Treatment of small hepatocellular carcinoma with acetic acid percutaneous injection

A single French center experience

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SUMMARY

Percutaneous ablation using acetic acid is an attractive method because of its low morbidity and low number of sessions required to induce complete tumor necrosis. Moreover, the real-time fluoroscopy CT scan could improve the technique by improving distribution of the necrotizing agent within the tumor.

Aim — To determine the feasibility and the long-term results of the acetic acid percutaneous injection under CT fluoroscopy guidance in a series of cirrhotic patients with small hepatocellular carcinoma in a single French center.

Methods — One hundred and two patients with hepatocellular carcinoma were evaluated for treatment between 1999 and 2000. The selection criteria for fluoroscopy CT scan-directed percutaneous acetic acid ablation were: 1) one to three nodules < 5 centimeters; 2) Child-Pugh class < 13; 3) prothrombin index > 40% and platelet count > 50000 per mm$^3$ and 4) contraindication to both resection and liver transplantation. Post treatment follow-up included ultrasonography, magnetic resonance and alphafetoprotein levels every 3 months. Recurrence and survival rates were estimated using the Kaplan-Meier method.

Results — Forty-nine patients (48%) could benefit from a curative treatment, most of them (37/49) being eligible for fluoroscopy CT scan-directed percutaneous acetic acid. The mean follow up was 24.4 ± 2.7 months. Complete tumor necrosis was achieved in 28 patients (76%) after a mean of 1.6 sessions. In these 28 patients, the recurrence rates were 34% and 48% and survival rates were 76% and 70%, at 24 and 36 months, respectively. No serious complications occurred during or after the treatment.

Conclusions — Percutaneous ablation using acetic acid using CT fluoroscopy guidance may be considered as a short term efficient, low risk treatment and can be applied even in patients with ascites or severe hemostatic abnormalities. However, the high rate of recurrence and the early occurrence of multifocal hepatocellular carcinoma underline the limits of this method as well as of all other percutaneous strategies.

Introduction

Patients with hepatocellular carcinoma diagnosed at an early stage should be considered for curative treatments. These include liver transplantation, surgical resection and percutaneous techniques of tumor ablation [1]. Liver transplantation is thought to be the most effective treatment for hepatocellular carcinoma patients upon cirrhosis because it treats both the tumor and the underlying disease [2]. However, a minority of patients can undergo liver transplantation due to the lack of donors and the fact that most patients in this setting are over 65 years old and there are often associated diseases. Surgical resection is currently restricted to patients with a single asymptomatic hepatocellular carcinoma, a preserved liver function and no portal vein invasion [3]. The technique for percutaneous techniques of tumor ablation is currently restricted to patients with a single asymptomatic hepatocellular carcinoma, a preserved liver function and no portal vessel invasion [3]. Moreover, the real-time fluoroscopy CT scan could improve the technique by improving distribution of the necrotizing agent within the tumor.

La destruction tumorale par injection percutanée d’acide acétique est une méthode intéressante en raison de sa faible morbidité et du faible nombre de séances. La technique peut être améliorée par l’utilisation de la fluoroscopie qui permet une distribution optimale de l’agent nécrosant dans la tumeur.

Objetif — Déterminer les résultats à long terme de l’injection percutanée d’acide acétique sous fluoroscopie dans une série française de malades cirrhotiques avec un petit carcinome hépatocellulaire.

Méthodes — Cent deux malades avec un carcinome hépatocellulaire miniaturisé ont été évalués en vue d’un traitement. Les critères retenus pour l’injection percutanée d’acide acétique sous fluoroscopie étaient : 1) un à trois nodules de carcinome hépatocellulaire < 5 centimètres ; 2) Score de Child-Pugh < 13 ; 3) taux de prothrombine > 40 % et plaquettes > 50 000 par mm$^3$ et 4) contre-indication à la résection et à la transplantation. Le suivi après traitement comprenait une échographie abdominale, une imagerie par résonance magnétique et un dosage d’γ-foetoprotéine tous les 3 mois. Les taux de récidive et de survie étaient estimés par la méthode de Kaplan-Meier.

