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POLICY STATEMENT

EASL Policy Statement on Liver Cancer Screening

SUMMARY

In Europe, the number of deaths from liver cancer has doubled in the past 30 years. Screening for liver cancer with an ultrasound examination every six months is an established method to reduce mortality resulting from liver cancer. EASL guidelines recommend that screening for liver cancer is offered to patients with chronic liver disease, but the European Commission's Group of Chief Scientific Advisors (GCSA) find that there is insufficient evidence for such a recommendation. Consequently, there is no political support for EASL's recommendation. This Policy Statement addresses this urgent problem, defining a strategy towards aligning EASL guidelines, patient preferences, and policy recommendations.

PROBLEM STATEMENT

The number of deaths from liver cancer[1] has increased dramatically over the past decades. According to the Global Burden of Disease studies, the number of people in Europe who are diagnosed with liver cancer has risen from 26,000 in 1990 to 50,000 in 2019, doubling in 30 years (1, 2). This increase is best explained by an ageing population with a growing prevalence of chronic liver disease. The number of people in Europe who die from liver cancer has increased in parallel with the number who are diagnosed with HCC, from 26,000 in 1990 to 48,000 in 2019 (2), and the fact that incidence and mortality are almost identical demonstrates that the vast majority of patients with liver cancer die from liver cancer.

The high and increasing mortality from liver cancer is an urgent problem, as detailed in EASL's "10 asks to improve liver cancer care in Europe", an open letter to the European Commission, the European Parliament, and the European Council (3).

Around 80–90% of patients with liver cancer have an underlying chronic liver disease, most of them in a disease stage with extensive fibrosis in the liver, i.e. cirrhosis. The dominant chronic liver diseases are viral hepatitis B and C, alcohol-related liver disease, and non alcohol-related fatty liver disease. The strong relationship between chronic liver disease and liver cancer has important implications:

1. Prevention and treatment of chronic liver disease equates to primary prevention of liver cancer.
2. Screening for liver cancer is not "population-based cancer screening". Rather it is restricted to patients with chronic liver disease and therefore counts as "targeted cancer screening" (4).

Prevention and treatment of chronic liver diseases are addressed by EASL's Clinical Practice Guidelines for the relevant liver diseases (5-8), and primary prevention of chronic liver diseases is also addressed by other EASL Policy Statements (3, 9, 10). The problem addressed by this Policy Statement is the lack of support for liver cancer screening from the European Union despite the urgency and widespread support of patients and clinicians. This Policy Statement is prompted by the European Council's process to extend screening recommendations beyond the current ones that cover breast, colorectal, and cervical cancer.

1 In this document, "liver cancer" refers to hepatocellular carcinoma (HCC), which is the commonest type of primary liver cancer, constituting around 90%. The second most common type of primary liver cancer, cholangiocarcinoma, is not covered by this Policy Statement. Rarer primary liver cancers and metastases to the liver are not covered, either.

Europe's Beating Cancer Plan, launched by the European Commission in 2021, announced certain flagship initiatives to reduce deaths from cancer (11). Among the flagship initiatives were efforts that will reduce the prevalence of chronic liver diseases and thus provide primary prevention of liver cancer. They included "reducing harmful alcohol consumption", "improving health promotion through access to healthy diets and physical activity", and "preventing cancers caused by infections". The Beating Cancer Plan also included a flagship initiative to improve early detection of cancer. This initiative will update the European Council recommendation on cancer screening from 2003, and it will be informed by a report from the European Commission's GCSA (11) .

That GCSA report, now published (4), includes considerations about extending the screening recommendation beyond what is currently recommended, which is screening for breast, colorectal, and cervical cancer. Specifically, the GSCA recommend providing screening for lung cancer (to current and former smokers) as well as screening for prostate cancer, but their report does not address screening for liver cancer specifically (4). The GCSA report states that "cancers were selected based on disease burden, measured by overall mortality or disability-adjusted life-years, and where screening test performance has been investigated in large-scale trials".

