

## Comparison of two Transarterial Chemoembolization Strategies for Hepatocellular Carcinoma

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**Abstract.** *Aim: This retrospective study aimed to compare the efficacy of and tolerance to two center-related conventional transarterial chemoembolization (TACE) strategies in the management of unresectable hepatocellular carcinoma (HCC). Patients and Methods: All HCC patients in whom TACE was initiated in the two centers from June 2008 to July 2011 were included. The TACE strategy performed in center 1 was “on demand” with selective injections of idarubicin, whereas the TACE strategy in center 2 was based “on scheduled” non-selective injections of epirubicin. Toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Results: One hundred and fifty HCC patients were included. Median time to treatment failure was significantly higher in center 1, 13.1 months vs. 7.9 months in center 2 (hazard ratio, 2.32;  $p < 10^{-3}$  in multivariate analysis). Median overall survival was 21.1 months in center 1 vs. 18.4 months in center 2 ( $p = NS$ ). The proportion of grade  $\geq 3$  adverse events and mean hospitalisation duration for the overall TACE treatment were significantly greater in center 2 than in center 1: 56% vs. 32% ( $p < 0.01$ ) and  $14.2 \pm 7.2$  days vs.  $10.3 \pm 7.0$  days ( $p < 0.01$ ), respectively. Conclusion: Our results failed to show any significant survival differences between two center-related TACE strategies but showed a significantly smaller proportion of grade  $\geq 3$  adverse events and shorter*

*hospitalisation for the overall treatment when the “on-demand” strategy was used.*

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death in the world (1-2). Curative therapies (resection, local ablation, liver transplantation) can only be applied in patients with early-stage tumors, whereas transarterial chemoembolization (TACE) is the standard-of-care in intermediate-stage HCC patients (3).

Conventional TACE (cTACE) associates the injection of an chemotherapeutic agent emulsified with lipiodol into the feeding artery(ies) of the tumor followed by embolization. One of the key theoretical advantages of TACE is exposure of the tumor to high concentrations of the chemotherapeutic agent. Even though TACE has improved survival in unresectable HCC patients compared with supportive care or systemic chemotherapy (4-7), there is great variability in survival rates in patients treated with TACE and the optimal TACE strategy is not yet known (8).

This lack of standardisation in TACE for HCC is clearly illustrated by the TACE strategies adopted in two French centers: the nature of the chemotherapeutic agent, the injection selectivity and the treatment schedule vary widely from one center to the other. This study, therefore, aimed to compare efficacy and tolerance in two center-related TACE strategies in the management of unresectable HCC.

### Patients and Methods

*Patients.* All patients diagnosed with HCC or with HCC recurrence after curative therapies in whom TACE was initiated from June 2008 to July 2011 in two French University Hospitals (Clermont-Ferrand

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and Dijon) were included. The inclusion criteria were as follows: confirmed diagnosis of HCC according to American Association for the Study of Liver Diseases criteria (9), Eastern Cooperative Oncology Group Performance Status (ECOG PS)  $\leq 2$ , preserved liver function (Child-Pugh class A or B7), platelet count  $>50 \times 10^9/l$ , left ventricular ejection fraction  $>50\%$ , in the absence of symptoms (encephalopathy, ascites), portosystemic shunts, hepatofugal blood flow, thrombus within the main portal vein, extrahepatic metastases, concomitant malignancy, renal failure (serum creatinine level  $\geq 150$   $\mu\text{mol/l}$ ), allergy to iodine-containing agents and pregnancy.

