Radiofrequency ablation of hepatocellular carcinoma in patients with cirrhosis

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SUMMARY
Radiofrequency is an effective therapeutic modality for patients with hepatocellular carcinoma. However few data are available with regard to the complication rate, the feasibility and long term survival.

Aims — To assess the response rate and complications of radiofrequency in cirrhotic patients with hepatocellular carcinoma.

Patients and methods — Eighteen patients were enrolled. Each nodule was treated subcutaneously. Treatment response was assessed by computed tomography performed at 24 hours in 10 patients and every 3 months in all patients. Necrosis of the tumor was considered complete when hypodensity was homogeneous.

Results — Thirty hepatocellular carcinoma nodules with a mean tumor size of 30 mm, were treated by 1.3 radiofrequency sessions. Complete necrosis was achieved in 89%, greater for nodules < 30 mm (100%) than for nodules ≥ 30 mm (80%). After a median follow up of 10.6 months, survival rate was 50%. Death was related to tumor involvement in 28%, to cirrhosis complications in 17% and to non liver-related disease in 5%. Three major treatment-related complications occurred (10%): subcapsular hematoma, sustained severe pain and peritoneal dissemination. All three complications were related to subcapsular location.

Conclusion — Radiofrequency may be considered as an alternative treatment to percutaneous ethanol injection for hepatocellular carcinoma; however, subcapsular location has to be excluded when considering the observed morbidity. Prospective studies are warranted to evaluate the efficacy and morbidity of this treatment in hepatocellular carcinoma.

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Hepatocellular carcinoma (HCC) is one of the five leading causes of cancer in the world [1, 2]. The incidence is increasing due to the large number of persons infected with the hepatitis C virus (HCV) [3, 4]. HCC develops in most cases in patients with underlying chronic liver disease: alcoholic cirrhosis, post-hepatitis B or C cirrhosis, or hemochromatosis. An association with cirrhosis usually worsens the prognosis of HCC. Complications include ascites or hemorrhage aggravating the prognosis and limiting therapeutic options. The frequent occurrence of multiple lesions also contributes to poor prognosis. Curative treatment can be proposed for only 5% of the patients.

There are several therapeutic options for patients with a single lesion: liver transplantation, surgical resection, alcoholization, or radiofrequency ablation. Tumor characteristics (size and number) and liver function are two determining factors for decision making [5]. When liver function is preserved and the tumor measures less than 3 cm, surgical resection can be proposed as first line treatment [6]. Liver transplantation can be performed if liver function is impaired or if the localization or the
number of the tumors contraindicates resection: single tumor measuring = 5 cm or less than 3 tumors measuring = 3 cm [7]. For Child A patients, alcoholization appears to provide results comparable with surgery in terms of complication rate, recurrence, or survival [8] and can be proposed for small tumors measuring < 5 cm.

Different studies on radiofrequency ablation have demonstrated that this method provides good short-term results (table I). Its long-term efficacy, complication rate, and practical modalities remain to be determined.

The purpose of this study was to report our preliminary efficacy and complication results with radiofrequency ablation of HCC in cirrhosis patients.

Table I – Radiofrequency ablation of hepatocellular carcinoma in patients with cirrhosis.

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>HCC (n)</th>
<th>HCC size (mm)</th>
<th>Single tumor [%]</th>
<th>Necrosis [%]</th>
<th>Local recurrence [%]</th>
<th>Intra hepatic recurrence [%]</th>
<th>Complications [%]</th>
<th>Mean follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curley et al. [9]</td>
<td>110</td>
<td>149</td>
<td>2.8 PC 4.6 L</td>
<td>77</td>
<td>—</td>
<td>3.6</td>
<td>45</td>
<td>12</td>
</tr>
<tr>
<td>Francica et al. [10]</td>
<td>15</td>
<td>20</td>
<td>2.8</td>
<td>73</td>
<td>75</td>
<td>0</td>
<td>31</td>
<td>6</td>
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<tr>
<td>Rossi et al. [11]</td>
<td>39</td>
<td>54</td>
<td>&lt; 3</td>
<td>96</td>
<td>80-100</td>
<td>5</td>
<td>36</td>
<td>—</td>
</tr>
<tr>
<td>Rossi et al. [12]</td>
<td>23</td>
<td>26</td>
<td>2.5</td>
<td>88</td>
<td>97</td>
<td>4</td>
<td>21</td>
<td>—</td>
</tr>
<tr>
<td>Nicolli et al. [13]</td>
<td>47</td>
<td>52</td>
<td>2.9</td>
<td>74</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Allgayer et al. [14]</td>
<td>12</td>
<td>15</td>
<td>3.2</td>
<td>92</td>
<td>83</td>
<td>—</td>
<td>—</td>
<td>8</td>
</tr>
</tbody>
</table>

HCC: hepatocellular carcinoma.

