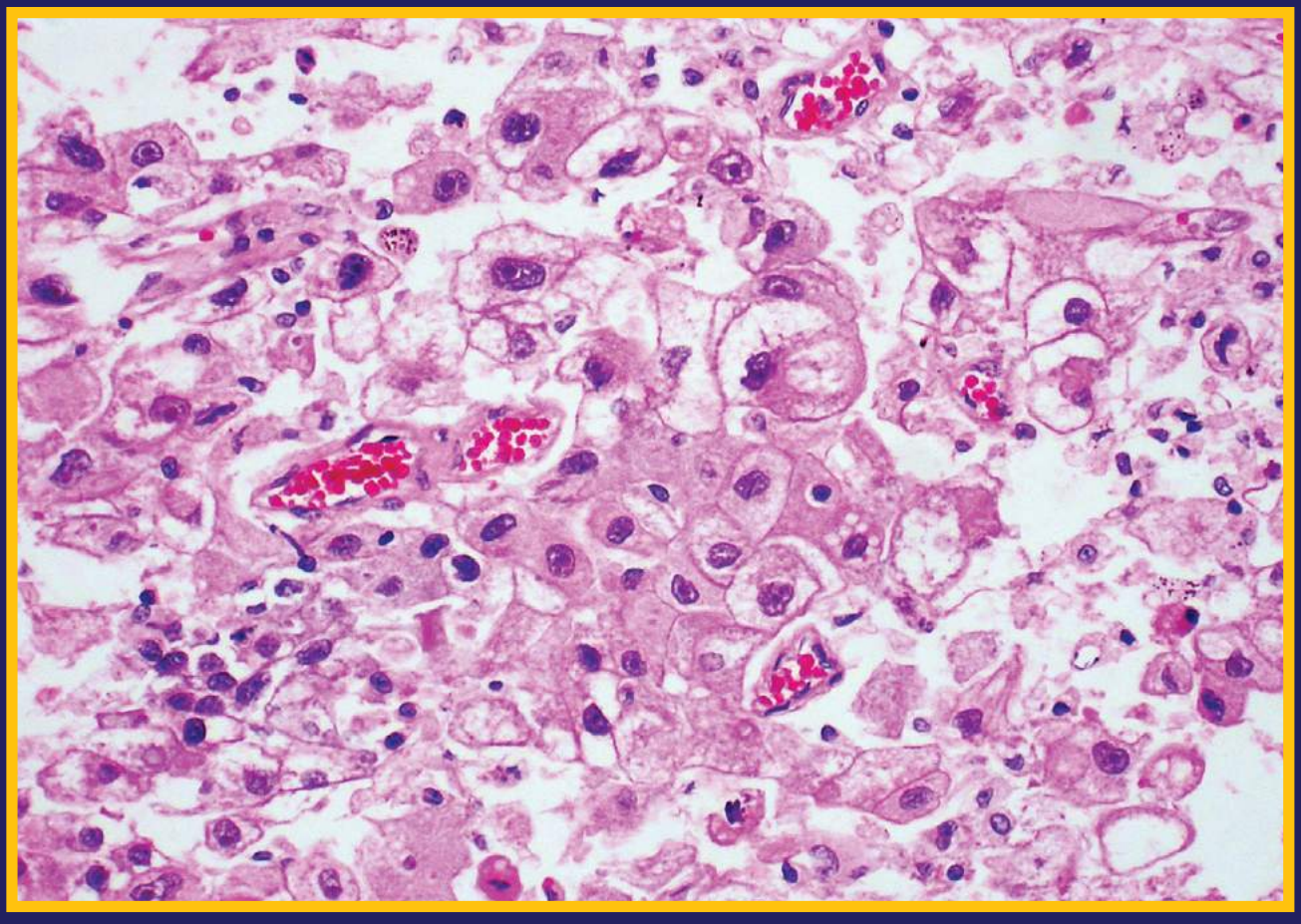
Meeting the Challenges of Hepatocellular Carcinoma in Federal Medicine



