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Evaluation of Screening Program for Hepatocellular Carcinoma at a Single Center

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Abstract

Background: Hepatocellular Carcinoma (HCC) is the seventh most common cancer in the world is, a form of liver cancer that starts in the cells of the liver. The best way to increase the chances of survival for people at high risk for HCC is to detect it early through regular monitoring. For monitoring purposes, it is recommended to conduct ultrasound exams every four to six months, sometimes in combination with alpha-fetoprotein tests.

Aim of the Work: Assess the HCC surveillance and its ability to detect HCC patients early on and improve their management.

Patients and Methods: The study involved 300 patients of Hepatocellular Carcinoma (HCC) investigated at Menoufia University's the Institute of National Liver in Egypt. Patients were evaluated using the Liver Cancer of Barcelona Clinic (BCLC) staging system. Furthermore, the patients were classified into three surveillance categories: No surveillance, routine surveillance, and sporadic surveillance.

Results: A substantial difference statistically among the groups that received and did not receive surveillance with consideration for the stage of Hepatocellular Carcinoma (HCC) in particular was found. Patients who were observed usually got their diagnoses earlier. Those who were not under surveillance frequently had advanced cases of Hepatocellular Carcinoma upon diagnosis (HCC).

Conclusion: High-risk patients were regular investigated for having HCC is necessary for early disease detection, appropriate therapy, and improved survival. Consistent monitoring with AFP and ultrasound allows for early detection of HCC.

Keywords: HCC; Surveillance; Screening; AFP

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Introduction

Globally, hepatocellular carcinoma is the third leading cause of cancer related deaths, and among malignant tumors in general, it ranks sixth. The Child-Turcotte-Pugh score and cancer stage are two of several factors that influence the prognosis and potential treatments for HCC. Possible treatments include surgical excision of the malignant lesion, ablation methods, or liver transplantation. If curative management cannot be applied, further options include trans arterial chemoembolization, external radiation, and selective internal radiation therapy can be used. Systemic treatments are usually used to treat advanced HCC [1-3].

Liver cancer patients' prognosis is highly dependent on factors such as tumor stage and their responsiveness to curative therapy. A median five-year survival rate of over 70% is achieved for patients diagnosed with early-stage Hepatocellular Carcinoma (HCC) who undertake curative treatment. A median lifetime of just one to two years is typical for patients in the latter stages of cancer when therapy focuses on symptom management instead of cancer removal. The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of Liver Diseases advocate frequent ultrasonography screenings for liver cancer in patients with cirrhosis (EASL). These tests are frequently performed alongside α-Fetoprotein (AFP) [2,3].

Because early identification increases overall survival rates, treatment length, and the chance of curative therapies, routine Hepatocellular Carcinoma (HCC) screenings should be performed on all cirrhotic patients. The efficacy of HCC screening, however, remains a matter of contention [4]. According to the research, the chances of early diagnosis and survival are both enhanced by

regular HCC testing [5,6]. Conversely, some researchers ask for the overall benefit of HCC screening in liver cirrhosis patients. For example, a case-control research did not discover that screening for Hepatocellular Carcinoma was associated with a lower risk of (HCC) related deaths [7].

Factors like intervals of surveillance and accuracy of screening tools play a role in the effectiveness of HCC screening [8].

It is unknown if Hepatocellular Carcinoma (HCC) monitoring programs are effective or if Egyptian patients adhere to them in order to detect the disease at an early stage. It is essential to understand the real use of HCC screening in order to evaluate its total impact. Therefore, this study was conducted to evaluate the surveillance program for HCC and its effectiveness in the early detection and management of HCC patients.

Patients and Methods

Study population

Researchers from Egypt's National Liver Institute (Menoufia University) performed the analysis and description of this retrospective study. Hepatocellular Carcinoma (HCC) was diagnosed in 384 patients between January and August 2022.

