DIGESTIVE CANCERS EUROPE

ELPA European Liver Patients' Association

LIVER CANCER: **NO PATIENT LEFT BEHIND**

White paper calling for increased equality of best practice implementation in the prevention, diagnosis and management of liver cancer across Europe

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EXECUTIVE SUMMARY

We are at a crossroads in our fight against liver cancer in Europe. Unfortunately, it is a fight we are currently losing. Every year, more than 87.000 European citizens are diagnosed with liver cancer, while around 78.000 die from the disease.

Increasing rates of hepatitis B and C infection, rising alcohol consumption, and rising numbers of people with obesity are all contributing to a 'perfect storm' of factors leading to increasing rates of liver cancer in Europe. Liver cancer can be challenging to diagnose due to lack of early symptoms, and difficult to treat due to its complexity and because many patients also have a second disease, cirrhosis of the liver.

However, there is hope. Many of the risk factors associated with liver cancer are preventable or modifiable. We are learning much more about how and when to screen for liver cancer or its associated risks, and if liver cancer is diagnosed early through screening, then the prognosis for patients is significantly better. Treatments are continuing to improve.

Survival rates in countries where best practices are being implemented are significantly higher. However, there are wide disparities across EU countries in terms of implementation of best practices and corresponding survival rates. The socio-economic and regional disparities in liver cancer care across different countries is a cause for concern. In addition, across Europe, data availability is limited and, in many cases, fragmented within European countries, emphasising the need for the collection and availability of high-quality information via cancer registries.

At DiCE and ELPA, we call upon all stakeholders across Europe to work together to ensure that best practices are implemented at every stage of the patient pathway in each country, giving every patient the best possible opportunity of a positive outcome.

WE PROPOSE A RANGE OF RECOMMENDATIONS ACROSS FIVE KEY AREAS, AIMING TO OPTIMISE:

While we acknowledge that not every country or region will be able to tackle every recommendation immediately, each should assess which ones can be addressed or would deliver the greatest impact at a national or regional level. **Together, we can ensure that everyone has access to best practice care. And no patient is left behind.**

PURPOSE OF THIS WHITE PAPER

The purpose of this document is to assist health policy-makers from across Europe in identifying the key priority areas of unmet need in their area, with a view to implementing best practices for liver cancer patients, based on the currently available evidence.

Readers of this white paper should be aware that all recommendations contained within are intended to provide information and guidance. Any recommendations should be adapted to local regulations and/ or capacities, infrastructure and cost-benefit strategies.

This white paper has been developed based on extensive research of recent data, expert consultation and existing expertise within DiCE and ELPA.

ABOUT DiCE AND ELPA

Digestive Cancers Europe (DiCE) and the European Liver Patients Association (ELPA) are two European patient advocacy umbrella organisations, who have joined forces to improve the outcomes and quality of life of liver cancer patients across Europe.

DiCE and ELPA have similar and complementary goals of contributing to early diagnosis, advocating best practices in public health and treatment, improving the quality of life for patients, and saving lives from liver cancer.

Working together, the two organisations are focusing on health policy at the European level, while encouraging their 60+ collective local Member groups to start developing patient support for liver cancer patients and carers throughout their journey.

DiCE

Digestive Cancers Europe (DiCE) is the European umbrella organisation of 32 national Members representing patients with digestive cancer – colorectal, gastric, liver, oesophageal, pancreatic and rare digestive cancers. Our mission is to contribute to the early diagnosis of and decreased mortality from digestive cancers and to increase the overall survival and quality of life of patients.

ELPA

The European Liver Patients' Association - ELPA was established by patients, is governed by patients, and represents patients. Nowadays, ELPA counts 31 members from 25 different countries. It has 8 working groups aimed at stimulating expert patients to acquire knowledge in a specific field of liver disease. Regarding liver cancer, ELPA's suggestion of reducing and eliminating hepatitis B and C to lower liver cancer incidence was included in Europe's Beating Cancer Plan.

You can find out more about DiCE and ELPA at their respective websites.

LIVER CANCER: WHAT IS IT, AND WHY DOES IT NEED URGENT ATTENTION?

What is liver cancer?

Primary liver cancer is cancer that started in the liver. The liver is an essential organ in the body with many important functions, including synthesis of plasma proteins such as albumin and clotting factors, and taking toxins and other harmful substances from the blood and breaking them down into safer forms.

There is more than one kind of primary liver cancer. The two main types are:

- Hepatocellular carcinoma (HCC). This is the most common form of liver cancer in adults. Around 85–90% of all liver cancers are HCCs (Vogel et al., 2019).
- Intrahepatic cholangiocarcinoma (otherwise known as bile duct cancer). About 15% of primary liver cancers are intrahepatic cholangiocarcinomas (Bañales et al., 2020). These cancers start in the cells that line the small bile ducts (tubes that carry bile to the gallbladder) within the liver.

There are also some other rare forms of liver cancer.

It is important to note that there are some quite significant differences between HCC and cholangiocarcinoma in terms of disease characterisation, prevention, diagnosis, treatment and prognosis. While there are significant challenges and unmet needs associated with all forms of liver cancer, for the purpose of this white paper, we will focus on HCC. This is to ensure clarity and to seek progress against the most common form of liver cancer first.

