Factors affecting post-treatment outcomes in patients with hepatocellular carcinoma

Mahmoud Saif-Al-Islam[a], Hamdy S. Mohamed[b], Emad A. Ahmed[c], Safaa Khalaf[a]

Departments of, [a]Tropical Medicine and Gastroenterology, [b]Internal Medicine, [c]General Surgery, Faculty of Medicine, Sohag University, Sohag, Egypt

Correspondence to Emad A. Ahmed, MD, PhD, Department of General Surgery, Faculty of Medicine, Sohag University, Sohag 82524, Egypt
Tel: +20 106 163 2696;
fax: +0934596010;
e-mail: dr.emadali@hotmail.com

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Background
Hepatocellular carcinoma is considered the most common primary liver tumor with increased morbidity and mortality worldwide. Therefore, we aimed to retrospectively analyze the clinical outcomes among patients with hepatocellular carcinoma treated with different treatment modalities and detect the possible factors that could affect these post-treatment outcomes.
Participants and methods
This study included patients that matched our eligibility criteria for a period of 5 years, starting from June 2015 to June 2020. Patients were followed up at postoperative first 3 months and 1 year. The authors categorized the types of post-treatment outcomes as favorable and unfavorable. According to the modified Response Assessment Criteria for Solid Tumors, the favorable outcomes included patients who were cured or had stable disease. Conversely, the unfavorable outcomes included patients who deteriorated or had a recurrence.
Results
Among 407 patients, 142 were cured at the first 3 months, 73.2% maintained cured, while 26.8% developed local recurrence after 1 year of therapy. About 47.7% of the included patients deteriorated in the first post-treatment after 3 months. The mortality rate was 41.8% during the 5-year postoperatively.
Conclusion
A fewer number of the hepatic focal lesion, small-sized lesion, early-to-intermediate stages of disease severity, and higher hemoglobin level were the only independent predictors of a favorable outcome.

Keywords:
Barcelona Clinic Liver Cancer, hepatocellular carcinoma, liver cancer, tumor response

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Introduction

Hepatocellular carcinoma (HCC) is a global health problem with a wide variation in its epidemiology [1]. HCC accounts for 90% of all primary malignant hepatic focal lesions and represents the sixth most common cancer worldwide [2,3]. Initial staging systems of HCC are beneficial for selecting the appropriate treatment and determining the overall prognosis of the disease. However, not all the staging systems combine the clinical features that reflect the liver disease's severity, tumor features, and overall patient-performance status [4] The Barcelona Clinic Liver Cancer (BCLC) staging system represents the best classification to correlate with the patient's condition, the severity of the disease, and hepatic function [5].

According to the BCLC treatment algorithm, surgical resection, liver transplantation (LT), radiofrequency ablation (RFA), and percutaneous ethanol injection (PEI) are chosen for very early (stage 0) or early (stage A) disease as potentially curative treatments [6,7]. For patients with intermediate-stage disease (stage B), transarterial chemoembolization (TACE) is recommended as a tumor-control treatment to establish local control and palliation [8]. Patients with advanced HCC (stage C) have limited treatment options, including systemic therapies that could provide minimal clinical benefit. Sorafenib is considered the only systemic agent that could extend the overall survival (OS). Up till now, the best supportive care is the only available option for patients in stage D [9,10].

Tumor responses in treated HCC patients were generally assessed according to the WHO guidelines and the Response Assessment Criteria for Solid Tumors version 1.1 (RECIST 1.1) based on tumor size and number [11] Recently, modified RECIST (mRECIST) criteria [12] have been introduced for HCC, and these criteria take into account the tumor viability based on arterial enhancement and single linear summation, which ultimately simplify the European Association for the Study of the Liver (EASL) criteria. EASL and mRECIST criteria

differ from each other according to the number of target lesions (all vs ≤2) and the calculation method (bidimensional vs unidimensional), respectively [13]. Therefore, mRECIST is commonly used as a response assessment tool and offers strong predictive value for OS analysis for different HCC therapies [14].

