Effect of surveillance for hepatocellular carcinoma on tumor staging and treatment decisions in Egyptian patients

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Abstract

Purpose Egyptian hepatocellular carcinoma (HCC) patients present at advanced stages. We aimed to study the influence of surveillance versus non-surveillance on HCC staging and the potential therapeutic options.

Methods A retrospective study to evaluate the effect of surveillance on early detection of HCC among cirrhotic patients from 2003 to 2008. Patients examined every 6 months using ultrasound and α -fetoprotein (α -FP) (group A) and those diagnosed with those that present for the first time symptomatically or incidentally (group B). Groups were compared for α -FP level, tumour characteristics, severity of liver disease; tumour staging was evaluated by Okuda, CLIP and BCLC staging systems, in addition to the potential therapeutic options.

Results Group A comprised 122 HCC cases and group B 473. Surveillance improved HCC detection: at the stage of single nodule in 62.3% in group A versus 52.2% in group B, ($P = 0.046$) and reduced the percentage of HCC with

portal vein thrombosis in 16.4 versus 33.8%, ($P = 0.000$) and the percentage of α -FP >400 ng/ml in 19.5 versus 32.6%, ($P = 0.006$) in groups A and B, respectively. Surveillance doubled the detection of HCC at early stage of BCLC (25.4 vs. 11.9% $P = 0.000$) and doubled the patients' chance for loco-regional ablation (12.3 vs. 5.9%, $P = 0.015$) and liver transplantation (10.7 vs. 3.2%, $P = 0.001$) in groups A and B, respectively.

Conclusion HCC surveillance increases early detection of HCC and doubled the chances for curative options. Implementation of both HCC surveillance and cadaveric liver transplantation programs should be recommended in Egypt.

Keywords HCC surveillance · HCC management · HCC treatment decision

Introduction

Worldwide, hepatocellular carcinoma (HCC) accounts for 80% of primary liver neoplasms, represents the fifth most common cancer in the world, and the third most common cause of cancer-related death [1]. The increased prevalence of HCC is related to the prevalence of hepatitis B virus (HBV) (450 million) and hepatitis C virus (HCV) (170 million) infections and the growing incidence of fatty liver diseases due to metabolic derangements [2] and alcohol abuse. HCC mainly occurs in patients with chronic hepatitis C and cirrhosis, with an annual incidence of 3–5% [3]. The prognosis is poor unless HCC is diagnosed and treated early.

In Egypt, there is a growing incidence of HCC (10–120/100,000) [4], which represents the leading cause of death from all other cancer sites [5]. HCC has nearly doubled over the last decade from 4.0% in 1993 to 7.2% in 2002

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among patients with chronic liver disease (CLD) [6]. HBV and HCV infections are the most important risk factors associated with progression from chronic hepatitis to cirrhosis and, eventually, to HCC.

Hepatocellular carcinoma is a neoplasm with a dismal prognosis, in part, due to the fact that diagnosis is frequently made at an advanced tumor stage precluding effective treatment. Recently, survival after diagnosis has improved [7], which is attributed to advances in diagnostic techniques and to the application of various curative treatment options (surgical resection, liver transplantation, and percutaneous ablation). A survival rate exceeding 50% at 5 years indicates that HCC is detected at an early stage, including patients with solitary nodules of 5 cm or less or up to three nodules each 3 cm or less [8].

Since the hepatocarcinogenetic process may evolve for years in a stepwise fashion from premalignant to overt HCC [9], detection of early, better treatable tumors is made possible by surveillance of patients at-risk. The two most common tests used for screening are ultrasonography (US) of the liver and serum α -FP level either individually or in combination.

The frequency of surveillance is based on the tumor growth rate. According to a study in Chinese patients with HCC, the most rapidly growing HCCs take less than 4.6 months to grow to 3 cm [10]. Therefore, the optimal interval is unknown, but is thought to range between 6 and 12 months.

In countries implementing surveillance programs, a noticeable switch in the tumors can be detected at stages amenable to potentially curative treatments [8]. In contrast, at more advanced stages, there is uncertainty whether any treatment approach may enhance survival [11]. Most cases of HCC develop on top of cirrhotic liver; thus, both the severity of underlying liver disease and the tumor stage determine the outcome of the patients [12].