What causes liver cancer?

HCC most commonly occurs in people with chronic liver disease, such as cirrhosis caused by hepatitis B, hepatitis C, heavy alcohol consumption or an accumulation of fat in the liver. Other risk factors for liver cancer include age, smoking, and obesity.

The fact that patients have two different liver diseases makes management of patients particularly complex, requiring multidisciplinary care.

WHAT IS LIVER DISEASE? CAUSES, PROGRESSION INTO CHRONIC LIVER DISEASE AND CIRRHOSIS

There are many different causes of liver disease, which may be linked with liver cancer. Some of the most common include:

Alcohol-related liver disease: Caused by regularly drinking too much alcohol.

Non-alcoholic fatty liver disease: Frequently linked to being overweight, which may cause fat to build up in the liver and might lead to liver inflammation.

Hepatitis: Infection of the liver caused by a virus.

Cirrhosis: a late-stage liver disease in which healthy liver tissue is replaced with scar tissue and the liver is permanently damaged.

What is the impact of liver cancer in Europe?

> **Europe has the largest burden of liver disease in the world, with the burden expected to grow across many countries (Pimpin et al., 2018). This is expected to increase the burden of liver cancer in Europe.**

Liver cancer is the ninth most frequent cancer type in Europe with 87.630 new cases diagnosed in 2020 and the number of cases is projected to increase (ECIS, 2020).

But it is the outcomes of people who are diagnosed with liver cancer that is perhaps the most troubling. Liver cancer is the seventh most common cancer-related cause of death, accounting for 78.400 deaths per year in Europe (ECIS, 2020).

Survival rates for liver cancer are relatively low. For example, 2013-2017 data from England shows that 40,0% of males and 34,6% of females survive liver cancer for at least one year, but this falls to 13,7% and 10,7% surviving for five years or more (UK Office for National Statistics, 2019).

For those living with the disease, quality of life can suffer. Although few studies have been published on it, liver cancer has been shown to have a significant and clinically important impact on quality of life (Li et al., 2019).

The problem is unfortunately getting worse, with the incidence of liver cancer increasing in Europe. While decreasing trends in new cases have been reported in some Asian countries, such as China and Japan, where cases were traditionally high because of high levels of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, respectively, in many European countries a notable and alarming increase in liver cancer cases is being observed. This is attributed to high alcohol intake, obesity and high levels of HCV infection and a lack of prevention programmes. In addition, the migration of large numbers of people from countries with high prevalence of HBV is changing disease burden profiles in Europe (Sharma et al., 2015).

Worryingly, Europe has the highest per capita alcohol consumption and alcohol-related loss of disability-adjusted life years (DALYs) of any of the global World Health Organisation (WHO) regions. Obesity has increased markedly over the past four decades and as a result, non-alcoholic fatty liver disease (NAFLD) is an increasingly prevalent liver disease in Europe (Pimpin et al., 2018), pushing the incidence of liver cancer higher.

In terms of financial costs, liver cancer costs around €4 billion each year in Europe, of which €1,2 billion relates to direct costs (Hofmarcher and Lindgren, 2020).

Liver cancer: specific considerations

There are some specific considerations to bear in mind when planning approaches to managing liver cancer:

HCC patients usually have another liver disease, and possible co-morbidities, meaning multidisciplinary care is essential:

HCC usually develops in patients with liver disease – such as cirrhosis – that compromises liver function, which makes management of these patients particularly complex. Many HCC patients suffer from decreased liver function, and sometimes liver failure is the cause of mortality without cancer progression (Sinn et al., 2019). Co-morbidities such as other chronic medical conditions, cardiovascular complications, autoimmune disease, etc. should be considered. Hence, a multidisciplinary approach for the management of HCC is the best practice and should be the standard of care.

Many cases of HCC are preventable, but early diagnosis is challenging:

Because several risk factors associated with liver cancer are related to lifestyle, many liver cancer cases are preventable. It is estimated in the UK that as many as 49% of liver cancer cases are preventable compared to 38% of all cancer cases (Cancer Research UK, 2015). However, early diagnosis is challenging. It is often hard to find liver cancer early because signs and symptoms often do not appear until it is in its later stages and national screening programmes are not in place in Europe. In 75% of cases, the tumour is already at an advanced stage at diagnosis. This suggests more focus should be placed on prevention as a means of improving outcomes in liver cancer.

There are specific treatment challenges:

Early diagnosis is crucial due to better therapeutic options. As well as the challenges associated with treating advanced disease, there are several other specific challenges with treating liver cancer. Transplants offer the opportunity of cure, but they are rare given the lack of donor organs, and the procedure is challenging. In addition, traditional chemotherapy – a mainstay of treatment for most cancers – is not effective in liver cancer.

Liver cancer has social stigma challenges:

Unlike most cancers, liver cancer (and liver diseases more generally) carries negative social connotations. As is the case with lung cancer, many assume it is the patient's own 'fault'. This may present challenges

for patients and may make it harder to prioritise liver cancer among policymakers.