**TACE technique.** In center 1, an emulsion of idarubicin 10 mg/5 ml (Zavedos®; Pfizer, Paris, France) and lipiodol 10 ml (Lipiodol Ultra-Fluide®, Guerbet, Aulnay-sous-Bois, France) was perfused as selectively as possible in 10 min. The emulsion was prepared by the interventional radiologist just before injection by passing the mixture from one 30-ml syringe to another 10 times *via* a 3-way tap. In cases of bilobar disease, each lobe was treated alternately at an interval of 6 weeks. The tumor was evaluated after each session and patients were treated “on demand”. In center 2, two thirds of an emulsion of epirubicin 50 mg/25 ml (Epirubicine; Hospira, Meudon-la-Forêt, France) and lipiodol 15ml were perfused in 10 min into one lobe and the remaining third was perfused into the other lobe. Patients received repeated sessions ( $3 \pm 1$ ) at fixed intervals (2 months) until the planned number of sessions was reached or until a complete radiological response was achieved.

**Efficacy and toxicity.** Time to treatment failure (TTF) was defined as the time between the first TACE session and treatment discontinuation for any reason, including tumor progression, treatment toxicity, patient’s preference or death (10). Progression-free survival (PFS) was defined as the time between the first TACE session and tumor progression or death from any cause. Overall survival (OS) was defined as the time from the first TACE session until death from any cause (10).

Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTC AE) version 4.0 (11) within 2 months of each TACE session. TACE-related mortality was defined as death from a complication within 4 weeks of each TACE session.

**Statistical analysis.** Categorical variables were described using percentages. Continuous variables were expressed as means and standard deviations (SDs). To compare baseline patients’ characteristics between the two centers, the Fisher’s exact test for categorical variables and the Kruskal-Wallis rank test for continuous variables were used.

Survival curves were plotted using the Kaplan Meier method and described using medians with 95% confidence intervals (95% CIs). For each efficacy criterion (TTF, PFS, OS), a univariate analysis using the log rank test was performed. Variables with a *p*-value  $< 0.20$  were included in the final Cox multivariate models to identify independent TTF and survival predictors. ECOG PS was not introduced into the models because this variable was already incorporated into the BCLC staging system (all of our patients were classified BCLC C on the sole criterion of an ECOG PS  $\geq 1$ ). Akaike’s Information Criterion was used to choose the final model. A *p*-value  $< 0.05$  was considered statistically significant. All statistical analyses were performed using the Stata software version 12.0 (Stata corporation, College Station, TX, USA).

## Results

**Patients and treatment.** One hundred and fifty patients were included; 60 patients in center 1 and 90 in center 2. Baseline patients’ characteristics are presented in Table I. There were no significant differences between the two centers’ patients, except for higher frequencies of both metabolic etiologies for cirrhosis and bilobar disease in center 1.

The total number of TACE sessions in the study was 372. The mean number of TACE sessions was not significantly different between the two centers:  $2.4 \pm 1.3$  in center 1 *vs.*  $2.6 \pm 1.4$  in center 2 ( $p=0.25$ ). Mean hospitalisation duration for all stays related to TACE sessions was  $9.7 \pm 5.7$  days in center 1 *vs.*  $13.0 \pm 6.6$  days in center 2 ( $p<0.01$ ). Mean hospitalisation duration for the overall TACE strategy (including stays for management of TACE-related toxicities) was  $10.3 \pm 7.0$  days in center 1 *vs.*  $14.2 \pm 7.2$  days in center 2 ( $p<0.01$ ).

**Efficacy.** At the time of the study closure, 88 (59%) patients had died. The frequency of subsequent treatments administered after TACE sessions (transplantation, resection, radiofrequency ablation, percutaneous ethanol injection) was 20% in center 1 and 14% in center 2 ( $p=0.35$ ). Median TTF was 13.1 months (95% CI=7.1-15.9) in center 1 *vs.* 8.1 months (95% CI=6.7-11.8) in center 2 ( $p=0.15$ ) (Figure 1a). In multivariate analysis, the independent risk factors of shorter TTF were center 2 *vs.* 1 (HR=2.32;  $p<0.01$ ), total tumor size (HR=1.08 per cm;  $p<10^{-3}$ ), ALP level (HR=1.03 per 10 IU/ml;  $p<0.01$ ) and albumin level (HR=0.96 per g/l;  $p=0.05$ ) (Table II).

