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ORIGINAL ARTICLE

Quality of life and survival analysis of patients undergoing transarterial chemoembolization for primary hepatic malignancies: a prospective cohort study

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Abstract

Introduction: Transarterial chemoembolization (TACE) is indicated for primary hepatic tumours when resection or local ablation are not feasible. Patients undergoing TACE have a better survival than best supportive therapy. However, there is paucity of prospective studies on the quality of life (QOL) after TACE for primary hepatic malignancies, especially in the Western world.

Purpose: The primary aim of the present study was to determine if TACE impacts on the QOL of patients affected by primary hepatic tumours, and to assess treatment efficacy in a prospective cohort of patients treated at a tertiary Canadian university medical centre.

Methods: From September 2005 to December 2010, 48 candidates for TACE underwent at least one TACE session. Data on their QOL, tumour response, serum alpha fetoprotein (AFP) and survival were prospectively collected every 3–4 months.

Results: The overall QOL of patients undergoing TACE did not decline during the first 12 months after treatment. A decline was observed in the physical health domain after the third TACE that coincided with the increasing size of the largest tumour and a rise in the serum AFP levels. Psychological, social and environmental domains remained stable throughout the treatment period. Multivariate analysis revealed that tumour focality, AFP levels and model of end-stage liver disease (MELD) scores were associated with long-term survival ($P = 0.001$, $P = 0.01$, $P = 0.02$, respectively). The overall survival at 12, 36 and 48 months were 72%, 28% and 12%, respectively.

Conclusion: TACE is an effective palliative intervention for unresectable and non-ablatable primary liver tumours without affecting the QOL of patients even when repeated interventions are performed.

Keywords

hepatocellular carcinoma, cholangiocarcinoma, transarterial chemoembolization, quality of life, alpha-fetoprotein, survival

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most frequent cancer in the world and the third most common cause of cancer-related mortality.[1] Although more common in Asia and Africa, its incidence is increasing in the Western world.[2] According to the Surveillance and Epidemiology End Results (SEER) registries in the United States, the average age adjusted incidence of HCC increased from 1.3 per 100 000 in 1978 to 1980 to 6.6 per 100 000 in 2002.[3] Similarly, the incidence of intrahepatic cholangiocarcinoma is rising in most countries and it represents the second

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most common malignancy of the liver after HCC.[4] At the time of diagnosis, the vast majority of patients are not surgical candidates and palliative modalities such as local ablation and transarterial chemoembolization (TACE) are the only possible treatments.[5]

TACE is indicated when a resection or local ablation are not feasible or for patients waiting for a liver transplantation.[6] It combines the injection of antineoplastic agents with the selective obstruction of the arteries feeding the tumour causing cell necrosis while preserving normal liver parenchyma.[7] More recently, TACE has found a role as a neo-adjuvant strategy for resectable patients with HCC[8] and for selected cases of unresectable cholangiocarcinoma.[9] A partial response has been observed in 17% to 61.9% of cases,[10] although a complete response is very rare (0%–4.8%).[8]

As the majority of patients undergoing TACE suffer from a terminal disease, preventing liver decompensation and maintaining an acceptable quality of life (QOL) during their treatment is as important as prolonging their survival. In the past decade, only a few studies, mainly from Asia, have measured the QOL of patients undergoing TACE for primary hepatic tumours. Asian patients are well known to have different risk factors than in Western countries.[11–14] Therefore, the main objective of this prospective study was to assess the impact on the QOL and survival of patients undergoing sequential sessions of TACE in a tertiary university hospital in North America.

Patients and methods

Patient population

All patients referred to the Queen Elizabeth II Health Sciences Centre (Halifax, Nova Scotia, Canada) and diagnosed with unresectable and non-ablatable HCC or cholangiocarcinoma were considered candidates for this study. Patients affected by HCC were triaged to their therapeutic algorithm according to the Barcelona Clinic Liver Cancer (BCLC) staging criteria.[15] Patients with cholangiocarcinoma were treated with TACE only if unable to undergo hepatic resection or local ablation for one of the following reasons: tumour size, tumour location or the presence of severe comorbidities. All participants were recruited from hepatology, oncology and surgical clinics. Written consent was obtained from each participant or from their next of kin when affected by visual, hearing or other significant cognitive impairments. The local ethic review board approved the study protocol as it followed the ethical principles for medical research involving human subjects according to the Declaration of Helsinki developed by the World Medical Association.

