J Cancer Sci Clin Ther 2020; 4 (4): 382-392 *DOI: 10.26502/jcsct.5079080*

Research Article

Effect of Transarterial Chemoembolization in Hepatocellular Carcinoma with Respect to Tumor Size: A Prospective Observational Study

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Received: 02 August 2020; **Accepted:** 03 September 2020; **Published**: 01 October 2020

Citation: Muhammad Sohaib Asghar, Sarah Kamran Akbani, Noman Ahmed Khan, Syed Jawad Haider Kazmi, Mohammed Akram, Rumael Jawed, Maira Hassan, Uzma Rasheed. Effect of Transarterial Chemoembolization in Hepatocellular Carcinoma with Respect to Tumor Size: A Prospective Observational Study. Journal of Cancer Science and Clinical Therapeutics 4 (2020): 382-392.

Abstract

Hepatocellular carcinoma is ranked as the sixth most common cancer globally. It also accounts for the second leading determinant of cancer-related mortalities worldwide. In the present day, transarterial chemoembolization (TACE) is the treatment modality of preference for high burden hepatocellular carcinoma. Our study aims to report the efficacy of TACE and alterations in laboratory parameters in patients of hepatocellular carcinoma before and after undergoing TACE in lieu with size >3 cm or <3 cm of the tumor. This prospective observational study was prosecuted in medicine, gastroenterology and hepatology department including 167 patients who were previously diagnosed with hepatocellular

carcinoma by radiological imaging, and have undergone TACE. The mean age of the study population is 53.89 ± 10.58 with females elder than males (p=0.038). The most frequent cause was Hepatitis C (p<0.001). Total bilirubin was found more in <3 cm tumor size (p=0.052) while decreased platelets were more a feature of >3cm tumor size (p=0.050). After TACE, bilirubin levels were remarkably improved in <3 cm tumor size, while INR and Platelets equally improved in both the groups and serum albumin and serum sodium was comparatively more improved in >3cm tumor size. Serum creatinine worsened in <3cm tumor size while improved in >3 cm tumor size, and SGPT was indifferent in <3cm tumor size and worsened in >3cm tumor size. Mean meld score was found improved in both the study groups however, greater improvements were seen in >3cm tumor size group. Downstaging of child-pugh classes was statistically significant in both the study groups (p<0.001).

Keywords: TACE; Child-Pugh; Hepatoma; Tumor; MELD; Severity markers

1. Introduction

Hepatocellular carcinoma has a vital role in cancer incidence and mortality [1]. Occurrence of hepatocellular carcinoma keeps on prevailing in many countries [2]. The approximate calculation of new cases yearly is over 500, 000 and annual occurrence is between 2.5 and 7% of patients with liver cirrhosis [2]. Hepatitis B and C are predominant risk factors of hepatocellular carcinoma [3]. Hepatocellular carcinoma is ranked as the sixth most common cancer globally [4, 6]. It also accounts for the second leading determinant of cancer-related mortalities worldwide [5, 6]. The phenomenon of hepatocellular carcinoma is directly in correspondence with age, regardless of the fact, in the endemic areas of viral hepatitis, it might present in adolescents [7]. Hepatocellular carcinoma depicts gender prevalence for males, who are distressed in comparison to females, although this predominance is credited due to excessive exposure of men to prime risk factors [7]. The number of new cases that have been speculated is 564, 000 comprising of 398, 000 of men and 166, 000 in women [8]. The endemic areas at potential risk are located in Eastern Asia, Middle Africa, and some countries of Western Africa [8]. The predisposing and relative factors of hepatocellular carcinoma other than chronic liver disease, hepatitis B, and C are heavy alcohol consumption, Aflatoxin exposure, cigarette smoking, iron overload, use of oral contraceptives, and anabolic steroids [9]. There is diversity in the display of hepatocellular carcinoma, asymptomatic throughout its proceeding stages usually masking the early detection of cancer [6]. The marked salient features of hepatocellular carcinoma are abdominal pain (53%), mass (34%), and ascites (20%) [10]. The majority of sufferers suffer from common associated features that are cirrhosis (63%) and hepatitis surface antigen (HbsAg) (52%) [10]. Patients of hepatocellular carcinoma encountering paraneoplastic syndromes commonly have bulky tumor volume and elevated serum alpha-fetoprotein [11]. Paraneoplastic syndromes manifest as hypercholesterolemia, hypoglycemia, hypercalcemia, and erythrocytosis [11]. The crucial complications of hepatocellular carcinoma are due to its affliction towards vessels leading to thrombotic events presenting as upper gastrointestinal bleed, esophageal varices, and portal vein thrombosis [12]. Other complications worsening the prognosis of hepatocellular carcinoma are hepatic encephalopathy and ascites [12].