Patients and methods

Material

We used the Radionics® system which is composed of a radiofrequency generator (maximum power 200 V, frequency 450kHz), an electrode needle, a cooling pump, and dispersion plates. We used a single electrode needle (17G) if the tumor measured less than 3 cm or a cluster electrode (3 needles) for larger tumors. The Watson Marlow cooling pump circulates a cold saline solution within the system to cool the electrode needle. Dispersion plots (comparable to cauterizer plates) close the electrical circuit with the electrode needle.

Principle

The electrode needle was inserted through the tumor, the distal tip coming flush with the edge of the tumor opposite the entry point. The current delivered was increased to a maximal level without increasing tissue resistance. The needle contact temperature was held below 25°C by the cooling circuit. Concomitant ultrasonography visualized the onset of hyperechogenicity in contact with the needle that progressively occupied the entire tumor volume. The radiofrequency wave was applied for fifteen to twenty minutes to reach a temperature of about 60°C within the tumor. At the end of the procedure, the current and cooling system were stopped with the needle left in place to measure the final temperature after disconnecting the generator. The needle was then withdrawn or left in place for a second thermo-ablation session, or displaced as needed to treat another tumor.

Methods

Ultrasonography (US) was performed the day before the ablation procedure to establish landmarks and verify tumor accessibility and absence of a new localization (figure 1). All HCC were treated percutaneously under US-guidance (figure 2). General anesthesia was used for all patients who remained in the recovery room for 2 hours after the procedure. Mean hospital stay was 48 hours. Two patients required pre-treatment platelet transfusion due to thrombopenia. Fifteen patients were treated with a single 17G needle and three with a triple-cluster needle. For patients with two tumors, all were treated during the same session. Two patients had four tumors requiring two different sessions several days apart. A duel-phase helical CT-scan was used for the radiological follow-up with a first CT 24 hours after the procedure for ten patients to analyze early complications (figure 3). Routine follow-up scans were then performed every three months to assess tumor response (figure 4). Necrosis was considered to be total when the scan visualized a hypodense zone without contrast enhancement. Presence of contrast enhancement was considered suggestive of residual tumor tissue or recurrence.

Patients

Eighteen male patients with cirrhosis, mean age 65.4 ± 6.7 years (range, 55 - 76 years) were treated between September 1999 and July 2000 by radiofrequency ablation of one or several HCC nodules (less than five tumors in all cases). Histological proof of HCC was obtained after fine needle aspiration biopsy. In all, 30 HCC tumors were treated. The cause of cirrhosis was alcohol in 14 patients (77%), hepatitis B virus (HBV) in 2 (11%), and hemochromatosis in 2 (11%). Viral replication was present in one of the two HBV carriers who was given antiviral treatment. Four patients had had prior treatment: surgical resection (n = 3), chemoembolization (n = 1). Liver transplantation was performed later in two other
patients. The Child-Pugh grades were: A, 14 patients (77%); B, 2 patients (11%); C, 2 patients (11%). Mean prothrombin level was 78 ± 17\% (range, 55-100). Serum bilirubin was 30 ± 21 µmol/l (range, 9-92), ALAT activity 90 ± 115 IU/l (range, 16-484), serum creatinine 94 ± 22 µmol/l (range, 63-150). Alpha-fetoprotein was elevated in 25% of patients.

Statistics

Quantitative data were expressed as mean ± standard deviation and range. Comparisons between groups were performed with Student’s t test and Fischer’s exact test for quantitative variables. Survival curves by tumor size and number were plotted with the Kaplan Meier method and compared with the log rank test. Significance was set at 0.05.

