

The evaluation for clinical prognostic factors of primary liver cancer treated by transcatheter arterial chemoembolization

Congcong Jiao¹, Hongzong Si², Lianhua Cui^{1*}

¹Department of Public Health, Qingdao University Medical College, Qingdao, 266071, China

²Institute for Computational Science and Engineering, Laboratory of New Fibrous Materials and Modern Textile, The Growing Base for State Key Laboratory, Qingdao University, Qingdao, 266071, China

Abstract: Transarterial arterial chemoembolization (TACE) is the most widely used treatment for unresectable primary liver cancer (PLC). The aim of this study was to find out main factors that impact the prognosis of PLC patients treated with TACE. 59 patients with PLC were obtained from Affiliated Hospital of Qingdao University Medical College from February 2006 to August 2010. All patients received a routine invasive strategy with TACE of Affiliated Hospital of Qingdao University Medical College. Then these patients were followed up for 2 years (from March 2008 to April 2011). The results showed that patient survival following a first TACE therapy at 1, 2 and 3 years was 42.7%, 22.0% and 3.4% respectively and the median overall survival time is 7.8 months. On univariate analyses, overall survival differed on AFP $\geq 400\mu\text{g/l}$, portal vein tumor thrombosis, serum albumin, and metastasis. On multivariate Cox regression, three independent predictors of decreased overall survival were identified: AFP $\geq 400\mu\text{g/l}$, metastasis and serum albumin $\geq 36\text{g/l}$.

Keywords: Prognosis; Primary liver cancer; Transarterial chemoembolization

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* Corresponding Author: Lianhua Cui, qdlhcui@163.com

1. Introduction

Primary liver cancer (PLC) or most commonly known as hepatocellular carcinoma (HCC), is the fifth most common neoplasm and the third most common cause of cancer-related death in the world [1]. With 7.18% of the entire population carry the hepatitis B virus in China, Chinese patients account for >55% of new cases of HCC worldwide and HCC is a leading cause of cancer-related death among Chinese population [2]. PLC is also a high malignancy with insidious onset, invasive fast-growing, high recurrence rate and fatality. The first-line treatment for HCC is liver transplantation or surgical resection [3]. HR is technically difficult for treating huge HCC because extensive resection is usually required, which may be associated with high risk of mortality and poor prognosis. In patients with large or multiple lesions, Transarterial arterial chemoembolization (TACE) is used frequently for the treatment of HCC when other curative treatment is not possible [4].

We all know that the liver has a dual blood inflow supply through the portal vein (supply most of the blood to the liver) and the hepatic artery (only a supportive role) in normal liver. However, the hepatic artery practically becomes the sole supplier of blood to the tumor in HCC. TACE exploited this anatomic configuration precisely, the hepatic artery is used as a roadway to treat the tumor in TACE, and the nontumorous liver is least affected. The rationale for TACE is that the intra-arterial injection of a chemotherapeutic drug such as doxorubicin or

cisplatin followed by embolization of the blood vessel will result in a strong cytotoxic effect enhanced by ischemia [5]. But in real clinical practice, the recurrence rate is higher in patients received TACE and intrahepatic recurrence rates were up to 60 percent have been reported. Moreover, many studies revealed that TACE achieved a significantly shorter survival time than hepatic resection [6,7].

Herein, the aim of this study was to investigate the overall survival curves of PLC patients after TACE treatment by Kaplan-Meier. The Cox's proportional hazard model was used to identify the best combination of significant prognosis factors. This study evaluated the efficacy of TACE in treatment of PLC and find out main factors that impact the prognosis of PLC patients after TACE treatment.

2. Methods

2.1. Subjects

A written consent was obtained from all patients before enrollment in the study, and Qingdao university medical college ethics committee approved the protocol. 59 patients with Primary liver cancer (PLC) were obtained from Affiliated Hospital of Qingdao University Medical College from February 2006 to August 2010. All the patients with integrated clinical data underwent Transarterial chemoembolization (TACE) as their initial treatment. The diagnosis of Primary liver cancer was confirmed by liver histopathology, but if histopathology was not

available, by two imaging modalities, such as ultrasound [US], magnetic resonance imaging [MRI], computed tomography, and/or Alpha fetoprotein (AFP) ≥ 400 ng/mL. The patients with 1 or more exclusion criteria were eliminated from the cohort: 1) serious cardiac, lung, and kidney diseases; 2) HCC patients with patients with Child Pugh C were also excluded from HCC group; 3) the patients who received other therapy before or after treatment were also excluded from CHB and HCC groups.

