Turk J Gastroenterol *2015; 26: 498-505*

Multidisciplinary decision making in the management of hepatocellular carcinoma: A hospital-based study

LIVER

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Original Article

ABSTRACT

Background/Aims: To evaluate the short-term outcome of the decision taken by the Hepatoma Board for the treatment of Hepatocellular carcinoma (HCC).

Materials and Methods: This was a prospective descriptive study involving 74 patients with HCC diagnosed by the known criteria. The decisions taken by the Hepatoma Board for the 74 patients were as follows: 1- surgical resection (7 patients), 2- local ablative therapy (LAT) (22 patients), 3- conventional transarterial chemoembolization (TACE) (24 patients), and 4- palliative supportive care (21 patients).

Results: The short-term mortality rate was 25.7% of the total patients. The success rate was nearly equal in LAT (68.2%) and surgery (71.4%), whereas the success rate was approximately 33.3% in TACE. There was no difference in the mean total bilirubin level before and after LAT, surgery, or TACE ($p>0.05$ for each). There was a significant decrease in the mean serum albumin level after TACE ($p=0.000$). There was a decrease in the mean alpha fetoprotein level after surgery and LAT ($p=0.033$) for surgery and ($p=0.048$) for LAT.

Conclusion: The management of HCC is better performed through a multidisciplinary team decision. Surgery has comparable outcome to LAT but is more invasive. According to our local experience, conventional TACE has a success rate of 33.3%.

Keywords: Multidisciplinary team, management of HCC, short-term outcome.

INTRODUCTION

Primary liver cancer is the fifth most common cancer worldwide and is responsible for 600,000 deaths each year; hepatocellular carcinoma (HCC), a primary liver cancer, accounts for 85%–90% of all primary liver cancers (1).

HCC is a common disorder worldwide. The incidence of HCC is increasing in Egypt mostly because of the increasing prevalence of viral hepatitis (2).

To coordinate and optimize the care of HCC, a multidisciplinary team (MDT) has been developed (3). Improved outcomes of HCC management through the establishment of an MDT have been documented in the literature (4, 5). An MDT for HCC management (Hepatoma Board) at the Assiut University Tertiary Hospital was started in 2012 by the participation of hepatologists, oncology surgeons, and interventional radiologists.

Aim of the work to evaluate the short-term outcome of the decision taken by the Hepatoma Board for the treatment of HCC.

MATERIALS AND METHODS

This was a prospective descriptive study. It was conducted in the Department of Tropical Medicine and Gastroenterology in a Tertiary Care Hospital.

The current study included 74 patients with HCC on the background of cirrhotic liver over a 16-month period. Patients who were diagnosed to have HCC based on the known criteria, were evaluated by the Hepatoma Board.

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Received: May 24, 2015 **Accepted:** August 14, 2015 **Available Online Date:** October 26, 2015
 • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2015.0158

Methods

The Hepatoma Board conducted a weekly meeting in the Department of Tropical Medicine and Gastroenterology with the participation of hepatologists (4 participants), oncology surgeons (2 participants), and interventional radiologists (2 participants).

Patients who were diagnosed to have HCC based on the known criteria (either in the Department of Tropical Medicine and Gastroenterology, in the outpatient clinic of the same department, or in the Internal Medicine Department, Tertiary Care Hospital) were re-evaluated by the Hepatoma Board.

The residents from the Department of Tropical Medicine and Gastroenterology initially meet the patients for obtaining their complete history, conducting clinical examination, facilitating patient enrollment into the Hepatoma Board system, and collecting patient data. Then, a complete assessment will be performed; both management and follow-up visits are scheduled and completed.

