When the cancer community in Europe talks of neglected cancers it usually means relatively rare or uncommon types, of which there are many. But conspicuous in the list are two digestive cancers that are both deadly, not uncommon and increasing in impact – liver and pancreatic. The current EU joint action, Innovative Partnership for Action Against Cancer (iPAAC), has addressed neglected cancers, in particular with work on new care and treatment indicators for pancreatic cancer, yet although primary liver cancer is also classed as neglected it has received less attention. Pressure for much more action is, however, now growing.

This year's liver cancer awareness month, held every October, saw multiple events and publications that aimed to fill gaps in awareness of the disease and in delivering the standard of care. Among them was an urgent call by Digestive Cancers Europe (DiCE) and the European Liver Patients Association (ELPA), which have pooled their respective strengths in treatment and prevention, and which say that Europe is losing the fight against liver cancer.

Rates of risk factors such as hepatitis C infection, alcohol consumption, and obesity are rising, leading to 78,000 deaths in Europe each year from an incidence of 87,000.
The International Agency for Research on Cancer (IARC) predicts that by 2040, the death rate in Europe will rise above 101,000 with an incidence of 109,000. It is the major countries that account for by far the highest numbers, current and future – France, Italy, Russia, Germany, the UK and Spain, in descending order. New cases of liver cancer are expected to rise by almost 35% in France, and 40% in Spain, by 2040. Smaller countries may see even higher rises, albeit from a lower baseline.

While these numbers are still lower than for pancreatic cancer – which is projected to take the lives of 168,000 people in Europe by 2040, putting it on track to become the third leading cause of cancer-related deaths in the EU countries, after lung and colorectal – the rise in estimated liver cases in Europe is certainly troubling.

Deadly but preventable

There are similar percentage rises in mortality and incidence for pancreatic cancer in Europe, and both liver and pancreatic have something else in common: they are mostly detected only at advanced stages, and have among the lowest survival rates of all cancers. In most countries, fewer than 15% of people diagnosed with liver cancer survive for five years.

> Liver cancer differs significantly from pancreatic cancer in one important aspect: it is amenable to prevention and screening

Liver cancer differs significantly from pancreatic cancer in one important aspect: it is amenable to prevention and screening owing to its risk factors. In that respect it has more in common with the biggest killer, lung cancer, which for many years was viewed fatalistically by healthcare systems, also owing to its late detection and poor outlook, but of course has the preventable risk factor of smoking and now the possibility of low-dose CT screening (if controversies can be ironed out).

There's another common factor with lung, which is new treatment options. While surgery is the preferred curative strategy, this can be carried out only in a small minority of patients. Liver cancer is also one of the few tumours for which cytotoxic chemotherapy has little effect, at least in HCC, the most common type, which has no doubt contributed to its status as a neglected disease. But for

about a decade there has been an effective targeted therapy in advanced disease, and now there are several targeted agents and also an immunotherapy in play. Responses remain highly variable, however, and much remains to be done in trials and in optimising sequencing of drugs. There are also a number of interventional radiological and radiotherapy techniques, and even liver transplantation, and techniques used on the liver cross over into the treatment of liver metastases from other cancers, principally colorectal, which are much more common than primary disease.

Liver disease comes first

Two virtual events took place towards the end of October. One was the launch of a white paper at a masterclass by DiCE and ELPA, Liver cancer, no patient left behind, which covers all aspects of care; the other was a meeting held by the European Association for the Study of the Liver (EASL), Beating liver cancer in Europe, which focused mainly on prevention and early detection, and benefited from parliamentary support from Slovenia, which currently holds the EU presidency and has a track record in promoting high-level European cancer policy (see two parts here and here.)

A key point highlighted in these and other recent events is that liver cancer occurs mainly because the liver first suffers from other diseases, and all such liver conditions including cancer are a substantial burden in Europe. A Lancet commission on the UK, for example, reported that mortality attributable to liver diseases has risen four-fold between 1980 and 2013, with liver disease likely to overtake heart disease as the leading cause of years of working life lost (see also a final paper about 'unacceptable failures' to tackle liver disease in the UK).

> A rise in non-alcoholic fatty liver disease related to a rise in obesity, diabetes and high blood pressure has become a cause of cancer

Looking at Europe, a Lancet-EASL commission has noted that, while alcohol-related liver disease is the major cause of cirrhosis in many European countries, there is also an increasing incidence of non-alcoholic fatty liver disease related to a rise in obesity, diabetes and high blood pressure, which has become both a cause of cancer and also an indication for transplantation. There is also a synergy between obesity and alcohol – a high body mass index can increase toxicity of alcohol on the liver.