Outcomes vary considerably across Europe:

The current and historical epidemiology of liver disease varies between countries within Europe. For example, Finland and the UK have observed staggering increases in liver disease mortality over the last 40 years, while the inverse is true for countries such as France and Italy, where liver disease mortality began declining in the 1970s and has kept falling, largely because of effective policy and population-level measures (Pimpin et al., 2018).

CALL TO ACTION

Liver cancer represents a significant unmet need in Europe, which is often overlooked. There are wide disparities across Europe when it comes to prevention, diagnosis, treatment, knowledge of liver cancer and patient involvement. These inequalities can be seen in access to prevention programmes, in rates of early cancer detection, diagnosis, treatment, survival and measures to improve quality of life of cancer patients and survivors.

The socio-economic and regional disparities in liver cancer care across different countries is a cause for concern. In addition, across Europe, data availability is limited and, in many cases, fragmented within European countries, emphasising the need for the collection and availability of high-quality information via cancer registries.

At DiCE and ELPA, we call upon all stakeholders across Europe to work together to ensure that best practices are implemented at every stage of the patient pathway in each country, giving every patient the best possible opportunity of a positive outcome.

WE PROPOSE A RANGE OF RECOMMENDATIONS ACROSS FIVE KEY AREAS, AIMING TO OPTIMISE:

1. **KNOWLEDGE**
2. **PREVENTION**
3. **EARLY DIAGNOSIS**
4. **TREATMENT AND CARE**
5. **PATIENT INVOLVEMENT AND EMPOWERMENT**

While we acknowledge that not every country or region will be able to tackle every recommendation immediately, each should assess which ones can be addressed or would deliver the greatest impact at a national or regional level.

Together, we can ensure that everyone has access to best practice care. And no patient is left behind.

SUMMARY OF RECOMMENDATIONS

GOAL	AREA	RECOMMENDATION
 **OPTIMISE KNOWLEDGE**	**Research on liver disease**	• Fund and enable more research on key areas (e.g. biomarkers, liquid biopsy and hepatitis C vaccine) that could make a significant difference to patient outcomes.
	Data sharing	• Drive better collection and analysis of liver cancer big data, utilising cancer registries.
 **OPTIMISE PREVENTION**	**Viral hepatitis**	• Adhere to the Action plan for the health sector response to viral hepatitis in the WHO European Region, ensuring equitable access to recommended prevention, testing, care and treatment services for all, including: – Implement mass HBV immunisation (for all newborns and high-risk groups) – Control HCV transmission (including raising awareness of link with unprotected sex and needle-sharing)/ improve screening of high-risk populations, and offer treatment – Ensure equitable access to therapies for HBV and HCV infections
	Lifestyle risk factors – alcohol smoking and obesity	• Implement the EU Beating Cancer Plan (BECA) to reduce the harmful consequences of chronic alcohol consumption, smoking and obesity, and promote healthy lifestyles from an early age.
 **OPTIMISE EARLY DIAGNOSIS**	**Screening**	• Improve implementation of screening programmes to identify at-risk populations, following the EASL guidelines and/ or ESMO guidelines. Patients at high risk of developing HCC should be entered into surveillance/ screening programmes. All individuals at high risk should be screened by use of abdominal ultrasound examinations every 6 months. • Monitor the outcomes of the LiverScreen initiative to understand if detection of advanced liver fibrosis in high-risk groups within the general population, using transient elastography as screening tool, is a valid screening approach.

OPTIMISE TREATMENT AND CARE

Multidisciplinary teams

- Ensure equal opportunity for management by a multidisciplinary team (MDT) involving hepatologists, pathologists, interventional radiologists, oncologists, hepatobiliary and transplant surgeons, nurses, and general practitioners.
- Investigate the potential for online consultations to plug gaps in MDTs.

Treatment

- Ensure the EASL and/ or ESMO treatment guidelines are fully implemented where possible, ensuring treatment is not delayed during evaluation, when the tumour can advance rapidly.
- Assess outcomes and recommendations from the BECA/ EU platform to improve access to cancer medicines to understand which elements can be implemented in liver cancer to improve early access.

OPTIMISE PATIENT INVOLVEMENT AND EMPOWERMENT

Patient health literacy and support

- Utilise standardised nomenclature around liver cancer across Europe.
- Ensure liver cancer patients and carers/ families are informed about patient organisations in their country immediately after diagnosis. If there are no organisations in the country, direct them to DiCE/ ELPA.
- Raise awareness of increased risk of liver cancer among family members and encourage sharing this information with HCPs.

Patient involvement in research

- Ensure liver cancer research incorporates the patient perspective e.g. endpoints that reflect the most meaningful outcomes for patients.
- Ensure there is a systematic approach to collecting real-world patient experiences and needs throughout the patient pathway.

SYNERGIES WITH OTHER EU PLANS AND GUIDELINES

> **We appreciate that there are many other stakeholders and organisations working in this area and there is no value in "reinventing the wheel" or contradicting other guidance.**

We have therefore developed this white paper with other recent leading guidance – such as the EU Beating Cancer Plan and the latest European Association for the Study of Liver (EASL) Clinical Practice Guidelines – in mind. In those areas where our reports overlap, our recommendations direct the reader to the relevant report.