Hepatocellular carcinoma due to its late diagnosis and masking of symptoms significantly alter liver function tests as claimed by statistical data analysis [13]. This hindrance in the early detection of hepatocellular carcinoma leads to a diminished response to systemic chemotherapy [14]. This is

higher incidence of undetected hepatocellular carcinoma nullify patients from opting curative treatment [14]. To enhance survival rates in the patients of hepatocellular carcinoma, multiple treatment modalities are available categorized in the surgical and non-surgical categories according to the severity of the disease [14]. Surgical modalities opted for eliminating hepatocellular carcinoma are Surgical resection (SR), Percutaneous ablative therapy by radiofrequency (RFA), Percutaneous ethanol injection (PEI), and Liver transplant (LT). Other modalities are contemplated as palliative therapies, comprising of Transarterial Chemoembolization (TACE) and radioembolization for intermediate stages, systemic therapy in the form of Sorafenib for late stages [15]. Transarterial chemoembolization (TACE) is a manifestation of intraarterial catheter dependent chemotherapy that specifically imparts high dosages of cytotoxic medications to neoplasm collaborating with the impact of ischemic necrosis generated by arterial embolization [16]. Transarterial chemoembolization is an invasive procedure, was pioneered by Dr. Sven-Iver Seldinger in 1953, A Swedish radiologist native of Mora Municipality, Dalarna County [17]. Transarterial chemoembolization secondly called radioembolization or targeted internal radiation therapy, comprising of targeted intraarterial administration of microspheres laden with radioactive compounds mostly Yttrium or Lipiodol tagged with iodine or rhenium, through a percutaneous approach [18]. Transarterial chemoembolization (TACE) is executed by injection of single or numerous chemotherapeutic medications following catheterization of neoplasm loaded arteries, amalgamed by embolization of similar arteries in place of acquiring enhancing impact of cytotoxicity and ischemia [19].

Transarterial chemoembolization encompasses two methodologies since 2004, which is Conventional TACE (cTACE) and TACE with drug-eluting beads (DEB-TACE) [20, 21]. Conventional TACE (cTACE) favors transcatheter carriage of chemotherapeutic drugs using Lipodol mediated colloid along with an embolizing drug to gain significant effects of ischemia and cytotoxicity [20-23]. TACE with drug-eluting beads (DEB-TACE) procedure permits the therapy to be transported directly into the liver by the fusion of minuscule beads with chemotherapy agent Doxorubicin conveyed to neoplasm through the arterial catheter [20, 21, 24, 25]. Transarterial chemoembolization (TACE) is opted for patients at stage B with intermediate hepatocellular carcinoma as quoted by one of the persistently sought criteria for staging Hepatocellular carcinoma, that is, Barcelona Clinic Liver Cancer (BCLC) using factors comprising of tumor staging, liver function status, physical status, functional status, and cancer-associated symptoms [26]. Transarterial chemoembolization (TACE) is a commodity availed for patients standing at the score of Child Pugh's B and Child Pugh's C as quoted by the most sought classification of the staging of liver failure in hepatocellular carcinoma known as "Child Pugh's" which is based on five stipulations: 1) Albumin levels, 2) Prothrombin time/International Nationalization Ratio, 3) Ascites, 4) Encephalopathy and 5) Bilirubin levels [27].

