HCC Surveillance

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Hepatocellular carcinoma (HCC) is probably the epitome of a screening target, with a well-defined high-risk population, accessible screening methods, and multiple curative-intent treatments available for early disease.

Keywords: hepatocellular carcinoma ; ultrasound surveillance ; sectional imaging ; early detection

1. Introduction

As of 2020, hepatocellular carcinoma (HCC) represents a major cause of morbidity and mortality, especially among patients with chronic liver disease. Available reports rank primary liver cancer as the sixth most common type of malignancy, disproportionally accounting for the fourth place in cancer-related mortality [1]. While these figures appear to be relatively stable throughout the recent years, the field is facing unprecedented effervescence, with rapid shifts occurring on multiple levels of knowledge.

Thus, the most consequential clinical dilemmas remain: why is HCC surveillance needed and what is the best approach to do it? The reason for them being the most consequential is straightforward. Even though new data is constantly emerging regarding new therapeutic regimens, the beneficial increments are still relatively small. HCC remains a diagnosis marked by high fatality rates, as proven by an incidence to mortality ratio desolately close to 1 [2]. In this light, the cornerstone of HCC survival remains early detection. This statement is backed by clear-cut data, early diagnosis rendering a 5-year survival exceeding 70%, compared to intermediate and advanced stage diagnosis which leads to a dismal, less than 20%, survival [3][4]. More explicitly, new data has shown that patients diagnosed and treated in the earliest Barcelona Clinic Liver Cancer (BCLC)—0 stage had an 86.2% 5-year survival, with a significant decrease in survival with upstaging −69.0% for BCLC A and 49.9% for BCLC B [5]. These figures dramatically drop when analyzing survival for late stage, BCLC C and D HCC, where survival is rarely above 12 months and 3 months, respectively [3][6].

Cancer surveillance programs aim to detect tumors at an early stage, when they are treatable with curative intent, thus improving survival [7]. However, the evidence for a survival benefit associated with HCC screening in patients with cirrhosis remains controversial due to the paucity of level I evidence to prove it [8]. There are only two randomized controlled trials, dichotomizing patients into screening and no screening groups, published on a large Chinese Hepatitis B Virus (HBV) cirrhosis cohort, one of them showing a 37% decrease in liver cancer-related mortality for the screening group [9].

Most of the research investigating HCC surveillance and mortality consists of observational cohort studies, the majority being retrospective. A meta-analysis of 47 observational studies found that surveillance improved detection of early-stage HCC (odds ratio [OR]-2.08), increased curative treatment rates (OR-2.24), and improved survival (OR-1.90), but there are several potential caveats [10]. In this light, the strength of the evidence supporting these screening programs remains disputable, especially with regards to mortality [11].

Future randomized controlled trials (RCTs) would provide the finest evaluation of surveillance impact, but appear to be unethical by all current standards, as most patients prefer surveillance [12]. Though high-quality data are lacking, there are currently no proposed alternatives to surveillance. With important improvements in HCC treatment over recent years, surveillance is likely to be beneficial.

The current standard of practice for HCC surveillance is bi-annual ultrasound (US) screening, per major society guidelines consensus [13][14][15][16][17]. However, the effectiveness of the ongoing screening strategies can be significantly improved.

The main advantages of US surveillance are its accessibility, non-invasive character, repeatability, and patient tolerance. Yet, even if its effectiveness is assumed based on empirical grounds, the enrollment in regular follow-up programs remains astoundingly low, even in developed countries with otherwise praised medical systems. Available reports suggest that less than one-third of the patients with cirrhosis are either included in or compliant with HCC screening programs [18]

[19], with further discrepancies occurring with regards to social status or liver disease etiology [20][21]. Not least, data suggest that less than half of patients with cirrhosis are regularly followed-up in specialized hepatology units, which places an increased burden on primary care providers to stay knowledgeable and updated with the diagnostic and therapeutic approach to an already complex issue [22].

2. Surveillance Techniques and Ongoing Strategies for HCC

Surveillance of HCC requires repeated applications of screening tools in patients at risk, aiming to reduce disease-related mortality. The outcome of surveillance is determined by the incidence of HCC in the target population, the availability and acceptance of efficient diagnostic tests, and the effective treatment [23]. The techniques used in HCC surveillance include imaging and serological examinations. The most widely used imaging method is abdominal ultrasound (US). It is indicated in patients at risk of developing HCC, notably cirrhotic patients and patients with chronic HBV infection, as long as their liver function is sufficient to allow for a therapeutic approach [24][25].

Currently, US surveillance is recommended by the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), and the Asian Pacific Association for the Study of the Liver (APASL) [13][14][15][16][17]. Multidetector CT (Computed Tomography) or dynamic MR (Magnetic Resonance) imaging are generally not cost-effective for surveillance but may be used in specific circumstances. Their indications and limitations will be discussed later in our review.

The use of tumor markers (especially alpha-fetoprotein, AFP) alone is currently not recommended for HCC screening, but the combination of AFP and B-mode US is endorsed by Eastern countries [15][16]. To increase accuracy, a value > 200 ng/dl is recommended as a threshold for surveillance purposes [16]. However, in patients with previous curative treatment for HCC, or those successfully treated with antivirals, the cut-off of 20 ng/dl appears to be more valuable [26]. Interesting new data shows that longitudinal changes in AFP may have better accuracy than a single value > 20 ng/dl [27].

The combination of US + AFP can lead to a 6% gain in the early HCC detection rate, but at the cost of false-positive results [28]. A large meta-analysis showed no benefit in early detection and receipt of curative therapy rates if AFP was added to B-mode US surveillance [10]. In contrast, in a population exceeding 1500 cirrhotic patients, AFP > 20 ng/dl used together with US surveillance increased the sensitivity of HCC detection up to 99.2% [29].