All patients were subjected to the following

1 Complete history-taking process involving age, sex, residence, disease duration, and performance status.
2 Thorough general examination including presence or absence of pallor, jaundice, lower limb edema, flapping tremor, and disturbed conscious level as well as its grade.
3 Thorough abdominal examination with specific emphasis on the presence of dilated abdominal veins; liver size, consistency, and tenderness; splenomegaly; and presence as well as the amount of ascites.
4 Laboratory Investigations include the following: complete blood count (CBC), complete liver function tests, serum urea and creatinine levels, prothrombin time, and International normalized ratio (INR), and alpha fetoprotein (AFP) level.
5 Radiological assessments: a- abdominal US with special stress on the number, site, and size of focal lesions; portal vein (PV) diameter and the presence or absence of PV thrombosis; ascites and its degree as well as splenic size. b- triphasic CT abdomen searching for the criteria of HCC (focal lesion with early enhancement in the arterial phase and rapid washout in the porto-venous phase as well as its number and size) and the presence or absence of vascular invasion as well as collaterals and the amount of ascites.
6 Esophagogastroduodenoscopy for the evaluation of portal hypertension severity in patients undergoing surgical resection.

The Decision taken by the Hepatoma Board for 74 patients were as follows

1. **Surgical Resection** in seven patients for HCC cases with the following criteria:
   a. performance status 0; b- Child–Pugh grade A; c- single HCC with a diameter of ≤3 cm; and d- no evidence of portal hypertension (radiological ± endoscopic).
2. **Local ablative therapy (LAT)** in 22 patients; radiofrequency ablation (RFA) in six patients and ethanol injection in 16 patients) for HCC cases with the following criteria:
   a. performance status 0, 1; b- Child–Pugh grade A, B; c- ≤3 HCC and each HCC not exceeding 4 cm in diameter; and d- in RFA, the HCC is not near the major vessels, biliary radicles, gall bladder, and surface.
3 **Transarterial chemoembolization (TACE)** in 24 patients for HCC cases with the following criteria:
   a. performance status 0, 1; b- Child–Pugh grade A, B; c- HCC, multi-nodular or large sized; and d- no evidence of vascular invasion.
4. **Palliative supportive care** in 21 patients for HCC cases with the following criteria:
   a. performance status 0–3; b- any Child–Pugh grade; c- either single or multiple HCC regardless of their size; and d- evidence of vascular invasion or distant metastasis.

Follow-up to predict the short-term outcome

During the Hepatoma Board meetings, cases were discussed and treatment plans were formulated according to the Barcelona Clinic Liver Cancer staging strategy (6) with some modifications because liver transplantation is still in the primitive stage in our region. The patients were subjected to the following (3 months after each procedure): 1- laboratory analysis, 2- abdominal ultrasonography, and 3- triphasic multislice abdomen CT. We use the response evaluation criteria in solid tumors (RECIST) for the evaluation of the response.

Exclusion criteria

Of the 152 patients with HCC along with liver cirrhosis who attended the Hepatoma Board meeting of the Tertiary Care Hospital over a 16-month period, only 74 were selected for our study. Other patients (n=78) were excluded because of the following reasons: 1- lack of follow-up, 2- follow-up at another institute after undergoing the procedure, and 3- death before undergoing the procedure.

Statistical analysis

Statistical Package for the Social Sciences (SPSS, version 16; SPSS Inc; Chicago, IL, USA) software was used for statistical analysis. The results were shown as mean±standard deviation and percentages. Comparisons of categorical variables were performed using Fisher's exact or chi-square test. Comparisons of continuous variable before and after each procedure were performed using paired samples t-test. Wilcoxon signed-rank test was used for non-parametric statistics while comparing two related samples. A p value of <0.05 was considered to be statistically significant while interpreting results.

Ethical considerations

Approval from the Ethics Committee of the Faculty of Medicine was obtained. Each patient was required to sign an informed

written consent form before starting the study. Confidentiality was assured for all patients.

RESULTS

Table 1 showed the demographic data of the study group. More than 80% of the study patients were males and two-third of the study patients belonged to rural areas. More than 70% of the patients were above the age of 55 years. The suggested etiology of liver cirrhosis and HCC were HCV, HBV, and combined HCV and HBV infections in 56.8%, 2.7%, and 2.7% of the patients, respectively.

Decision of the Hepatoma Board for the management of HCC of the study group was shown in Table 2.

Figure 1 showed the short-term outcome after the procedures (3 months after each procedure). The success of the selected procedures was noticed in 28 patients (37.8%); however, 22 patients (29.7%) needed another procedure. The short-term mortality rate was at 25.7% (19 out of 74) and approximately 84.2% of deaths were among the patients who received palliative treatment (16 out of 19).

