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Multicentre randomised phase III trial comparing Tamoxifen alone or with Transarterial Lipiodol Chemoembolisation for unresectable hepatocellular carcinoma in cirrhotic patients (Fédération Francophone de Cancérologie Digestive 9402)

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ABSTRACT

The FFCD 9402 multicentre phase III trial was designed to compare the effects of the combination of Transarterial Lipiodol Chemoembolisation (TACE) and tamoxifen with tamoxifen alone on overall survival and quality of life in the palliative treatment of hepatocellular carcinoma with cirrhosis. From 1995 to 2002, 138 patients were randomised between the two groups. One hundred and twenty three patients were eligible including 61 in the Tamoxifen group and 62 in the TACE group. Baseline characteristics were similar: Child-Pugh class A: 70%, alcoholic cirrhosis: 76%, Okuda stage I: 71%, multinodular tumour: 70% and segmental portal vein thrombosis: 10%. At 2 years, the overall survival was 22% and 25% in the Tamoxifen and TACE groups ($P = .68$), respectively. Multivariate analysis identified four independent prognostic factors for survival: α-fetoprotein (AFP) > 400 ng/mL ($P = .008$), abdominal pain ($P = .011$), hepatomegaly ($P = .023$) and Child-Pugh score ($P = .032$). The Spitzer Index level assessing the quality of life during follow-up did not differ between the two groups ($P = .70$). Amongst patients with stage Okuda I, the 2-year overall survival was 28% in the Tamoxifen group and 32% in the TACE group ($P = .58$). In this subgroup, two prognostic factors were statistically significant for survival: AFP > 400 ng/mL ($P = .004$) and Spitzer Index ($P = .013$) as shown by multivariable analysis.

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In conclusion, this study suggests that TACE improves neither the survival nor the quality of life in patients with HCC and cirrhosis.

1. Introduction

The prognosis of hepatocellular carcinoma (HCC) is poor because curative therapies are dedicated to a small proportion of patients with early stage of the disease.[1] At intermediate or advanced stages there is no standard treatment.[1,2] Transarterial Lipiodol Chemoembolisation (TACE) is a controversial intervention with still uncertain efficacy,[3–9] even if the two most recent randomised controlled clinical trials (RCT) identified overall survival (OS) benefit.[8,9] Two meta-analyses [10,11] showed that chemoembolisation significantly improved OS although a third meta-analysis[12] failed to demonstrate a significant advantage. The efficacy of antiestrogen therapy in advanced HCC is also controversial. In the early 1990s, a positive effect was attributed to tamoxifen.[13,14] However, the recent meta-analyses of Llovet and colleagues[11] and Nowak and colleagues[15] and a large RCT,[16] concluded that tamoxifen therapy did not provide any significant survival benefit.

Thus, we conducted a French multicentre randomised controlled phase III trial to compare the effect of the

