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Transcatheter arterial embolisation versus no treatment in cirrhotic patients with hepatocellular carcinoma: a retrospective comparative study

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Abstract. To evaluate the effectiveness of transcatheter arterial embolisation (TAE) as a treatment of hepatocellular carcinoma (HCC) complicating cirrhosis, the survival of 27 untreated patients and 57 TAE-treated patients was compared. Clinical features, laboratory findings and tumour stage were comparable in the two groups of patients. TAE was undertaken with epirubicin, iodised oil and gelatine esponge. Cumulative survival rates at 6, 12, 24 and 36 months were 0.59, 0.47, 0.17 and 0.08 in the untreated group, and 0.87, 0.75, 0.40 and 0.19 in the TAE-treated group ($P = 0.01$). Patients with Child's grade B cirrhosis and patients with tumour smaller than 25 % of the liver volume responded better to TAE. Twenty-four untreated patients and 25 TAE-treated patients died during the follow-up. The complication rate and mortality rate of TAE were 28 % and 1.7 % respectively. TAE prolongs the survival of patients with HCC complicating cirrhosis; prognosis depends on tumour stage and the degree of hepatic function impairment.

Key words: Chemoembolisation – Embolisation, hepatic artery – Hepatocellular carcinoma – Iodised oil

Introduction

Transcatheter arterial embolisation (TAE) is an accepted therapy for unresectable hepatocellular carcinoma (HCC). When compared with classical studies on the natural history of HCC [1–3], TAE is very effective in improving patient survival [4–8]. Recent observations [9–12] have enhanced our understanding of untreated HCC, mostly because an early diagnosis is nowadays possible with ultrasonography and serum testing; also these observations showed a spontaneous survival better than classical studies. A reappraisal of the validity of TAE should therefore take these data into account.

In order to verify the effectiveness of TAE we compared the survival rates of two homogeneous groups of patients with HCC complicating cirrhosis, one of which received no specific therapy while the other received TAE as primary treatment.

Methods

Untreated patients

Twenty-seven cirrhotic patients with histologically proven HCC (21 men, 6 women; mean age 63.3 years ± 8.3 SD) were observed at our University Hospital during the period 1987 to 1990. All patients were evaluated with ultrasonography and dynamic CT; they refused any specific antitumoral therapy and fulfilled the following criteria: Okuda stage I or II; patency of the portal vein, with preserved portal flow as assessed by duplex ultrasound; non-specific anticancer therapy.

Angiography was performed in only a few cases; no patients underwent hepatic arterial administration of iodised oil. According to Child's grading, cirrhosis was classified as grade A in 11 cases, grade B in 12 cases and grade C in 4 cases. HCC was unifocal in 14 cases and multinodular in 13 cases; 7 patients (4 with Child's grade A cirrhosis, 3 with grade B) with a small HCC were suitable for hepatic resection but refused surgery.

TAE-treated patients

Fifty-seven cirrhotic patients with HCC (50 men, 7 women; mean age 60.9 years ± 9.4 SD) underwent TAE between April 1989 and October 1992, according to previously reported criteria [6]; all patients were ineligible for surgery or percutaneous ethanol injection, and gave their informed consent. There were 11 patients with Child's grade A cirrhosis, 40 with grade B and 6 with

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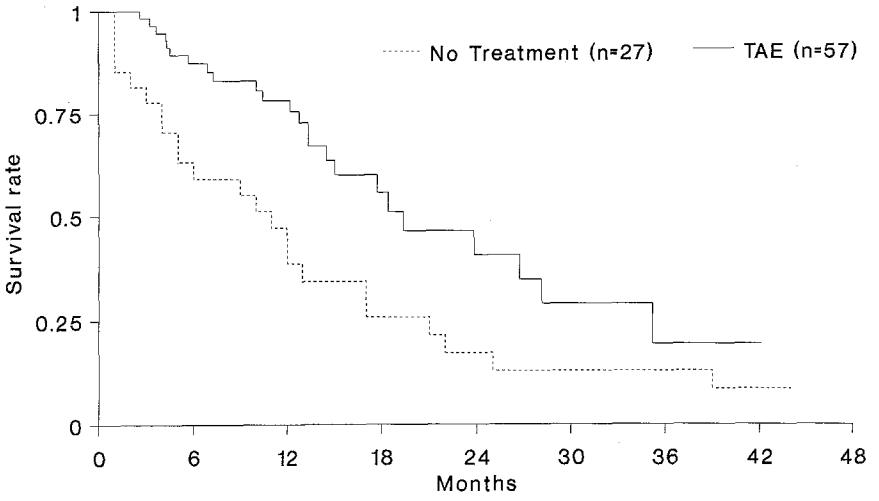