Table 1. Demographic and Baseline laboratory data of the study group

Variable	Total Number (74)
Age in years *	
Mean±SD (Range)	58.61±7.57 (41–79)
Distribution of HCC patients according to age groups	
Age<55 years	22 (29.7%)
Age≥55 years	52 (70.3%)
Sex	
Male/Female	60 (81.1%)/14 (18.9%)
Residence	
Rural/Urban	48 (64.9%)/26 (35.1%)
Child–Pugh grade	
Child A/B/C	33 (44.6%)/33 (44.6%)/8 (10.8%)
Viral markers	
HBV/HCV/HBV & HCV/Not done	2 (2.7%)/42 (56.8%)/2 (2.7%)/28 (37.8%)
Total bilirubin (mg/dL) **	1.74±1.60
Albumin (g/dL) **	3.26±0.78
International normalized ratio (INR) **	1.31±0.20
Alpha fetoprotein (AFP) (ng/mL) [§]	416.50±735.91
Normal	7 (9.5%)
Raised	67 (90.5%)

SD: standard deviation; HCC: hepatocellular carcinoma; HBV: hepatitis B viruses; HCV: hepatitis C virus
Data are expressed as number and percentage.
*Data are expressed as mean±SD and range.
**Data are expressed as mean±SD.
[§]Data are expressed as number, percentage, and mean±SD.

Surgical resection was performed in seven patients and the success rate was approximately 71.4% (5 out of 7 patients), while the other two patients (28.6%) developed small hepatoma at the 3-month follow-up that was treated with PEI (Table 3). One patient reported post-operative empyema that was treated by a combination of antibiotic and aspiration with successful response.

LAT was performed by either RFA or percutaneous ethanol injection (PEI) in 22 patients and the success rate was approximately 68.2%; other procedures were needed in 27.2% of the patients (Table 3). RFA was performed in eight patients and success was achieved in six (75%) patients; one patient needed another session of RFA and the other needed TACE. PEI was performed in 14 patients and success was achieved in nine of those patients (64.3%), while another session of PEI was needed in two patients, TACE was needed in one patient, palliative treatment was need in one patient, and one patient died.
TACE was performed in approximately 24 patients and success was achieved in eight patients (33.3%); 14 patients (58.4%) needed another procedure (TACE) and 2 patients died (8.3%) (Table 3).

Table 2. Decision of Hepatoma Board for the management of the study group

Decision	Total Number (n=74)	Percentage (%)
Surgery (Resection)	7	9.5
Local ablative therapy	22	29.7
RFA	8	36.4
PEI	14	63.6
TACE	24	32.4
Palliative	21	28.4

Data are expressed as number and percentage.
RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; TACE: transarterial chemoembolization

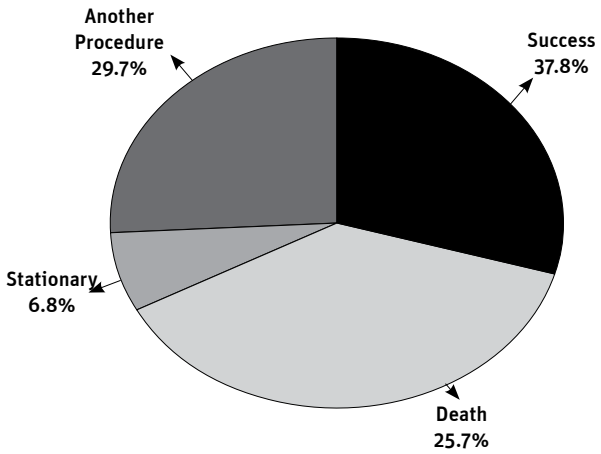

Figure 1. Short-term outcome after the procedures.