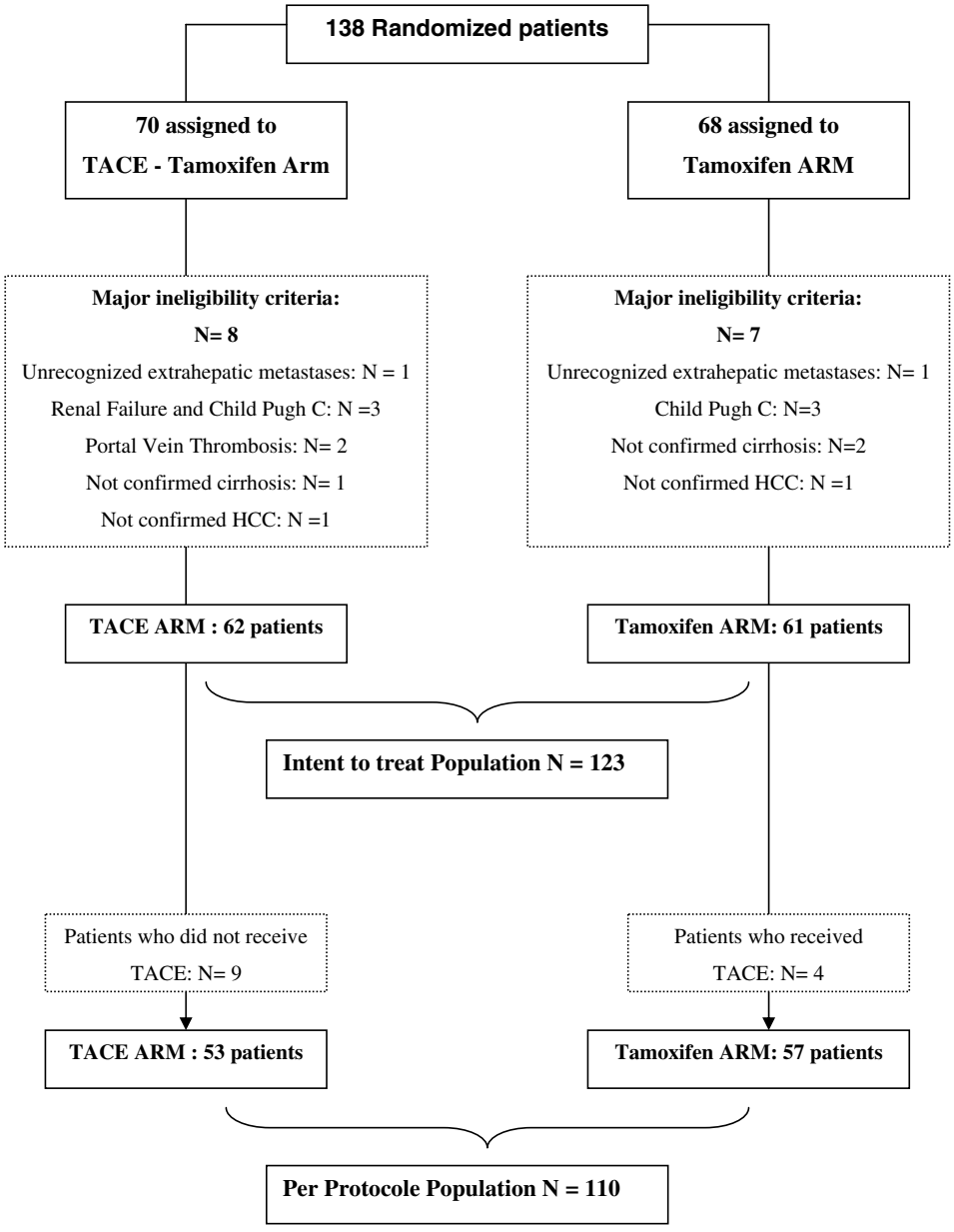

Fig. 1 – Trial flow-chart.

Table 1 – Baseline characteristics of patients in the TACE and the Tamoxifen groups

	TACE group, N = 62	Tamoxifen group, N = 61
Demography		
Age, years[a]	64.9 (7.3)	63.9 (7.0)
Sex, men	52 (84)	55 (90)
Causes of cirrhosis		
Alcohol	45 (73)	48 (79)
Hepatitis C virus	6 (10)	7 (11)
Hepatitis B virus	3 (5)	3 (5)
Other	7 (11)	3 (5)
Tumour-related symptoms		
Jaundice	3 (5)	7 (11)
Ascitis	8 (13)	8 (13)
Abdominal pain	13 (21)	10 (16)
Hepatomegaly	41 (66)	39 (64)
Biochemistry		
Serum bilirubin[a] (mg/L)	15.3 (9.9)	14.4 (9.1)
Prothrombin activity[a] (%)	78.9 (10.9)	80.9 (12.5)
Serum albumin[a] (g/L)	37.1 (5.7)	38.1 (5.8)
α-Foetoprotein concentrations[a] (ng/mL)	188 (353)	153 (296)
Tumour stage		
Uninodular	20 (32)	17 (28)
Multinodular		
Unilateral[b]	15 (24)	20 (33)
Bilateral[b]	27 (44)	24 (39)
Disease characteristics		
Child-Pugh class		
A	46 (74)	40 (68)
B	16 (26)	19 (32)
Okuda stage		
I	46 (74)	42 (69)
II	16 (26)	19 (31)
Diameter main nodule ⩾5 cm	36 (58)	41 (67)
Involved liver volume >50%	8 (13)	7 (11)
Segmental portal thrombosis	7 (11)	6 (10)
Performance and quality of life		
WHO[c] performance status		
0	18 (33)	27 (49)
1	32 (58)	26 (47)
2	4 (7)	2 (4)
3–4	1 (2)	0 (0)
Missing	7	6
	N = 48	N = 46
Spitzer QoL Index[a]	8.33 (1.4)	8.78 (1.3)

a Mean (SD).
b 1 or 2 lobes.
c World Health Organization.

TACE-tamoxifen with tamoxifen alone on OS and quality of life (QoL) in patients with unresectable HCC.

2. Patients and methods

2.1. Selection of patients

Inclusion criteria were patients with liver cirrhosis (diagnosis of cirrhosis was obtained by histopathology, clinical presentation or laboratory findings) and unresectable HCC based on biopsy, or persistently elevated serum α-fetoprotein (AFP) levels (>500 ng/mL) with one typical imaging finding (ultrasonography, CT scan or magnetic resonance imaging). These criteria were near from the Barcelona criteria.[1] A signed informed consent was required.

Exclusion criteria were age older than 75 years, advanced liver disease (Child-Pugh class C),[17] advanced HCC (Okuda stage III),[18] portal vein thrombosis (trunk and primary branches) or arteriovenous shunting, extrahepatic metastases, renal failure (serum creatinine level >120 μmol/L or creatinine clearance <80 mL/s), platelet count $<50 \times 10^9$/L, prothombin activity <50% and cardiac ejection fraction <35%.