Other serological tests that have been used or are under investigation for HCC diagnosis are lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) and des-gamma-carboxyprothrombin (DCP) [14]. A Korean study revealed that, when combined with AFP, AFP-L3 significantly increased the detection sensitivity from 62% (AFP alone) to 79% (AFP and AFP-L3) at a very early stage. The Japanese Society of Hepatology uses AFP in combination with DCP as a surveillance technique. DCP seems to be correlated with tumor size, with superior performance to AFP, and is also associated with a more aggressive phenotype [15].

Several other biomarkers have been proposed as a screening tool in HCC including proteins (e.g., mRNAs), metabolites, extracellular vesicles, circulating free DNA, or circulating tumor cells [30]. Discussing all these biomarkers is beyond the purpose of this paper. Nevertheless, from bench to bedside there is still a long road ahead.

With regards to optimal surveillance schedule, most of the available data converges towards a 6-month interval. The previously mentioned Italian database revealed a significant decrease in failure rates from annual to bi-annual visits (41.3% vs. 32.2%), regardless of other features [31]. These findings are reinforced by a large-scale retrospective analysis from Taiwan [32], which compared bi-annual follow-up, to annual and less frequent visits and concluded that shorter visit intervals were associated with lower 5-year mortality. However, the benefit of decreasing the interval below 6-months is questionable, as data suggest that HCC detection (<3 cm) and overall survival did not significantly improve if a 3-month interval was implemented [33]. No difference in either HCC incidence or in prevalence of tumors ˂ 30 mm in diameter (79% versus 70%, p ˂ 0.30) was observed between the randomized groups [33]. The 6-month interval is therefore currently recommended by all major society guidelines, as previously mentioned.

Finally, it is important whom to offer the surveillance program for HCC. The at-risk population has been well-defined and comprises: all cirrhotic patients, regardless of etiology and disease severity (except for Child–Pugh C patients—only those awaiting liver transplantation), non-cirrhotic HBV patients at intermediate or high risk of HCC and non-cirrhotic F3 patients, regardless of etiology [14]. Risk among those populations is very variable and can be further stratified and refined using information gained through liver stiffness and risk scores assessment (see below).

3. Ultrasound Aspects of HCC Discovered during Screening

We can all agree that US is a powerful screening tool for HCC. It is a noninvasive and literally risk-free procedure; inexpensive and ubiquitously available; and not least, it is a patient-friendly procedure [34]. However, several clinical dilemmas still exist even now, after several decades of US screening in HCC.

What are the ultrasound features of HCC? What should one be looking at? The aim of US examination in the screening process is to detect nodules that may represent early or very early HCC. When searching for nodules, two main features are important: the US aspect and the size of the nodule. Most of the small HCCs (<2 cm) are hypoechoic, but HCC may also appear as an iso or even as a hyperechoic nodule. One study that included 153 consecutive small HCC patients found that 76.4% were hypoechoic, 17% were hyperechoic, 3.3% were isoechoic and 3.3% had nodule-in nodule pattern. This echogenicity distribution was similar in the 2–3 cm range. Patients with a hyperechoic pattern displayed a trend towards lower AFP levels, younger age, and a higher prevalence of hepatitis C—related cirrhosis. The prevalence of well-differentiated tumors was identical (55.6% and 54.5%) in the hypoechoic and hyperechoic subgroups [35]. Another study has shown that the prevalence of hyperechoic small HCC nodules may be as high as 24% [36]. The main differential diagnosis includes haemangioma and dysplastic nodules. Considering this, small hyperechoic lesions detected in cirrhotic livers should be managed similarly to hypoechoic nodules [35].

In clinical practice we can encounter other US features such as: (a) nodules with a halo; these nodules tend to have a higher chance of becoming HCC; (b) if one nodule has ill-defined margins and during follow-up transforms into a nodule with well-defined margins the probability of HCC increases; (c) the appearance of vasculature on color flow US during follow-up is also a worrisome feature; and (d) hyperechoic nodules have a lower chance of becoming HCC [37]. Other US features of HCC discovered during surveillance are large, multinodular, diffuse tumors with or without portal vein thrombosis (PVT). Sometimes the only US sign of an HCC is PVT [38].

In a multicenter study the size of nodules detected during an active surveillance was mostly either <2 cm (42,7%) or between 2–3 cm (40.3%), only 17% being larger than 3 cm (39). The probability for one nodule to be HCC increases with size. The percentages definitely diagnosed as HCC for lesions < 1 cm, 1–2 cm, 2–3 cm, > 3 cm were 68.7%, 91.5%, 94.9% and 97.1% respectively [39]. There is an old saying in liver cancer community that any nodule larger than 1 cm in a cirrhotic liver should be considered as HCC until otherwise proved [40]. From this perspective, we diagnose HCC using US every day in our routine clinical practice. However, we cannot be 100% certain that a nodule depicted by US is indeed HCC, as other contrast-enhanced imaging methods, such as CT or MRI are needed for certification. CT and MRI are used for tumor characterization and staging [14] but can also be used for supplementary nodule detection. Of note, most of the nodules < 10 mm in size detected by US are not malignant [41]. For such tumors, US is valuable in the follow-up strategy, and if a nodule increases in size beyond 10 mm, it should prompt further investigations, such as a CT scan and/or MRI. How to manage these findings is very nicely highlighted in the current European guidelines [14] and it is beyond the purpose of this review. Here, we would like to familiarize the reader with the possible dynamic changes in the US characteristics of such nodules. During the follow-up, the most important US alarm feature is the increase in size. It is not clear how the other above mentioned US features can help in decision making. Whether to continue follow-up until they become greater than 10 mm or to start early additional investigation should be investigated in future studies.

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