

Radiofrequency Ablation as Locoregional Therapy for Unresectable Hepatic Malignancies: Initial Results in 24 Patients with 5-Years Follow-Up

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ABSTRACT

Radiofrequency ablation (RFA) is one treatment modality for unresectable liver metastases. Patients with hepatic malignancies ($n=24$) underwent elective RFA. All tumors were ablated with a curative intent, with a margin of 1 cm, in a single session of RFA. The median diameter of tumor was 3.1 cm (range 1.7–6.9 cm). Studied patients were not candidates for resection due to multifocal hepatic disease, extrahepatic disease, proximity to major vascular structures or presence of cirrhosis with functional hepatic reserve inadequate to tolerate major hepatic resection. Complete tumor necrosis was achieved in 87.5% and tumor recurred in 3 patients (12.5%) with lesions larger than 5 cm. Distant intrahepatic recurrence was diagnosed in another 4 (16.7%). Distant metastases were found in 7 (29.2%) patients. Four of these 7 patients had also distant intrahepatic recurrence of disease. Two and 5-years survival rates were 41.7% (10 patients) and 8.3% (2 patients) respectively. RFA is safe and effective option for patients with unresectable hepatic malignancies smaller than 5 cm without distant metastatic disease. RF ablation resulted in complete tumor necrosis in 87.5% with 2 and 5-years survival rates much higher than with chemotherapy alone or only supportive therapy, when survival is measured in weeks or months. If RFA is unavailable, percutaneous ethanol injection therapy can be done but with inferior survival rates.

Key words: radiofrequency ablation, liver metastases, recurrence, percutaneous ethanol injection, mortality

Introduction

Metastasis is the most common neoplasm in an adult liver, and the liver is the second most common site for metastatic spread, after the lymph nodes. Analyzing the data from 9,700 consecutive autopsies in patients with 10,736 primary cancers, Pickren et al found that liver metastases were present in 41%¹. They found that the primary sites most commonly metastasizing to the liver are the eye (77.8%), pancreas (75.1%), breast (60.6%), gallbladder and extrahepatic bile ducts (60.5%), colon or rectum (56.8%), and stomach (48.9%). Most metastatic tumors likely arise in the liver as a result of primary shedding into vascular system². It is not uncommon, particularly in patients with colorectal adenocarcinoma, for liver to be the only site of metastatic disease. Liver metastases are synchronously present in 20–30% of patients undergoing primary resection of colorectal cancer³. Approximately 60% of colorectal cancer patients will de-

velop metastatic disease, with the liver being the most common site for metastatic disease⁴. Previously more patients were defined as having unresectable metastatic disease because of factors concentrated on the lesions to be removed and patient factors rather than the liver that would remain. These criteria were based on criteria made by Ekberg et al. which included: four or more metastases within the liver, additional extrahepatic metastatic disease, large size of hepatic metastases, and the inability to achieve a resection margin of at least 1 cm⁵. Today, in an era of better adjuvant therapy and imaging modalities, survival difference between patients who had one to three metastases and patients who had four or more metastases as long as they underwent an R0 (i.e., microscopically negative) resection are lacking⁶. Also extrahepatic disease should be precisely defined. Direct tumor extension into extrahepatic region pathophysiolo-

gically does not present further metastatic potential rather bigger liver metastasis. Thus, resection of liver metastasis with direct extrahepatic extension has reported 5-year survival rates of 10%⁷. Despite all these improvements in selection criteria for liver resections huge number of patients with primary or metastatic hepatic malignancy are not candidates for surgical resection, and an ablation techniques to control and potentially to cure liver disease must be used.

