EASL Updates Liver Cancer Guidelines

Recommendations now include multiple systemic medications in addition to surgery and local therapies.

April 13, 2018 By Liz Highleyman

The European Association for the Study of the Liver (EASL) presented updated clinical practice guidelines for the management of hepatocellular carcinoma (HCC) during a special session at the International Liver Congress yesterday this week in Paris. The full guidelines are now available online.

An expert panel made up of hepatologists, oncologists and other specialists developed the recommendations based on an extensive review of relevant studies focusing on advances since the guidelines were last updated in 2012.

Over years or decades, chronic hepatitis B or C virus infection, heavy alcohol consumption, fat accumulation in the liver and other causes of liver injury can lead to development of liver cirrhosis and HCC.

About 42,200 people in the United States will be diagnosed with liver cancer and about 30,200 people will die from it this year, according to the American Cancer Society. Globally, it is the fifth most common cancer and the second leading cause of cancer-related death. HCC accounts for around 90 percent of all liver cancers.

(Cancers that arise elsewhere in the body and metastasize, or spread to the liver are not considered to be liver cancer).

Liver cancer is often detected late and it is difficult to treat. Depending on its stage, HCC may be treated with surgery to remove part of the liver (known as resection), liver transplantation, local radiation or other therapies to destroy tumors, or systemic drugs—or a combination of these. But many people experience continued disease progression or recurrence and survival is typically measured in months.

HCC Prevention

With regard to liver cancer prevention, the panel recommended hepatitis B vaccination for all newborns and people in high-risk groups. Government health agencies should implement policies to prevent hepatitis B and C transmission, curb alcohol abuse and “encourage lifestyles that prevent obesity and metabolic syndrome,” the panel wrote.

Antiviral therapies that suppress hepatitis B virus and cure hepatitis C are recommended, as they have been shown to prevent progression to cirrhosis and development of HCC. Even after cirrhosis is present, antiviral therapy can reduce the likelihood of progression to liver cancer, though the risk is not completely eliminated.

The panel members addressed the controversy around whether HCC recurrence is more likely in people who are cured of hepatitis C using direct-acting antivirals (DAAs). Panel chair Peter Galle, MD, of University Medical Center in Mainz, Germany, who presenting an overview of the guidelines, said that growing evidence suggests the apparent effect is due to the patient population—sicker people were treated first with DAAs—but it remains an area of concern.

In a recommendation that drew considerable appreciation, the panel said that coffee has been shown to decrease the risk of HCC in people with chronic liver disease and coffee consumption should be encouraged.

“Coffee has a sort of chemopreventive quality,” Galle said. “There are uncertainties related to the amount and caffeinated versus decaffeinated, and there is no reason to think it has an effect on exiting tumors.”

Surveillance and Diagnosis

The panel recommended better screening programs to identify people at risk for liver cancer. Regular surveillance is strongly advised for people with liver cirrhosis, with a weak recommendation for those with advanced (stage F3) liver fibrosis. Some hepatitis B patients without cirrhosis are also considered to be at intermediate or high risk for HCC. The role of surveillance for non-cirrhotic people with NAFLD is not yet clear.

Abdominal ultrasound every six months is recommended. The panelists noted that accurate biomarkers for early detection of HCC are still lacking. Alfa fetoprotein (AFP) is sometimes used, but is “suboptimal in terms of cost-effectiveness for routine surveillance of early HCC,” they wrote.

Noninvasive imaging can be used to diagnose people with cirrhosis who have larger tumors ($\geq$1 cm), but for most others pathological evidence from a biopsy should be used to confirm a diagnosis. Computed tomography and MRI scans are the preferred imaging methods. People at high risk for HCC with tumors smaller than 1 cm should undergo follow-up screening no less than every four months. Repeat biopsies are advised for people with inconclusive results.

Surgery and Local Therapies

A majority of the guidelines document is devoted to various forms of liver cancer treatment, starting with surgery and so-called loco-regional therapies that aim to destroy tumors within the liver.

“Surgery is the mainstay of hepatocellular carcinoma treatment, leading to the best outcomes of any treatment available in well-selected candidates,” with five-year survival rates of 60 to 80

percent, according to the panel.

Liver resection and liver transplantation are the first options for people with early tumors, according to the guidelines. Surgery can often be useful for more advanced HCC as well, especially if other therapies can shrink tumors before the operation. Resection is not considered suitable for people whose cancer has invaded major blood vessels in the liver.

