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ORIGINAL RESEARCH

Hepatocellular Carcinoma Surveillance—Experience from Croatian Referral Centre for Chronic Liver Diseases

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Abstract
Purpose For patients at high-risk of developing hepatocellular carcinoma (HCC), biannual ultrasound surveillance has long been recommended, in order to detect the tumor in the early, potentially curative stages. However, globally reported HCC surveillance rates vary greatly, ranging from as low as 1.7 to as high as 80%. Our aim was to assess the utilization of surveillance with biannual ultrasound in high-risk Croatian patients and to identify the factors that impact the implementation of the recommended protocol.
Methods This retrospective study included 145 newly diagnosed HCC patients in the period from January 2010 to September 2015. We identified low-risk and high-risk patients. The latter were further subdivided into the regular biannual ultrasound surveillance group and the non-surveillance group. The groups were compared according to demographic characteristics and BCLC stage at the time of HCC diagnosis.
Results Among 145 patients, 80 patients were classified as high-risk according to EASL criteria. During the relevant period, 28.7% underwent regular surveillance, while 71.25% did not. Younger patients were more likely to undergo surveillance (OR 0.935 CI 0.874–0.999; $p = 0.05$). The patients who underwent regular surveillance had a higher chance of being diagnosed at a curative stage (BCLC 0 or A) (OR 3.701 CI 1.279–10.710; $p < 0.05$).Gender was not a predictor of participation in the regular surveillance protocol. Among the high-risk patients who did not undergo regular surveillance, 56.1% were not aware of the chronic liver disease prior to the HCC diagnosis.
Conclusion HCC surveillance is still underutilized in high-risk Croatian patients despite its obvious benefits possibly due to the untimely diagnosis of the chronic liver disease.

Keywords Hepatocellular carcinoma · Surveillance · Ultrasonography

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide and the incidence is expected to grow in the upcoming years. It represents more than 90% of primary liver cancers and most commonly occurs in the setting of the cirrhotic liver. It is more frequent in Asian and African countries with higher hepatitis B (HBV) and hepatitis C (HCV) prevalence as opposed to the western world. However, the countries of the western world are facing a growing number of HCC cases, mainly due to the increase in HCV infected individuals and high prevalence of both alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD), the "disease of the modern man" [1–5].

There are several HCC staging classifications, including TNM, OKUDA, Clip, Barcelona-Clinic Liver Cancer (BCLC), CUPI, JIP, GETCH, with the BCLC classification being the most commonly used in European countries. It takes into account the overall tumor mass as well as the patient's performance status and the prognosis of the underlying liver disease. Besides being a classification system, it can also serve

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as a basis for therapeutic procedures and the prediction of 5-year survival [1].

HCC is a difficult to treat, chemoresistant and radioresistant tumor. However, if detected in the early stages, BCLC stage 0 (one nodule smaller than 2 cm) and BCLC stage A (one nodule or three nodules smaller than 3 cm), a surgical approach can be potentially curative. For this reason, technically adequate biannual ultrasound surveillance has long been recommended by EASL–EORTC Clinical Practice Guidelines (European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer) as the most appropriate test to preform surveillance in high-risk individuals [1].

Due to the aforementioned, the discrepancies between worldwide reported surveillance rates ranging from as low as 1.7 to as high as 80% are worrisome [6, 7]. There are many determinants of ineffective surveillance including both patient- and physician-related factors and potentially the model of health care systems of different countries, but to our knowledge, studies on the latter have not been published [8].

In Croatia, a country with a national social health insurance fund and health care accessible to all citizens [9], the incidence of HCC is rising from reported 8.7/100000 in 2003 to 11.1/100000 in 2013 [10, 11]. The aim of this study was to assess the utilization of biannual ultrasound surveillance in the high-risk Croatian patients and, as a secondary end-point, to identify the factors that impact the implementation of the recommended protocol.

Patients and Methods

This retrospective study was conducted at the University Hospital Centre Zagreb, Croatian Referral Centre for Chronic Liver Diseases. We reviewed electronic charts of patients discharged from January 2010 to September 2015 with ICD-10 diagnosis C22 ("malignant neoplasm of liver and intrahepatic bile ducts") from three hospital departments: Department of Oncology and Radiotherapy, Department of Surgery and Department of Internal Medicine.

In all included patients, HCC diagnosis and BCLC staging were made according to the guidelines published by EASL [1].

The reasons for hospital admission included admission through emergency room due to symptomatic HCC and referral from primary or secondary health care practices or our center's ultrasound unit, because of the newly discovered liver mass.

