

A Retrospective Study on Different Treatment Modalities of Hepatocellular Carcinoma in Assiut Governorate

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Abstract: Introduction: the management of HCC in assiut governorate is affected by many factors that would affect the choice and effectiveness of treatment. Aim of the work: to identify the different lines of management of HCC and factors associated with them. Methods: retrospective study that included 146 patients with primary hepatocellular carcinoma (HCC), admitted to Assiut university hospital and El Rajhi hospital during the period from January 2012 to December 2014. Results: the main lines of HCC management included 5 lines: surgery (resection/transplantation), local ablation, TACE, chemotherapy and Best supportive care. The most significant factors that affected treatment choice and results were Child pugh score, primary tumor size and multiplicity. Conclusion: The best cure rate was found in small or single lesions or child pugh score A managed with surgical resection. TACE was the most widely used modality. lesions more than 5 cm or multiple lesions or child pugh score B or C were associated with chemotherapy and best supportive care.

Keywords: hepatocellular carcinoma, epidemiology, upper Egypt, treatment modalities

1. Introduction

Hepatocellular carcinoma is the fifth most common type of cancer and the third most common cause of cancer-related mortality in the world. Over 80% of HCC develops in cirrhotic liver, and is mainly attributable to chronic viral infection with hepatitis B or C. The great majority of HCC cases occur in developing countries with a very high incidence in Asia and Sub-Sahara Africa. However, its incidence is increasing in Japan, United States, and other western countries with the rise of infection with hepatitis C (Nordenstedt et al., 2010 and Yang and Roberts, 2010).

HCC has a rising incidence in Egypt mostly due to high prevalence of viral hepatitis and its complications. It ranks second and sixth most common cancer among men and women respectively (Omar et al., 2013).

Theoretically, the best treatment for HCC is liver transplantation, which offers the potential to both resect the entire potentially tumor-bearing liver and eliminate the cirrhosis if present (Majnoet al., 1997, Belghiti, 2005, Ravaioliet al., 2008, Choti, 2009 and De Luna et al., 2009)

Liver resection has generally been accepted as the first treatment of choice for HCC. however, the associated cirrhosis limits the extent of surgery and increases the risk of postoperative liver failure and recurrence. (Facciutoet al., 2009 and Belghitiet al., 2003).

The limited treatment options for patients with unresectable HCC have led to the emergence of other liver directed therapies including thermal ablative techniques (radiofrequency ablation [RFA] and microwave), percutaneous ethanol injection (PEI), cryoablation, local administration of cytostatic drugs, and intrarterial embolization techniques such as selective intrarterial radioembolization therapy, transarterial

embolization (TAE), and transarterial chemoembolization (TACE) (Schwartz et al., 2007).

The present study is an epidemiologic retrospective one that aimed at identification of different treatment modalities of hepatocellular carcinoma in Assiut Governorate and to identify the factors that affect the choice and effectiveness of each modality.

2. Patients and Methods

The present study is an epidemiologic retrospective one that aimed at determining the bulk of the problem in our area and to identify the results of different treatment modalities. It was carried out on all patients presented to liver hospital and clinical oncology unit in Assiut University Hospital and were diagnosed as HCC during the period from 2012 to 2014

All patients' files were reviewed for clinical, laboratory, imaging data and staging according to Child-Pugh classification system, The different modalities of treatment were reviewed and recorded including Surgery For resectable tumors and locoregional treatment for unresectable tumors and metastatic disease.

All files also were reviewed for assessment after the end of treatment and the response were defined according to WHO criteria as: complete response (CR), partial response (PR), minimal response (MR) and progressive disease (PD).

The present study included 146 patients: 111 male and 35 female (aged between 46 and 77 years) with primary hepatocellular carcinoma (HCC), at Assiut university hospital and El Rajhi hospital during the period from January 2012 to December 2014, diagnosed by Triphasic spiral CT scan based on their early arterial enhancement and late portal venous washout.

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3. Results

As shown in table1, The majority of patients were males (79.2%); Patients were equally distributed around the age of 60yrs (52% above 60 and 48% were below); Hepatitis C-V was associated with more than 90% of cases; and Child Pugh score of A in 60% of cases and the primary diagnosis of a single lesion was made in 60% of cases.

