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POLICY STATEMENT

EASL Policy Statement
Risk-based surveillance for hepatocellular carcinoma among patients with cirrhosis

SUMMARY

Hepatocellular carcinoma (HCC) is a type of liver cancer that predominantly develops in patients with cirrhosis of the liver. The number of Europeans who die from HCC is increasing, reaching 78,400 in 2020, and HCC surveillance of patients with cirrhosis aims to reduce this number. The term 'HCC surveillance' means that screening for HCC is done at regular intervals.

Current recommendations say that HCC surveillance should be done with an ultrasound examination of the liver every 6 months, but too many patients do not receive this standard of care. This Policy Statement argues for risk-based surveillance as a superior strategy to prevent deaths from HCC.

Risk-based surveillance means that the decision to screen, the interval between screening tests, and the type of screening test can be varied according to the level of individual risk of developing HCC; it builds on our evolving understanding of who will and who will not develop HCC.

With this strategy we will identify a high-risk group who must absolutely receive HCC surveillance and will be the center of our attention. We will also identify a low-risk group who may not need HCC surveillance at all.

Our current knowledge suggests that the high-risk group will include 5% to 10% of patients while the low-risk group will include 20%, and simulation studies have shown that risk-based surveillance provides better value for money than our current one-size-fits-all recommendation.

Therefore, risk-based surveillance has the potential to reduce not only deaths from HCC but also the costs of offering HCC surveillance.

INTRODUCTION

This EASL Policy Statement about risk-based surveillance for hepatocellular carcinoma (HCC) among patients with cirrhosis was drafted and revised by the EASL Task Force for Liver Cancer and ultimately approved by the EASL Governing Board. It extends the EASL Policy Statement on Liver Cancer Screening,[1] advocating for a particular screening strategy: risk-based surveillance. Risk-based surveillance for HCC means that the intensity of screening and the screening test can be varied according to the level of individual risk in order to achieve a more favorable balance of benefits and harms at the individual as well as the population level.[2]

EASL Clinical Practice Guidelines recommend that patients with cirrhosis are screened for HCC with an ultrasound exami-

-nation of the liver every 6 months.[3] Patients who receive this standard of care are said to be under HCC surveillance. Other patients not only receive substandard care, they also receive highly variable care: Follow-up in outpatient clinics, access from primary care to diagnostic examinations, and waiting times vary across countries and healthcare systems. One goal of European standards of care is to ensure that no patient is left behind.

We do not currently have data that will allow us to compare survival between European cirrhosis patients who are under surveillance vs. not under surveillance, but it has been shown that patients' survival time from the time of HCC diagnosis is much longer in countries with strict adherence to European surveillance standards, exemplified by Japan and Taiwan, than in Europe and other countries.[4, 5] This finding indicates that our European patients with HCC would live longer and better if we followed our own guidelines.

PROBLEM STATEMENT

HCC is a type of cancer that originates in the liver and almost exclusively develops in patients who have already developed cirrhosis of the liver. The cost of HCC in Europe is €4 billion per year.[6] What is worse, the number of Europeans who die from HCC is increasing, in 2020 reaching 23,000 in Central-Eastern Europe, 10,500 in Northern Europe, 21,200 in Southern Europe, and 23,700 in Western Europe – a total of 78,400 deaths.[7]

One important way to prevent those deaths is to diagnose HCC earlier so that more effective treatments can be given. That is the purpose of HCC surveillance which is offered to patients with cirrhosis.[1] Although EASL guidelines recommend HCC surveillance, less than half of the European patients who should receive surveillance actually receive it.[8] That is the problem we address in this statement, and risk-based surveillance is our proposed solution.

THE BASIS FOR RISK STRATIFICATION

All liver cells have the potential to turn malignant and become an HCC. This process is vastly accelerated in the liver of a patient with cirrhosis, but it does not progress at the same rate in all cirrhotic livers. For example, the rate is much faster in men with cirrhosis than in women with cirrhosis. If patients with cirrhosis could live indefinitely, they would all eventually develop HCC – but of course they don't: Patients with cirrhosis live only 5–10 years after they are diagnosed with cirrhosis, on average. Among cirrhosis patients there is large variation in survival time. To provide a few examples, older patients have shorter survival time than younger patients; patients with other chronic diseases (e.g., cardiovascular disease or diabetes) have shorter survival time than patients without chronic diseases;[9] and patients with more advanced cirrhosis have shorter survival time than patients with less advanced cirrhosis. The crux of the matter is that many patients with cirrhosis die before an HCC can develop and grow to a size that can be detected, let alone grow to a size that is fatal.