Transarterial chemoembolization (TACE) has been recommended for ages as the criterion conventional for palliative treatment of unresectable hepatocellular carcinoma and has been outlined to boost the 5 years survival rates in contrast with supportive therapy [28-31]. As proposed by Barcelona Clinic Liver Cancer (BCLC), Transarterial chemoembolization (TACE) is prioritized as the first-line treatment for unresectable intermediate-stage hepatocellular carcinoma (stage B) [28-31]. Transarterial chemoembolization (TACE) is a guarded and controlled mechanism but there are countable heinous complications associated, the ones reported are Tumor rupture, Liver

abscess, bile leak, Hepatic failure, Gastrointestinal hemorrhage/ulceration, and Pulmonary embolism [32-34]. Approximate contraindications to the employment of transarterial chemoembolization (TACE) include contrast allergy, renal impairment, coagulopathy, cardiac dysfunction [35, 36]. Irrevocable contraindications to the usage of transarterial chemoembolization (TACE) include acute derangement of baseline liver functions, anaphylactic reactions to iodinated contrast, portal vein thrombosis, and infiltration due to extrahepatic metastasis [35, 36]. The aim of this study is to trail the downstaging of tumor from Child Pugh's B and C to Child Pugh's A and B by beneficial effects of transarterial chemoembolization (TACE), to evaluate the role of transarterial chemoembolization (TACE) in maintaining the model for end-stage liver disease score (MELD) below 15 to avoid liver transplantation. The secondary objectives were to determine whether the improvement of the severity of the liver disease is seen greater in tumor size >3cm or <3cm.

2. Materials and Methods

This prospective observational study was prosecuted in medicine, gastroenterology and hepatology department at DOW University Hospital, one of the prestigious and top-notch hospitals imparting health care facilities to the patients paying a visit to the hospital institution. After inclusions and exclusions of terminologies, we finalized the proforma which is split into two sections, the first section comprises demographic data containing the name (optional), age, gender, and any comorbidities currently suffered (apart from hepatoma). The second section is additionally split into a few sub-categories including parameters of Child Pugh's score, that is, the Patient's laboratory parameters before and after TACE. All the findings after investigating the parameters mentioned above will be captivated on inclusion as baseline findings before undergoing the process of TACE. Any dramatic or remote changes in findings during and after the process of TACE will be recorded. All the patients who are previously diagnosed with hepatocellular carcinoma by radiological imaging were part of our study, and have undergone TACE, while those who died during the study period were omitted from the study. The sample size of 169 was enumerated by using 5% as a margin of error, 95% as a confidence interval, 100 as population size, and 50% as response distribution. Two patients during the study period had opted for liver transplantation, hence omitted from the final results, hence a final sample size of 167 patients was collected through non-probability consecutive methods. All the data was then assembled, entered, and analyzed using SPSS 25.0 software version, and outcomes were obtained respectively.

3. Results

The mean age of the study population is 53.89 ± 10.58 with females elder than males (p=0.038). The two study groups were comparable with age, gender, and comorbidities as shown in Table 1. The most frequent cause was Hepatitis C (p<0.001). The child pugh's classification was also comparable amongst the two study groups. Total bilirubin was found more in <3 cm tumor size (p=0.052) while decreased platelets were more a feature of >3cm tumor size (p=0.050). The rest baseline labs were comparable in both study groups as shown in Table 2. Table 3 has shown a follow up of comparative labs after TACE in both the study groups. Almost all the laboratory investigations and determinants of child pugh's scoring shown improvement post TACE procedure. Notably, bilirubin levels were remarkably improved in <3cm tumor size, while INR and Platelets equally improved in both the groups and serum albumin and serum sodium were comparatively more improved in >3cm tumor size. Serum creatinine worsened in <3cm tumor size while improved in >3 cm tumor size, and SGPT was indifferent in <3 cm tumor size and

worsened in >3cm tumor size. Mean meld score was found improved in both the study groups however, greater improvements were seen in >3cm tumor size group. Before the TACE procedure, the child pugh scoring of <3cm tumor size group showed the highest individuals in class C category and that of >3cm tumor size group were in the class B category. After TACE procedure, the downstaging of child class was observed greater in tumor size >3cm with one-half falling in child class A, and one-third in child class B. While, downstaging also occurred in tumor size <3cm with 46% study participants now falling in child class B and 36% in child class A. Overall, downstaging of child pugh classes was statistically significant in both the study groups ($p<0.001$).