Résultats — Un traitement curatif était possible chez 49 patients. Parmi ces malades, 37 étaient éligibles pour un traitement percutané par injection d’acide acétique sous fluoroscopie. Le suivi moyen était de 24,4 ± 2,7 mois. La nécrose tumorale complète a été obtenue chez 28 patients (76 %) après une moyenne de 1,6 séances (1-3). Les taux de récidive étaient 34 % et 48 % et les taux de survie étaient de 76 % et 70 % à 24 et 36 mois, respectivement. Aucune complication sévère n’était observée durant ou après l’injection.

Conclusions — La destruction tumorale par injection percutanée d’acide acétique sous fluoroscopie est un traitement efficace à court terme, à faible risque et peut être réalisée en présence d’une ascite modérée ou d’anomalies sévères de l’hémostase. Cependant, le taux élevé de récidives et l’apparition précoce de carcinomes hépatocellulaires multifocaux soulignent les limites de cette méthode mais aussi de tout autre traitement percutané.
hypothesis [3, 4]. As for liver transplantation, a restricted number of patients are eligible for resection mostly because of deteriorated hepatic function or poor general condition. Therefore, percutaneous ablation is the only curative therapeutic option for a majority of patients.

Percutaneous ethanol injection has been the most widely used technique of percutaneous tumor ablation [5-7]. Other methods such as percutaneous injection of acetic acid, radiofrequency, laser, microwaves, and cryosurgery, have been developed over the past few years. Currently, radiofrequency is thought to be the first-line treatment for small non-surgical hepatocellular carcinoma. Indeed, this approach requests fewer treatment sessions than percutaneous ethanol injection [8, 9]. Percutaneous injection of acetic acid may also be an interesting method for the same reason [10]. Furthermore, the recently described real-time fluoroscopy computed tomography (CT) scan might improve the percutaneous injection of acetic acid results by allowing an optimal distribution of the necrosing agent throughout the entire nodule [11, 12].

The aim of the present study was therefore to determine the feasibility and the long-term results of the percutaneous injection of acetic acid under CT fluoroscopy guidance (FPAI) in cirrhotic patients with small hepatocellular carcinoma from a single French center.

Patients and methods

Study population

Between January 1999 and December 2000, 102 consecutive patients with hepatocellular carcinoma with cirrhosis were evaluated in the Department of Hepatology of the Hôpital Saint Antoine in Paris. The optimal therapeutic option was determined after careful clinical, laboratory and imaging assessment, by a multidisciplinary committee including hepatologists, liver surgeons and radiologists.

Patient selection

Candidates for liver transplantation were patients with a single hepatocellular carcinoma less than 5 cm in diameter or with 3 or less than 3 nodules measuring less than 3 cm without extrahepatic and vascular spread. Surgical resection was restricted to patients with a single hepatocellular carcinoma nodule of less than 50 mm, Child-Pugh class A, normal bilirubin and no portal hypertension. Patients eligible for FPAI presented with the following criteria: 1) one to three hepatocellular carcinoma nodules smaller than five centimeters in diameter; 2) Child-Pugh class < 13; 3) prothrombin index > 40% and platelet count > 50 000 per mm3 and 4) contraindication to both partial hepatectomy (age > 70 years, portal hypertension, Child-Pugh score > 7 or major liver atrophy) and liver transplantation (persistent alcohol intake, age > 65 years, medical history of cardiac, renal or pulmonary disorders). Patients with multifocal tumors and Child-Pugh score ≥ 7 were treated by chemoembolization. Finally, patients with end-stage disease received palliative medical treatment, including tamoxifen or systemic chemotherapy.

