Results of radiofrequency ablation of liver tumors: experience of 134 cases

Resultados da ablação por radiofreqüência de tumores hepáticos: experiência de 134 casos

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ABSTRACT

Objective: To study radiofrequency ablation of primary and metastatic liver tumors. **Methods:** The authors present a series of 134 cases, 63 females and 71 males with a mean age of 61.2 years, in whom radiofrequency ablation was used either by laparotomy or percutaneously to treat 203 lesions. The group was composed of 51 cases of hepatocellular carcinoma, four cases of cholangiocarcinoma, and cases of hepatic metastases, as follows: 64 of colorectal cancer, 6 of neuroendocrine tumors, 5 of breast cancer, 1 case of pancreas cancer, 1 of kidney cancer, 1 of endometrial cancer and 1 of leiomyosarcoma. **Results:** Procedure-associated morbidity/mortality was 24.8 and 3.7%, respectively. Recurrence was observed in 12.7% within a mean time of 10.5 months. **Conclusions:** Radiofrequency ablation is a safe procedure and can be used in patients with impaired hepatic function. For metastatic diseases, it does not replace surgery but it can be associated with other procedures, such as surgery and transarterial chemoembolization, or after recurrence, leading to greater probability of remaining disease-free.

Keywords: Liver/pathology; Liver neoplasms/pathology; Liver neoplasms/secondary; Carcinoma, hepatocellular/surgery; Catheter ablation/methods; Follow-up studies

RESUMO

Objetivo: Estudar a ablação de tumor primário e metastático do fígado por radiofreqüência. **Métodos:** Foram estudados 134 casos, sendo 63 mulheres e 71 homens com uma média de idade de 61,2 anos, nos quais a ablação por radiofreqüência foi aplicada por via percutânea ou por meio de laparotomia no tratamento de 203 lesões. O grupo foi composto por 51 casos de carcinoma hepatocelular, 64 casos de metástase de tumor colorretal, seis casos de metástases de carcinoma neuroendócrino, cinco casos de metástase de tumor de mama, quatro casos de colangiocarcinoma; um caso de metástase de tumor de pâncreas; um caso de metástase de tumor renal, um caso de metástase de tumor de endométrio e um caso de metástase hepática de leiomiosarcoma. **Resultados:** A morbidade associada ao método foi de 24,8% e a mortalidade de 3,7%. Observou-se uma taxa de recorrência após o procedimento de 12,7% em média 10,5 meses após a ablação. **Conclusões:** A ablação por radiofreqüência é um procedimento seguro, que pode ser utilizado em pacientes com reserva hepática comprometida. Nas doenças metastáticas o procedimento não substitui a cirurgia, porém pode ser utilizado associado a outros métodos como a cirurgia, quimioembolização transarterial e aumentando com isto as chances do paciente em ficar livre de doença.

Descritores: Fígado/patologia; Neoplasias hepáticas/patologia; Neoplasias hepáticas/secundário; Carcinoma hepatocelular/cirurgia; Ablação por cateter/métodos; Seguimentos

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common solid tumor in the world with an estimated incidence of one million new patients per year. Additionally, after lymph nodes, the liver is the second major target of metastases of other solid tumors. This is particularly common in patients with colorectal adenocarcinoma, in whom the metastatic disease affects mostly the liver. Unfortunately, only 5 to 15% of new patients diagnosed with HCC or

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hepatic metastasis of colorectal cancer undergo a curative resection, which is considered the gold standard treatment for such tumors. Patients with disease limited to the liver may not be candidates to resection due to multifocal lesions, proximity of tumor to the main vascular branches or to biliary structures preventing resection with safe margins, as well as to potentially unfavorable tumor biology, such as the presence of more than four liver metastases or inadequate hepatic functional reserve associated to concurrent cirrhosis[1]. In those cases, one alternative treatment is radiofrequency ablation (RFA), which has been widely used due to its potential benefits, including decreased mortality and morbidity[2].

The purpose of the RFA is to induce thermal damage to the tissue by means of electromagnetic energy. To this end, the patient becomes part of a closed circuit that includes the radiofrequency generator, the electrode needle and grounding pads, thus generating an electrical field alternating with the patient's tissue. Because of the high electrical resistance in the tissue involving the electrode, the ions present in it suffer agitation in an attempt to follow the different directions of the alternating current. This agitation results in frictional heat around the electrode, and the discrepancy between the small area of the electrode needle and the large area of the ground pads causes heat generation to be concentrated around the needle[3].