Table1 The clinical information of patients with primary liver cancer.

Variables	Groups	Number	%
Sex	M	49	83.1
	F	10	16.9
Age	≥ 50	20	33.9
	< 50	39	66.1
AFP	≥ 400 ug/l	30	50.8
	< 400 ug/l	29	49.2
PVTT	N	45	76.3
	Y	14	23.7
Metastasis	N	52	88.1
	Y	7	11.9
Albumin	≥ 36 g/l	20	33.9
	< 36 g/l	39	66.1
TNM stage	I + II	16	27.1
	II + III	43	72.9
Tumor size	≥ 6 cm	15	25.4
	< 6 cm	44	74.6
ALT	≥ 64 U/L	29	49.1
	< 64 U/L	30	50.9
AST	≥ 42 U/L	13	22
	< 42 U/L	46	78
CEA	≥ 3.4 ng/ml	33	55.9
	< 3.4 ng/ml	26	44.1
CA199	≥ 39 U/ml	30	50.9
	< 39 U/ml	29	49.1

2.2. TACE Procedure

Each patient was discussed in a team meeting to decide the appropriate approach. All patients received a routine invasive strategy with TACE of Affiliated Hospital of Qingdao University Medical College. With the patient under local anesthesia, a 4F-to-5F French catheter was introduced into the abdominal aorta via the superficial femoral artery using the Seldinger technique. Compound emulsion of iodine oil and chemotherapeutic were injected by percutaneously inserting a microcatheter into the femoral artery of the patient under fluoroscopic guidance (X-ray) that corresponds to the artery of the liver. Digital subtraction angiography (DSA) was applied to confirm the size, location, extent and

blood flow condition of the tumor. Meanwhile, DSA can provide useful information about portal vein tumor thrombosis and super-select the major blood supply for hepatic cancer. When applicable, the artery feeding the tumor was cannulated in a superselective approach. Then, gelatin sponge slurry was infused until the arterial branches beyond the catheter tip were densely filled with gelatin sponge slurry.

2.3. Follow-up

All the enrolled patients were followed up for 2 years (from March 2008 to April 2011). During 2 years follow-up, 45 patients died and 14 patients survival. The survival time is from diagnosis to dead or last investigation. During 2 years, patients underwent follow-up liver function testing, serum AFP determination, chest radiography and liver imaging by CT, MRI, and ultrasonography. Meanwhile, General condition scale was used to assess patient's general situation, such as sex, age, occupation, marital status, accompanied disease, past disease history, family heredity history and so on.

2.4. Statistical analysis

All statistical analyses were performed by using SPASS17.0 and P value less than 0.05 was considered to indicate a significant. The rate and constituent ratio were compared by the chi-square test; overall survival (OS) was the end point of the survival analysis and was estimated with Kaplan-Meier curves and tested with the log-rank test; COX regression model was establish to analysis the independent factors on the survival prognosis of patients.

3. Results

3.1. Preoperative details

A total of 59 subjects were enrolled (49 male and 10 female). All 59 patients in the study had been diagnosed with primary liver cancer. There were 14 patients with portal vein tumor thrombus, 7 patients with extrahepatic metastasis, 54 patients with HBsAg positive and 29 patients with Alpha fetoprotein (AFP) positive. Demographic and etiology data of these subjects are shown in Table 1.

3.2. Survival Analysis of Patients after TCEA treatment

Patient survival following a first TACE therapy at 1, 2, and 3 years was 42.7%, 22.0%, and 3.4% respectively in the study cohort. Fifty-nine patients with a measured Tmax/Lmean were analyzed using the Kaplan-Meier curve. The median overall survival time of patients is 7.8 months (95%CI: 5.35-10.24). The Kaplan-Meier curve of overall survival according to a low and high Tmax/Lmean is shown in Fig. 1. According to the Kaplan-Meier curve, survival rates of primary liver cancer patients with interventional

therapy drop quickly within three months after treatment and that drop more gently after three

months of therapy.

Table 2 Prognostic indicators and survival rate for PLC patients treated with TACE.