Table 3. Relation between decision and outcome

	Outcome							
	Success (n=28) (37.8%)		Death (n=19) (25.7%)		Another procedure (n=22) (29.7%)		Stationary (n=5) (6.8%)	
Decision	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Surgery (Resection) (n=7)	5	71.4	0	0.0	2	28.6	0	0.0
Local ablative therapy (n=22)	15	68.2	1	4.6	6	27.2	0	0.0
TACE (n=24)	8	33.3	2	8.3	14	58.4	0	0.0
Palliative (n=21)	0	0.0	16	76.2	0	0.0	5	23.8

Data are expressed as number and percentage.
n: number; TACE: transarterial chemoembolization

Table 4. Comparison between different decisions according to outcome

	Outcome			
	Success (n=28)		No success (n=46)	
Decision	**No.**	**%**	**No.**	**%**
Surgery (Resection) (n=7)	5	71.4	2	28.6
Local ablative therapy (n=22)	15	68.2	7	31.8
TACE (n=24)	8	33.3	16	66.7
Palliative (n=21)	0	0.0	21	100.0

Data are expressed as number and percentage.
n: number; TACE: transarterial chemoembolization

Palliative treatment was performed in 21 patients either because of the multiplicity of HCC, vascular invasion, or advanced Child–Pugh grade. On the follow-up of this group of patients, it was found that 16 patients died (76.2%) either because of gastrointestinal bleeding or hepatic encephalopathy or hepatorenal syndrome, whereas the remaining five patients (23.8%) showed a stationary course of the disease (Table 3). The success rate was nearly equal in LAT (68.2%) and surgery (71.4%), while it was approximately 33.3% in TACE (Table 4 and Figures 2-4).

The mean total bilirubin level before and after each procedure was shown in Table 5 (A). There was no difference in the mean total bilirubin level before and after LAT (p=0.995). Although with regard to surgery, there was a slight increase in the mean bilirubin level after resection but the difference was not statistically significant (p=0.086). Also, in TACE, there was an increase in the mean bilirubin level after the procedure but the difference was not statistically significant (p=0.263). During the follow-up of the patients who were managed by palliative treatment, there was an increase in the mean bilirubin level (p=0.048).

The mean serum albumin levels before and after the procedures were shown in Table 5 (B). There were no statistically significant differences in the mean serum albumin levels before and after LAT, resection, and palliative therapy; however,

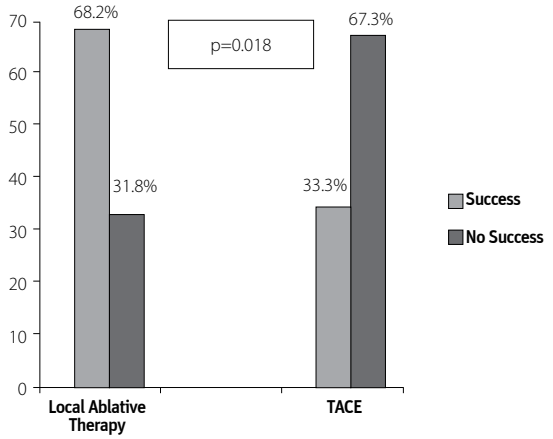

Figure 2. Comparison between local ablative therapy and TACE according to outcome.
TACE: transarterial chemoembolization

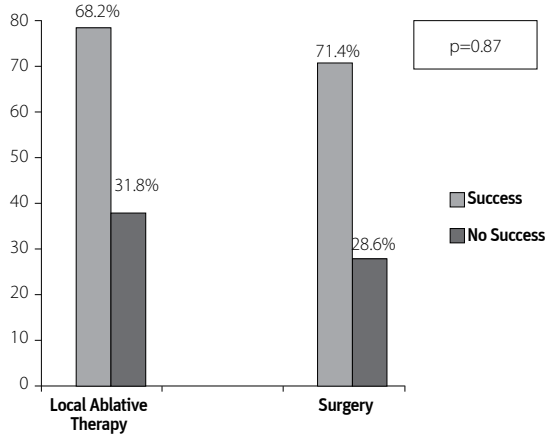

Figure 3. Comparison between local ablative therapy and surgery according to outcome.

in TACE, there was a statistically significant decrease in mean serum albumin level after the procedure (p=0.000).