2.2. Randomisation

After checking the eligibility criteria, randomisation was performed at the Fédération Francophone de Cancérologie Digestive (FFCD) data centre in Dijon, France. A stratified by centre and Okuda stage minimisation procedure was used.[19] The protocol was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale d'Alsace no. 1 (February 14, 1995) and endorsed by Good Clinical Practice.

2.3. Treatment procedure

Tamoxifen was administered orally at a daily dose of 20 mg in both arms. TACE was prepared by mixing epirubicin 50 mg (Farmorubicine, Pharmacia SAS, Saint-Quentin-en-Yvelines, France) with 15 mL lipiodol (Lipiodol Ultrafluid, Laboratoire Guerbet, Aulnay-sous-Bois, France) in a volume ratio of 1:1. Embolisation was performed by injection of Gelfoam cubes. Following the procedure, patients received 3–4 L/d of intravenous fluid, i.v. furosemide and analgesics if needed. Ceftriaxone (2 g/d) was administered intravenously for 2–3 d and then orally for 7–8 d. The first course of TACE was performed within 7 d following randomisation. TACE was repeated every 2 months until tumour stabilisation (stable size of the lipiodol deposition zones by two consecutive CT scans or prolonged normalisation of serum AFP levels). After checking for the absence of hepatic insufficiency, an additional TACE was performed following a 2-month period for

Table 2 – Reasons for stopping treatment in the TACE and the Tamoxifen groups

	TACE group, N = 62 N (%)	Tamoxifen group, N = 61 N (%)
Death	19 (33)	42 (79)
Liver failure	11 (19)	3 (6)
Patient refusal	8 (14)	1 (2)
Arterial hepatic obstruction	7 (12)	0 (0)
Portal thrombosis	5 (9)	2 (4)
Drop out	1 (2)	2 (4)
>10 courses of TLC	1 (2)	0 (0)

Patients could have more than one reason for treatment stopping.

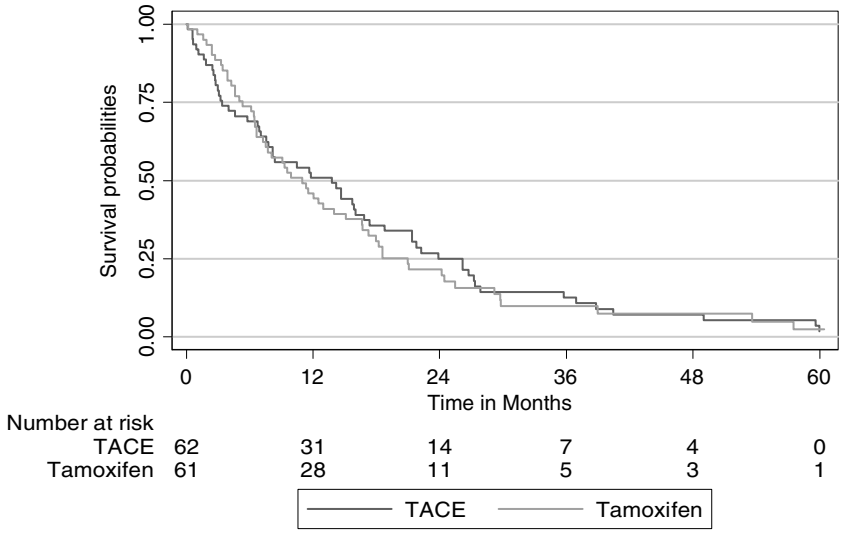

Fig. 2 – Overall survival amongst Okuda I and II patients in the TACE and the Tamoxifen groups (intent-to-treat N = 123).

all patients. Later on, courses were repeated following 4 months and then every 6 months. When serum AFP level and/or tumour size increased again, TACEs were again repeated every 2 months. TACE was stopped according to patient's refusal, no lipiodol retention on CT scan after the third course, poor hepatic function (Child-Pugh class C), extrahepatic spread (except pedicular lymph nodes), occlusion of the main portal vein, irreversible hepatic arterial occlusion and >10% decrease in cardiac ejection fraction. Whatever the outcome, the total number of TACEs was limited to 10. Tamoxifen was discontinued in case of intolerance or vascular event.

2.4. *Assessment of outcome*

The primary end-point was OS calculated from the date of randomisation until death (all causes) or last follow-up.

Secondary end-point was QoL evaluated by the Spitzer QoL Index[20,21] every 2 months during 3 years until stopping the treatment or until 10 cures of TACE was done and then every 3 months until death. A score of 0 (worst) to 10 (best) was calculated following the assessment of five dimensions related to activity, daily life, health perceptions, social support and behaviour.

