HCC Screening: A Prospective Cohort Study to Compare Sensitivities of Helical CT with Dual Phase to Ultrasound as a Screening Tool for Heptocellular Carcinoma Detection in a High Risk Population

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A. Study Purpose and Rationale

Hepatocellular Carcinoma (HCC) is the 5th most common cancer worldwide. There are approximately 500,000 new cases worldwide annually. In the United States HCC comprises 84% of all primary liver cancers and the incidence of the disease has been increasing with approximately 10,000 new cases of HCC occurring annually in the United States (El-Serag, 2004). Survival rates for HCC are poor. 1 year and 3-year relative survival rates for HCC from 1998-2000 were 36% and 17% respectively (El-Serag *et al*., 2001). The overall median survival is only 7 months and is even less in those presenting with symptomatic disease (Lovett J., 1999)

The primary risk factor for HCC is cirrhosis, with incidence of disease depending on the etiology of cirrhosis. The prevalence of cirrhosis in persons with HCC is about 80-90% in autopsy series. The incidence of HCC in cirrhotics is approximately 3-5% per year. All causes of cirrhosis may be complicated by HCC but approximately 80% of all cases of HCC worldwide are accounted for by chronic Hepatitis C (HCV) or Hepatitis B (HBV) infection. The 5-year cumulative incidence of HCC in HBV and HCV-related cirrhosis is 15% and 10% respectively (Fattovich G. *et al.* 2002). In addition alcoholic cirrhosis, hereditary hemochromatosis, Primary Biliary Cirrhosis (PBC) and Primary Sclerosing Cholangitis (PSC) are also associated with increased risk of developing HCC. There is also increasing evidence that Nonalcoholic Steatohepatitis (NASH) may be associated with HCC (Fattovich *et al.,* 2004).

Screening for HCC in patients with cirrhotic liver disease is currently common practice; however, there is little evidence that screening provides any benefit. Screening for HCC makes intuitive sense. The disease has a high incidence in identifiable patient populations. There are non-invasive tests that can detect the disease and detection of HCC at an earlier stage affords more treatment options and a better prognosis. However, no randomized trial has been performed in a Western population to demonstrate the efficacy of screening for HCC. In addition, to a scarcity of data regarding the effectiveness of screening there is little data regarding the best method for screening.

There have been studies in Asian populations showing a benefit to screening. However, HCC is a different epidemiologic disease in Asia, occurring at an earlier age and often without evidence of cirrhosis, owing to the high rate of neonatal transmission of HBV that is rare in the United States. Zhang *et al.,* (2004) randomized nearly 19,000 persons with chronic hepatitis in China to screening with AFP and US or no screening. The screened group had more cases of HCC detected. The cancers were detected at an earlier stage and HCC mortality was significantly decreased in the screened group. Based on the above study and similar Asian studies as well as retrospective studies performed in Western populations it has become common practice in the United States to screen with the use of the serum marker alpha-fetoprotein (AFP) and an ultrasound (US) of the liver on a 6 to 12 month basis.

Sherman *et al.* (1995) performed a prospective trial in which he screened a cohort to 1,069 chronic carriers of HBV with AFP or AFP and US every 6 months for a mean 26 months of follow up. Sensitivity and specificity were determined to be 64.3% and 91.4% for AFP > 20 and 78.8% and 93.8% for US in this study. However, subjects in this study with negative tests did not receive further work-up to assess for occult disease raising questions as to how accurate the sensitivities calculated in this study are. Pateron *et al* (1994) performed a cohort study using 188 French subjects with ultrasound examination of the liver and determination of blood alpha-fetoprotein and des-gamma-carboxyprothrombin levels every 6

months for a median follow up was 36 months. Sensitivity of US was determined to be 71%, but this study was similarly flawed. Studies looking at patients on a liver transplant waiting list that were studied by US prior to transplantation showed sensitivities of US of 50-58%. (Gambarin-Gelwan M *et al*, 2000 & Dodd GD *et al*, 1992)

Do better screening tools exist? Conventional CT has not been shown to be more sensitive for HCC than US (Gambarin-Gelwan M *et al*, 2000). However, recent studies have indicated that helical CT might be. Helical CT is a more advanced form of CT that is able to perform more cuts of the imaged area in a shorter amount of time. Currently, helical CT can image the entire hepatic bed in less than 8 seconds. This allows for imaging of the hepatic bed while IV contrast is in the arteries feeding the liver (arterial phase) as well as a second phase when the IV contrast enters the portal vasculature (delayed portal phase). Most HCC lesions receive the majority of their blood supply from the arterial vasculature, whereas the liver receives the majority of its blood supply from the portal vasculature. Thus, using both phases can be helpful in picking up HCC lesions.

Colagrande S *et al*, (2003) prospectively screened 36 cirrhotic patients with resected HCC for recurrence. Patients were screened with US and helical CT as well as AFP. Helical CT was able to pick up recurrent lesions earlier than US did. Laghi *et al*, (2003) evaluated 77 patients with 140 foci of HCC. Sensitivities were determined to be 87.1% with a PPV of 94.0%. Iannaccone R *et al.*, (2005) studied 250 patients with and without HCC by helical CT. Sensitivity was shown to be 92.8% when a delayed phase to assess the portal vasculature was performed in addition to the arterial phase.