From the patients' medical history, we recorded demographic data, etiology of the liver disease, and anamnestic data on previous surveillance protocols. The patients were classified into two main groups: high-risk patients and low-risk patients. Classification criteria for high-risk patients were as follows: Child–Pugh class A and class B cirrhosis, Child–Pugh class C cirrhosis on OLT (orthotopic liver transplantation) waiting list, non-cirrhotic HBV carriers with active hepatitis or family history of HCC, non-cirrhotic HCV carriers with Metavir F3 fibrosis. For the low-risk patients, criteria were as follows: patients with HCC in non-cirrhotic liver, not-HBV infected liver, HCV carriers Metavir score F0-F2, and patients with Child–Pugh C cirrhosis not on OLT list.

High-risk patients were further subdivided into those diagnosed with HCC during regular surveillance, defined as biannual liver ultrasound, and those diagnosed with HCC either accidentally or after admission into the emergency room due to symptomatic HCC. The latter group included both patients with known liver disease who underwent irregular ultrasounds performed in intervals longer than 6 months and patients who did not have a liver ultrasound performed prior to the HCC diagnosis.

Statistical analysis was performed in SPSS v.17 (IBM Corp., Armonk, NY). Numerical variables were tested for normality of distribution using D'Agostino-Pearson Test. Categorical variables were compared with chi-square test. Normally distributed variables were presented as the arithmetic mean standard deviation and Student's t test was used to compare the two groups. Multinominal logistic regression was applied. In all tests, a two-tailed p value < 0.05 indicated statistical significance.

This study was approved by the ethics committee of the University Hospital Centre Zagreb (approval number—02/21 AG) and was conducted in compliance with the Helsinki Declaration.

Results

In the investigated time period, we have identified 145 newly diagnosed HCC patients. Three patients were excluded due to inadequate medical records making a total of 142 subjects who were analyzed in our study. Table 1 shows the baseline characteristics of our enrolled patients.

Among the studied population, 66.9% (95/142) of patients diagnosed with HCC were classified as high-risk. Overall, this group did not differ significantly from the low-risk group according to age at HCC diagnosis (65.9 ± 8.4 vs 68.1 ± 13.1, $p > 0.05$) or according to gender (M/F 78/17 vs 33/14, $p > 0.05$).

We have further stratified the high-risk group based on their participation in the surveillance protocol. At this point, we had to exclude 15 additional patients because their medical records did not contain adequate anamnestic data. Baseline characteristics of the analyzed high-risk patients are summarized in Table 2.

Table 1 General characteristics of the entire studied group ($N = 142$)

N	142
Gender	
Female (n)	31
Male (n)	111
Average age at the time of HCC diagnosis (years)	66.49 ± 10.27
High-risk patients	66.9% (95/142)
Low-risk patients	33.0% (47/142)
HCC in cirrhotic liver	25.5% (12/47)
HCC in non-cirrhotic liver	74.5% (35/47)
Etiology of the liver disease in high-risk patients	
Alcoholic liver disease	31.6% (30/95)
Hepatitis B	9.5% (9/95)
Hepatitis C	26.3% (25/95)
Hepatitis B+ hepatits C	2.1% (2/95)
Other	28.4% (27/95)
Cryptogenic	2.1% (2/95)

Values are presented as mean ± SD or as percentages

Of high-risk patients, 28.7% (23/80) underwent regular biannual ultrasound surveillance.

Younger patients were more likely to undergo surveillance (OR 0.935 CI 0.874–0.999; $p < 0.05$), while gender was not a predictive factor of the participation in the surveillance protocol (OR 2.316 CI 0.575–9.338; $p > 0.05$).

Furthermore, we have evaluated the tumor stage at the time of HCC diagnosis. When compared to the patients who did not participate in the surveillance protocol, surveilled high-risk patients were 3.701 times more likely to be diagnosed in the curative (BCLC 0+A) stage of the disease (CI 1.279–10.710; $p < 0.05$). Table 3 shows the distribution of the BCLC stage at the time of HCC diagnosis in surveilled and non-surveilled high-risk patients.

Irrespective of the surveillance status, when compared to the low-risk patients, the high-risk patients were more commonly diagnosed in the curative stage of HCC, but the difference was not statistically significant (high-risk BCLC 0+A vs. low-risk BCLC 0+A, 31.7 vs 22.2%, $p > 0,05$).

In the high-risk group that did not undergo regular surveillance (57/80), 59.6% (34/57) of them, prior to the HCC diagnosis, were not diagnosed with the chronic liver disease. ALD was present in 38.2% of these patients, 17.6% had viral hepatitis and in 38.2% of patients, the etiology of the liver disease was not established. Among patients who were not diagnosed with the chronic liver disease prior to HCC diagnosis, 67.6% (23/34) presented with at least one complication of portal hypertension. Hypersplenism was found in 44.1% (15/34), ascites in 44.1% (15/34), esophageal varices in 41.1% (14/34), and encephalopathy in 2.9% (1/34) of patients.

