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Validation of AFP Model as a Predictor of Response, Recurrence and Survival in HCC Patients Underwent Locoregional Treatment

Mohamed Kamal Shaker, Heba Mohamed Abdella, Mohamed Mahmoud Mahmoud El Tabbakh & Mohamed Atef Abu Hashima *

Department of Tropical Medicine, Faculty of Medicine, Ain Shams University

***Corresponding Author:** Mohamed Atef Abu Hashima, **Phone No.:** (+2) 01113501412, **E-mail:** midoatif.2014@gmail.com

ABSTRACT

Background: incidence of hepatocellular carcinoma (HCC) has rapidly increased worldwide. HCC is the sixth most common malignancy and the third most common cause of cancer related death. Since HCC usually develops in a damaged liver, the prognosis of HCC depends not only on tumor progression but also on the degree of liver dysfunction. In Egypt, HCC constitutes 70.48% of all liver tumors among Egyptians. **Aim of the Work:** to validate the use of AFP model as a predictor of response, recurrence and survival in hepatocellular carcinoma patients after locoregional treatment. **Patients and Methods:** this study was conducted at Tropical Medicine department and HCC clinic, Ain Shams University Hospitals. The study was approved by the Research and Ethics Committee of Ain Shams University, Cairo, Egypt in accordance with local research governance requirements. **Results:** according to this classification 130 patients are for RFA and 70 patients are for TACE but actually 132 patients underwent TACE and 68 patients underwent RFA this could be explained by the facts that some lesions are large in size (>4cm) and others are located near main bile duct, intestinal loop or blood vessel so RFA couldn't be done. **Conclusion:** AFP model may be a predictor of response, recurrence and survival in HCC patients undergoing locoregional treatment (TACE or RFA) but more studies with larger sample size are needed to validate its use.

Keywords: Hepatocellular Carcinoma - Locoregional Treatment - Alpha Fetoprotein

INTRODUCTION

Approximately 70%–90% of patients with HCC have an established background of chronic liver disease and cirrhosis, with major risk factors for developing cirrhosis including chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease, and nonalcoholic steatohepatitis (NASH) [(1)]. Additional risk factors for developing HCC include intake of aflatoxin-contaminated food, diabetes, obesity, certain hereditary conditions such as hemochromatosis, and other metabolic disorders [(2)]. HCC diagnosis was based on histological criteria and/or imaging techniques, as proposed by the American Association for the Study of Liver Diseases. For the diagnosis of HCC, nodules found on ultrasound surveillance that are smaller than 1 cm should be followed up with ultrasound at 3-month intervals. Lesions larger than 1 cm in diameter should be evaluated by dynamic magnetic resonance imaging or helical multidetector computed tomography (CT) scan using contrast. If the appearance is typical for HCC, no further investigation is required [(3)]. There are different treatment modalities for HCC. Resection may benefit certain patients, albeit mostly transiently. Many patients are not candidates given the advanced stage of their cancer at diagnosis or their degree of liver disease and, ideally, could be cured by liver transplantation. Globally, only a fraction of all patients have access to transplantation, and, even in the developed world, organ shortage remains a major limiting factor. in these patients, local ablative therapies, including radiofrequency ablation (RFA), chemoembolization, and potentially novel chemotherapeutic agents, may extend life and provide palliation [(4)]. Recently, the French study group for LT reported on a new predictive model for HCC recurrence, namely the AFP model which was based on tumor staging and AFP values at listing. Adding AFP to tumor size and number increased the accuracy for predicting recurrence post liver transplantation. The AFP model was shown to be superior to Milan criteria in predicting recurrence in a training set of HCC patients, and was subsequently validated in a cohort of French patients followed prospectively under the control of the French organization for organ sharing. On these grounds, the AFP model was officially adopted in January 2013 in France for selecting HCC candidates [(5)]. However, the alpha feto protein model has not been studied on HCC patients undergoing locoregional treatment as regard response to treatment, HCC recurrence and survival.

AIM OF THE WORK

To validate the use of AFP model as a predictor of response, recurrence and survival in hepatocellular carcinoma patients after locoregional treatment.

