ORIGINAL ARTICLE

Outcome of inoperable hepatocellular carcinoma patients receiving transarterial chemoembolisation: a real-life retrospective analysis in a Hong Kong regional hospital

CME

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Objective To evaluate survival and prognostic factors in patients with advanced hepatocellular carcinoma treated by transarterial chemoembolisation in a real-life clinical practice setting.

Design Retrospective study.

Setting Regional hospital, Hong Kong.

Patients Patients with inoperable hepatocellular carcinoma diagnosed from January 1998 to December 2003 who received transarterial chemoembolisation.

Results A total of 74 patients were identified, and had a median survival of 214 days. The cumulative survival rates at 1, 2, and 3 years were 28%, 12%, and 7%, respectively. By multivariate analysis, superselective cannulation performed in transarterial chemoembolisation (hazard ratio=0.47; 95% confidence interval, 0.23-0.95; P=0.034), embolisation with gelfoam (0.30; 0.11-0.80; P=0.017), and treatment intervals of more than 45 days (0.33; 0.15-0.72; P=0.006) were independent predictors of good survival. Child-Pugh grade B cirrhosis (hazard ratio=5.62; 95% confidence interval, 2.11-14.97; P=0.001), and high pre-treatment serum alpha-fetoprotein level (2.93; 1.50-5.73; P=0.002) were independent predictors of poor survival.

Conclusions In real-life clinical practice, survival of patients with inoperable hepatocellular carcinoma remains grave despite treatment. Patients with Child-Pugh grade A cirrhosis or with low pre-treatment alpha-fetoprotein level are more suitable for this form of treatment. The procedure should be performed with superselective cannulation and embolisation with gelfoam.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world. In Hong Kong, it ranks as the second major cause of cancer deaths, and among male inhabitants it has an incidence of 33 cases per 100 000/year.[1] Despite advances in modern medicine, most tumours are diagnosed at an advanced stage even with surveillance.[2,3] Untreated HCC is uniformly fatal. A recent study showed that the 1-year survival rate was 7.8%.[4] Radical therapy by surgical resection, percutaneous ablation, or liver transplantation remains the treatment of choice. Unfortunately, late diagnosis, vascular involvement, and underlying cirrhosis preclude curative therapy in the majority of patients.[2,5-7] Among various modalities of palliative treatment for HCC, transarterial chemoembolisation (TACE) is the only strategy showing survival bene t in randomised controlled trials and a meta-analysis.[8-10] In these clinical trials strict patient selection criteria were used, whereas data pertaining to real clinical practice are scarce. Therefore, the objective of the present study was to determine survival and prognostic factors in patients with unresectable HCC who were treated with TACE in a regional Asian hospital.

Methods

Study design

Patient selection

From January 1998 to December 2003, Tuen Mun Hospital patients with HCC (International

Key words
Carcinoma, hepatocellular; Chemoembolization, therapeutic; Liver neoplasms; Prognosis; Survival rate

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不能動手術而接受肝動脈化療栓塞術的肝細胞癌患者的治療效果：香港地區醫院的現實生活回顧分析

目的 評估在一個現實生活的臨床實踐環境裏，末期肝細胞癌患者接受肝動脈化療栓塞術治療的生存率和預後因素。

設計 回顧研究。

安排 地區醫院，香港。

患者 1998年1月至2003年12月期間，因不能動手術而接受肝動脈化療栓塞術的確診肝細胞癌患者。

結果 共74名患者接受栓塞術，生存時間的中位數為214天。1、2和3年的漸增生存率分別為28%、12%和7%。根據多元分析，肝動脈化療栓塞時使用的超選擇性套管插入術（風險比=0.47；95%置信區間，0.23-0.95；P=0.034）、利用泡棉進行栓塞（0.30；0.11-0.80；P=0.017），和治療間隔時間超過45天（0.33；0.15-0.72；P=0.006）都是有利患者生存的獨立預測因素。肝硬化屬Child-Pugh B級（5.62；2.11-14.97；P=0.001）和術前血清alpha-胎蛋白水平較高（2.93；1.50-5.73；P=0.002）則是不利生存率的獨立預測因素。

結論 在現實生活的臨床實踐中，不能動手術的肝細胞癌患者縱使接受治療，他們的生存率都不高。肝硬化屬Child-Pugh A級或術前alpha-胎蛋白屬低水平的患者較適合此種栓塞術，並應以超選擇性套管插入術和泡棉進行。