Procedure

The FPAI procedure has been recently reported [14]. Briefly, a 22 Gauge Chiba end-hole needle was introduced percutaneously into the tumour under CT fluoroscopy guidance. Treatment was performed under local anaesthesia. An intermittent discontinuous CT fluoroscopic technique combined with dynamic manual table movement from the lower to the upper pole of the lesion allowed analysis of acetic acid diffusion in the lesion. Injection was performed using a mixture of 50% acetic acid and nonionic contrast material (iohexol 300; Nycomed Amersham SA, Buckinghamshire, UK) at a ratio of 5:1. The theoretical volume of 50% acetic acid for injection was calculated based on V = 4/3 p (R + 0.5)2 x 1/3, where V is the volume of acetic acid and R the radius of the nodules in centimetres [14]. A minimum volume of 3 ml 50% acetic acid was injected no matter the size of the lesion. The acetic acid was injected slowly by a syringe connected to the needle via an extension tube, under CT monitoring. If some areas where no contrast material remained visible in the lesion, the needle was further repositioned to achieve a more homogenous distribution. In case of diffusion of contrast material outside the lesion, the injection was stopped and the needle position adjusted accordingly. Usually, patients were hospitalized 24 hours for the procedure.

Follow-up

Post-treatment follow-up included ultrasound and magnetic resonance imaging (MRI) and determination of a-foetoprotein (aFP) levels every 3 months after the initial FPAI session. The short-term effects of ablation were assessed using MRI 3 months after each FPAI session. If the lesion had residual arterial hypervascularity after the initial FPAI session, a further session of FPAI was performed and was evaluated 3 months later with MRI. If the lesion was inactive, the FPAI was discontinued and the follow-up was pursued as described above. Previous data in the literature showed that one to three radiofrequency ablation and percutaneous acetic acid injection sessions are usually sufficient to obtain complete tumor necrosis [9, 10, 15-17]. Therefore, if the complete necrosis of tumor was not obtained after a maximum of three sessions, FPAI was considered to be a failure in terms of therapeutic benefit compared with other percutaneous methods and the patient was treated by alternative therapy. The local recurrence was defined by the re-enlargement of the nodule more than 3 months after complete tumor necrosis and characteristic features of arterial vascularization in the nodule. This diagnosis was confirmed by incidental visualization using two imaging techniques (e.g. CT scan and MRI). The occurrence of a new tumor was defined by the appearance of one or more hepatocellular carcinoma nodules located more than 2 cm from the initial nodule or in other segments of the liver. The recurrence was referred to as early or late if the tumor reappeared less or more than eighteen months after the initial tumor necrosis. The endpoints were cumulative survival, recurrence rate and cancer-free survival rate.

Statistical analysis

The results are expressed as means ± SE. Cumulative survival rate, rate of recurrence and cancer-free survival rate were calculated from the onset of hepatocellular carcinoma treatment using Kaplan-Meier method. Factors associated with recurrence were investigated using Fisher’s exact test for categorical variables (gender, Child score) or Mann-Whitney’s test for continuous variables (age, initial number of nodules, size of principal tumor, number of sessions and total acetic acid volume injected). A P value < 0.05 was considered significant.

Results

Patient characteristics

Between January 1999 and December 2000, 102 consecutive cirrhotic patients with hepatocellular carcinoma(s) were evaluated for treatment. Among these patients, forty-nine patients (48%) were eligible for curative treatment according to the criteria defined in the Methods section: liver transplantation was performed in 2 patients, surgical resection in 10 patients and FPAI in 37 patients. Fifty-three other patients (52%) received palliative treatment: chemoembolization in 27 cases and medical treatment in 26 cases (figure 1).