The median PFS was 8.4 months (95% CI=6.3-11.7) in center 1 *vs.* 10.3 months (95% CI=7.4-11.8) in center 2 ( $p=0.52$ ) (Figure 1b). In case of progression, 28% and 24% of patients were retreated with TACE in center 1 and 2, respectively ( $p=0.63$ ). In multivariate analysis, independent risk factors of shorter PFS were total tumor size (HR=1.07 per cm;  $p<10^{-3}$ ) and GGT level (HR=1.01 per 10 IU/ml;  $p<0.01$ ) (Table II).

The median OS was 21.1 months (95% CI=16.0-not achieved) in center 1 *vs.* 18.4 months (95% CI=14.7-22.9) in center 2 ( $p=0.43$ ) (Figure 1c). In multivariate analysis, independent risk factors of mortality were total tumor size (HR=1.06 per cm;  $p=0.01$ ), ALP level (HR=1.05 per 10 IU/ml;  $p<0.01$ ) and BCLC C classification (HR=3.21;  $p<0.01$ ) (Table II).

**Toxicity.** Six TACE-related deaths occurred, 2 (3%) in center 1 and 4 (4%) in center 2 ( $p=NS$ ). In center 1, one patient rapidly developed acute liver and renal failure and died 15 days after the first TACE session; another patient died 10 days after the first TACE session from septic shock. In center 2, three patients developed acute liver and renal failure and died 15 and 28 days after the first TACE session

Table I. Patients' characteristics.

	Center 1 (n=60)	Center 2 (n=90)	All (n=150)	p-Value
Gender (male gender)	50 (83%)	83 (92%)	133 (89%)	0.12
Age (years)	66.5±8.8	66.7±8.0	66.6±8.3	0.86
Etiology				
Alcohol	38 (64%)	69 (76%)	107 (72%)	0.14
Viral hepatitis	14 (24%)	18 (20%)	32 (22%)	0.68
Metabolic	18 (31%)	8 (9%)	26 (17%)	<0.01
Normal liver	4 (7%)	6 (7%)	10 (7%)	1.00
Other	6 (10%)	7 (8%)	13 (9%)	0.77
Bilobar disease	31 (52%)	18 (20%)	49 (33%)	<10 <sup>-3</sup>
Total tumour size (mm)	82±50	86±48	84±49	0.35
Maximal node size (mm)	50±31	57±39	54±36	0.54
AFP (ng/ml)	1486±4165	2409±12585	2031±9999	0.20
Child-Pugh score A	48 (81%)	76 (84%)	124 (83%)	0.41
BCLC stage				0.52
A	19 (35%)	25 (28%)	44 (31%)	
B	29 (54%)	48 (55%)	77 (54%)	
C	6 (11%)	15 (17%)	21 (15%)	
Recurrence	13 (22%)	15 (17%)	28 (19%)	0.52
Liver enzymes				
Bilirubin (µmol/l)	17±11	17±12	17±12	0.72
ALT (IU/l)	51±32	64±164	59±129	0.16
AST (IU/l)	60±50	78±135	70±109	0.34
GGT (IU/l)	283±340	223±201	247±266	0.51
ALP (IU/l)	122±71	135±94	130±86	0.27
PT (%)	78±17	80±16	79±16	0.64
Albumin (g/l)	34±7	35±6	35±7	0.22

Data are n (%) or mean±SD. ALT, Alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; GGT, gamma-glutamyl transferase; PT, prothrombin time; SD, standard deviation.