Classi cation of Diseases Code 155.0) treated with transarterial oily chemoembolisation (TOCE, International Classi cation of Diseases Code 99.25) were identi ed using the Hong Kong Hospital Authority Clinical Management System database. This hospital is a regional acute tertiary medical centre with 1405 beds; in 2006 it served 1 095 400 inhabitants. The hospital has more than 10-year experience in managing HCC using a multidisciplinary approach that includes: surgeons, interventional radiologists, clinical oncologists, and hepatologists. The medical records of all adult (18-80 years) patients were reviewed retrospectively. Patients with a diagnosis of HCC made by (1) histology acquired by ne-needle aspiration, (2) elevated alpha-fetoprotein (αFP) level exceeding 200 ng/mL, and (3) typical computed tomography (CT), magnetic resonance imaging, and/or hepatic arterial angiography features were identi ed.

Patients were considered clinically inoperable based on the presence of vascular invasion, extreme tumour size (>6 cm), poor liver function (Child-Pugh grade B or C), multiplicity of tumour (>3 nodules), patient preference or other signi cant co-morbidities that could complicate surgery for HCC. Patients were excluded if any of the following conditions occurred: Child-Pugh grade C cirrhosis, tumour with main portal vein involvement, history of ruptured tumour or extra-hepatic spread, history of previous treatment for HCC (including percutaneous ablation or surgery), total serum bilirubin level of more than 50 mol/L, or serum creatinine level of greater than 200 mol/L.

Treatment procedure

All TACE followed a standard protocol and was performed by experienced interventional radiologists after obtaining informed consent from the patients. Serum biochemistry, αFP level, clotting pro le, and complete blood picture were checked in each patient at baseline before every TACE session. All patients were fasted and pre-medicated with intravenous antibiotics. Hepatic arteriography was performed to de ne the size and location of the tumour. The tip of the catheter was placed distal to gastro-duodenal artery or in either the right or left branch of the hepatic artery. Cisplatin (DBL, Mayne-Pharma, Australia) and lipiodol (Lipiodol Ultra uid, Guerbet, Aulnay-sous-Bois, France) were prepared as an emulsion with a ratio of 5:6, and infused according to the vascularity and extent of the tumour as determined by the hepatic arteriogram performed before each session. The infusion was continued until there was a reduction of arterial blood ow. If technically feasible, the tumour-supplying arteries were superselectively cannulated for further infusion of the chemo-agent. In patients with huge vascular tumours or in the presence of arterio-portal shunting, the feeding arteries were embolised with 1 mm pellets of gelfoam (Spongostan, Ferrosan, Johnson and Johnson Medical Limited, England). The aim was to reduce arterial blood ow without totally occluding the vessel. Patients were then kept in hospital overnight for clinical and biochemical observation. To assess the tumour size and degree of lipiodol uptake, a follow-up CT scan of the liver was arranged 2 weeks after each TACE session. In cases of poor lipiodol uptake, a second course of TACE was undertaken. Alternative treatment options were considered for cases with a persistently poor response. For patients in whom lipiodol uptake by the tumour was good, TACE would be performed serially in order to achieve a satisfactory response. Generally, TACE was repeated every 4 to 8 weeks. Liver biochemistry, αFP level, renal function, as well as tumour and treatment details (Table 1) were logged during the study period. Conditions that led to cessation of TACE included: total serum bilirubin level increasing to above 50 mol/L, poor control of the tumour, patient s wishes, tumour invasion of the main portal vein, extra-hepatic metastasis, extensive arteriovenous shunting, or complete radiological resolution of the tumour with normalisation of the αFP level. Patients were followed up at intervals of 4 to 8 weeks.

Outcome

The main outcome of interest was overall survival, calculated from the date HCC was diagnosed to the time of death. The mean interval between sessions was de ned as the time difference between the rst and last sessions divided by the total number of the sessions minus one. Adverse reactions after TACE were also recorded. Post-embolisation reactions were de ned as: hyperthermia, abdominal pain or vomiting (sometimes associated with elevated transaminase levels) during the 2 days following TACE. Liver failure after TACE was de ned as the occurrence of hepatic encephalopathy, refractory ascites, or an elevation of total serum bilirubin level to more than 50 mol/L.