The most widely used staging systems include the Okuda system [13], which proposed three stages (I, II, and III) with different prognosis that is easily calculated by clinicians; the Cancer Liver Italian Program (CLIP) score [14], which has developed as a prognostic staging system; and the Barcelona-Clinic Liver Cancer (BCLC) classification [15], which has emerged as the standard classification in HCC clinical management.

Currently, HCC surveillance program has not been implemented in Egypt. The rate of HCC detected during routine surveillance of patients with cirrhosis compared with those diagnosed at first presentation symptomatically or incidentally has not been evaluated. Accordingly, we were motivated both to study the impact of surveillance versus non-surveillance strategy on HCC staging and to link the result of tumor stage with the potential therapeutic modalities available in Egypt.

Patients and methods

The study is a retrospective comparative study conducted at Cairo Liver Center. The center is a private institution caring for patients with liver disease, and has implemented a surveillance program in the form of US and serum α -FP level every 6 months for all patients with liver cirrhosis irrespective of the Child–Pugh grade.

Patients

All CLD patients who complied with the screening program from January 2003 to December 2008 and in whom HCC was diagnosed by the program were included in the study as the intervention group (group A). All patients who were not following the program but were diagnosed with HCC on first presentation during the study period were taken as the control group (group B).

Patients in both groups were subjected to thorough history taking and clinical examination, with emphasis on the presence of jaundice, ascites, portal hypertension, splenomegaly, esophageal varices, and encephalopathy.

The following biochemical variables were determined at the time of diagnosis: serum albumin and bilirubin concentrations, prothrombin activity, and alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels, in addition to HCV Ab, HBsAg, and serum α -FP level (cutoff value = 20 ng/mL). Tumor characteristics (size, number, and site) were detected by US and spiral computed tomography (CT), in addition to magnetic resonance imaging (MRI). Esophagogastrosocopy for evaluation of portal hypertension was done when needed.

Methods

Diagnosis of HCC was established according to the following criteria: A focal lesion found on US examination which is 2 cm or less on top of liver cirrhosis was further investigated by triphasic CT scan or MRI with contrast. If the appearances are typical of HCC (i.e., hypervascular with washout in the portal/venous phase) in both techniques, the lesion was diagnosed as HCC. If the findings are not characteristic or the vascular profile is not coincidental among techniques, the biopsy of the lesion is performed if no contraindication to biopsy.

If the nodule is larger than 2 cm at initial diagnosis and has the typical features of HCC on a dynamic imaging technique, the diagnosis of HCC is established. Alternatively, if the AFP level is more than 200 ng/mL, biopsy is not required. However, if the vascular profile on imaging is not characteristic or if the nodule is detected in a non-cirrhotic liver biopsy is performed.

The effect of the screening program on improving patients' chances of survival was evaluated as follows:

- The ability of the program in early detection of HCC cases measured as the percentage with single lesion, the percentage without portal vein thrombosis (PVT), the percentage with AFP level of less than 400 ng/mL, and the percentage detected at an early stage by the Child–Pugh, Okuda, CLIP, and BCLC classifications.
- The ability of the program to increase the patients' chances for treatment measured as the percentage of detected patients eligible for curative care.

The percentage in group A versus group B was estimated and compared. Chi-square test was used to detect significant associations, and Fisher's exact test was used when chi-square statistics was not valid; *t* test was used to detect significant differences between means.

The following tumor staging systems were applied on HCC patients in groups A and B:

1. Okuda scoring system includes bilirubin, albumin, and ascites parameters, along with an assessment of the tumor extent in the liver of more or less than 50% of the liver area involved [13].
2. CLIP score includes the Child–Pugh score parameters and an assessment of tumor extent in the liver, the presence or absence of PVT, and the level of AFP. For simplification of statistical analysis, we expressed CLIP score into three categories: early, CLIP score 0; intermediate, CLIP score 1–3; and advanced, CLIP score 4 or more [14, 16].
3. The BCLC classification uses variables related to tumor stage, liver functional status, physical status, and cancer-related symptoms and links the four stages described with a treatment algorithm [3, 15] to classify

tumor into early, intermediate, advanced, and terminal stages. The treatment options were guided by the BCLC algorithm for treatment.

4. The feasibility of potential liver transplantation was evaluated according to the “Milan criteria” excluding age: either one nodule smaller than 5 cm or fewer than three lesions smaller than 3 cm, in the absence of macrovascular invasion, was estimated to be within the criteria [17].