Noteworthy, several factors could affect the post-treatment outcomes in patients with HCC. Therefore, in this study, we aimed to retrospectively analyze the clinical outcomes among patients with HCC treated with different therapy modalities according to the BCLC classification and detect the possible factors that could affect these post-treatment outcomes.

Participants and methods

This study is a retrospective observational study that was a part of the collaboration between the Sohag University Hospital (SUH), the Faculty of Medicine, Sohag University, and the Sohag Oncology Institute (SOI), Sohag, Egypt. Ethical committee approvals for the study were obtained. Because of the retrospective nature of this study, the requirement for informed consent was waived. The study protocol was registered at ClinicalTrials.gov with Number: NCT04553458. The analysis was performed utilizing the 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)' statement [15].

Setting and participants

This work was conducted at the tropical medicine and gastroenterology, internal medicine, and general surgery departments. This study included patients that matched our eligibility criteria for a period of 5 years starting from June 2015 to June 2020. The study's purpose was to retrospectively analyze the clinical outcomes among patients with HCC treated with different treatment modalities according to the BCLC classification and detect the possible factors that could affect the post-treatment outcomes.

Eligibility criteria

All adult patients diagnosed with HCC based on a contrast-enhanced cross-sectional imaging study 'triphasic computed tomography (CT) or dynamic MRI' criteria or according to a histopathological diagnosis were included. Exclusion criteria were limited to severely ill patients with other system comorbidities, patients with extrahepatic metastasis, and those who dropped from the follow-up list after treatment.

Data collection

The patients' data were extracted and retrospectively reviewed from both hospitals' databases (SUH and SOI). During the recruitment period, 407 patients were diagnosed with HCC admitted to our departments and followed-up in SUH and SOI outpatient clinics.

Pretreatment data

Demographic criteria of the included participants were collected. We analyzed the routine laboratory tests and α-fetoprotein levels as a tumor marker for all patients. The liver state was evaluated by the Child–Turcotte–Pugh (CTP) scoring system (A, B, and C). Diagnostic imaging, including ultrasonography, CT, and MRI before implementing a specific treatment regimen, was reviewed. Hepatic focal lesion site, size, and numbers and the portal vein state were identified. Staging for BCLC (0, A, B, C, or D) was determined. When a true-cut needlebiopsy was taken for diagnosis, a histopathological report documenting HCC was studied (12 cases).

Applied treatment modalities

According to the BCLC classification, the treatment modalities for HCC patients include tumor ablation and surgical resection for patients with stages 0 and A. TACE was preserved for patients in stage B. Sorafenib administration in stage C patients and essential life support for terminal stage D patients were applied.

In our study, we analyzed two ablation procedures using an RFA or through PEI. Some treatment modalities were used in combinations. LT as a treatment option is not available at SUH or SOI, and some candidate patients refused the transferal to a transplantation center in other districts. Therefore, LT was not included as a treatment modality among our patients in this study.

Follow-up data

All patients were followed up in the outpatient clinics, and the triphasic CT abdomen was scheduled every three months for the first year after treatment.

Study variables and measurements

According to the mRECIST criteria, a complete response is defined as the disappearance of all target lesions with no arterial enhancement. A partial response is identified when there is a decrease of at least 30% of viable target lesions' diameters. Progressive disease is defined as an increase of at least 20% in the diameters of viable tumors or new lesions' appearance. The stable condition is described when the remaining viable tumor is neither decreased to sufficiently reach a

partial response nor adequately increased to qualify for the progressive disease [12].

We analyzed different preoperative clinicopathological and laboratory data and the chosen type of therapy and correlated them with post-treatment outcomes. Therefore, we categorized the post-treatment outcomes as favorable and unfavorable. The favorable outcomes included patients who were cured or had stable disease. Conversely, the unfavorable outcomes included patients who deteriorated or had a recurrence.

