

# Survival and prognostic factors in patients with hepatocellular carcinoma treated by percutaneous ethanol injection: A 10-year experience

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The treatment of early and intermediate stage hepatocellular carcinoma (HCC) is still debated. Surgical treatments are considered to be the only curative procedures available, and only for a minority of patients. Percutaneous ethanol injection (PEI) is an established technique for the ablation of HCC nodules, and shows survival rates similar to those of resection. The efficacy of PEI in patients with biopsy-proven viral cirrhosis and small to intermediate inoperable HCC was evaluated. One hundred twenty-seven patients (85 men, 42 women, mean age 63 years, range 51 to 92 years, 115 hepatitis C virus-positive, 12 hepatitis B virus-positive) were enrolled between January 1993 and December 2002. They all underwent a standard PEI procedure and were prospectively followed-up. Overall median survival rate was 28 months (range six to 112 months). The following parameters were associated with a significantly longer survival: nodule diameter smaller than 30 mm ( $P=0.0480$ ), the presence of a perinodular boundary ( $P=0.0008$ ), serum alpha-fetoprotein less than 20 ng/mL ( $P=0.0104$ ), a Child-Pugh A class score ( $P<0.0001$ ) or a Cancer of the Liver Italian Program score of 0 ( $P<0.0001$ ) and the presence or absence of small esophageal varices ( $P=0.013$ ). The 19 patients with all these favourable characteristics showed an overall median survival of 61 months. An alpha-fetoprotein below 20 ng/mL was associated with significantly longer disease-free survival ( $P=0.0009$ ). The Child-Pugh and Cancer of the Liver Italian Program scores were effective in predicting prognosis of these patients. In conclusion, PEI still represents a safe and economically sound treatment for HCC.

**Key Words:** Ablative therapy; Cirrhosis; HCC; PEI; RFA; TACE

There is still no agreement on the best standard treatment for patients with inoperable small- to intermediate-sized hepatocellular carcinoma (HCC) (1,2), and the treatment of early and intermediate stage HCC is still a source of debate (3). At present, the only potentially curative treatments for HCC are considered to be either partial hepatectomy or orthotopic liver transplantation (OLT) (2,4,5). Unfortunately, OLT is available for only a minority of patients, particularly in

La survie et les facteurs pronostiques chez les patients atteints d'un carcinome hépatocellulaire traité par injection d'éthanol percutané : Une expérience sur dix ans

Le traitement des phases précoce et intermédiaire du carcinome hépatocellulaire (CHC) demeure controversé. Les traitements chirurgicaux sont considérés comme les seules interventions curatives disponibles, et seulement pour une minorité de patients. L'injection d'éthanol percutané (IEP) est une technique établie pour l'ablation des nodules de CHC et assure des taux de survie similaires à ceux de la résection. L'efficacité de l'IEP chez les patients atteints d'une cirrhose virale confirmée par biopsie et un CHC petit à modéré a été évaluée. Cent vingt-sept patients (85 hommes, 42 femmes, âge moyen de 63 ans, plage de 51 à 92 ans, 115 positifs au virus de l'hépatite C, 12 positifs au virus de l'hépatite B) ont été enrôlés entre janvier 1993 et décembre 2002. Ils ont tous subi une IEP standard et fait l'objet d'un suivi prospectif. Le taux de survie médian global était de 28 mois (plage de six à 112 mois). Les paramètres suivants s'associaient à une survie beaucoup plus longue : diamètre des nodules inférieur à 30 mm ( $P=0,0480$ ), présence d'une liaison périnodulaire ( $P=0,0008$ ), alpha-fœtoprotéine sérique inférieure à 20 ng/mL ( $P=0,0104$ ), score Child-Pugh de classe A ( $P<0,0001$ ) ou score du programme italien de cancer du foie de 0 ( $P<0,0001$ ) et présence ou absence de petites varices œsophagiennes ( $P=0,013$ ). Les 19 patients présentant toutes ces caractéristiques favorables ont profité d'une survie médiane globale de 61 mois. Une alpha-fœtoprotéine inférieure à 20 ng/mL s'associait à une survie sans maladie considérablement plus longue ( $P=0,0009$ ). Les scores de Child-Pugh et du programme italien de cancer du foie permettaient de prédire le pronostic de ces patients. Pour terminer, l'IEP continue de constituer un traitement sûr et économiquement solide du CHC.

underdeveloped or poor countries in which cirrhosis and HCC are common diseases (6). Even in countries where OLT is available, many of the patients affected by HCC often withdraw from OLT waiting lists because of increased tumour growth or spread (7); others are not considered to be eligible for OLT after having undergone other therapies such as local ablative or systemic therapies. Although liver resection apparently insures the best local control of the disease, it is quite a

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risky procedure in cirrhotic patients; only a minority of them can undergo surgery because of the cirrhosis itself (8).