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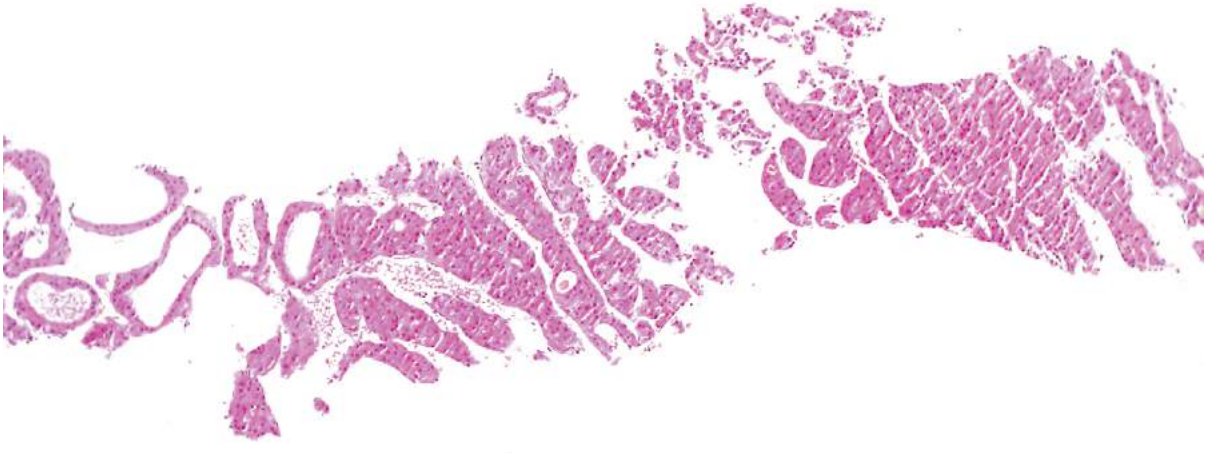

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Cover image and table of contents image: Histopathology of hepatocellular carcinoma

VA Continues to Improve Management of Deadly Hepatocellular Carcinoma

WASHINGTON—With the number of veterans being diagnosed with hepatocellular carcinoma continuing to rise, the VA has implemented several new initiatives to improve outcomes for patients with this aggressive cancer.

The most common type of liver cancer, HCC is the third-leading cause of cancer-related death worldwide. In recent years, most kinds of cancer have seen significant drops in incidence and mortality rates in the United States, but hepatocellular carcinoma remains an outlier.

Nationally, new diagnoses of liver cancer rose 38% between 2003 and 2012, and the number of deaths increased 56% in the same period, according to the national Centers for Disease Control and Prevention. The upward trend accelerated over time, with the incidence rate rising an average of 2.3% per year from 2008 to 2013 and the mortality rate increasing an average of 2.8% per year for men and 3.4% for women.

No healthcare system has seen the impact of the dramatic rise in HCC more clearly than the VA. In 2000, the VA had 1,361 patients diagnosed with the disease. By 2005, the number of veterans diagnosed with HCC had more than tripled to 4,989, according to the VA. By 2015, the number had doubled again, reaching 11,250. The number of veterans with HCC receiving care declined slightly to 9,905 in 2018 but is expected to resume its upward trend.

"HCC is different from most other cancers. Where the numbers for lung cancer, for instance, have remained relatively stable, HCC is skyrocketing now because of fatty liver disease," said David Ross, MD, PhD, MBI, national director of the VA's HIV, Hepatitis, and Related Conditions Programs and associate clinical professor of medicine at the George Washington University School of Medicine and Health Sciences in Washington. *(See article on page 9 for more information.)*

A 'Perfect Storm'

The largely male, baby boomer demographics of veterans who receive care through the VA apparently created a "perfect storm" for HCC. The cancer affects men at twice the rate seen in women, and chronic infection with the hepatitis C virus poses the highest risk of HCC for patients in the United States. Approximately 75% of U.S. cases of hepatitis C are found in individuals born between 1945 and 1965, a cohort with five times the risk of the infection compared to other age groups. As of 2016, approximately 180,000 veterans had been diagnosed with chronic hepatitis C infection.

A number of other factors increase the risk of HCC, and many of them also occur disproportionately in veterans, including diabetes, metabolic syndrome, obesity, alcohol use disorder and nonalcoholic fatty liver disease.

Because of the elevated risk of HCC in its patient population, the

"HCC is different from most other cancers. Where the numbers for lung cancer, for instance, have remained relatively stable, HCC is skyrocketing now because of fatty liver disease."

—David Ross, MD, PhD, MBI

VA has adopted a number of processes designed to identify and monitor those at greatest risk, standardize diagnosis and better manage treatment.

Screening for and treatment of hepatitis C have formed the cornerstone of VA's HCC prevention efforts. With HCV nearly eliminated in the VA *(see article on page 11)*, new questions have arisen about how else to stem the rising tide of liver cancer.

"We need to continue to follow patients who have cirrhosis or other conditions that increase the risk of HCC like problem drinking or hepatitis B or nonalcoholic fatty liver disease," Ross told *U.S. Medicine.*

Eighty percent of individuals diagnosed with HCC have cirrhosis, and the presence of cirrhosis in individuals with known risk factors can increase their risk of developing HCC between eight-and 25-fold, according to the American Association for the Study of Liver Disease. Consequently, the AASLD recommends surveillance using ultrasound with or without AFP every six months for adults with cirrhosis who are eligible for HCC treatment, a protocol followed by the VA.