Bias assessment

All records were independently reviewed by an assessment committee, which included certified surgeons and gastroenterologists. All members of this committee were blinded to the study participants' baseline risk factor information.

Statistical analysis

Continuous variables were expressed as the median and interquartile range, while categorical variables were presented as numbers and percentages. Quantitative variables were compared using the Mann–Whitney test. For qualitative variables, Pearson's χ^2 tests were used after assumptions have been verified. A 95% confidence interval was reported for both measures. Multivariate logistic regression analysis was performed to identify the predictors of favorable outcomes. A P value less than 0.05 was considered statistically significant. All statistical tests were performed using IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY).

Results

Participants and descriptive data

From June 2015 to June 2020, 407 patients with HCC matched our eligibility criteria and were included in our study. The demographic criteria of all participants are summarized in Table 1. The majority of hepatic focal lesions were single (67.3%), less than 3 cm in diameter (35%), and present at the right lobe (49.4%). No mortality among patients for the first 3 months after the different treatment modalities, while 89 patients died at 1 year (21.9%). The selected treatment options for all participants were applied according to the BCLC staging system. Potentially curative treatment options (RFA, liver resection, PEI, and combined RFA+PEI) were chosen for 168 patients (41.27%). In contrast, tumor-control treatment (TACE, combined TACE, and RFA, sorafenib, chemotherapy) was used to treat 136 patients (33.4%), while symptomatic treatment was given to 103 patients (25.3%).

Outcome data and main results

Among 142 patients cured at the first 3 months, 73.2% maintained cured, while 26.8% developed local recurrence after 1 year of therapy. About 47.7% of patients deteriorated in the first post-treatment after 3 months. The mortality rate was 41.8% during the first year postoperatively. Follow-up map for the included participants at 3-month and 1-year follow-up period is detailed in Table 2.

Clinical criteria in patients with favorable and unfavorable outcomes are detailed in Table 3. They elicited statistically significant factors predicting favorable outcome, which include CTP class A (P<0.001), BCLC stage A (P<0.001), the single hepatic focal lesion (P<0.001), left hepatic lobe focal lesion (P<0.001), less than 3 cm (P<0.001), absence of portal vein thrombosis (P<0.001), and absence of ascites (P<0.001).

Moreover, patients with favorable outcomes had significantly higher hemoglobin level, platelet count, albumin, significantly lower leukocyte count, serum bilirubin, α-fetoprotein levels, and a lower percentage of HBsAg positivity (Table 4). Additionally, treatment options, such as surgery, combined RFA+PEI, and RFA, had highly significant favorable treatment outcome among the treated patients (100, 82.8, and 78.4%, respectively; P<0.001), while the significant unfavorable outcome was found with symptomatic treatment (P<0.001), chemotherapy (P<0.001), sorafenib (P=0.002), and combined RFA+TACE (P=0.032) (Table 5).

Multivariate analysis for the significant values was performed. A fewer number of the hepatic focal lesion, small-sized lesion, early-to-intermediate stages of disease severity, and higher hemoglobin level were the only independent predictors of favorable outcome (Table 6).

Discussion

HCC is an aggressive malignancy that occurs mostly in patients with liver cirrhosis and commonly presents in advanced stages [1]. There is a wide variety of treatment options for patients with HCC, some were considered a potentially curative treatment, including surgical resection, LT, and local tumor ablation therapy. Others were considered as tumor-control treatments like TACE and systemic therapy [16]. Selection of the suitable treatment line depended on many factors such as tumor site, size, and number, extrahepatic spread, and the underlying liver function [1].