The key reports we reference in this white paper are:

- The EU Beating Cancer Plan, which sets out a new EU approach to cancer prevention, diagnosis, treatment, and care. It will tackle the entire disease pathway, from prevention to quality of life of cancer patients and survivors, focusing on those actions where the EU can add the most value. As such, there are many synergies with this white paper, including the call to promote cancer prevention, to highlight the role of obesity, smoking and alcohol consumption in cancer, and to boost diagnosis and treatment. Specifically for liver cancer, the Beating Cancer Plan commits to helping to ensure access to vaccination against Hepatitis B and to treatments to prevent liver cancers associated with the Hepatitis C virus.
- The latest EASL Clinical Practice Guidelines, and ESMO Clinical Practice Guidelines, which both provide recommendations around diagnosis, treatment and other elements of clinical practice. The EASL and ESMO guidelines very comprehensively define the use of surveillance, diagnosis and therapeutic strategies recommended for patients with HCC, and we defer to these guidelines on all topics of clinical best practice.
- The Action plan for the health sector response to viral hepatitis in the WHO European Region, which was the first action plan of its kind addressing all five hepatitis viruses with a particular focus on HBV and HCV, with an overall objective of eliminating viral hepatitis as a public health threat in the European Region by 2030.

RECOMMENDATIONS

1. Optimise knowledge

RESEARCH

Compared to other cancers, liver cancer has often been "forgotten" and there has been a lack of investment into research (British Liver Trust, 2017). Liver cancer deaths have continued to increase and in general, we haven't seen the improvements in treatments that we have for other cancer types. The recent approval by the European Medicines Agency of an immunotherapy-based treatment provides hope for liver cancer patients and reinforces the need for further research to find advanced treatment options similar to those available for other cancer types.

Unlike some other cancers, which may be caused by a small number of clearly defined genetic mutations, liver cancer has complex mechanisms, which can vary between different disease stages and patients, which has challenged the discovery of therapeutic targets until now.

Some specific areas of required future research include:

- **Biomarkers:** Overall, there is a need for more reliable biomarkers for HCC, as those currently available lack sensitivity and specificity. For example, the current gold-standard biomarker, serum alpha-fetoprotein, has a sensitivity of roughly only 70% (Cartlidge et al., 2017). Where molecular biomarker-driven treatments are a reality in many other cancers, they are far from becoming a reality in liver cancer. Biomarker research is vital.
- **Liquid biopsy:** Traditional liver biopsy remains the gold standard to diagnose liver diseases including liver cancer, but they have several limitations – they are invasive for patients and can be very painful, and are costly for health systems. In addition, there is a small risk in tumour biopsy of spreading the tumour further through, the so-called "needle track seeding" (Shyamala et al., 2014). Liquid biopsy is emerging as a superior alternative – it is more convenient, readily and repeatedly accessible, safe, cheap, and provides a more detailed molecular and cellular representation of the individual patient's disease (Barrera-Saldaña et al., 2020). More research is needed to understand the full potential of liquid biopsy in a real-world setting as a source of biomarkers for diagnosis, prognosis, and prediction of therapeutic response in liver cancer.
- **Hepatitis C vaccine:** Hepatitis B and C are major risk factors for liver cancer. While there is an effective vaccine available for hepatitis B, there is no current vaccine for hepatitis C. In total, there are approximately 71 million people with HCV infection, which is estimated to cause about one in five of all deaths from liver cancer. The journey toward the elimination of HCV has just begun, and program development and operational research are just emerging (Ward et al., 2020).

More research is urgently needed to improve prevention and access to treatments for patients to ultimately improve outcomes.

RECOMMENDATIONS:

- Fund and enable more research on key areas (e.g. biomarkers, liquid biopsy and hepatitis C vaccine) that could make a significant difference to patient outcomes.

DATA

Evaluating the burden of disease and appropriate response, depends highly on the quality and quantity of data available. The wide geographic variation across Europe in the availability of high-quality cancer registry data leads to uncertainties associated with disease burden estimates.

Common data quality issues for the liver cancer burden estimation are: 1. miscoding of liver metastases as primary liver cancers, 2. underreporting of liver cancer on death certificates - likely due to the relatively poor diagnostic ability in liver cancer compared to other cancers (Lin, 2020), and 3. underestimation of liver cancer due to lack of diagnostic capacity (Global Burden of Disease Liver Cancer Collaboration, 2015).

In general, across Europe, there is often still a lack of good comparable data. Increasing the availability of comparable national health databases and registries is central to improving research opportunities, policy evaluation and future priority setting. For international clinical trials or international comparisons among clinical registries, it is of the highest importance that health record systems are interoperable within Europe.

Improving the quality of liver cancer data will help to identify and compare trends in HCC incidence, mortality and survival across Europe, identify and compare the causes of the rising incidence of HCC and identify inequalities in incidence, survival and treatment across Europe.

RECOMMENDATION:

- Drive better collection and analysis of European-wide liver cancer data, utilising cancer registries.