To confirm a diagnosis of HCC, the American Association for the Study of Liver Diseases came up with criteria (AASLD) [2]. Patients were eligible to participate in the trial if they did not meet the following criteria: They could not have serious co-morbidities, a history of cancer (other than HCC), be under the age of 18, or not have access to surveillance data. Following the exclusion of 84 patients who did not fulfil the study's eligibility criteria, a final sample size of 300 patients were selected for participation. Study protocol adhered to the standards laid out in the Declaration of Helsinki, and the National Liver Institute's Institutional Review Board at Egypt's Menoufia University gave its approval.

Definition of surveillance intensities

For the purposes of this research, HCC surveillance was defined as obtaining serum AFP results from a minimum of one ultrasonography liver imaging test (within one month) for monitoring purposes within two years previous to HCC diagnosis. The study participants were classified into three categories based on the frequency of surveillance: Non-surveillance, regular surveillance, and irregular surveillance.

Regular surveillance: According to the guidelines of Liver Diseases' American Association (AASLD), Hepatocellular Carcinoma (HCC) is often monitored with a battery of ultrasounds and Alpha-Fetoprotein (AFP) tests once every six months, doing regularly for two years prior to an HCC diagnosis [2].

Irregular surveillance identified patients who had been under observation for a minimum of two years before of their HCC diagnosis, with monitoring intervals of more than six months.

Non-surveillance: All patients who did not undergo any investigation within 2 years prior to HCC diagnosis.

Demographic and clinical characteristics

Personal and clinical information was gathered at the time of diagnosing Hepatocellular Carcinoma (HCC), which included details such as age, gender, and functional capacity as determined by the Eastern Cooperative Oncology Group (ECOG) standards for the individual [9], conditions including diabetes and hypertension, along with history of drug use, blood transfusions, or operations, and a family history of jaundice, are all potential risk factors, bleeding tendencies, vomiting blood, or dark stool, the reason for chronic liver disease, and the presence of cirrhosis, were also noted.

Records of laboratory investigations were obtained, including AFP level at diagnosis, viral markers (HCV, HBV), and radiology data (including the presence of liver cirrhosis, ascites, and splenic diameter). Assessment of liver cirrhosis stage was performed using the Child-Pugh classification [10].

Tumor characteristics

Tumor characteristics were evaluated, including size and number, using liver dynamic (CT) or (MRI). The assessment also took into account indicators such as Portal Vein Thrombosis (PVT), blood vessel infiltration, spread to surrounding lymph nodes, and the degree of distant metastases. The staging technique of Liver Cancer Barcelona Clinic (BCLC) was utilized with these parameters to determine the Performance Status (PS), score of Child-Pugh, and radiologic extent of the tumor [11].

The cases were classified into five stages according to BCLC:

- Stage 0 (very early stage)

- Stage A (early stage)

- Stage B (intermediate stage)

- Stage C (advanced stage)

- Stage D (end-stage disease)

Treatment modalities

The treatments were documented after giving it to the patients. Curative treatments for Carcinoma of Hepatocellular (HCC) included transplantation of liver meeting the criteria of Milan, resection surgery, ablation of radiofrequency, or injection of percutaneous ethanol [12].

Statistical analysis

Information was entered, processed, and analyzed using SPSS for Windows®, version 26, which is a Statistical Package for the Social Sciences (IBM, SPSS Inc, Chicago, IL, USA). Percentages and frequencies were included in the numerical data that we totaled up. To determine if the numerical data was normally distributed, the Kolmogorov-Smirnov test was employed. Both the median (range) and the mean ± standard deviation were used to display the results, depending on the data's distribution.

Chi-Square test, or Monte-Carlo test was utilized for comparison between three or more groups with categorical variables. With normally distributed quantitative variables, the one-way ANOVA test was utilized for group comparisons; when the data did not exhibit a normal distribution, we applied the Kruskal-Walli's test. A significance level of less than 0.05 was used to determine statistical significance for all tests.