The Spitzer Index was assessed by the patient or the clinician to prevent missing data due to cancer progression and/or poor health status.[22–28]

2.5. *Follow-up*

For both arms, patients were followed up 1 month post-randomisation and then every 2 months during 3 years or until completion of 10 TACEs. Complete physical examination, liver function tests, prothrombin activity, serum AFP, renal function, intercurrent events and Child-Pugh score were collected. Ultrasonography, CT scan and cardiac ejection fraction were performed every 3 months, and bone scintigraphy every 6 months. TACE-related adverse effects were recorded within 2 weeks following the procedure.

2.6. *Statistical analysis*

Our study was initially designed to detect an increase in 2-year OS amongst Okuda I patients (74 patients per arm) and in 1-year OS amongst Okuda II patients (54 patients per arm) from 20% in the tamoxifen regimen to 40% in the chemoembolisation arm (bilateral type I error = 5% and type 2 error = 20%). Post hoc due to the slow recruitment, the trial was designed to test an increase in 2-year OS amongst Okuda I and Okuda II patients from 15% in the tamoxifen arm to 35% in the TACE arm. It was required to observe 90 events and to include 120 patients in 7 years.

Data were analysed with Stata v8 software on an intent-to-treat principle (excluding patients with major non-eligibility criteria). At inclusion, the clinical variables and prognostic factors were described as mean (standard deviation) or frequencies.

Survival curves were estimated using Kaplan–Meier method[29] and compared by the log-rank test. Univariate relative hazard ratio and 95% confidence interval (CI) were calculated using Cox's proportional hazards model.[30] Univariate significant clinical factors ($P \leqslant .05$) and randomisation stratification criteria (Okuda Stage and centre dichotomised according to median of the number of included patient per centre) were retained for multivariate Cox analysis.

As exploratory analysis, the same analyses were repeated amongst the Okuda I (univariate and multivariate) and II subgroups (univariate).

As confirmatory analyses, OS was also compared amongst per-protocol (patients who receive at least one dose of randomised treatment) and amongst all included population (full intent-to-treat analysis including eligible and non-eligible patients).

QoL was compared at baseline and then longitudinally by a mixed model analysis of variance for repeated measurement with first-order autoregressive correlation matrix including time effect, treatment and Okuda stage.[31] Using Kaplan–Meier estimate, we calculated the time until definitive global health score deterioration defined as the time between ran-

Table 3 – Univariate analysis of overall survival amongst Okuda I and II patients

	N	Median overall survival (months)	Relative hazard of death [confidence interval, CI 95%]	P, log-rank
Treatment				
Tamoxifen	61	11.0	1	.68
TLC	62	13.8	.93 [.6–1.3]	
Okuda stage				
I	88	15.1	1	<.0001
II	35	4.3	2.48 [1.6–3.7]	
α-Fetoprotein (AFP)				
<400 ng/mL	85	14.7	1	<.0001
⩾400 ng/mL	37	6.4	2.56 [1.7–3.9]	
Child-Pugh class				
A	86	15.7	1	.0001
B	35	6.4	2.17 [1.4–3.3]	
Abdominal pain				
Absent	100	14.2	1	.0001
Present	23	5.8	2.65 [1.6–4.4]	
Bilirubin serum				
⩽30 mg/L	112	12.5	1	.0001
>30 mg/L	11	2.4	3.38 [1.8–6.4]	
Ascite				
Absent	107	12.5	1	.01
Present	16	3.9	1.93 [1.1–3.3]	
WHO performance status				
0	45	18.0	1	
1–4	65	7.6	1.63 [1.1–2.4]	.015
Spitzer Index[a]	94		.66 [.6 –.8]	<.0001
Diameter main tumour				
<5 cm	46	16.0	1	.013
⩾5 cm	77	8.1	1.62 [1.1–2.4]	
Hepatomegaly				
Absent	43	17.3	1	.03
Present	80	8.4	1.55 [1.0–2.3]	
Involved liver volume > 50%				
No	108	12.5	1	.041
Yes	15	4.0	1.78 [1.0–3.1]	
Albumin serum				
⩽ 30 g/L	16	7.6	1	.08
>30 g/L	107	12.1	.63 [.4–1.1]	
Alcoholic cirrhosis				
Absent	29	11.6	1	.21
Present	93	11.5	1.33 [.8–2.1]	
Centre				
>6 included patients	103	12.1	1	.34
⩽6 included patients	20	8.2	1.28 [.8–2.1]	
Segmental portal vein thrombosis				
Absent	107	11.3	1	.43
Present	13	17.3	.78 [.4–1.4]	
Localisation				
Uninodular	37	15.7	1	.47
multinodular	86	11.0	1.16 [.8–1.7]	
Age				
<65 years	58	11.8	1	.69
⩾65 years	65	11.3	.93 [.6–1.3]	

Table 3 – *continued*

	N	Median overall survival (months)	Relative hazard of death [confidence interval, CI 95%]	P, log-rank
Sex				
Men	107	11.5	1	.97
Women	16	12.6	.94 [.5–1.7]	

a Spitzer Index range from 0 to 10 and relative hazard of death was given for an increase of one point of Spitzer score.

domisation and the first score decrease without any further QoL score improvement or any further available QoL data. It was censored at the last follow-up in case of no score deterioration.

