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Hepatic Oncology

The efficacy and effectiveness of hepatocellular carcinoma surveillance in patients with cirrhosis

Amit G Singal^{*1}

“A lack of randomized data supporting hepatocellular carcinoma surveillance in patients with cirrhosis does not equate to a lack of efficacy.”

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related death worldwide [1]. Patients with cirrhosis are at the highest risk for developing HCC, with an annual risk of 2–6%, and HCC is one of the leading causes of death in these patients. Prognosis for HCC is dependent on tumor stage at diagnosis, with curative options only available for early stage HCC. Transplantation and liver resection yield 5-year survival rates approaching 70% in patients with early-stage tumors, whereas those diagnosed at advanced stages only have palliative treatment options, with a median survival of less than 1 year [2].

Several societies, including the American Association for the Study of Liver Diseases, National Comprehensive Cancer Network and Veterans Affairs (VA) recommended HCC surveillance in patients with cirrhosis to improve early tumor detection and overall survival [2]. However, other societies, such as the United States Preventive Services Task Force (USPSTF), believe current data are insufficient to provide a recommendation for HCC surveillance

in patients with cirrhosis. These disparate society recommendations have spurred questions regarding the benefits of HCC surveillance in patients with cirrhosis. In this commentary, we will discuss the efficacy and effectiveness of HCC surveillance to improve early tumor detection and overall survival in patients with cirrhosis.

Is HCC surveillance efficacious?

Overall, HCC surveillance fulfills all criteria established by the World Health Organization (WHO) for a surveillance program. HCC disease burden is an important health problem, there is an identifiable target population, surveillance is accepted by patients and providers, surveillance achieves an acceptable level of accuracy, there are standardized recall procedures, surveillance is affordable, there is an advantage of treating occult HCC and surveillance reduces mortality [3].

Abdominal ultrasound, the backbone of HCC surveillance testing, is safe and efficacious for early tumor detection. Ultrasound is cheap, widely available, noninvasive and poses no risk of radiation

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¹Dedman Scholar of Clinical Care, Division of Digestive & Liver Diseases, UT Southwestern Medical Center, 5959 Harry Hines Blvd, POB1 Suite 420, Dallas TX 75390-8887 USA.

^{*}Author for correspondence: Tel.: +1 214 645 6029; Fax: +1 214 645 6294; amit.singal@utsouthwestern.edu

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or contrast exposure. Its sensitivity for early-stage tumors ranges from 29 to 100%, with a meta-analysis demonstrating a pooled sensitivity of 63% (95% CI: 49–76%) in patients with cirrhosis [4]. Using α -fetoprotein in combination with ultrasound raised sensitivity for early HCC to 69% (95% CI: 53–81%), although this difference was not statistically significant.

The best evidence for HCC surveillance improving survival comes from a large randomized controlled trial (RCT) among patients with chronic hepatitis B infection [5]. In this study with over 19,000 HBV carriers randomized to surveillance ($n = 9757$) or no surveillance ($n = 9443$), patients in the surveillance arm had a significantly higher proportion of HCC detected at an early stage (61 vs 0%, $p < 0.001$). Surveillance resulted in a higher rate of curative therapy (47 vs 8%, $p < 0.001$) and significantly lower mortality rate (83.2 vs 131.5 per 100,000, $p < 0.001$). These data cannot be directly extrapolated to patients with cirrhosis for several reasons including a lower sensitivity of surveillance tools in a cirrhotic nodular liver, less availability of curative treatments, and higher competing risk of non-HCC mortality. However, a lack of randomized data supporting HCC surveillance in patients with cirrhosis does not equate to a lack of efficacy. Colonoscopy is widely accepted for colorectal cancer screening without randomized data, based on level II evidence and extrapolation of fecal occult blood test data [6]. We must consider that the same case may be true for HCC surveillance. In fact, several prior cohort studies have demonstrated patients with cirrhosis detected by surveillance have higher rates of early tumor detection, curative treatment and better overall survival than those who had not undergone surveillance [7]. The survival benefit associated with HCC surveillance remains significant in the subset of studies that adjust for lead-time bias.