Screening Questions

Questions about the need for such frequent screening remain, however. "There is not a randomized controlled trial showing that surveillance for liver cancer prolongs life," Ross noted.

"There is a lack of high quality data," agreed Fasiha Kanwal, MD, MSHS, an investigator in the Clinical Epidemiology & Comparative Effectiveness Program at the Center for Innovations in Quality, Effectiveness and Safety at the Michael E. DeBakey VAMC, chief of the Gastroenterology and Hepatology Section at the Baylor College of Medicine, both in Houston, and editor-in-chief of *Clinical Gastroenterology and Hepatology*.

FY Year	Number Dx with HCC
2000	1,361
2005	4,989
2010	9,017
2015	11,250
2017	10,679
2018	9,905

Source: VSSC Advanced Liver Disease Data Cube

"As a clinician who cares for these patients, though, we know that finding liver cancer early on will prolong life" Kanwal said. "And, it's hard to randomize screening; patients want it."

VA researchers have developed a number of new models for determining who would benefit most from ongoing surveillance. "The models revolve on cirrhosis or no cirrhosis. If no cirrhosis, does the patient have other risks? Alcohol use could be a factor," Kanwal noted.

Particularly for patients for whom ongoing monitoring is clearly appropriate, "it's not enough to do surveillance," Ross added. "We have to move quickly, if we find something to evaluate. Not everything is liver cancer. In the majority of cases, if we find a lesion, we can make a decision without doing a biopsy."

That's possible because most cases of HCC now are diagnosed using radiology, Kanwal said. Imaging allows physicians and patients to avoid painful liver biopsies, which can cause dangerous bleeding and other complications.

In an effort to avoid delays in treatment and to standardize the technical aspects of diagnosis, imaging and management, the VA held a meeting of liver experts in March at the Miami VAMC. The goal is that "every VISN/VAMC uses the same optimized way to image and interpret liver lesions," Ross explained.

Once HCC is diagnosed, information about the liver lesion goes into the patient record and a registry that can be viewed across the VA.

Nationwide access to the information makes assessing risks and next steps easier. "We have tumor boards set up in a large number of VAMCs already, and we're on track to setting them up for every center," Ross noted.

The tumor boards gather multidisciplinary teams of experts to evaluate what's best for the particular patient. "Liver cancer can be cut out, or we could use radiation or chemotherapy. It all depends on the specifics," he said.

The VA's initiatives to better manage liver disease and HCC have already made a notable difference. They have reduced the time from diagnosis to treatment from three months to four weeks, Ross noted, "which makes a difference in whether patients live or die from this cancer. It's been an incredible success so far."

Rising Rates of Nonalcoholic Fatty Liver Disease Drive Up Hepatocellular Carcinoma Cases

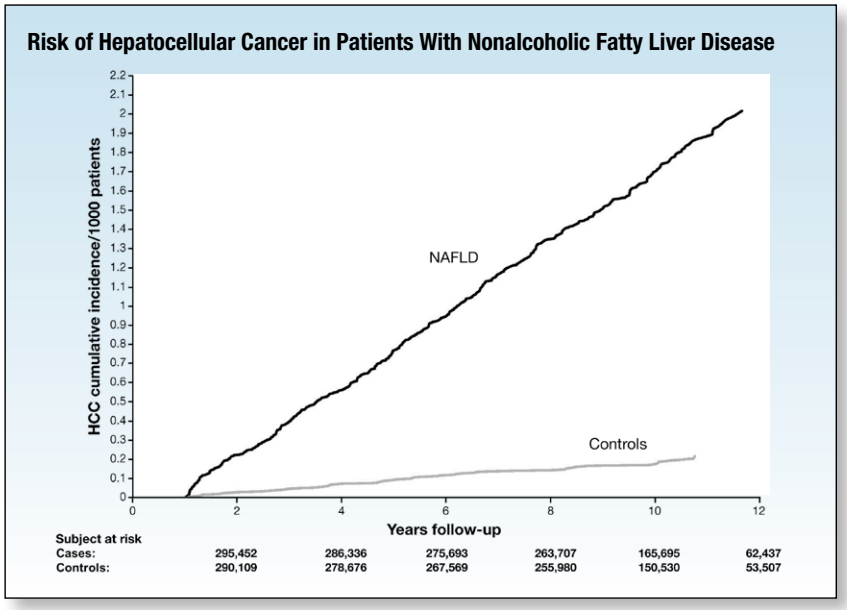
HOUSTON—A new epidemic appears poised to overtake hepatitis C as the leading cause of hepatocellular carcinoma.