Among those previously diagnosed with liver disease (25/57), 24% underwent irregular liver ultrasound scans and 64% of patients did not undergo liver ultrasound at all.

Among the low-risk patients, 74.5% (35/47) developed HCC in non-cirrhotic liver (NCL), while 25.5% (12/47) of patients had Child–Pugh C cirrhosis and were not on the OLT list. Patients with HCC in NCL were younger in comparison to the low-risk patients with Child–Pugh C cirrhosis (average age 67.14 ± 13.07 vs 70.92 ± 13.26; $p > 0.05$), but older when compared to the high-risk patients (67.14 ± 13.07 vs 65.92 ± 8.38; $p > 0.05$). However, the difference did not reach statistical significance either case. A known risk factor for liver damage (hemochromatosis, peliosis hepatis, ALD) was present in 20% (7/35) of patients with HCC in NCL.

Table 2 Baseline characteristics of high-risk patients stratified according to their participation in the biannual ultrasound surveillance protocol

	Surveillance		p value
	Yes ($N = 23$)	No ($N = 57$)	
Gender (m/f)	18/5	50/7	$p > 0.05$
Age at the time of diagnosis (years)	63.04 ± 5.58	67.11 ± 9.43	$p > 0.05$ (0.057)
Alcoholic liver disease N (%)	7 (30.4%)	20 (35.1%)	$p > 0.05$
Hepatitis B N (%)	4 (17.4%)	4 (7%)	
Hepatitis C N (%)	8 (34.8%)	13 (22.8%)	
Cryptogenic N (%)	1 (4.3%)	1 (1.7%)	
Cirrhosis N (%)	22 (95.6%)	55 (96.5%)	
Child–Pugh			
Child–Pugh A	12 (52.2%)	24 (42.1%)	[a]$p > 0.05$
Child–Pugh B	9 (39.1%)	30 (52.6%)	
Child–Pugh C	0 (0%)	0 (0%)	

Values are presented as mean ± SD. For comparison of numeric values, Student's t test was used. For comparison of categorical values, Fisher's exact test or chi-square test were used, as appropriate

[a] Based on $n = 80$ due to missing data

Table 3 Distribution of the BCLC stage at the time of HCC diagnosis in surveilled and non-surveilled high-risk patients

BCLC stage	Surveilled high-risk patients (%)	Non-surveilled high-risk patients (%)
BCLC 0	4.3	1.8
BCLC A	47.8	22.8
BCLC B	34.8	28.1
BCLC C	13.0	42.1
BCLC D	0	3.5

Discussion

Reported HCC surveillance rates vary greatly among different countries as well as surveillance definitions used in different studies. Current recommendation, which is considered a standard of care, is biannual ultrasound exam for the high-risk patients and the interval is based on the HCC median duplication time of 170 days [1, 12]. Asian studies report rates of regular surveillance ranging from 17 to 56.5% [13, 14]. Studies from the USA report rates ranging from as low as 1.7 to as high as 80% in tertiary referral centers, while a large meta-analysis published in 2012 reported a pooled surveillance rate of 18.4% [6, 7, 15–18]. A study from Canada reported a surveillance rate of 77%; however, the definition of regular surveillance was annual ultrasound [19]. European data is scarce, ranging from 3% in Norway to 61.6% in Italy [20–22]. In our cohort of patients, 28.7% of the high-risk patients underwent a regular biannual ultrasound and this can be regarded as underutilization of the surveillance program. We must emphasize that our results do not reflect the rates of patients followed solely by hepatologists in tertiary referral center since our cohort of patients is heterogeneous and includes patients referred to our center from primary and secondary health care institutions. Indeed, studies show that patients with advanced liver disease treated by subspecialists are more likely to receive regular surveillance as opposed to patients treated by primary care physicians [6, 7, 15]. However, due to the burden of liver disease, referral of all the high-risk patients to tertiary institutions is not possible and the role of primary care physicians in identifying and monitoring these patients is crucial for early HCC detection. Our study showed that failure to recognize cirrhosis may be a significant reason for not entering the surveillance program as has been noticed by other authors [6, 7, 20, 23, 24]. This problem is further emphasized by the fact that the majority of HCC patients without prior diagnosis of chronic liver disease presented with signs of long-standing portal hypertension, namely hypersplenism, that should have pointed into the direction of liver disease work-up. We have found that the patient age was the sole predictor of participation in the surveillance protocol, with younger patients being more likely to receive biannual ultrasound. Literature reports lower rates among patients with better liver function and non-viral cirrhosis, particularly in those with ALD that have not achieved abstinence, as opposed to patients infected with HBV and HCV [17, 21, 22, 25]. Unfortunately, our cohort of patients was too small to draw conclusions on this matter. In the USA, ethnicity was a determinant of surveillance use [6, 18] as well as socioeconomic status, with lower rates in underinsured patients [7, 15]. Since 1990, Croatia has had a national social health insurance fund (Croatian Health Insurance Fund), with mandatory health insurance with modest co-payments for complementary health insurance that covers all medical expenses. In this health care system, primary, secondary, and tertiary health care is accessible to all citizens [9]. Therefore, even though socioeconomic status was not a parameter included in our study, it should not be a barrier to any of the standard diagnostic procedures.