HCC ablation by means of percutaneous ethanol injection (PEI) under ultrasound (US) guidance is considered to be one of the most established regional therapies for nonadvanced HCC in patients with liver cirrhosis (9). This technique results in a long-term survival rate that is considered to be comparable with that of surgical resection (9,10). The PEI survival curves that have been reported in several studies appear to be better than those of patients who undergo surgery; this seems to be the case even in the absence of adverse prognostic factors (2). The recurrence rate after PEI is lower than that following surgery and the procedure itself is absolutely safe (9). In addition, its economic cost is low. These facts make this procedure attractive, especially for underdeveloped or poor countries in which cirrhosis and HCC are common diseases. Moreover, surgery requires careful patient selection, given that the results can be severely affected by the general condition of the patient. In fact, patient selection for PEI is simple. It is essentially based on tumour size and on the position of the tumour within the liver parenchyma. Prognosis is based on the Child-Pugh score (11).

Although newer ablative techniques such as radiofrequency ablation (RFA), cryoablation and laser interstitial ablation are now available for the treatment of HCC, PEI still represents a valid choice given that it is an inexpensive, easy-to-perform procedure (12).

RFA has recently been demonstrated to be as effective as PEI, even if it presents a slight, although not significant, trend to an increase in the number and severity of complications (12). Moreover, because PEI is a relatively inexpensive technique, it can be carried out even in clinical centres, as long as they are equipped with basic US equipment and minimally skilled operators (9). On the other hand, RFA requires skilled operators and rather expensive equipment.

Some other therapeutic modalities that are now widely proposed for the treatment of small to intermediate stage HCC, such as transarterial embolization (TAE) and transarterial chemoembolization (TACE), still require more investigation. Many important questions concerning TACE remain unanswered. Among these are patient selection criteria, the type of cytotoxic agents to be used and, most importantly, whether TACE is as effective in improving overall survival as it is in temporarily stopping cancer growth (13-15). In addition, repeated TACE procedures may result in a deterioration of cirrhotic liver function (13).

TAE and TACE of HCC are widely used, although several randomized controlled trials have not provided any definitive evidence regarding improvement in survival (16-18). Recently, TACE has been compared with conservative or symptomatic treatment; significant improvement in patient survival was demonstrated in carefully selected patients. However, the patient control groups in the studies received only symptomatic treatment (14,19,20). Because TAE and TACE are beneficial in controlling tumour growth, they may be useful in 'bridging' selected patients to OLT. There is also a trend to using this technique in cirrhotic patients in combination with PEI or RFA (21).

A considerable number of new scoring systems have recently been proposed for prognosis and outcome prediction in cirrhotic patients with HCC (22-28). However, the Child-Pugh score (11) is still, in general and according to our own

clinical experience, a useful tool for predicting prognosis in cirrhotic patients. A newer scoring system, the Italian Cancer of the Liver Program (CLIP) score, should be considered one of the most useful (24). It is generally considered to be a reliable predictor of survival in cirrhotic patients. However, it is not yet generally accepted because it does not offer better reliability than other systems in terms of prognosis (29,30).

The present study was performed to evaluate the survival and most predictive prognostic factors in a group of patients with viral liver cirrhosis and small to intermediate HCC, who were treated with PEI and followed up prospectively.

## PATIENTS AND METHODS

Of the 611 consecutive cirrhotic patients with HCC screened in the University of Florence School of Medicine between January 1993 and December 2002, 127 cirrhotic patients (42 women and 85 men; mean age: 63 years; range 51 to 92 years) with small to intermediate HCC but without any extrahepatic diffusion of the disease were enrolled in the study.

Patient criteria for inclusion in the present study were based on the presence of a single nodular HCC lesion that was smaller than 30 mm or the presence of multiple (up to three) nodular HCC lesions that had not exceeded 50 mm as the sum of the maximum diameter of each single lesion. All participants had confirmed class A or B liver cirrhosis according to the Child-Pugh score (11). The CLIP score (24) was also calculated. All participants in the study had a CLIP score of 2 or less. No patients with portal vein thrombosis, extrahepatic metastases, any symptom related to gastrointestinal bleeding, a prothrombin time of less than 16 s or a platelet count that was lower than  $40 \times 10^9/L$  were included in the study.

All patients had been judged to be unsuitable for OLT and/or surgical hepatic resection due to the liver cirrhosis, the presence of lesions in locations that were not amenable to hepatic resection, the coexistence of other diseases and/or no compliance with surgical procedure. No patient had been previously treated with PEI.

The decision to offer PEI instead of surgery to these patients was made after a thorough and careful assessment study of each case with a surgeon and a radiologist.

The OLT program was started in our region in 1997, and because of the scarcity of donors and the number of potential recipients, the waiting list since then has been roughly one year long. Informed patients are rarely willing to wait one year before doing something affecting their disease. Moreover, when the study was started, HCC was not considered to be a good indication for OLT. Milan criteria were published only in 1996 (31). Resection was considered to be too risky by the surgeon, and without evidence of a real advantage compared with PEI. Only recently were TAE and TACE shown to improve overall survival in patients with HCC and liver cirrhosis, although results of these procedures are still controversial (14,19).

Once they had been informed of their diagnosis and prognosis, all patients gave their consent to PEI rather than undergo surgery. Patient consent was obtained after a clear, thorough explanation of the program, its goals, the procedure and risks to be undertaken.