Results

Characteristics of patient

The research involved 300 patients, with a mean age of 58.16 years, ranging from thirty-two to seventy-nine years. The group comprised 243 men (81%) and 57 women (19%) (Table 1).

Among the patients diagnosed with Hepatocellular Carcinoma

Table 1: Relation between the type of surveillance and demographic criteria, clinical data.

Variables	No surveillance (N=221)	Regular surveillance (N=45)	Irregular surveillance (N=34)	Test of significance	P value
Age (Years)	62.23 ± 10.24	62.47 ± 7.47	62.50 ± 6.91	F=0.337	0.853
Sex					
Males	181 (81.9%)	33 (73.3%)	29 (85.3%)	MC=4.620	0.329
Females	40 (18.1%)	12 (26.7%)	5 (14.7%)		
Causes of liver disease					
HCV	218 (98.6%)	41 (91.1%)	31 (91.2%)	χ^2 =2.885	0.577
HBV	8 (3.6%)	1 (2.2%)	0 (0%)	MC=10.345	**0.022***
Bilharziasis	11 (5%)	1 (2.2%)	0 (0%)	MC=2.502	0.644
NAFLD	7 (3.2%)	2 (4.4%)	0 (0%)	MC=2.268	0.687
Co-morbidities and risk factors					
Smoking	30 (13.6%)	3 (6.7%)	5 (14.7%)	MC=5.245	0.244
DM	89 (40.3%)	15 (33.3%)	7 (20.6%)	MC=6.775	0.148
HTN	57 (25.8%)	12 (26.7%)	1 (2.9%)	MC=0.286	**0.036***
IHD	9 (4.1%)	0 (0%)	0 (0%)	MC=3.317	0.506
Alcohol	3 (1.4%)	0 (0%)	0 (0%)	MC=1.083	0.897
Drug or surgical history					
DAAS	133 (60.2%)	29 (26.4%)	25 (73.5%)	χ^2 =8.409	0.078
Blood transfusion	40 (18.1%)	12 (26.7%)	10 (29.4%)	MC=20.645	**<0.001***
Surgery	32 (14.5%)	5 (11.1%)	0 (0%)	MC=7.255	0.123
Interferon	3 (1.4%)	0 (0%)	1 (2.9%)	MC=2.346	0.672
Combined oral contraceptive	3 (1.4%)	0 (0%)	0 (0%)	MC=1.083	0.897
Child-Turcotte Pugh score					
CHILD A	116 (52.5%)	43 (95.6%)	33 (97.1%)	MC=50.901	**0.002***
CHILD B	54 (24.4%)	2 (4.4%)	1 (2.9%)		**0.005***
CHILD C	51 (23.1%)	0 (0%)	0 (0%)		**0.010***
Performance status stage					
0	68 (30.8%)	44 (97.8%)	33 (97.1%)	MC=**107.123**	**<0.001***
1	109 (49.3%)	1 (2.2%)	1 (2.9%)		**<0.001***
2	16 (7.2%)	0 (0%)	0 (0%)		0.542
>2	28 (12.7%)	0 (0%)	0 (0%)		0.336

F: One-Way ANOVA test; c2: Chi-square test; MC: Montecarlo test; *: Statistically significant (p<0.05)

(HCC), 280 had an infection with the Hepatitis C Virus (HCV) (93.3%). Ten patients, or 3.3% of the total, developed HCC as a result of Hepatitis B Virus (HBV) infection, while nine patients had NAFLD (3%). Among the individuals infected with HCV, 187 (62.3%) were received Direct-Acting Antiviral medications (DAAs).

All patients were diagnosed with cirrhosis at the time of HCC diagnosis. According to the Child-Pugh classification, 192 patients (64%) were classified as class A, 57 (19%) as class B, and 51 (17%) as class C.

Regarding surveillance, 45 patients (15%) underwent regular surveillance, 34 (11.3%) had irregular surveillance, and 221 (73.7%) had no surveillance.