"Nonalcoholic fatty liver disease is the next big thing in the epidemiology of liver cancer," said Fasiha Kanwal, MD, MSHS, an investigator in the Clinical Epidemiology & Comparative Effectiveness Program at the Center for Innovations in Quality, Effectiveness and Safety at the Michael E. DeBakey VAMC in Houston.

Nonalcoholic fatty liver disease is a subtype of liver steatosis, which is characterized by fat that accounts for more than 5% of the liver mass. When steatosis occurs without evidence of excessive alcohol consumption, specific hereditary disorders or medications known to increase fat buildup in the liver, it is classified as NAFLD.

NAFLD appears closely connected to metabolic syndrome, affecting up to 75% of patients with diabetes, 80%-90% of obese patients and 90% of individuals with hyperlipidemia. NAFLD develops asymptomatically in many patients, and 80% of patients with NAFLD have normal alanine transaminase values, the most common liver function test.

Just how many Americans have nonalcoholic fatty liver disease remains a matter of some debate. According to the American Liver Foundation, nearly one-third of adults and 10% of children have NAFLD, about twice the rate seen in 2000.



Source: Gastroenterology 2018 155, 1828-1837.e2DOI: (10.1053/j.gastro.2018.08.024)

Research conducted at the Brooke Army Medical Center at Fort Sam Houston in Texas, however, suggests that nearly half of all adults in the United States actually might have it.[1]

The Army study enrolled 400 adult outpatients, and ultrasound examination found that 46% had NAFLD. Nearly three-quarters of diabetic patients had NAFLD, and almost a quarter of them had progressed to nonalcoholic steatohepatitis, in which the liver becomes inflamed.

Even the high rate of NAFLD seen in this study could represent an underestimation. Recent guidelines note that "steatosis at 30% is the accepted lower limit where steatosis can be detected reliably by ultrasound (currently the most commonly used diagnostic test for fatty liver)."[2]

Researchers agreed, though, that NAFLD has become the most common chronic liver disease in the world and that its increasing prevalence will contribute to rising rates of hepatocellular carcinoma.

"While patients with nonalcoholic fatty liver disease have a smaller risk of HCC than patients with hepatitis C, it affects so many more people," Kanwal told *U.S. Medicine*.

The rising rates will hit the VA especially hard. The VA's success in treating hepatitis C means VA "will be seeing HCV less and less, while fatty liver disease will be more and more of a problem," predicted David Ross, MD, PhD, MBI, national director of the VA's HIV, Hepatitis, and Related Conditions Programs and associate clinical professor of Medicine at the George Washington University School of Medicine and Health Sciences in Washington, DC.

Eightfold Risk

Research by Kanwal and her colleagues at the VA and Baylor found that veterans with biochemically apparent NAFLD had almost eight times the risk of developing HCC as veterans who did not have fatty liver.[3]

Their retrospective study compared the risk of HCC in 296,707 veterans diagnosed with NAFLD at 130 VA facilities between Jan. 1, 2004, and Dec. 31, 2008, to a sex- and age-matched cohort of 296,707 veterans without NAFLD. Only 0.4% of NAFLD patients had a diagnosis of cirrhosis at the start of the study, and just 1.4% were diagnosed with cirrhosis during the study.

As of Dec. 31, 2015, 545 patients developed HCC, 490 in the NAFLD group and 55 in the control group. On an unadjusted basis, "patients with NAFLD had an 8.6-fold higher risk of HCC than controls," which persisted on multivariable analysis, according to the study led by Kanwal, who is also chief of the Gastroenterology and Hepatology Section at the Baylor College of Medicine in Houston, and editor-in-chief of *Clinical Gastroenterology and Hepatology*.

In addition, the authors found some subgroups of NAFLD patients had significantly higher risk than others. The incidence of HCC was more than five times higher in men than women (0.22 vs. 0.04 per 1,000 person years) and more common in Hispanic veterans across all age groups than in non-Hispanic patients. Risk of HCC increased substantially after age 65.

Per 1,000 patient years, the annual incidence of HCC in NAFLD patients with cirrhosis was 10.63 compared to 0.08 for veterans with NAFLD but no cirrhosis and 0.02 for veterans without NAFLD. Hispanics with cirrhosis faced the greatest risk, with an annual incidence of 23.76 per 1,000 patient years. Twenty percent of the veterans who developed HCC, however, had no cirrhosis.

High levels of fibrosis as indicated by high FIB-4 scores were associated with a nearly 10-fold increase in HCC risk in the absence of a cirrhosis diagnosis. The researchers determined that the highest risk occurred in patients with high FIB-4 and cirrhosis (13.55 per 1,000 patient years).

Based on these findings, the researchers suggested that FIB-4 scores and presence of cirrhosis "can be easily applied in clinical practice to identify the at-risk groups for targeted evaluation and risk modification among the masses of individuals with NAFLD."