The number of tumour nodules and absence of portal vein thrombosis were confirmed on the basis of upper abdominal US scans and contrast-enhanced dynamic computed tomography (CT) scan findings. Tumour size, defined as the maximum diameter of the lesion, was assessed by upper abdominal US scans. Extrahepatic metastases were investigated and excluded by means of clinical assessment, chest x-ray, abdominal US, contrast-enhanced dynamic

CT and bone scintigraphy. The diagnosis of HCC was histologically proven in all patients.

The demographic and clinical features of patients are summarized in Table 1.

No patient had had renal failure, recent (within six weeks) gastrointestinal bleeding, hepatic encephalopathy or evidence of any disseminated intravascular coagulation. The diagnosis of disseminated intravascular coagulation was excluded by repeated platelet counts and measurements of fibrinogen levels as well as by normal D-dimer concentrations in at least two plasma samples that had been obtained just before blood sampling. Blood samples and a 24 h urine collection were obtained to evaluate liver and renal function in each subject. HIV infection was excluded in all patients on the basis of the absence of specific antibodies in the sera.

The study protocol was approved by the local Ethics Committee and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

### PEI

Sterile 100% ethanol was injected through a 22- or 23-gauge needle that had been inserted percutaneously into the nodule under US guidance. PEI was performed once per session. The patient underwent one or two sessions per week. A maximum of four to six sessions was needed to ablate the tumour during the program. The volume of ethanol to be injected was calculated according to the formula proposed by Shiina et al (32) and the number of treatment sessions depended on tumour size.

Follow-up contrast enhanced dynamic CT and upper abdominal US scans were performed one month after completion of PEI treatment and every three months thereafter until completion of the study. A lesion treated by PEI was considered to be fully ablated when it did not show any enhancement by contrast-enhanced liver CT. Upper abdomen US scan, alpha-fetoprotein (AFP) level evaluation, clinical examination and evaluation of liver function parameters were also carried out at those times.

Recurrent HCC, including local recurrence and the appearance of lesions at other liver sites, was diagnosed on the basis of either typical findings or dynamic contrast-enhanced CT and US, and confirmed by histopathological findings of specimens obtained by percutaneous liver biopsy, when not contraindicated. If a viable tumour was found, PEI was repeated. If no residual tumour was found, the patients underwent periodical monitoring as described above. Neoplastic seeding after PEI procedure was detected by physical examination, US scans, AFP serum level determination and, if necessary, biopsy (if not contraindicated) and histopathological examination. The choice of the treatment for recurrence was based on tumour size and stage, hepatic reserve and the patient's general condition and compliance.

### Statistical analysis

Actuarial survival curves were calculated by the Kaplan-Meier method and compared with the log-rank test. Differences were considered to be significant when two-sided  $P < 0.05$ . Data were analyzed using GraphPad Prism version 3.02 (GraphPad Software Inc, USA).

Pretreatment variables were chosen because of possible effects on prognosis: choices were based on previous studies or our own clinical experience. The pretreatment clinical and pathological variables that were evaluated for any effect on survival in this study included patient- and tumour-related variables. Patient-related factors included sex, the Child-Pugh score of cirrhosis and

**TABLE 1**  
**Demographic and clinical characteristics of the patients enrolled in the study**

	n (%)
Maximum tumour size (mm)	
≤30	80 (63.0)
30–50	47 (37.0)
Number of hepatocellular carcinoma nodules	
Single	98 (77.2)
Multiple	29 (22.8)
Total bilirubin (μmol/L)	
≤34	70 (55.1)
>34	57 (44.9)
Albumin (g/L)	
≤35	100 (78.7)
>35	27 (21.3)
Platelet count	
<50×10 <sup>9</sup> /L	15 (12.0)
50×10 <sup>9</sup> /L–100×10 <sup>9</sup> /L	32 (25.1)
>100×10 <sup>9</sup> /L	80 (62.9)
Alpha-fetoprotein (ng/mL)	
<20	80 (63.0)
20–100	28 (22.0)
>100	19 (15.0)
Child-Pugh classification	
A	79 (62.2)
B	48 (37.8)
Cancer of the Liver Program classification	
0	60 (47.2)
1	57 (45.0)
2	10 (7.8)

the presence of gastroesophageal varices. Tumour-related variables included the type (solitary or multiple nodules) and diameter of the tumour, and the presence or absence of a perinodular boundary. Each variable was divided into two or three subgroups (Table 2).

Survival was measured from the first session of the PEI treatment until death from HCC or to the last day of follow-up. Surviving patients or those who had died from diseases other than HCC were defined as censored cases. All P values presented in the present report are two-tailed;  $P \leq 0.05$  was considered to be significant.

### RESULTS

Cirrhosis was hepatitis C virus (HCV)-related in the majority of patients (115 patients, 90.6%), while the hepatitis B surface antigen was positive in the remaining 12 patients (9.4%). No patient had both the hepatitis B surface antigen and the anti-HCV antibody. None were known to have abused ethanol or drugs during the six months before the study or during it.