The mean levels of INR before and after the procedures were shown in Table 5 (C). There was an increase in the mean INR level after palliative therapy and TACE when compared with

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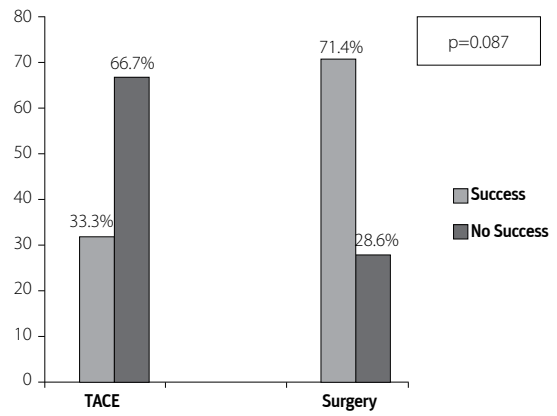

Figure 4. Comparison between TACE and surgery according to outcome. TACE: transarterial chemoembolization

the mean levels before the procedures (p=0.046 and 0.003, respectively). On the other hand, there were no statistically significant differences in the mean levels of INR after surgery and LAT when compared with the mean levels before the procedures (p=0.114 and 0.128, respectively).

The mean levels of AFP before and after the procedures for patients with raised values were shown in Table 5 (D). There was a significant decrease in the mean levels of AFP after surgery and LAT (p=0.033 and 0.048, respectively). Although in patients treated by TACE, there was a non-significant decrease in the mean levels of AFP (p=0.968), in patients treated by palliative therapy, there was a non-significant increase in the mean AFP level (p=0.068).

DISCUSSION

HCC patients have a broad range of management options, including resection, ablation, transplantation, chemoembolization, and systemic chemotherapy (7). As such, the manage-

Table 5. Changes in the laboratory data of the study group before and after interventions

Decision	No.	Pre Mean±SD	Post Mean±SD	p
(A) Total bilirubin before and after intervention				
Surgery (Resection)	7	1.02±0.44	1.23±0.41	0.086
Local ablative therapy	21	1.27±0.91	1.27±0.62	0.995
TACE***	22	1.73±1.77	2.09±1.25	0.263
Palliative**	5	1.78±0.88	2.12±0.99	0.048*
(B) Serum albumin before and after intervention				
Surgery (Resection)	7	3.92±0.38	3.57±0.41	0.291
Local ablative therapy[§]	21	3.34±0.50	3.25±0.49	0.290
TACE***	22	3.41±0.67	2.83±0.80	0.000*
Palliative**	5	2.56±1.23	2.32±1.01	0.266
(C) INR before and after intervention				
Surgery (Resection)	7	1.12±0.11	1.23±0.22	0.114
Local ablative therapy[§]	21	1.27±0.13	1.29±0.24	0.128
TACE***	22	1.27±0.16	1.59±0.47	0.003*
Palliative**	5	1.31±0.13	1.64±0.45	0.046
(D) AFP before and after intervention for patients with raised values				
Surgery (Resection)	7	271.93±78.18	59.26±64.98	0.033*
Local ablative therapy[§]	21	224.97±65.93	71.44±55.92	0.048*
TACE	22	620.94±328.46	314.00±149.02	0.968
Palliative[#]	5	752.50±242.05	925.84±272.65	0.068

SD: standard deviation
(A, B, C)
Paired sample t-test; *Statistically significant difference (p<0.05)
[§]One patient died; **sixteen patients died
*** Two patients died; INR: international normalized ratio
D
Wilcoxon signed-rank test; AFP: alpha fetoprotein
[#]AFP level was only followed in 5 of 21 patients because 16 died before the short-term follow-up
TACE: transarterial chemoembolization

ment of HCC often involves many subspecialist providers (8). HCC patients require MDT management to select treatments according to tumor stage, performance status, and hepatic function (9).