One of such ablative techniques is radiofrequency ablation (RFA) which uses energy of 450 to 500 KHz for hyperthermic ablation of liver tumors. Once cells are heated above 50 °C, cells membrane melt and fuse, and with continued heating, protein denaturation and cell death occurs^{8,9}. Radiofrequency electricity is the type of electrical energy used in the standard operating room electrosurgical machines. The size of ablated area is determined largely by current's intensity and length, the gauging of electrode tip and the duration of energy applied¹⁰. The current intensity that can be used is limited by tissue carbonization around needle tip, which can result in sharp rise in tissue impedance and thus interruption of the radiofrequency wave flow. This limits the area of tissue that can be ablated by a single probe. Tissue vascularization is also an important factor that determines the volume of tissue ablated¹¹. Like other heat ablation methods, complete necrosis of highly vascular tumors may be impeded by the cooling effect of blood. The Pringle maneuver during RFA is an effective measure to reduce the cooling effect of blood¹². Another way to reduce hepatic blood flow is RFA with balloon occlusion of the hepatic artery¹³. RFA with the conventional single needle electrode can ablate tumors smaller than 2 cm, but ablating of larger tumors is possible with recent technical improvements¹⁴. The use of expandable electrode with multiple hooks can create overlapping ablation fields up to 7 cm^{14,15}.

Until the introduction of RFA technique for treatment of unresectable liver metastases the patients in University Hospital Center Zagreb were treated by chemotherapy and supportive, life-maintaining measures with death occurring in weeks or months after the diagnosis. In this study, we report our initial results in 24 patients with primary or metastatic hepatic malignancies treated with RFA of their liver tumors with prolonged survival rates compared to patients receiving only chemotherapy and/or supportive treatment.

Patients and Methods

Patients

Between January 1, 1999, and January 1, 2001, 24 patients with hepatic malignancies underwent elective RFA for 32 tumor nodules. There were 15 (62.5%) men and 9 (37.5%) women with median age of 65. Eighteen patients (75%) had liver metastases from colorectal carcinoma, 3 (12.5%) from breast carcinoma, 1 (4.2%) from lung carcinoma and 2 (8.3%) had hepatocellular carcinoma. All patients except patients with hepatocellular carcinoma un-

derwent surgical therapy for primary lesions. Seventeen patients (70.8%) underwent ablation of a solitary tumor, 5 patients (20.8%) underwent ablation of 2 tumors and 3 patients (8.4%) received ablation of 3 tumors in a single session of RFA. Two patients with hepatocellular carcinoma had underlying cirrhosis. None of our patients had previous hepatic resection or transarterial chemoembolization. All patients received chemotherapy according to the type of primary tumor. We aimed at ablation of all tumors with a curative intent, with a margin of 1 cm, in a single session of RFA. The median diameter of tumor was 3.1 cm (range 1.7–6.9 cm). Studied patients were not candidates for resectional therapy due to multifocal hepatic disease, extrahepatic disease, proximity to major vascular structures or presence of cirrhosis with functional hepatic reserve inadequate to tolerate major hepatic resection.

All patients underwent baseline evaluation including history and physical examination, serum laboratory tests consisting of complete blood count, platelets, coagulogram profile, renal panel, electrolytes, albumin, total bilirubin, alkaline-phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum tumor markers such as alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) and computed tomography (CT) of the abdomen.

All patients had histological confirmation of hepatic malignancy from prior intraoperative biopsy or CT scan conformation of hepatic lesions. The same battery of serum blood tests and CT of the abdomen were obtained the day before and after RFA procedure.

Technique of RFA

All our patients were treated surgically during operative procedure. Intraoperative ultrasonography was used to locate intraparenchymal lesions and to guide the RFA needle. Superficial lesions were easily identified and palpated and needle was inserted directly without ultrasound. Patients were monitored up to two years after treatment.

RF ablation was achieved using RF generator RITA 1500 (RITA Medical Systems, Mountain View, CA, USA) and multiple array needles. Electrode needle is StarBurst XL, 14 Gauge, which contains 9 individual hook-shaped arms and 5 thermocouples attached to the 15-cm-long insulated cannula. Lesions from 3–5 cm could be ablated with this electrode. Generator could supply up to 150W of power at 460 kHz with multi-point temperature feedback and post-ablation conformation of lethal temperatures.

Depending on the size and site of the tumor, each ablation cycle lasted 8 to 12 minutes. During the procedure, a needle electrode with an uninsulated tip and an insulated needle shaft is inserted into the tumor. A flux of high-frequency alternating current passes through the uninsulated needle tip into the surrounding tissue, generating rapid vibration of the ions in the tissue and frictional heat¹¹. Tissues are heated not by conduction of heat directly, but by causing electrons in the tissue to vi-

brate back and forth at a high frequency. After ablation of the tumor, the needle track was thermocoagulated by continuing radiofrequency current in a manual mode when the needle was withdrawn slowly.