The majority of patients had a single tumour nodule (77.2%). Only 29 (22.8%) had two nodular lesions, and no patient had three nodules. The size of the treated tumours (considered as the sum of the maximum diameters of each single lesion if multiple lesions were present) ranged from 30 mm to 50 mm with a mean value ( $\pm$  SD) of 37.4 $\pm$ 9.6 mm. Complete tumour necrosis was achieved in all patients according to the findings of contrast-enhanced CT that was performed one month after the completion of PEI treatment,

**TABLE 2**  
**Survival of patients according to each prognostic factor considered in the present study**

Variable	Survival rate (%)				P
	1 year	3 years	5 years	10 years	
Age (years)					
≤60	82.8	62.3	25.0	0	0.8342
>60	88.5	48.1	27.4	0	
Sex					
Male	85.7	50.0	24.3	0	0.4001
Female	90.3	55.0	33.0	0	
Varices					
Absent or small	89.4	56.6	32.8	0	0.0139
Present	80.6	36.0	9.0	0	
Maximum tumour size (mm)*					
≤30	88.5	59.7	30.3	0	0.0480
30–50	85.1	37.6	20.9	0	
Number of hepatocellular carcinoma nodules					
Single	85.5	52.3	25.3	0	0.9218
Multiple	93.1	48.7	37.9	0	
Fibrotic boundary					
Present	89.3	59.7	33.7	0	0.0008
Absent	81.3	28.0	8.0	0	
Child-Pugh classification					
A	94.9	62.4	40.0	0	<0.0001
B	74.5	33.5	5.6	0	
Cancer of the Liver Program classification					
0	93.2	58.7	37.5	0	<0.0001
1	82.2	53.1	20.5	0	
2	80.0	0	0	0	
Platelet count (×10 <sup>9</sup> /L)					
<50	90.9	45.5	45.5	0	0.4818
50–100	82.4	45.1	18.8	0	
>100	92.7	56.6	25.4	0	
Alpha-fetoprotein (ng/mL)					
<20	92.3	62.0	33.9	0	0.0104
20–100	78.6	44.0	17.3	0	
>100	78.9	20.7	13.8	0	

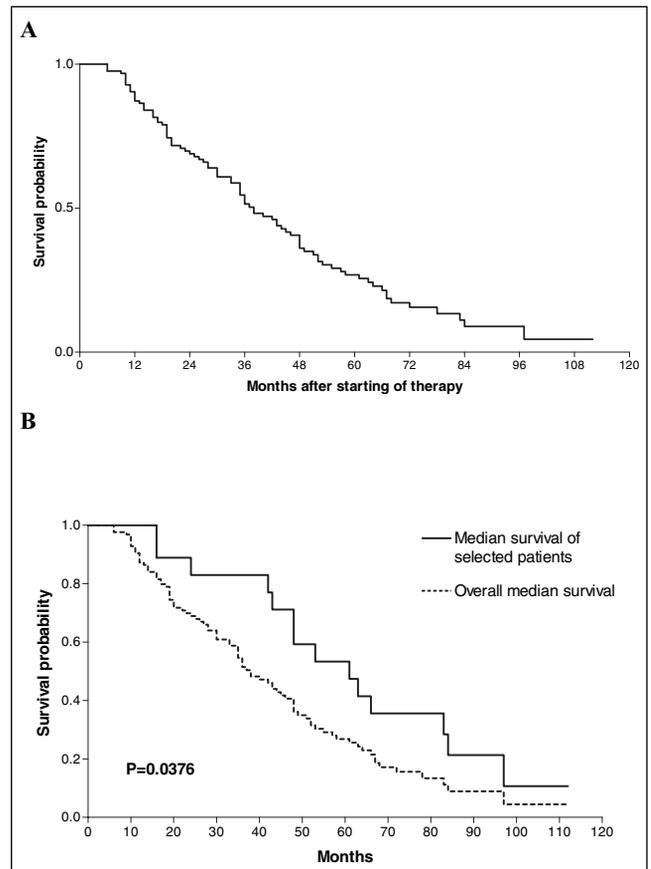
\*Size is reported as the sum of the diameters of the lesions.

and no new lesion was found in other sites of the liver parenchyma.

Local recurrence or a new lesion in other areas of the liver parenchyma was observed in 89 of 127 patients (70.1%) at least six months after the last PEI treatment. Local recurrence was observed in 17 patients (19.1%). New lesions in other areas of the liver parenchyma were observed in 72 patients (81.9%). Of the 156 nodules that were treated, a local recurrence was observed in 14 of the 95 lesions with a diameter of less than 30 mm (14.7%) and in 15 of the 47 lesions with a diameter of 30 mm to 50 mm (31.9%). A statistically different percentage of recurrences was observed in lesions with a diameter from 30 mm to 50 mm compared with those up to 30 mm (P=0.0169).