That might be a direction the VA pursues as it retools its advanced liver disease program to reflect the changing needs of patients, particularly in light of some evidence that NAFLD-related HCC is 20% more deadly than HCC of other etiologies.[4]

"NAFLD is coming of age, not just in the VA, but nationally," Ross told *U.S. Medicine*. We are expanding the scope of what we are doing in terms of advanced liver disease and focusing on how do we connect with veterans with risk of liver disease. We want to ensure we don't lose the gains seen against hepatocellular carcinoma by putting into place an integrated system not seen in other healthcare systems."

[1] Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, Landt CL, Harrison SA. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology.* 2011 Jan;140(1):124-31.

[2] National Guideline Centre (UK). Non-Alcoholic Fatty Liver Disease: Assessment and Management. London: National Institute for Health and Care Excellence (UK); 2016 Jul. (NICE Guideline, No. 49.) 6, Diagnosis of NAFLD.

[3] Kanwal F, Kramer JR, Mapakshi S, Natarajan Y, Chayanupatkul M, Richardson PA, Li L, Desiderio R, Thrift AP, Asch SM, Chu J, El-Serag HB. Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease. *Gastroenterology.* 2 Dec;155(6):1828-1837.e2.

[4] Zoler ML. VIDEO: NAFLD increasingly causing U.S. hepatocellular carcinomas. Diabets:HUB. MDedge. April 27, 2015.

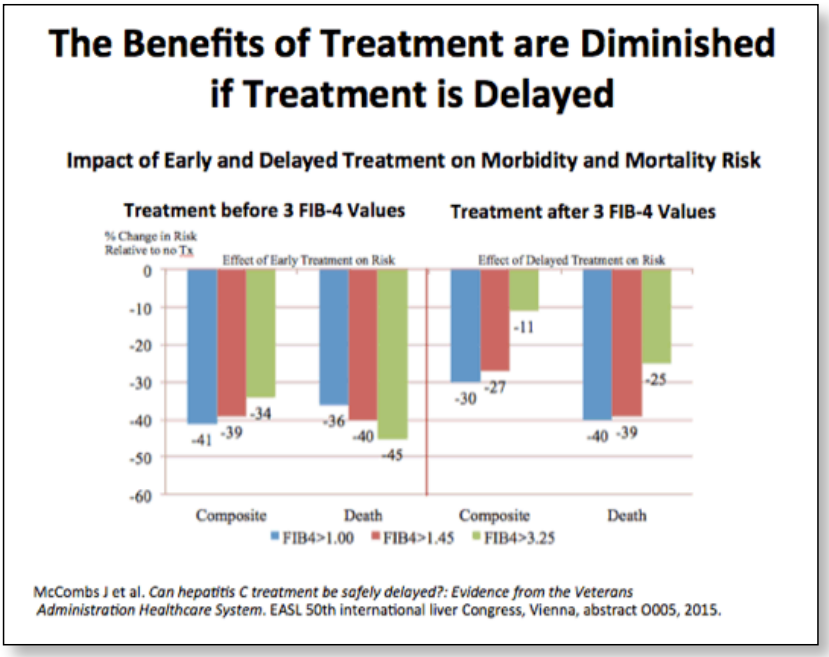
HCC Risk Remains for Some, Even After Hepatitis C Is Cured

HOUSTON—The VA has announced that it expects to eliminate hepatitis C in all veterans willing and able to receive treatment by May of this year.

Successful treatment for HCV also dramatically reduces the risk of hepatocellular carcinoma and other complications. The VA reported last month that "the overall death rate one year after treatment reduced to 80% among veterans in VA care with HCV. Veterans cured of HCV with [direct-acting antivirals] were also 84% less likely to develop liver cancer."

Direct-acting antivirals first came on the market in 2014, enabling all-oral treatment of HCV in eight to 12 weeks with few adverse effects and achieved sustained virological response or cure in 94% to 95% of patients. Those drugs represented a huge step forward compared to previous therapies, which required weekly injections of interferon, with its significant physical and psychiatric side effects, and had cure rates of 35%-55%, depending on the therapy and genotype of hepatitis C.

Starting in early 2014, the VA aggressively pursued the goal of eliminating HCV among all veterans in care, at one point starting treatment for a new patient an average of nearly every minute of every work day. So far, 116,000 veterans have been treated with direct-acting antivirals, and 96,654 have been cured. Fewer than 27,000 veterans who receive care through the VHA remain to be treated.



McCombs J et al. *Can hepatitis C treatment be safely delayed?: Evidence from the Veterans Administration Healthcare System.* EASL 50th international liver Congress, Vienna, abstract O005, 2015.