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PATIENTS AND METHODS

This study was conducted at Tropical Medicine department and HCC clinic, Ain Shams University Hospitals. The study was approved by the Research and Ethics Committee of Ain Shams University, Cairo, Egypt in accordance with local research governance requirements. **Study design and settings:** A retrospective and prospective cohort study. **Participants:** All newly diagnosed patients with HCC who were fit for locoregional treatment (TACE, RFA) according to BCLC: Retrospectively: from 4/2012 till 4/2017. Prospectively: from 5/2017 till 12/2017. The enrolled patients had been followed up till death or till the end of the study (5/2018). **Inclusion criteria:** 1) Proved diagnosis of HCC according to AASLD practice guidelines [6]. 2) Patients underwent RFA for HCC with BCLC (The Barcelona-Clinic- Liver-Cancer staging system) stage A with no eligibility or ability to do transplantation or resection. 3) Patients underwent TACE for HCC with BCLC stage A or B. **Exclusion criteria:** 1) Presence of extra-hepatic metastasis or gross vascular invasion. 2) Child class C patients or BCLC stage C or D. 3) Patients who lost follow up. 4) Any other medical co morbidities as (heart failure, renal failure, respiratory failure…). **The following parameters were retrieved and documented from the records of the patients. *Pre-treatment assessment:* 1) Full personal history taking and thorough clinical examination. 2) Laboratory investigations including**: Complete blood picture. Liver profile including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, serum bilirubin, serum albumin, and prothrombin time (PT), alpha fetoprotein (AFP) level, etiology of the underlying liver disease viral, autoimmune, etc (HCV Ab, HBS Ag, HBcAb, ANA), fasting blood sugar, 2hr post prandial blood sugar and HbA1c (if available), renal function tests (Serum creatinine), **1. Radiological investigations:** Abdominal ultrasound: for liver texture, echogenicity and presensce of HFL. Triphasic spiral abdominal CT scan: to confirm the diagnosis of the HCC by Presence of arterial enhancement of the focal lesion followed by wash-out in porto-venous and delayed phase. MRI abdomen with diffusion if inconclusive or atypical CT criteria. **2. Liver biopsy** if non-cirrhotic liver or inconclusive imaging. ***Then,*** The AFP model was calculated for each patient enrolled in the study before intervention,and the patients were classified into two groups according to alpha feto protein model: Low risk group (<2) and high risk group (>2) in both RFA and TACE patients. **Radiofrequency ablation (RFA):** The patients who underwent RFA should have HCC with Barcelona-Clinic- Liver-Cancer staging system (BCLC) stage A with no eligibility or ability to do transplantation or resection i.e. Child A or B with single tumor not greater than 5 cm in the largest dimension; multiple tumors (maximum 3 nodules) non greater than 3 cm; no portal venous thrombosis and extra-hepatic metastasis, the tumor or tumors should be visualized with ultrasound (US) and accessible via the percutaneous route. This procedure was carried-out in the interventional radiology unit, Ain-Shams University Hospital. The radiofrequency device used was cool tip RF system, valley lab USA, Mass-with maximum power output capability of 200 W and produces a 480 kHz waves, with display parameters including: impedance, current, power and temperature. RF electrodes used was cooled-tip electrode needle. There were two types of perfusion RF electrodes, single which used for ablating lesion ≤3cm and cluster which used for ablating lesions 3-5 cm in diameter. Subcostal approach was generally used for left lobe lesions. However, for right lobe lesions either subcostal or intercostal approaches were used. The patients were placed in supine. All patients underwent this procedure had general anesthesia in the form of propofol 1% infusion with 10 cm infiltration local anesthesia at the site of electrode entry. This procedure was done under ultrasound guidance in all patients. **Trans-arterial chemoembolization (TACE):** The patients who underwent TACE should have HCC with Barcelona-Clinic- Liver-Cancer staging system (BCLC) stage B i.e. Child A or B with single tumor greater than 5 cm in the largest dimension; or multi-nodular tumors (> 3 nodules); with no eligibility or ability to do transplantation or resection; no portal venous thrombosis and extra-hepatic metastasis. Trans-arterial chemoembolization (TACE) was performed either via selective proper hepatic artery or super-selective catheter placement according to tumor location. The catheter was percutaneously inserted through the femoral artery with tip fixation method. After diagnostic hepatic angiography and redistribution of hepatic arterial flow to single arterial supply, the catheter was inserted. In each case, the infusion was an emulsion of duxirubicin 50-100 mg mixed with 10 cc lipidol. The volume infused was divided approximately between segments or lobes

