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Tackling a Killer: New Therapies at the VA vs. Rising Rates of Hepatocellular Carcinoma

by Annette Boyle | Sep 16, 2025

The last 20 years have seen a significant drop in the incidence and mortality of most cancers in the U.S., but liver cancer has largely defied that trend. Incidence rates for hepatocellular carcinoma (HCC), which accounts for up to 85% of all liver cancers, have tripled since 1980, making it the fastest-growing malignancy by incidence in the U.S.

A recent photo of U.S. Marines conducting a safety walk of the driving course during a combat vehicle operator training at Marine Corps Base Camp Lejeune, NC. Contaminated water at the base between 1953 and 1987 has been linked to hepatocellular carcinoma (HCC.} (U.S. Marine Corps photo by Cpl. Apollo Wilson)

While new therapies including tyrosine kinase inhibitors like lenvatinib and immune checkpoint inhibitors such as ipilimumab, nivolumab and atezolizumab have started to improve survival rates, the number of deaths continues to rise. As a result, liver cancer ranks as the sixth most common cancer and the third deadliest nationwide.

And that's in the general population. For veterans, the rates are worse. Veterans face a five-fold higher incidence of hepatocellular carcinoma (HCC), making it an area of intense research for the VA.

Service-related and other factors contribute to the increased risks in veterans. The VA considers HCC a presumptive condition for many veterans. Under the Sergeant First Class Heath Robinson

Honoring our Promise to Address Comprehensive Toxics Act (PACT Act), Congress extended eligibility for VA health care to veterans who served during the Gulf War era and post-9/11 veterans exposed to burn pits who develop a gastrointestinal cancer of any type.

This determination was based on an Institute of Medicine study that found an association between liver damage and HCC and exposure to chemicals frequently detected at burn pit sites, including carcinogens and other toxins. Veterans who served in Iraq, Afghanistan, Djibouti, Kuwait, Saudi Arabia, Somalia and selected other locations after August 2, 1990, are presumed to have been exposed to burn pits.

In addition, for veterans who served more than 30 days at Camp Lejeune/Marine Corps Air Station New River between 1953 and 1987, liver cancer is explicitly listed as a presumptive condition linked to solvent-contaminated water.

Older veterans, in particular, have another major risk—chronic hepatitis C virus (HCV), which increases the likelihood of developing HCC about 1000%. Three out of four cases of HCV in the United States occur in individuals born between 1945 and 1965, who have five times the risk of the infection seen in other age groups.

Prior to 2014, veterans were three times more likely to have chronic hepatitis C infection compared to the general population. Vietnam Era veterans might have had increased exposure to the virus from the needle-free jet gun injector used to administer vaccinations quickly to thousands of troops from the late 1950s through the 1990s. While not formally recognized as a risk factor, jet gun use was associated with an outbreak of hepatitis B in the 1980s.

Researchers first discovered post-transfusion cases of hepatitis that were not caused by hepatitis A or hepatitis B in the 1970s, but scientists did not isolate the hepatitis C virus until 1989. As blood supplies were not screened for the virus until 1992, blood transfusions could also have transmitted HCV to veterans.

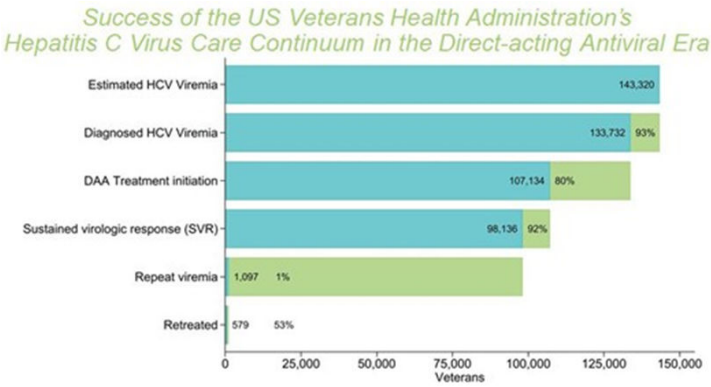
Those risks and the large number of Vietnam era veterans in care at the VA resulted led to an explosion of HCV cases at the VA.