"This is an incredible public health success story," pointed out Fasiha Kanwal, MD, MSHS, an investigator in the Clinical Epidemiology & Comparative Effectiveness Program at the Center for Innovations in Quality, Effectiveness and Safety at the Michael E. DeBakey VAMC, chief of the Gastroenterology and Hepatology Section at the Baylor College of Medicine, both in Houston, and editor-in-chief of *Clinical Gastroenterology and Hepatology.*

"Within the VA, we have documented that the risk of hepatocellular carcinoma was increasing 10-fold among patients with HCV until very recently. Direct-acting antivirals are very, very effective and safe and have had a huge impact on HCC as well as HCV," Kanwal told *U.S. Medicine*.

Risk Reduction

"Patients who achieve a sustained virological response with direct-acting antivirals have a 60% to 75% reduction in HCC risk," Kanwal said. "Every study has found a similar, remarkable reduction in risk of HCC. That's a major difference in a disease in

which nearly everyone who has it dies."

That reduction in risk should not lead to complacency, however. "Treatment reduces risk, but it doesn't drop to zero," Kanwal noted. Two groups continue to have a significantly elevated risk of HCC even after treatment.

"In patients who had already developed advanced fibrosis or cirrhosis before eradicating chronic hepatitis C, a residual risk of these complications unfortunately persists even after viral eradication. This is particularly true of the risk of hepatocellular carcinoma," explained Akbar K. Waljee, MD, director of the Inflammatory Bowel Disease Program at the VA Ann Arbor Healthcare System, associate director of the Michigan Integrated Center for Health Analytics and Medical Prediction and associate professor in internal medicine at the University of Michigan.

Between 30% and 40% of veterans treated for HCV had cirrhosis at the time of treatment. "Risk remains high in this group," said Kanwal, "and clinicians should consider liver cancer surveillance."

A VA study quantified just how much higher the risk for this group is. Led by George Ioannou, MD, MS, of the VA Puget Sound Healthcare System and professor of gastroenterology at the University of Washington in Seattle, the study found that patients who had cirrhosis prior to successful treatment had an HCC incidence rate eight times that of patients who did not have cirrhosis, 1.97 per 100 patient-years vs. 0.24 per 100 patient-years.[1]

FY Year	Number treated and estimated % cured
2014*	37,000 (cure rate not available**)
2015	30,936 (94%)
2016	38,358 (94%)
2017	28,473 (95%)
2018	17,350 (95%)

* January 2014-Oct 2015
** Cure rates were not able to be determined for FY2019, because cure rates can only be determined for veterans meeting the following criteria; 1) A minimum of *12 weeks* must have passed since the veteran stopped HCV treatment and 2) The veteran must have had an HCV viral load test drawn at least 12 weeks after treatment stopped. Thus, cure data is collected cumulatively as veterans complete their treatment course and are scheduled to return to VA for follow-up lab testing as part of their routine care.

Source: VA

In keeping with these findings, American Association for the Study of Liver Disease guidelines note that "the risk of HCC for patients with HCV-related cirrhosis who develop SVR after DAA treatment is lowered, but not eliminated, and therefore patients with cirrhosis and treated HCV should continue to undergo surveillance."

Patients who do not achieve sustained virological response following treatment for HCV constitute the second group that continues to have a higher risk of HCC. A VA study led by Kanwal determined that achieving SVR reduced the risk of HCC by 68% in patients with cirrhosis and 82% in those without cirrhosis compared to patients who did not achieve SVR.[2]

Achieving SVR

Ongoing surveillance is only recommended for patients who fail to achieve SVR and also have cirrhosis.

"The beneficial effect comes from attaining SVR," Kanwal reiterated. But patients who previously failed treatment with an interferon-based therapy or one of the direct-acting antivirals do necessarily have to resign themselves to a higher risk forever.

"More than 95% now achieve cure within one round, but patients can repeat treatment if the first course fails," she said.

The opportunity to receive treatment before developing complications, let alone twice, distinguishes HCV care at the VA.

"We should try to treat patients before they progress to cirrhosis," Kanwal said. "That's not an issue in the VA, but outside of the VA, treatment is often restricted to those who have cirrhosis. That misses the point; those patients remain at risk for HCC. You don't have to worry about HCC progression if you treat HCV early."

[1] Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. *J Hepatol.* 2017 Sep 5. pii: S0168-8278(17)32273-0.

[2] Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents. *Gastroenterology.* 2017 Oct;153(4):996-1005.e1.

Federal Medicine Clinicians Now Have Many More Treatment Options for HCC

RICHMOND, VA—For more than a decade after the U.S. Food and Drug Administration approved sorafenib for hepatocellular cancer, treatment options for the aggressive malignancy remained static. That changed dramatically in the last 24 months as five drugs received approval for HCC—nivolumab, regorafenib, pembrolizumab, lenvatinib and cabozantinib.