Risk-based surveillance takes advantage of our understanding of the characteristics that affect the rate of HCC progression and/or affect the patient's survival time. We cannot foresee our patients' future, but we can divide them into groups according to the probability that they will develop and ultimately die from HCC.[10-16] That insight is the basis for risk-based surveillance (Figure 1). The aim is to offer HCC surveillance to patients who are likely to develop an HCC that will grow to a fatal size before the patient dies from other causes (the high-risk group), and to not offer HCC surveillance to the others who are likely to die before an HCC affects their survival time or quality of life (the low-risk group).

HCC SCREENING TESTS

Screening tests aim to identify HCCs in patients with cirrhosis without symptoms suggestive of HCC. Ideally, HCCs are identified while they are still small and there is a good chance that they can be completely removed. An ultrasound examination of the liver is the standard screening test because it is cheap, fast, and widely accessible. Its downsides are that the quality of the examination is highly dependent on the skills of the examiner, and that it is not good at identifying HCCs that are small.[17] Blood-based biomarkers, best known among them alpha-fetoprotein, can improve the detection of small HCCs.[17, 18] Unfortunately, both ultrasound imaging and current biomarkers suffer from an inability to distinguish HCCs from other nodules in the liver. This lack of specificity can be harmful to patients because they will need further examinations, usually a CT scan, occasionally a biopsy.[19, 20] The risk of harm is higher and the chance of benefit lower for patients who have a low risk of developing HCC.[21]

The ideal screening test is both very sensitive (few HCCs over-looked) and very specific (few non-HCC nodules mistaken for HCC). The best one available is an MRI scan of the liver, and it can be tweaked to focus on HCCs in a way that reduces the scan time.[22] It remains more expensive and less accessible than ultrasound and blood-based screening tests, but MRI screening may provide value for money among the high-risk group of patients with cirrhosis. Other patients should be screened with an ultrasound examination of the liver, as currently recommended. In the future, blood-based biomarkers will likely replace ultrasound because blood sampling does not require hospital contact at all, and because blood samples give the same result no matter who draws the blood.[23]

Risk-based surveillance divides patients with cirrhosis into three groups according to the importance of conducting HCC surveillance: The high-risk group must absolutely be surveilled, and more costly screening tools than ultrasound are justified, e.g., MRI; the low-risk group may not need surveillance at all; and the remaining intermediate-risk group should be offered surveillance according to current EASL guidelines (Figure 1).

THE PROMISE OF RISK-BASED SURVEILLANCE

Most patients with cirrhosis are not offered the recommended surveillance for HCC.[8] The reasons include lack of awareness, lack of adherence, and lack of access. Risk-based surveillance will allow us to direct awareness, adherence, and access to those patients who stand to benefit the most from HCC surveillance. It is neither practically nor economically feasible to offer MRI-based surveillance to all patients with cirrhosis, but it is feasible to offer it to a small group of high-risk patients. It is equally feasible to increase awareness about HCC surveillance in this high-risk group—awareness among patients and among clinicians.

Risk-based surveillance has been studied intensively in breast cancer screening,[2,24,25] and the European Commission's Group of Chief Scientific Advisors suggests that "MRI screening could be considered for women categorized as having particularly dense breasts";[2] that is an example of risk-based surveillance because having dense breasts is a risk factor for cancer, and MRI screening is better at finding small cancers than the standard mammography screening.[2]

In management of patients with cirrhosis, a Scottish study found that risk-based surveillance could increase the benefits and reduce the harms of HCC surveillance,[21, 26] and a simulation study found that it was also a cost-effective strategy.[27] A survey study found that United States clinicians were receptive to risk-based surveillance instead of the current one-size-fits-all surveillance,[28] and we see no reason why European clinicians should be less accepting. Additionally, Chinese studies have reported that risk-based surveillance is superior to a one-size-fits-all approach to follow-up among patients who have had surgery for HCC.[29, 30] These studies in cirrhosis and in other healthcare fields demonstrate that risk-based surveillance has strong potential.

THRESHOLDS

Risk-based surveillance divides patients in three groups according to their risk of HCC, but there is currently no consensus on the thresholds that delineate the groups. Present EASL guidelines recommend HCC surveillance to patients with cirrhosis who have a risk of HCC of 1.5% per year or higher.[3] Simulation studies have suggested that ultrasound-based HCC surveillance remains cost-effective at lower risks, so that all patients with cirrhosis and a risk of HCC above 0.4% per year should be offered surveillance.[31] There are, fortunately, many patients with a lower risk than that, and we should be able to safely exclude them from HCC surveillance. For example, researchers divided 482 Scottish patients with cirrhosis into three groups—low, medium, or high risk—and they did this using four different risk-stratification tools.[21] When they divided patients using the aMAP score, a widely recommended tool,[12, 13] the low-risk group included 7.6% of the patients, and none of them developed HCC. Moreover, only 1 patient in the medium-risk group developed HCC, and this group included 28.8% of all patients. So, only 1 of 172 patients in the low- or medium-risk groups that included 7.6% + 28.8% = 36.4% of all patients developed HCC. With the three other risk-stratification tools, the low-risk group included 9.3%, 9.7%, or 38% of patients, respectively. This example demonstrates that we can indeed identify a low-risk group, but we are not yet sure how to do this best. It is plausible that a low-risk group with no need for HCC surveillance can include 20% of our patients with cirrhosis (Figure 1). That will be good for them, and it will also be good for our healthcare systems.