Study design

From September 2005 until December 2010, 48 consecutive patients who satisfied the inclusion criteria underwent a total of 105 TACE sessions. All participants were presented at a multidisciplinary weekly meeting where medical oncologists, hepatologists, surgeons and interventional radiologists discussed and obtained a consensus on the best treatment strategy for each patient. For patients referred for TACE, the location and number of suspected primary liver tumours were recorded prospectively. Multifocal tumours were defined as multiple lesions identified on imaging tests in several segments of the same hepatic lobe and bilobar involvement was defined when both hepatic lobes were involved according to the Brisbane terminology of liver anatomy.[16] In the presence of bilobar disease, chemoembolization of the lobe with the largest tumour burden was performed first followed by treatment of the contralateral lobe after 3–4 months. QOL questionnaires, physical examination, radiological abdominal studies with i.v. contrast injection, chest radiographs and haematological and chemistry blood tests were obtained per protocol at the time of diagnosis and then before all TACE procedures. TACEs were performed every 3 to 4 months by dedicated interventional radiologists unless extrahepatic disease, liver decompensation or significant side effects occurred. Patients who had transient liver decompensation or who developed systemic infection or bone marrow suppression during the duration of this study were re-evaluated every 3 to 4 months, or more often if necessary, and considered candidates for a repeat TACE if they satisfied the original inclusion criteria.

All data were prospectively collected by the primary investigators or by a study coordinator and entered into a digital database with secure access to protect patients' confidentiality. Intention-to-treat analysis of the QOL data was performed by comparing changes occurring over time to the baseline values obtained prior to the first intervention.

TACE procedures

All patients underwent TACE according to a standard protocol. Abdominal contrast computerized tomography (CT) or magnetic resonance imaging (MRI) studies were obtained within 4 weeks before each therapeutic intervention. All patients were admitted to the hospital the night before TACE, fasted overnight and were required to stay for a minimum of one night after the procedure. Intravenous (i.v.) fluid hydration and parenteral antibiotic prophylaxis with cefazolin (or vancomycin/clindamycin if allergic) and metronidazole were administered before arterial groin catheterization. Post TACE all patients received 4–8 mg of i.v. ondasentron to prevent nausea and vomiting associated with sedatives and chemotherapy used during the procedure. Patients affected by viral hepatitis B received lamivudine therapy before and after TACE to prevent hepatitis flare ups. A selective 4- or 5-French catheter was introduced by cannulating the common femoral artery and a visceral angiography was carried out to assess the arterial blood supply to the liver and confirm patency of the portal vein. Depending on the size, location and arterial supply of the tumour, the tip of the catheter was advanced into the right or left hepatic artery or super-selectively when possible using microcatheters. In super-selective TACEs, the distal portion of the sub-segmental artery feeding the tumours were injected with chemotherapy agents and embolized to evoke neoplastic necrosis on a small area of the liver, thus avoiding damage to normal

parenchyma. Chemoembolization of only one lobe of the liver for each TACE session was carried out after mixing doxorubicin hydrochloride (75 mg/m^2 body surface area) with 10 ml of lipiodol (ethiodized poppy seed oil, EZ-EM®; Montreal, Quebec, Canada) for patients with HCC and gemcitabine (1500 mg/m^2 body surface area) for patients with cholangiocarcinoma. Polyvinyl alcohol particles were then injected if the chemoembolized artery territory did not show stagnant flow. During the period between 2009 and 2010, doxorubicin eluting beads were used to perform TACE in patients affected by HCC who were randomized in an international multicentric controlled trial comparing drug eluting beads chemoembolization vs. conventional TACE. Before discharge, all patients underwent baseline post-treatment CT without parenteral contrast injection to assess the distribution of lipiodol in the tumour or with intravenous dye injection to assess the vascularity of the neoplastic lesions for patients treated with drug eluting beads.

Primary aim of the study

The primary aim of the present study was to determine if the QOL of patients undergoing TACE for unresectable and non-ablatable primary hepatic tumours had a significant decline over time in comparison with their pre-intervention state.

Secondary aims of the study

The secondary aims of the study were to assess 5-year overall survival and if there were survival differences according to focality, lobar distribution, tumour response by response evaluation criteria in solid tumours (RECIST) criteria and[10] variation in serum AFP levels in all patients undergoing at least one TACE.

Inclusion and exclusion criteria

Patients included in the present study were all adults able to give written consent or for whom consent was obtained by their next of kin, affected by non-resectable and non-ablatable HCC or cholangiocarcinoma in the presence of compensated liver function (Child–Pugh A or B)[17] with an Eastern Cooperative Oncology Group (ECOG) performance status between 0 to 2[18] and without radiological evidence of extra-hepatic disease.