2. Optimise prevention

Prevention is more effective than any cure. The major causes for liver cancer are highly preventable (Global Burden of Disease Liver Cancer Collaboration, 2017). Prevention is also the most cost-effective, long-term cancer control strategy.

Many liver cancers could be prevented by tackling known risk factors for this disease.

VIRAL HEPATITIS

Infections by HBV and HCV are the main risk factors for HCC development (Llovet et al., 2021).

In Europe, HBV and HCV are highly prevalent. It is estimated that 13,3 million people in Europe live with chronic hepatitis B (1,8% of adults) and an estimated 15 million people with hepatitis C (2,0% of adults) – that's about 1 in every 50 people living with either disease (WHO, 2021).

The numbers are increasing and likely to increase considerably further. In Europe, increasing prevalence of liver cancer may be partly attributed to chronic HBV infection, particularly in countries that implemented the preventive anti-HBV vaccine relatively late, and in countries with significant numbers of immigrants from endemic HBV regions such as Asia and North Africa. In addition, before the late 80s, blood transfusions were not thoroughly checked for HCV infection. Now there is a clinical lag time from HCV infection epidemics of the 1970s and 1980s, with these individuals now developing liver cirrhosis with the associated higher HCC risk.

Many of these infections may not show symptoms for a long time, sometimes decades, and slowly damage the liver. Globally, at least 60% of liver cancer cases are due to late testing and treatment of viral hepatitis B and C (WHO, 2018).

There are effective available strategies against viral hepatitis. HBV vaccination has dramatically reduced infection rates among children in Europe (WHO – HBV, 2017). Rapid progress in the development of treatments for chronic viral hepatitis infections in recent years has made it possible to cure chronic HCV infection in more than 90% of patients, and to effectively control chronic HBV infection through suppression of viral replication. Curative therapies for HCV infections reduce HCC risk by ~70% (Kanwal et al., 2017).

However, gaps in implementation remain. While most EU Member States have successfully implemented universal childhood HBV immunization programmes, HBV vaccination coverage still remains low in many countries among high-risk populations, such as prisoners, men who have sex with men and sex workers (WHO, 2017). In addition, the migration of large numbers of people from countries with high prevalence of HBV is changing disease burden profiles in Europe (Sharma et al., 2015).

Affordability and sustainability of HCV treatment, as well as treatment access remain major obstacles in most Member States (WHO, 2017).

In 2016, Member States in the European Region adopted the Action Plan for the Health Sector Response to Viral Hepatitis in the WHO European Region. They also committed to the global goal of eliminating viral hepatitis as a public health threat by 2030.

Adherence with this plan is vital, not only to control and reduce the spread of viral hepatitis, but to reduce the risk of liver cancer that follows it.

RECOMMENDATIONS:

- Adhere to the Action plan for the health sector response to viral hepatitis in the WHO European Region, ensuring equitable access to recommended prevention, testing, care and treatment services for all, including:
  - Implement mass HBV immunization (for all new-borns and high-risk groups)
  - Control HCV transmission (including raising awareness of link with unprotected sex and needle-sharing)/ improve screening of high-risk populations, and offer treatment
  - Ensure equitable access to therapies for HBV and HCV infections

LIFESTYLE RISK FACTORS: ALCOHOL, SMOKING AND OBESITY

As well as viral hepatitis, there are several other key modifiable risk factors for liver cancers, including alcohol intake, smoking and obesity.

Alcohol in particular is expected to become the leading cause of liver cancer in Europe. The amount of alcohol consumed by people in EU countries is higher than the rest of the world (WHO, 2019) and the incidence of many alcohol related digestive cancers, including liver cancer, is on the increase.

Indeed, it is already estimated that alcohol abuse accounts for 40% to 50% of all liver cancers in Europe and a recent meta-analysis showed that the risk for liver cancer increases by 16% with consumption of three or more drinks per day up to 22% with consumption of six or more drinks per day (Healio, 2017).

Meanwhile, HCC risk is 66% higher in current smokers than non-smokers (Abdel-Rahman et al., 2017). Tobacco use represents an important public health issue worldwide, but particularly in Europe, where the highest levels of tobacco-use prevalence (over 29%) have been reported (WHO – Tobacco, 2019).

Finally, weight problems and obesity are increasing at a rapid rate in most of the EU Member States, with estimates of 51,6% of the EU's population (18 and over) overweight (Smith, 2014). Compared to having a normal body mass index (BMI), being overweight is associated with a 21% increased risk of liver cancer (Campbell et al., 2016).

However, awareness of the link between these modifiable risk factors and liver cancer is low. For example, according to a Eurobarometer survey, one in ten EU citizens is not aware of the connection and one in five does not even believe that there is a link between cancer and drinking alcohol (Eurocare, 2020).

The EU Beating Cancer Plan lays out several measures for Member States to help reduce the high prevalence in alcohol, tobacco and obesity-related cancer deaths.

For alcohol, the report calls for implementation of a wide range of policies such as reductions in alcohol affordability and availability, limits on advertising and promotion, and raising awareness about the risk of alcohol consumption and cancer.

For tobacco, the report calls to make product regulation stricter, to revise EU minima taxation rates for tobacco products, to address tobacco advertisement, promotion and sponsorship in social media and online services, and support Member States in implementing the WHO Framework Convention on Tobacco Control.