Demographic data					**p-value**
1	Age (in years)	Age Group	<50 years	>50 years	-
		Total	70 (41.9%)	97 (58.1%)	
		Males	42 (46.2%)	49 (53.8%)	0.225**
		Females	28 (36.8%)	48 (63.2%)	
		Tumor size <3cm	32 (39.0%)	50 (61.0%)	0.457**
		Tumor size >3cm	38 (44.7%)	47 (55.3%)	
2	Mean age (in years)	53.89 ± 10.58			-
		Males: 52.37 ± 11.43	Females: 55.72 ± 9.20		0.038*
		Tumor size <3cm: 54.35 ± 9.48	Tumor size >3cm: 53.45 ± 11.58		0.586*
3	Gender	Males: n=91 (54.5%)	Females: n=76 (45.5%)		-
		Tumor size <3cm: n=47 (57.3%)	Tumor size <3cm: n=35 (42.7%)		0.471**
		Tumor size >3cm: n=44 (51.8%)	Tumor size >3cm: n=41 (48.2%)		
4	Comorbidities (other than Hepatoma)	Frequency of Diseases	Tumor size <3 cm	Tumor size >3 cm	-
	Abbreviations:	DM: 24.6% (n=41)	30.5% (n=25)	18.8% (n=16)	0.089^
	DM: Diabetes Mellitus	HTN: 12.0% (n=20)	12.2% (n=10)	11.8% (n=10)	
	HTN: Hypertension	DM+HTN: 10.2% (n=17)	12.2% (n=10)	8.2% (n=7)	
	CKD: Chronic Kidney Disease	DM+CKD: 3.6% (n=6)	4.9% (n=4)	2.4% (n=2)	
	Hep B: Hepatitis B virus	HTN+CKD: 3.6% (n=6)	6.1% (n=5)	1.2% (n=1)	
	Hep C: Hepatitis C virus NAFLD: Non-Alcoholic fatty	DM+HTN+CKD: 1.2% (n=2)	1.2% (n=1)	1.2% (n=1)	
	liver disease	CKD: 3.6% (n=6)	2.4% (n=2)	4.7% (n=4)	
	HCC: Hepatocellular carcinoma	No comorbidities: 41.3% (n=69)	30.5% (n=25)	50.8% (n=44)	
5	Known cause of HCC	Hep B: 14.4% (n=24)	2 (2.4%)	22 (25.9%)	<0.001^
		Hep C: 43.1% (n=72)	9 (11.0%)	63 (74.1%)	
		NAFLD: 15.0% (n=25)	23 (29.1%)	2 (2.3%)	
		Alcohol: 4.2% (n=7)	7 (8.9%)	0 (0.0%)	
		No identified cause: 23.4% (n=39)	38 (48.1%)	1 (1.1%)	

6	Tumor size	<3cm: n=79 (47.3%)	>3cm: n=88 (52.7%)	-
7	Child Pugh's Class	Class A: n=11 (13.9%)	Class A: n=17 (19.3%)	0.415**
		Class B: n=30 (38.0%)	Class B: n=37 (42.0%)	
		Class C: n=38 (48.1%)	Class C: n=34 (38.6%)	

* indicates independent sample t-test, ** indicates Fisher's exact test, *** indicates chi-square test.

Table 1: Demographic data of the study population (n=167).

