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# Suboptimal Knowledge of and Surveillance for Hepatocellular Carcinoma by Primary Care Providers

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# **Abstract**

**Background & Aims**—A large proportion of patients with cirrhosis are seen only by their primary care provider (PCP). Surveillance for hepatocellular carcinoma (HCC) therefore depends on PCPs in these cases. We aimed to assess PCP knowledge and practice of HCC surveillance.

**Methods**—We contacted a random sample of 1000 North Carolina PCPs by mail. All received an introductory letter, followed by a 12-item questionnaire addressing HCC surveillance knowledge and practice.

**Results**—Three hundred ninety-one PCPs (39%) completed the survey; 89% saw patients with cirrhosis in their practice, but only 45% screened for HCC. Among PCPs who screened, the most common methods were ultrasound analysis and measurement of [α] fetoprotein (66%). Reasons for surveillance included supported by evidence (72%), recommended by medical societies (42%), and malpractice liability for not surveilling (26%). Of PCPs who did not screen, 84% referred to gastroenterologists for surveillance decisions, 24% were unaware of recommendations, 8% were uncertain of the benefits, and 8% were concerned over cost. Hepatic resection and liver transplantation were identified as effective therapies by 67% and 56% of PCPs, but all other effective therapies were identified by less than half (transarterial chemoembolization by 42%,

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MTL: acquisition of data

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radiofrequency ablation by 35%, sorafenib by 26%). Ability to identify at least 1 effective therapy was independently associated with surveillance (odds ratio, 2.1; 95% confidence interval, 1.1–4.0)

**Conclusions**—Most PCPs see patients with cirrhosis, but only a minority screen for HCC. PCP knowledge of effective HCC therapy options is suboptimal. Efforts to enlist PCPs in HCC surveillance may be best served by increasing their knowledge of effective therapies.

#### Keywords

therapy; screening; hepatitis C; hepatitis B; cirrhosis

# INTRODUCTION

Hepatocellular carcinoma surveillance is recommended by all three major hepatology societies.(1-3) Nevertheless, surveillance rates remain well below 50% and in some populations as low as 12%.(4-7) Among the many steps needed for surveillance to be accomplished, physician education and incorporation of surveillance into their practice are critical. As expected, hepatologists and gastroenterologists tend to believe in surveillance and are more likely to routinely order it for their cirrhotic patients (5, 7) but only 20-50% of such patients are seen by such subspecialists. (7, 8) Primary care providers (PCPs) see most of the remainder.

Therefore, if surveillance is to have any chance of reaching more than 50% of cirrhosis patients, enlistment of PCPs will be necessary. Only 3 studies have investigated the practice and knowledge of HCC surveillance amongst PCPs and these 3 focused primarily on PCPs who see a high number of Asian patients or on surveillance for viral hepatitis rather than HCC surveillance. (9-11) Therefore we sampled PCPs from the entire North Carolina Medical Board database and limited our questionnaire to HCC surveillance only.

# **METHODS**

#### Institutional Review of Research

Our research project and protocol were reviewed and approved by the University of North Carolina Institutional Review Board prior to initiating this study.

#### Subjects

We used the North Carolina Medical Board database to identify practicing primary care providers (physicians and doctors of osteopathy) in North Carolina. A random sample of 1000 PCPs was identified. This sample represented 14% of North Carolina PCP's (12),(13)

## Survey

Survey methodology is based on the tailored design method.(14) All subjects received an introductory letter, followed by the questionnaire in a separate mailing. The questionnaire consisted of 8-items addressing knowledge and use of HCC surveillance guidelines as well as identification of HCC therapies. Basic demographics and practice information requested was limited to gender, years in practice, major affiliations (e.g. academic facility, Veterans

Affairs, private practice) and their ability to see Medicaid covered patients. We purposely did not request more specific information that would lengthen the questionnaire, compromise anonymity and potentially lower the response rate. Therefore we did not collect information on practice location, type of service area (rural versus urban), training, or specific type of practice (i.e. group versus solo, family practice versus internal medicine) or personal perceptions of surveillance efficacy. Such limiting of variables did not allow us to construct a conceptual behavioral model for the decision to recommend surveillance. Instead, we focused on self-reported rate of surveillance, and the modality and interval recommended. We also asked about knowledge of HCC therapies because they have changed substantially in the last decade and remain a primary justification for surveillance. No pre-testing or validation of this brief survey were done. A \$10 cash incentive was included to reduce non-response bias and was given regardless of whether the PCP completed the questionnaire or not. A reminder/gratitude postcard was mailed to all subjects, followed by the mailing of a second questionnaire for non-responders. Addressed return envelope with pre-paid postage was included.