Fig. 1. Cumulative survival rate of untreated and TAE-treated patients with HCC complicating cirrhosis ($P = 0.01$)

Table 1. Comparison of the essential features of untreated patients and TAE-treated patients

	Untreated patients	TAE-treated patients	*P* value
Number	27	57	
Mean age (yr)[a]	63.3 ± 8.3	60.9 ± 9.4	NS
Male/female	3	7	NS
Albumin (gm/l)[a]	35.4 ± 5.3	37.7 ± 4.5	NS
Total bilirubin (mg/dl)[a]	1.60 ± 0.96	1.34 ± 0.90	NS
Prothrombin time (%)[a]	64 ± 12	72 ± 9	NS
Ascites	12	14	NS
Child's grades			
A	11	11	
B	12	40	0.065
C	4	6	
Tumour/liver volume			
< 25 %	15	32	
25 %–50 %	6	15	NS
> 50 %	6	10	

NS, not significant
[a] Values are the mean ± SD

grade C. HCC was unifocal in 21 cases, multinodular in 35 cases and diffuse in 1 case.

Ninety-nine TAEs were performed (range 1–6, mean 1.7 TAE per patient) using epirubicin (Farmorubicina, Farmitalia, Carlo Erba, Milan, Italy), iodised oil (Lipiodol UF, Guerbet, Aulnay sous Bois, France) and gelatine sponge. The mean epirubicin dose per procedure was 47 mg ± 15 (SD); the volume of iodised oil ranged from 5 to 15 ml.

Repetition of TAE was precluded by worsening of hepatic insufficiency in 9 cases, extrahepatic tumour spread in 6 cases, low patient compliance in 4 cases and portal vein thrombosis in 1 case.

All patients were evaluated with abdominal CT prior to TAE, at 2 weeks after each TAE and then every 3 months.

Therapeutic effect

Response to TAE was evaluated by tumour volume change for patients with a CT follow-up of 3 months at least. Complete response was assessed by the disappearance of the lesion, partial response by a decrease in its size of more than 50 %, no change by a decrease in its size of less than 50 %, and progressive disease by tumour growth or evidence of extrahepatic metastases.

Statistical analysis

An unpaired Student's t-test and chi-squared test (with Yates' correction when appropriate) were used to compare features of untreated and TAE-treated patients. Survival distribution function was calculated with the actuarial product-limit estimator using SAS (SAS Institute, Inc.) software; survival of the two groups was compared with a log-rank test. Statistical analysis was considered significant when the P value was less than 0.05.

Results

The two groups of patients did not differ statistically with regard to essential clinical features, serum chemistry values and histopathological data (Table 1).

Survival

Survival rates (± SE) at 6, 12, 24 and 36 months were 0.59 (± 0.095), 0.47 (± 0.097), 0.17 (± 0.077), and 0.08 (± 0.057) in the group of untreated patients (median survival 10.2 months) and 0.87 (± 0.045), 0.75 (± 0.063), 0.40 (± 0.098) and 0.19 (± 0.103) in the group of TAE-treated patients (median survival 18.5 months) (Fig. 1). The actuarial survival of the two groups of patients was significantly different ($P = 0.01$).

According to Child's cirrhosis classification the difference in survival was significant for patients with grade B cirrhosis ($P = 0.0001$) (Fig. 2), whereas in terms of hepatic