3. Results

From May 1995 to June 2002, 138 patients in 15 French centres were randomly assigned to the TACE group (70 patients) or the Tamoxifen group (68 patients). Eligible patients were 62 in the TACE group and 61 in the Tamoxifen group (Fig. 1). The two groups were well balanced with respect to demographic, clinical or biological characteristics (Table 1). The majority of patients (76%) had alcoholic cirrhosis with well-compensated liver function (Child-Pugh class A: 70%) and Okuda stage I (71%) with multinodular tumour (70%).

3.1. *Chemoembolisation treatment and adverse events*

In the TACE group, 9 patients did not receive at least one course and 53 patients underwent TACE with a mean number of courses per patient of 2.8 (SD: 2.3). In the Tamoxifen group 1 patient received two courses and 3 patients five courses of TACE. The most common adverse effects, occurring at least

Table 4 – Multivariate analysis of overall survival amongst Okuda I and II patients and Okuda I patients

	Okuda I/II RR [CI 95%]	P multivariate Cox	Okuda I RR [CI 95%]	P multivariate Cox
	N = 93		N = 67	
Treatment				
Tamoxifen	1	0.32	1	0.43
TLC	0.78 [0.5–1.3]		0.78 [0.4–1.4]	
Okuda stage				
I	1	0.69		
II	1.14 [0.6–2.1]			
AFP				
<400 ng/mL	1	0.008	1	0.001
⩾400 ng/mL	2.11 [1.2–3.7]		3.53 [1.7–7.3]	
Abdominal pain				
Absent	1	0.011	1	0.068
Present	2.36 [1.2–4.6]		2.28 [0.9–5.5]	
Hepatomegaly				
Absent	1	0.025	1	0.32
Present	1.74 [1.1–2.8]		1.31 [0.8–2.3]	
Child-Pugh class				
A	1	0.017	1	0.077
B	1.97 [1.1–3.4]		1.84 [0.9–3.6]	
Centre				
>6 included patients	1	0.08	1	0.052
⩽6 included patients	1.84 [0.9–3.6]		2.36 [1.0–5.6]	
Spitzer Index[a]	0.87 [0.7–1.1]	0.25	0.71 [0.5–0.9]	0.022
WHO performance status				
0	1	0.47	1	0.74
1–4	1.22 [0.7–2.1]		.90 [0.5–1.7]	
Diameter main tumour				
<5 cm	1	0.59	1	0.16
⩾5 cm	1.15 [0.7–1.9]		1.59 [0.8–3.0]	

a Spitzer Index range from 0 to 10 and relative hazard of death was given for an increase of one point of Spitzer score.

once, were fever (79%), abdominal pain (77%), liver failure defined as the determination of Child-Pugh score >9 (43%) and the increase of creatinine >120 μmol/L (17%).

The reasons for discontinuation of treatment are displayed in Table 2.

4. Survival

4.1. *Intent-to-treat analyses*

By 1 August 2004, 58 and 56 had, respectively, died in the TACE and the Tamoxifen groups. The median follow-up was 12.4 months in the TACE group and 11.0 months in the Tamoxifen group. OS (Fig. 2) did not differ according to treatment arm ($P = .68$, log-rank test). At 1 and 2 years, the survival rates were 51% (95% CI, 38–63%), and 25% (15–37%) in the TACE group and 46% (33–58%) and 22% (12–33%) in the Tamoxifen group ($P = .68$). The median OS was 13.8 months (95% CI, 7.6–16.8) in the TACE group and 11.0 months (95% CI, 7.3–15.1) in the Tamoxifen group.

Univariate analysis identified 12 significant prognostic factors (Table 3) while multivariate Cox model highlighted four independent prognostic variables (Table 4): AFP level ($P = .008$), abdominal pain ($P = .011$), hepatomegaly ($P = .025$) and Child-Pugh class ($P = .017$).

