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Geriatrics CRC Project, 12/19/13

Are we adequately screening at-risk patients for hepatocellular carcinoma in the outpatient setting?

A. Study Purpose and Rationale

Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer deaths worldwide[1] and ninth leading cause of cancer deaths in the US[2]. HCC is known to be an aggressive disease with a high fatality rate as evidenced by similar rates of deaths per year and incidence.[3] As the rates of HCC are expected to increase every year, physicians are faced with a challenge to better detect and treat this devastating disease.

Patients who develop HCC usually do not have pathognomonic symptoms beyond those of chronic liver disease making an early clinical diagnosis difficult. When worsening symptoms of decompensated liver disease arise, HCC is often advanced and in many cases untreatable with a 5-year survival of only 0-10%.[4] This raises a need to routinely screen at-risk patients for HCC in order to detect smaller tumors earlier with a chance for early initiation of treatment and better prognosis. Modern imaging techniques facilitate the ability to detect HCC at a smaller size earlier, while the development of treatments for early-stage HCC support the need for earlier detection. However, despite the benefits of surveillance of at-risk populations, the prevalence of adequate surveillance is low. In two large studies of Veterans Administration (VA) patients with cirrhosis, regular surveillance in patients with cirrhosis was performed in only 2-12% of patients.[5,6]

HCC is unique from other cancers in that it has specific epidemiologic distributions and defined etiologies making it easier to identify patients who are at-risk. Published 2011 guidelines on the management of hepatocellular carcinoma by the American Association for the Study of Liver Diseases (AASLD) recommends surveillance for specific groups of patients in whom the risk of HCC is increased.[7] These at-risk groups have specific clinical characteristics that can be easily identified by physicians facilitating their entry into surveillance programs. Currently, the AASLD 2011 guidelines recommend ultrasonography every 6 months.[7] The surveillance interval does not have to be shortened for patients at higher risk of HCC. This is a non-invasive and cost-effective method that can be easily implemented as a sustainable surveillance program for at-risk patients.[8]

The Associates in Internal Medicine (AIM) clinic at the Columbia University Medical Center (CUMC) is a resident staffed primary care clinic that provides health care services to a predominantly low-income, minority patient population local to Washington Heights in New York City. The prevalence of liver disease is high among this population given increased risks for HCV, HBV, and HIV. In the AIM clinic patient population, are we identifying these at-risk patients and initiating HCC surveillance programs according to published AASLD guidelines? Given that rates of HCC surveillance in the US are low resulting in later diagnosis of HCC and increased

morbidity and mortality, it is important to ensure increased HCC surveillance in the outpatient setting.

AIM 1: This study aims to identify at-risk AIM patients and determine current rates of HCC surveillance in these patients with the goal to increase the frequency of HCC surveillance according to AASLD guidelines. A retrospective chart review will be conducted to identify at-risk patients and determine current rates of HCC surveillance over the past year. Once the rates of HCC surveillance are determined, we will create a QI intervention that will help increase surveillance rates.

The rates of HCC is 2-7 times higher in men versus women and the incidence of HCC in women peaks at 2 decades later in age than in men.[9,10] It is thought that men tend to have higher rates of exposure to liver carcinogens such as smoking and alcohol than women predisposing them to a higher risk of liver injury. Regardless of differences in incidences, results from the Surveillance, Epidemiology, and End Results (SEER) database from 1998 to 2001 show that the 3 year survival is similar for men and women who undergo surgical resection, transplant, and radiofrequency ablation.[11] Given that men are thought to be more predisposed to developing HCC due to increased liver injury risk factors and higher HCC incidence, men may be entered into surveillance programs more frequently than women. However, the mortality from HCC is equal between both genders making surveillance equally important for both genders.

AIM 2: In this study, we aim to compare rates of surveillance in men versus women.

Hepatitis B Virus (HBV) is most commonly known to be associated with HCC and may prompt physicians to more aggressively survey for HCC as compared to other risk factors for HCC. However, HCC due to Hepatitis C Virus (HCV) is becoming a rising cause of cancer-related death in the US.[12] As rates of HCV increase in the US while HCC mortality remains unchanged, it will become even more important to adequately survey patients with HCV who are at-risk.[12]

AIM 3: This study will compare rates of HCC surveillance between patients with HBV versus patients with HCV.