Table 1: General features of study cases(n: 146)

	No.	%
Age groups		
≤ 60 years	76	52.05
> 60 years	70	47.9
Sex		
Male	111	79.2
Female	35	20.8
Tumor size		
≤ 5 cm	121	82.8
> 5 cm	25	17.2
Hepatitis		
HCV	121	82.2
HBV	13	8.9
Mixed	6	4.1
Negative	6	4.1
Cirrhosis		
Yes	133	91.05
No	13	8.9
Child Pugh score		
A	88	60.27
B	51	34.9
C	7	4.7
AFP		
≤ 400	82	56.1
> 400	64	43.8
Single/Multiple		
Single	87	59.58
Multiple	59	40.4

In table 2 and in figure 1; the frequency of different treatment options is displayed where TACE was the most commonly used option followed by local ablation and chemotherapy

Table 2: Frequency distribution of treatments

Treatments	N	%
Resection/transplantation	20	14
Local ablation	35	23.9
TACE	40	26.9
Chemotherapy (weekly gemzar)	31	21.2
Best supportive care	20	14

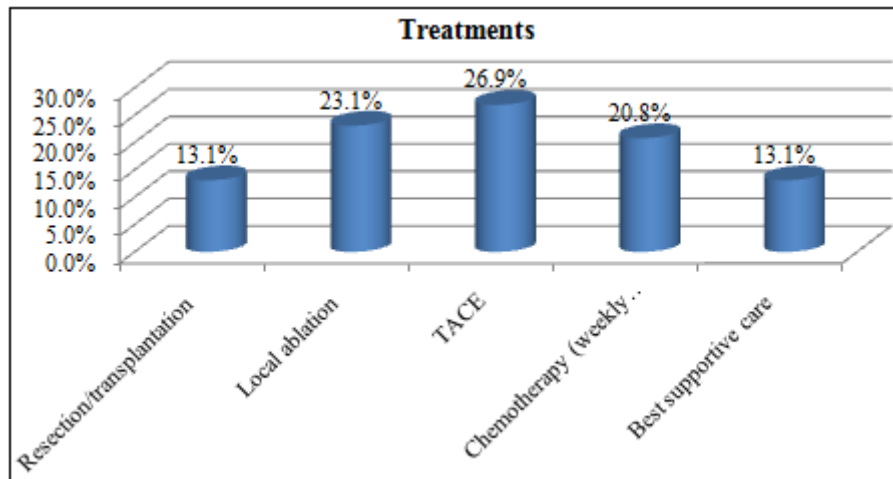


Figure 1: Frequency distribution of treatment

The results of different treatment options are shown in figure 2 where complete response was significantly associated only with surgical resection while progressive disease was most

likely with best supportive care and chemotherapy.

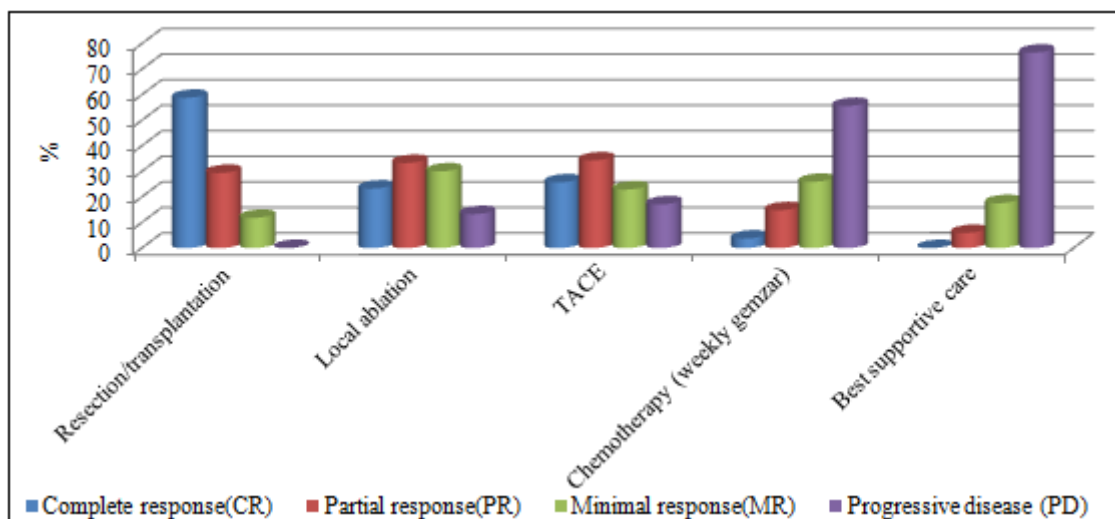


Figure 2: Outcome of different treatment modalities

There is high statistically significant difference between child pugh score of the patient and TACE as a modality of treatment (P value 0,0001) but no statistically significant difference with other modalities of treatment (table 3)

Table 3: Relation between Child Pugh score and different treatment modalities

	Child pugh score						P. value
	A (t;88)		B (t;51)		C (t;7)		
	No.	%	No.	%	No.	%	
Resection/transplantation	13	14.8	7	13.7	0	0.0	0.551
Local ablation	22	25	12	23.5	1	14.3	0.812
TACE	27	30.7	13	25.4	0	0.0	0.0001**
Chemotherapy (weekly gemzar)	21	23.8	10	19.7	0	0.0	0.312
Best supportive care	5	5.7	9	17.6	6	85.7	0.231

