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Compliance With Hepatocellular Carcinoma Surveillance Guidelines Associated With Increased Lead-Time Adjusted Survival of Patients With Compensated Viral Cirrhosis

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BACKGROUND & AIMS: Semi-annual surveillance for hepatocellular carcinoma (HCC) is recommended for patients with cirrhosis. We aimed to determine how compliance with HCC surveillance guidelines affects survival times of patients with hepatitis C virus– or hepatitis B virus–associated compensated cirrhosis who developed HCC. **METHODS:** We collected data from the prospective ANRS CO12 CirVir study, from March 2006 through June 2012, on 1671 patients with biopsy-proven

viral cirrhosis and no previous liver complications who were undergoing surveillance for HCC at 35 centers in France. Only 216 patients who developed HCC during follow-up were included in the analysis. Patients were considered to be compliant with surveillance guidelines if the time between their last surveillance image evaluation and diagnosis of HCC were fewer than 7 months and noncompliant if this time was 7 months or longer. **RESULTS:** HCC was detected in 216 patients, at a median follow-up time of 59.7 months. Of these patients, 140 (80.5%) were Barcelona Clinic Liver Cancer stage 0/A, 135 (69.9%) received first-line curative treatment (15 underwent transplantation, 29 underwent resection, 89 received percutaneous ablation, and 2 received resection and percutaneous ablation), and 129 (60.0%) were compliant with surveillance guidelines. Seventy-nine of the patients with HCC died; 49 deaths were associated with tumor progression. After lead-time adjustment, overall survival (OS) time was longer in patients compliant with surveillance guidelines (median OS time, 53.2 months) than noncompliant patients (median OS time, 25.4 months) ($P = .0107$); this difference remained significant even when we changed lead time assumptions. In multivariate analysis adjusted for a propensity score, compliance with HCC surveillance guidelines was associated with low tumor burden, allocation of curative treatment, and increased OS time compared with noncompliance (hazard ratio for OS, 2.19; 95% confidence interval, 1.16–4.14; $P = .0150$). **CONCLUSIONS:** In an analysis of data from the ANRS CO12 CirVir cohort, we associated compliance with HCC surveillance guidelines (fewer than 7 months between image evaluations) with early diagnosis, allocation of curative treatment, and longer adjusted OS of patients with hepatitis C virus– or hepatitis B virus–associated compensated cirrhosis and a diagnosis of HCC.

Keywords: Liver Cancer; Screening; Early Detection; Curative Treatment.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

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Monitoring for hepatocellular carcinoma (HCC) in patients with cirrhosis, based on bi-annual ultrasound examination, is recommended by international guidelines.[1–3] Surveillance aims to detect tumors at an early stage when they are amenable to curative therapy so as to improve survival, which should be the endpoint of all screening policies.[4] However, the evidence of a survival benefit associated with implementing HCC surveillance remains controversial. The only randomized controlled trial supporting HCC surveillance using abdominal ultrasound every 6 months derived from a large trial on Chinese patients with chronic hepatitis B virus (HBV) infection, but numerous limitations and biases affecting this work were acknowledged.[5]

Numerous observational studies have compared survival in patients with HCC detected during surveillance vs those with HCC diagnosed incidentally. Kansagara et al[6] performed a systematic review that focused on the impact of HCC screening in chronic liver disease, and reported only weak evidence regarding the impact of HCC screening on mortality. While it is accepted that surveillance enables the identification of early-stage HCC, the degree to which systematic screening might be translated into survival benefits over clinical diagnosis remains uncertain. Additional retrospective studies, including an analysis of lead-time bias, have concluded that surveillance for HCC was an independent predictor of survival.[7–9] However, the retrospective design of these studies limited the strength of the evidence. A well-designed randomized controlled trial, either comparing surveillance vs no surveillance or 6-month vs 12-month timeframes would be ideal to settle the controversy, but the implementation of such a trial might be impractical or unethical. In addition, the evaluation of periodical screening with 6-month schedule based on the idea of time since last negative imaging finding before the diagnosis of HCC has not been fully quantified.

The aim of this work was therefore to assess the impact of compliance with HCC surveillance guidelines on tumor burden at diagnosis, allocation of curative treatment, and lead-time adjusted survival in patients with compensated viral cirrhosis included in the large, prospective, multicenter ANRS CO12 CirVir cohort in France,[10–13] using a propensity score analysis to account for potential influential factors at the time of last normal imaging.

Methods

The study has been sponsored and funded by the ANRS (France Recherche Nord & sud Sida-HIV Hépatites). The protocol was approved by an Ethics Committee (Comité de Protection des Personnes, Aulnay-sous-Bois, France) and complied

Abbreviations used in this paper: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IPCW, inverse probability of censoring weighted; IQR, interquartile range; US, ultrasound.

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