Future directions will study how effectively QI intervention increases HCC surveillance rates according to AASLD guidelines. This will involve a prospective controlled study that will compare rates of HCC surveillance in physicians who receive QI intervention versus physicians who do not receive QI intervention.

B Study Design and Statistical Analysis

Retrospective Chart Review:

1. Identify AIM resident clinic patients indicated for HCC surveillance as outlined by AASLD guidelines over past year (Jan 1 2013 to Dec 31, 2013) using retrospective chart review.
   - Asian males over 40 years old who are carriers for HBV,
   - Asian females over 50 years who are carriers for HBV,
   - HBV carriers with family history of HCC,

- African/North American Blacks with HBV,
- Cirrhotic HBV carriers,
- HCV cirrhotic patients,
- Stage 4 primary biliary cirrhosis,
- Genetic hemochromatosis and cirrhosis,
- Alpha 1 antitrypsin deficiency and cirrhosis,
- Other cirrhosis

Definitions for chart review.

- HBV carrier is defined as HBe antigen positive or HB surface antigen positive.
- HCV positivity is defined as positive HCV antibody or elevated PCR for HCV RNA.
- Cirrhosis is defined as cirrhotic appearing liver on histology or abdominal imaging in light of signs of cirrhosis including: ascites, varices, splenomegaly, hepatic or portal vein thrombosis, thrombocytopenia, elevated PT/INR, elevated bilirubin, low albumin.
- HCC surveillance is one abdominal ultrasound within the last year.
- Alternate surveillance includes AFP levels, CT, or MRI.

2. Collect additional data fields as outlined in the Data Collection Form (See Addendum A).

3. Statistical Analysis

- Male versus female HCC surveillance rate comparison using chi-squared proportion for 2 groups.
- Hypothesis: At-risk males are more frequently surveyed for HCC than at-risk females.

	Male (n=100)	Female (n=100)
Surveillance	70%	50%
No Surveillance	30%	50%
Sample sizes needed for each group	n = 103	n = 103

- HBV versus HCV HCC surveillance rate comparison using chi-squared proportion for 2 groups.
- Hypothesis: Patients with HBV are more frequently surveyed for HCC than patients with HCV.

	HBV (n=60)	HCV (n=120)
Surveillance	50%	30%
No Surveillance	50%	70%
Sample sizes needed for	n = 76	n = 152

each group		

4. Create QI intervention in EMR that helps physicians identify which of their patients are indicated for surveillance and educates physicians on guideline recommended surveillance.

5. Total length of time needed is 6-9 months.

Future Directions:
Prospective Chart Review:
1. Half of residents at AIM clinic will receive QI intervention. ½ of residents will receive no QI intervention.
2. Collect post-intervention rates of HCC surveillance after QI intervention initiated for at-risk patients versus no QI intervention
3. Statistical Analysis:
- Use chi-squared for 2 groups to compare rates of HCC surveillance between QI intervention group and no QI intervention group.
- Use chi-squared for 2 groups to compare rates of HCC surveillance pre QI intervention and post-QI intervention in QI intervention group.

C. Study Procedures
No procedures will be conducted during this retrospective data analysis.

D. Study Drugs
N/a

E. Medical Device
N/a

F. Study Questionnaires
A form will be used to help collect data from retrospective chart review. See Addendum A.

G. Study Subjects
AIM Resident Clinic patient population. Inclusion criteria includes adult AIM clinic patients seen in continuity or walk-in clinics by NYPH-CUMC residents.

H. Recruitment of Subjects
Project will need permission from AIM clinic to collect data. No recruitment needed for retrospective chart review.
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I. Confidentiality of Study Data
All data will be coded in the study database and each patient will be assigned a unique ID number. Only Dr. Rajani Sharma will have access to these codes liking patient to ID number and this information will be secured according to CUMC IT policies. All devices used to access

data will be protected according to CUMC IT policies. All study personnel will have HIPAA training certificates.