“Rates of hepatocellular carcinoma, cirrhosis of the liver, and liver failure were skyrocketing among veterans in VA care with HCV,” David Ross, MD, PhD, MBI, Director, VA HIV, Hepatitis, and Related Conditions Programs, told U.S. Medicine in a previous conversation. “VA data and research showed that cure of HCV decreased death from all causes, not just liver disease.” Based on that data, the VA launched an aggressive program to eliminate HCV in veterans in 2014.

The VA had offered HCV treatment for years, but earlier therapies proved hard to tolerate and often ineffective. “The new direct-acting antivirals were much more effective (cure rates up to 95%) and

much less toxic than standard treatments," Ross added. "They also shortened the time needed for treatment from 12 months of injections and pills to as little as eight weeks of taking one pill a day."

Starting in early 2014, the VA aggressively pursued the goal of eliminating HCV among all veterans in care. By 2019, it had cured more than 100,000 veterans. That represents 80% of those diagnosed with HCV and nearly 92% of veterans treated achieved sustained virologic response. Younger veterans and those with unstable housing or alcohol or substance use disorders were least likely to initiate or complete therapy.[1]



Click to Enlarge: Success of the U.S. Veterans Health Administration's Hepatitis C Virus Care Continuum in the Direct-acting Antiviral Era

Source: Clinical Infectious Diseases

Curing HCV cut the likelihood of veterans developing HCC by 84% and reduced all-cause death rates by up to 50%, according to the VA. After sharply rising for more than a decade, the HCV treatment program dramatically reduced the number of veterans diagnosed with HCC annually. Peaking at a high of 11,250 in 2015, new diagnoses fell 80% in six years.

Coinfection with Hepatitis B and D Increases Risk

Worldwide, another form of hepatitis is a major risk factor for HCC, especially for individuals who contract hepatitis B (HBV) at birth through their mother or in early childhood. Consequently, the American Association for the Study of Liver Disease (AASLD) recommends testing women for hepatitis B during every pregnancy and vaccinating all newborns for hepatitis B, along with high-risk adults. The U.S. Centers for Disease Control and Prevention (CDC) also recommends screening all adults for hepatitis B using a triple panel test including HBsAg, anti-HBs (anti-surface antibody), and anti-HBc (anti-core antibody) at least once. In particular, individuals with chronic HCV and signs of chronic liver disease should also be screened.[2]

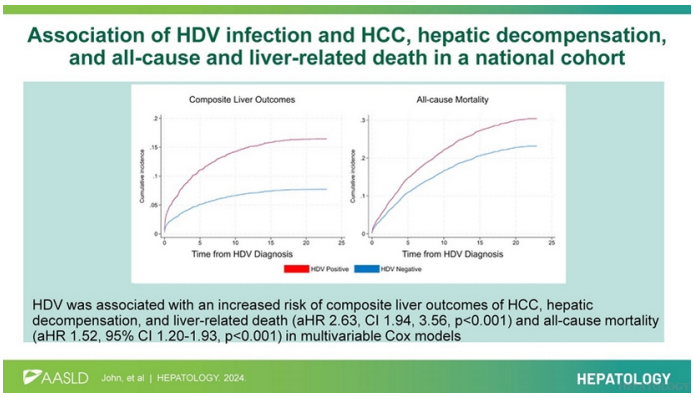
Overall, individuals with chronic HBV have a 10% and 25% risk of developing HCC. HBV can progress to fibrosis, cirrhosis and then HCC, but HCC can also occur in individuals with HBV who do not have cirrhosis. On an annual basis, 2% to 4% of patients with HBV with cirrhosis progress to HCC, as do 1% of those without cirrhosis.

Of even greater concern, hepatitis D, which occurs only in patients who already have chronic HBV, more than doubles the risk of hepatic decompensation, HCC, and liver-related mortality compared to HBV alone, based on a study of 4817 veterans by researchers from the Miami; Richmond, VA; Palo

Alto, CA; Pittsburgh, Washington D.C., and Long Beach, CA, VAMCs. In light of these findings, the researchers recommended widespread testing for hepatitis D.[3]

Alcohol Remains a Major Risk Factor for HCC

Alcohol use significantly increases the risk of all liver diseases and accounts for 15% to 30% of all HCC cases globally. A study released by Rand this summer found that 9% of veterans met the criteria for alcohol use disorder, with the rate as high as 21% among veterans aged 18 to 49.[4] A variety of psychosocial therapies are recommended for AUD, along with the FDA-approved medications acamprosate, naltrexone and disulfiram. The VA/DoD guidelines recommend naltrexone plus topiramate, an epilepsy medication, for veterans with moderate to severe AUD.