To ensure anonymity, all questionnaires were given an alphanumeric code. The master key linking code to subject name was used only at the mail out and receipt portion of the study to determine who should receive a second chance mailing. Data collection (receipt of questionnaires) was closed 90 days after the last mailing was completed. Thereafter the master key was destroyed and no further questionnaires were collected or mailed out.

# **Analysis**

Demographic, practice information, and survey responses were analyzed using basic descriptive statistics (e.g. means, medians, proportions, standard deviations). We used Pearson Chi-Square and T-test where appropriate to compare PCPs who screened and those that did not. Logistic regression was used to identify independent variables associated with surveillance.

#### **RESULTS**

#### Subjects (PCPs)

Of the 1000 PCPs to whom we mailed letters and questionnaires, 391 (39%) completed the questionnaire and mailed it back to us. Two PCPs answered questions in an incongruent or unclear manner and had to be discarded (one PCP indicated not seeing cirrhotic patients yet did surveillance; another did not answer whether they saw cirrhotic patients, but indicated they do not screen.) Characteristics of the remaining 389 PCPs is shown in Table 1. The vast majority was in private practice and saw Medicaid patients. Nearly 90% saw cirrhotic patients in their practices.

#### Hepatocellular carcinoma (HCC) surveillance

Of the 345 PCPs that saw cirrhotic patients, only 45% recommended HCC surveillance. There were no significant differences between those PCPs who do recommend surveillance (n = 156) from those who don't (n = 189) in terms of gender, years in practice, practice affiliation and whether they see Medicaid patients. The most common means of surveillance

used was liver ultrasound and alpha-fetoprotein measurement. (Figure 1) The most common interval for surveillance was 12 months. (Figure 2) Nearly three quarters of those who provide surveillance do so because they felt evidence supported it (Table 2). When asked to identify barriers to surveillance, 54% identified poor patient adherence and 53% identified patient financial constraints, 49% lack of insurance and 32% insurance constraints on coverage. Only 5% identified lack of available surveillance services (e.g. radiology) as a barrier.

Among those who do not recommend surveillance, the vast majority (84%) defer to subspecialists to decide or carry out surveillance (Table 3). However, 46 (24%) were unaware of any surveillance recommendations, while only 15 (8%) felt the benefit of surveillance was uncertain. Only 4% identified cost as a reason for not recommending surveillance.

#### Knowledge of HCC therapies and association with surveillance

Of the 345 PCPs who see cirrhosis patients, 230 (67%) identified resection as an effective therapy for HCC, but only 192 (56%) identified liver transplant. (Table 4) Other effective treatments were identified less frequently. PCPs who were able to identify at least one modality as an effective therapy were more likely to screen with an odds ratio of 1.9 (p = 0.04). On multivariate analysis (controlling for PCP gender, practice setting, years in practice and whether they see Medicaid patients), the association between identifying at least one effective therapy and recommending surveillance remained significant (OR 2.1, 95% confidence interval 1.1 - 4.0). None of the other variables were significantly associated with recommending surveillance.

#### DISCUSSION

While formally recommended by hepatology societies for nearly a decade, less than half (25-42%) of cirrhotic patients receive HCC surveillance according to several studies.(4-7) Such low rates may be because 20-50% of cirrhosis patients are not seen by gastroenterologists who tend to recommend surveillance more than PCPs.(7, 8) Even after being seen by a gastroenterologist, patients may see their PCP more frequently, especially in remote regions where the distance to a subspecialist is greater. If surveillance is to ever have a sustainable rate over 50%, enlistment of PCP help will probably be necessary. However, data regarding PCP knowledge and beliefs regarding HCC surveillance are limited.

Our study indicates that only 45% of primary care providers who see cirrhosis patients in North Carolina recommend surveillance. About 70% of PCPs who screen, do so because they feel evidence supports it. Forty-two percent understood that some medical associations recommend it. Of the majority that do not screen, 84% deferred to subspecialists to recommend or consider surveillance, and 24% were unaware of surveillance recommendations. Only resection and transplantation were correctly identified as effective therapies by more than half of all respondents (67% and 56% respectively). (Table 4) Only 35% identified RFA, even though data suggest it rivals resection in efficacy and is significantly less morbid. (15-17). Similarly, only a minority of PCPs identified TACE and sorafenib despite randomized controlled trials (RCT) showing survival benefit.(18, 19)

Those PCP's able to identify at least one effective treatment were twice as likely to recommend surveillance.

Of those who do surveillance, US and AFP, in combination, was most commonly used, and 12 months the most common interval. (Figures 1 & 2). These data may reflect older AASLD recommendations of 2005 in which AFP was mentioned as an alternative option, if US is suboptimal or unavailable, and the suggested interval was up to 12 months. In 2010, the AFP was completely dropped and the interval limited to 6 months.