There is high statistically significant difference between size of the tumor (more or less than 5 cm) and local ablation (P value 0.001), also significant with best supportive care (P value 0.001) as modalities of treatment. but no statistically significant difference with other modalities (table 4)

Table 4: Relation between tumor size and treatment options:

	Size				P. value
	<=5 cm		>5 cm		
	No.	%	No.	%	
resection/transplantation	17	14	3	12	0.897
local ablation	35	28.9	0	0.0	0.001**
TACE	33	27.2	7	28	0.701
Chemotherapy (weekly gemzar)	24	19.8	7	28	0.612
best supportive care	12	9.9	8	32	0.01*

** Statistically significant difference (p<0.01)

In single lesion/cases the most commonly used modalities were TACE and local ablation, while chemotherapy and best supportive care were least used. In cases with multiple lesions: local ablation, chemotherapy and best supportive care were most commonly used while resection and TACE were the least used. (table 5)

Table 5: Relation between tumor multiplicity and treatment modalities

	Single/multiple				P. value
	Single		Multiple		
	No.	%	No.	%	
Resection/transplantation	14	16	6	10.2	0.369
Local ablation	22	25.3	13	22.03	0.355
TACE	35	40.3	5	8.4	<0.001**
Chemotherapy (weekly gemzar)	8	9.2	23	40	<0.001**
Best supportive care	8	9.2	12	20.4	0.016*

** Statistically significant difference (p<0.01)

4. Discussion & Conclusion

In the present study about 52% of the patients were between 50 and 60 years old, this generally agreed with (El-seraget et al., 2007) which stated that Hepatocellular carcinoma rarely occurs before the age of 40 years and reaches a peak at approximately 70 years of age, also agreed with (Mohammed et al., 2000 and Shaker et al., 2013).

There was a figure of 79% males which is generally agreed with (WHO,2008) which stated that Liver cancer is the fifth most common cancer in men worldwide (523,000 cases per year, 7.9% of all cancers) and the seventh in women (226,000 cases per year, 6.5% if all cancers). Also agreed with (El-Serag and Rudolph, 2007) which stated that Rates of liver cancer among men are two to four times as high as the rates among women. Shaker et al., (2013) also agrees with our study. This is mostly explained by higher incidence of HCV in males than females.

At admission, about 91% of the cases had liver cirrhosis which agreed with Sangiovanniet al., (2006) who stated that All etiologic forms of cirrhosis may be complicated by tumor formation, and that the risk is higher in patients with hepatitis infection. Overall, one-third of cirrhotic patients will develop HCC during their lifetime, Velasquez et al., (2003) and El Serag(2001) also agrees with our study.

On the other hand, in our study 82% of the cases had hepatitis C, 9% hepatitis B, 4% mixed, those percentages were different from worldwide studies as according to (EASL – EROTIC clinical practice guidelines, 2012): approximately

54% of cases worldwide can be attributed to HBV infection (which affects 400 million people globally) while 31% can be attributed to HCV infection (which affects 170 million people), leaving approximately 15% associated with other causes.

Reviewing the literature agrees with the impression that the underlying type of viral infection type differs widely in different zones of the world according to different communities characteristics:

HCV infection confers the highest risk of HCC in patients with cirrhosis, with an annual incidence ranged between 2% and 8 % (*Bruix and Sherman, 2005*). While the incidence of HBV-related HCC has decreased after the initiation of a universal vaccination program (*El-Serag 2011*).

In our study: In about 60% of cases child pugh score was A, while it was B in about 35%, C in about 5% of the cases, this can simply be explained as the majority of cases were studied at el Rajhi hospital which were admitted to hospital with criteria consistent with planning for major or minor surgical procedure that included patients in relatively good general condition or in early stages of disease.

AFP was less than 400 in 56% of the cases of the present study, most worldwide studies recommend AFP level with high cutoff points as 400ng/ml to be a good prognostic predictor in HCC patients only if dependent on other factors as tumor size (large cutoff as 5 cm) (*Huoet al., 2004*)

Single lesions were found in about 60% of cases and multiple lesions in 40% and this agreed with *Kumar et al., (2008)* & *Shaker et al., (2013)* which stated that single lesion is the most common presentation in HCC with almost similar percentages.

In the present study we found highly significant difference between tumor size and sex (p value 0.001) this could be explained by increased exposure to risk factors in males; hepatitis C or B, smoking, alcohol, *Yu MW et al., (2005)* also genetics and sex hormones as estrogen and androgen were found to play a role in hepatocarcinogenesis (*Nagasue N et al., 1985*). It may be also explained by the common belief that males in poor communities are usually late complainers than women.