Decisions about liver resection in people with cirrhosis should be based on factors including liver function, portal hypertension, how much of the liver would be left after surgery and overall health status and comorbidities. Laparoscopic surgery and other less invasive approaches are recommended if available.

Recurrence is common after surgery and follow-up is recommended every three to four months during the first year. Neoadjuvant (starting before surgery) or adjuvant (starting after surgery) therapies are not recommended to prevent recurrence because they have not been yet been shown to improve outcomes, but the panel encouraged further clinical trials using new drugs such as checkpoint inhibitors.

The guidelines extensively discuss liver transplantation, including donor organ allocation policies and living donor transplants. However, the shortage of donor livers severely limits the availability of this option.

The guidelines also go into detail about local ablation techniques. Radiofrequency thermal ablation is the standard of care for people with early HCC not suitable for surgery, and it can replace surgery as first-line treatment for those with very early cancer. Ethanol injection is another option, and microwave ablation shows some promise, but there is little evidence to support external beam radiation therapy, according to the panel.

Transarterial chemoembolization (TACE) involves injection of chemotherapy drugs and blockage of blood vessels that supply a growing tumor. It is the most widely used primary treatment for unresectable HCC, but it is not indicated for people with decompensated liver disease, metastatic liver cancer or kidney dysfunction.

Selective internal radiation therapy, also known as radioembolization, uses radioactive beads to target tumors. Although studies have shown that this approach has a good safety profile and can control local tumors, it has not yet demonstrated an overall survival benefit compared with systemic therapy.

Systemic Therapies

Systemic therapies, or drugs that affect the whole body, have seen the most evolution since the previous guidelines, but promising newer agents are still considered experimental and not included in this version. The number of drugs that are either approved or under consideration for liver cancer has risen from one in 2012 to at least half a dozen.

The systemic drugs recommended in guidelines are all targeted therapies that interfere with kinases, a large family of enzymes that play a role in processes that allow cancer to grow and spread.

Nexavar (sorafenib) is the standard first-line systemic therapy for people with advanced HCC or those with early tumors who are either considered unsuitable for or experience disease progression despite loco-regional therapies. It is the only first-line systemic HCC therapy approved by the Food and Drug Administration (FDA).

The EASL guidelines also recommend Lenvima (lenvatinib) as an alternative first-line therapy for advanced HCC and good liver function. To date, Lenvima is FDA-approved for advanced kidney cancer and thyroid cancer, but not for liver cancer.

Stivarga (regorafenib), which the FDA approved for liver cancer in April 2017, is recommended as second-line treatment for people who experience disease progression on Nexavar. Cabozantinib—FDA-approved as Cabometyx tablets for advanced kidney cancer and Cometriq capsules for metastatic thyroid cancer—has also been shown to improve survival in this group.

Galle noted that Eli Lilly recently announced results from a study showing that Cyramza (ramucirumab), a VEGF inhibitor that blocks blood vessel formation, increased overall survival and progression-free survival in liver cancer patients with high AFP levels. It is currently FDA- approved for advanced stomach cancer, colorectal cancer and non-small-cell lung cancer. He said this would be added in a footnote to the guidelines.

EASL does not yet recommend immunotherapy for liver cancer. Last September the FDA approved Opdivo (nivolumab) as second-line therapy for people with HCC who were previously treated with Nexavar, but it is not yet approved for this indication in Europe.

Opdivo is a monoclonal antibody that blocks PD-1, a receptor on T cells that plays a role in regulating immune function. Some tumors can use PD-1 to turn off immune responses against them, and drugs that block PD-1 can restore T-cell activity. FDA approval was based on promising findings from the CheckMate 040 trial, which showed that Opdivo led to tumor shrinkage or disease stabilization in just over half of treated patients. But the EASL panel noted that this was an uncontrolled Phase II study, and awaits Phase III data.

Targeted therapies and immunotherapies work very well for some people, but show little effectiveness for others. Experts do not yet know how to predict which patients will benefit and the development of predictive biomarkers is one of the most active areas of cancer research

The panel emphasized that the new EASL recommendations are intended to guide clinical practice where all possible resources and therapies are available. The members acknowledged that providers will have to make adjustments to account for local regulations, drug availability, provider capacity, infrastructure and cost-benefit analyses.

Click here to read the full EASL hepatocellular carcinoma guidelines.

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