A complication was defined as any adverse event after RFA, excluding pain or a transient febrile response after the procedure. Treatment mortality was defined as any death within 30 days of the RFA treatment. Response to ablation was assessed by a helical computed tomography (CT) scan 1 month after ablation. Successful treatment was encountered when complete ablation was achieved. Complete ablation is defined as the absence of any contrast-enhancing lesion indicating residual tumor at the ablation site in the postablation CT scan. All patients had monitoring of serum alpha fetoprotein (AFP) and carcinoembryonic antigen (CEA) level, chest x-ray, and CT scan of the abdomen every 3 months to detect intrahepatic recurrence or distant metastasis. Local recurrence was defined as tumor recurrence within or at the periphery of the ablated lesion in the subsequent CT scans after complete ablation was documented in the first postablation CT scan. Distant intrahepatic recurrence was defined as a new tumor that appeared in the liver separate from the ablated area. Extrahepatic recurrence referred to any recurrence outside the liver.

Two year survival rate was defined as the treatment efficacy for this method and this subpopulation of patients with unresectable metastatic disease. Also 5-year survival rate was calculated.

Results

A total of 24 patients have been treated on the RFA protocol during the study period of 24 months. Follow-up was 5 years. Intraoperative bleeding from RFA needle track was noted in 6 patients (25%) of the needle electrode withdrawals. In all cases it was minimal and easily controlled with cauterization. There have been no deaths after RFA treatment in these 24 patients. None of the patients developed renal insufficiency or a coagulopathy after RFA treatment. The serum liver function tests (AST, ALT) were elevated for 5 days and returned to baseline values in all patients by the postoperative day 12.

Response to ablation was assessed by a helical computed tomography (CT) scan 1 month after ablation. Tumor has recurred at the site of RFA in 3 patients (12.5%) with tumors ≥ 5 cm. In other words, complete tumor necrosis was achieved in 87.5% of patients. Distant intrahepatic recurrence was diagnosed in another 4 patients (16.7%). Distant metastases were found in 7 (29.2%) patients. Four of these 7 patients had also distant intrahepatic recurrence of disease.

Serum tumor marker (AFP or CEA) was elevated before the procedure in 17 patients (70.8%). After RFA in 9 patients, serum tumor markers did not return to baseline value and 7 of them developed new metastatic lesions.

After 24 months 10 patients were alive (41.7%). Seven of 14 patients that died in this period were patients with

diagnosed distant metastatic disease. After 5-years only 2 patients were alive (8.3%) and both with primary colorectal carcinoma.

Discussion

Studies have demonstrated that patients with untreated hepatic metastases from colorectal carcinoma have a 31% survival rate at 1 year, 7.9% at 2 years, 2.6% at 3 years, and 0.9% at 4 years^{16,17}. Although the median survival of patients with untreated disease ranges from 6–12 months, the addition of chemotherapy regimens improves median survival to 20 months¹⁶.

It must be stressed that surgical resection is the standard treatment for patients with localized colorectal liver metastases, with reported 5-year survival rates up to 58%¹⁸. Despite the advent of more efficient chemotherapeutic protocols and the progress in surgical techniques, such as portal vein embolization, hepatic artery infusion chemoembolization, cryoablation, microwave coagulation therapy, laser-induced thermotherapy or hepatectomy, many patients with hepatic malignancies still have unresectable disease. One of procedures for the treatment of unresectable hepatic malignancies is RFA. RFA devices are designed to destroy larger areas of tissue. It can be performed percutaneously, laparoscopically or through laparotomy^{19–27}. A percutaneous approach has advantage that it is minimally invasive and patient may be treated on an outpatient basis, usually under conscious sedation. There are, however, limitations to percutaneous approach. Tumor must be apparent on transabdominal ultrasonography to be targeted under ultrasonic guidance. Lesions near the dome of the liver are often poorly seen, and there is concern that treatment of lesions on the periphery of the liver may damage adjacent viscera. Poor visualization and respiratory motion may hinder accurate targeting of lesions such that multiple ablations are often needed to treat even small tumors¹⁹. However, laparoscopic or open approach may be necessary in patients with high risk of bleeding from severe coagulopathy, large HCC (≥ 5 cm), superficial nodules adjacent to other visceral organs at risk of thermal injury, or deeply located lesions not accessible to percutaneous puncture.