Patients were excluded if younger than 18 years of age, unable to provide written consent, affected by advanced liver dysfunction (Child–Pugh class C) or renal impairment (defined as serum creatinine above 180 μmol/l), allergic to i.v. dye, or when diagnosed with extra-hepatic disease, with main portal vein (PV) or main branch PV thrombosis, and if affected by neutropenia (neutrophil count equal or less than 1000/ml) or thrombocytopenia (platelet count equal or less than 50 000/ml).

Diagnosis of primary hepatic tumours

A diagnosis of HCC was made when one cross-sectional study (triphasic contrast abdominal CT scan or MRI) was suggestive for HCC in the presence of serum AFP above 100 ng/ml. Alternatively, HCC was diagnosed when two contrast-enhanced cross-sectional studies showed the presence of hypervascular tumours with portal vein washout. When a diagnosis was not established using non-invasive modalities, a percutaneous liver biopsy of the most accessible tumour was obtained according to the guidelines of the American Association for the Study of Liver Diseases (AASLD).[19] A diagnosis of cholangiocarcinoma was made by tissue diagnosis obtained by a true cut liver biopsy in all patients before undergoing TACE.

Variables collected at the time of diagnosis

The following demographic and clinical variables were collected at the time of enrolment: patients' age, gender, weight, height, body mass index (BMI) and body surface area (BSA), which were used to calculate the amount of chemotherapy agent infused during each TACE session. Clinical variables included the risk factors contributing to the development of primary hepatic tumours, histology when available, the measurement of the main diameter of the largest tumour nodule, the presence of multicentric or multilobar tumours and the total number of nodules. Haematological parameters included a coagulation profile, renal and liver function tests, the model of end-stage liver disease (MELD) at the time of diagnosis,[20] serum AFP levels, the presence of vascular tumour involvement by radiological characteristics or by histology, interventions performed before and after each participant's inclusion such as ablation, resection or liver transplantation and the total number of TACE sessions for each patient.

Variables collected during therapy

After the first TACE session, the following variables were collected at interval of 3–4 months in addition to the quality of life questionnaires: the size of the largest tumour nodule treated by TACE on the most recent cross sectional radiology study, hematological parameters, coagulation profile, renal and liver function tests and the serum AFP levels.

Quality-of-life questionnaire

Patients were requested to complete the baseline World Health Organization QOL questionnaire (WHOQOL-BREF)[21] fully and without assistance, and were given adequate time to complete this task before reviewing their disease status and treatment plan. Patients were then requested to complete the questionnaire during each visit scheduled every 3 to 4 months in accordance with the guidelines set forth in the WHOQOL-BREF Manual. The WHOQOL-BREF was chosen as the instrument to assess QOL because it is comprehensive, it has been validated in several countries, it is easy to administer and it is relatively short in comparison with other similar instruments. The WHOQOL-BREF contains a total of 26 questions divided into four domains: physical, psychological, social and environmental health. Attributes incorporated within the physical health domain of the WHOQOL-BREF include: activities of daily living, dependence on medicines or medical aids, energy and fatigue, mobility, pain and discomfort, sleep and rest and work capacity. Attributes incorporated within

the psychological health domain are: body image and appearance, negative and positive feelings, self-esteem, spirituality, religion and personal beliefs, thinking, learning, memory and concentration. Measurements of social health domain include personal relationships, social support and sexual activity. Features incorporated in the environmental health domain are: financial resources, freedom, physical safety and security, health and social care, home environment, opportunities for acquiring the new information and skills, participation in and opportunities for recreation, physical environment and transportation.

Raw scores were scaled in a positive direction (i.e. higher scores denote higher QOL) then data were transformed in scores on a 0–100 scales using validated conversion.[21] Questionnaires which contained more than 20% of missing data were discarded as recommended by instruction provided in the manual of WHOQOL-BREF.

Tumour staging

The largest tumour nodule identified, using contrast cross-sectional abdominal imaging tests, was sized for each patient at the time of diagnosis and before each TACE by one of the primary investigators (K.M.E.). All the measurements were performed using an electronic scale in millimeters provided by the software used by the radiology department at our institution (IMPAX Web1000®; Agfa, Mortsel, Belgium). TNM classification (AJCC, 7th edn)[22] was used to stratify tumours according to their largest diameter.

Follow-up

Every 3–4 months, all patients were evaluated with physical examinations, chest radiographs, serial radiological studies with parenteral contrast infusion in addition to haematological and biochemical tests including serum AFP. Patients were censored if alive at the time of the closure of the present study, when they had undergone liver transplantation, or if they were lost at follow-up. The time of censoring was defined as the last date of documented follow-up. Missing data were minimized by contacting patients, their families or their primary physicians by phone or by letters. Patient's date of demise was confirmed by death certificate, from the prospective provincial tumour registry or by contacting patients' primary doctors or their next of kin. Follow-up data were available for all participants.