For obesity, the report focuses heavily on preventing childhood obesity, including a revision of the EU school fruit, vegetables and milk scheme to make healthy products more available to children. The Cancer Plan will also launch the “HealthyLifestyle4All” campaign in 2021, involving key sectors promoting sport, physical activity and healthy diets.

RECOMMENDATIONS:

- Implement the EU Beating Cancer Plan to reduce the harmful consequences of chronic alcohol consumption, smoking and obesity, and promote healthy lifestyles from an early age.

3. Optimise diagnosis

Early detection of liver cancer in people who are at risk (e.g. liver with advanced fibrosis/ cirrhosis) by offering screening programs provides the best chance of beating cancer and saving lives and reducing costs – but it is challenging due to lack of early symptoms.

CONFIRMING DIAGNOSIS WITH ABDOMINAL ULTRASOUND OR OTHER RADIOLOGICAL, NON-INVASIVE METHODS

Staging of HCC is important to determine outcome and planning of optimal therapy. One of the key methods of staging HCC is through the Barcelona Clinic Liver Cancer (BCLC) staging system (see below).

BCLC staging system (from EASL guidelines)

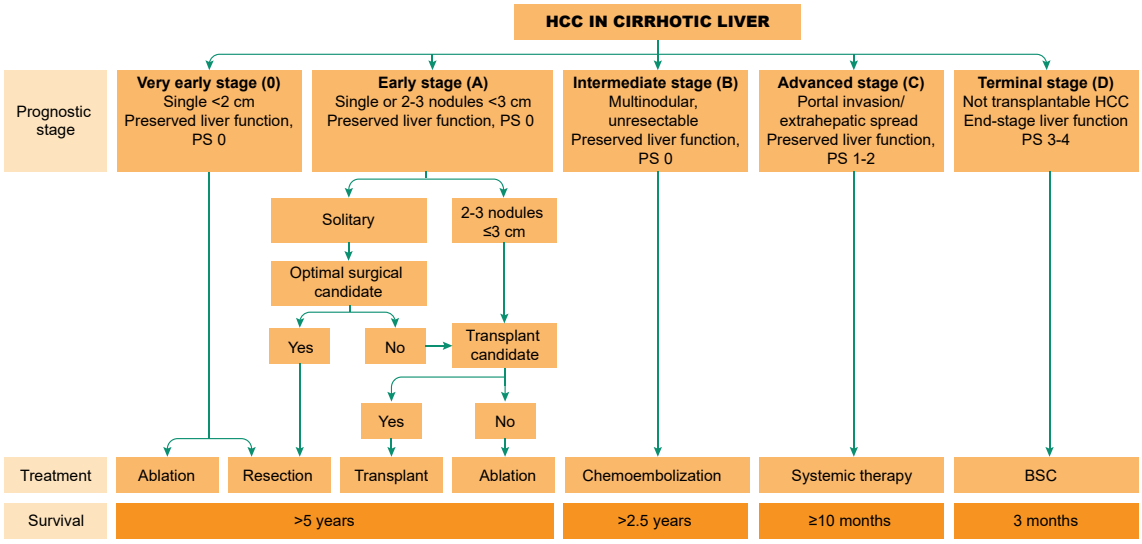

Fig. 1. Modified BCLC staging system and treatment strategy. BSC, best supportive care; PS, performance status'.

More than 60% of liver cancer patients are diagnosed with late-stage disease, resulting in reduced survival time. For Stage C HCC, median survival is between 4 and 11 months. For Stage D HCC, median survival is less than four months (EASL Clinical Practice Guidelines, 2018).

In contrast, patients diagnosed with early-stage disease have a relatively good prognosis. For Stage 0 HCC, with treatment, between 70% and 90% of patients will survive for 5 years or more. For Stage A, with treatment, between 50% and 70% of patients will survive for 5 years or more (EASL Clinical Practice Guidelines, 2018).

However, the symptoms of liver cancer are quite nonspecific, especially in the early stages. A series of tests therefore need to be conducted to establish a diagnosis and evaluate the state of the liver/ possible tumour.

The question then is who do you test and how?

National screening vs targeted screening

Very few countries worldwide have introduced a nationwide liver cancer screening program. There are a few exceptions, such as Japan, China, and South Korea. There is a particularly high burden of disease in these countries, largely due to a high prevalence of hepatitis B and C. The national liver cancer screening program in South Korea – as an example – is for groups at high risk of contracting hepatitis B, hepatitis C, or other liver diseases using liver ultrasonography and serum alpha-fetoprotein measurement. Screening programmes in these countries have been proven to have a significant impact in reducing liver cancer incidence (Oh, 2020).

European countries do not have general population screening (it is not recognised as being needed), but rather screening of at-risk populations in the majority of countries. The EASL guidelines state that patients at high risk of developing HCC should be entered into screening programmes. The EASL and ESMO guidelines state that screening should be performed by experienced personnel in all high-risk populations using abdominal ultrasound every six months.