Hepatitis B and C infections are also significant in Europe; the hepatitis C virus, which has been more prevalent in EU member states than Hep B, causes chronic hepatitis in 60–70% of infected people, of whom 5–20% will develop cirrhosis and 1–5% will contract HCC, although this typically takes up to 30 years. The good news is that hepatitis C is now curable in most people. The European Network for Hepatitis B and C Surveillance is the key source on prevalence.
As Abid Suddle, a hepatologist at King's College Hospital, noted at a British Liver Trust event, it is non-alcoholic fatty liver disease that is set to be a leading cause of liver cancer in the west and the perception of cirrhosis as mainly associated with alcohol is far from accurate. A major difficulty, he noted, is that liver disease tends to develop silently with no symptoms over a long time, and without abnormalities in blood tests that may be ordered by GPs and others checking on other conditions. So the challenge is two-fold: detecting liver disease that may develop into cancer, and detecting cancer itself.

The DiCE/ELPA white paper cites evidence that Europe has the biggest liver disease burden globally, which may indicate that the projections for increased cancer incidence in the region are

based on solid ground. There is much to consider in public health to reduce liver disease and also cancer with alcohol policies (such as pricing), tackling the pandemic of obesity among Europeans, and viral hepatitis vaccination and treatments. But alcohol policies are lagging those in smoking, which have finally turned the tide on male smoking rates at least, while there is little progress in reducing the numbers of overweight children and adults through measures such as a tax on sugar (and the Covid-19 pandemic may have exacerbated unhealthy eating). The potential for stigmatising patients owing to drinking or weight is also clear.

Hepatologists push for screening

As liver cancer patients usually have two diseases – cancer and the condition that caused it – the physicians with particular responsibility for, and interest in, treatment are hepatologists (liver specialists), and many are playing a leading role in multidisciplinary cancer teams (MDTs) and in stepping up calls for better policies. It's similar to the way that respiratory physicians have taken on much of the heavy-lifting in quality initiatives in lung cancer.

> Lack of early detection of cancer in the context of liver disease is the universal frustration for hepatologists and others in the MDT

Lack of early detection of cancer in the context of liver disease is the universal frustration for hepatologists and others in the MDT, especially as there is good evidence of better outcomes for those undergoing surveillance by ultrasound, which is the current tool used to detect tumours and can be coupled with a blood test for a tumour emitting alpha-fetoprotein (AFP). The recommended screening interval is six months for those with cirrhosis and also those with hepatitis B infections without cirrhosis. There is also work on monitoring earlier fibrosis before it develops into the more serious scarring in cirrhosis (see the LiverScreen project).

So screening is important in patients with high-risk liver disease, but Europe is way behind countries such as Japan and Taiwan in using surveillance, as reflected in a big gap in median survival – 60 months in Japan, for example, compared with just 24 months in Europe, in figures cited by Pierre Nahon, a hepatologist at Jean Verdier Hospital in Paris. In France about 75% of patients are diagnosed at advanced stages, with less than two years survival. Many liver cancers are only picked up when they become symptomatic at an emergency stage – about 30% in the UK, for example, noted Suddle. Surveillance programmes have been in place in countries such as Japan for some time, but they do have high rates of HCC and higher risk.

Nahon notes that surveillance is recommended in a number of guidelines, including from ESMO and EASL, so it should be a standard of care. But comparing screening in clinical trials against what happens in routine care in hospitals in Belgium and France has also shown that adherence to recommendations may be low in Europe, he noted. In a study with 100% screening, 61% of HCC patients were eligible for curative treatment, but 20% screening in 'real life' led to only 24% at curative stage. The standard in all the guidelines is six-monthly surveillance of cirrhosis patients with ultrasound with or without the alpha-fetoprotein blood test; diagnosis is usually made with further imaging with CT or MRI, and also biopsy.

Liver specialists want to raise the profile of surveillance to improve compliance and early detection through education of patients and their healthcare providers. Identifying those who have liver conditions such as non-alcoholic fatty disease who are on course to develop cirrhosis and possibly

HCC is certainly a major challenge. As Nahon points out, up to 30% of Europeans have this type of condition, so this is a huge population, but there are algorithms that primary care providers can use to identify people who may have cirrhosis and need to be referred to a liver clinic for surveillance. EASL issued updated guidelines this year on non-invasive tests for evaluating liver disease, which includes a proposed algorithm for primary care.

They also recognise that better tools are needed to improve the sensitivity of the current ultrasound/blood test regime, which misses up to half of early cancers. Other imaging methods and new biomarkers are under research, as are ways to personalise screening so it is more cost effective. One such trial starting next year in France is Fastrak, which is comparing six-monthly ultrasound with ultrasound+MRI to detect smaller tumours. Nahon also points out that the level of evidence for current screening is low as, understandably, patients with cirrhosis won't agree to be randomised into a no-surveillance arm, but there is consensus that it remains a strong recommendation, despite the usual drawbacks of screening, such as false-positives.