Statistical analysis

Summary statistics were constructed for the baseline values, using frequencies and proportions for categorical data, and means and standard deviations (SD) for continuous variables. Categorical outcomes were analysed using the chi-square test or Fisher's exact test when appropriate. Continuous variables were compared using the Mann–Whitney or Kruskal–Wallis test. All statistical tests were two-tailed and a *P*-value of less than 0.05 was considered significant. For time-to event outcomes, the distributions of time to the first event were compared using the log-rank test; the Kaplan–Meier method was used to estimate the absolute risk of each event for each group, and hazard ratios and 95% confidence intervals (CIs) were estimated using the Cox proportional hazard model. To identify the baseline and clinical variables associated with the overall survival time, multivariable analyses were performed using the Cox proportional hazard model with a stepwise selection procedure. The stepwise procedure was set at the threshold of 0.10 for inclusion and 0.05 for exclusion. Repeated measures analysis of variance (ANOVA) was performed to test for trends in QOL measures taken after TACE sessions over time, controlling for baseline QOL measure taken before the first TACE session. This was done for each of the four health domains. All statistical analyses were performed with the intent to treat methods using SPSS 18.0 statistical software (SPSS Inc., Chicago, IL, USA) or SAS (version 9.2; SAS Institute Inc., Cary, NC, USA).

Results

Patients' characteristics

Table 1 outlines the demographic and clinical characteristics of the study population. The mean age of participants was 61.1 years (SD = 9.0) with the majority being males (87.5%). The most common predisposing factor of HCC was hepatitis C virus infection (34.7%) followed by alcoholic cirrhosis (32.7%). Two patients (4.1%) were diagnosed with unresectable cholangiocarcinoma and received gemcitabine[9] chemotherapy during their TACEs.

Chemoembolization treatment

According the patient's clinical response to TACE and tumor characteristics on CT, the decision was made to proceed for another TACE session when there was evidence of enhancing viable tumour without lipiodol deposition, tumour growth or the development of new tumours. Five patients (10.4%) were deemed still transplantable after TACE and underwent cadaveric liver transplants. All patients underwent at least one TACE with 12.5% of participants undergoing three or more sessions. The median number of chemoembolizations per patient was 1.7. The time interval between subsequent TACE procedures was determined using patient-specific clinical and radiological factors; the mean interval between TACE 1 and TACE 2 was 18 weeks (SD = 8.0), and TACE 2 and TACE 3 was 22 weeks (SD = 5.9) (Table 1). Only two patients had more than 3 TACE sessions (5 and 6 interventions respectively).

The mean size of the treated tumours was 5.2 cm (SD = 3.2) with a single mass detected in 54.2%. Thirty patients (62.5%) received TACE for a right lobe HCC whereas 16 (33.3%) received TACE for bilobar lesions (Table 2). The average MELD score and AFP levels before the first TACE session were 8.5 (SD = 3.2) and 8775.9 ng/ml (SD = 34 346.4), respectively (Table 2).

Quality-of-life measures

The transformed scores of the WHOQOL-BREF questionnaires for physical, psychological, social relationships and environmental

Table 1 Study population characteristics

Variable	Values
Age, years (SD)	61.1 (9.0)
Gender, male (number, percentage)	42 (87.5)
Risk factors for a primary hepatic tumour (number, percentage)	
Viral hepatitis C	17 (35.4%)
Viral hepatitis B	2 (4.2%)
Non-alcoholic stato-hepatitis	4 (8.3%)
Alcohol	16 (33.3%)
Other	5 (10.4%)
Body mass index (average, SD)	28.3 (5.3)
Body surface area, m^2 (average, SD)	1.94 (0.23)
Candidates for liver transplantation (number, percentage)	21 (43.7%)
Number of patients transplanted (number, percentage)	5 (10.4%)
Prior interventions for hepatic tumour (number, percentage)	
RFA	6 (12.5%)
Histological diagnosis (number, percentage)	10 (20.8%)
Radiological diagnosis (number, percentage)	38 (79.2%)
Tumour type (number, percentage)	
Hepatocellular carcinoma	46 (95.8%)
Intrahepatic cholangiocarcinoma	2 (4.2%)
Total number of TACE procedures	105
Number of TACE procedures per patient (mean, SD)	1.7 (1.0)
Number of tumours per patient (mean, SD)	2.1 (1.6)
Total number of TACE procedures (number, percentage)	
Left lobe	2 (4.2%)
Right lobe	30 (62.5%)
Both lobes	16 (33.3%)
Mean follow-up (months, SD)	12.3 (10.4)
Mean interval between TACE 1 and TACE 2 (weeks, SD)	18 (8.0)
Mean interval between TACE 2 and TACE 3 (weeks, SD)	22 (5.9)
Mean interval between TACE 3 and TACE 4 (weeks, SD)	13 (1.4)