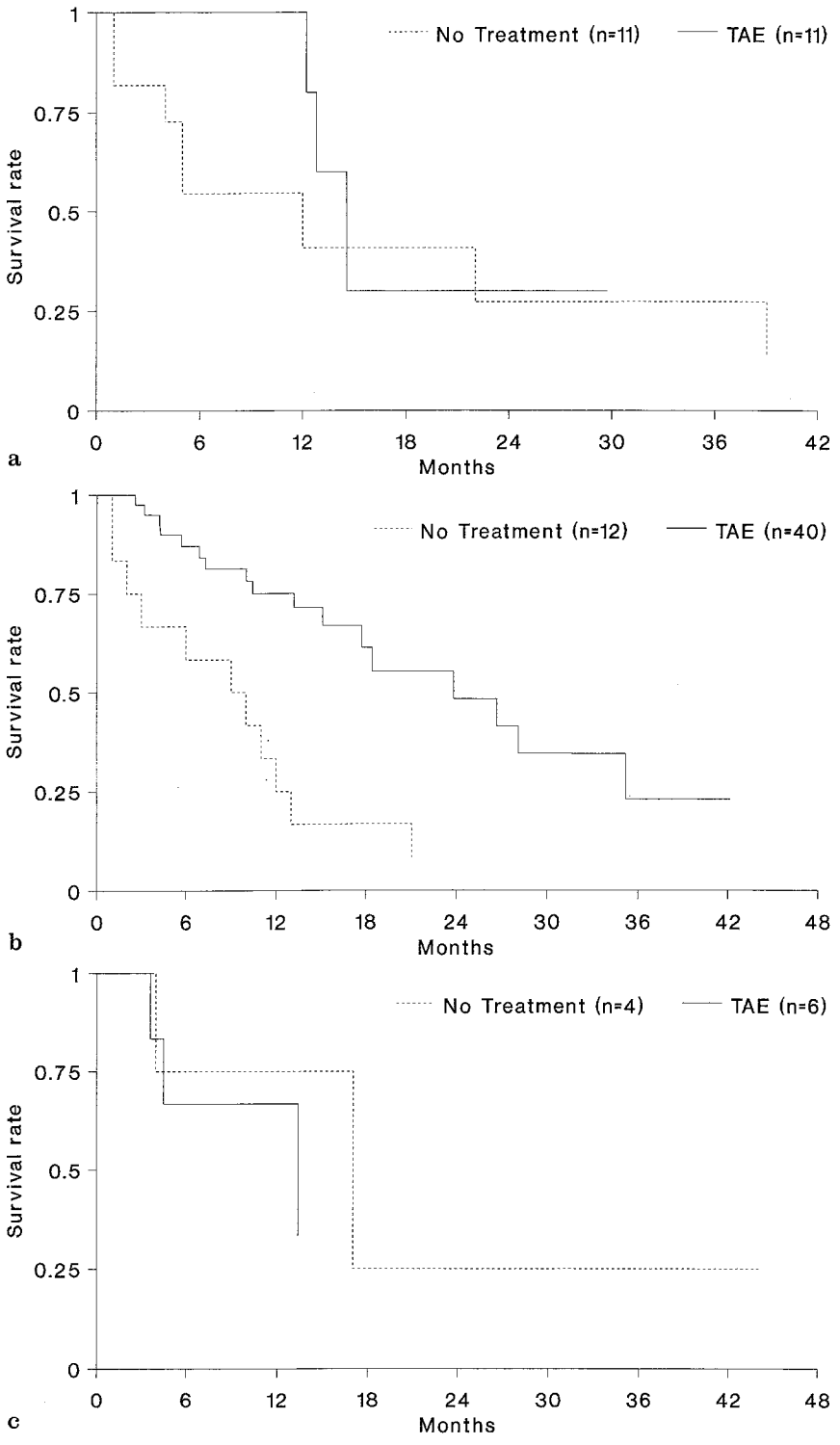

Fig. 2 a–c. Actuarial survival rates of untreated and TAE-treated patients according to Child's classification: **a** grade A ($P = 0.20$); **b** grade B ($P = 0.0001$); **c** grade C ($P = 497$)

tumour replacement a difference was observed only in patients with the smallest tumours ($P = 0.05$) (Fig. 3).

Cause of death; complications of TAE

Tables 2 and 3 show the distribution of the causes of death according to Child's grades and the hepatic tumour replacement initially assigned. Twenty-four untreated patients died during follow-up, all from hepatic failure. Twenty-five TAE-treated patients died from hepatic failure (19 cases), rupture of oesophageal varices (2 cases), rupture of the tumour, hepatic abscess, cardiac arrest or cachexia (1 case each).

Hepatic failure developed after TAE, and precluded further TAE treatment, in 9 patients (initially classified as grade A in 1 case, grade B in 6 cases and grade C in 2 cases); all underwent one procedure alone.