Results

The study included 122 patients in group A, male/female (101/21), with a mean age of 52.3 ± 8.02 years, whereas group B was composed of 473 patients, male/female (404/69), with a mean age of 56.8 ± 9.5 years. The predominant risk factors for underlying liver disease were HCV (71 vs. 78%) and HBV (22 vs. 18%) in groups A and B, respectively. The median serum α -FP level in group A was 48.7 ng/mL, which was significantly lower than 101.8 ng/mL in group B. The mean size of solitary lesions in group A was significantly smaller than that detected in group B (3.7 ± 2.4 vs. 5.8 ± 3.5 cm, $p = 0.000$). Table 1 presents the characteristics of HCC cases.

Regarding the frequency of surveillance episode used in group A, 61.5% of patients were diagnosed with HCC by less than ten times screening episodes, whereas 73.8% of the patients were diagnosed with HCC by less than 15 times examination.

The screening program appeared to be successful in early detection of HCC cases (Table 2). The program could improve detection of HCC at the single-nodule stage in 62.3% in group A versus 52.2% in group B ($p = 0.046$).

Table 1 Characteristics of HCC patients admitted to Cairo Liver Center, January 2003–December 2008

	Group A (<i>n</i> = 122)	Group B (<i>n</i> = 473)	<i>p</i>
Mean age (years)	52.3 ± 8.02	56.8 ± 9.52	0.000
Male/female	101/21	404/69	0.471
Frequency of HBV infection (%)	22	18	0.295
Frequency of HCV infection (%)	71	78	0.119
Median α -fetoprotein (ng/mL)	48.7	101.8	–
Mean number of FHLs	1.52 ± 0.5	1.62 ± 0.487	0.0448
Mean size of solitary lesions	3.7 ± 2.4	5.8 ± 3.5	0.000
Site of FHL (left lobe/right lobe/bilobar)	15/91/16	63/319/91	0.244
Bilobar involvement (%)	13.1	19.2	0.116
Child–Pugh class A/B/C	32/38/52	94/133/246	0.2
Okuda stage I/II/III (%)	28.7/42.6/28.7	20.3/49.3/30.4	0.1
CLIP: early/intermediate/advanced (%)	15.6/64.8/19.6	10.1/55.69/34.3	0.005
BCLC: very early/early/intermediate/advanced/terminal (%)	1.6/23.8/21.3/9.8/43.5	1.7/10.2/17.9/18.6/51.6	0.001

Early CLIP score 0; intermediate CLIP score 1–3; advanced CLIP ≥ 4 ; FHL focal hepatic lesion

Table 2 Screening program improved detection of HCC at early stage in patients admitted to Cairo Liver Center, January 2003–December 2008

	Group A (<i>n</i> = 122)	Group B (<i>n</i> = 473)	<i>p</i>
Single nodule	62.3	52.2	0.046
Adverse prognostic factors			
Portal vein thrombosis	16.4	33.8	0.000
α -Fetoprotein > 400 ng/mL	19.5	32.6	0.006
Okuda stage I	28.7	20.3	0.046
BCLC early stage	25.4	11.9	0.0001
CLIP early stage	15.6	10.1	0.091

PVT was detected in 16.4% in group A versus 33.8% in group B ($p = 0.000$), and AFP level of more than 400 ng/mL was reported in 19.5% in group A and 32.6% in group B ($p = 0.006$). This indicates that screening could reduce both the percentage of HCC cases with PVT and the percentage of HCC cases with AFP level of more than 400 ng/mL.

As shown in Table 2, the surveillance was successful in early staging of HCC cases. The prevalence of Okuda stage I was reported in 28.7% in group A versus 20.3% in group B. The prevalence of early CLIP score was higher in group A (15.6%) than in group B (10.1%), but results did not mount statistical significance. According to BCLC classification; very early/early HCC cases represented 25.4% in group A and 11.9% in group B ($p = 0.000$). Child–Pugh stage A score was higher in group A (26.2%) than in group B (19.9%), but results did not reach statistical significance.