The efficacy of surveillance, a measure of the degree to which one procedure obtains the expected result under standardized conditions, has been largely demonstrated. Patients in biannual surveillance program are more likely to be diagnosed in the early stages of the disease when curative treatments, including liver resection and liver transplantation, are an option [8, 17–20, 22, 26–31]. However, we have still found a high proportion of patients undergoing surveillance diagnosed in advanced stages of the disease. These missed early tumors, along with other aforementioned factors that affect surveillance implementation, impact the effectiveness of surveillance.

Ultrasound is an operator-dependent technique and detection of early HCC in heterogeneous cirrhotic liver tissue with regenerative nodules, with both high sensitivity and specificity, requires expertise. It has been reported that subclinical HCC can be detected by ultrasound with a sensitivity of 94−95% but this drops to 63% for early HCC. On the other hand, studies from expert centers report sensitivity as high as 82 to 91% with specificity > 90%. Reported detection rates have been increasing over time, largely due to improvement of the available equipment [8, 16, 19, 32]. Hence, it is pivotal to standardize the requirements on both skill and experience of the ultrasonographers as well the equipment used for the centers where the surveillance is performed.

HCC arises mostly on the grounds of liver cirrhosis with the most common etiologies being ALD, HCV, and

HBV [22]. Throughout Europe, including Croatia, alcohol consumption is decreasing [33]. Nevertheless, per capita consumption is still high, 10.2–12.2 l of pure alcohol as reported by WHO [34]. In Europe, the prevalence of chronic HBV infection ranges from 0.1 to 7%, but it is declining due to universal HBV vaccination offered since 1991. HCV prevalence ranges from 0.4 to over 3.5% in some Mediterranean countries [35]. Even though the overall reported incidence and prevalence of hepatitis B and C in Croatia is low and HBV vaccination has been mandatory since 1999, viral hepatitis is a significant health burden with estimated 25,000 persons chronically infected with HBV and 40,000 persons chronically infected with HCV [36]. These data are reflected by our findings of the alcoholic liver disease being the most common etiology of the liver disease underlying HCC, followed by HCV infection. We also believe that in a significant proportion of patients diagnosed with cryptogenic cirrhosis, alcohol consumption may have been disregarded or underreported.

Literature reports that 10−20% of HBV-, HCV-negative patients develop HCC in non-cirrhotic liver; however, some degree of liver damage or risk factors for liver injury are usually present, [37, 38]. We have found a slightly higher number of patients developing HCC in NCL, reasons for which are not entirely clear. Even though BCLC was not developed for staging HCC in NCL it correlates with patients' survival and was therefore used in this study [38]. Consistent with previous reports, these patients are older and diagnosed in more advanced stages of the disease. Despite seemingly large figures, even with the presence of risk factors such as alcohol consumption, there are no grounds to recommend surveillance.

Despite the major limitation of our study, its retrospective nature and collection of data from anamnestic records, we have gained a general insight into HCC surveillance in Croatia and identified the drawbacks that are consistent with the worldwide reports. Another possible limitation is a relatively small sample size which explains why some of our results were borderline statistically significant. As this was a single-center experience, its external validity is also questionable. Further prospective and multicentric studies are needed.

HCC surveillance seems to be underutilized and high-risk patients go unrecognized while the incidence of HCC is growing. In order to improve effectiveness, a multidisciplinary approach is mandatory. It entails primary care physicians with a crucial role in identifying high-risk patients, encouragement of patients with known cirrhosis to adhere to the biannual ultrasound protocol by both specialists and subspecialists and standardization of the requirements for the diagnostic procedure per se.

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Compliance with Ethical Standards This study was approved by the ethics committee of the University Hospital Centre Zagreb (approval number—02/21 AG) and was conducted in compliance with the Helsinki Declaration.

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