4.2. *Okuda I subgroup analyses (88 patients)*

At the date of analyses, 42 (91%) and 38 (91%), respectively, died in the TACE and Tamoxifen arm. At 1 and 2 years, the

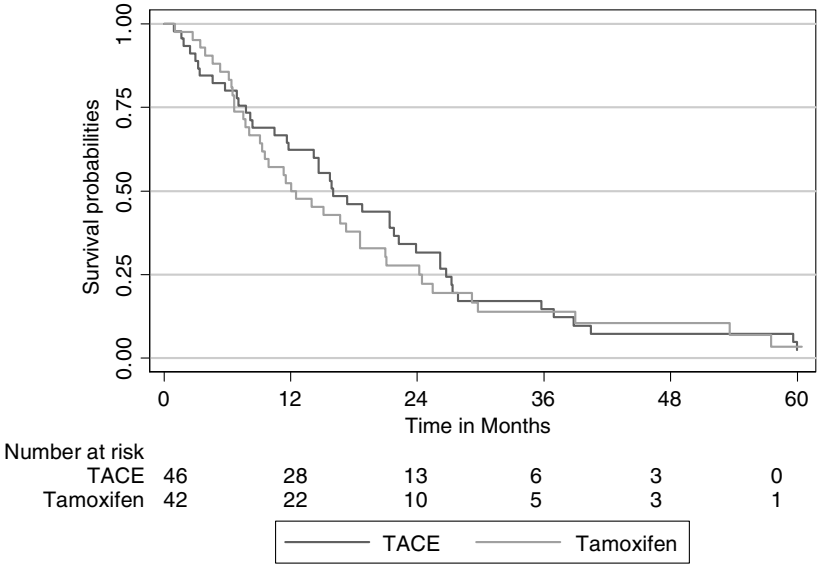

Fig. 3 – Overall survival amongst Okuda I patients in the TACE and the Tamoxifen groups (intent-to-treat N = 88).

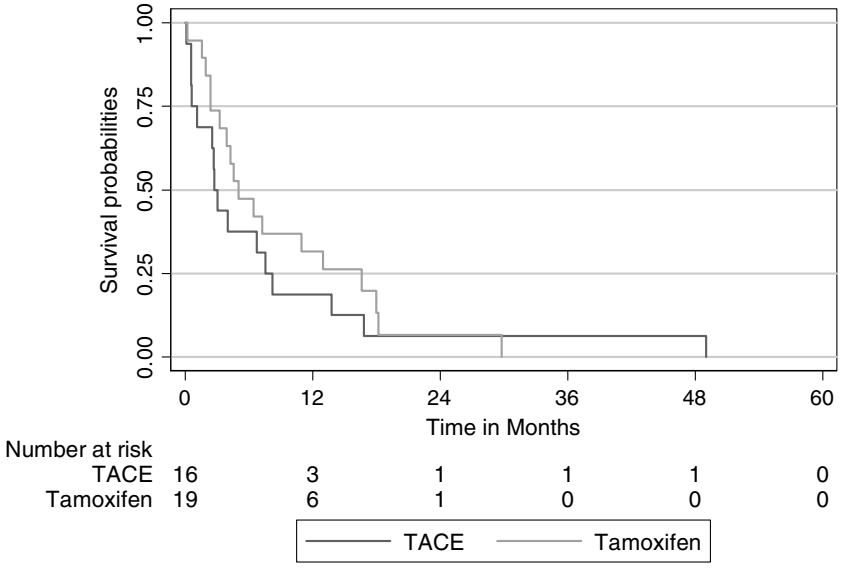

Fig. 4 – Overall survival amongst Okuda II patients in the TACE and the Tamoxifen groups (intent-to-treat N = 35).

Table 5 – Complications present at the time of death in the TACE and the Tamoxifen groups

	TACE group, N = 62	Tamoxifen group, N = 61
	N (%)	N (%)
Hepatic failure		
No	33 (55)	29 (48)
Yes	27 (45)	31 (52)
Cachexia		
No	37 (62)	37 (62)
Yes	23 (38)	23 (38)
Extra hepatic metastasis		
No	50 (83)	51 (85)
Yes	10 (17)	9 (15)
GI haemorrhage		
No	51 (85)	53 (88)
Yes	9 (15)	7 (12)
Portal vein thrombosis		
No	55 (92)	51 (85)
Yes	5 (8)	9 (15)
Others		
No	42 (70)	43 (72)
Yes	18 (30)	17 (28)

survival rates were 62% (46–75%) and 32% (19–46%) in the TACE group, and 52% (36–66%) and 28% (15–42%) in the Tamoxifen group (P = .58), respectively (Fig. 3). Median OS was 16 months (95% CI, 11.6–22.3) in TACE and 12.1 months (95% CI, 9.1–18.6) in Tamoxifen arms. As shown by multivariate Cox analysis (Table 4): AFP level (P = .001), Spitzer Index (P = .022) and centre (P = .05) have an independent prognostic value.

4.3. *Okuda II subgroup analyses (35 patients)*

At the date of analyses, 16 (100%) and 18 (95%), respectively, died in the TACE and Tamoxifen arms. At 1 and 2 years, the survival rates were 19% (5–40%) and 6% (0.4–25%) in the TACE group, and 32% (13–52%) and 7% (0.4–25%) in the Tamoxifen group (P = .42), respectively, (Fig. 4). The median OS was 2.8 months (95% CI, 0.6–7.6) in TACE and 5 months (95% CI, 2.4–13) in the Tamoxifen arms.