Effective treatment of HCC is often stymied by late diagnosis, advanced disease and other complications. The VA estimates that fewer than "50% of patients with HCC undergo definitive treatment because of age, liver function, general medical condition, and patient refusal."

Transplantation is widely recognized as the treatment most likely to offer a cure for HCC, but relatively few patients meet the Milan guidelines for suitable candidates. A chronic shortage of livers further restricts the number of patients who can benefit from transplantation. Resection may also be curative, though the VA viral hepatitis and liver disease website notes that "less than 20% of HCC patients are good candidates for surgical resection."

For example, patients who aren't candidates for surgery have localized treatment options, including transcatheter arterial chemoembolization, radiofrequency ablation, brachytherapy, percutaneous injection of ethanol or ascetic acid, and hepatic artery chemotherapy.

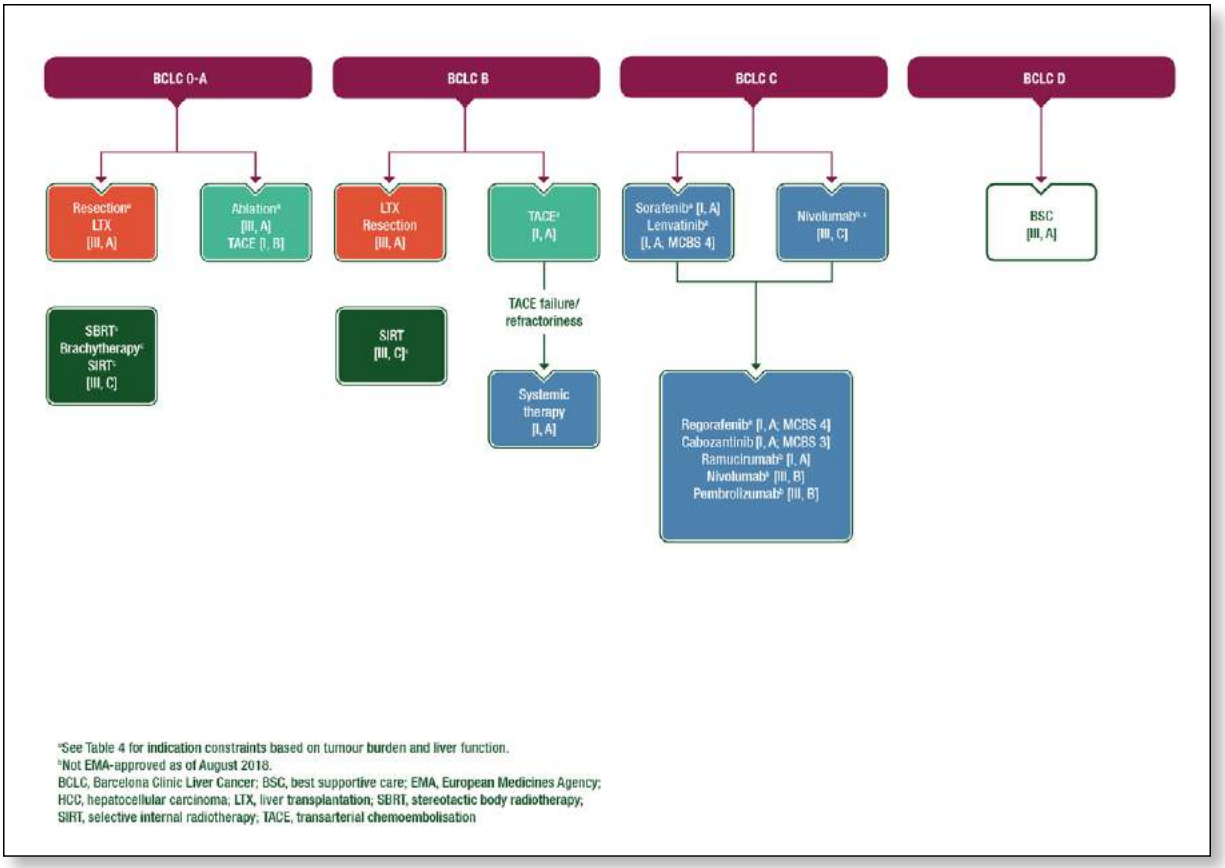
More Options

For patients with large or multiple tumors or metastases, however, the options have been quite limited. Until recently, sorafenib, which gained FDA approval for advanced HCC in 2007, has been the only systemic chemotherapy shown to extend survival for patients with unresectable HCC. The SHARP clinical trial showed sorafenib, an oral multikinase inhibitor, extended overall survival from 7.9 months to 10.7 months compared to no treatment, a 31% improvement.[1]