#	Laboratory investigations	All patients (n=167)	Grouping variables		p-value
			Tumor size <3cm (n=79)	Tumor size >3cm (n=88)	
1	Total Bilirubin (mg/dl)	3.62 ± 5.48	4.49 ± 7.23	2.84 ± 3.02	0.052
2	Direct Bilirubin (mg/dl)	2.00 ± 3.24	2.48 ± 4.24	1.57 ± 1.86	0.068
3	Indirect Bilirubin (mg/dl)	1.65 ± 2.35	2.00 ± 3.07	1.33 ± 1.36	0.064
4	International normalized ratio	1.88 ± 1.77	1.98 ± 1.75	1.79 ± 1.79	0.502
5	Platelet counts (10^9/L)	121.87 ± 82.64	135.10 ± 83.11	110.00 ± 80.84	0.05
6	Serum Albumin (g/dl)	2.61 ± 0.69	2.58 ± 0.72	2.63 ± 0.67	0.648
7	Serum Sodium (mEq/L)	132.58 ± 6.55	132.21 ± 6.29	132.90 ± 6.80	0.496
8	Serum Creatinine (mg/dl)	1.45 ± 1.25	1.60 ± 1.61	1.33 ± 0.80	0.162
9	Alanine Transaminase (IU/L)	54.49 ± 45.42	53.56 ± 42.75	55.32 ± 47.92	0.803
10	Mean MELD score	20.35 ± 8.62	21.38 ± 8.90	19.42 ± 8.30	0.143

P-Value calculated by independant sample t-test.

Table 2: Comparison of severity markers amongst the patients of Hepatocellular carcinoma (at inclusion).

#	Laboratory investigations	Tumor size <3cm (n=79)		p-value	Tumor size >3cm (n=88)		p-value
		Before TACE	After TACE		Before TACE	After TACE	
1	Total Bilirubin (mg/dl)	4.49 ± 7.23	1.81 ± 2.67	0.003*	2.84 ± 3.02	1.57 ± 1.96	0.002*
2	Direct Bilirubin (mg/dl)	2.48 ± 4.24	0.93 ± 1.78	0.003*	1.57 ± 1.86	0.69 ± 1.24	<0.001*
3	Indirect Bilirubin (mg/dl)	2.00 ± 3.07	0.87 ± 0.95	0.003*	1.33 ± 1.36	0.87 ± 0.85	0.010*
4	International normalized ratio	1.98 ± 1.75	1.30 ± 0.42	0.001*	1.79 ± 1.79	1.20 ± 0.33	0.002*
5	Platelet counts (10^9/L)	135.10 ± 83.11	180.01±81.99	0.001*	110.00 ± 80.84	195.43 ± 80.99	<0.001*
6	Serum Albumin (g/dl)	2.58 ± 0.72	3.05 ± 0.65	<0.001*	2.63 ± 0.67	3.25 ± 0.56	<0.001*
7	Serum Sodium (mEq/L)	132.21 ± 6.29	134.50 ± 5.50	0.012*	132.90 ± 6.80	136.82 ± 4.37	<0.001*
8	Serum Creatinine (mg/dl)	1.60 ± 1.61	1.79 ± 1.51	0.420*	1.33 ± 0.80	1.20 ± 1.24	0.437*
9	Alanine Transaminase (IU/L)	53.56 ± 42.75	54.27 ± 32.32	0.911*	55.32 ± 47.92	62.60 ± 36.76	0.272*
10	Mean MELD score	21.38 ± 8.90	16.24 ± 8.86	<0.001*	19.42 ± 8.30	11.77 ± 6.66	<0.001*

11	Child Pugh Class	A: n=11 (13.9%)	A: n=29 (36.7%)	0.156**	A: n=17 (19.3%)	A: n=44 (50.0%)	<0.001^
		B: n=30 (38.0%)	B: n=37 (46.8%)		B: n=37 (42.0%)	B: n=29 (33.0%)	
		C: n=38 (48.1%)	C: n=13 (16.5%)		C: n=34 (38.6%)	C: n=15 (17.0%)	

*P-value calculated by paired; ** P-value calculated by chi-square test. sample t-test; ** P-value calculated by chi-square test.

Table 3: Comparison of severity markers before and after TACE (3 months after inclusion into the study).