according to tumor distribution. The entire procedure was performed under local anesthesia. **Follow up of the patients:** Patients were followed up by AFP, laboratory investigations and triphasic spiral CT performed 1 month after RFA or TACE to evaluate the response and then every 3 months to evaluate the recurrence. The response criteria were defined using modified RECIST to assess hepatic or extra-hepatic tumor [7]. **In modified RECIST**, CR was disappearance of any intratumoral arterial enhancement in all target lesions; PR was at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions; SD was any cases that do not qualify for either partial response or progressive disease and PD was an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started. **At the end of the study, the calculated model was used to assess:** 1) The response to treatment in both RFA and TACE group in low and high risk groups. 2) Hcc recurrence in both RFA and TACE group in low and high risk groups. 3) Overall survival in both groups. Disease free survival ***(DFS)*** was calculated from the time of the procedure to the time of disease recurrence. Overall survival ***(OS)*** was calculated from the time of intervention to death or last follow-up visit. **Data management and statistical analysis:** Data collected was subjected to revision and introduction to a personal computer, where data management was conducted using Statistical Package for Social Sciences (SPSS) software computer program version 20.

RESULTS

Table (1): Descriptive data of the studied groups

		RFA	TACE	Test value	P-value	Sig.
		No. = 68	No. = 132			
Age	Mean±SD	58.04 ± 6.30	57.28 ± 7.46	0.722•	0.471	NS
	Range	44 – 75	33 – 77			
Sex	Female	25 (36.8%)	30 (22.7%)	4.436*	0.035	S
	Male	43 (63.2%)	102 (77.3%)			

NS: Non significant; S: Significant; HS: Highly significant
*: Chi-square test; •: Independent t-test
P-value >0.05 Non significant
P-value <0.05 significant
P-value <0.01 highly significant

The mean age in both groups was around 58 years old with male predominance in HCC patients accounting for 63.2% in RFA group and 77.3% in TACE group.

Table (2): Laboratory data of the studied groups

		RFA	TACE	Test value	P-value	Sig.
		No. = 68	No. = 132			
CBC						
Hg(g/dl)	Mean±SD	12.20 ± 1.76	12.59 ± 2.06	-1.331•	0.185	NS
TLC (10^3/uL)	Mean±SD	5.19 ± 1.89	5.84 ± 1.70	-1.777•	0.077	NS
PLT (10^3/uL)	Median(IQR)	111.5 (81.5 – 146.5)	122 (85.5 – 165)	-0.968‡	0.333	NS
	Range	15 – 580	29 – 731			
Liver Profile						
ALB (g/dL)	Mean±SD	3.43 ± 0.56	3.43 ± 0.54	0.071•	0.943	NS
BILI (mg/dL)	Mean±SD	1.07 ± 0.48	1.14 ± 0.45	-0.968•	0.334	NS
AST (IU/L)	Median(IQR)	56 (41 – 76)	56 (36 – 78)	-0.025‡	0.980	NS
ALT(IU/L)	Median(IQR)	46 (36 – 71)	50 (34 – 82)	-0.640‡	0.522	NS
INR	Mean±SD	1.21 ± 0.18	1.22 ± 0.17	-0.656•	0.512	NS
PT (sec.)	Mean±SD	15.13 ± 2.06	14.69 ± 2.52	0.882•	0.379	NS
AFP (IU/mL)	Median(IQR)	32 (9.65 – 133.5)	39.5 (13.2 – 301.5)	-1.651‡	0.099	NS
HCV	Negative	8 (11.8%)	14 (10.6%)	0.062*	0.804	NS
	Positive	60 (88.2%)	118 (89.4%)			
Kidney Function						
S.CREAT (mg/dL)	Mean±SD	0.93 ± 0.24	0.87 ± 0.22	1.621•	0.107	NS

NS: Non significant; S: Significant; HS: Highly significant
*: Chi-square test; •: Independent t-test
P-value >0.05 Non significant
P-value <0.05 significant
P-value <0.01 highly significant

As regard liver profile the mean level of total bilirubin in RFA group was 1.07±0.48 mg/dl while in TACE group was 1.14 -+ 0.45.Also the mean level of INR was 1.21 -+ 0.18 in RFA group while in TACE group it was 1.22-+0.17 all without reaching statistical significance. Median AFP level was 32 IU/ml in RFA group and 39.5 in TACE group with no statistically significant difference between both groups. Most of the patients included in the study were HCV +ve where 88.2% of RFA and 89.4% 0f TACE were HCV+ve. 12 patients of both groups were HBSAg +ve representing 6% of total number of patients. No statistically significant difference between the two groups as regard CBC and kidney function.

