the third most common malignancy in females and males, after breast, prostate and lung cancer, respectively (24). In Germany, CRC is the second most common cancer in women and men after breast or prostate cancer.

Approximately 66,000 new cases were diagnosed in 2000 (25). Most deaths due to CRC can be attributed to metastases and, in many patients, the liver is the initial or only site. Patients without any treatment of CRC have a poor prognosis. According to the literature, the 5-year survival rates are below 1% and the median survival is less than 12 months (2-4, 7, 26, 27).

Surgical resection of hepatic metastases is considered the only potentially curative option for patients suffering from metastatic spread limited to the liver. However, the majority of patients may not be eligible for surgery because of extensive disease with widespread metastases, tumor load in the liver or co-morbidity (8, 10, 11). If metastasectomy was applicable, several authors demonstrated 5-year survival rates between 25 and 40% in appropriately selected patients (2, 3, 5, 6, 8, 13). Unfortunately, in many patients, metastases are numerous and widely distributed within the liver parenchyma, rendering metastasectomy unfeasible.

Over the last 10-15 years, percutaneous, image-guided, tumor ablation using radiofrequency, laser or microwave energy has received increasing attention as a promising alternative for the treatment of focal malignant liver disease (28-40). These techniques allow for in situ tumor ablation.
destruction and are mainly used in cases in which "classic" surgical procedures can not be applied any more. Furthermore, thermal tumor ablation has the additional advantage of being easily repeatable, less expensive, with less hospitalization time and reduced morbidity in comparison to surgery (20, 41).

Solbiati et al. treated 117 patients with 179 metastatic lesions from CRC. These metastases ranged from 0.6 to 9.6 cm in diameter. The treatments were performed with percutaneously-inserted, internally-cooled RF electrodes with 2.5-4.0 cm of exposed tip. The procedures were guided and monitored by ultrasound. The estimated 1-, 2- and 3-year survival rates were 93%, 69% and 46%, respectively. In 39% of all metastases treated local recurrence was observed, but no local recurrence was detected later than 18 months after treatment. The disease-free survival 1 and 2 years after RFA was 49% and 35%, respectively (42).

Recently, Gillams et al. reported on 354 liver metastases treated with RFA in 167 patients with CRC. The size of the metastases ranged from 1 cm to 12 cm. Thirty-one percent of the patients treated had stable extra-hepatic disease. The procedures were performed with internally water-cooled single or triple cluster electrodes, depending on the tumor size. The treatment monitoring was performed with both ultrasound and CT. In 21% of the patients with follow-up examinations available, local recurrence was detected. For patients with less than the arbitrarily chosen number of 5 metastases smaller than 5 cm in size and no evidence of extra-hepatic disease, the 5-year survival was 26%. For all patients, including those with numerous metastases and/or extrahepatic disease, the 1-, 3- and 5-year survivals were 71%, 21% and 14%, respectively, from the time of first thermal ablation (43).

Our results suggest that RFA of CRC metastases is safe, easily repeatable and can result in patient outcomes comparable with the results of surgical resection. One-, 2- and 3-year survival rates were 96%, 71% and 68%, respectively. These results are superior to those results published by Solbiati et al. (42). Although almost 70% of our patients received systemic chemotherapy prior, parallel or subsequently to RFA, it seems unlikely that chemotherapy alone can be responsible for the 3-year survival of 68%. The 5-year survival for untreated patients and for those on 5-FU and folinic acid chemotherapy is less than 3%. The impact of local thermal ablation to the liver in patients with extra-hepatic tumor manifestation remains unclear. In our study, patients with active extra-hepatic tumor spread were excluded from RFA. However, the presence of a few, asymptomatic, e.g., pulmonary, metastases with no evidence of further tumor manifestation was not considered to be an absolute contraindication for RFA. This issue has been addressed by Elias et al., who reported on a 5-year survival of 20% in patients with incomplete surgical resection of liver metastases and known extra-hepatic disease (44).

In 18% of all metastases treated, local recurrence was observed, with the highest probability occurring during the first 8 months after treatment and a second peak at 22 months after RFA. No local recurrence was detected later than 22 months after the procedure. This local recurrence rate is comparable to those published by Gillams et al. (43), however, our local recurrence rate was substantially lower when compared with the data provided by Solbiati et al. There are several facts that affect the volume of coagulation necrosis achieved, including electrode shape and design, the parameters of the RF generator, tumor localization, ablation time and tissue perfusion. In comparison with the study described before, we used multitened expandable electrodes, which are supposed to achieve ablation areas of increased size. Furthermore, we extended the ablation time to 30 - 45 minutes for each cycle to gain a sufficient energy deposition. In our experience, all but the smallest metastases require multiple overlapping RFA to achieve complete coagulation necrosis. Therefore, the time necessary for creating overlapping ablation areas easily exceeded the time limit reported by other authors. In our study, we exclusively used CT and, especially, CT-fluoroscopy for monitoring and guiding the procedure. The use of intra-procedural CT has been previously validated (45, 46). Recently published articles showed that, when compared with power Doppler ultrasound, contrast enhanced CT is superior in the detection of residual tumor after local ablative treatment. However, the reported sensitivity of contrast-enhanced ultrasound for the detection of residual tumor is almost equivalent to that of contrast-enhanced helical CT (47, 48).

Conclusion

The results of this study indicated that RFA of liver metastases is an effective, safe and repeatable procedure. Since we included patients who were not candidates for surgery and we report results concerning survival comparable to the results provided by surgical series, we hope to increase the acceptance of RFA for liver lesions. However, more comprehensive clinical trials need to be conducted in order to evaluate the role of RFA in the treatment of malignant liver lesions as compared to surgical resection.

References