In our study, we found a preponderance of male sex among HCC patients. HCC was 2–4 times more

Table 1 Patients' characteristics

Variables	*n* (%)
Age (years)	60 (55–66)
Sex (male/female)	275/132
Child–Pugh classification	
A	133 (32.7)
B	193 (47.4)
C	81 (19.9)
Tumor criteria	
Hepatic focal lesion site:	
Right lobe	201 (49.4)
Left lobe	94 (23.1)
Both	112 (27.5)
Hepatic focal lesion size (cm)	4 (3–7)
<3 cm	142 (35)
3–5 cm	139 (34)
>5 cm	126 (31)
Hepatic focal lesion number	
Single	274 (67.3)
Two	45 (11.1)
Multiple	88 (21.6)
Portal vein	
Patent	343 (84.3)
Thrombosed	64 (15.7)
Ascites	165 (40.5)
Laboratory tests	
White blood cells ($\times 10^3$/dl)	5.4 (4.1–7.4)
Hemoglobin (g/dl)	12 (10.3–13.3)
Platelets ($\times 10^3$/dl)	128 (97–210)
Prothrombin time (s)	13.7 (12.9–15.4)
Prothrombin concentration (%)	80 (65–92)
INR	1.2 (1–1.4)
Total bilirubin (mg/dl)	1.5 (0.9–2.3)
Albumin (g/dl)	3 (2.7–3.5)
Creatinine (mg/dl)	0.9 (0.8–1.1)
Alfa fetoprotein (ng/dl)	262 (19.6–1080)
Serology	
HCV Ab	358 (88)
HBsAg	57 (14)
Three-month outcome and mortality	
Favorable outcome	186 (45.7)
Cure	142 (34.9)
Stable	44 (10.8)
Unfavorable outcome	221 (54.3)
Deteriorate	194 (47.7)
Local recurrence	18 (4.4)
De novo recurrence	9 (2.2)
One-year outcome and mortality	
Alive	318 (78.1)
Cure	113 (27.8)
Stable	32 (7.9)
Deteriorate	133 (32.7)
Local recurrence	40 (9.8)
Death	89 (21.9)

HCV, hepatitis C virus; HBsAg, hepatitis-B surface antigen; INR, International Normalized Ratio.

common in men than women [17]. The higher incidence of HCC among men could be attributed to variations in hepatitis carrier state, sexual hormone effect, immune responses, and genetic considerations [18]. Additionally, our study showed that hepatic focal lesions were most frequently found in the liver's right lobe. These findings were running parallel to previous studies, where a higher percentage of the focal lesion was present in the right lobe than the left or both lobes [19,20]. As cirrhosis is a premalignant condition and represents the most important risk factor for progression to HCC, cirrhotic changes were found to be more extensive in the right lobe of the liver [8,21,22]. This was documented by biopsies from the right hepatic lobe that exhibited more necroinflammation and fibrosis than biopsies taken from the left lobe [23–25].

Curative treatment options were provided to 41.27% of our patients, 5% were subjected to hepatic resection, while 36.27% were selected for local tumor-ablative measures. RFA was the first treatment choice for 111 (27.27%) of the included HCC patients. Similarly, RFA was the first reported HCC treatment in Japan [26].

About 45.7% of our participants had favorable outcomes at 3 months of post-treatment follow-up. They were subjected to different treatment modalities with a reasonable cure rate (35%). About 73.2% of the cured patients maintained cure state after 1 year of therapy, while local recurrence was recorded in only 26.8% of patients. Compared with previous studies, these results were considered satisfactory [26–28].

Patients with favorable outcomes in this study showed CTP class A, BCLC stage A, favorable tumor criteria as a single focal lesion, left hepatic lobe focal lesion, small diameter, and absence of portal vein thrombosis, and a significantly lower median value of α-fetoprotein level. Similarly, Bryant and colleagues found that patients with favorable responses had fewer tumor numbers and smaller lesions. But, on the other hand, they reported an insignificant difference between the favorable and poor-response groups regarding AFP values [29].