SD, standard deviation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Table 2 Tumour and laboratory variables at diagnosis

Tumor and laboratory variables at diagnosis	Value
Tumour characteristics (number, percentage)	
Single tumour	26 (54.2%)
Multiple tumours	22 (45.8%)
Size of the largest tumour, cm (mean, SD)	5.2 (3.2)
Location of tumour (number, percentage)	
Left lobe	2 (4.2%)
Right lobe	30 (62.5%)
Bilobar	16 (33.3%)
Radiological vascular tumour invasion (number, percentage)	
Present	6 (12.5%)
Absent	42 (87.5%)
TNM classification (AJCC, 7th Edition) (number, percentage)	
T1	10 (20.8%)
T2	15 (31.3%)
T3a	19 (39.5%)
T3b	4 (8.3%)
White blood count × 10(9)/l (mean, SD)	6.1 (2.2)
Red blood cells × 10(120/l (mean, SD)	4.0 (0.5)
Platelets × 10(9)/l (mean, SD)	149 (101.0)
INR (mean, SD)	1.2 (0.2)
Potassium mmol/l (mean, SD)	4.1 (0.4)
Sodium mmol/l (mean, SD)	136 (3.4)
Creatinine µmol/l (mean, SD)	79.6 (20.5)
Total bilirubin µmol/l (mean, SD)	25 (18.8)
Albumin g/l (Mean, SD)	33.5 (4.6)
MELD (mean, SD)	8.5 (3.2)
Serum alpha fetoprotein level (mean, SD)	8 775.9 (34 346.4)

SD, standard deviation; MELD, model of end-stage liver disease.

wellbeing domains were obtained at the time of diagnosis and before each TACE session. The overall trend of each domain was followed throughout the treatment period controlling for the baseline QOL measured before the first TACE. There were no statistically significant temporal trends for any of the four health domain QOL measures at the alpha = 0.05 level. As represented in Fig. 1, the overall QOL of patients undergoing repeat sessions of TACE remained stable over time, although a trend towards a decline of the physical health domain was observed after patients underwent at least three interventions ($P = 0.08$) that coincided approximately to 1 year after the first treatment.

Tumour response

For most of the patients, there seemed to be a disease-stabilizing effect on the tumour size by the RECIST criteria[10] with a concomitant decline of the serum AFP levels measured at 3, 6, 9 and 12 months. Although not statistically significant, the reduction in serum AFP and tumour size persisted for 6–9 months after the first therapy and progression of the disease was observed after the third session of chemoembolization as represented in Fig. 2.

Survival

The median survival of this cohort was 22 months (95% CI = 16.6–27.3) and the overall survival probability at 12, 36 and 48

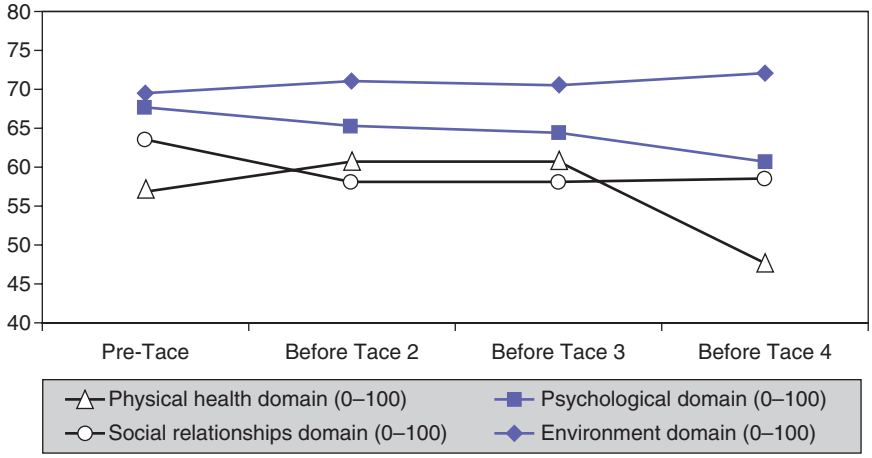

Figure 1 Graphical representation of the trends of the quality of life (QOL) of patients undergoing transarterial chemoembolization (TACE) for primary hepatic tumours. A repeated measures analysis of variance for the temporal trend of each domain did not reveal any statistical significance when controlling for the baseline value measured before the first TACE