Click to Enlarge: HDV was associated with an increased risk of composite liver outcomes of HCC, hepatic decompensation, and liver-related death (aHR 2.63, CI 1.94, 3.56, p<0.001) and all-cause mortality (aHR 1.52, 95% CI 1.20-1.93, p<0.001) in multivariable Cox models

Source: AASLD John, et al Hepatology June 2025

Binu John, MD, and colleagues in the Veterans Analysis of Liver Disease (VALID) Group of Investigators published a study in the June issue of the American Journal of Gastroenterology that indicated another medication could reduce the risk of HCC in veterans with harmful alcohol use. In 8,040 veterans using glucagon-like peptide-1 receptor agonists (GLP-1RAs) to treat type 2 diabetes who had positive AUDIT-C screens without cirrhosis, GLP-1 RAs reduced the risk of a composite of liver outcomes (HCC, decompensation and liver-related mortality) 30% and cut the risk of death 57%, while also reducing the likelihood of a subsequent positive screen for alcohol use disorder 25%. Semaglutide, specifically, halved the risk of liver disease and reduced the mortality risk by 67%.[5]

Hard to Detect Metabolic Conditions Increase Risk, Create Screening Challenges

Other factors are now driving up HCC diagnoses.

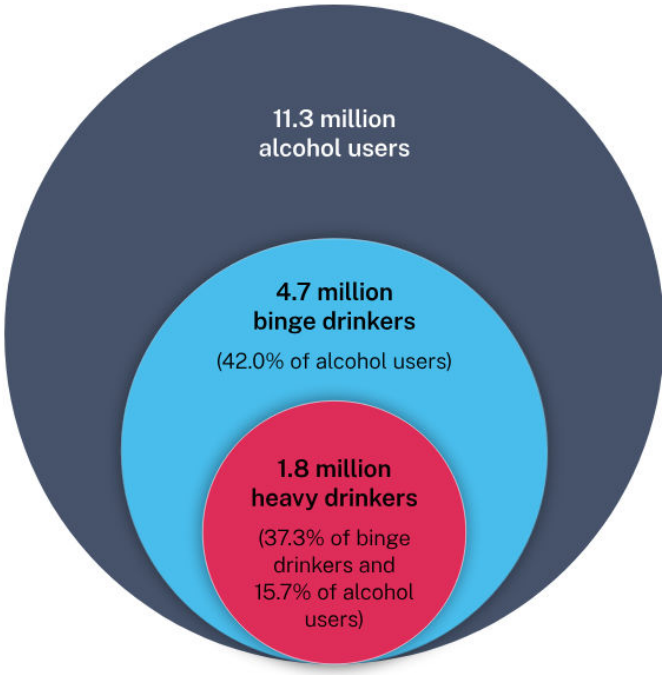
"Now that we can better treat viral liver diseases, we're increasingly observing hepatocellular carcinoma in patients with MASLD (metabolic-associated steatotic liver disease)," said Tamar Taddei, chief of Gastroenterology at VA Connecticut Healthcare System and professor of Medicine (Digestive Diseases) at Yale School of Medicine.

MASLD, previously called non-alcoholic fatty liver disease (NAFLD), is a chronic liver disease characterized by hepatic fat accumulation unrelated to alcohol use along with at least one cardiometabolic risk factor, such as obesity, type 2 diabetes, hypertension or dyslipemia. MASLD often has no symptoms and so frequently goes undiagnosed.

A recent study led by Sebastian Niezen, MD, of the VA Pittsburgh Healthcare System with colleagues at 10 other VAMCs indicated that 45% of veterans had risk factors for MASLD and may be undiagnosed, slightly higher than the national estimate of MASLD in 30% to 40% of adults.[6]

About 75% of people who are overweight and 90% of those who are obese or have hyperlipidemia have MASLD, as do more than 70% of individuals with diabetes.

Figure 1. Past-Year Alcohol Use Among Veterans, 2023



SOURCE: Features data from SAMHSA, undated-a.