Last August, lenvatinib received FDA approval for first-line use in unresectable HCC. Another multikinase inhibitor, lenvatinib showed noninferiority to sorafenib in the multicenter, global phase 3 REFLECT trial, which enrolled 1,492 treatment-naïve patients. In that study, median overall survival was 13.6 months with lenvatinib vs. 12.3 months with sorafenib, indicating an 8% reduction in mortality risk for lenvatinib. Lenvatinib also significantly extended median progression-free survival to 7.4 months from 3.7 months, a 34% improvement. More patients responded to lenvatinib compared to sorafenib as well, 24.1% versus 9.2%.[2]

"Sorafenib has a higher incidence of hand-foot syndrome (which is the

The VA estimates that fewer than "50% of patients with HCC undergo definitive treatment because of age, liver function, general medical condition, and patient refusal."



Source: Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Vogel A, Cervantes A, Chau I et al. Ann Oncol 2018; 29 (Suppl 4): iv238–iv255.

most disabling side effect to treat) while lenvatinib has more hypertension, proteinuria and hypothyroidism. I personally find the latter easier to manage," said Binu John, MD, MPH, associate professor of Medicine, Virginia Commonwealth University, and director of liver transplantation and the liver cancer program at Hunter Holmes McGuire VAMC, Richmond, VA.

In choosing between the two, "some could argue that, if patients progress on sorafenib, they have multiple options, since all trials on regorafenib, cabozantinib and anti-PD1 [agents] were done in patients who progressed post-sorafenib or were intolerant. There is no such data with lenvatinib, since it just got approved," John told *U.S. Medicine*.

The other drugs received approval for use in the second- or subsequent lines, which raises new questions about appropriate sequencing. "Regorafenib, nivolumab and cabozantinib are all options," John said. "I think the enthusiasm for pembrolizumab may be diminished after the early release of the Phase 3 study, which was negative, although we have not seen it in print."

Pembrolizumab received FDA approval in November 2018, but in February, its manufacturer reported that the KEYNOTE-240 trial failed to significantly extend survival compared to best supportive care plus placebo in previously treated patients with advanced HCC.

Regorafenib gained second-line approval in April 2017 based on the RESORCE trial, which enrolled 573 patients. That trial showed that regorafenib improved median progression free survival to 3.1 months from 1.5 months for placebo and

overall survival to 10.6 months from 7.8 months. Grade 3 or 4 treatment-related adverse events that occurred at much higher rates in the regorafenib group than among the placebo group included hypertension (15% vs. 5%) and hand-foot skin reaction (13% vs. 1%).[3]

The data on regorafenib "is impressive, but it is a drug that is difficult to manage," John noted.

Nivolumab received accelerated approval in late 2017 for use after progression on or intolerance of sorafenib. The Phase 1/2 CheckMate-040 trial with 154 patients found that 14.3% of patients responded to nivolumab, and duration of response ranged from 3.2 months to more than 38.2 months. Among responders, 91% continued to respond for more than six months, and 55% responded for at least 12 months.[4]

An ongoing head-to-head trial has stimulated interest in nivolumab. "We are awaiting the Phase 3 Checkmate-459 data comparing sorafenib and nivolumab," John said. "If that is a positive study, nivolumab will become first line."

Most recently, cabozantinib emerged as a second-line treatment option following soratenib. Approved in January 2019, cabozantinib is another multiple tyrosine kinase inhibitor. The Phase 3 CELESTIAL trial with 707 patients was stopped early, based on strong interim results. Cabozantinib demonstrated a 24% reduction in mortality risk and a median improvement in overall survival from 8.0 months to 10.2 months compared with placebo.[5]

> ***"Regorafenib, nivolumab and cabozantinib are all options. I think the enthusiasm for pembrolizumab may be diminished after the early release of the Phase 3 study, which was negative, although we have not seen it in print."***
>
> — Binu John, MD, MPH

When combined with the improvement in median progression survival, 5.2 months vs. 1.9 months, cabozantinib demonstrated a 56% reduction in the risk of disease progression or death. Nearly two-thirds of patients in the cabozantinib group had either partial response or stable disease compared to one-third of patients receiving placebo.

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[2] Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G,Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet.* 2018 Mar 24;391(10126):1163-1173.

[3] Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt G, Han G; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2017 Jan 7;389(10064):56-66.

[4] El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017 Jun 24;389(10088):2492-2502.

[5] Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, Cicin I, Merle P, Chen Y, Park JW, Blanc JF, Bolondi L, Klümpen HJ, Chan SL, Zagonel V, Pressiani T, Ryu MH, Venook AP, Hessel C, Borgman-Hagey AE, Schwab G, Kelley RK. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *N Engl J Med.* 2018 Jul 5;379(1):54-63.

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