Variables	Groups	Number	Survival rate (%)			OS(months)	Z	OR	P
			1	2	3				
AFP	<400ug/l	29	58.6	37.9	6.9	17.1	11.69	2.64	0.001
	≥400ug/l	28	28.6	7.1	0	4.9			
PVT	N	45	48.9	26.7	4.4	9.0	5.31	2.07	0.024
	Y	13	23.1	7.7	0	5.0			
Metastasis	N	51	49.0	25.5	3.9	9.0	5.47	2.41	0.025
	Y	7	0	0	0	5.1			
Albumin	≥36g/l	19	47.4	36.8	9.5	19.8	4.71	1.84	0.033
	<36g/l	39	60.5	15.8	0	7.8			

3.3. Prognostic factors for PLC patients after TCEA treatment

This study collected the multiple factors that affect overall survival of patients with primary liver cancer, such 31 variables as gender, age, smoking, drinking, infection history, inheritance, TNM staging, portal vein tumor thrombosis, metastasis, HBsAg, AFP, carcino-embryonic antigen(CEA), carbohydrate antigen 19-9(CA199), alanine aminotransferase (ALT), aspartate aminotransferase (AST). On univariate analyses (Table 2), overall survival differed on AFP≥400μg/l, portal vein tumor thrombosis, serum albumin, and metastasis. On multivariate Cox regression (Table 3), overall survival was not affected by portal vein tumor thrombosis. Other three independent predictors of decreased overall survival were identified: AFP≥400μg/l (OR=2.316, 95% CI: 1.214–4.418), metastasis (OR=2.792, 95% CI: 1.121–6.953), serum albumin≥36g/l (OR=2.056, 95% CI: 1.100–3.843).

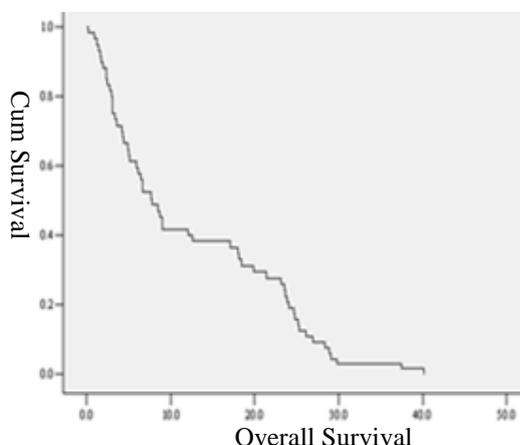


Figure 1. Analysis of overall survival.

4. Discussion

Primary liver cancer (PLC) is a common malignancy worldwide and has poor prognosis. As we know, transarterial chemoembolization (TACE) is recommended as the standard therapy for Barcelona Clinic Liver Cancer (BCLC) stage B patients with large/multifocal HCC [8]. Past studies have focused on differences in overall survival of PLC patients after treatment with TACE [9,10], but little information were available on survival and prognostic factors of PLC patients after treatment with TACE. In this study, we evaluated the survival prognostic factors of PLC subjects after treatment with TACE. A total of 59 subjects diagnosed with PLC were analyzed. Survival estimates were performed with Kaplan–Meier methods. Cox’s proportional-hazards model estimated the death risk (hazard ratio (HR)) of prognostic factors. The median overall survival time of patients is 7.8 months (95%CI: 5.35-10.24). The prognostic indicators associated with higher risk of all-cause deaths are AFP≥400μg/l (OR=2.316), metastasis (OR=2.792), serum albumin≥36g/l (OR=2.056). The results reflect that metastasis, advanced serum AFP and serum albumin has an ad- verse effect on survival for PLC patients after treatment with TACE.

In the study by Yin et al [11], The 1-, 2-, and 3-year OS rates and median survival were 51.8%, 34.8%, 18.1% and 14 months (range 5–47 months), respectively in TACE group. A RCT from Japan showed a median OS of 21 months in the TACE group [12]. In this series, the 1-year, 2-year and 3-year OS rates and median survival were 42.7%, 22.0%, 3.4% and 7.8 months (95%CI: 5.35-10.24) after TACE respectively. However, the etiological factors of HCC in these studies were significantly different. Such as, the proportion of HBsAg (+) in the HCC patients was 13.9% in the Japanese study while it was 91.5% in our study. This may explain the relatively poor outcomes observed in our study.

Table 3 The results of multivariate analysis by Cox regression.