A total of 24 patients have been treated on the RFA protocol during 24 months. All patients underwent open surgical procedure. That approach allows detection of peritoneal metastases and extrahepatic invasion that may not be diagnosed even with extensive preoperative imaging²⁸. In addition, open procedures allow usage of intraoperative ultrasound for the detection of small tumor nodules not identified by preoperative imaging. Such additional nodules are fairly common, as shown in a recent study that identified new tumor lesions in 5 (18.5%) of 27 patients with HCC 5 cm or smaller undergoing laparoscopic ultrasonography before RFA²⁶. The extent of the coagulative necrosis is accurately assessed by CT scan, or MRI. Study demonstrated that almost all treated lesions increase in size from the preoperative CT scan. This reflects that tumor, as well as a surrounding rim of

normal liver tissue, has been ablated. Failure to demonstrate that increase in size was a risk factor for recurrence.

There have been no early postoperative deaths (within 30 days) after RFA treatment. Complete tumor necrosis was achieved in 87.5% of patients. Using contrast CT scan, several studies have shown similar complete tumor necrosis in 80 to 90% of HCC smaller than 3 to 5 cm after single session of RFA^{25,26,29,30}. The complete ablation rate for larger tumors is less favorable: a study of RFA for 126 HCC 3.1 to 9.5 cm reported a complete necrosis rate of 48% even with the use of cluster electrodes. Larger lesions are at increased risk for recurrence, perhaps because of the increased odds of incompletely treating one surface during multiple overlapping ablations. Also, larger lesions are seen on ultrasound to be irregular, often with small satellite lesion at their periphery. This implies that the actual volume of tumor on a microscopic level may be larger than it appeared grossly, either on preoperative CT scan, or on laparoscopic ultrasonographic examination. This could easily explain a greater risk of recurrence among larger lesions³¹. Local tumor recurrence was evident in 3 patients (12.5%) with tumors larger than 5 cm. Distant intrahepatic recurrences were diagnosed in another 4 (16.7%). These results are similar as in other studies³². Distant metastases were found in 7 (29.2%) patients. Previous studies have reported highly variable local recurrence rates associated with RFA, ranging from 2%²⁷ to 60 %³³. Curley et al. reported the lowest local recurrence rate of 1.8% in one of the largest series published²⁷. Local recurrences were evident at a median follow-up time of 6 months and were associated with ablation of larger tumors. It is possible that the rate of local recurrence may be reduced by specific interventions. For example, newer probes have been developed to produce larger spheres of coagulation necrosis. Now we deploy the electrode in several overlapping ablation sites to encompass tumors greater than 5 cm in diameter as it was proposed by others^{34–36}.

After 24 months 10 patients were alive (41.7 %). Survival rate in our series is similar to that reported in the literature¹⁸. Seven of 14 patients that died in this period had distant metastatic disease with primary colorectal carcinoma. Our results confirm previous conclusions that patients with distant metastatic disease of colorectal carcinoma should be omitted from this protocol because they do not benefit with RFA procedure. In our series 2 patients with primary colorectal carcinoma with unresectable hepatic metastases were alive after 5 years (8.3%). It is lower than in other series such as Siperstein et al. which reported 5-year survival rate of 18.4%³⁷.

RFA is often compared to percutaneous ethanol injection which is one modality that has also been used to

treat unresectable liver malignancy in some institutions. Studies have shown that 4 to five 5 sessions per tumor need to be performed to achieve complete necrosis in 80% of tumors. The mean total procedure time for each session was approximately 30 minutes^{38–40}. Our study demonstrates that treatment with RF ablation can result in complete tumor necrosis in about 90% of patients which is higher than that could be achieved with PEI. An additional and important advantage of RFA over PEI is that fewer treatment sessions were required to achieve this result. Therefore, RF ablation is preferred treatment for patients with unresectable hepatic malignancy where such option is available. In case where RFA gadget is not available PEI is an adequate replacement. The similar results could be accomplished at much lower cost.