and 30 days after the second TACE session. A fourth patient died in center 2 from gastrointestinal bleeding after the first TACE session. Sixty-nine (46%) patients presented at least one grade ≥3 AE after one or more TACE sessions. The proportion of patients who presented at least one grade ≥3 AE was significantly higher in center 2 than in center 1 (56% vs. 32%;  $p<0.01$ ) but did not differ in terms of distribution per grade (Table III). The majority of TACE-related grade ≥3 AEs occurred after the first session. The proportion of patients in center 1 and center 2 who presented at least one grade ≥3 AE after the first, second and third TACE session was 22% vs. 40% ( $p=0.02$ ), 10% vs. 20% ( $p=0.17$ ) and 18% vs. 19% ( $p=1$ ), respectively. The most common grade ≥3 AEs were an elevation of liver enzyme levels: ALT, AST, GGT and ALP and/or total bilirubin. They accounted for 46% of all grade ≥3 AEs and were most often transient, with patients recovering pretreatment levels within one or two weeks. Other noteworthy grade ≥3 AEs were sepsis/febrile neutropenia, pain, oedemato-ascitic decompensation and thrombopenia. Finally, the nature of the grade ≥3 AEs did not differ between the two centers.

## Discussion

The optimal TACE strategy is far from being clearly defined as, in particular, the chemotherapeutic agent, the vector and the frequency of sessions have yet to be determined (8). The OS rate of HCC patients treated with TACE remains low (<30% at 3 years) and there is, therefore, a need for a TACE strategy that improves survival. We, therefore, conducted this retrospective study in order to compare the efficacy and toxicity of two French center-related cTACE strategies. The main differences between the two strategies were the nature of the chemotherapeutic agent (idarubicin vs. epirubicin), the frequency of sessions (on demand vs. scheduled at fixed intervals) and the type of injection (selective/hypersselective vs. lobar). These major differences illustrate the heterogeneity that exists worldwide between TACE practices.

With a median OS of approximately 20 months, our result was comparable with those observed in the literature on cTACE (13-14). Even though the center variable was not statistically associated with OS or PFS in multivariate analysis, TTF was significantly higher in center 1 and OS tended to be higher in center 1. It has already been shown