Results

Laboratory results (PT, serum bilirubin, serum ALAT, serum creatinine) were not significantly different for tumor size and tumor number. The clinical features and response to treatment are presented in tables II and III according to tumor size and number.

Tumor size and number

Thirty HCC tumors, mean size 29.8 ± 10.7 mm (range, 15-50 mm) were treated by radiofrequency ablation (table II). Fifteen tumors measured less than 30 mm (mean, 21 mm; range, 15-25 mm) and 15 tumors measured more than 30 mm (mean, 36 mm; range, 30-50 mm). Ten patients (55%) had a single tumor, six (33%) two tumors, and two (11%) four tumors (table III).

Fig. 2 – Patient n° 1: ultrasonography during treatment by radiofrequency.

Fig. 3 – Patient n° 1: computed tomography 24 hours after treatment by radiofrequency.

Fig. 4 – Patient n° 1: computed tomography six months after treatment by radiofrequency demonstrates no evidence of local recurrence.
Cluster electrodes were used for lesions of 50, 40, 45 and 20 (n = 2) mm in size, in three patients. Mean duration of the treatment sessions, including patient installation, insertion of the needle and delivery of the radiofrequency wave, was 49 ± 13 mm (30 - 90 min). Mean duration of the radiofrequency wave was 17 ± 4 min for tumors measuring less than 30 mm and 21 ± 8 min for tumors measuring more than 30 mm. Mean hospital stay was 48 hours (range, 24 - 120 hours).

Response rate

The overall rate of complete necrosis after radiofrequency ablation was 89%. It reached 100% for tumors measuring less than 30 mm and was 80% for tumors measuring more than 30 mm. There was no significant difference by tumor size (P = 0.1) or number of tumors (P = 0.65) (Table II and III).

A second radiofrequency session was performed in four patients to treat a recurrence and in two others who had multiple tumors. The total number of sessions was 1.3 ± 0.5 (range, 1-2) per patient and 1.1 ± 0.3 per tumor.

Complications

Six patients (33%) developed complications (Table II). Four patients suffered pain during hospitalization, associated with fever in two and with hiccups in one. The pain persisted for five weeks in one of these patients. In two patients with pain who had tumors measuring less than 30 mm, the scan identified large hypodense areas. Intraparenchymal hemorrhage was observed eight weeks after the radiofrequency session for one subcapsular tumor. This patient experienced sudden onset pain controlled by analgesics. One final patient developed an intraperitoneal hemorrhage secondary to massive peritoneal carcinomatosis eight months after radiofrequency treatment. The initial tumor measured 40 mm and had been treated with a single needle (Figure 5). A second radiofrequency session was required to treat residual tumor tissue. This patient had thrombopenia (42,000/mm3) and had had a platelet transfusion.

The overall complication rate was 20% per tumor; three minor complications (10%) and three major complications (10%).

Recurrence (Tables II and III)

Local recurrence

Residual tumor tissue was observed in three patients with tumors all measuring more than 30 mm (10% local recurrence).

Intrahepatic recurrence

Five patients developed new hepatic localizations visualized on the follow-up scans (27% intrahepatic recurrence). All five patients had one tumor measuring more than 30 mm.

Follow-up

Mean follow-up was 10.6 ± 5.7 months (range, 3-24 months). Two patients were lost to follow-up. At last follow-up nine patients (50%) had died: five (28%) due to progression of their HCC, three (17%) due to a complication of cirrhosis, one (5.5%) due to an extra-hepatic cause (Table II).

Median survival was 14 ± 2 months in patients with tumors measuring less than 30 mm and 10.5 ± 2.1 months for those with tumors measuring more than 30 mm (P = 0.05) (Figure 6). Fifty percent of the patients (n = 9) had died at one year follow-up. Two patients had undergone liver transplantation. The first transplant recipient had four tumors. The histology study of the liver found three sterilized tumors and one small island of residual cells in the fourth tumor. This was a subcapsular tumor that had bled 8 weeks after radiofrequency treatment. The second transplant recipient had been treated for two tumors. The 3-month scan showed peripheral enhancement in one of the two tumors suggested tumor residue which was not confirmed at the pathology examination of the whole liver.

Discussion

Radiofrequency ablation for HCC in patients with cirrhosis is an interesting therapeutic alternative whose place among treatment options remains to be clearly defined.