We could not compare the survival rate using RFA and patients with unresectable hepatic disease left without treatment, because methodologically it is very difficult to find case controls, but 42% 2-year survival rate is very satisfactory for patients with unresectable hepatic malignancy and is similar to other studies^{41,42} as is 5-year survival rate of 8.3%³⁷. Natural history of unresectable primary HCC is measured in weeks (range 7.6–16.6) depending on the tumor stage⁴³. Systemic chemotherapy was administered according to the type of tumor. Metastatic hepatic disease from colorectal origin was treated with oxaliplatin and/or irinotecan.

RFA seems to be safe and effective treatment technique for patients with unresectable hepatic malignancies smaller than 5 cm and without distant metastatic disease. This conclusion will change with further development of RFA equipment with possibilities of ablation of larger lesions. RF ablation results in complete necrosis in 80–90% with 2-year and 5-year survival rate of 42% and 8% respectively which is much higher than without treatment when survival is measured in weeks⁴² and months or with chemotherapy alone when median survival is 20 months⁴⁴. It must be always offered to patients with unresectable disease as treatment of choice when indicated. If this modality is unavailable, percutaneous ethanol injection can be done, with two disadvantages: the results are inferior and PEI requires more treatment sessions than RFA (with higher possibility of intra- and postoperative complications), but is a safer procedure in inexperienced hands.

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RADIOFREKVENCIJSKA ABLACIJA KAO LOKALNO-REGIONALNA TERAPIJA NERESEKTABILNIH HEPATALNIH METASTAZA: POČETNI REZULTATI KOD 24 BOLESNIKA TIJEKOM 5-GODIŠNJEG PRAĆENJA

S A Ž E T A K

Radiofrekvencijska ablacija (RFA) jedan je terapijski modalitet za liječenje neresektabilnih jetrenih metastaza. Bolesnici sa jetrenim metastazama (n=24) podvrgnuti su elektivnoj RFA. Ablacija svih jetrenih metastaza vršena je u svrhu izlječenja (kurativno) sa 1 cm zdravog ruba tijekom jedne (jedine) operacije. Srednji promjer tumora iznosio je 3,1 cm (rang 1,7–6,9 cm). Bolesnici podvrgnuti zahvatu nisu bili kandidati za resekcijski zahvat zbog: multifokalnih jetrenih metastaza, ekstrahepatalne proširenosti bolesti, blizine velikih krvnih žila ili prisutne ciroze sa nedovoljnom hepatalnom rezervom koja bi preostala nakon resekcije. Kompletna tumorska nekroza postignuta je u 87,5%, a rekurencija tumora pojavila se u 3 (12,5%) bolesnika i to kod metastatskih lezija većih od 5 cm. Udaljena intrahepatalna rekurencija dijagnosticirana je u 4 bolesnika (16,7%). Udaljene metastaze verificirane su u 7 (29,2%) bolesnika. Kod 4 od tih 7 bolesnika također je bila prisutna i udaljena intrahepatalna rekurencija bolesti. Dvogodišnje i 5-godišnje stope preživljenja iznosile su 41,7% (10 bolesnika) i 8,3% (2 bolesnika). Tijekom 24 mjeseca praćenja, preživljenje je iznosilo 41,7% (10 bolesnika). RFA je sigurna i efikasna metoda kod bolesnika sa neresektabilnim hepatalnim metastazama manjim od 5 cm bez udaljene metastatske bolesti. RFA je rezultirala sa kompletnom tumorskom nekrozom u 87,5% slučajeva sa 2- i 5-godišnjim stopama preživljenja znatno dužim u odnosu na primjenu isključivo kemoterapije ili supportive terapije kada se preživljenje mjeri u tjednima ili mjesecima. Ako RFA nije dostupna također je moguće primjeniti perkutanu instlaciju etanola koja daje ipak lošije rezultate.