#### No relationship was found between treatment failure and AFP serum level

Sixty-five of the patients with recurring HCC were given PEI treatment again. Twenty-three patients with HCC recurrence did not meet the PEI criteria and received TACE. Hepatic



**Figure 1)** Overall median survival of the whole group of 127 enrolled study patients (A) and overall median survival curve of patients with the following optimal characteristics (B): a nodule with a diameter <30 mm and a perinodular bound, a serum alpha-fetoprotein of less than 20 ng/mL, a Child-Pugh A class score or a Cancer of the Liver Program score of 0 and the absence of small esophageal varices compared with the whole group of 127 enrolled study patients

resection was performed in only one patient, in whom the new HCC nodule was small and placed in a site within the liver parenchyma that was amenable to surgical resection. Two patients (1.5%) experienced a subcutaneous seeding of HCC as a consequence of PEI treatment or liver biopsy. They both underwent surgery and further recurrence of the tumour at the subcutaneous site did not occur.

At the time of writing, 88 patients (69.3%) had died: 43 (33.8%) due to the progression of HCC, 30 (23.6%) because of hepatic failure or variceal bleeding (without HCC progression) and 15 (11.8%) because of other causes that were not directly related to HCC. No patient had died within 30 days of the PEI administration. The median follow-up period from completion of PEI treatment was 33 months.

Overall median survival time was 28 months (range six to 112 months) (Figure 1). The differences in survival among the various subgroups with each prognostic factor were evaluated using log-rank tests. Median survival and one-, three- and five-year survival rates based on the considered prognostic factors are shown in Table 2.

The median survival (32 months, range six to 112 months) of the patients with absent or small varices (n=96) (32 months, range six to 112 months) is longer, even if not significantly, compared with the median survival (23 months,

range 10 to 77 months) ( $P=0.059$ ) of the group of patients with large varices ( $n=31$ ).

The presence of a lesion with a diameter of less than 30 mm ( $P=0.048$ ), an AFP serum level that was less than 20 ng/mL ( $P=0.0104$ ), a class A Child-Pugh score ( $P<0.0001$ ), the absence or presence of small esophageal varices ( $P=0.0139$ ) and the presence of a perinodular boundary ( $P=0.0008$ ) were among the prognostic factors associated with longer survival (Figure 2). Using the CLIP score or the Child-Pugh score, it is possible to observe that the better prognosis was in the CLIP 0 and 1 groups (Figure 2). Considering only the 19 patients who met the criteria of best prognosis, the overall median survival was 61 months (Figure 1). It is noteworthy that two of these patients survived longer than eight years (97 and 112 months, respectively).

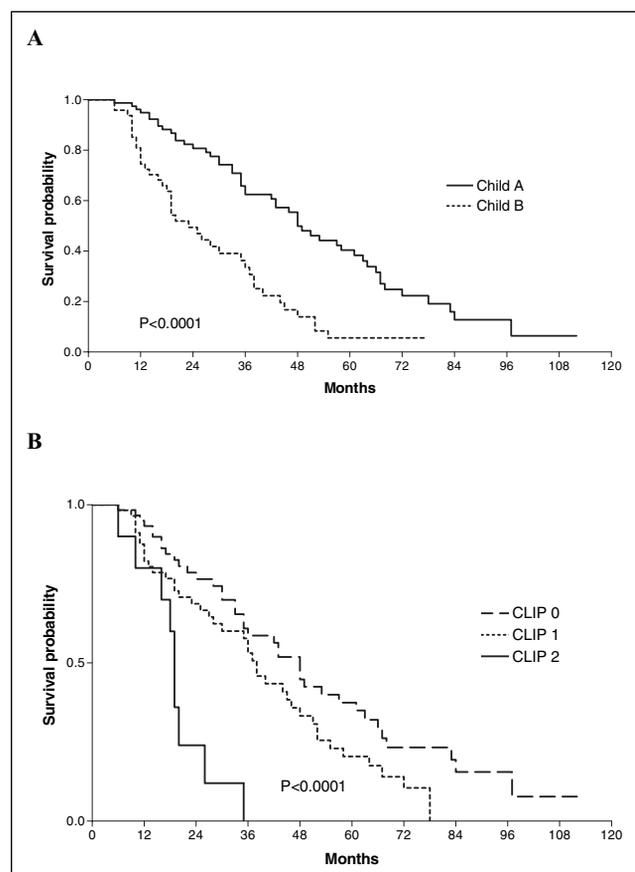
It is important to note that, considering the above mentioned prognostic factors, the group of patients with an AFP serum level less than 20 ng/mL before the PEI procedure had significantly longer survival and a lower rate of disease progression (Figures 3 and 4).

## DISCUSSION

Today, PEI is considered to be an alternative therapeutic strategy to surgery in cirrhotic patients with inoperable small to intermediate stage HCC (3). According to several studies reported in an extensive review (9), this technique is considered to be safe. It is generally associated with very low mortality (0.09% in the largest study) and low morbidity rates (9). This treatment can also be considered economically sound (9). In Italy, the cost of the entire treatment by PEI is approximately US\$1,000, while that of partial resection is approximately US\$30,000. OLT costs approximately US\$125,000 (9). Patients who undergo PEI are generally treated on an outpatient basis because most of them can carry out normal daily life activities, even as soon as a few hours after the procedure (9). The technique can also be performed in patients with poor liver function providing they have an acceptable coagulation profile. PEI does not result in any loss or important damage to non-neoplastic parenchyma, as is often the case in multisegmental resection or TACE.