Tableau II. – Characteristics and treatment response according to tumor diameter of patients treated by radiofrequency for hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>HCC (n)</th>
<th>HCC size (mm)</th>
<th>Single tumor (%)</th>
<th>Necrosis (%)</th>
<th>Local recurrence (%)</th>
<th>Intra hepatic recurrence (%)</th>
<th>Complications per patient (%)</th>
<th>Survival at last follow-up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC all size</td>
<td>18</td>
<td>30</td>
<td>29</td>
<td>55</td>
<td>89</td>
<td>10</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>HCC &lt; 30 mm</td>
<td>7</td>
<td>15</td>
<td>21</td>
<td>57</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>HCC 30 mm</td>
<td>11</td>
<td>15</td>
<td>36</td>
<td>54</td>
<td>80</td>
<td>20</td>
<td>45T</td>
<td>36</td>
</tr>
</tbody>
</table>

*P < 0.05: between HCC < 30 and HCC > 30 mm; HCC: hepatocellular carcinoma.

Tableau III. – Characteristics and treatment response according to tumor number of patients treated by radiofrequency for hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>HCC (n)</th>
<th>HCC size (mm)</th>
<th>Necrosis (%)</th>
<th>Local recurrence (%)</th>
<th>Intra hepatic recurrence (%)</th>
<th>Complications per patient (%)</th>
<th>Survival at last follow-up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC Single tumor</td>
<td>10</td>
<td>10</td>
<td>30</td>
<td>87</td>
<td>20</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>HCC Multiple tumors</td>
<td>8</td>
<td>20</td>
<td>30</td>
<td>94</td>
<td>5</td>
<td>25</td>
<td>50</td>
</tr>
</tbody>
</table>

*P < 0.05: between HCC < 30 and HCC > 30 mm; HCC: hepatocellular carcinoma.
The technique provides real efficacy since the rate of tumor necrosis is estimated at 90% for tumors measuring less than 3 cm and about 70% for those measuring 3 to 5 cm \[15\]. Radiofrequency ablation was compared with alcohol injection in one randomized study \[16\] that included 86 patients with 112 tumors measuring less than 3 cm. Complete necrosis was observed in 80% of the cases after a mean 4.8 ethanol injections while this rate reached 90% after 1.2 radiofrequency sessions.

The efficacy of radiofrequency ablation depends on the size of the tumor and the degree of cellular differentiation. Tumor necrosis is complete in 70% of the cases for well-differentiated tumors measuring 3 to 5 cm, in 25% for well-differentiated tumors measuring more than 5 cm and in 45% for poorly-differentiated tumors measuring 3 to 5 cm \[15\]. This size-related effect is confirmed in our study where the rate of necrosis was 80% for tumors measuring more than 3 cm (mean 3.6 cm) and 100% for those measuring less than 3 cm (mean 2.1 cm). In our series, the percentage of necrosis in tumors measuring more than 3 cm was greater than that found by Livaraghi et al. \[8\], probably due to the smaller mean tumor size (3.6). The efficacy of radiofrequency ablation was also well demonstrated in our two liver transplant recipients since the histology study of the explanted livers found that 5 of the 6 radiofrequency-treated tumors had been sterilized (83%). Goldstein et al. \[17\] reported similar findings. In their study, 8 transplanted patients had had radiofrequency treatment before transplantation. There was no residual tumor tissue in 7 of the 8 explanted livers (87%).

The short-term efficacy of radiofrequency ablation is thus clearly demonstrated for tumors measuring less than 5 cm, but the long-term effect and the influence of treatment on survival remain to be ascertained. Curley et al. \[9\] evaluated recurrence rate and survival at a mean 19 months in 110 patients with cirrhosis and HCC. The recurrence rate at the end of this follow-up was 48%: local recurrence in 3% of the cases and a new localization in 45%. Concerning survival, 25% of the patients died with recurrent disease, 25% had recurrence but were alive at last follow-up, and 50% were recurrence-free. The results of our series show that 50% of the patients had died at a mean follow-up of 10.6 months and that half of the deaths were related to disease progression. All of the fatal cases involved tumors measuring more than 30 mm. The survival rate is significantly lower in patients with tumors measuring greater than 30 mm probably because of the high intrahepatic recurrence rate (45%). Similarly, Khan et al. \[18\] reported a 43% rate of intrahepatic recurrence at two years in patients who had large tumors (> 30mm) compared with 18% for those with small tumors (< 30mm). It thus appears clear that prognosis in patients with tumors measuring = 30 mm remains poor, despite control of local tumor spread. Liver function also appears to influence survival in our study since 17% of the patients died from a complication of their cirrhosis. In order to improve the survival rate, we propose careful patient selection based on tumor size and liver function.

