Cost Effectiveness of Alternative Surveillance Strategies for Hepatocellular Carcinoma in Patients With Cirrhosis

KARIN L. ANDERSSON,* JOSHUA A. SALOMON,‡ SUE J. GOLDIE,‡ and RAYMOND T. CHUNG*

*Gastrointestinal Unit, §Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; and the ‡Program in Health Decision Science, Harvard School of Public Health, Boston, Massachusetts

Background & Aims: **The increasing incidence of hepatocellular carcinoma (HCC) in the United States has significant health and economic consequences. Ultrasound (US) surveillance is recommended for patients with cirrhosis because of their high risk of HCC and improving treatment outcomes for small tumors. We assessed the costs, clinical benefits, and cost effectiveness of US surveillance and alternative strategies for HCC in cirrhosis using a computer-based state transition model with parameters derived from available literature.** ***Methods:*** **Our model compared a policy of no surveillance with 6 surveillance strategies in cirrhotic patients ages 50 years and older in the United States: (1) annual US, (2) semiannual US, (3) semiannual US with α-fetoprotein, (4) annual computed tomography (CT), (5) semiannual CT, and (6) annual magnetic resonance imaging. The number of screening tests needed to detect one small HCC, cost per treated HCC, lifetime costs, quality-adjusted life expectancy, and incremental cost-effectiveness ratios were calculated.** ***Results:*** **Semiannual US surveillance for HCC in cirrhosis increased quality-adjusted life expectancy by 8.6 months on average, but extended it nearly 3.5 years in patients with small treated tumors. Semiannual US surveillance had an incremental cost-effectiveness ratio of $30,700 per quality-adjusted life year (QALY) gained, and was more cost effective than the alternative surveillance strategies using a threshold of $50,000 per QALY gained. The incremental cost-effectiveness ratios for the combined α-fetoprotein/US and annual CT strategies exceeded $50,000/QALY unless the sensitivity and specificity of US decreased to less than 65% and 60%, respectively.** ***Conclusions:*** **Semiannual US surveillance for HCC in cirrhotic patients improves clinical outcomes at a reasonable cost.**

The incidence of hepatocellular carcinoma (HCC) in the United States has doubled over the past 2 decades, resulting in an estimated 1 billion dollars in direct and indirect health care costs.[1,2] Because the prognosis of advanced HCC is poor, surveillance for the detection of small tumors in high-risk populations has become common practice. The majority of gastroenterologists use semiannual ultrasound and the serum tumor marker α-fetoprotein (AFP) to detect HCC in cirrhotic patients,[3] of whom 2% to 8% develop the tumor annually.[4,5] Studies suggest that surveillance detects tumors at earlier stages and improves survival.[6,7] Recent guidelines from the American Association for the Study of Liver Diseases advocate annual or semiannual surveillance with ultrasonography (US) in cirrhosis.[8] Because its sensitivity and specificity are limited, the use of AFP is recommended only when ultrasound is unavailable.

The cost effectiveness of HCC surveillance with US alone in a general population of cirrhotic patients has not been evaluated in the United States. Surveillance with AFP and US, or with computed tomography (CT), has been shown to be cost effective in select populations such as liver transplant candidates and hepatitis C cirrhotic patients.[9–14] With improvements in treatment options for small tumors and the diagnostic accuracy of radiologic imaging, routine surveillance for HCC in cirrhosis is more likely to provide benefit.

In recent years, local ablative therapies such as radiofrequency ablation have permitted patients with advanced liver disease or comorbidities that preclude resection or transplantation to be treated successfully.[15] Liver transplantation is not only a viable treatment for HCC, but changes to the Model for End-Stage Liver Disease scoring system now give patients with small tumors priority in the transplant process. For patients meeting the Milan criteria, those with a single HCC less than 5 cm or no more than 3 tumors each smaller than 3 cm, long-term survival posttransplant approaches that observed for non-malignant indications.[16] As survival improves, the consequences of missing small HCC grow.

The range of available screening modalities for HCC also has expanded. Although US is recommended for surveillance, CT is used increasingly frequently for surveillance by clinicians.[3] CT or magnetic resonance imaging (MRI) may be more sensitive in detecting small HCC.[17,18] The relative performance and costs of these tests in surveillance program has not been evaluated formally.

With the imminent peak in hepatitis C cirrhosis and the increasing incidence of nonalcoholic fatty liver disease, the burden of HCC is expected to grow. In light of potentially more effective, yet expensive, diagnostic tests and treatments, we used the best available data to estimate the benefits, costs, and cost effectiveness of US alone compared with alternative surveillance strategies for HCC in cirrhosis.

Abbreviations used in this paper: AFP, α-fetoprotein; CT, computed tomography; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life year; US, ultrasound.

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Methods

Analytic Overview

We developed a computer-based Markov model (TreeAge Pro software 2005; TreeAge Software, Inc, Williamstown, MA) to simulate surveillance, diagnosis, and treatment of HCC in a cohort of patients with compensated cirrhosis. In comparison with no surveillance, we assessed: (1) annual US, (2) semiannual US, (3) semiannual US with AFP, (4) annual CT, (5) semiannual CT, and (6) annual MRI surveillance. Model outcomes included the number of screening tests needed to diagnose one small HCC, cost per treated HCC, lifetime costs, quality-adjusted life expectancy, and incremental cost-effectiveness ratios (2004 US$ per quality-adjusted life year [QALY] gained). We adopted a health system perspective and followed the recommendations of the Panel on Cost-Effectiveness in Health and Medicine. One-way and 2-way sensitivity analyses were performed to identify individual parameters with the greatest influence on our results.