The screening appeared to be successful in increasing the patients' chances to curative treatment and decreasing the number of patients in need of palliative treatment or patients in terminal stage in whom symptomatic treatment is the only option (Table 3; Fig. 1). The screening had more than double power to identify patients at early stages eligible for radiofrequency and liver transplantation ($p = 0.015$, $p = 0.001$, respectively) in group A than in group B, and results were highly significant. Regarding chemoembolization, there was neither difference in the two groups regarding the size of focal hepatic lesion nor the number of focal hepatic lesions indicated for chemoembolization for both groups. Group A 5.5 ± 2.8 versus 6.4 ± 3.26 ($p = 0.272$) and 1.73 ± 1.14 versus 1.49 ± 1.1 ($p = 0.27$). Although surveillance increased the number of cases indicated for chemoembolization, results did not mount statistical significance (21.3% in group A vs. 18.0% in group B, $p = 0.398$). Surveillance reduced significantly the number of patients indicated for new agents in favor of application of curative treatment (9.8% in group A vs. 18.6% in group B; $p = 0.012$). However, 43.4% in group A

Table 3 The ability of the screening program to improve chances of patients admitted to Cairo Liver Center for treatment of HCC, January 2003–December 2008

	Group A (<i>n</i> = 122)	Group B (<i>n</i> = 473)	<i>p</i>
Curative treatment (very early and early)			
Resection	2.5	2.7	0.578
Liver transplantation	10.7	3.2	0.001
Percutaneous ethanol injection/ radiofrequency ablation	12.3	5.9	0.015
Palliative treatment (intermediate and advanced)			
Chemoembolization	21.3	18.0	0.398
New agents	9.8	18.6	0.021
Symptomatic (terminal)	43.4	51.6	0.109

versus 51.6% in group B ($p = 0.109$) were terminal patients and would be treated symptomatically.

Discussion

Currently, the incidence of HCC seems to be increasing tremendously in Egypt as pointed out by many studies [6, 18]. In developed countries, the prognosis of HCC has improved over the past two decades, where 30–40% of cases are diagnosed at early stages when curative treatments can be initiated [7]. Potentially curative treatments include surgical resection and liver transplantation, with reported 5-year survival of 50–70% [7]. Hence, the objective of HCC surveillance was to detect HCC at potential curative stages in order to both decrease mortality from the disease and provide improvement of survival duration.

In this study, we compared the characteristics of a series of HCC detected during surveillance and HCC diagnosed symptomatically or incidentally at first presentation and found that many adverse tumor factors, such as high α -FP level of more than 400 ng/mL and PVT (32 vs. 19.5%, 33.8 vs. 16.4%), were higher in the non-surveillance group. This is consistent with the results of Yuen et al. [19], who found that patients in whom HCC was diagnosed by screening had a lower median α -FP level (111 vs. 825.5 ng/mL), smaller mean size of solitary lesions (3.7 ± 2.4 vs. 5.8 ± 3.5 cm), and lesser chance of bilobar involvement, diffuse HCC, PVT, and metastasis among screened patients versus unscreened patients, respectively. Similarly, Farinati and Gianni [20], in a study of 280 Italian patients, showed that patients in whom HCC was diagnosed by screening had an earlier tumor staging than unscreened patients, resulting in a mean gain in survival of 16 months even after adding 10 months to the survival for the unscreened patients.

Fig. 1 Potential therapeutic options among HCC patients in groups A and B

Observational studies suggest that HCCs detected during surveillance were smaller and hence more likely to be a solitary lesion than those that present symptomatically or incidentally [21, 22]. Surveillance would improve the opportunity for early detection of HCC, consequently, HCC patients whose disease is detected as a result of surveillance are more likely to receive curative treatment. In a large study from China, the biannual screening reduced HCC mortality by 37% compared with the control group [23].

In the present study, surveillance resulted in detection of more solitary HCCs at early stage, in the absence of vascular invasion, whether by Okuda or BCLC system. Conforming to results of prospective, randomized, controlled study from Shanghai, HCC screening of more than 17,800 patients with hepatitis B resulted in a higher proportion of tumors diagnosed at the subclinical stage and undergoing surgical resection than the control group [24]. It is well known that the absence of clinically relevant portal hypertension and normal bilirubin levels are key predictors of survival in patients with single tumors undergoing resection [25]. In the present study, finding of smaller tumor was associated with doubling of eligibility for locoablative modalities rather than increased referral for surgery. In concurrence with a study involving 118 French patients showed that screening programs cannot effectively identify potentially resectable HCCs [26]. In contrast, eligibility for surgical resection is quite low even in our surveillance group, being less than 5% in both groups, which is quite lower than those reported elsewhere (10–30% of HCCs are amenable to “curative” surgical resection at the time of diagnosis) [27]. The lower resection rate in our group was attributed to the presence of significant portal hypertension as well as disturbed liver functions.