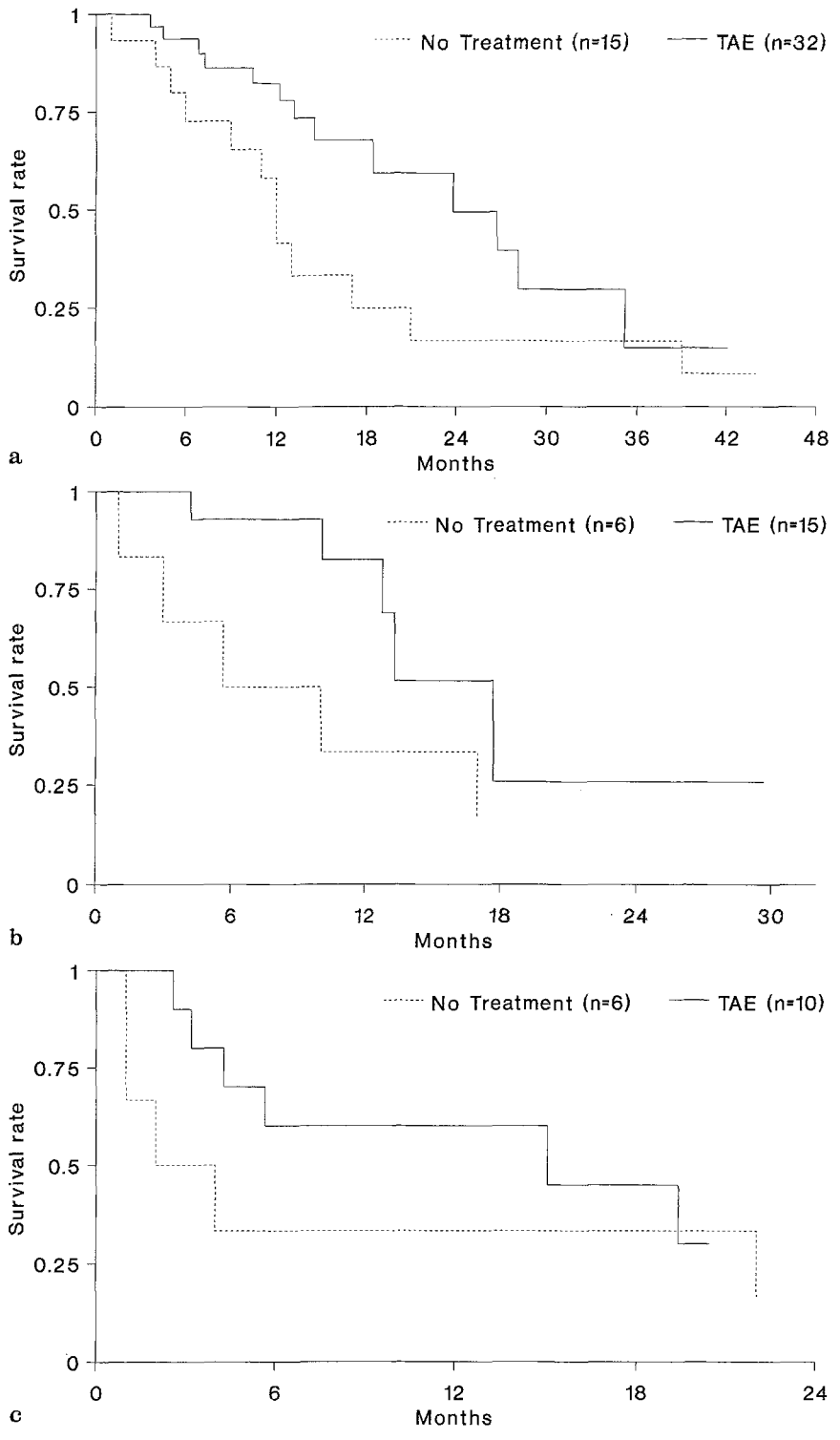

Fig. 3a–c. Actuarial survival rates of untreated and TAE-treated patients grouped according to hepatic tumour replacement: **a** hepatocellular carcinoma (HCC) size less than 25% of the liver ($P = 0.05$); **b** HCC size between 25% and 50% of liver ($P = 0.12$); **c** HCC size greater than 50% of the liver ($P = 0.23$)

Twenty TAE-related complications occurred in 16 patients (28%): prolonged fever (6 cases), cholecystitis (3 cases), ascites (3 cases), focal pancreatitis (2 cases), prolonged pain (2 cases), bleeding peptic ulcer, leucopenia, hepatic abscess and splenic infarction (1 case each). All but one of the complications were conservatively treated and had a favourable outcome; the patient with hepatic abscess after TAE underwent multiple transcutaneous drainage but died from sepsis 1 month after the chemoembolisation (mortality rate 1.7%).