The HCC-MDT (Hepatoma Board) at this Tertiary Care Hospital was established in 2012 with the participation of hepatologists, oncology surgeons, and interventional radiologists. This study that included 74 patients with HCC on top of with liver cirrhosis disclosed and proved some important observations. First, more than 80% of the study patients were males and two-third of the study patients belonged to rural areas. Second, the mean age was 58.61±7.57 with more than 70% of patients with HCC along with liver cirrhosis were presented after the age of 55 years. Our results were similar to the results of Abdel-Wahab et al. (10) (2007). They reported that HCC is more common among males (male to female ratio was 5:1) and rural residents (77%). The mean age in their study was 54.26±9.2 years.

Our results were also similar to the results of Stacy et al. (8) (2013) who reported that the majority of HCC patients who were treated at the Johns Hopkins University School of Medicine (JHH) were males (77.7%) and the median age was 57 years (52–65 years).

The etiology of liver cirrhosis and HCC in our study was hepatitis C virus (HCV) infection in approximately 56.8% of the patients, hepatitis B virus (HBV) infection in approximately 2.7% of the patients, and combined HCV & HBV infection in approximately 2.7% of the patients.

In Abdel-Wahab et al. (10) (2007), the etiology of liver cirrhosis and HCC was hepatitis C in 76.6%, hepatitis B in 3.3%, and mixed B & C in 3.6% of the patients. The prevalence of HCV in their study was higher than that in our study because in our study, there were 28 patients (37.8%) in whom hepatitis markers were not performed. HCV is a risk factor for HCC in Egypt (11).

The decision of the Hepatoma Board for the management of HCC patients in our study was as follows: hepatic resection in 9.5%, LAT in 29.7%, TACE in 32.4%, and palliative therapy in 28.4%. Our results were different from those of Abdel-Wahab et al. (10) (2007). In lower Egypt. They reported that liver resection was performed in 25.8%, TACE in 17.2%, LAT in 14%, and mixed treatment in 3.5% of the patients, and that conservative treatment was performed in 38.7% of the patients. The cause of the above mentioned difference may be the late presentation of several patients in our study (upper Egypt compared with lower Egypt) or different culture as some patients in our study were eligible for resection but they asked for another modality and were shifted to LAT as well as some patients were not fit for surgery.

Non-cirrhotic patients or Child–Pugh A cirrhotic patients with good liver function, one nodule, and normal portal pressure are eligible for surgical resection. As a result of these guidelines, few HCC patients benefit from this method. Approximately 10%–15% of newly diagnosed HCC patients in Asia undergo resection therapy. In western countries, only 5%–10% are candidates for resection (12-14).

Of the 22 patients who were subjected to LAT in our study, 15 (68.2%) achieved success on short-term follow-up with survival and without recurrence or complications. Seven patients (31.8%) needed another procedure and one patient died.

HCC patients who are not surgically fit should be subjected to LATs. This technique could be performed either through percutaneous approach as in our study or through a laparoscopic approach (15). There are two common types of LATs: RFA and PEI. RFA is used more commonly and replaced PEI because of proven efficacy with regard to the survival and recurrence with few sessions of treatment. RFA induces coagulative necrosis of the tumor with safety margins around the lesion (16).

RFA was more effective in the treatment of small HCC (diameter: 2–3 cm) and short-term outcomes are excellent. Also, local recurrence rate after RFA was low and the rates of disease-free and overall survival was higher (17).

Of the seven patients who were subjected to resection, five (71.4%) achieved success with regard to the short-term follow-up with survival. Two patients (28.6%) needed another procedure (PEI). The success rate was nearly equal in LAT (68.2%) and surgery (71.4%) in the current study.

There was no significant difference in the mean total bilirubin or albumin levels before and after LAT or surgery. However, there was a decrease in the mean AFP levels after LAT and surgery when compared with the mean levels before these procedures.

Comparison of RFA and surgical resection in two randomized controlled trials revealed no significant differences between them with regard to recurrence-free or overall survival; however, RFA was associated with lower complication rates (18,19).

HCC patients in the early stage who are not eligible for liver transplantation or resection are preferentially treated with percutaneous ablation that is considered as a minimally invasive option with low mortality, low complication rates, and good outcomes in overall survival (20, 21).

Unresectable HCC was initially managed by TACE (22). TACE is recommended as the standard of care for intermediate stage HCC without vascular invasion or distant metastases (23).