Patients in the regularly monitored group exhibited significantly better overall health compared to both the inconsistently monitored and non-monitored groups (P<0.001). Furthermore, Child-Pugh class (A *vs.* non-cirrhotic) and MELD scores were significantly more favorable in the regularly monitored group compared to the inconsistently monitored and non-monitored groups (all P<0.001).

Tumor characteristics

In 64.4% of patients who were monitored regularly, Hepatocellular Carcinoma (HCC) was found at an early stage (stage 0 or A) according to the BCLC staging system. The percentages in the groups that did not undergo monitoring (26.9%) and those in the irregular surveillance group (40.5%; both P<0.001) were significantly different. Moreover, when contrasted with the group that did not undergo monitoring, the irregular surveillance group had a significantly greater percentage of early-stage diagnoses (P<0.001) (Table 2 and Figure 1).

When comparing the regular surveillance group to both the irregular surveillance and non-surveillance groups, lymph node invasion was found less often in the regular group (P<0.001). In addition, the non-surveillance group had a significantly higher frequency than the group that had irregular monitoring (P<0.001).

Diffuse or infiltrative tumors were more commonly detected in the non-surveillance group, followed by the irregular surveillance

Table 2: Relation between surveillance of the patients and tumor characteristics and its management.

Variables	No surveillance (N=221)	Surveillance (N=79)		Test of significance	P value
		Regular surveillance (45)	Irregular surveillance (34)		
Very early stage (0)	**1 (0.5%)**	**11 (24.4%)**	**0 (0%)**	MC=179.458	0.015*
Early stage (A)	**2 (0.9%)**	**20 (44.4%)**	**0 (0%)**		<0.001*
Intermediate stage (B)	**31 (14%)**	**14 (3.2%)**	**33 (97.1%)**		<0.001*
Advanced stage (C)	**135 (61.1%)**	**0 (0%)**	**1 (2.9%)**		<0.001*
Terminal stage (D)	**52 (23.5%)**	**0 (0%)**	**0 (0%)**		<0.001*
number of lesions					
1 focal lesion	39 (17.6%)	24 (53.3%)	9 (30.4%)	MC=45.306	**0.002***
2 focal lesions	70 (31.7%)	13 (28.9%)	12 (35.3%)		0.108
3 focal lesions	6 (2.7%)	4 (8.9%)	0 (0%)		0.46
Infiltrating	13 (5.9%)	0 (0%)	0 (0%)		0.752
Multicentric	93 (42.1%)	4 (8.9%)	13 (38.2%)		**0.001***
Tumor size	6 (2–19.5)	2.5 (1–6.5)	6.5 (2.5–11)	KW=52.40	**<0.001***
AFP level at diagnosis (ng/ml)	455 (1.3–40000)	15 (1.7–1650)	406 (3.2–44777)	KW=31.789	**<0.001***
PV invasion	171 (77.4%)	0 (0%)	1 (2.9%)	MC=137.937	**<0.001***
LN invasion	128 (57.9%)	0 (0%)	1 (2.9%)	MC=76.333	**<0.001***
Metastases	73 (33%)	0 (0%)	1 (2.9%)	MC=76.333	**<0.001***
management decision					
Ablation	5 (2.4%)	24 (53.3%)	0 (0%)	MC=23.489	**<0.001***
Liver transplantation	1 (0.5%)	3 (6.7%)	2 (6%)		**0.246**
TACE	29 (13.1%)	16 (35.6%)	30 (88.2%)		**<0.001***
Sorafenib	134 (60.6%)	0 (0%)	1 (2.9%)		**<0.001***
Supportive TTT	52 (23.5%)	0 (0%)	0 (0%)		**<0.001***
Surgical Resection	0 (0%)	2 (4.4%)	1 (2.9%)		**0.362**

MC: Montecarlo test; *: Statistically significant (p<0.05)

and regular surveillance groups. There were significant differences observed among all three groups in relation to this discovery.