Therapeutic effect of TAE

Response to TAE was evaluated in 46 patients. A complete response was never observed; a partial response was found in 5 patients, no change of tumour volume in 22 patients, and progressive disease in 19 patients.

Table 2. Distribution of the causes of death according to the Child's grade initially assigned

Cause of death	Untreated group (24/27)			TAE-treated group (25/57)		
	A (9/11)	B (12/12)	C (3/4)	A (3/11)	B (18/40)	C (4/6)
Hepatic failure	9	12	3	1	14	4
Bleeding from OV					2	
Other causes				2	2	

OV, oesophageal varices

Table 3. Distribution of deaths according to the hepatic volume replaced by tumour

	Untreated group (24/27)	TAE-treated group (25/57)
< 25 %	12/16	13/32
25–50 %	6/6	5/15
> 50 %	6/6	7/10

Discussion

Transcatheter chemoembolisation has become the procedure of choice for treating cirrhotic patients with HCC not suitable for surgical resection or percutaneous ethanol injection. Efficacy of TAE is usually assessed by comparison with historical reports on the natural history of untreated HCC [1–3], since only a few studies were tailored to the comparison with untreated patients, particularly in Western countries [3, 12–15]. To the best of our knowledge only one study was designed to verify the efficacy of TAE in a randomised trial [14], the result being discouraging; nevertheless the results of this study should be very carefully evaluated, since not all patients were cirrhotic and the survival rate was not a subset according to Child's classification.

The results of the present study indicate that TAE is an effective therapy for patients with inoperable HCC, and confirm the findings of other authors [5, 8, 13, 15, 16]. Child's grade A cirrhosis does not affect long-term survival after TAE (Fig. 2a); nevertheless, although statistical analysis does not support a difference in our series (but a type II error cannot be excluded), 1-year survival shows a very good trend in the TAE-treated group.

On the other hand, patients with grade B cirrhosis are the best responders to TAE at long-term follow-up, as reported also by Ohnishi et al. [13]. No definitive conclusions can be drawn for Child's grade C patients because of the small number of cases recruited in the present study.

With regard to tumour size, TAE is shown to be very effective palliation for confined HCC not suitable for surgical resection or percutaneous ethanol injection, the 3-year survival being significantly better than the spontaneous survival in our series. Conversely, we did not observe a significant improvement in survival for patients with large HCC treated with TAE. Nevertheless, the trend of survival after TAE seems to be more favourable than spontaneous survival: therefore, although further experience is needed, TAE should be recommended for patients with large HCC for which other therapeutic options are not always available.

TAE is burdened by a high periprocedural complication rate, the mortality rate being clinically acceptable. Most complications, both minor and major, are usually controlled with conservative treatment. A further complication may be the increased impairment of hepatic function in the long term; in the present series cirrhosis decompensated some months after TAE in 9 patients, 8 of which were in Child's classes B or C at enrolment.

A tumoral response to chemoembolisation, evaluated as the change in tumour volume, was only occasionally observed in the present series, but it does not seem to be related to survival [14]. However, as we evaluated tumour size with a CT scan alone, the necrosis rate after TAE was very difficult to assess because of the high enhancement from Lipiodol retention. Moreover it is well known that TAE induces a coagulation necrosis of HCC [17, 18] which entraps the iodised oil, making tumour density of no use in terms of necrosis and the tumour size stable for a long period. Nevertheless oil retention by the tumour correlates well with survival [7].

Spontaneous survival rates of patients with HCC vary in the reported series [2, 3, 7, 9, 10]. Differences in spontaneous survival in previous reports can be related to early diagnosis, therapeutic amelioration of the cirrhosis and its complications (such as sclerotherapy for gastro-oesophageal varices) and different geographic features of HCC. Therefore, great care should be exercised in comparing the results of a study with historical controls.

In conclusion, TAE is a palliative therapy effective in prolonging the survival of patients with HCC complicating cirrhosis; prognosis is usually related to tumour size and liver function impairment. The complication rate of TAE is high, but both minor and major complications can be controlled with conservative treatment; mortality is exceedingly low.

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