The thermal damage caused by RFA heat depends on both duration of heating and the temperature achieved in the tissue. Heating at 55 °C for four to six minutes causes irreversible cell damage, whereas at between 60 and 100 °C, it causes immediate tissue coagulation with irreversible damage to mitochondrial and cytosolic enzymes. Therefore, the main purpose of ablation therapy is to reach and maintain temperatures between 55 and 100 °C, for at least four to six minutes, in the entire target volume[3].

OBJECTIVE

To study patients with positive histological diagnosis of primary liver malignancies who were elegible for treatment by radio frequency ablation.

METHODS

This was a prospective, non-randomized study, carried out between April 2000 and August 2008, analyzing 134 patients with a positive histological diagnosis of primary or metastatic liver malignancy, with no clinical, radiological or intraoperative evidence of extrahepatic disease, who were eligible for treatment according to the RFA protocol, as shown in Table 1. Some patients were considered as having unresectable liver disease based on number of tumors or bilobular distribution of tumors (although some patients underwent disease resection in one lobe and tumor RFA in the remaining lobe); proximity of tumor to crucial vascular structures preventing resection with a safe margin; presence of cirrhosis; and inadequate functional hepatic reserve to tolerate a major hepatic resection. Despite the possibility of performing resection, it was decided to carry out RFA in another group of patients, as a bridge to transplantation.

Following the protocol proposed by Curley et al.[4] , the patients eligible for this study, regardless of response to other treatment modalities, included those who had not received chemotherapy or radiotherapy for at least four weeks before RFA; had a life expectancy ≥ three months with a Zumbroad status ≤ 1; CHILD A or B cirrhosis; plasma bilirubin < 3.0 mg/dl, creatinine ≤ 2.0 mg/dl, serum albumin > 3 mg/dl and prothrombin time not lower than 50% compared to the normal; no history of hepatic encephalopathy, abnormal mental status, active infection and ascites.

The patients whose tumor invaded the right or left (or both) main biliary duct were excluded due to possible destruction of the duct during RFA.

All patients underwent a basic evaluation, including history and physical examination, complete laboratory tests (complete blood count, platelet count, blood coagulation profile, renal function, electrolytes, liver function, including albumin, ALT, AST, alkaline fosfatase, gamma-GT, bilirubins and appropriate plasma tumor markers, such as alphafetoprotein – AFP and carcinoembrionic antigen – CEA). Moreover, imaging examinations were performed as follows: ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) assessing the abdomen and pelvis, as well as chest X-ray. After the RFA, imaging examinations were requested one month after treatment and every three months until completion of a two-year period, followed by subsequent controls every six months (Figure 1).

Patients with only one or two tumor nodules with good puncture window were approached with CT-guided percutaneous RFA. All other patients were surgically treated by means of an open surgical procedure in which the intraoperative US was used for positioning the RFA needle in the lesions to be treated. There were no cases treated by laparoscopic approach in this current series.

In the first cases, the generator system RF 2000 manufactured by Radiotherapeuthics Corp. (Mountain View, CA, USA) was used. Later, the RITA Medical Systems® generator, and more recently, Cool-Tip™ radiofrequency system USA has been utilized for being