Of course, these studies have limitations including length-time bias, lead-time bias and potential selection bias. The best, if not only, way to address these concerns would be to perform an RCT among patients with cirrhosis; however, this may prove to be difficult. An RCT in Australia among patients with cirrhosis was terminated given poor enrollment, as patients refused potential randomization to an arm without HCC surveillance after informed consent [8]. Similarly, many healthcare providers may refuse to support an RCT given ethical concerns of

withholding surveillance from some patients. Even short of these data, current data suggest HCC surveillance is efficacious for improving early tumor detection and overall survival in patients with cirrhosis.

Is HCC surveillance effective?

Whereas efficacy defines the performance of HCC surveillance under ideal and controlled circumstances, effectiveness represents its performance under ‘real-world’ conditions. Several steps must occur for an efficacious intervention to be effective in clinical practice; therefore, an efficacy trial can overestimate an intervention’s effect when implemented in clinical practice. For example, a gap between the efficacy and effectiveness for HCC surveillance may exist due to lack of provider recommendation, poor access to surveillance tests, poor patient adherence, differences in patient characteristics and/or differences in test performance [9].

Surveillance utilization and the effectiveness of surveillance tests are two important factors influencing the effectiveness of HCC surveillance in clinical practice. A recent modeling study found surveillance utilization and sensitivity rates must exceed 34 and 42%, respectively, for HCC surveillance to be associated with a survival benefit [10]. Currently, HCC surveillance is performed in less than 20% of patients with cirrhosis in the United States, with lower rates among patients followed by primary care providers than those seen by gastroenterologists [11]. Underuse of HCC surveillance is associated with higher rates of advanced tumor presentation, when treatment options are limited and survival significantly worse [12]. Equally problematic is the variable effectiveness of surveillance tests, given the operator-dependent nature of ultrasound. Although ultrasound is efficacious for early tumor detection, its effectiveness is substantially lower with a sensitivity of 32% for early HCC [13]. In fact, inadequate sensitivity of surveillance tools is one of the most common reasons for late stage tumor detection among patients followed in tertiary care centers [14].

There is a clear and urgent need for interventions to address these shortcomings. Prior data suggest these interventions should be aimed at the provider or system level. Patients report high levels of acceptance and willingness to participate in HCC surveillance [15]. In contrast, providers report several barriers to effective HCC surveillance, including difficulty identifying at-risk

patients with cirrhosis, suboptimal levels of knowledge about HCC surveillance guidelines, and time constraints given competing clinical concerns [16,17]. A recent quasi-study evaluating a clinical reminder for HCC surveillance within the VA health system demonstrated increased surveillance rates from 18.2 to 27.6%; however, this rate still falls below the minimum cut-off at which HCC surveillance becomes beneficial [18]. Further in-reach and outreach interventions, such as those used in colorectal cancer screening, may serve to further improve HCC surveillance rates in the future [19]. Similarly, there is hope that HCC biomarkers can increase early tumor detection rates in clinical practice. For example, one prior study suggested using α -fetoprotein in combination with surveillance ultrasound increased sensitivity for early HCC in clinical practice (32 vs 63%, $p < 0.001$) [13]. The Early Detection Research Network (EDRN) is an ongoing multicenter study evaluating novel HCC biomarkers, which may further increase the sensitivity of HCC surveillance tools in the future [20].

Conclusion

Even in the absence of level I data, there are strong and consistent data suggesting HCC surveillance is efficacious for early tumor detection and improving survival in patients with cirrhosis. However, the effectiveness of HCC surveillance in clinical practice is currently limited given low utilization rates and suboptimal sensitivity of current tests for early tumor detection. Interventions are needed to optimize effectiveness and provide the maximum benefits of HCC surveillance to patients in clinical practice.

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