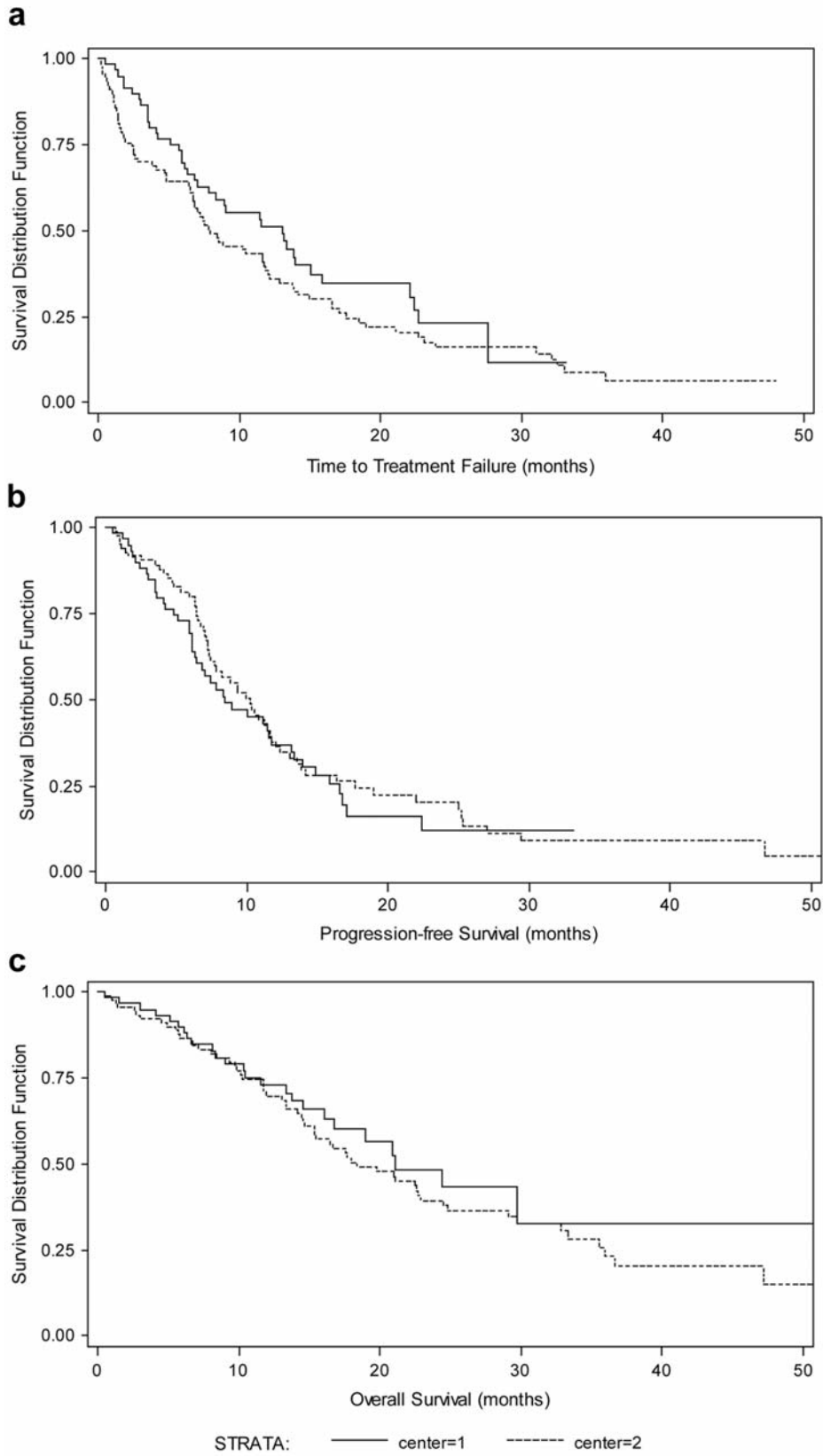


Figure 1. Kaplan-Meier estimated (a) time to treatment failure, (b) progression-free survival, (c) overall survival curves by center.

Table II. *Multivariate Cox regression models.*

Variable	Time to treatment failure		Progression-free survival		Overall survival	
	HR (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value
Center 2 ( <i>vs.</i> 1)	2.32 (1.34-4.02)	<0.01				
Total tumor size (cm)	1.08 (1.03-1.13)	<10 <sup>-3</sup>	1.07 (1.03-1.11)	<10 <sup>-3</sup>	1.06 (1.01-1.11)	0.01
BCLC classification C ( <i>vs.</i> A/B)					3.21 (1.50-6.87)	<0.01
ALP (IU/L ×10)	1.03 (1.01-1.06)	<0.01			1.02 (1.01-1.08)	<0.01
Albumin (g/l)	0.96 (0.91-0.99)	0.05				
GGT (IU/L ×10)			1.01 (1.00-1.02)	<0.01		

ALP, Alkaline phosphatase; BCLC, Barcelona Clinic Liver Cancer; ECOG PS score, Eastern Cooperative Oncology Group performance status; GGT, gamma-glutamyl transferase; HR, hazard ratio; 95%CI, 95% confidence interval.

that total tumor size and the GGT level were independent factors of shorter PFS and that total tumor size, the ALP level and BCLC C classification were independent factors of mortality in HCC patients treated with TACE (3,15-16). We also observed that the proportion of patients with grade ≥3 AEs was significantly higher in center 1 and that most of the grade ≥3 AEs in the 2 centers occurred after the first cTACE session, being hepatic. This notion of serious toxicity mainly associated with the first cTACE session has already been described (17). We can suppose that patients who are well enough to receive the first cTACE session without any serious AEs would also present good tolerance after further cTACE sessions even if there is also evidence suggesting that the repetition of cTACE sessions with an aggressive schedule increases the occurrence of serious AEs (16).