Table (3): Different classification systems in the study groups

		RFA	TACE	Test value	P-value	Sig.
		No. = 68	No. = 132			
CHILD	Mean±SD	5.76 ± 0.79	5.67 ± 0.72	0.883•	0.378	NS
	Range	5 – 9	5 – 8			
	A	59 (86.8%)	119 (90.2%)	0.526	0.468	NS
	B	9 (13.2%)	13 (9.8%)			
BCLC	0	11 (16.2%)	6 (4.5%)	27.450*	0.000	HS
	A	49 (72.1%)	64 (48.5%)			
	B	8 (11.8%)	62 (47.0%)			
MELD	Mean±SD	9.72 ± 2.96	9.83 ± 2.60	-0.277•	0.782	NS
	Range	6 – 19	6 – 18			

NS: Non significant; S: Significant; HS: Highly significant
*: Chi-square test; •: Independent t-test

Most of the patients who underwent RFA were child A (86.8%) and BCLC A (72.1%) and the mean MELD score was 9.72-+2.96 while in patients who underwent TACE most of the patients were child A (90.2%) but 48.5% of the patients were BCLC A and 47% were BCLC B and the mean MELD score was 9.83-+2.6 with highly statistical significant difference in BCLC classification (P=0.00). No statistically significant difference between the two groups as regard child and MELD scores.

Table (4): Milan criteria and AFP model in the study groups

		RFA	TACE	Test value	P-value	Sig.
		No. = 68	No. = 132			
Milan	Within Milan	61 (89.7%)	71 (53.8%)	25.802*	0.000	HS
	Outside Milan	7 (10.3%)	61 (46.2%)			
Number of nodules	Median(IQR)	1 (1 – 1)	1 (1 – 2)	-2.822‡	0.005	HS
	Range	1 – 4	1 – 6			
Size of largest nodule	Mean±SD	2.64 ± 0.88	4.32 ± 1.99	-6.638•	0.000	HS
	Range	1.4 – 4.5	1 – 12			
AFP model	Median(IQR)	0 (0 – 2)	2 (1 – 3.5)	-4.637‡	0.000	HS
	Range	0 – 5	0 – 7			

NS: Non significant; S: Significant; HS: Highly significant
*: Chi-square test; •: Independent t-test; ‡: Mann Whitney test

About 89.7% of patients in RFA group were within milan criteria while only 53.8% of TACE patients were within milan criteria with high statistical significance (P = 0.00). The range of number of nodules in RFA patients was 1-4 while in TACE it was 1-6 with high statistical significance (P = 0.005). The mean size of largest nodules in RFA patients was 2.64 ± 0.88 while in TACE was 4.32 ±1.99 with high statistical significance (P = 0.00). The median AFP model in RFA was 0 while in TACE it was 2 with high statistical significance (P = 0.00).

Table (5): Response to treatment, recurrence and survival in the study groups

		RFA	TACE	Test value	P-value	Sig.
		No. = 68	No. = 132			
Response	Complete response	61 (89.7%)	107 (81.1%)	3.099	0.377	NS
	Partial response	6 (8.8%)	21 (15.9%)			
	Stationary disease	0 (0.0%)	2 (1.5%)			
	Progressive disease	1 (1.5%)	2 (1.5%)			
Recurrence	No recurrence	26 (41.9%)	27 (25.2%)	5.087	0.024	S
	Recurrence	36 (58.1%)	80 (74.8%)			
Recurrence free survival (months)	Median (IQR)	6 (3 – 13.5)	9.5 (3 – 16.5)	-0.960	0.337	NS
	Range	3 – 47	3 – 36			

NS: Non significant; S: Significant; HS: Highly significant
*: Chi-square test; ‡: Mann Whitney test

Regarding response to treatment about 89.7% of RFA group achieved complete response while 81.1 % achieved complete response in TACE group with no statistically significant difference. About 74.8% of patients in TACE group witnessed recurrence while recurrence occurred in 58.1 in RFA group with statistically significant difference (P=0.024).