4.4. *Confirmatory analyses*

Per protocol analysis (N = 110; Fig. 1) confirmed that OS did not differ (log-rank P = .1211, HR Tam versus TACE = 1.36 [0.92–2.01]). Amongst all included patients (N = 138; Fig. 1), OS did not differ according to treatment arm (log-rank test P = .41; HR Tam versus TACE = 1.16 [0.82–1.65]).

4.5. *Complications present at the time of death and the length of hospital stay*

Hepatic failure was the main complication present at the time of death in each arm (Table 5). The mean total hospital stay was significantly longer in patients receiving TACE treatment (P = .003) corresponding to 32.5 d (SD: 28.1) in TACE and 17.8 d (SD: 25.6) in Tamoxifen group.

4.6. *Quality of life*

The means of Spitzer Index filled in were similar between the two arms during the follow-up (Fig. 5A). The mixed model analysis of variance highlighted that QoL did not differ between the two treatments (regression coefficient $\beta = -0.03$, P = .919). The

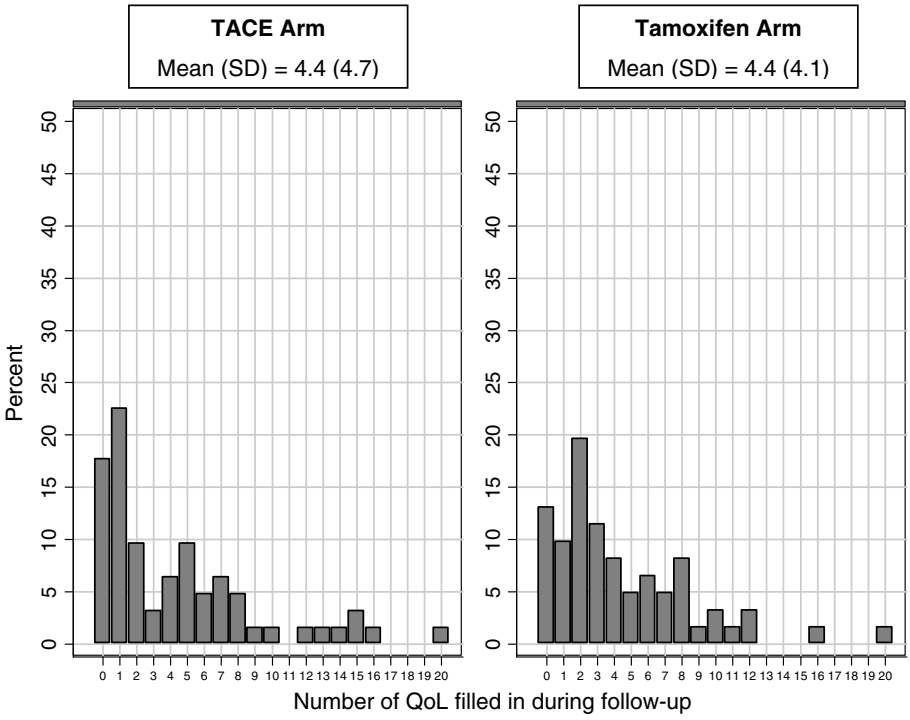

Fig. 5A – Percent of number of QoL filled in during follow-up according to TACE and the Tamoxifen groups.

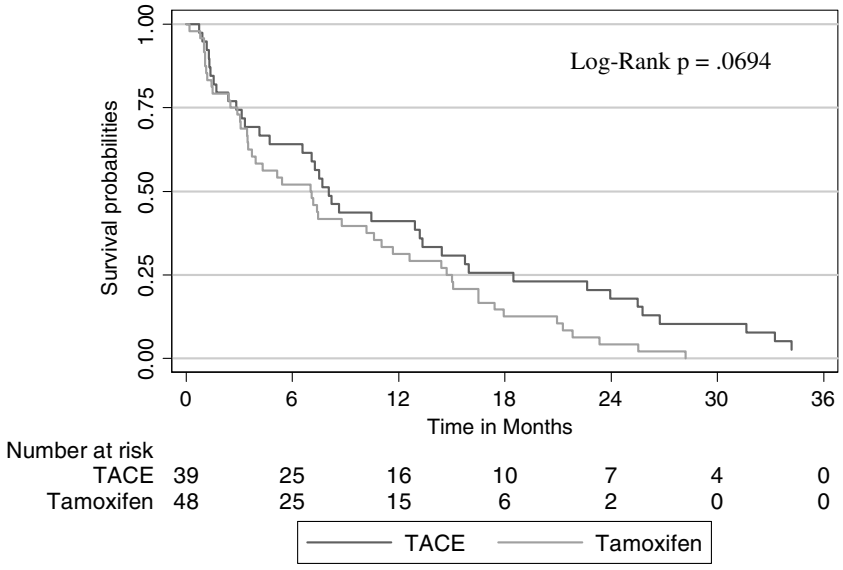

Fig. 5B – Time until definitive quality of life deterioration (Kaplan–Meier estimate) (B) amongst Okuda I and II patients in the TACE and the Tamoxifen groups.

