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 mm3 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.
technique combined with dynamic manual table movement from the under local anaesthesia. An intermittent discontinuous CT fluoroscopic 
the tumour under CT fluoroscopy guidance. Treatment was performed 
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carcinoma nodules smaller than five centimeters in diameter; 2) Child-
FPAI presented with the following criteria: 1) one to three hepatocellular 
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hepatocellular carcinoma nodule of less than 50 mm, Child-Pugh class 
vascular spread. Surgical resection was restricted to patients with a single 
hepatic 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, labora-
tory 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 vas-
cular spread. Surgical resection was restricted to patients with a single 
hepatocellular carcinoma nodule of less than 50 mm, Child-Pugh class 
¿ 7, 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 chemother-
apy.

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

ABBREVIATIONS:

FPAI : fluoroscopy CT scan-directed percutaneous 
acetic acid injection
aFP : alpha-fetoprotein
MRI : magnetic resonance imaging
CT : computed tomography

dlucer 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, radiofre-
dency, laser, microwaves, and cryosurgery, have been de-
veloped over the past few years. Currently, radiofrequency is 
thought to be the first-line treatment for small non-surgical hepato-
cellular carcinoma. Indeed, this approach requests fewer treat-
ment 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 necrotizing 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.

Follow-up

Post-treatment follow-up included ultrasound and magnetic reso-

nance imaging (MRI) and determination of a-fetoprotein (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 percuta-
aneous acetic acid injection sessions are usually sufficient to obtain 
complete tumor necrosis [9, 10, 15-17]. Therefore, if the complete necro-
sis of tumor was not obtained after a maximum of three sessions, FPAI 
was considered to be a failure in terms of therapeutic benefit as compa-
red with other percutaneous methods and the patient was treated by 
alternative therapy. The local recurrence was defined by the re-enlarge-
ment 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 coincidental 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 seg-
ments 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 
ons 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 prin-
cipal 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 evalu-
ated for treatment. Among these patients, forty-nine patients 
(48%) were eligible for curative treatment according to the crite-
ria defined in the Methods section: liver transplantation was per-
formed 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 treat-
ment 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 hepatocellu-
lar carcinoma was established by the concomitant finding of 
2 imaging techniques showing a nodule of more than 2 cm asso-


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Treatment of small hepatocellular carcinoma with acetic acid

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 ± 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).
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 hepatocellular carcinoma. 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 upper right quadrant (16.2%). It is noteworthy that no toxic cholangitis was observed. Finally, we observed one case of neoplastic seeding along the needle track (1/41 sessions, 2.4%) which was treated by surgical resection.

**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 using radiofrequency ablation [8, 9, 17]. The low number of FPAI sessions has therefore the advantage of

<table>
<thead>
<tr>
<th>Complications</th>
<th>Number of patients (%)</th>
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<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 (13.3)</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>Flushes</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