J. Potential Conflict of Interest
None

K. Location of the Study
CUMC AIM Resident Clinic

L. Potential Risks
Surveillance may result in liver biopsy with rare complications such a needle-track seeding of cancerous cells during needle aspiration cytology, bleeding, or introduction of infection. Trans-jugular liver biopsy is also rarely associated with complications such as perforation of hepatic capsule or cholangitis.

M. Potential Benefits
Potential benefits include Increased surveillance for HCC according to AASLD guidelines, earlier diagnosis of HCC, and early initiation of treatment.

N. Alternative Therapies
N/a

O. Compensation to Subjects
No compensation will be provided to subjects.

P. Costs to subjects
Subjects will not incur any additional costs as a result of participating in the study.

Q Minors as Research Subjects
N/a

R. Radiation or Radioactive Substances
N/a

References:
1. El-Serag, HB and Rudolph, KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007; 132 (7): 2557-2576.

2. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009; 27:1485.

3. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 61:69.

4. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003; 362:1907–1917.

5. Davila JA, Henderson L, Kramer JR, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. Ann Intern Med 2011; 154:85.

6. El-Serag HB, Kramer JR, Chen GJ, et al. Effectiveness of AFP and ultrasound tests on hepatocellular carcinoma mortality in HCV-infected patients in the USA. Gut 2011; 60:992.

7. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-1022.

8. Wong GL, Wong VW, Tan GM, et al. Surveillance programme for hepatocellular carcinoma improves the survival of patients with chronic viral hepatitis. Liver Int 2008;28:79–87.

9. McGlynn KA, Tsao L, Hsing A, Devesa SS and Fraumeni JF Jr. International trends and patterns of primary liver cancer. Int. J. Cancer 2001; 94: 290-296.

10. Parkin DM, Bray F, Ferlay J, and Pisani P. Global cancer statistics, 2002. CA Cancer J. Clin 2005; 55: 74-108.

11. Wong RJ, Corley DA. Survival differences by race/ethnicity and treatment for localized hepatocellular carcinoma within the United States. Dig Dis Sci. 2009;54(9):2031-2039.

12. El-Serag, HB. Hepatocellular Carcinoma. NEJM 2011; 365: 1118-1127.

Addendum A: Data Collection Form

Name_____
DOB_____
MRN_____
Age _____
Sex_____
PCP_____

Risk Factor Assessment:
Race:
[] Asian [] Af Am [] Hispanic [] Caucasian [] Other

Age:
[] >40 years [] > 50 years

HBV:
[] Pos HBe Ag [] Pos HBV SAg
HBV VL_____
[] Family history of HCC?

HCV:
[] Pos HCV Ab
HCV VL_____

HIV:
[] Positive [] Negative

Cirrhosis:
[] Positive histology for cirrhosis
[] Positive Abdominal imaging for cirrhosis (US, CT, or MRI)
[] ascites
[] varices
[] splenomegaly
[] hepatic or portal vein thrombosis
[] Thrombocytopenia
[] Elevated PT/INR
[] Elevated bilirubin
[] Decreased albumin
[] Prior history of variceal bleeding
[] Prior history of encephalopathy
[] Abnormal LFTs
[] Abnormal coagulation tests
[] CBC

Other rarer disease:
[] Hemochromatosis
[] Primary Biliary Cirrhosis (stage 4)
[] Alpha 1 anti-trypsin deficiency

Current Therapies for liver disease:
[] lactulose
[] rifaximin
[] spironolactone
[] furosemide
[] HBV medications
[] HCV medications
[] HIV medications - HAART

Overall Assessment for HCC Surveillance
[] Risk of HCC is increased and the patient should receive surveillance
[] Risk of HCC is increased, but benefit of surveillance is uncertain.
[] No increased risk of HCC

What kind of surveillance did the patient receive?
[] 1 Abdominal US in past year
[] 2 Abdominal US in past year
[] >2 Abdominal US in past year
[] Alternating AFP and Abdominal US
[] Abdominal CT in past year
[] MRI in past year
AFP measurements in past year_____