Statistical analysis

Continuous variables were expressed as mean/median and standard deviations. Categorical variables were expressed as percentages. Overall survival was calculated by Kaplan-Meier plots.[11] The log rank test was applied to compare different patient subgroups. Data were censored at the time of death. Univariate analysis was performed by the Cox regression method to identify parameters that affected survival.[12] Hazard ratios and 95% con dence intervals (CIs) were derived from the Cox proportional hazards models results. All signi cant prognostic factors identi ed from the univariate analysis were entered into a Cox regression model for multivariate analysis, to indicate independent prognostic factors for survival. A P value of less than 0.05 was considered signi cant. Data were analysed using the Statistical Package for the Social Sciences, Windows version 11.5.0; SPSS Inc, Chicago IL, US.

Results

Patients' characteristics

One hundred and twenty-one patients with inoperable HCC who underwent TACE were identi ed. Forty-seven patients who had already had operations or percutaneous treatment, or who had extra-hepatic spread were excluded. Baseline patient and tumour characteristics, and TACE parameters are shown in Table 1. None of the patients had main portal vein obstruction, and 14 (19%) had normal baseline serum αFP levels. In all, 323 TACE sessions were performed on remaining 74 studied patients, and the mean treatment interval was 35 days.

TABLE 1. Baseline patient and tumour characteristics

Characteristic*	Patients
Male/female	64 (86%)/10 (14%)
Median age (range, SD) [years]	57.6 (38-80, 10.8)
History of alcohol intake	36 (49%)
HBV/HCV	60 (81%)/3 (4%)
Presence of symptoms	63 (85%)
Presence of varices†	14 (19%)
Child-Pugh grading Non-cirrhotic A B	 14 (19%) 40 (54%) 20 (27%)
HCC diagnosed by screening programme	7 (9%)
No. of tumour Solitary Multinodular	 27 (36%) 47 (64%)
Bilobar tumour	30 (41%)
Median tumour size (range, SD) [mm] <50 >50	91 (11-190, 42) 18 (24%) 56 (76%)
Portal vein invasion Right Left	 10 (14%) 8 (11%)
Mean total serum bilirubin level (range, SD) [μmol/L] <20 >20	18.2 (4-43, 10) 48 (65%) 26 (35%)
Mean baseline albumin level (range, SD) [g/L] <35 >35	33.7 (21-43, 6) 46 (62%) 28 (38%)
Mean baseline αFP level (range, SD) [ng/mL] <200 >200	15 164 (2-70 700, 24 470) 23 (31%) 51 (69%)
Mean serum creatinine level (range, SD) [μmol/L]	86.8 (56-151, 17)
Mean serum alanine transaminase level (range, SD) [U/L]	72.5 (14-265, 46)
Mean No. of TACE sessions (range, SD)	5 (1-20, 5)
Mean dose of cisplatin/session (range, SD) [mg]	10 (2-29, 6)
Mean dose of lipiodol/session (range, SD) [mL]	13 (1.8-36, 8)
Mean total treatment duration (range, SD) [days]	220 (28-1040, 247)
Mean treatment interval (range, SD) [days]‡	35 (14-85, 15)
Embolisation with gelfoam	56 (76%)
Post-embolisation syndrome	46 (62%)
Superselective cannulation	26 (35%)
New portal vein invasion development	4 (5%)
New metastasis development	5 (7%)

* SD denotes standard deviation; HBV hepatitis B virus; HCV hepatitis C virus; HCC hepatocellular carcinoma; αFP alpha-fetoprotein; and TACE transarterial chemoembolisation
† Available in 25 patients with upper endoscopy performed
‡ Available in 56 patients

Treatment termination

Twenty-three (31%) of the patients stopped their treatment due to deteriorating liver function, and three due to extensive arterio-venous shunting. Three others stopped treatment because of (i) main hepatic artery occlusion, (ii) hepatic artery pseudoaneurysm, and (iii) brain metastasis, and the remaining three were lost to follow-up.