The characteristics of the 37 patients treated by FPAI are shown in table I. Forty five hepatocellular carcinoma nodules had been treated by acetic acid (table II). Most patients had one hepatocellular carcinoma nodule. The diagnosis of hepatocellular carcinoma was established by the concomitant finding of 2 imaging techniques showing a nodule of more than 2 cm asso-
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...associated with arterial hypervascularization in 19 patients. The diagnosis of hepatocellular carcinoma was established by a single positive imaging technique showing a hypervascularized nodule associated with an aFP level more than 400 ng/mL in 4 patients. Eventually the diagnosis of hepatocellular carcinoma was established by ultrasound guided liver biopsy in the 14 others patients. None of these patients had an aFP level \( > 400 \) ng/mL.

**FPAI procedure**

When CT fluoroscopy monitoring showed a heterogeneous distribution of acetic acid in the treated lesions after injection (figure 2a), the needle was repositioned in order to improve the distribution of the agent throughout the entire nodule (figure 2b). A mean number of 2.5 (range: 1 to 10) different needle positions within each lesion was necessary. Spread of acetic acid outside the lesion occurred in 35 of the 60 FPAI procedures. In this situation, the injection was discontinued and the needle was immediately repositioned within the lesion to complete the procedure. The average CT fluoroscopic time was 1 min 52 sec (range: 52 sec-3 min 49 sec).

**Treatment Efficacy**

The mean follow-up period was 24.4 \( \pm 2.7 \) months. Medium and long-term results of FPAI could not be evaluated in 9 patients (24.3%) for the following reasons: 7 patients developed a multifocal hepatocellular carcinoma in the 3 months after the beginning of FPAI, 1 patient developed a lung cancer with adrenal and mediastinal metastases and died early and, in one patient, a complete tumour necrosis could not be obtained despite a correct FPAI procedure.

Successful FPAI, defined by the complete tumor necrosis and the absence of vascular activity, was achieved in 28 patients (75.7%). In all these patients, the tumor size decreased following FPAI. A mean of 1.6 FPAI sessions (range: 1-3) was sufficient to obtain the complete tumor necrosis: a single session in 18 patients (64.3%), two sessions in 7 patients (25%) and three sessions in 3 patients (10.7%). The mean volume of acetic acid injected during each FPAI session was 8.4 mL (range: 2-30 mL).

**Recurrence rate and survival**

In the 37 treated patients, recurrence rates were 60% at 36 months (figure 3). The survival and cancer-free survival rates were 58% and 32% at 36 months, respectively (figure 4).

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**Table I.** – Characteristics of the 37 patients with hepatocellular carcinoma treated by acetic acid percutaneous injection under CT scan fluoroscopy.

<table>
<thead>
<tr>
<th>Variables</th>
<th>N = 37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (range)</td>
<td>68.4 (34-85)</td>
</tr>
<tr>
<td>M / F ratio</td>
<td>27/10</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
</tr>
<tr>
<td>• HCV / HBV + HDV</td>
<td>15/1</td>
</tr>
<tr>
<td>• Alcoholic liver disease</td>
<td>18</td>
</tr>
<tr>
<td>• Hemochromatosis</td>
<td>1</td>
</tr>
<tr>
<td>• Hemochromatosis + alcohol</td>
<td>1</td>
</tr>
<tr>
<td>• Primary biliary cirrhosis</td>
<td>1</td>
</tr>
<tr>
<td>Ascites</td>
<td>5</td>
</tr>
<tr>
<td>Prothrombin index ( \geq 60 ) %</td>
<td>13</td>
</tr>
<tr>
<td>Serum bilirubin ( \leq 25 ) ( \text{nmol/L} )</td>
<td>10</td>
</tr>
<tr>
<td>Platelet count ( &lt; 80000 ) ( \text{per mm}^3 )</td>
<td>12</td>
</tr>
<tr>
<td>Esophageal varices grade 2 or 3</td>
<td>14</td>
</tr>
<tr>
<td>Child-Pugh class: A/B/C</td>
<td>28/7/2</td>
</tr>
<tr>
<td>aFP values ( \leq 400 ) ( \text{ng/mL} )</td>
<td>4</td>
</tr>
</tbody>
</table>

**Table II.** – Characteristics of 45 nodules among 37 patients with hepatocellular carcinoma treated by acetic acid percutaneous injection under CT scan fluoroscopy.