Click to Enlarge: Past-Year Alcohol Use Among Veterans, 2023

Source: Features data from SAMHSA, undated-a

One in four people with MASLD progress to metabolic-associated steatohepatitis (MASH, previously called non-alcoholic associated steatohepatitis or NASH), according to the American Liver Foundation. In MASH, fat accumulation causes liver inflammation and scarring or fibrosis, which can advance to cirrhosis, liver failure and HCC. About 2% of people with MASH develop HCC each year and MASLD/MASH account for an estimated 38% of HCC cases today.

About 40% of cases of MASLD-associated cases of HCC occur in patients without cirrhosis, Dimitrios Moris, MD, MSc, PhD, and other researchers at the Durham VAMC and Duke University found. Cirrhosis has been the primary factor considered in screening for HCC, as more than 90% of patients who develop HCV- or alcohol-related HCC first progress to cirrhosis.[7]

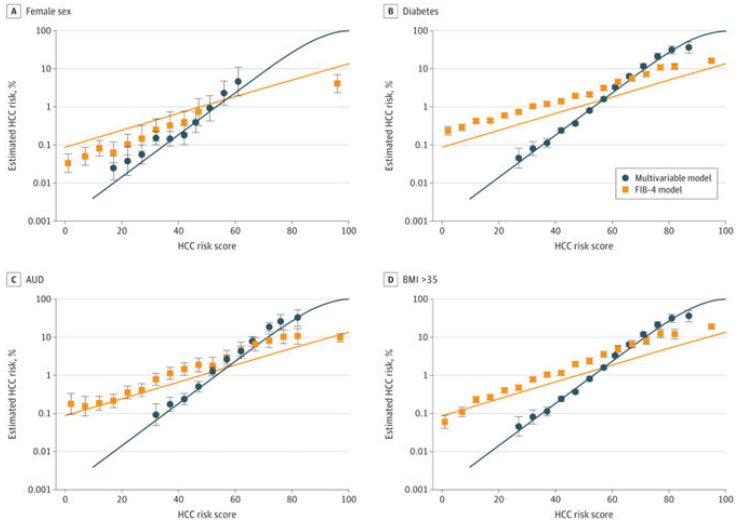
MASLD "is harder to detect, and we're seeing liver cancer emerge in these patients even before cirrhosis develops," Taddei noted. "We want to understand the liver cancer risk in these populations."

Taddei and colleagues at the VA and Yale University School of Medicine, developed an HCC risk score for patients without cirrhosis or viral hepatitis using the Fibrosis-4 index along with age, sex, race, ethnicity, body mass index, diabetes status, smoking status, and alcohol use. Notably, most HCC

cases analyzed using the model had FIB-4 less than 3.25, the conventional cutoff for higher risk of advanced fibrosis.[8]

"This clinical score provides primary care clinicians with a straightforward tool to assess whether to be concerned about liver cancer or liver disease," Taddei noted. "The earlier we in specialty care receive these consultations, the more effectively we can address the risk factors for liver cancer. If this score prompts clinicians to consider liver health, I consider it a success."

Another screening tool under development by the VA researchers in Miami; Richmond, VA; New Haven, CT, and Philadelphia, applies a natural language processing algorithm to VA electronic health records to identify undiagnosed veterans with MASLD and MASLD with increased alcohol intake (MetALD). They conducted a retrospective study of data from 817,657 participants in the VALID cohort from Jan. 1, 2013, to Dec. 31, 2022. The rule-based algorithm searched records for imaging evidence of hepatic steatosis then combined those results with identification in the records of cardiometabolic risk factors and harmful alcohol use indicators. The team validated the algorithm with a blinded review of randomly selected charts.[9]



Click to Enlarge: HCC Lines were estimated using risk scores obtained from the development sample. Subgroup data points from Kaplan-Meier estimates are shown for a minimum of 10 patients with HCC events and 5 who were at risk for HCC at the end of follow-up. Circle represents multivariable model, and square represents Fibrosis-4 Index (FIB-4) model. Error bars represent 95% CIs. AUD indicates alcohol use disorder; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Source: JAMA Network Open

The team, which included both Taddei and John, reported that 53.5% of the veterans had some form of steatotic liver disease—36.5% had MASLD, 12.1% had MetALD, and 4.7% had alcohol-associated steatotic liver disease. The 36.5% discovered to have MASLD indicates massive underdiagnosis when compared to the 2.8% of veterans in the cohort with ICD 9/10 codes for the condition. Chart review supported the results of the NLP analysis, finding 96% sensitivity and 90% specificity.