Radiofrequency is an effective technique that can replace alcoholization if the morbidity can be controlled. Currently, the rate of complication after radiofrequency ablation remains high, between 6 and 12% depending on the study, compared with 3 to 5% after injection of alcohol \[19\]. The complication rate appears to be unusually high in our series because we included all adverse effects associated with treatment. The commonly reported complications include hemorrhage, infection, and pain. Minor complications such as pain requiring analgesics, or fever are relatively frequent, each reported for example in 25% of the patients by McGregor and Dodd \[20\]. We had three major complications, i.e. 10% of the treated tumors. In order to reduce morbidity, the limitations on indications for radiofrequency ablation should be outlined in detail.

Fig. 5 – a) Patient n° 2: hepatocellular carcinoma: ultrasound before treatment. b) Patient n° 2: hepatocellular carcinoma in computed tomography before treatment.

Fig. 6 – Survival curves according to tumor diameter.
Currently accepted contraindications for transcutaneous radiofrequency ablation include large tumors (> 5 cm), overly numerous tumors (> 4), and tumors lying close to the bile ducts, or a hollow organ. Surgery could be considered as an alternative for these patients. We used the transcutaneous approach exclusively. A bleeding subcapsular lesion resulting in acute pain in one patient and a case of peritoneal dissemination also following treatment of a subcapsular tumor were also observed here. The radiofrequency treatment in the patient who developed peritoneal carcinomatosis had been conducted during a period of severe thrombopenia but under the cover of a platelet transfusion. The 24 scan showed a small area of hemorrhage within the tumor that may have favored dissemination. This type of complication could be prevented by not using the transcutaneous approach for subcapsular lesions if there is not a sufficient amount (about 1 cm) of healthy parenchyma for protection [21]. Hemorrhage is more frequent after fine-needle biopsy of subcapsular tumors [22]. We therefore recommend to avoid radiofrequency ablation in patients who have important coagulation disorders (PT < 50%, platelets < 70,000/mm³). Lovet el al. [23] recently reported four cases of dissemination (12.5%) along hepatic track. These authors used a single 17 G Radionics® needle. Dissemination was associated with subcapsular tumor (< 1 cm from the hepatic capsul; p = 0.009), poor degree differentiation (p = 0.02), and the alpha-fetoprotein level (P = 0.02). These authors did not report on the frequency of dissemination in patients with coagulation disorders. Although these results were not confirmed by Livraghi et al. [24], they underline that the use of radiofrequency should be avoided in patients on the transplantation waiting list, particularly if they have a subcapsular tumor and severe coagulation disorders.

The current rate of complications after radiofrequency ablation is higher than after alcoholization. If a rigorous technique is applied in selecting patients however, this rate could probably be reduced by experienced operators. Radiofrequency treatment has the advantage of requiring a small number of sessions (1.2 on the average) compared with alcoholization (4.8 on the average). The cost for material is about 500 euros per needle, which remains a limiting factor. At the present time, it appears indispensable to conduct a medicoeconomic analysis in order to determine the respective place of radiofrequency ablation, alcohol injection and surgical resection in the treatment of HCC.

**Conclusion**

Radiofrequency treatment has been found to be particularly effective in terms of tumor destruction in cirrhosis patients with HCC. 100% tumor necrosis for tumors measuring < 30 mm and 80% for tumors measuring = 30 mm. Radiofrequency ablation is thus a supplementary therapeutic alternative for the treatment of HCC. In order to reduce the rate of complications related to the transcutaneous approach, it would appear advisable to not treat subcapsular lesions by radiofrequency if the safety margin is insufficient or if the patient presents important coagulation disorders.

**REFERENCES**