Analyses of our data showed that both the mortality and the morbidity rates appeared to be even lower than those of other studies in which the PEI outcome had been analyzed (9,10). No deaths occurred during the 30 days following the procedure. No major complications were observed following the procedure. The only negative side effect during and immediately after PEI was the presence of pain. However, the pain was always mild and self-limiting. Repeated treatment did not affect either the mortality rate or morbidity of our patients. The survival of Child-Pugh class A patients was higher than that of class B. The CLIP score was also able to predict patient prognosis: CLIP 0 subjects had a better prognosis than CLIP 1 and 2 patients. Despite the existence of newer survival and outcome prediction models (23-27) for cirrhotic patients with or without HCC, the data presented in this study confirm that the Child-Pugh score is still valid. Even 30 years after its creation, it is an efficacious tool for predicting patient survival (33).

Based also on our own clinical experience, several deaths in HCC patients seem to be more related to cirrhosis and its complications (such as portal hypertension and liver failure) rather than to HCC itself. This may explain why the Child-Pugh score can compete well with newer models in predicting HCC patient prognosis.

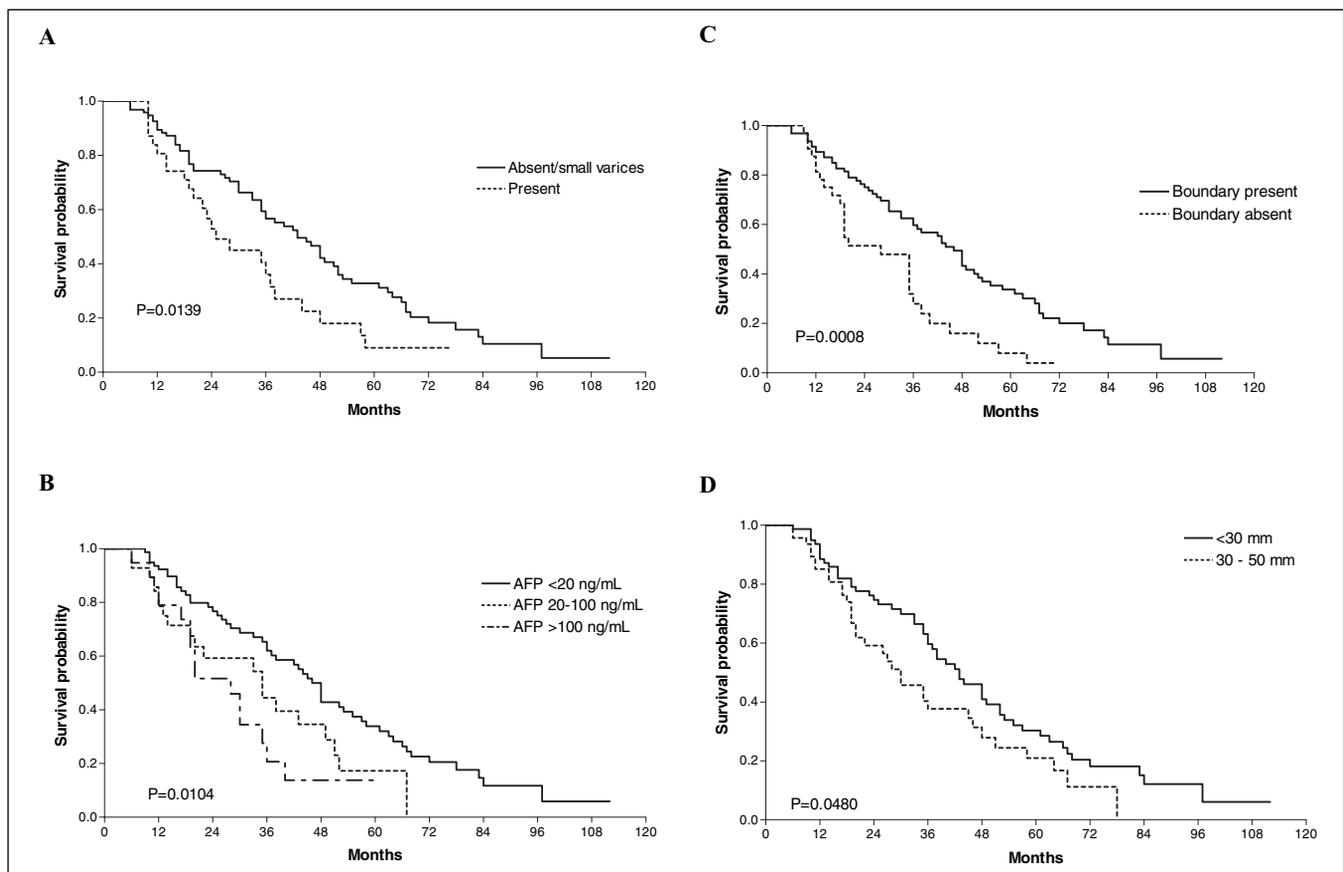


**Figure 2** Survival probability of patients according to the Child-Pugh (Child) score (A) or the Cancer of the Liver Program (CLIP) score (B)

A comparison of the risk factors involved in PEI and in newer ablative therapies such as RFA (regardless of any benefits) clearly indicates that such factors are minimal with PEI, while RFA still entails some degree of risk (34).