The rational for the use of TACE in the management of HCC was based on the angiogenic activity of this tumor. Through a transarterial catheter, a cytotoxic chemotherapeutic agent

emulsified with Lipiodol was infused intra-arterially followed by the embolization of the feeding vessels (24). The success of TACE was measured by the maximum and sustained retention of the chemical agent.

Drug eluting beads (DEB-TACE), although not yet the standard, are becoming increasingly popular largely because of the decreased side-effect profile in comparison with the standard TACE cocktail of drugs. DEB-TACE delivers small beads that have been soaked for several hours, generally in doxorubicin. The loaded beads occlude the feeding vessels of HCC and the anticancer drug is gradually released, thereby creating tumor necrosis and increasing chemotherapeutic concentrations locally (25).

In our study, conventional TACE was performed in approximately 24 patients and success was achieved in eight patients (33.3%); 14 patients (58.4%) needed another procedure (another TACE) and two patients died (8.3%). There was an increase in the mean bilirubin and INR levels after the procedure, while there was a statistically significant decrease in the mean serum albumin level after the procedure. There was also a decrease in the mean AFP levels after TACE.

TACE allows local tumor control in 15%–60% of the unresectable HCC cases with 5-year survival rates between 8% and 43% (26). The variability in the results of TACE is likely explained by the fact that intermediate stage HCC covers a broad spectrum of the disease burden, and that there is a variability in the chemotherapeutic agents and embolization materials administered to patients; in addition, the procedure is performed in both Childs A and Childs B liver disease populations. With regard to the patients with HCC who had Child–Pugh B, recurrent disease and lesion in both hepatic lobes had improved outcomes with the use of DEB-TACE (23). DEB-TACE causes fewer side-effects than conventional TACE. There was a longer time to progression for DEB-TACE than that for conventional TACE (27). All patients in our study had HCC on top of with liver cirrhosis and were subjected to conventional TACE that may be the reason for the low outcome of TACE.

Limitations, drawbacks, and shortcomings: 1- small sample size and 2-we did not perform liver transplantation for potential HCC candidates because at the time of the study, liver transplantation was not the available modality of treatment for HCC in our location as well as because of financial reasons.

CONCLUSION

The management of HCC is better provided through MDT decision to offer treatments according to tumor stage, performance status, and hepatic function. Surgery has comparable outcome to LAT (71.4% versus 68.2%) but is more invasive. According to our local experience, conventional TACE has low success rate (33.3%). Hepatic decompensation was observed more frequently in patients who were managed by conventional TACE than in patients managed by surgery or RFA. The short-term mortality rate was 25.7% of the total HCC (19 out of 74) patients and approximately 84.2% of the deaths were among the patients who received palliative supportive treatment (16 out of 19 patients).

Recommendations

1. Screening programs for high-risk groups for HCC should be applied aiming for the early diagnosis of HCC where curative therapy is an available option.
2. Management of HCC should be based on MDT decision to provide the best treatment for the patient.
3. LAT (mainly RFA) has good results in tumor ablation and patient survival if performed by experts.
4. Surgery has comparable outcome to LAT but is more invasive.
5. TACE should be performed in selected patients and by expert to avoid increase in hepatic decompensation.
6. Considerable effort is required to make liver transplantation an available modality of treatment for HCC worldwide.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Faculty of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.Z., N.A.M., M.O.A.M.; Design - S.Z., N.A.M., M.O.A.M., A.A.B., H.M.A.S.; Supervision - S.Z., N.A.M., M.O.A.M., H.M.H.; Materials - S.Z., N.A.M., M.O.A.M., H.M.A.S., H.M.H.; Data Collection and/or Processing - A.A.B., N.A.M., M.O.A.M., A.M.M.S.; Analysis and/or Interpretation - S.Z., N.A.M., A.A.B., A.M.M.S., H.M.A.S.; Literature Search - N.A.M., A.A.B., M.O.A.M., A.M.M.S., H.M.A.S.

Acknowledgements: The research team would like to acknowledge all staff members in Hepatoma Board in the Department of Tropical Medicine and Gastroenterology, Assiut University.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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