Proportions of patients with grade ≥3 AEs described in cTACE studies are heterogeneous, most of them reporting proportions between 20% and 50% (18-22). Given the prospective collection of AEs in the two arms (drug-eluting beads and cTACE), the phase II randomized PRECISION V trial may serve as a standard for the comparison of AEs (23). In one center of our study, the 32% of grade ≥3 AE compares favourably with the 30% of serious AEs (defined as events resulting in death, immediately life-threatening, resulting in permanent/significant disability/incapacity, requiring or extending in patient hospitalization or congenital anomaly/birth defects) reported in the doxorubicin cTACE arm of the PRECISION V trial. We may think that two main factors explain the significantly higher frequency of grade ≥3 AEs we observed in one center: first, the absence of selectivity of the injection in this center: this relationship has been described in the past (22); second, as patients received approximately the same number of sessions in the two centers and as serious AEs occurred mainly after the first session, the chemotherapeutic agent itself. To date, only two randomized controlled trials were designed to compare chemotherapeutic agents for TACE of HCC (doxorubicin *vs.* epirubicin) but they failed to demonstrate superiority in survival (24, 25).

Table III. *Transarterial chemoembolization-related adverse events.*

	Center 1 (n=60)	Center 2 (n=90)	<i>p</i> -Value
All sessions			
All grade ≥3 AEs, n (%)	19 (32)	50 (56)	<0.01
Grade 3 AEs, n (%)	12 (20)	25 (28)	0.49*
Grade 4 AEs, n (%)	5 (8)	21 (23)	
Grade 5 AEs, n (%)	2 (3)	4 (4)	
First session			
All grade ≥3 AEs, n (%)	19 (32)	50 (56)	0.02
Second session			
All grade ≥3 AEs, n (%)	4 (10)	13 (20)	0.28
Third session			
All grade ≥3 AEs, n (%)	4 (18)	9 (19)	1

\*Fischer exact test: there were no significant differences between the two centres in terms of distribution per grade 3, 4 or 5. AE, adverse event.

Epirubicin is an anthracycline widely used for TACE of HCC, as reported in the systematic review published by Marelli *et al.* the most widely used chemotherapeutic agents in this indication were doxorubicin (36%), cisplatin (31%) and epirubicin (12%) (8). The use of idarubicin in center 1 is based on the finding that in a preclinical study comparing the cytotoxicity of 11 chemotherapeutic agents (including the most frequently used for TACE) on three human HCC cell lines, this anthracycline was by far the most cytotoxic (26). The superiority of idarubicin (especially over doxorubicin and epirubicin) was observed most notably on the SNU-449 cell line, known for its resistance to various chemotherapeutic agents (27). The greater cytotoxicity of idarubicin can be explained by two different mechanisms. First, idarubicin has higher hepatic penetration than other anthracyclines (28). This may be related to its highly lipophilic nature, which facilitates intracellular penetration through the cell membrane composed of a double layer of lipids. Second, idarubicin has the ability to overcome the multidrug resistance (MDR) system (29).

The MDR mechanism consists in pumping drugs out of cells and is classically observed in HCC (30, 31). Both its highly lipophilic nature and its ability to overcome MDR could account for the greater accumulation of idarubicin in HCC cells and, therefore, its greater efficacy. In our study, we found no significant survival benefit in the center using idarubicin but only a benefit in terms of tolerance. The highly lipophilic nature of idarubicin is responsible for its great accumulation in the hepatocytes, thereby minimizing systemic AEs of the drug. The better tolerance may explain the significantly shorter median overall hospitalisation duration observed in the center with “on-demand” selective/hyperselective injections of idarubicin. These two criteria, serious toxicity and hospitalisation duration, are of major importance as TACE remains a palliative procedure in HCC patients.

In conclusion, our results failed to present any differences in terms of PFS or OS between TACE strategies performed in two French centers. A significantly higher proportion of patient with grade  $\geq 3$  AEs was observed in one center, probably explaining the significantly longer median hospitalisation for the overall TACE strategy in this center.

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