Two studies reported higher rates of surveillance among PCPs (79-89%), but the PCPs in these studies were highly biased toward increased HCC awareness. Both studies targeted PCPs from communities with high proportions of Asians who have significantly higher prevalences of hepatitis B infection and consequent cirrhosis. Also, PCPs in these studies may recommend surveillance more often because supporting evidence is stronger (Level I, RCT data) for surveillance in hepatitis B related liver disease (20) than cirrhosis from other etiologies (Level II, observational, cohort data) (21). One study surveyed 11 San Francisco clinics with a patient population that is 25% Asian.(10) Moreover, 1 in 4 of the PCPs themselves were Asian and half had patient panels that were >25% Asian. The other study surveyed 3 Northern California counties, but again 1 in 4 of the PCPs were Asians, 43% spoke an Asian language and 30% of their catchment was Asian.(9) Such PCP groups will have an increased interest in HCC surveillance compared to PCPs from other areas of the U.S. The nation as a whole is only 5% Asian.(22) The only other study examining PCPs focused primarily on surveillance for hepatitis C and B infections.(11) HCC surveillance questions were limited and did not specify the presence or absence of cirrhosis. None of the three studies asked about HCC therapies or whether respondents actually see cirrhosis patients in their practices.

We focused on HCC surveillance and therapy. We surveyed a random sample of PCPs from across the state of North Carolina. Therefore, our data are more representative of communities with Asian prevalence closer to the national average. Only 2.5% of North Carolina are of Asian descent.(13) Unlike prior surveys we also asked whether PCPs actually saw cirrhosis patients in their practice. Such determination is critical since PCPs may render an opinion on HCC surveillance but never actually see a cirrhotic patient. Some may divert cirrhosis patients away from their clinic, or work in clinics where cirrhosis patients are rare (e.g. student health clinics).

We also wanted to understand PCP knowledge of HCC therapies because effective therapies are arguably the most compelling justification for surveillance.(1, 23) HCC therapies have evolved greatly in the last 12 years. Our survey suggests that PCP knowledge of more recently established treatments is relatively poor compared to established surgical interventions. Filling this knowledge gap regarding RCT data for TACE, RFA and sorafenib, could increase surveillance rates by PCPs since the ability to identify at least one effective therapy was independently doubled the odds of surveillance. Also, over 80% of PCPs who do not screen deferred the decision to subspecialists, and despite some controversy in the literature regarding HCC surveillance recommendations, (23-25) only 8%

did not screen because the "benefit is uncertain". Therefore, a large number of PCPs may recommend surveillance, if guidance and education are provided.

Our study is limited by a response rate (39%) that is lower than prior HCC surveillance surveys of PCPs (62-71%).(9, 10) As mentioned, these prior studies targeted Asian community PCPs who very likely have a deeper knowledge and interest in HCC. Our response rate is more in line with less targeted provider surveys. An analysis of 130 surveys of US health care professionals, conducted from 1996 to 2005 yielded a median response rate of 51% with an interquartile range of 38-65%.(26) Moreover, the response rate for health care professionals declined significantly with the percent of surveys having >60% response falling from 63% prior to 2000 to 35% in 2005-2008.(27) PCPs who see pertinence in a survey and have increased knowledge of the topic tend to respond more often, hence the higher response rates in the studies from California.(9, 10, 28) Such a response bias in our study would make our surveillance and knowledge of therapy rates *overestimates* of the true rate amongst PCPs in our state. Moreover, recall bias by those who said they recommend surveillance may further overestimate the rate.

Our survey is also limited in scope. The questionnaire was purposely kept brief to limit the non-response rate. Many other variables needed for a full behavior model such as PCP access to subspecialists and volume of cirrhotic patients seen were not included. Thus, therapy knowledge that was associated with surveillance may be merely a surrogate for other more pertinent variables not captured in our survey.

Our study provides the only data on HCC surveillance and knowledge of HCC therapy in an unselected population of PCPs who see cirrhotic patients in practices not enriched with Asians. The data suggest that HCC surveillance rates and knowledge of therapies are low. It also suggests an opportunity to increase community surveillance rates by closing the gap in knowledge, particularly regarding effective therapy options. Moreover the majority of PCPs who do not screen may be amenable to surveillance if educated and guided by subspecialists. Enlisting PCP help in initiating surveillance may eliminate unnecessary referral for opinion and certainly will help with sustaining surveillance once started. It is probably the only practical way to increase and sustain surveillance rates on a broader scale.