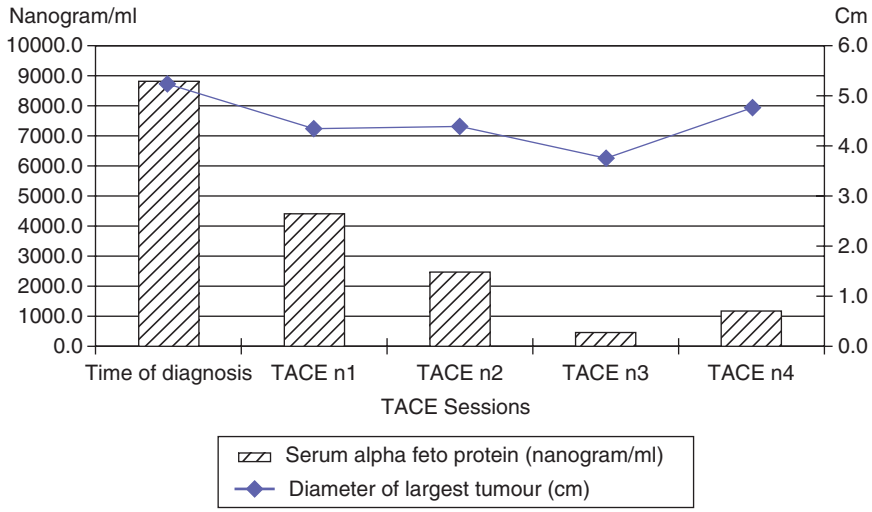

Figure 2 Interval changes of the tumour with the largest diameter and levels of serum alpha fetoprotein. Both variables did not show any statistical difference over time although there was a decline in the serum tumour marker level and the largest diameter of the tumour treated by TACE (P = NS)

months was 72, 28 and 12% respectively (Fig. 3). At univariate analysis, patients affected by a single tumour vs. multifocal disease or by involvement of one lobe vs. both lobes had significant better survival rates after TACE ($P < 0.05$) (Fig. 4a–b). To determine the effect of other potential prognostic factors associated with survival post TACE, a backward stepwise selection in the Cox proportional hazard regression model was performed including important clinical variables such as: age, tumour size, presence of multicentric and multilobar disease, vascular invasion, MELD score and serum AFP. Among them, the presence of multiple tumours ($P = 0.001$), a MELD score above 8 ($P = 0.01$) and serum AFP levels above 100 ng/ml ($P = 0.02$) at the time of diagnosis were all associated with a significantly worse outcome after TACE.

Discussion

Kato and colleagues described TACE for the first time in 1981.[23] Although there is consensus in terms of improved tumour response after TACE, the results on survival benefit remained controversial until 2002 when two trials demonstrated a survival advantage for patients undergoing treatment in comparison to best supportive care.[24,25] A recent systematic review[26] has confirmed that TACE improves the overall survival for patients with unresectable and non-ablatable HCC; however data on the longitudinal variations of the QOL of subjects undergoing treatment remains very scarce especially in Western countries.

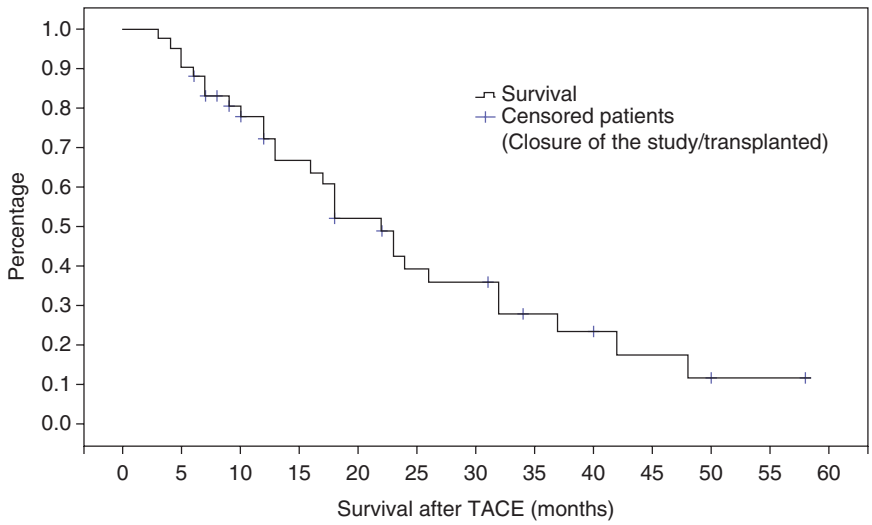

Figure 3 Overall survival after treatment with transarterial chemoembolization (TACE) for primary hepatic tumours

As the majority of patients with primary hepatic tumours diagnosed in Europe and North America are cirrhotic, treatment modalities are more likely to be dictated by the function of the liver rather than by the tumour stage. Quite often clinicians taking care of cirrhotic patients with primary hepatic tumours have to face the difficult decision to determine if the treatment is worth the potential risk of provoking liver decompensation with the possibility of a rapid decline of patients' QOL, or in the worst case scenario, causing irreversible organ failure and premature death.