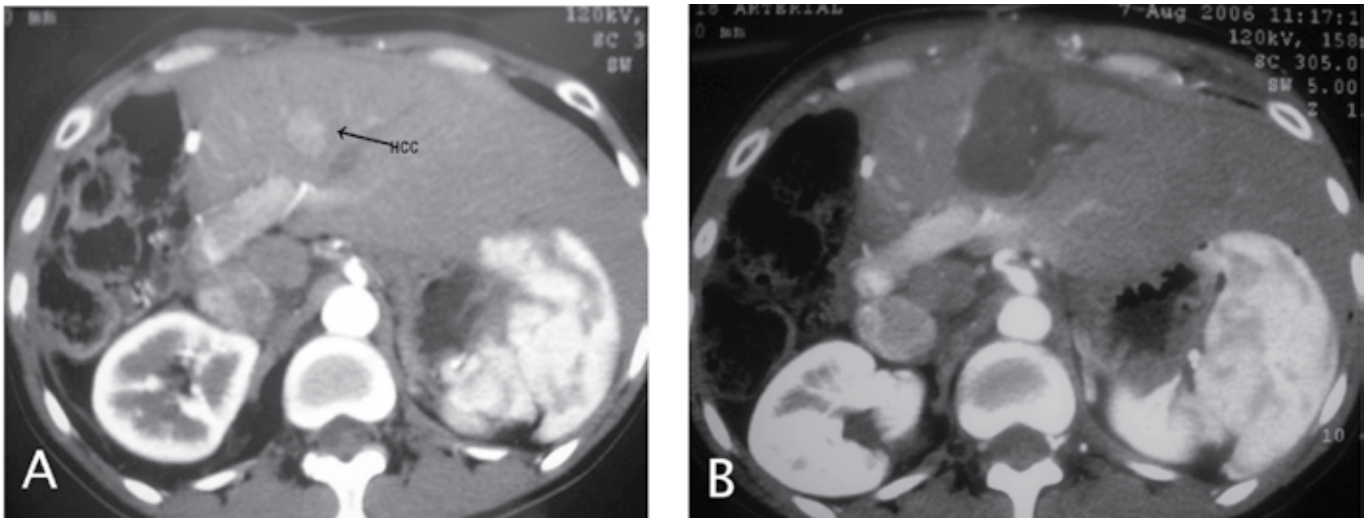

Figure 1. Computed tomography of hepatic lesion before (A) and after (B) after radiofrequency ablation. Hepatocellular carcinoma after right hepatectomy in a noncirrhotic liver

a single needle without the umbrella, which facilitates its insertion during the intraoperative period.

RESULTS

We assessed 134 patients, of which 63 were females and 71 were males, aged 28 to 88 years of age and mean age of 61.2 years. The diameter of lesions varied between 2 and 4.9 cm, with a mean value of 3.64 cm and the mean number of lesions treated was 1.5, ranging from one to five. The types of lesions are described in Table 1.

Table 1. Cases treated by radiofrequency ablation in the study

Diagnosis	Number of patients (%)
Colorectal cancer metastasis	64 (47.7)
Hepatocellular carcinoma	51 (38)
Neuroendocrine tumor metastasis	6 (54.4)
Breast cancer metastasis	5 (3.7)
Cholangiocarcinoma	4 (2.9)
Leiomyosarcoma metastasis	1 (0.7)
Pancreas cancer metastasis	1 (0.7)
Kidney cancer metastasis	1 (0.7)
Endometrial cancer metastasis	1 (0.7)

In 80 patients only RFA was performed. In the remaining 54 cases, the RFA was accompanied by resections, intraoperative injection of alcohol and other procedures with a total of 115 combined procedures, as shown in Table 2. Of 134 patients in the study, 113 had the RFA performed by laparotomy and 21 by percutaneous appproach. The liver segments treated are described in Table 3; the segments more often approached were IV, VII and VIII. The mortality rate was 3.5%. Two patients had cirrhosis, presented progression of hepatic diseases, were treated for HCC and died from 10 to 13 months after the procedure. One patient had colorectal hepatic metastasis, and seven months later presented pulmonary metastases and evolved to death. The only case that was directly related to the method was an 88-year-old patient who suffered extensive burns in the

Table 2. Other treatments associated with radiofrequency ablation

Procedures	Number of cases
Cholecystectomy	29
Hepatic biopsy	34
Nodulectomy	19
Left hepatic segmentectomy	14
Injection of absolute alcohol	5
Right hepatectomy	4
Enterectomy	3
Splenectomy	2
Chemoembolization before RFA	2
Partial pancreatectomy of body and tail	2
Ligation of the right portal vein	1
Resection of segments VI/VII	1
Rectosigmoidectomy	1
Hilum lymphadenectomy	1

Table 3. Hepatic segments (according to Couinaud) treated by radiofrequency ablation

Hepatic segment	Number of lesions per segment
I	7
II	5
III	6
IV	39
V	10
VI	11
VII	50
VIII	42
Total	170

lower limbs, in which the plaques were placed, due to grounding problems in the operation room, and died due to infection and renal failure caused by myoglobinuria.

The rate of local relapse was 17.6%, and it occurred at an interval of 6 to 18 months after the procedure (mean of 10.5 months after the RFA), as shown in Table 4. As to the relation between the size of lesions and local relapse, it was observed that 11 patients (11.8%) of the laparotomy group presented local relapse, and in 81.8% of such cases the lesions were larger than 3 cm. In the percutaneous group, the rate of relapse was 45% (nine patients) and, in the group with lesions < 3 cm, the reported incidence was 55.5%; in the group > 3 cm, the incidence was 44.5%. The overall morbidity rate was 26.5%.

DISCUSSION

Most liver tumors when diagnosed are no longer resectable, and RFA, in some cases, is the only chance of cure or even palliation for both primary and secondary tumors[5]. The limitations to surgical resection can be classified and related to the tumor, to lesions that are very large, poorly located, multiple, involving crucial vascular structures or associated to the extrahepatic disease, or related to the patient, which include the related comorbidities, old age and insufficient liver function, especially in those with cirrhosis and borderline function[4]. These cases receive alternative treatments, minimally invasive therapies such as RFA and alcohol injection, which are able to destroy the tumor with a much lower number of deaths or serious complications than surgical resection[4,6].