Furthermore, applying Milan criteria, transplantation represented the best therapeutic option for 10.7% in group A versus 3.2% in group B patients. Milan criteria are considered to be too restrictive and can be expanded without impact on posttransplantation survival. Retro- and

prospective studies yielded results in favor of application of expanded criteria (UCSF criteria) for liver transplantation for HCC. Adoption of these criteria would have increased the number of curative liver transplantation in our series.

Surveillance increased the number of cases indicated for chemoembolization, but results did not mount statistical significance (21.3% in group A vs. 18.0% in group B, $p = 0.398$).

In the current study, most HCC patients presented at the terminal stage by BCLC classification in both groups A and B (43.4 vs. 51.6%) ($p = 0.065$). This may be related to high percentage of advanced liver cirrhosis cases (Child–Pugh class C) in both groups, with many complications of cirrhosis that have altered their general performance status in addition to the differences in the intrinsic growth rates of tumors precluding any treatment apart from symptomatic treatment. Besides, in many group B patients, HCC was diagnosed because of symptom development that prompted them to seek medical care and was found to have a dismal prognosis (0–10%; 5-year survival) [3]. Advanced cirrhosis may partly explain the high frequency of portal thrombosis even in the surveyed group. Although many factors interplay to induce PVT, such as the low portal vein velocity, the previous interventional treatment of portal hypertension besides the low platelet count altogether may induce nontumoral PVT, and the tumor itself may cause portal vein invasion. It is usually very difficult to discriminate malignant from benign PVTs by the currently available noninvasive modalities [28].

Thus, surveillance would tend to identify slower growing tumors rather than aggressive tumors [29], and we estimated that the doubling time of tumor size ranges from 1 to 19 months, with a median of 4–6 months. It has been suggested that because of the unpredictable tumor growth rate, screening should be done more frequently (3-month intervals) in a high-risk population [30]. In contrast, a recent randomized trial aimed at comparing the frequency of surveillance (3 vs. 6 months) in 1,200 patients with cirrhosis concluded that US-based screening performed

every 3 months does not improve the diagnosis and treatment of small HCCs [31]. However, in Egypt, owing to the high prevalence of HCV and subsequent rise in its prevalence, 3-month interval screening looks suitable, although appears more costly, but merits further evaluation. Eventually, multicenter trials are needed to indicate the best surveillance period for the Egyptian population.

Therefore, the current available data seem to indicate that implementing screening programs improves the outcome for patients in terms of increasing the chance of successful treatment and prolonging survival [20, 21, 24, 32]. In countries where HCC is of low prevalence, screening for HCC may not be cost-effective. The cost-effectiveness should increase for countries with a high prevalence of HCC [33], such as Egypt.

In order for surveillance to be successful, it should be accompanied by implementation of nationwide cadaveric transplantation program. But religious, legal, cultural, and social constraints on cadaveric liver transplantation have forcibly limited the transplantation program to be solely dependent on living donor liver transplantation (LDLT). Currently, LDLT is the only option available in Egypt, which began on 2001, and the overall HCC cases represented around 20%. Besides, it remains hampered by limited availability of proper donors and high expenses that make it an out-of-reach operation to most of eligible patients. Hence, implementation of cadaveric liver transplantation would increase the chance of HCC cases eligible for transplantation.

It is worth to mention that the overall survival rate of patients was difficult to estimate precisely because of the absence of a competent national health insurance system and poor compliance of most of the patients, especially in the terminal stages of the disease. In general, the predicted overall survival time was shorter in symptomatic patients with adverse prognostic factors and patients at advanced and terminal stages of the disease.

Finally, one of the main objectives from the study was to provide the health policy makers with an evidence-based proof of the importance of HCC surveillance among patients with cirrhosis. However, the only limitation of this study was the inclusion of a small sample size of HCC patients from a single center that does not represent the nationwide population. Accordingly, multicenter studies are needed to emphasize the urgent need for HCC surveillance program.

In conclusion, HCC surveillance increases the chance of early detection of HCC and doubles the chances for curative options, including locoablation therapy and liver transplantation. Furthermore, to improve the chances of curative options, implementation of both HCC surveillance and cadaveric liver transplantation programs should be recommended in Egypt.

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