The EASL guidelines identify the following groups as being high-risk:

- Cirrhotic patients, Child-Pugh stage A and B
- Cirrhotic patients, Child-Pugh stage C - possible candidates for liver transplantation
- Non-cirrhotic HBV patients at intermediate or high risk of HCC
- Non-cirrhotic fibrosis stage F3 patients, based on an individual risk assessment

The ESMO guidelines state that screening is warranted in all patients with cirrhosis irrespective of its aetiology, as long as liver function and comorbidities allow curative or palliative treatments (Vogel et al., 2018).

The ESMO guidelines also highlight that patients with HCV infection and advanced fibrosis remain at increased risk for HCC even after achieving sustained virological response following antiviral treatment and, thus, should remain in a surveillance programme.

We defer to these leading guidelines, which state that implementation of screening programmes to identify at-risk candidate populations should be improved, and that patients at high risk of developing HCC should be entered into surveillance/ screening programmes.

Screening methods

Currently, imaging has become the first choice for the diagnosis of liver cancer. Ultrasound (US) is a major, sustainable HCC surveillance method as it provides inexpensive, real-time, and non-invasive detection. It has been shown that patients with liver cancer who received US three times or more during the 2 years preceding their liver cancer diagnosis had a higher 5-year survival probability (Chiang et al., 2017).

The EASL guidelines state that surveillance should be performed by experienced personnel in all high-risk populations using abdominal ultrasound every six months.

Use of transient elastography for screening of wider at-risk groups

Fibrosis occurs when the liver is repeatedly and continuously injured. Liver fibrosis might be progressive and advanced liver fibrosis is a risk factor for the development of HCC with up to 90% of cases occurring on the background of a cirrhotic liver (O'Rourke, 2018).

Transient elastography is a non-invasive technique that uses both ultrasound and low-frequency elastic waves to quantify liver fibrosis. One study showed that liver stiffness of more than 24 kPa was an independent risk factor for developing new liver cancer in HCV patients (Ebrahim et al., 2020).

There may be value in screening additional at-risk patients – for example those with hepatitis C and individuals with fatty liver disease – for liver fibrosis to identify those at high risk for liver cancer.

The ongoing LiverScreen initiative (a financed European project in which ELPA participates) aims to set up a targeted, easy-to-use, cost-beneficial screening program for detection of liver fibrosis in high-risk groups within the general population, using transient elastography as a screening tool.

The outcomes from LiverScreen will help us to understand the value of this approach and whether it should be adopted as general practice across Europe.

RECOMMENDATIONS:

- Improve implementation of screening programmes to identify at-risk populations, following the EASL guidelines and/ or ESMO guidelines. Patients at high risk of developing HCC should be entered into surveillance/ screening programmes. All individuals at high risk should be screened by use of abdominal ultrasound examinations every 6 months.
- Monitor the outcomes of the LiverScreen initiative to understand if detection of advanced liver fibrosis in high-risk groups within the general population, using transient elastography as screening tool, is a valid screening approach.

4. Optimise treatment and care

MULTIDISCIPLINARY EXPERT CARE

Multidisciplinary teams (MDTs) are widely recognised as a best practice approach in managing cancer but are particularly relevant for the management of HCC. Because most HCCs develop in the setting of chronic liver disease, risk of death involves tumour - and non-tumour-related factors (Naugler et al., 2019). No single treatment strategy can be applied to all patients with HCC, necessitating a multidisciplinary approach to tailor a management plan based on tumour burden, extent of metastasis, severity of hepatic decompensation, comorbid medical conditions, functional status, cancer-related symptoms, and patient preferences (Wang et al., 2017).

A multidisciplinary approach has been proven to be associated with improved survival of liver cancer patients (Sinn et al., 2019). In addition, it must be taken into account that the tumour may advance, and patients may need sequential therapy.

The best approach to optimize the management of HCC is one that utilizes a core multidisciplinary liver tumour board, consisting of hepatologists, pathologists, interventional radiologists, oncologists, hepatobiliary and transplant surgeons, nurses, and general practitioners (Siddique et al., 2017). The EASL guidelines state that every liver cancer patient should be discussed in multidisciplinary teams to fully capture and tailor individualised treatment options (EASL Clinical Practice Guidelines, 2018).

However, this is a challenge that requires organisational and cultural changes and must be led by competent health managers who can improve teamwork within their organisations (Specchia et al., 2020). It is thought that the MDT approach is not currently applied uniformly throughout Europe.

RECOMMENDATIONS:

- Ensure equal opportunity for management by a MDT involving hepatologists, pathologists, interventional radiologists, oncologists, hepatobiliary and transplant surgeons, nurses, and general practitioners.
- Investigate the potential for online consultations to plug gaps in MDTs.

TREATMENT

The right treatment when given at the right time can improve liver cancer patients' recovery, survival and quality of life.

Best practice treatment of liver cancer is multidisciplinary, and multimodal treatment options are chosen generally on an individualised basis according to the complex interplay of tumour stage and the extent of underlying liver disease, as well as the patient's overall general health.

Key modalities of cancer treatment include surgery, localised approaches such as transarterial chemoembolisation (TACE) and selective internal radiation therapy (SIRT), non-systemic treatments, such as radiation therapy, and systemic treatments through pharmaceutical agents for more advanced disease.