Other VA researchers have focused on developing better biomarkers for HCC. A team led by Hashem El-Serag, of the Michael E. DeBakey VAMC in Houston, former president of the American Gastroenterological Association, and chair of department of medicine at the Baylor College of

Medicine, conducted a meta-analysis of biomarker studies for HCC along with his Baylor colleague Fouad Jaber. Of the externally validated algorithms, they noted that GALAD, which incorporates gender, age, alpha-fetoprotein (AFP), the lens culinaris agglutinin-reactive fraction of AFP (AFP-L3%) and prothrombin induced by vitamin K absence-II (PIVKA-II) significantly increased sensitivity for HCC detection compared to AFP alone and other combinations, but also increased false positives by 20% to 30%.[10]

Serum AFP levels above 400ng/mL have previously been considered diagnostic for HCC, particularly when combined with imaging, but up to half of patients with HCC have normal AFP levels at diagnosis. In addition, other conditions can elevate AFP, including pregnancy, other cancers and cirrhosis.

Seeking to improve on AFP and GALAD, El-Serag and colleagues at the DeBakey VAMC developed the HCC early detection screening (HES) algorithm version 2, which includes age, alanine aminotransferase level, platelet count, etiology as well as AFP level and rate of AFP change in the prior year, if available.[11]

The team prospectively tested HES V.2.0 and other algorithms in 2,331 patients from eight Texas liver clinics, all of whom had cirrhosis; 72.8% of participants were male and 78.4% were white. During the follow-up period, 125 participants developed HCC.

Chart Title: Overall comparative accuracy of biomarker scores

Time before HCC diagnosis	AFP	GALAD	HES V2.0
Any time	38.4 (27.3, 50.6)	40.0 (29.8, 52.7)	47.2 (35.3, 52.2)
6 months	37.2 (18.5, 56.0)	48.8 (30.0, 70.4)	52.4 (28.3, 61.0)
12 months	39.1 (23.8, 53.9)	40.6 (26.8, 58.1)	47.8 (32.7, 56.7)
24 months	33.0 (21.4, 45.5)	38.0 (26.6, 51.5)	51.0 (36.1, 55.1)

Source: Sensitivity (true-positive rate, %) with 95% bootstrap CIs at a fixed false-positive rate of 10% for detecting any HCC (n = 125) in the overall cohort (non-HCC, n = 2206) Source: El-Serag HB, Jin Q, Tayob N, et al. HES V2.0 outperforms GALAD for detection of HCC: A phase 3 biomarker study in the United States. Hepatology. 2025;81(2):465–475. doi: 10.1097/HEP.0000000000000953

In women, HES v2.0 dramatically improved the sensitivity for detection of HCC compared to AFP, at 50.3% at any time prior to diagnosis vs. 29.4%, and increasing true positives by nearly 250% at 24 months, 55.0% vs. 22.2%. It also significantly outperformed GALAD in women.

Diagnosing HCC

Because of the issues with AFP noted above, AASLD does not recommend AFP for HCC diagnosis. It also does not recommend diagnosis based on other biomarkers or liquid biopsy, pending additional validation studies.[12]

For patients with suspected HCC, the AASLD recommends CT/MRI imaging to capture arterial phase hyperenhancement, delayed phase washout, capsule appearance and tumor size. While imaging can be diagnostic on its own in some circumstances, biopsy is recommended in patients without cirrhosis or HBV. AASLD also notes that "HCC biopsies can be informative of molecular and immune classes of HCC, oncogenic mutations associated with immune excluded phenotypes, and gene signatures predictive of response to immunotherapy. Even if in few circumstances, histology can capture mixed HCC-cholangiocarcinoma among LR-5 cases, a feature with significant clinical implications."

HCC treatment options continue to expand

Patients with early-stage HCC with a single tumor within the liver that is "technically resectable and/or within transplantation criteria, is most effectively managed with local therapies, such as partial hepatectomy, liver transplantation, ablation, radiation, or transarterial therapies," according to the overview of HCC treatment written by Moris and his colleagues.