<table>
<thead>
<tr>
<th>Number of nodules</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean size of nodules <a href="range">mm</a></td>
<td>27.2 (9-50)</td>
</tr>
<tr>
<td>Number of patients with 1 / 2 / 3 nodules</td>
<td>30/5/2</td>
</tr>
<tr>
<td>Number of nodules according to size:</td>
<td></td>
</tr>
<tr>
<td>• 15-20 mm</td>
<td>14</td>
</tr>
<tr>
<td>• 21-30 mm</td>
<td>19</td>
</tr>
<tr>
<td>• 31-40 mm</td>
<td>8</td>
</tr>
<tr>
<td>• 41-50 mm</td>
<td>4</td>
</tr>
</tbody>
</table>
If the analysis was restricted to 28 patients who have responded to the treatment (e.g., in whom a complete tumor necrosis was obtained), the recurrence rate was 34% at 24 months and 48% at 36 months. The overall survival rate was 74% at 24 months and 70% at 36 months. However, the cancer-free survival rate reached 41% at 36 months (Figure 5). Among the 12 patients who developed tumor recurrences, 5 patients had a single local recurrence and seven patients had a multifocal hepatitis C virus. No predictive factor of the recurrence was identified in this study (Table III).

Complications

No serious complications occurred during or after FPAI. Thirteen patients (35.1%) had minor side effects (Table IV). After acetic acid injection, most patients presented with transient pain of the skin.
Discussion

The aim of our study was to evaluate the feasibility and the long term results of FPAI in hepatocellular carcinoma treatment in a single French center. We show that: a) FPAI is a low-risk procedure even in patients with ascites or coagulation impairment; b) one or two FPAI sessions are sufficient to obtain a complete tumor necrosis in most cases; c) the 36-month survival rate of patients treated by FPAI is similar to those reported in patients treated by surgery or other percutaneous ablation techniques. However, this original technique was only applicable to one third of our patients and its restricted efficacy was illustrated by frequent recurrences and early undetected multifocal hepatocellular carcinoma.

Percutaneous ethanol injection and percutaneous acetic acid injection are usually performed under ultrasound guidance. The advantages claimed for ultrasound include real-time monitoring and its low cost [18]. In fact, ultrasound may sometimes be limited to precisely evaluate the extent of agent distribution and needle positioning, since a markedly hyperechoic area immediately appears after the injection. Fluoroscopy monitoring enables an accurate evaluation of acetic acid distribution and detection of any acetic acid leaks, may limit the adverse effects of the procedure. This advantage has been also observed for percutaneous ethanol injection by analyzing the pattern of ethanol distribution within the lesion [19]. A potential disadvantage of CT fluoroscopy may be the exposure to radiation. To avoid this problem, an extension tube between needle and syringe were used and needle positioning was performed using intermittent CT fluoroscopy [20]. Thereby, the average CT fluoroscopic time remained below 1 minute by patient.

No major complications were observed. This is probably related to the small number of sessions, the small volume of acetic acid injected and the very careful fluoroscopy CT scan monitoring of acetic acid distribution in tumors. We observed one case of neoplastic seeding in the needle tract eighteen months after the treatment. However, the liver biopsy performed just before FPAI may have contributed to the tumor seeding in this patient. Altogether, FPAI-related complications appear to be quite similar to those reported for percutaneous ethanol injection [10, 16, 18].