Adverse effect

The complications of TACE are listed in Table

TABLE 2. Complications following 323 courses of transarterial chemoembolisation (TACE) in 74 patients

Complication	No. (%) of various complications post-TACE sessions	No. (%) of patients with each complication
Abdominal pain	86 (27)	47 (64)
Vomiting	24 (7)	29 (39)
Post-embolisation reactions	83 (26)	41 (55)
Elevated transaminase level	64 (20)	36 (49)
Liver failure	4 (1)	4 (5)
Hepatic artery dissection	1 (0.3)	1 (1)
Creatinine level >150 μmol/L	1 (0.3)	1 (1)
Groin haematoma	2 (0.6)	2 (3)

TABLE 3. Univariate analysis of prognostic factors in 74 patients treated with transarterial chemoembolisation (TACE)

Variable	Survival			
	Median (days)	1-Year (%)	2-Year (%)	P value
Tumour size (mm)				
<50	336	44.4	33.3	0.019
>50	183	23.2	5.4	
Child-Pugh grading				
B	123	20	10	0.044
Non-B	273	31.5	13	
Baseline bilirubin level (μmol/L)				
<20	274	33.3	14.6	0.006
>20	121	19.2	7.7	
Baseline α-fetoprotein level (ng/mL)				0.049
<200	334	43.5	17.4	
>200	183	21.6	9.8	
No. of TACE sessions				
<5	151	12.5	1.8	<0.001
>5	532	77.8	44.4	
Dose of cisplatin/session (mg)				
<10	274	38.3	19.1	0.002
>10	151	11.1	0	
Dose of lipiodol/session (mL)				
<15	273	35.8	17	0.008
>15	151	9.5	0	
Treatment interval (days)				
<45	214	21.4	9.5	0.001
>45	532	78.6	35.7	
Embolisation with gelfoam				
Negative	92	5.6	0	<0.001
Positive	274	35.7	16.1	
Superselective cannulation				
Negative	183	18.8	6.3	0.005
Positive	335	46.2	23.1	

2. Forty-one (55%) of the patients experienced post-embolisation reactions, which ensued in 83 (26%) of the TACE sessions. Four patients had liver failure. One patient had a hepatic artery dissection. No patient experienced aggravation of ascites, hepatic encephalopathy, gastro-intestinal bleeding, cholecystitis, ruptured HCC, or liver abscess.

Survival

The median survival of these patients was 214 (range, 28-1887; standard deviation [SD], 367) days. The 1-year, 2-year, and 3-year survival rates were 28%, 12%, and 7%, respectively. Three patients were lost to follow-up 3 months, 9 months and 15 months, respectively after their last TACE sessions and were treated as censored cases, while the remaining 71 studied patients were all dead at the time of analysis. The main cause of death in these patients was liver decompensation (44 patients); four (5%) experienced irreversible liver failure after their latest TACE sessions (already having received 1-3 sessions), all of whom died within 11 to 22 days. Three of them experienced segmental portal vein invasion and one had a tumour size exceeding 90 mm. Two of the latter had αFP levels >70 700 ng/mL, though all four had normal pre-TACE prothrombin times and bilirubin levels (<28 mol/L). One patient died of irreversible renal failure after the second TACE session, and another from an undetermined cause (3 days after the second TACE session). In both cases death was considered procedure-related. In 12 patients death was tumour-related, and the remaining 13 died of other causes (chest infection, stroke, myocardial infarction, and sepsis).

Predictive factors for survival

According to the univariate analysis with the log rank test, 10 factors related to survival were identi ed (Table 3).

The above-mentioned factors (except No. of TACE sessions) were included in the multivariate analysis with the Cox regression model. Five out of nine factors were identi ed as statistically signi cant independent predictors of survival. They were: TACE performed with superselective cannulation, embolisation with gelfoam, treatment intervals of more than 45 days, non Child-Pugh grade B disease, and low pre-treatment serum αFP level (Table 4).

Discussion

Transarterial chemoembolisation was proven to be bene cial for patients with unresectable HCC in a number of non-randomised, case-control studies.[13-15] A few local studies demonstrated a 1-year survival ranging from 49% to 86%.[16-18] Two recent randomised controlled studies demonstrated a survival bene t from TACE in patients with inoperable HCC. Lo et al[8] randomised 79 Chinese patients, including 21 with segmental (but not main trunk) portal vein occlusion, into two groups (TACE and conservative treatment). This study clearly showed a 1- and 2-year survival bene t for TACE of 57% and 31%, respectively. Llovet et al[9] also demonstrated a survival bene t, with 1- and 2-year survival rates in favour of TACE of 82% and 63%, respectively. A meta-analysis