A large body of literature has shown that TACE improves the overall survival of patients with primary liver tumours who are not surgical candidates,[4,9,25,27] but still there are only a few prospective studies[12,13,28] that have analysed the trend of the QOL of these patients. None have assessed the potential relationship between QOL, tumour response and overall survival. Without any doubts, during the past decade health care providers have been paying more attention to measuring the QOL of patients undergoing oncological treatments. Several previous studies have shown that for patients with terminal diseases, their overall survival might not be as important as maintaining a good level of functional status.[29–32] In light of these findings, QOL assessment has become more critical when the likelihood of a cure is low as in advanced HCC.[28] In these circumstances, QOL has been increasingly used as an outcome measure for the evaluation of different palliative treatments where the goal is to improve or maintain patients' ability to live the best possible life within the constraint of their disease. Unfortunately, for HCC the assessment of QOL has occurred mostly in the context of randomized controlled trials testing the safety and the effectiveness of new therapies in comparison to the standard therapy already in use and very limited data is available for patients treated outside these trials.[28]

Recognizing these limitations, Wible *et al.*[12] have studied a prospective cohort of patients treated with TACE for non-surgical HCC in the USA. They recruited 73 subjects who underwent 163 surveyed TACE sessions and used the Short Form-36 (SF-36) Health Survey Forms (Version 1)[33] to evaluate potential changes in the QOL of patients undergoing TACE every 4 months. In this previous study, patients reported a significant improvement in their QOL at 4 months after the first TACE although at 8 and 12 months the reported differences of QOL did not reach statistical significance and became almost non-existent after 1 year. One of the most important findings was that there was no trend towards deterioration of patients' overall QOL over the 12-month period even if a large proportion of patients had Child–Pugh class B and C liver dysfunction for whom some deterioration of their QOL would have been expected for the natural progression of the tumour and liver disease.

These findings were also confirmed in our study where the majority of patients had compensated cirrhosis with an average MELD score of 8. In our population, patients tolerated selective TACE sessions well and were discharged from the hospital after only 1 or 2 days during which they were treated for hydration or pain control. The most common immediate side effect after TACE was the development of some degree of post-embolization syndrome that occurred in about 40% to 50% of patients. Severe side effects such as the development of a hepatic abscess (one patient) and transient liver decompensation with the development of ascites responsive to diuretics occurred in five patients. These findings were similar to previous data reported by our group.[34] In patients with bilobar disease the decision was made to start with the lobe showing the most tumour burden and then re-evaluate according to the tumour response as well as patient's tolerability to the procedure. A step-wise approach was performed in order to prevent liver decompensation which could occur when bilateral simultaneous TACEs are performed.