A statically significant bigger number of patients in the regular group of surveillance underwent potentially curative treatments compared to those in the irregular groups of surveillance and non-surveillance. Treatments such as liver transplantation meeting Milan criteria, resection of surgery, ablation of radiofrequency, or injection of percutaneous ethanol were more regularly selected as original therapies for HCC among patients in the regular group of surveillance in relation to those in the groups of irregular surveillance and non-surveillance (P<0.001 for all comparisons).

Discussion

Leading medical bodies like AASLD, EASL, and APASL recommend that people who have cirrhosis on their livers and those who are at high risk but do not yet have the disease. Undergo regular ultrasound screening, potentially alongside AFP testing, every six months. The frequency of these screenings should be tailored to individual health status, access to healthcare services, and financial considerations [13,14]. Studies indicate that conducting surveillance for Hepatocellular Carcinoma (HCC) every six months can enhance the ability to detect early-stage cancer by a 70% sensitivity [13,15]. Hepatocellular Carcinoma (HCC) and its risk factors are on the rise in Egypt, prompting experts to recommend a four-month reduction in monitoring intervals [16].

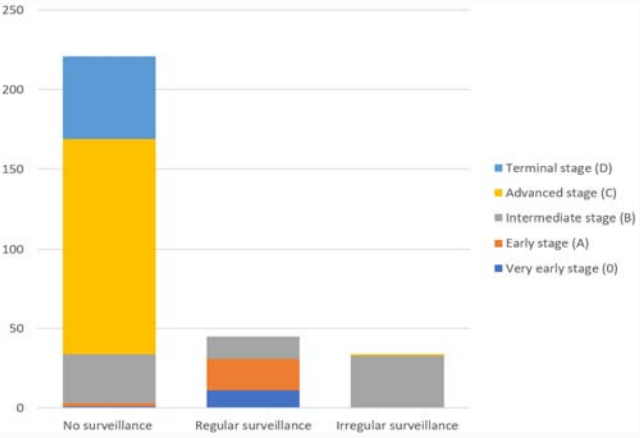

Figure 1: Relation between type of surveillance and stage of HCC.

Our study aimed to assess the efficacy of the HCC surveillance program in detecting patients at an early stage, enabling prompt treatment. Three hundred patients undergoing therapy for Hepatocellular Carcinoma (HCC) at the National Liver Institute's oncology clinic at Egypt's Menoufia University were part of the study. The ages of the patients ranged from 32 to 79 years, with an average of 58.16 years. The cohort consisted of 243 men, accounting for 81% of the total, and 57 women, accounting for 19%.

Carrilho et al. conducted research that involved 1,405 patients with HCC from various locations in Brazil over a period of 6 years. They found that men made up 78% of the patients in their study [17]. This fact agrees with our findings.

Smoking, diabetes, Hepatitis C Virus (HCV) infection, occupational exposures, and hormonal effects are all factors that increase the likelihood of adverse outcomes, which may explain why there are more men in this group.

In our study, we found that 38 individuals were smokers, making up 12.7% of the total cases. El Azm et al. highlighted that heavy smoking is widely recognized as a significant risk factor for non-B non-C Hepatocellular Carcinoma (HCC) in Egypt [18]. Another research study has identified smoking as a significant risk factor for Hepatocellular Carcinoma (HCC) in Egypt [19].

Infection of Hepatitis C Virus (HCV) was causing Carcinoma of Hepatocellular (HCC) most common, affecting 280 patients (93.3%) in our study. Hepatitis B Virus (HBV) Infection was discovered in 10 patients (3.3%), while the disease of Non-Alcoholic Fatty Liver (NAFLD) was present in 9 patients (3%). These findings align with Ezzat et al. research, which also highlighted HCV as liver cancer most common cause in Egypt, despite a declining incidence. HBV remains the second most significant cause. They emphasized the importance of mass vaccination campaigns to prevent HBV and reduce its public health impact [20].

Regarding the current study, DAAS were used by 187 cases (62.3%), Blood transfusion in 72 cases (24%) while 27 cases (12.3%) previously underwent surgeries.