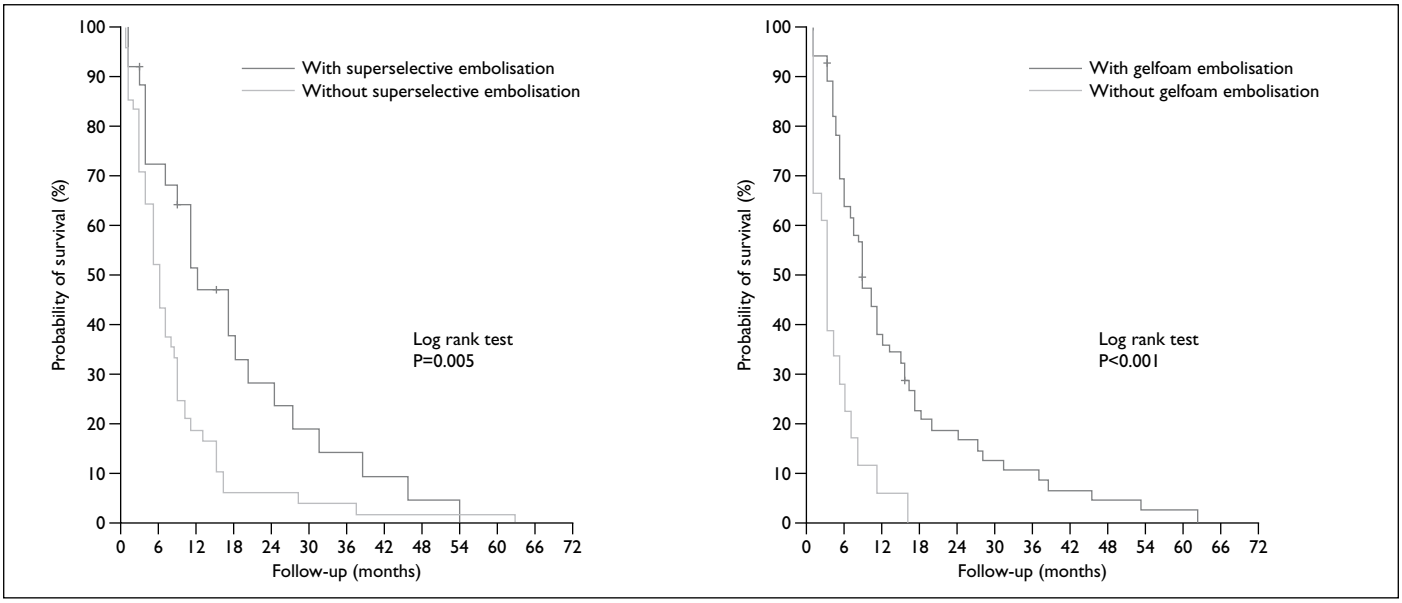

FIG. Survival curves of the 74 patients

with an overall sample size of 898 patients showed that arterial embolisation signi cantly improved 2-year survival when compared to conservative treatment (odds ratio=0.53; 95% CI, 0.32-0.89; P=0.017).[10] On the other hand, data on real clinical practice were scarce, and this was the reason we performed this study.

Surprisingly, the survival of our patient cohort (28% at 1 year; median survival 214 days) was better than in those treated conservatively (8% at 1 year; median survival 90 days, as quoted in another recent local study[4]). Compared to subjects in other existing studies (Table 5[8,9,16]), ours had: (1) larger tumour at the time of diagnosis, (2) higher mean serum αFP levels, and (3) a higher percentage with symptoms. Presence of constitutional symptoms was an independent prognostic factor.[9] By all these characteristics, our cohort had more advanced malignancies than those of others. These differences could be related to the social status of our patients, as they all resided in the northwest district of Hong Kong, where the average income is lower than elsewhere in the territory.[19] A substantial number of new immigrants from Mainland China also reside in our district, and probably had a lower education level, poor self-awareness of well-being, higher family burdens, and longer working hours. Collectively, these features might have delayed presentation to medical services and eventually resulted in late treatment.