Acetic acid is a more efficient necrotizing agent for cells and collagen septa in hepatocellular carcinoma than absolute ethanol [21]. Consistent with this, the percutaneous ablation methods using acetic acid require smaller injection volumes and fewer sessions as compared to percutaneous ethanol injection [9, 10, 16, 22]. One to two FPAI sessions (depending on the size of nodules) were indeed enough to induce a complete tumor necrosis in 75% of our patients. In comparison, the number of treatment sessions was usually 3 to 6 sessions for hepatocellular carcinoma ≥ 2 cm and 8 to 10 for 2- to 3.5-cm hepatocellular carcinoma in previous studies using percutaneous ethanol injection [10, 16, 18, 22] while 1 to 3 sessions were sufficient when using radiofrequency ablation [8, 9, 17]. The low number of FPAI sessions has therefore the advantage of

Table IV. – Complications of treatment by acetic acid percutaneous injection in 37 patients with hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild pain in right upper quadrant</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Elevated transaminase activities (5 to 20 N)</td>
<td>5 (13.5)</td>
</tr>
<tr>
<td>Moderate fever (38°C-38.5°C)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Partial pneumothorax</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Myoglobinuria</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Flashes</td>
<td>1 (2.7)</td>
</tr>
<tr>
<td>Subcutaneous neoplastic seeding</td>
<td>1 (2.4)</td>
</tr>
</tbody>
</table>

N: fold upper the normal range

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short duration of hospitalization, reduced medical costs and treatment-related discomfort.

The 3-year survival in patients with small hepatocellular carcinoma in the present study is similar to that observed in the percutaneous acetic acid injection reported from Japanese series [10, 15, 16]. Although our study was not designed to compare FPAI with other percutaneous methods for the hepatocellular carcinoma treatment, we observed that, in terms of survival, our results are similar to those reported for percutaneous ethanol injection treatment. The overall-3-year survival rate for patients with small hepatocellular carcinoma treated with percutaneous ethanol injection ranged from 55% to 88% [8, 18]. Recent data have suggested that radiofrequency ablation was more effective than percutaneous ethanol injection in the treatment of small hepatocellular carcinoma in cirrhosis [8, 9, 17]. To our knowledge, there are only two randomized controlled trials reporting a higher local recurrence-free survival and event-free survival with hepatocellular carcinoma < 5 cm after radiofrequency ablation than after percutaneous ethanol injection [8, 9]. In an Italian study, the overall survival rates after 1 and 3 years were 96% and 88%, respectively, in the percutaneous ethanol injection group, and 100% and 98%, respectively, in the radiofrequency group (P = 0.138) [8]. Lin et al. [9] confirm these results and show that radiofrequency ablation yielded better clinical outcomes than conventional and higher-dose in treating hepatocellular carcinoma 4 cm or less. Nevertheless, this technique is not entirely free from complications and appropriate experience and optimized treatment protocols are needed [23, 24]. Further trials are needed to establish the long-term efficacy and the morbidity of this recent procedure.

Even in well-selected patients, long-term survival after FPAI is curtailed by a high recurrence rate (48% at 36 months). Local as well as mainly multifocal recurrences were observed and occurred within 17 months (range: 6-48 months) after FPAI session. Unexpectedly, none of the following criteria (e.g. the age of patients, injected volume of acetic acid, Child Pugh class, size or number of tumors) were predictive of recurrence in the present study. Our results are overall similar with those reported in the literature for percutaneous acetic acid injection: 10% of patients developed local recurrences and new hepatocellular carcinoma lesions occurred elsewhere in the liver in 38 to 42% of patients at 2 years [10, 15, 16]. Such a recurrence rate is not a specific drawback of FPAI, since it is also common in patients treated with other percutaneous treatments or surgical resection [3, 26-29].

While FPAI was only applicable to less than 40% of our patients, it may be considered as an interesting percutaneous treatment for non-surgical small hepatocellular carcinoma, mainly because of its low morbidity and low number of sessions. However, the high rate of recurrence and the early occurrence of multifocal hepatocellular carcinoma underline the limits of this method as well as of all other percutaneous strategies.

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REFERENCES