# **Acknowledgments**

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# **Abbreviations**

| AFP | alnha | fetoprotein |  |
|-----|-------|-------------|--|
| AFF | апрпа | retobrotem  |  |

**CT** computerized tomography

**HCC** hepatocellular carcinoma

MRI magnetic resonance imaging

**PCP** primary care provider

**RFA** radiofrequency ablation

**TACE** transarterial chemoembolization

**U.S.** United States of America

**US** ultrasound

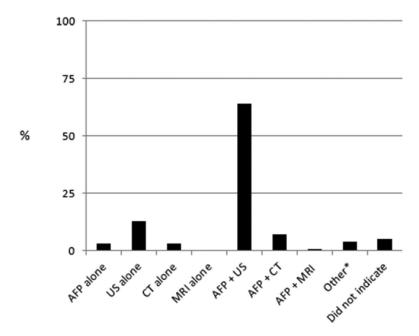
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**Figure 1.** Modality of HCC surveillance used by those primary care providers who screen (n = 156). \* "Other" category for modality: 2 PCPs indicated they would do what the subspecialist recommends, while 4 used AFP, US, CT and MRI in various combinations and alternating fashion (e.g. AFP + US every 6 months and CR or MRI every 2 years).

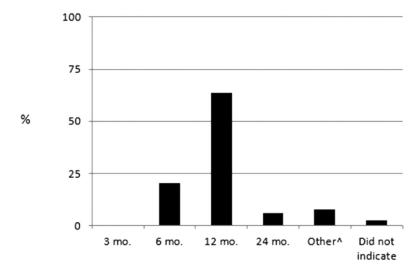


Figure 2. Interval of HCC surveillance used by those primary care providers who screen (n = 156).  $^{\land}$  "Other" category for interval: 2 PCPs gave ranges of 6-12 months, 5 indicated taking cues from subspecialists and 8 gave unclear answers for interval (e.g. "depends" and "periodically" and "if liver enzymes rise"). AFP = alpha-fetoprotein, US = ultrasound, CT = computerized tomography, MRI = magnetic resonance imaging.

Table 1

Characteristics of primary care providers (n = 389)

| Characteristic                                  |     |        |
|---|-----|--------|
| Male, n (%)                                     | 234 | (60.2) |
| Years in practice (mean, standard deviation)    | 22  | (9.9)  |
| Primary affiliation, n (%)                      |     |        |
| Private practice                                | 313 | (80.5) |
| Academic setting                                | 47  | (12.1) |
| Veterans Affairs hospital or clinic             | 13  | (3.3)  |
| Health maintenance organization (HMO)           | 4   | (1.0)  |
| Other (not specified by respondent)             | 12  | (3.1)  |
| Encounter cirrhotic patients in practice, n (%) | 345 | (88.7) |

Table 2

Reasons for recommending HCC surveillance among those PCPs that screen, n = 156 (respondents asked to choose all that apply)

|   | n   | %  |
|---|-----|----|
| Evidence supports surveillance for HCC              | 112 | 72 |
| Surveillance is recommended by medical societies    | 65  | 42 |
| Not surveillance would pose a malpractice liability | 41  | 26 |
| Surveillance for HCC is cost-effective              | 26  | 17 |
| Other*  | 12  | 8  |
| Did not give a reason                               | 4   | 3  |

<sup>\*</sup> Other reasons given: Affects treatment options; it is standard with our cirrhosis clinic; It's what I would do; patients request it; r/o liver lesion affecting labs etc.; recommended by consultant (gastroenterologist or hepatologist).

Table 3

Reasons for not recommending HCC surveillance among those PCPS that do not screen, n = 189 (respondents asked to choose all that apply)

|   | n   | %  |
|---|-----|----|
| Refer cirrhotic patients to consulting provider | 158 | 84 |
| Did not know it was recommended                 | 46  | 24 |
| Benefit of surveillance is uncertain            | 15  | 8  |
| Too costly                                      | 8   | 4  |
| * Other   | 8   | 4  |
| Did not give a reason                           | 0   | 0  |

<sup>\*</sup> Other reasons given: Transient population; I screen the hepatitis C cirrhotics/not usually the alcoholic cirrhotics; Not sure of latest recommendations; See few cirrhotics + usually terminal or followed by specialists; Only check with hep C; Ultrasound often done as diagnosis of cirrhosis evolving; Usually do not live long enough; I intend to but some slip through

Table 4

Effective HCC therapies identified by PCPs who see cirrhosis patients, n = 345 (respondents asked to choose all that apply)

|   | n   | %  |
|---|-----|----|
| Hepatic resection                                   | 230 | 67 |
| Liver transplantation                               | 192 | 56 |
| Transarterial chemoembolization                     | 146 | 42 |
| Radiofrequency ablation                             | 121 | 35 |
| Sorafenib   | 91  | 26 |
| Did not identify any choices as effective therapies | 50  | 15 |