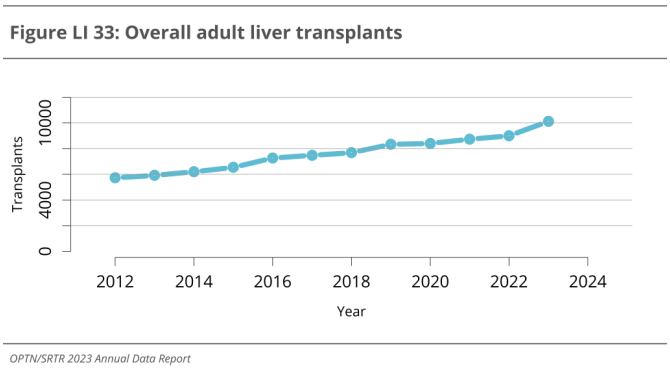
Resection is generally recommended in patients without portal hypertension who have preserved liver function, good performance status and just one tumor, if they will have adequate functional liver post-surgery. It is the preferred option for patients without cirrhosis and for those with compensated cirrhosis for whom at least 30% of the remnant will be non-cirrhotic. Moris and his colleagues note that data also supports "consideration of surgical resection among patients with multinodular HCC," especially when they have three or fewer nodules of 3 cm or less.

Liver transplant is an option for patients with up to three small, localized liver tumors or one tumor with no dimensions larger than 5 cm and no macrovascular invasion. The adoption of these parameters established by the Milan criteria, dramatically improved transplant outcomes, said the Durham VAMC/Duke team, and liver transplantation "is now considered to provide the best long-term outcomes for patients who present with transplantable HCC, with five-year survival exceeding 70% and recurrence rates less than 10%–15%."

Liver transplantation might also become an option for patients who are successfully downstaged using transarterial chemoembolization (TACE), transarterial radioembolization (TARE), resection or radiofrequency ablation (RFA) to meet the Milan criteria or expanded Milan criteria.

Advances in machine perfusion technology that better preserve donated livers nearly doubled the number of liver transplants performed in the U.S. between 2012 and 2024, rising from 5,921 to 11,458.[13,14] This greater access and the associated shorter wait time may change the calculus of resection versus transplantation for multidisciplinary teams treating veterans, given the significantly greater benefit of transplantation.

Moris and colleagues noted that "the survival benefit [of transplantation] is most profound in patients who have multifocal disease within Milan criteria (specifically, a greatest tumor dimension <3 cm without major vascular invasion), with a HR of 0.39 (95% CI, 0.30–0.50) relative to resection.



Click to Enlarge: Overall Adult Liver Transplants

Source: OPTN/SRTR 2023 Annual Report

Adjuvant therapies are not recommended in patients undergoing resection or ablation. While initial results of the phase 3 Imbrave050 clinical trial suggested that atezolizumab plus bevacizumab extended recurrence-free survival compared to surveillance, updated results at 35.1 months showed the RFS benefit was not sustained. "While IMbrave050 was the first RCT in the adjuvant arena to show significant benefit in recurrence-free survival at the first interim analysis, on subsequent analysis, this benefit was no longer demonstrated. This trial provides a cautionary note to assessing data at early interim time points and underscores the importance of designing an interim analysis that is robust enough to call a trial positive as per conventional stopping rules," said Taddei and colleagues in a critical update to the AASLD practice guidelines in July.[15]

In veterans with locally advanced HCC, transarterial therapies including TARE and TACE are recommended, along with transarterial embolization, TACE with drug-eluting beads. Ablation, SBRT, proton-beam radiotherapy have also shown effectiveness with less concern for liver injury than classical external beam radiation therapy,

"SBRT has shown control rates ranging from 95% to 100% up to one or two years after treatment, and it has also been used as a bridge to [liver transplant] to provide tumor downstaging or stabilization of disease while waiting for an organ," said the Durham VAMC/Duke team. "It is important to note that these studies often under-represent patients with CTP scores greater than B7; and, when included, they typically receive lower doses of radiation because of concerns about liver toxicity. For this reason, caution should be exercised when treating patients with significant underlying hepatic dysfunction."

Metastatic Disease Requires Systemic Therapy

Treatment of patients with unresectable HCC who are not eligible for locoregional therapy and those with metastatic disease at diagnosis or in recurrence relies on systemic therapy. The first systemic therapy, sorafenib, received FDA approval in 2007 and reigned alone for a decade. Since 2017, however, several new therapies have gained approval. These include the targeted therapies lenvatinib, regorafenib, ramucirumab and cabozantinib. Multiple immune checkpoint inhibitors (ICIs) have also been approved—pembrolizumab, nivolumab, ipilimumab and the combinations atezolizumab plus bevacizumab and durvalumab plus tremelimumab.