4. Discussion

Transarterial chemoembolization (TACE) reformed the treatment of hepatocellular carcinoma when it was pioneered in the ’90s. In the present day, transarterial chemoembolization is the treatment modality of preference for high burden hepatocellular carcinoma. Innumerable case reports and retrospective studies have reported the concrete efficacy of TACE in curing carcinoma of the liver. Our study aims to report the efficacy of transarterial chemoembolization and alterations in laboratory parameters in patients of hepatocellular carcinoma before and after undergoing TACE in lieu with size >3cm or <3cm of the tumor. Miscellaneous studies reported mean age of patients suffering from hepatocellular carcinoma >50 years, concurrent with outcomes of our study [19, 37, 38, 39], but insufficient studies also reported mean age <50 years thus quoting results dissimilar to our study [40, 41]. Considerable studies cited increased age when compared to our study thus contradicting our finding [42-44], while the trivial study had its median correlating with our study [45]. Hepatocellular carcinoma has increased affinity towards the male gender, conclusion declared by abundant studies, thus coinciding with the outcome of our study [19, 37, 39, 40, 42]. Our study pronounced hepatitis C as the known cause of hepatocellular carcinoma, an outcome concurrent with findings cited by countable studies [19, 38, 40, 42, 44, 46, 47], while equivalent studies reported hepatitis B as a prominent cause of carcinoma thus contravening our outcome [39, 40, 41, 43, 45, 48]. Infrequent studies indicated diabetes mellitus as the most prominent co-morbid present in patients suffering from hepatocellular carcinoma, finding corresponding with our study [46, 47]. Many of the sufferers included in our sample population were devoid of any co-morbidity.

Extensive studies concluded an ample number of sufferers of hepatocellular carcinoma categorized in Child Pugh’s class A, an outcome opposing result of our study inferring mass of sufferers categorized in Child Pugh’s class C [19, 37, 38, 40, 43, 45, 46]. Multiple studies concluded liver tumor as high-burden hepatocellular carcinoma in terms of size of the tumor with >3 cm tumor size reported by significant studies, corresponding with our outcome [37, 44, 45], while negligible study reported tumor size <3 cm thus contradicting our finding [43]. Extensive studies conducted observing the effect of TACE on laboratory parameters of patients suffering from hepatocellular carcinoma reported increased median values of total bilirubin when compared to our study [37, 40, 44, 48], while equivalent studies cited decreased values [19, 39, 43, 46], both outcomes contravening our study. The median value of platelet count in multiple studies was found to be coinciding with values calculated by our study [37, 39, 46], while some studies also reported declined values [19, 38].

Substantial studies conducted observed median values of serum albumin increased when compared to our results [19, 37, 39, 40, 43, 44, 48]. Decreased median values of serum creatinine were detected in various studies opposing findings noted in our study [19, 39, 46]. One study reported median value of alanine transaminase similar to value demarcated by our study, thus correlating with our outcome [37], while few studies quoted decreased values [19, 46], and an infrequent study detected increased alanine transaminase compared with our study [40]. The majority of studies regulated were indicative of increased INR in patients suffering from hepatocellular carcinoma, therefore median values are similar to our study [37, 39, 43, 44]. A study detected the median value of mean meld score diminished when paralleled with the value of our study, therefore, contrasting our outcome [43]. Another study regulated by Katayama et al had an entirely different perspective regarding prognosis and overall survival among patients of hepatocellular carcinoma electing for the procedure of TACE, suggestive of the number of tumors present in the patient of stage B of BCLC staging system as a predictive factor for prognosis rather than the size of the tumor [49].

5. Conclusion

Our study highlights the efficacious effects of transarterial chemoembolization in curing high burden hepatocellular carcinoma measuring >3cm or above and prominent downregulating alterations were observed in laboratory parameters, scores, and staging criteria. A significant decline in levels of INR, bilirubin, and creatinine was witnessed along with a decrease in meld score in patients with tumor size >3cm opting for the procedure of TACE. The majority of sufferers with tumor size >3cm and categorized in Child Pugh's class C had improvements and transcended to class A and B proving the efficiency of TACE in curing high burden hepatocellular carcinoma.

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