Lower platelet count, deterioration in the liver function, higher AFP, and hepatitis-B virus were associated with unfavorable outcomes among our patients. Similarly, Zhang *et al.* [30] reported that thrombocytopenia was associated with poor survival and high recurrence rate, especially in patients with platelet count less than $100 \times 10^3/mm^3$. Conversely, Scheiner *et al.* [31] found that thrombocytopenia was associated with a better outcome in patients with advanced HCC, and antiplatelet therapy may benefit in managing HCC. Regarding the platelet count, there is a bidirectional relation between platelets and cancer cells. Tumor cells stimulate platelet formation and aggregation, while

platelets through selective mediators stimulate tumor growth and metastasis [32]. Moreover, abnormal albumin and bilirubin levels in patients with HCC were associated with poor prognosis and increased incidence of PVT [33,34].

In this study, all patients who were subjected to surgical resection had favorable outcomes. Hepatic resection was considered to have the best outcome for BCLC stage A HCC [35]. Furthermore, we found that RFA achieved a favorable outcome in 78.4% of HCC patients, and this percentage was raised to 82.8% in the group subjected to combined RFA and PEI (7.1%). Li *et al.* [36] stated that combined RFA+PEI was the optimal ablative treatment strategy with significant favorable OS and a significantly reduced local recurrence rate. Performance of PEI before RFA diminishes the heat-sink effect. Also, PEI induces tissue-coagulative necrosis and obliteration of small vessels [37]. Moreover, radiofrequency energy heated the ethanol, resulting in increased tissue necrosis [38], and produced a larger ablation zone with a better safety margin than RFA alone [39–41].

This study described those independent predictors of favorable outcomes that were small-sized lesions, fewer tumor numbers, and early-to-intermediate BCLC stages of disease severity. Similarly, many studies reported that a smaller hepatic focal lesion size was a significant predictor of favorable response [29,42–46]. However, these previous studies were conducted on patients treated with TACE only. Other studies

Table 2 Follow-up map for participants at 3-month and 1-year follow-up period

	3-month follow-up, *n* (%)	1-year follow-up, *n* (%)				Died
		Cure	Stable	Deteriorate	Local recurrence	
Cure	142 (35)	104 (73.2)	0	0	38 (26.8)	0
Stable	44 (10.8)	0	28 (63.6)	12 (27.3)	0	4 (9.1)
Deteriorate	194 (47.7)	2 (1)	4 (2)	107 (55.2)	0	81 (41.8)
Local recurrence	18 (4.3)	5 (27.8)	0	9 (50)	2 (11.1)	2 (11.1)
De novo recurrence	9 (2.2)	2 (22.2)	0	5 (55.6)	0	2 (22.2)
Total	407	113 (27.8)	32 (7.9)	133 (32.7)	40 (9.8)	89 (21.9)

Table 3 Comparison of demographic, clinical, and radiographic features in different treatment outcome

Variables	Favorable outcome: 186 (45.7) [*n* (%)]	Unfavorable outcome: 221 (54.3) [*n* (%)]	*P* value
Age (years)	60 (55–65)	60 (55–67)	0.338
Sex (male/female)	124/62	151/70	0.722
Child–Pugh classification			
A	83 (62.4)	50 (37.6)	0.000
B	97 (50.3)	96 (49.7)	
C	6 (7.4)	75 (92.6)	
BCLC			
Stage A	140 (79.5)	36 (20.5)	
Stage B	36 (38.3)	58 (61.7)	0.000
Stage C	2 (3.7)	52 (96.3)	
Stage D	8 (9.6)	75 (90.4)	
Hepatic focal lesion number			
Single	156 (57)	118 (43)	
Two	18 (40)	27 (60)	0.000
Multiple	12 (13.6)	76 (86.4)	
Hepatic focal lesion site			
Right lobe	93 (46.3)	108 (53.7)	
Left lobe	71 (75.5)	23 (24.5)	0.000
Both	22 (19.6)	90 (80.4)	
Hepatic focal lesion size (cm)	3.5 (3–4)	5 (3.5–8)	
<3 cm	87 (61.3)	55 (38.7)	0.000
3–5 cm	75 (54)	64 (46)	
>5 cm	24 (19)	102 (81)	
Portal vein			
Patent	186 (54.2)	157 (45.8)	0.000
Thrombosed	0	64 (100)	
Ascites	53 (32)	112 (68)	0.000

BCLC, Barcelona Clinic Liver Cancer.