Alcohol injection has been used in the chemical ablation of nodular type HCC and it was used in this study as adjuvant treatment in patients partially responsive to RFA or as a way to optimize the ablation results by promoting an increase of the treated area[7].

A recent study[8] showed that the alcohol injection prior to the RFA, in cases of HCC, allows the achievement of a volume of coagulation necrosis that is significantly higher than RFA without alcohol ($p < 0.001$), and it must be routinely employed whenever possible. A higher rate of complete ablation was achieved by open route than by percutaneous route[9] (86 *versus* 57%), but it did not reach a statistically significant difference. However, some studies report better safety in the application of RFA by open surgery and this approach must be performed whenever there is a large tumor, especially if larger than 5 cm, because the rate of complete ablation of these tumors is only 25%, with an increased risk of peritoneal implantation in the needle path[9-10].

It has been recently[11] described that 64% of cases managed by percutaneous RFA therapy presented intrahepatic tumor relapse after treatment. Such failures were detected both locally, at the primary site

Table 4. Relapse after radiofrequency ablation

Tumor	Site of tumor treated by RFA (seg)	Size (cm)	Approach	Associated treatments	Relapse (months after RFA)
BCM	IV/VIII	5	Percutaneous	No	8
HCC	VI	4.9	Percutaneous	No	6
HCC	V	2	Percutaneous	No	10
CRM	IV	4	Percutaneous	No	8
HCC	IV/VIII	2	Percutaneous	No	18
CHOL	IV	3	Percutaneous	No	12
CRM	VII	2.5	Percutaneous	No	12
CRM	VIII	3.5	Percutaneous	No	12
HCC	II/IV/V/VI	2.5	Percutaneous	No	7
NTM	VI/VII/VIII	4	Laparotomy	Left segmentectomy	13
NTM	VI/VII	3	Laparotomy	No	18
CHOL	IV	4	Laparotomy	No	13
CRM	VII	4	Laparotomy	No	11
HCC	VII	4	Laparotomy	No	8
HCC	VI	5	Laparotomy	No	6
HCC	VII	4	Laparotomy	No	18
HCC	VI/VII	4	Laparotomy	No	10
CRM	VIII	3	Laparotomy	Nodulectomy	7
HCC	VIII	4	Laparotomy	Nodulectomy in segment VI and alcohol injection in segment V	10
CRM	I/VIII	4	Laparotomy	Nodulectomy in II/VI	6
CRM	I/IVb	3	Laparotomy	No	8

BCM = breast cancer metastasis; HCC = hepatocellular carcinoma; CRM = colorectal metastasis; CHOL = cholangiocarcinoma; NTM = neuroendocrine tumor metastasis; RFA = radiofrequency ablation

of ablation, and regionally, in the liver. There was an index of locoregional relapse of 53% in a series of 110 HCC patients treated with RFA[12]. In the first report of this service about the use of RFA, a relapse rate of 20.5% was found, two cases of HCC in which the relapse took place at the same spot of treatment and one case of regional hepatic relapse in a patient with neuroendocrine liver metastasis[13].

The relapse rate was 17.6% and in a recent prospective study[14] about predictive factors of survival in patients with liver metastasis of colorectal tumors after RFA, 135 patients with metastases who were not candidates to resection were studied, and the following factors had an impact on the results: CEA levels < 200 ng/ml, with 34 months of survival after treatment *versus* 16 ($p = 0.01$), and size of lesion, with survival of 38 months in cases where the dominant lesion was up to 3 cm, 34 months in lesions sized between 3 and 5 cm, and 21 months in those where the lesion was > 5 cm ($p = 0.03$). Additionally, tumors > 5 cm had a predictive factor of mortality with a risk of death 2.5 times higher when compared to those cases where the largest tumor was not > 3 cm ($p = 0.05$).

Tumor size has been pointed as a predictive factor of relapse after RFA[11]. Patients with tumors > 4 cm have a relapse rate of 60%, and the rate increases with tumor size, reaching 100% relapse in tumors > 6 cm. It was also shown that medium-sized and/or non-infiltrating tumors were successfully treated more often than large and/or infiltrating neoplasms[15-16].