TABLE 4. Multivariate analysis on 74 patients with unresectable hepatocellular carcinoma

	P value	Hazard ratio	95% Confidence interval
Superselective cannulation	0.034	0.47	0.23-0.95
Gelfoam embolisation	0.017	0.30	0.11-0.80
Dosage of lipiodol	0.157	2.22	0.74-6.69
Dosage of cisplatin	0.236	2.11	0.61-7.25
Treatment interval	0.006	0.33	0.15-0.72
Size of tumour	0.497	1.33	0.59-2.99
Child-Pugh grade B	0.001	5.62	2.11-14.97
Baseline serum bilirubin	0.246	0.59	0.24-1.44
Baseline serum α-fetoprotein	0.002	2.93	1.50-5.73

TABLE 5. Comparison of different studies involving transarterial chemoembolisation

	Lo et al[8]	Llovet et al[9]	Yuen et al[16]	Present study
Predominant tumour size (cm)	7*	5†	4*	9*
Serum α-fetoprotein level	505 ng/mL*	-	172 ng/L*	2222 ng/mL* 15 164 ng/mL†
Symptomatic patients	70%	-	-	85%

* Median
Mean

This study con rmed that high baseline serum αFP level and Child-Pugh grade B cirrhosis are independent predictive factors of poor survival. Moreover, embolisation with gelfoam and having superselective cannulation were associated with enhanced survival (Fig), which was consistent with a previous study showing that TACE was superior to transarterial chemotherapy without embolisation.[20,21] In this study longer treatment intervals were also related to better survival, which could be due to more satisfactory tumour response after each TACE session. However, regularly scheduled TACE is not

recommended. Ernst et al[22] showed that when the latter approach was compared to TACE that was repeated according to tumour response, regular scheduling was associated with more complications and a lower survival rate. Moreover, in our study superselective cannulation was demonstrated to be a favourable predictive factor. Patients who underwent segmental or subsegmental arterial embolisation had a better prognosis than those having less-selective embolisation. Matsui et al[23] showed that the survival rates of the 82 patients in their cohort who had subsegmental embolisation was 100% at 1 year and 73% at 3 years. In the present study, tumour size was not predictive of survival. Notably, a study of patients with huge HCCs (>10 cm) demonstrated a survival bene t; a 42% 1-year survival in those having TACE versus 8% in controls.[24] Therefore, presence of a huge tumour should not preclude TACE. In the present study, it was also noted that having more TACE sessions was associated with better survival. However, having more sessions may have been merely a consequence of longer survival. For this reason, this variable was not included in our multivariate analysis. Remarkably, in this retrospective study in a regional hospital, only about 10% had their HCC diagnosed by regular screening; the majority being symptomatic at the presentation. Yuen et al[25] found that screening for HCC can identify tumours at an early stage and resulted in a higher proportion receiving treatment. In our study, TACE was a relatively safe intervention. Although minor complications such as post-embolisation reactions were common, no patient experienced major post-TACE complications such as ascites, hepatic encephalopathy, gastro-intestinal bleeding, cholecystitis, or liver abscess. Chan et al[26] investigated the complications of TACE, in which a minority of patients (1-3%) experienced major complications including: gastro-intestinal bleeding, liver abscess, ascites, and hepatic encephalopathy. Acute liver failure was observed in 28% (17/60) of their patients. We identi ed four such patients (5%) in our series, all of whom died in the same episode of liver failure, which could have been due to the advanced stage of their liver disease.

The retrospective nature of the present study based on information retrieved from hospital records may result in inter-observer bias, excessive reliance on non-standardised record keeping, and problems associated with missing data in hospital notes. In order to minimise the inter-observer variation, only the chief author reviewed and analysed the data. Generalisation of these results may also be limited, as the data were collected from only one centre. Despite these limitations, our study provides useful local data in a regional hospital with a speci c background relevant to our studied population.

Conclusions

Notwithstanding the bene ts demonstrated in randomised controlled trials, survival of patients with inoperable HCC undergoing TACE was still grave in real-life clinical practice. Nevertheless, we showed that this intervention is mostly bene cial to patients with preserved liver function and low pre-treatment αFP level, but not for those presenting late. We therefore suggest that strict patient inclusion criteria should be used, whereas poor socioeconomic state should not preclude TACE. Moreover, better survival was demonstrated in subjects having superselective cannulation or embolisation with gelfoam. As our study only included patients undergoing TACE and nil else, it is postulated that survival could be signi cantly improved with concurrent use of other treatment modalities (ablation techniques). With further trials and advances in medicine, we hope that patients with unresectable HCC will be able to enjoy better survival.

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