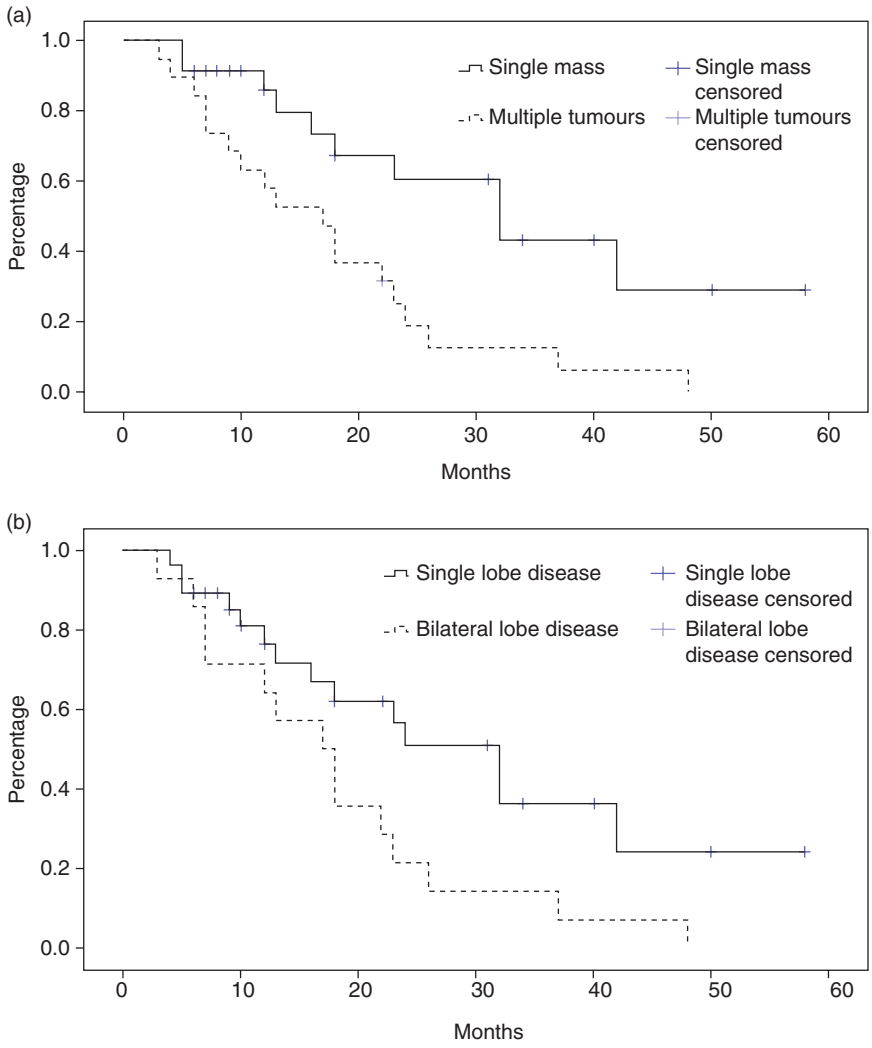

Figure 4 (a) represents the Kaplan–Meier survival curves of patients affected by single vs. multiple primary hepatic tumours ($P = 0.04$). Similarly, in (b), patients with tumour involvement of both hepatic lobes had a significant lower survival rate in comparison with individuals who had only one lobe involved by tumours ($P = 0.02$)

As previously shown by Wible *et al.*,[12] the most important finding of the present study was that the majority of patients were able to tolerate several TACE sessions without significant deterioration of their QOL. The QOL of the cohort remained stable for almost 1 year whereas a decline was observed only after the third TACE that coincided with progression of the tumours. The findings of the present study were similar to a recent study by Toro *et al.*[35] where the QOL of the group of patients receiving TACE declined 9 months after initiation of therapy. Yet, in this previous study all aspects of QOL were affected which was more evident on a longer follow-up period. With this aggressive chemoembolization approach, the overall survival of our population at 12, 36 and 48 months were 72%, 28% and 12% respectively. Our results confirmed that the survival benefit after TACE is observed even when patients had multiple tumours or bilobar disease although significantly better long-term survival was seen for patients with single tumours or multiple tumours involving only one lobe of the liver.

These findings are in line with the survival outcomes of the two large randomized controlled trials. Llovet *et al.*[25] reported 2-year survival rates of 63% for patients undergoing TACE vs. 27% for best supportive care. Lo *et al.*[24] reported 3-year survival rates of 26% and 3%, respectively. The present study has confirmed that a reduction in serum AFP,[36] repetition of TACEs,[37,38] low MELD score,[39] the absence of diffuse disease[40,41] and small tumour size[42] are all associated with a better prognosis.

One of the limitations of the present study was the relatively small number of patients and the fact that not all subjects underwent histological proof of HCC. Therefore, there is the potential risk that some patients treated with TACE were not affected by

primary malignant lesions of the liver, but rather benign entities such as adenomas, focal nodular hyperplasia, regenerative or dysplastic nodules that might appear as HCC by radiological criteria. Nevertheless, our protocol applied the diagnostic criteria for HCC suggested by the AASLD in which liver biopsy is not indicated for the diagnosis of HCC in the presence of confirming cross-sectional contrast enhanced radiological studies.[19]

The strength of the present study is that it is the only prospective observational study designed to assess both the QOL and overall survival of patients diagnosed with primary hepatic tumours treated with an aggressive TACE protocol where chemoembolization was performed every 3–4 months in a North American population. As patients characteristics are heterogeneous in different geographical areas, our study has shown that even in compensated cirrhotic patients, TACE not only provides overall survival benefits in comparison to best supportive care, but also does not impact negatively on their overall QOL.

Another important aspect is that the WHOQOL-BREF questionnaire was chosen because this instrument has been validated in several Countries outside North America and Europe and therefore our results could be generalizable to other geographical areas where socio-economic and patients' characteristics differ from our sample. In addition, it could be used for future studies to confirm or reject our findings in countries where the risk factors for primary liver tumours differ significantly from our population.

In summary, TACE for the treatment of primary unresectable hepatic neoplasms is a safe and effective therapy that prolongs life even in cirrhotic patients with compensated liver disease. It does not seem to negatively impact their QOL even when repeated treatments are performed for multiple liver tumours or for bilobar disease.

Conflicts of interest

None declared.

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