An analysis[17] of 273 patients undergoing RFA due to HCC was recently published, in whom the lesions > 2.5 cm represent the only independent variable with impact in the rates of local relapse, also showing that in cases of local relapse a new aggressive treatment towards complete destruction of the lesion increases the chances of survival of this group of patients. In the present series it was observed that, of the 21 cases of relapse, 12 tumors had a diameter ≥ 4 cm and that the right posterior segments, VII and VIII, were the most frequent sites of relapse, with 23.3%, followed by segment IV. There were nine cases of relapse in the group with HCC (17.6%), seven cases in the group with colorectal metastasis (10.9%), one case in the group with mammary gland metastases (20%), two in the group of neuroendocrine tumors (33.3%) and two cases of cholangiocarcinoma (50%).

In metastatic disease, such as neuroendocrine metastases, the RFA has been used mainly to complete the treatment of tumors in deep parenchyma or tumors that can not be surgically removed[18].

A recent prospective study[8] assessed 180 patients with single colorectal metastases, of whom 150 patients were submitted to resection and 30 patients were treated with RFA for not presenting clinical conditions to undergo conventional surgery or for not presenting enough hepatic remnant during preoperative tomographic evaluation. The rate of local relapse was markedly lower in the group undergoing resection compared to the group undergoing RFA, i.e., 5 and 37%, respectively ($p < 0.001$). Resection treatment was associated with better five-year relapse-free survival (92 *versus* 60%, $p < 0.001$), disease-free survival (60 *versus* 0%, $p < 0.001$) and overall survival (71 *versus* 27%, $p < 0.001$). In tumors > 3 cm, the relapse rate reached 31% in the RFA group and only 3% in the resection group, with $p = 0.001$. In view of these findings, the authors concluded that all efforts must be made with the scope of resecting those lesions, such as preoperative portal embolization, two-step resections, state-of-the-art chemotherapy and referral to centers specialized in hepatic surgery in order to offer a treatment with higher chances of disease cure. A new approach[19] uses RFA as an alternative to surgery for the treatment of relapsed liver tumor after hepatectomy.

Its safe performance[20] was recently assessed in a multicenter study in which 2,320 patients with 3,554 lesions were included. Six deaths (0.3%) were notified, including two deaths caused by multiple organ failure followed by intestinal perforation, one case of septic shock due to peritonitis caused by *Staphylococcus aureus*, one case of massive hemorrhage due to tumor rupture, another due to liver failure caused by stenosis of the right biliary duct and one case of sudden death due to unknown cause which occurred three days after the procedure. Fifty patients (2.2%) had severe complications. The results of this study confirm that the RFA is a procedure with low relative risk for treating focal liver tumors. Additionally, subcapsular lesions of HCC must be treated with caution since they are associated to high risk of important complications, especially tumor implantation[2]. Other complications were described[21] after data analysis of 3,670 patients collected from 82 published articles. The complications were intra-abdominal bleeding (1.6%), abdominal infection (1.1%), biliary fistula and strictures (1%), hepatic failure (0.8%), pleural and pulmonary complications (0.8%), vascular liver damages (0.6%), skin burns (0.6%) and thermal damage to adjacent organs (0.5%). The overall mortality rate was 0.5% and morbidity was 9%, regardless of how RFA was applied. Despite some minor complications, such as seromas, urinary tract infection and ascites, this series had a single case of biliary tract fistula (0.9%), in accordance with others reported[22]. A system of perfusion with cold saline solution (4°C) was used during ablation to avoid this type of damage and they were able to treat lesions

which were located at least 5 mm away from the biliary duct, and 12 out of 13 patients had no evidence of any biliary fistula or stenosis[23].

According to previously published data[24], imaging examinations performed one month later, and then at three-to-six-month intervals have been acceptable because this follow-up allows detection of tumor untreated regions before the tumor grow to a size in which re-treatment could no longer be performed. A measurable decrease of contrast uptake was shown in lesions that underwent successful ablation, which was indicated by a minimum increase in the Hounsfield unit density[25]. The study showed that the CT non-contrast phase is needed to assess the success of the RFA procedure.

CONCLUSIONS

RFA treatment, both for primary and metastatic liver diseases, is a safe, effective and fast procedure. The complications rates are acceptable especially when compared to those of surgical procedures in patients with impaired liver function. RFA must be used in selected cases, since surgical resection remains the definitive method for cure of liver tumors. We must be aware of the broad spectrum of complications found after the procedure for its appropriate detection and management. Bear in mind that the size of lesions and complete ablation are the key elements to achieve parity with surgical resection. RFA is a tool that requires advanced skills and must be used by experienced individuals to attain the best oncological outcomes.

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