Table 4 Comparison of baseline laboratory characteristics in different treatment outcomes

Variables	Favorable outcome: 186 (45.7%) [*n* (%)]	Unfavorable outcome: 221 (54.3%) [*n* (%)]	*P* value
White blood cells (×10^3/dl)	5.2 (4.25–7)	5.8 (4.1–8.2)	0.015
Hemoglobin (g/dl)	12.5 (11–13.7)	11.4 (9.5–13)	0.000
Platelets (×10^3/dl)	136 (98–224)	121 (85–187)	0.004
Prothrombin time (s)	13.8 (13–15.2)	13.5 (12.75–15.3)	0.824
Prothrombin concentration (%)	77 (66.65–89.25)	82.6 (65.75–95)	0.198
INR	1.2 (1.09–1.4)	1.2 (1–1.4)	0.185
Total bilirubin (mg/dl)	1.2 (0.9–1.8)	1.5 (1–3)	0.000
Albumin (g/dl)	3.2 (2.9–3.6)	3 (2.6–3.5)	0.005
Alfa fetoprotein (ng/dl)	93 (14.6–484)	318 (32–2555)	0.000
HCV Ab: *N* (%) within total HCV Ab positive	165 (46)	193 (54)	0.534
HBsAg: *N* (%) within total HBsAg positive	20 (36.1)	37 (63.9)	0.040

HBsAg, hepatitis-B surface antigen; HCV Ab, hepatitis-C virus antibody; INR, International Normalization Ratio; IQR, interquartile range.

Table 5 Comparison of treatment options between favorable and unfavorable outcomes

Variables	Favorable outcome: 186 (45.7%) [*n* (%)]	Unfavorable outcome: 221 (54.3%) [*n* (%)]	*P* value
RFA (*n*=111)	87 (78.4)	24 (21.6)	0.000
Surgery (*n*=20)	20 (100)	0	0.000
PEI (*n*=8)	5 (62.5)	3 (37.5)	0.278
Combined RFA+PEI (*n*=29)	24 (82.8)	5 (17.2)	0.000
Transarterial chemoembolization (*n*=56)	28 (50)	28 (50)	0.290
Combined RFA+TACE (*n*=12)	2 (16.7)	10 (83.3)	0.032
Sorafenib (*n*=10)	0	10 (100)	0.002
Chemotherapy (*n*=56)	12 (21.4)	44 (78.6)	0.000
Symptomatic treatment (*n*=105)	8 (7.8)	95 (92.4)	0.000

* (%) the percentages were calculated in relation to the total number of each variable (treatment options).
IQR, interquartile range; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Table 6 Multivariate analysis of variables predicting favorable outcome

	Comparison	Odds ratio	95% CI	*P* value
Hemoglobin level	Per every gm increase	0.82	0.7–0.97	0.020
Hepatic focal lesion number	Single versus multiple	3	1.2–7.7	0.005
Hepatic focal lesion size (cm)	≤3 cm versus >3 cm	1.36	1.2–1.56	0.000
Child–Pugh classification	Class A versus C	14.53	3.98–53.09	0.000
BCLC	Stage A versus stage B–D	0.115	0.07–0.67	0.014
	Stage B versus stage C–D	0.159	0.02–0.85	0.036

BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval.

described that the BCLC stage was also considered a significant prognostic factor for HCC outcomes [47,48].

The limitation of this study is that it was derived from an observational retrospective analysis. Therefore, further analysis of prospective randomized studies with a larger number of participants is strongly recommended.

Conclusion

A fewer number of the hepatic focal lesion, small-sized lesion, early-to-intermediate stages of disease severity, and higher hemoglobin level were the only independent predictors of a favorable outcome. Further analysis of prospective randomized studies with a larger number of participants is strongly recommended.

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Conflicts of interest
There are no conflicts of interest.

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