Following that, it states that "consideration of other cancer types where more targeted screening of high-risk individuals may be beneficial, such as liver or pancreatic cancer, is out of scope for this report"(4). Based on discussion with the GCSA[1], the reason that liver cancer screening is out of scope for the report is neither the disease burden nor the very targeted nature of liver cancer screening, but the lack of evidence that liver cancer screening reduces mortality from liver cancer.

The United States National Cancer Institute (NCI) under the National Institutes of Health (NIH) most recently reviewed the evidence for liver cancer screening in 2021, concluding – as did the European Commission's GCSA – that "screening of persons at elevated risk does not result in a decrease in mortality from hepatocellular cancer" (12). In their review of the literature on the effect of liver cancer on mortality, the NCI cites 17 studies, only one of which is an original article published in the past decade (13). This was a non-randomised study conducted within the United States Veterans Administration, and it found no association between screening and mortality from liver cancer (specifically, HCC). The NCI also points to another limitation in the rationale for screening: "20% to 50% of patients presenting with HCC have previously undiagnosed cirrhosis" (12), citing two studies published in 1990 (14, 15).

Despite the lack of a recommendation of liver cancer screening from the European Commission's GCSA, and therefore presumably also from the European Council, EASL continues to support liver cancer screening as detailed in its Clinical Practice Guidelines for HCC Management (16). EASL also supports efforts to screen high-risk groups for chronic liver disease (6, 7, 9, 10, 17), noting that an earlier diagnosis of chronic liver disease improves the chance to 1) offer curative treatment of chronic liver disease; 2) prevent progression to decompensated cirrhosis; and 3) implement liver cancer screening. If successful, these efforts will improve primary and secondary prevention of liver cancer.

This EASL Policy Statement addresses the problem that the European Commission's GCSA and the United States National Institutes of Health find insufficient evidence to recommend liver cancer screening of patients with cirrhosis. EASL is concerned that the lack of political support for its recommendation of liver cancer screening contributes to the meagre utilisation of liver cancer screening in clinical practice and to deaths resulting from liver cancer (18).

1 Online discussion during the meeting entitled "CANCER SCREENING - Update of Council recommendation on cancer screening" arranged by DG SANTE EU Health Policy Platform, 28 March 2022.

ETHICAL ISSUES

Considering that liver cancer screening of patients with cirrhosis is recommended by EASL and many national guidelines, it may be considered unethical to conduct a study in which some or all patients with cirrhosis are not offered screening.

A related issue is whether patients with cirrhosis would be willing to participate in a study in which they might not be offered liver cancer screening. There is some evidence that patients have a strong preference for screening (19, 20).

EVIDENCE-BASED STRATEGIES TO ADDRESS THE PROBLEM

The key strategy is to establish stronger evidence for the balance between benefits and harms of liver cancer screening.

1. Strengthen the evidence base for liver cancer screening of patients with cirrhosis. Current EASL guidelines state that the recommended screening modality is an ultrasound examination of the liver every six months, and that screening for liver cancer is recommended to patients with cirrhosis Child-Pugh class A and B and to patients with cirrhosis Child-Pugh class C who are awaiting liver transplantation (16). These patients, therefore, should be the target population for studies to strengthen the evidence base.

Studies may be randomised or non-randomised. Randomised studies provide the strongest evidence, but are difficult to carry out (4, 21), and their results will not be ready for many years. Non-randomised studies provide weaker evidence, but may provide adequate evidence if they use optimal methods and are large enough to provide precise estimates of efficacy and harms (22, 23). The study outcome can be all-cause mortality, mortality from liver cancer, or the liver cancer detection rate (4). Simulation studies may be helpful, but cannot stand alone because they are fully dependent on the validity of their assumptions, which are derived from existing randomised or non-randomised studies.