Variables ¹	Regression coefficient	P	OR	95% Confidence Interval	
				Lower	Upper
AFP	0.840	0.011	2.316	1.214	4.418
PVTT	0.517	0.137	1.678	0.848	3.320
Metastasis	1.027	0.027	2.792	1.121	6.953
Albumin	0.721	0.024	2.056	1.100	3.843

¹After adjusting for age, gender

This study evaluated the prognostic factors of overall survival after TECA for PLC. The impact of tumor markers, liver function parameters and clinicopathological variables representing the malignant potential of the tumor were studied in 59 patients after TECA. On multivariate Cox regression, we confirmed that AFP \geq 400 μ g/l, metastasis, serum albumin \geq 36g/l were predictors of poor outcome. Alpha-fetoprotein (AFP) is a glycoprotein, mainly from the yolk sac and embryo liver; serum AFP levels are very low in adults. A high serum AFP level has been associated with larger tumor size, bilobar involvement, massive or diffuse-type tumors, and portal vein tumor thrombus [13]. Serum AFP level is still regarded as the most important serum marker for HCC diagnosis today [14]. The serum AFP level not only has diagnostic value but also has predictive value for the prognosis of HCC. Results from other studies also showed the AFP level was an important prediction factor for the recurrence and prognosis of HCC after resection, TACE or radiofrequency ablation (RFA) treatment [15-18]. These results are consistent with our finding that preoperative serum AFP level has considerable predictive value for the prognosis of PLC patients treated with TACE.

To date, metastasis is still one of the main obstacles to the survival of patients with hepatocellular carcinoma (HCC) [19]. A large tumor diameter and extrahepatically expanding growth pattern are risk factors for the tumor rupture of HCC [20, 21], which is a life-threatening complication with a high mortality rate [22]. On the other hand, a large HCC is frequently accompanied by intrahepatic metastases, it is necessary to control the residual intrahepatic tumors to achieve long-term survival. In 2010, Andreana et al. had showed that Intra-hepatic metastasis is an effective predictor for risk of recurrence after curative resection [23]. Recently, Satoshi Yasuda et al. reported that the patient was able to achieve an acceptable survival of 18 months through an aggressive multimodal therapy combining hepatectomy for the main tumor and repeated TACE for intrahepatic metastases in the remnant liver [24]. In present study, metastasis has already been shown to be a risk factor for poor prognosis in PLC patients treated with TACE. The median survival time of 7 patients with metastasis was 5.1 months, while that of 52 patients without metastasis was 13.7 months.

Portal vein tumor thrombus (PVTT) in HCC is a common entity, the incidence of portal vein tumor thrombus is 44%–62.8% according to autopsy results [25] and 31.4%–34% according to clinical data [26]. PVTT may cause the interruption or reduction of the portal vein blood flow, which results in worsening of acute liver failure. Therefore PVTT is an independent predictor for poor overall survival rate [27]. Previous studies have reported the survival time after diagnosis of PVTT has been reported to be <3 months without treatment [28]. In the present case, The median overall survival time is 5.0 months in patients with PVTT, and patients with PVTT had a 1.7 times higher risk of death by univariate analyses. Serum albumin level, a critical inflammatory negative phase reactant, has been often investigated in the prognostic index models in patients with cancer. Therefore, we also demonstrate low serum albumin was one of the independent prognostic factors for the patients treated with TACE. That is in accordance with some results of previous studies, they have shown that serum albumin level may have an adverse prognostic impact on certain cancer types and different cancer stages and that hypoalbuminemia is associated with poor prognosis [29-31].

5. Conclusion

In conclusion, TACE is the most widely used treatment for unresectable PLC, The median overall survival time is 7.8 months in 59 PLC patients treated with TACE. This study evaluated the prognostic factors of overall and after TACE for PLC. By univariate analyses, overall survival differed on AFP \geq 400 μ g/l, portal vein tumor thrombosis, serum albumin, and metastasis. On multivariate Cox regression, overall survival was not affected by portal vein tumor thrombosis. Other three independent predictors of decreased overall survival were identified: AFP \geq 400 μ g/l, metastasis and serum albumin \geq 36g/l. Our findings further support that prognosis and treatment guidelines for TACE are insufficiently. More prognostic indices must be considered for select appropriate candidates for starting or repeating TACE.

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