Reig et al. observed early recurrence of HCC in patients treated with DAAs, which occurred in 27.6% of cases [21]. Contrary to this finding, other studies have reported no increase in recurrence following therapy with DAAs [22,23]. El Kassas et al. concluded that DAAs may play a role in the recurrence of HCC [24].

Amongst the included cases in our study, there were 79 cases who underwent surveillance for HCC. Amongst this group, there were 45 cases (56.9%) with regular surveillance, 34 cases (43.1%) with irregular surveillance.

A meta-analysis of 32 trials found that ultrasound has an overall sensitivity of 84% for detecting Hepatocellular Carcinoma (HCC) at any stage. On the other hand, its sensitivity for early-stage HCC detection was noticeably lower, at 47% [25].

Findings from a multiple study involving 374 patients indicated that screening identified 42% of Hepatocellular Carcinoma (HCC) cases diagnosed. Using ultrasonography for screening was connected to detecting tumors higher rates early, greater chances of receiving curative treatments, and improved survival compared to cases where cancer was found incidentally [26].

A combination of ultrasonography and Alpha-Fetoprotein (AFP) monitoring every four months for the detection of hepatocellular carcinoma has been supported by previous research in Egypt (HCC) [27]. Combining AFP monitoring with ultrasonography could improve surveillance for hepatocellular carcinoma, according to an Egyptian study with 514 patients suffering from chronic HCV infection (HCC). The study strongly recommended the establishment of a national surveillance program in Egyptian cirrhotic patients with HCV. This program should integrate both ultrasonography and AFP monitoring to enhance screening and notice HCC early effectively [28].

In the up-to-date study, a significant difference statistically between the cases with and without surveillance regarding the stage of HCC was found. The cases with regular surveillance were presented with earlier stages of the disease compared to the cases with no surveillance who presented by later stages of the disease. Also, surveillance was associated with smaller tumor size at presentation.

This aligns with the findings of Johnson et al., who noted variations in the rates of survival of Hepatocellular Carcinoma (HCC) comparing Hong Kong and Japan. When compared to Japan's stringent screening program, Hong Kong's program stands in sharp contrast. While the median survival time in Hong Kong was 17.8 months, it was 52 months in Japan [29].

Also included in this extensive retrospective study were the effects of various surveillance intervals on Hepatocellular Carcinoma high-risk patients (HCC). A 6-month screening interval is optimum for HCC surveillance, according to the study, since individuals with more spaced-out ultrasounds had reduced overall mortality rates [30].

Notable research was conducted by Zhang et al. among 18,816 Chinese patients who had hepatitis B infection recently or in the past. The number of people randomly assigned to the watch group was 9,373, while the number of people randomly assigned to the control group was 9,443. The research protocol included regular serum AFP testing and ultrasound imaging every six months for the study group. Even though participants only followed the surveillance regimen 60% of the time, they nevertheless reduced their chance of dying from Hepatocellular Carcinoma (HCC) by 37% [31].

Hepatocellular Carcinoma (HCC) generally exhibits a slow tumor growth rate, with median doubling times of 76.8 days for HCC associated with Hepatitis B virus, 137.2 days for HCC associated with Hepatitis C virus, and 99.8 days for HCC not linked to viral hepatitis. This extended doubling time provides multiple opportunities for ultrasound to detect the tumor, even if it was initially missed during screening, before it progresses to intermediate or advanced stages (BCLC stage B, C, and D) [32].

Likewise, the introduction of clinical reminder systems for physicians seems to enhance adherence to surveillance schedules in routine clinical practice [33].

Finally, at the end of our study, we conclude that is better to do surveillance by ultrasound and AFP every six months in high-risk cirrhotic patients as it is cost effective and better prognosis.

Conclusion

Regular surveillance of high-risk patients for developing HCC is of a great importance in early disease detection that enables proper management and improving survival. Regular surveillance with combined AFP and ultrasound every six months enables detection of HCC in earlier stages.

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