This strategy may be supplemented with the following two strategies:

2. Risk stratification among patients with cirrhosis, so that not all patients with cirrhosis are offered the same form of liver cancer screening. This strategy, known as risk-based screening (4), aims to achieve a better balance of benefits and harms of liver cancer screening. For example, patients with cirrhosis, obesity, and type 2 diabetes may be offered liver cancer screening using abbreviated MRI instead of ultrasound (24). Several models for risk stratification have been published (21), and it is possible that some patients with cirrhosis will be at such a low risk of liver cancer that they will not benefit from screening at all.

3. Screening for cirrhosis among patients at high risk of chronic liver disease so that liver cancer screening can be offered to the entire target population. This strategy addresses the problem that many patients are unaware of their cirrhosis until they are diagnosed with liver cancer, meaning that they could not have been offered screening for liver cancer although they are in the target population for liver cancer screening. Fulfilling this strategy, which is covered by EASL Clinical Practice Guidelines (6, 7, 16), would increase the number of cirrhosis patients offered liver cancer screening and thus reduce the number of deaths from liver cancer.

EVIDENCE IN FAVOUR OF SCREENING

There are four lines of evidence in favour of screening:

Firstly, one randomised trial conducted in China in the 1990s reported that liver cancer screening offered to patients with chronic hepatitis B infection reduced their mortality from liver cancer (25). This study has been criticised (26) and its relevance for current practice is questionable.

Secondly, many non-randomised studies have found lower mortality after liver cancer diagnosis for patients whose liver cancer was diagnosed through a screening programme than for patients whose liver cancer was diagnosed outside a screening programme. These studies have used a range of methods to reduce bias and confounding (18, 27-29).

Thirdly, mortality from liver cancer has been found to decline in countries that have successfully implemented liver cancer screening, such as Taiwan and Japan (30, 31).

Fourthly, cost-effectiveness analyses have found that liver cancer screening reduces mortality from liver cancer at an acceptable price (32-34).

OPPOSING EVIDENCE

Some non-randomised studies have found that liver cancer screening does not reduce mortality from liver cancer. For example, a Chinese study found that implementation of screening for liver cancer within a population of 68,551 people aged 35–64 years did not reduce mortality from liver cancer (35). More notably, the matched case-control study from the United States Veteran Administration referred to above found no association between liver cancer screening with ultrasound and/or alpha-fetoprotein and mortality from liver cancer among patients with cirrhosis and a MELD score below 20 (13). In another study the same research group used the same methodology to demonstrate that liver cancer screening reduced mortality from liver cancer among patients with chronic hepatitis B infection (36).

ALTERNATIVE STRATEGIES

A do-nothing strategy would plausibly result in more research in currently active research areas, i.e., research in pursuit of strategies 2 and 3 above, not in research in pursuit of strategy 1. This means that we would see more same-strength evidence for liver cancer screening, not stronger evidence.

EASL RECOMMENDATIONS AND ACTION STEPS

EASL aims to strengthen the evidence base for liver cancer screening of patients with cirrhosis. It will succeed through these actions:

- **Liaising with the European Commission's GCSA** (or another organisation with expert insight into evidence-based medicine and cancer screening) to identify the limitations of the existing evidence for liver cancer screening
- **Requesting advice from the GCSA** on study designs to overcome those limitations
- **Encouraging and supporting research** that follows this advice continuing to advocate for primary and secondary prevention of mortality from liver cancer, in collaboration with patient organisations and other stakeholders

In addition, EASL will encourage and support further research into questions whose answers are required by researchers who design randomised or non-randomised studies on the effect of liver cancer screening:

- Under which circumstances would patients be willing to participate in a randomised trial of liver cancer screening?
- Under which circumstances would clinicians be willing to let their patients participate in a randomised trial of liver cancer screening?
- How should we define "death from liver cancer"?

If EASL is successful with this strategy as outlined above, the European Commission, the hepatology community, patient organisations, and other stakeholders will be in a better position to recommend or to not recommend targeted screening for liver cancer offered to patients with chronic liver disease, to the ultimate benefit of our patients.

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