A highly significant difference was found between tumor size and Child Pugh score (p value 0.009). But no statistically significant difference between multiplicity of lesion and either hepatitis or child pugh score.

In our study, there was no statistically significant difference between alpha feto protein neither with tumor size nor multiplicity. This was in disagreement with other studies as that suggests strong correlation between AFP and size >5cm (*Abbasiet al., 2012*)

As regards different treatment modalities applied in Assiut university hospitals, we found that; TACE and Local ablation were the most common modalities of treatment (27% and 23%) while the least commonly used modality was surgery and BSC (13 % for each) on the other hand 21% of HCC

patients were subjected to chemotherapy "weekly gemzar". This generally agreed with *Weledjiet al., (2014)* who states that local ablation (using either radiofrequency ablation or percutaneous ethanol injection) and TACE are the 1st treatment option in HCC patients specially in cases with early stages HCC but not suitable for surgery and those cases represent the largest proportion of HCC patients, and also safe and effective option.

In our study we found that complete response was the most frequent result of resection/transplantation arm (58% of the patients) followed by TACE and local ablation this generally agreed with the report of the *Journal of Hepatology (2012)* with some limitations: it stated that liver resection is the treatment of choice for patients with maintained underlying liver structure and function and for patients with solitary tumors, if these conditions were applied complete response will be achieved in most cases, however the risk of recurrence is high on the long term. While with local ablation with radiofrequency or percutaneous ethanol injection it was considered the standard care for early stage patients with tumors not suitable for surgery, radiofrequency ablation is recommended in most instances as the main ablative therapy in tumors less than 5 cm. Ethanol injection is recommended in cases where radiofrequency ablation is not technically feasible (around 10-15%). In tumors <2 cm, with early Child pugh score, both techniques achieve **complete responses** in more than 90% of cases with good long-term outcome. Whether they can be considered as competitive alternatives to resection is uncertain

Progression response was most commonly met with Best Supportive Care arm (76.5%) followed by chemotherapy (55%) while it was 0% with resection arm. *Journal of Hepatology (2012)* stated that best supportive care usually results in disease progression due to the original advanced disease. Thus, it can't be involved in trials. Concerning chemotherapy, *Journal of Hepatology* also agreed with our study in that chemotherapy is not a recommended modality of treatment for HCC, the only standard systemic treatment is Sorafenib which couldn't be included in our study due to financial issues.

In this study, According to Child Pugh score the different treatment modalities were almost similarly used in Child's A and B while in Child's C the best supportive care was significantly commonly used. This was in agreement with *Journal of Hepatology (2012)* which clarified that almost all modalities of treatment whether surgery, local ablation, TACE or even systemic chemotherapy requires relatively good general condition and early Child's score (A, B) to be able to get satisfactory outcome, for patients with Child's score C, the only possible treatment option is Best supportive care.

In our study there was high statistically significant difference between tumor size of 5 cm or less and local ablation: this is simply explained by the fact that in the interventional procedure of local ablation patients are selected preoperatively to have tumor size less than 5 cm. On the other hand a significant value (P value 0.001) with best supportive care and tumor sizes larger than 5 cm is expected with this line. Also there was no statistically significant

difference with other modalities which were equally used in tumors smaller or larger than 5 cm: this statistical analysis maybe affected by the fact that cases with tumors larger than 5 cm were of much less number than cases with smaller tumors (21 vs 118).

The current study shows that in single lesion/cases the most commonly used modalities were TACE and local ablation, this disagreed with (*EASL-EORTC Clinical Practice Guidelines, 2012*) which approved liver resection as the first treatment choice for solitary tumor lesions, this disagreement maybe explained by the fact that in our community locoregional procedures are more safe and less complicated. In cases with multiple lesions, local ablation and chemotherapy were most commonly used. This agreed with (*EASL-EORTC Clinical Practice Guidelines, 2012*) which stated that locoregional treatment is the available option for multinodular tumor cases, chemotherapy is not recommended as a treatment choice in the guidelines but systemic treatment (sorafenib) is given to cases with tumor lesions beyond locoregional procedures, sorafenib couldn't be administered by patients in our study due to financial issues.

In Conclusion; The available treatment modalities in our area depend on many factors such as tumour size; multiplicity; Child-Pugh score and presence hepatitis in addition to the availability of surgical treatment options like liver-transplantation. As an area of low resources and low socio-economic standards: this seems to play an important role and would affect the timing of HCC detection; progress of investigations and ability to provide our patients with optimum care as much as can be done: finally all these factors would add to the prognostic module when the case is going to be counseled for best treatment options.

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