Table (6): Survival in study groups

		RFA	TACE	Test value	P-value	Sig.
		No. = 68	No. = 132			
Survival	Negative	43 (63.2%)	96 (72.7%)	1.908*	0.167	NS
	Positive	25 (36.8%)	36 (27.3%)			

NS: Non significant; S: Significant; HS: Highly significant
*: Chi-square test; ‡: Mann Whitney test

Twenty five patients (36.8%) of RFA patients survived till end of study while thirty six patients (27.3%) of patients who underwent TACE survived till the end of the study.

Table (7): Response, recurrence and OS in different child classes in RFA group

	RFA		Test value	P-value	Sig.
	CHILD A	CHILD B			
	No. = 59	No. = 9			

Response	Complete response	53 (89.8%)	8 (88.8%)	0.215	0.898	NS
	Partial response	5 (8.5%)	1 (11.1%)			
	Stationary disease	0 (0.0%)	0 (0.0%)			
	Progressive disease	1 (1.7%)	0 (0.0%)			
Recurrence	No recurrence	24 (45.3%)	2 (22.2%)	1.680	0.195	NS
	Recurrence	29 (54.7%)	7 (77.8%)			
OS (months)	Median (IQR)	14 (10 – 23)	18 (17 – 22)	-0.553	0.581	NS
	Range	3 – 47	5 – 26			

In RFA group, complete response was achieved in 89.8% and 88.8% of child class A and B respestivelly. 8.5% of child class A and 11.1 % of child class B showed partial response. None of the patients in both classes had stationary response and progressive disease happened in one patient in child class A but not in patients of child class B. 54.7 % of child class A witnessed recurrence with median OS of 14 months while 77.8% of child class B witnessed recurrence with median OS of 18 months all without reaching statistically significant difference.

Table (8): Response, recurrence and OS in different in different BCLC classes in RFA group

		RFA		Test value	P-value	Sig.
		BCLC A	BCLC B			
		No. = 49	No. = 19			
Response	Complete response	46 (93.9%)	12 (63.1%)	6.792	0.034	S
	Partial response	3 (6.1%)	6 (31.5%)			
	Stationary disease	0 (0.0%)	0 (0.0%)			
	Progressive disease	0 (0.0%)	1 (5.2%)			
Recurrence	No recurrence	23 (48.9%)	5(26.3%)	5.187	0.023	S
	Recurrence	24 (51.1%)	14 (73.7%)			
OS (months)	Median (IQR)	15 (10 – 22)	21 (8.5 – 24)	-0.414	0.679	NS
	Range	3 – 47	6 – 25			

In RFA group, complete response was achieved in 93.9% and 63.1% of BCLC class A and class B respectively. 6.1% of BCLC class A and 31.5% of BCLC class B showed partial response. None of the patients in both classes had stationary disease and only one patient of BCLC class B had progressive disease. 51.1% of BCLC class A and 73.3% of BCLC class B witnessed recurrence of the disease with OS 15 months and 21 months in BCLC class A and B respectively.

Table (9): Response, recurrence and survival indifferent child classes in TACE group

		TACE		Test value	P-value	Sig.
		CHILD A NO= 119	CHILD B NO =13			
Response	Complete response	97 (81.5%)	10 (76.9%)	0.933	0.817	NS
	Partial response	18 (15.1%)	3 (23.1%)			
	Stationary disease	2 (1.7%)	0 (0.0%)			
	Progressive disease	2 (1.7%)	0 (0.0%)			
Recurrence	No recurrence	26 (26.8%)	1 (10.0%)	1.357	0.244	NS
	Recurrence	71 (73.2%)	9 (90.0%)			
OS (months)	Median (IQR)	17 (13 – 22)	15 (12 – 22)	-0.363	0.716	NS
	Range	3 – 42	8 – 32			

In TACE group, complete response was achieved in 81.5% and 76.9% of child class A and class B respectively. 15.1% of child class A and 23.1 % of child class B showed partial response. Two patients of child class A had stationary disease but none of child class B. Recurrence occurred in 73.2% and 90% of child class A and class B respectively. OS in child class A was 17 months while in child class B was 15 months all without reaching statistically significant difference between the two groups.