MOVING FORWARD

The goal of HCC surveillance is to reduce the number of patients who die from HCC. Risk-based surveillance is a promising strategy that we believe performs better than the current one-size-fits-all approach to HCC surveillance. First, it defines a high-risk group that may be offered more intensive surveillance, resulting in a greater benefit from surveillance. Second, it defines a low-risk group that may not need surveillance at all, resulting in reduced costs and reduced harms from surveillance.

Risk-based surveillance is a vibrant research area, but many questions are still unanswered. First, there are questions about the thresholds and how to estimate patients' risk of HCC. Second, the attitudes of European patients and clinicians should be surveyed, and any concerns addressed. Third, the two strategies—risk-based vs. one-size-fits-all—could be compared head-to-head with respect to the numbers of deaths from HCC and the costs.

First and foremost, though, we need to raise awareness about the importance of HCC surveillance. This should be a concerted effort from politicians, patient organizations, professional organizations, and individual clinicians. It will be easier to accomplish if it can be targeted to a smaller high-risk patient group and the clinicians who care for them.

Figure 1

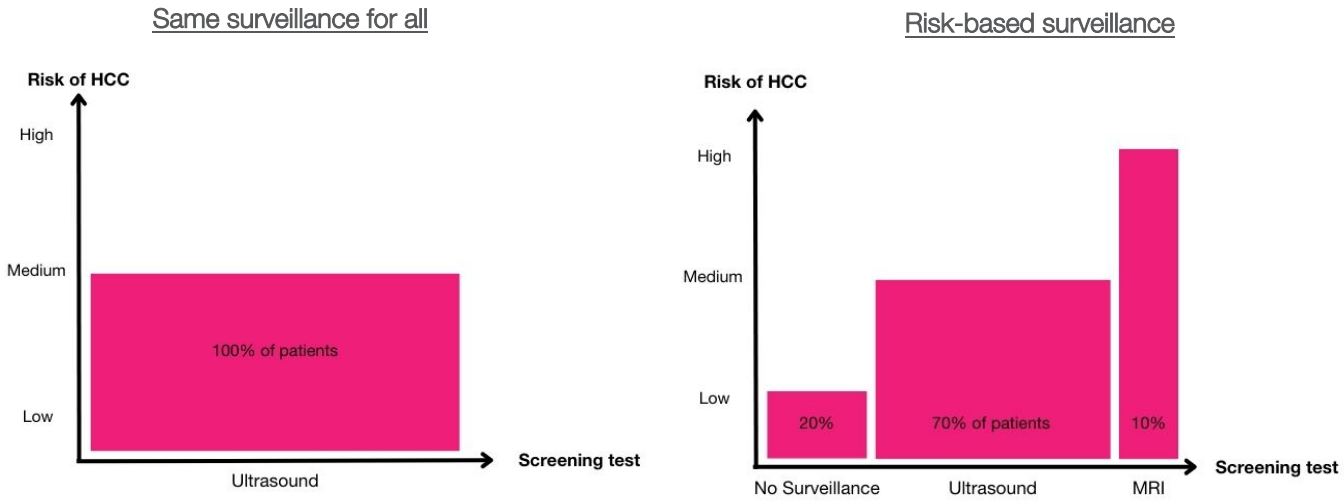

Figure 1. Current guidelines recommend surveillance for hepatocellular carcinoma (HCC) with an ultrasound examination for all patients with cirrhosis, so despite our expanding insight into risk factors for developing HCC it considers all patients to be at 'medium risk' (left). Risk-based surveillance promises to be a superior strategy: it tailors HCC surveillance to the patient's risk of developing HCC (right). With risk-based surveillance, ~20% of low-risk patients can be spared surveillance, and ~10% of high-risk patients can be offered intensified surveillance, e.g., with magnetic resonance imaging (MRI) as the screening test. Risk-based surveillance is expected to reduce the number of deaths from HCC and the costs of offering surveillance. Currently, the cost of HCC in Europe is €4 billion per year.

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