Complex and multidisciplinary

Treating liver cancer is complex and demands an expert MDT that assesses the cancer stage, liver function – this is a particularly critical indicator emphasised by MDT members – and fitness to undergo treatments. Such MDTs, which may be part of a hepato-pancreato-biliary unit, are starting to find their voice as an essential approach to care (see for example this US liver cancer tumour board discussion hosted by the Global Liver Institute, and papers such as here and here). But as with other common cancers there is no doubt large variability around Europe in the MDT approach (which DiCE/ELPA agree is likely in their white paper). A research-oriented MDT at Hammersmith Hospital in London, which is led jointly by a hepatologist and a medical oncologist, could be seen as a 'gold standard', and is claimed to be the UK's only specialised service providing such joint expertise at the head of the team.

ESMO updated its treatment guidelines this year, listing the wide variety of options now considered to be the standard of care. In early stages, according to the Barcelona Clinic Liver Cancer (BCLC) staging system, and also with liver function assessed with the Child-Pugh system, apart from surgery there can be a choice of transplantation, thermal ablation and transarterial chemoembolisation (TACE). Alternatives to the standard of care can also include radiotherapy (external and brachytherapy), and selective internal radiotherapy (SIRT – which uses radioactive beads). In the non-curative setting, ESMO has given the highest score in its Magnitude of Clinical Benefit Scale to the recently approved combination of the immunotherapy drug atezolizumab together with bevacizumab for a significant improvement in survival in HCC compared with the targeted agent sorafenib, which had been the only option for some time, but has also been joined by other inhibitors. But for BCLC stage D, where the liver has severe damage, or performance status is too poor, there is only best supportive care.

Given the complexities of liver disease and its diagnosis and subsequent treatment it is not surprising that survival rates differ widely among countries (see the Concord-3 study) and most patients are unlikely to have access to the full range of current treatment options, such as SIRT, outside of expert centres. It isn't just doctors who are vital MDT members – one important professional who spoke at the British Liver Trust event was Sarah Selemani, a clinical nurse specialist who has expertise in guiding patients through the journey with liver cancer; such nurses still aren't in place in many countries.

Access to curative treatments for HCC and survival in France

correlates with well-off areas such as Paris and the Riviera

As with other cancers such as lung, there can also be substantial variation within countries. Nahon presented a map of France, showing that access to curative treatments for HCC and survival correlate with well-off areas such as Paris and the Riviera.

The policy backdrop

The uptick in pressure to increase awareness of and treatments for liver cancer no doubt also correlates with the launch of the EU's Beating Cancer Plan and its Cancer Mission, as there is huge ambition in elements of the plan. There is an emphasis on prevention such as encouraging healthy lifestyles, which is particularly relevant for liver cancer. The plan also includes commitments on ensuring access to hepatitis B vaccination and to treatments to prevent liver and gastric cancers associated with hepatitis C, and the just published roadmap on the plan does include actions on the viruses. (EASL ran another event on the opportunities in the plan for hepatitis-related cancer prevention). Liver cancer advocates will be happy to see the roadmap also includes the promised inequalities registry and upgrading of comprehensive cancer centre infrastructure – the latter being one of the more ambitious moves.

Taking stock of the latest round of liver cancer initiatives also reveals a lot of ambition, but also concern. The DiCE/ELPA white paper is the most thorough of the crop, covering all bases in optimising knowledge, prevention, early diagnosis, treatment and patient involvement. It references the Beating Cancer Plan, EASL and ESMO guidelines and also an action plan for five types of viral hepatitis in the WHO European region, said to be the first plan of its kind with the aim of eliminating it as a threat by 2030.

In addition to well-referenced sections on lifestyle, screening and treatment, the paper includes important points on data, noting there is a lack of good quality comparative data among European countries in registries, and that there are common miscoding issues such as recording liver metastases as primary cancers, underestimation of liver cancer incidence due to lack of diagnostic capability, and under-reporting of liver cancer on death certificates. It also notes evidence that a multidisciplinary approach is associated with improved survival in HCC, and that the complexity of liver cancer is a challenge to health literacy – common language should be used around Europe.

The white paper's recommendations are complemented by 10 'asks' from EASL to improve liver cancer care and prevention, which invites people to sign an open letter aimed at European policymakers. Also included is a short report by the International Liver Cancer Network that reinforces calls for action.

There are other organisations, especially in the liver field, active in raising awareness about cancer. But there is a formidable set of issues that needs to be tackled to reverse the projected rise in incidence, not least the challenge on the prevention side in promoting an active, healthy population in diverse nations and where pronounced inequalities are evident.