Table (10): Response, recurrence and survival in different BCLC classes in TACE group

		TACE		Test value	P-value	Sig.
		BCLC A No= 64	BCLC B No= 68			
Response	Complete response	55 (85.9%)	54 (79.4%)	5.200	0.158	NS
	Partial response	9 (14.1%)	10 (14.7%)			
	Stationary disease	0 (0.0%)	2 (2.9%)			
	Progressive disease	0 (0.0%)	2 (2.9%)			
Recurrence	No recurrence	16 (29.1%)	13 (19.1%)	1.220	0.269	NS
	Recurrence	39 (70.9%)	51 (75%)			
OS (months)	Median (IQR)	17 (15 – 22)	14.5 (11 – 21)	-2.048	0.041	S
	Range	8 – 42	3 – 32			

In TACE group, complete response was achieved in 85.9% and 74.2% of BCLC class A and B respectively. 14.1% of BCLC class A and 19.4% of BCLC class B achieved partial response. Stationary disease as well as progressive disease occurred in two patients of BCLC class B. Recurrence occurred in 70.9% of BCLC class and 80.4% of BCLC class B all without reaching statistical significance. OS in BCLC class A was 17 months while in BCLC class B was 14.5 months with statistically significant difference between the two groups.

Table (11): AFP model as predictor of response, recurrence and survival in RFA patients

RFA		Low risk	High risk	Test value*	P-value	Sig.
		No. = 46	No. = 22			
Response	Complete response	43 (93.5%)	18 (81.8%)	3.170*	0.205	NS
	Partial response	3 (6.5%)	3 (13.6%)			
	Stationary disease	0 (0.0%)	0 (0.0%)			
	Progressive disease	0 (0.0%)	1 (4.5%)			
Recurrence	No recurrence	19 (44.2%)	7 (36.8%)	0.292*	0.589	NS
	Recurrence	24 (55.8%)	12 (63.2%)			

Recurrence free survival	Median(IQR) Range	6.5 (3 – 13) 3 – 47	6 (3 – 18) 3 – 26	-0.113‡	0.910	NS
OS (months)	Median(IQR) Range	13 (9 – 22) 3 – 47	18.5 (13 – 23) 6 – 35	-1.358‡	0.174	NS
Survival	Negative Positive	27 (58.7%) 19 (41.3%)	16 (72.7%) 6 (27.3%)	1.260*	0.262	NS

NS: Non significant; S: Significant; HS: Highly significant
*: Chi-square test; ‡: Mann Whitney test

In RFA group, complete response was achieved in 93.5% in low risk group (AFP < or equal 2) and 81.8% of high risk group (AFP >2). 6.5% and 13.6% achieved partial response in low risk and high risk group respectively. None of patients in both grouped had stationary disease and progressive disease occurred in one patient of high risk group. Recurrence occurred in 55.8% of low risk group and 63.2% of high risk groups. 41.3% of low risk group and 27.3% of high risk group survived till the end of the study.

Table (12): AFP model as predictor of response, recurrence and survival in TACE patients

TACE		**Low risk** **No. = 57**	**High risk** **No. = 75**	**Test value**	**P-value**	**Sig.**
Response	Complete response	52 (91.2%)	55 (73.3%)	7.532*	0.057	NS
	Partial response	5 (8.8%)	16 (21.3%)			
	Stationary disease	0 (0.0%)	2 (2.7%)			
	Progressive disease	0 (0.0%)	2 (2.7%)			
Recurrence	No recurrence	15 (28.8%)	12 (21.8%)	0.700*	0.403	NS
	Recurrence	37 (71.2%)	43 (78.2%)			
	Range	10 – 42	3 – 32			
Survival	Negative	37 (64.9%)	59 (78.7%)	3.089*	0.079	NS
	Positive	20 (35.1%)	16 (21.3%)			

NS: Non significant; S: Significant; HS: Highly significant
*: Chi-square test; ‡: Mann Whitney test

In TACE group, complete response was achieved in 91.2 %and 73.3% in low and high risk group respectively. While 8.8% of low risk group achieved partial response 21.3% of high risk group achieved it. Two patients of high risk group had stationary disease and another two patient of the same group had progressive disease. Recurrence occurred in 71.2% of low risk group and 78.2% of high risk group all without reaching statistical significance.