Implementing a life course approach for liver cancer patients, implies affordable access to treatments during the whole continuum of services, especially since most patients with liver cancer need sequential treatments.

However, the socio-economic and regional disparities in liver cancer care across different countries in Europe is a cause for concern. Both in terms of overall rate of availability of medicines and time to availability, the disparities across European countries are significant (Newton et al., 2021). This has been exacerbated by the COVID-19 pandemic, which has had a significant detrimental impact on cancer patients and their access to care (Vintura, 2021).

Unsurprisingly, survival rates are higher for HCC patients with easier access to care, probably reflecting progressive improvement in the effectiveness of health care services offered to these patients (Mazzuco et al., 2021).

While the challenges of liver transplant are clear due to shortage of donor organs, all other treatment options in the EASL treatment guidelines should be readily available to all patients.

The EU Beating Cancer Plan provides for an EU platform to improve access to cancer treatments as well as support for the cancer workforce through an inter-specialty training programme.

This will devise and test models for closer collaboration among stakeholders and will leverage, pool and share existing data using new digital tools.

RECOMMENDATION:

- Ensure the EASL/ ESMO treatment guidelines are fully implemented where possible, ensuring treatment is not delayed during evaluation, when the tumour can advance rapidly.
- Assess outcomes and recommendations from the EU Beating Cancer Plan/ EU platform to improve access to cancer medicines to understand which elements can be implemented in liver cancer to improve early access.

5. Optimise patient involvement and empowerment

HEALTH LITERACY AND SUPPORT

Socioeconomic status is linked with liver cancer outcomes. High area-deprivation and low education are linked with up to twofold (usually around 1,5) increased risk of liver cancer (Mihor et al., 2020).

Health literacy is a critical empowerment strategy to increase people's control over their health, their ability to seek out information, and their ability to take responsibility.

Health literacy has been shown to correlate directly with outcomes. For example, in patients who have undergone liver transplant, it was found that limited health literacy was often associated with more hospitalizations and poorer outcomes (Serper et al., 2015).

It has also been noted that in people with hepatitis B, hepatitis C, and cirrhosis, simple but formal education sessions significantly improved patient knowledge about their liver diseases (Surjadi et al., 2011; Mohamed et al., 2012; Volk et al., 2013).

The complexity of HCC can lead to inconsistencies in the description and interpretation of disease. Currently, varying terminology is used across Europe, which can lead to confusion for patients.

One of the determinants of health literacy is the capacity to obtain and process basic health information – readability is a vital yardstick for communication with patients (Gulati et al., 2018).

This is where patient organisations have an important role to play. Patient organisations with a focus on liver diseases and liver cancer can provide a wealth of information and support for patients. This information is written by specialised staff who use an easy-to-understand language, and all materials are reviewed by medical experts and patients.

In addition, patient organisations can bring together patients with liver cancer, facilitating one of the best ways of information and support – that provided from one patient to another.

One final area of consideration is the increased risk of developing liver cancer if individuals have a family history of liver cancer. One study showed that people with a positive family history of liver cancer have a 2- to 3-fold increase in their HCC risk (Turati et al., 2012). It is vital that family members of patients with liver cancer inform their primary care physicians about their family history.

RECOMMENDATIONS:

- Utilise standardised nomenclature around liver cancer across Europe.
- Ensure liver cancer patients and carers/ families are informed about patient organisations in their country immediately after diagnosis. If there are no organisations in the country, direct them to DiCE/ ELPA.
- Raise awareness of increased risk of liver cancer among family members and encourage sharing this information with HCPs.

PATIENT INVOLVEMENT IN RESEARCH

The active involvement of patients in cancer research has a positive impact on both the patient and research community, and the liver cancer research field is no exception to this.

A collaborative approach between researchers and patients allows to identify and understand the needs, gaps, and priorities in the liver cancer patient pathway. As a result, basic liver cancer research can be driven into translational discoveries, and more effective drugs and treatments can be generated and provided to patients.

By sharing good medical practices, the experience of patients with liver cancer improves. The use of patient-reported experience outcomes along with other forms of patient feedback, provides a valuable insight into what services are best for patients and a focus on service improvement efforts.

More patient involvement in research will reveal common challenges and barriers for patients.

RECOMMENDATIONS:

- Ensure liver cancer research incorporates the patient perspective, e.g. endpoints that reflect the most meaningful outcomes for patients.
- Ensure there is a systematic approach to collecting real-world patient experiences and needs throughout the patient pathway.

CONCLUSIONS

In this white paper, we have proposed a range of recommendations for liver cancer policy across five key areas, aiming to optimise knowledge, prevention, early diagnosis, treatment and care and patient involvement and empowerment.

We believe that increased focus on the highlighted areas of unmet need would drive significant improvements in outcomes for liver cancer patients.

At DiCE and ELPA, we call upon all stakeholders across Europe to work together to ensure that best practices are implemented at every stage of the patient pathway in each country, giving every patient the best possible opportunity of a positive outcome.

Together, we can ensure that everyone has access to best practice care. And no patient is left behind.

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