Model

A cohort of 50-year-old individuals representative of patients with cirrhosis in the United States enter the model and move through a series of health states designed to reflect important stages in the natural history of cirrhosis, tumor progression, and treatment (Figure 1).

Surveillance Algorithms and Treatment

To estimate the effect of surveillance, the model distinguishes between detected and undetected HCC. Depending on the accuracy and timing of surveillance and the tumor growth rate, HCC might be detected early or remain undetected until an advanced stage. Patients with compensated cirrhosis in whom small HCC was detected (defined as tumors meeting Milan criteria) were eligible for liver transplantation, resection, or local ablative therapies; whereas decompensated cirrhotic patients were eligible for transplant or local ablation. Patients with advanced tumors received only palliative care.

A number of assumptions were made in the base case including the following: (1) a positive US was evaluated with a dynamic imaging study, either triple-phase CT or MRI, as recommended by the American Association for the Study of Liver Diseases guidelines; (2) serum AFP level was considered positive if greater than 20 ng/mL cut-off level, and was evaluated with dynamic imaging even when the corresponding US was negative; (3) suspicious lesions found on imaging underwent a biopsy; (4) no additional imaging was performed before a biopsy in the CT or MRI strategies; and (5) patients with false-positive test results returned to their previous surveillance test and schedule once a biopsy confirmed their true disease status.

Data

Table 1 summarizes selected model parameters used in the model. A base-case value and plausible range was established for each model input based on published literature and expert assumptions. When several estimates were available, we prioritized estimates from larger, well-controlled, prospective studies in Western populations.

Natural history of cirrhosis. Based on large epidemiologic studies, the average life expectancy of compensated cirrhosis is between 10 and 13 years.[19] Between 5% and 7% of compensated cirrhotic patients progress to decompensated disease each year, developing ascites, variceal bleeding, or encephalopathy. The median life expectancy of decompensated disease is 2 years.[19–21] Because 20% of the annual excess mortality from cirrhosis is attributable to HCC, we adjusted mortality rates accordingly to avoid double-counting HCC deaths.[19–21] With this adjustment, predicted life expectancy for compensated cirrhosis in the model approximated that reported in the literature.

Incidence and progression of hepatocellular carcinoma. The annual incidence of HCC is approximately 5%, with a range of 2% to 8% in cohort studies of cirrhotic patients undergoing surveillance.[4–6,22,23] The median survival for patients with small or advanced HCC is 2 years or 6 months, respectively.[24–26] Tumor growth was assumed to be linear, with a doubling time between 117 and 195 days.[25,27,28] Based on this doubling time, approximately 40% of tumors progress from a limited to an advanced stage each year.

Surveillance test characteristics. The sensitivity of US for HCC surveillance ranges from 40% to 81% and its specificity ranges from 80% to 100%.[29–33] The sensitivity of triple-phase CT is higher (85%–90%), but its specificity is similar (80%–96%).[17,29,30,33–36] Serum AFP is far less sensitive (40%–65%) and specific (63%–94%) at the 20 ng/mL cut-off level.[37,38] The sensitivity and specificity of MRI approach 90%.[33,39,40] Because

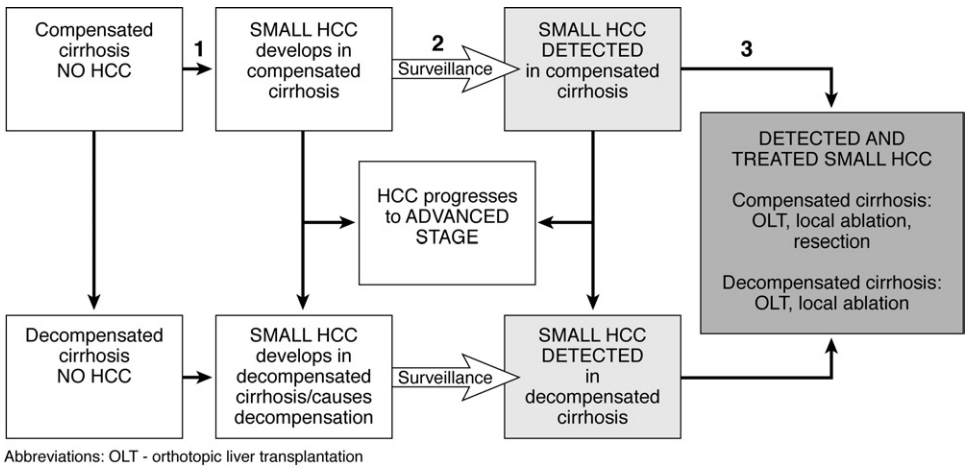

Figure 1. Simplified schematic of Markov health states. In each cycle, individuals may remain in the same health state, transition to the following state, or die from liver disease or unrelated causes. For example, transition 1 reflects cancer incidence; transition 2 is determined by the sensitivity of the surveillance modality; and transition 3 is the proportion of treatment-eligible tumors. Best available data were used to determine transitions. The grey boxes represent the possible benefit of surveillance: detection and treatment of small HCC.