DISCUSSION

Incidence of hepatocellular carcinoma (HCC) has rapidly increased worldwide. HCC is the sixth most common malignancy and the third most common cause of cancer related death [(8)]. Since HCC usually develops in a damaged liver, the prognosis of HCC depends not only on tumor progression but also on the degree of liver dysfunction [(9)]. In Egypt, liver cancer forms 23.81% of the total malignancies. HCC constitutes 70.48% of all liver tumors among Egyptians [(10)]. HCC represents approximately 90% of all primary liver cancer cases, shows a clear gender disparity towards males and is a major cancer in less developed regions, with a correlation to HBV surface antigen prevalence [(11)]. WHO and RECIST define standard measurement methods for converting radiology image observations into a quantitative and statistically tractable framework for measuring the response of tumor size to therapy. Both methods offer simple approaches to determining anatomic size and lesion changes during treatment as an indicator of response. Target lesions are measured using either the bilinear product approach (WHO) or single linear summation (RECIST) [(12)]. Recently AFP model proposed as prognostic tool which was designed in a French training cohort of HCC candidates, and tested further in an external, prospectively followed, validation set. The AFP model has been shown to be more accurate than Milan criteria for selecting HCC candidates in this French population and as a results, has been adopted as an official selection tool by the French organization for organ sharing (ABM) by 2013 [(13)]. However, the alpha feto protein model has not been studied on HCC patients undergoing locoregional treatment as regard response to treatment, HCC recurrence and survival. So our aim in this study is to validate the use of AFP model as a predictor of response, recurrence and survival in HCC patients after locoregional treatment. This study took place in tropical medicine department in Ain Shams University (Hepatoma Clinic) and included 68 patients underwent RFA and 132 patients underwent TACE retrospectively from April 2012 to April 2017 and prospectively from May 2017 to December 2017 with follow up 6 months for all patients. The AFP model was calculated for each patient enrolled in the study before intervention. The score is calculated by adding the individual