A recent multicentre study (34) involving 2320 patients with 3554 HCC lesions who had undergone RFA demonstrated that RFA must still be considered a rather complex procedure that requires substantial experience for it to be performed safely. The study reported six deaths (0.3%) among the patients studied. Fifty patients (2.2%) had additional major complications including peritoneal hemorrhage, neoplastic seeding, intrahepatic abscesses and intestinal perforation. A higher rate of major complications was correlated with repeated treatment. Minor complications were observed in less than 5% of the patients. The study concluded that RFA is a relatively safe procedure with a lower complication rate than the rate reported for surgery and equivalent to the rate reported for single-shot PEI. However, RFA showed a slight, although not significant, increase in mortality and morbidity without any increase in efficacy (34). Furthermore, the study concluded that additional refinement in technique and patient selection must be carried out to achieve the safety equivalent of multi-session PEI. We experienced two cases (1.5%) of seeding at the subcutaneous site after PEI. However, the patients underwent surgery and no further subcutaneous localization was present during follow-up.

The role of TAE and TACE as alternative therapeutic strategies for small and intermediate inoperable HCC has not



**Figure 3)** Survival probability of patients according to the absence or presence of small varices in comparison to the presence of large varices (A), alpha-fetoprotein (AFP) pretreatment level (B), the presence of a perimodular boundary (C) and the size of the lesion (D)

yet been definitively proven. Although the technical aspects of the procedure have significantly improved, there are still many unanswered questions regarding their efficacy. Besides having no definitive patient selection criteria, an ideal cytotoxic agent has not yet been identified. In addition, the optimal dose of ethiodized oil and the optimal frequency and timing of repeated treatment sessions are still a source of debate. Furthermore, significant survival benefits for patients that undergo TACE for intermediate HCC have been demonstrated when compared with those treated only symptomatically (14,19,20). TACE in combination with PEI has been reported to be superior to PEI alone in the treatment of patients with small HCC tumours, especially for patients with HCC tumours that measure less than 2 cm in diameter (35,36). Results of a combination of RFA and PEI have been similar to those achieved by the above-mentioned procedures (37).

Moreover, TAE and TACE require sophisticated angiographic equipment and a skillful radiologist, while PEI is easy to perform and requires a rather short training period.

The low rate of complications reported in the present study is mainly related to the technique by itself rather than the operator's skill, because our unit is also involved in postgraduate teaching. While the supervisors (Roberto Mazzanti, Umberto Arena) remained the same during the study, the operator periodically changed.

Finally, repeated TACE treatments may result in deterioration of liver function, especially in those patients with moderate

to severe liver dysfunction (38,39). The combination of limited TACE with PEI or TACE with RFA may avoid this risk and lead to improved survival (40). However, there is still no definitive evidence on this issue. The association of PEI and RFA demonstrated a higher five-year survival rate compared with TACE alone, but a lower one than the multisession PEI treatments (40). With respect to chemotherapy, we recently demonstrated that intra-arterial administration of 5-fluorouracil and folinic acid can be a therapeutic strategy for patients with inoperable locally advanced HCC (41).

It is interesting to note that the absence of a significant degree of portal hypertension and AFP serum level turned out to be the most important of the considered prognostic factors. In the present study, a significant degree of portal hypertension, expressed as the presence of large gastroesophageal varices, had a significant impact on patient survival. In our opinion, this is an important observation because it suggests that in cirrhotic HCC patients with the presence of portal hypertension, OLT should be considered the best therapeutic procedure because both surgical resection and ablative techniques do not produce any improvement in survival. OLT is considered to be the best treatment for patients who meet the Milan criteria (a solitary nodule smaller than 5 cm in diameter HCC or fewer than three tumours each smaller than 3 cm, younger than 60 years of age) with a five-year survival rate of approximately 75% (42). However, the time between candidacy and transplantation introduces a variable that is related to

survival: a waiting list that exceeds six to 10 months negates the increase in life expectancy provided by OLT due to the risks that patients face while on the waiting list (42). In Italy, the scarcity of donors and the number of patients with cirrhosis on waiting lists dramatically reduces the possibility of a patient with HCC undergoing OLT in comparison with other European Community countries (eg, Spain) (43).

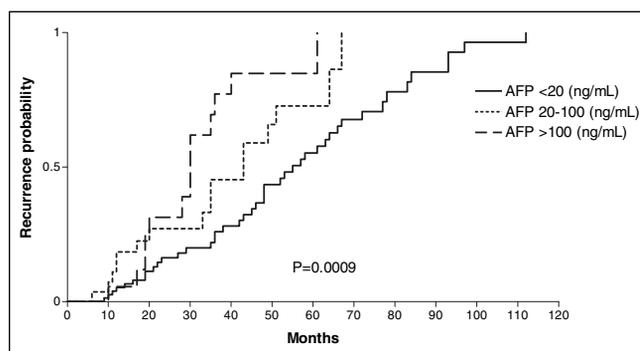
Because the OLT program was started in our region only four years after the beginning of the present study, a minority of our patients have had the chance to be evaluated for OLT. In our experience, the wait lasted more than 12 months. Moreover, it must be considered that the median age of patients of this study was only slightly under the upper age limit for OLT.