Spitzer Index decreased by 1% at each follow-up whatever treatment modality and Okuda stage ($\beta = -0.10$, $P = .025$). The QoL was lower amongst Okuda II patients ($\beta = -0.91$, $P = .007$) representing a 9% difference of theoretical range score.

The median time until definitive QoL deterioration was 8.1 months [4.1–13.3] in TACE arm and 7 months [3.5–10.6] in Tamoxifen arm ($P = .07$) (Fig. 5B).

5. Discussion

This study suggests that TACE improves neither survival nor QoL in patients with well-preserved liver function and Okuda stages I and II.

Our results were not in agreement with the two most recent RCT[8,9] and two meta-analysis.[10,11] However, they are consistent with two French trials.[5,7] The French studies were characterised by a large number of patients with alcohol-induced cirrhosis, whereas the Hong Kong and Barcelona trials included patients with hepatitis B or C virus-induced cirrhosis (Table 6). Furthermore, frequency of hepatic failure following TACE is higher in the French trials, reaching 43% in our study and 60% in the GRETCH study.[5] In contrast, hepatic failure in the Hong Kong and Barcelona trials[8,9] was only observed in 7% and 0% of patients, respectively.

In our study, the number of chemoembolisation sessions was approximately three. It was less than in a trial[8] but similar to that in other RCTs.[5,7,9] In the Llovet and colleagues study[9], TACE was delivered after 2 and 4 months, then every 6 months. Thus, the three first courses were delivered in not more than 10 months versus 6 months in our study. If in our trial, TACE was delivered every 2 months, patients were checked for the absence of hepatic insufficiency. The use of a different chemotherapeutic agent might have resulted in a better tolerance and efficacy of TACE; however, there is no evidence that doxorubicin is superior to the epirubicin used in our trial. Otherwise, patients had similar HCC and cirrhosis characteristics, but poorer performance status in our study. This could explain the differences, together with alcoholic aetiology (Table 6), between our results and those of Llovet and colleagues. Antiestrogen therapy was administered in both arms because when our study was initiated, a positive effect on HCC had been reported.[13,14] It was not confirmed later.[16]

The Child-Pugh score and AFP represented the main prognostic factors in our multivariate analyses. Child-Pugh score[32,33] or CLIP score (which included Child-Pugh)[34] has been already identified as prognostic factor. Amongst Okuda stage I patients, QoL was an independent prognostic factors, as other cancer localisations.[35–37] Our results did not reveal

Table 6 – Main characteristics of cirrhosis and hepatocellular carcinoma (HCC) in the chemoembolisation group of five recent randomised controlled trials (HBV: hepatitis B virus, HCV: hepatitis C virus)

Trials	N	Cirrhosis			HCC		
		Frequency (%)	Child-Pugh A (%)	Etiology	Multinodular (%)	Okuda I (%)	Segmental portal vein thrombosis (%)
GRETCH, 1995[5]	50	92	100	75% alcohol	38	94	2
Pelletier, 1998[7]	37	92	70	53% alcohol	–	69	0
Lo, 2002[8]	40	–	100	85% HBV	57	47	22
Llovet, 2002[9]	40	100	77	82% HCV	65	67	0
FFCD, 2006	62	100	74	73% alcohol	68	74	11

any difference of longitudinal QoL. Despite a moderate correlation with self-appraised QoL[38,39], Spitzer QoL index was assessed by the patient or the clinician.[21,22] Furthermore, unblinded assessment could have attenuated or exaggerate the difference by the occurrence of response shift and treatment expectations.[39] In contrast, clinicians can also provide useful QoL data.[40–42] QoL in both arms was probably over estimated.[26,43] Therefore, the use of time until definitive quality of life deterioration has been proposed[44] with the hypothesis that drop-out or death is associated with definitive QoL deterioration.

A major strength of our study is the large number of patients. However, achievement of planned statistical power to assess effect of TACE amongst Okuda sub-groups and the large number of patients with non-eligibility criteria had induced a major clinical variability and underlined heterogeneity of TACE practice in French centres. The use of Okuda classification to select patients was not optimal.[32,45] Recent classifications, e.g. the BCLC,[46] CLIP,[47] GRETCH[48] or the JIS [32] score were not available when our protocol was initiated.

In conclusion, our study failed to demonstrate the superiority of TACE in French population with mainly alcoholic HCC aetiology. A meta-analysis including our results should be carried out to quantitatively assess the contribution of this result to the literature on TACE efficacy.

Conflict of interest statement

None declared.

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