Targeted therapy leverages HCC's need for tyrosine kinase receptors to fuel its growth and spread. The mTKI sorafenib provided a three-month increase in overall survival (OS) compared to placebo in the SHARP study, the first drug to move the needle in advanced HCC.[16]

The REFLECT trial compared lenvatinib to sorafenib in 954 patients. Lenvatinib doubled the progression-free survival (PFS) for patients, 7.4 months vs. 3.7 months, a 34% reduction in risk, and nearly tripled the objective response rate (ORR), 18.8% vs. 6.5%. Lenvatinib demonstrated non-inferiority in OS compared to sorafenib with a median OS of 13.6 vs 12.3 months for sorafenib, (HR=0.92, 95% confidence interval [CI] 0.79–1.06), with the upper limit of the 95% CI for non-inferiority being 1.08. Based on these results, lenvatinib supplanted sorafenib as the preferred first-line option.[17]

Two combination immune therapies subsequently showed improved overall survival and ORR compared to sorafenib. In the IMbrave150 trial, atezolizumab (an anti-PD-L1) plus bevacizumab (an anti-VEGF) increased OS to 19.2 months compared to 13.2 for sorafenib, a 34% reduction in the mortality risk.[18] In the HIMALAYA trial, durvalumab (an anti-PD-L1) plus tremelimumab (an anti-CTLA-4) also proved superior to sorafenib in terms of OS, 16.5 months vs. 13.8, and ORR, 20.1% vs. 5.1%.[19]

Given the longer overall survival for the ICI combinations, guidelines from the American Association for the Study of Liver Disease, the American Society of Clinical Oncology and the National Comprehensive Cancer Network guidelines all recommend atezolizumab plus bevacizumab or durvalumab plus tremelimumab as the preferred first-line therapy for most patients with advanced or metastatic HCC. The guidelines recommend sorafenib and lenvatinib in the first line for patients unable to tolerate immune therapies because of autoimmune disorders and for those who have received liver transplants.

The 2025 NCCN guidelines for HCC also include tislelizumab and durvalumab, as category 1 first-line therapies and nivolumab plus ipilimumab and pembrolizumab as other options.

Cabozantinib and regorafenib are the category 1 NCCN recommendations for subsequent-line therapies, with other recommended regimens including any of the first-line options. A number of other immune therapies are recommended under specific circumstances.

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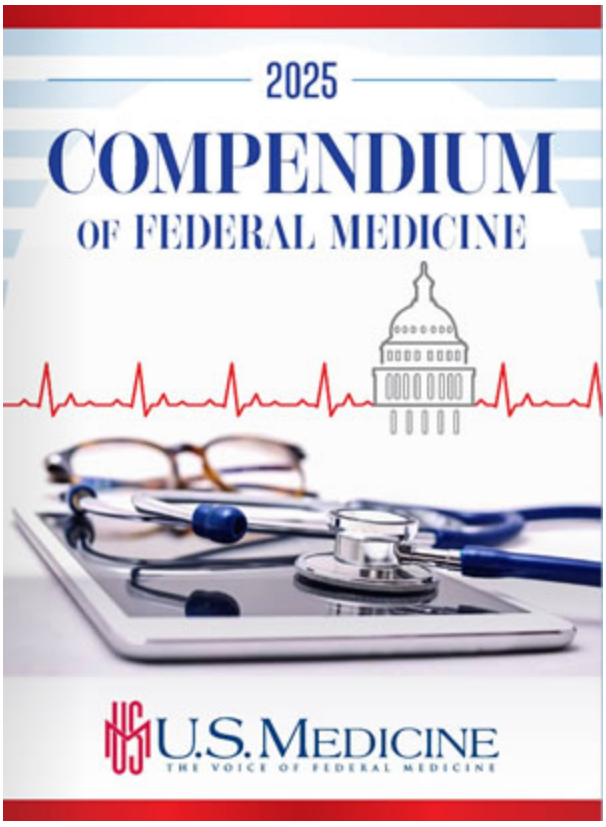

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