Even if a minority of our patients met the Milan criteria for OLT at the beginning of the study, once they were informed about their disease, the OLT procedure and the risk of a long wait for an OLT, most of them decided to undergo PEI. In our own clinical experience, seven of the 611 patients screened (1.1%) were conducted for OLT, but only three finally received OLT (0.4%).

With respect to other, newer, therapeutic modalities, recent data suggest that the administration of antiviral therapy (alpha interferon), in association with intrahepatic chemotherapy after HCC ablation, can be effective in reducing the rate of HCC recurrence (44). This strategy has also been associated with local ablation techniques with a reduction of HCC recurrence (45). According to these observations, the HCC recurrence rate after PEI treatment can be reduced, and this fact could be demonstrated by randomized studies.

Our patients, even if carefully selected, had a rather low median survival. This may be due, in part, to a relevant proportion of patients (26.4%) with large varices and several other small varices (significant portal hypertension). Patients with large varices had a lower median survival rate than did patients with varices that were small or absent; interestingly, this turned out to be of strong prognostic significance. This finding is not new, as others have shown how important portal hypertension is in the prognosis of patients with HCC (46). In addition, the mean age of our patients was 63; 48 (37.8%) of those were Child B and 91% had chronic HCV infection. Clearly, aged patients with a Child B cirrhosis are exposed to a higher risk of liver decompensation compared with younger patients with a well-compensated cirrhosis. It should be noted that 91% of patients included in this study had HCV-related cirrhosis. HCC is considered to be a late complication of chronic HCV infection, occurring in the advanced steps of the liver disease. Moreover, chronic HCV infection causes angiogenesis in the liver (47) and it has been shown in several cancers that angiogenesis is a marker of bad prognosis (48).

In the present paper, we also analyze the prognostic value of serum AFP. The presence of even a mild increase in serum AFP (above 20 ng/mL but less than 100 ng/mL) before PEI results in a worse prognosis in these patients. We can hypothesize that HCC nodules that produce AFP have a poorer prognosis because of more aggressive biological behaviour compared with those that do not produce it. However, because PEI completely ablates the HCC nodule, other hypotheses should be investigated. We may not exclude, for instance, that even a slight increase in the serum level of AFP could be considered as a marker of liver decompensation and/or portal hypertension (ie, because AFP is metabolized by liver, the increase in the



**Figure 4)** Probability of recurrence according to various alpha-fetoprotein (AFP) levels

AFP level may be due to the opening of intrahepatic shunts). It is possible that a slightly increased AFP level is a marker for the presence of disseminated HCC micronodules within the liver parenchyma that are not yet visible by US or CT. Moreover, AFP itself may also play a role in affecting patient survival. This protein, although generally known as a tumoural marker, was originally described as a protein with immunosuppressive action, and it may play a role in affecting the prognosis of cirrhotic patients as shown in early studies (49,50). However, the points raised by those early studies have not been further investigated. The present study was not designed to answer these questions. Still, the idea that AFP could act as a depressor of systemic defense against cancer is most intriguing. This should be considered when designing new prospective studies on therapeutic strategies of small HCC.

The results of the present study also confirm the role of the Child-Pugh classification in assessing the prognosis of patients with liver cirrhosis and HCC. A comparison of the Child-Pugh classification to a newer classification system, such as CLIP, shows both scores to be reliable in estimating patients' survival.

## CONCLUSION

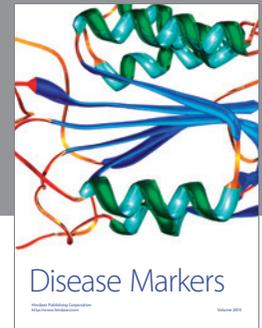
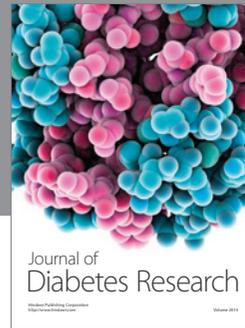
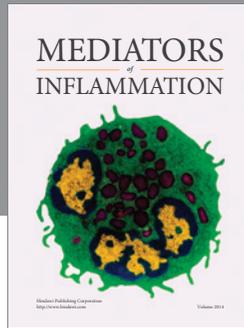
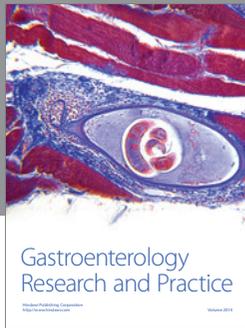
The results of the present study show that PEI still represents, even 20 years after its introduction, a safe and efficacious therapy for small and intermediate HCC, when used in selected patients. They also show that PEI is still one of the safest and lowest cost techniques for the treatment of small- and intermediate-stage HCC.

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