points for each obtained variable. A cut-off of 2 separates between patients at high and low risk of recurrence [14]. The patients were classified into low risk and high risk group for locoregional treatment according to the calculated alpha feto protein model. Then, patients were followed up by AFP, laboratory investigations and triphasic spiral CT performed 1 month after RFA or MRI for TACE to evaluate the response and then every 3 months to evaluate the recurrence. In our study the mean age in both groups was around 58 years old, there was male predominance in HCC patients accounting for 63.2% in RFA group and 77.3% in TACE group with statistical significance P-value (0.035). The Egyptian study that was held on 1313 Egyptian patients with HCC showed that the most frequent age category affected by HCC was between 51 and 60 years [15]. ***Morsy et al.*** [16] also found that mean age of HCC cases in Egypt was 55 years. Also in Egypt, in 2014, there were an estimated 125, 000 viremic individuals being newly diagnosed each year: 10% of those with chronic hepatitis, 30% of those with compensated cirrhosis, while the majority (60%) were diagnosed with decompensated cirrhosis or HCC [17]. A single-center prospective study of 1, 286 Egyptian patients with HCV cirrhosis estimated the annual incidence of HCC with 5.3% [18]. In our study most of the patients included were HCV +ve where 88.2%of RFA group and 89.4% 0f TACE group were HCV+ ve. Thermal ablation with radiofrequency is the standard of care for patients with BCLC 0 and A tumors not suitable for surgery. Thermal ablation in single tumors 2 to 3cm in size is an alternative to surgical resection based on technical factors (location of the tumor), hepatic and extrahepatic patient conditions [19]. In our study Most of the patients who underwent RFA were child A (86.8%) and BCLC A (72.1%) and the mean MELD score was 9.72-+2.96 and The range of number of nodules in RFA patients was 1-4 and The mean size of largest nodules in RFA patients was 2.64-+0.88. Also, TACE is recommended for patients with BCLC stage B and should be carried out in a selective manner [19]. While in our study most of patients who underwent TACE were child A (90.2%) but 48.5% of the patients were BCLC A and 47% were BCLC B and the mean MELD score was 9.83-+2.6 multiple expert panels have reached the consensus that patients with HCC should have a CTP score of A to be considered for aggressive therapies to facilitate assessment of the effect of treatment without the confounding issues of liver failure and death as a result of underlying poor hepatic reserve [20]. In RFA group child A patients achieved complete response in 89.8 % of cases, recurrence in 54.7% and OS 14 months while child B patients achieved complete response in88.9%, recurrence in 77.8% and OS 18 months All without reaching statistically significant difference between the two groups. While In TACE group child A patients achieved complete response in 81.5 % of cases, recurrence in 73.2% and OS 17 months while child B patients achieved complete response in 76.9%, recurrence in 90% and OS 15 months All without reaching statistical significant difference. The range of number of nodules in RFA patients was 1-4 while in TACE it was 1-6 with significant statistical difference (P = 0.005) and The mean size of largest nodules in TACE was 4.32 -+1.99 with high statistical significant difference (P = 0.00). This seminal publication from Milan, Italy, set criteria (single tumors ≤5 cm in diameter or no more than three tumors ≤3 cm in diameter) for OLT in patients with HCC, which was known as "Milan criteria" [21]. About 89.7% of patients in RFA group were within milan criteria while only 53.8% of TACE patients were within milan criteria with high statistical significance (P = 0.00). In our study the median AFP model in RFA was 0 while in TACE it was 2 with high statistically significant difference (P = 0.00). RFA has 2year local recurrence rate: 2–18% [22]. In our study, regarding response to treatment about 89.7% of RFA group achieved complete response, recurrence occurred in 58.1% and 36.8 % of patients survived till end with OS 20 months. Systematic review on conventional TACE has included 101 articles, with a total of 10, 108 patients. The objective response rate was 52.5% (95% CI43.6–61.5), and the overall survival (OS) was 70.3% at one year, 51.8% at two years, 40.4% at three years, and 32.4% at five years with a median OS of 19.4μmonths (95% CI 16.2–22.6) [7]**.** In our study, 81.1 % achieved complete response in TACE group and about 74.8% of patients witnessed recurrence while 0nly 27.3% survived till end of study with OS 18 months. In both RFA and TACE patients the median of recurrence free survival was 6 months with no statistical significant difference. AFP model is based on a scoring system (0–9 points), which

assigns values to: largest lesion diameter, number of HCC nodules as well as pre-LT AFP levels. A cut-off value of two points identifies patients with excellent survival and lower recurrence rate at 5 years, when tested according to the course of risk stratification during the waiting list, those patients moving from AFP >2 points to the low-risk group (≤2 points) after tumor treatment, had similar recurrence risk when compared to patients originally classified in the low-risk group [(14)]. The analyses in the subgroups of hepatitis B virus (HBV) and hepatitis C virus (HCV) patients showed similar results, and one can be surprised by the high incidence of 5-year recurrence in the HCV population with AFP score >2 (67.8%±3.0%) [(23)]. Serum AFP level has already been included in Hangzhou criteria and been used in the prognostic stratification of transplant candidates for HCC. In total, 100 and 1,000 ng/mL were used as cutoff values of AFP in some prognostic studies [(14)]. It has significance at predicting survival after liver transplantation. Changes in AFP while on the wait list also predicted post-transplant survival, and identifying these changes could facilitate better patient selection to optimize organ allocation and post-transplant outcomes [(24)]. In our study, In RFA group patients with AFP model score less than or equal 2 (low risk group) had higher complete response rate (93.5%) than high risk group (81.8%)And less recurrence rate (55.8%) in low risk group than (63.2%) in high risk group Also low risk group has a median recurrence free survival of 6.5 months And 58.7 % died by the end of the study while in high risk group RFS was 6 months and 72.7 % died All without reaching statistical significant difference. While in TACE, low risk group achieved complete response in 91.23% of patients while in high risk group it was 73.3%, recurrence was lower 71.2% while in high risk it was 78.2%. Also low risk group has a median recurrence free survival of 13months and 64.9 % died by the end of the study while in high risk group RFS was 6 months and 78.7%% died by the end of the study with statistical significance in OS and recurrence free survival.

CONCLUSION

AFP model may be a predictor of response, recurrence and survival in HCC patients undergoing locoregional treatment (TACE or RFA) but more studies with larger sample size are needed to validate its use.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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