However, not all studies of helical CT showed improved sensitivity for HCC. Peterson *et al*, (2000) performed a prospective direct correlation of helical CT findings with explanted liver specimen findings in 430 transplant recipients with cirrhosis. The prospective and retrospective rates of identifying HCC were 59% and 68%. This study did not use an arterial phase though, which may explain the poor sensitivities calculated in the trial. Additionally, helical CT has the potential to increase the false positive rate. Brancatelli G *et al*, (2003) studied single-detector helical CT screening in 1329 patients with cirrhosis who were referred for transplantation. They found a false positive rate of 8% within this group.

Based on the above data it seems possible that helical CT with dual phase may be a more sensitive test for picking up HCC as part of a screening program in a high risk population.

B. Study Design and Statistical Analysis

This trial will be designed to test the null hypothesis that ultrasound as at least 90% as sensitive as helical CT with dual phase in detecting HCC lesions as part of a screening program in a high-risk population. The study will be a non-randomized, un-blinded prospective cohort trial. All subjects will undergo conventional HCC screening (AFP and US q6 months). In addition, all subjects will undergo helical dual phase CT scheduled within 2 weeks of each US. Patients will be followed for 5 years in the screening program with 1 year of additional follow-up. Certified radiologists will evaluate all US and CT scans independently. Results will be reported to the subjects' primary caregiver as well as the study's principal investigator.

The primary outcome will be the determination if there is a significant difference in the sensitivity of US vs. CT scan in the diagnosis of HCC. Helical CT will be considered a 'gold standard' for the point of comparison.

A subpopulation of the study will undergo liver transplantation during this study. Based on the pathology of the explants it will be clear if these patients did or did not have HCC. Most patients with lesions of 1-2 cm on US or CT will have a tissue biopsy to determine of the lesion was HCC. Based on this subpopulation of subjects the sensitivity, specificity, PPV and NPV of both US and helical dual phase CT can be calculated. Another secondary analysis will be performed to compare the number of single lesions < 5cm found initially on US vs. CT.

Based on sensitivities of US for detecting HCC ranging from 50-80%, I will use an estimate of 75% for the sensitivity of US for the purposes of calculating the power for this study. Helical CT will be used as a 'gold standard' for comparison with US for the sake of computing the primary outcome. Given

the wide availability of helical CT, its relative safety and the importance of sensitivity on a screening test the null hypothesis will be that US is at least 90% as sensitive as helical CT for HCC in a screening program for cirrhotics. If the true sensitivity of US is 75% as estimated above then this study will need 56 subjects with HCC to find a significant difference with a power of 80% and an alpha of .05. Given that the annual incidence of HCC in the screened population is 3-5%, approximately 500 subjects will have to be enrolled and screened 10 times over a 5-year period in order ensure sufficient cases to properly power the study. This factors in the 'drop-out' of subjects who test positive for HCC and therefore will not receive future screening. This N will also permit an additional dropout of 7% per year due to either mortality, liver transplantation or loss to follow-up. Test for significance will be done by chi square analysis.

Secondary analysis of sensitivity, specificity, PPV and NPV will be calculated for both US and helical CT based on the subpopulation of subjects that have a tissue biopsy performed or receive liver transplantation.

	HCC present	HCC absent
Test +	TP	FP
Test -	FN	TN

Test sensitivity = TP/(TP + FN)
Test specificity = TN/(TN + FP)
PPV = TP/(TP + FP)
NPV = TN/TN + FN)

Secondary analysis will also be performed to compare number of single HCC lesions < 5 cm or 2 lesions each < 3 cm caught initially on US or helical CT. This comparison will also be performed with chi square analysis.

C. Study Procedure

Subjects will be recruited from the Gastroenterology and Liver Transplant Clinics at five medical centers in New York City. These centers currently follow a significant number of patients that are eligible for this study. As screening for HCC in cirrhotics is currently standard practice in all of the clinics that patients will be recruited from there should not be any major hurdles in recruiting a sufficient number of patients to conduct this study. There will be a primary site investigator at each site that will be responsible for working with the various providers in each clinic to determine which patients are eligible for the study and might be willing to participate. The investigator will approach the patient for informed consent only at the invitation of the patient's primary provider.

Once enrolled in the study, all patients will be assessed for the presence of HCC by AFP, US and helical CT. As most patients enrolled in the study will likely already be part of a screening program, this step will consist primarily in making sure screening is up to date and pursuing a baseline CT scan. Any subjects with evidence of HCC at initial screening will be excluded from the study. The results of the tests will be made known to the patient's primary provider.

All subjects without any serologic or radiologic evidence of HCC will be screened every 6 months with serum AFP, abdominal US and helical CT with dual phase. Radiologic studies will be read by separate and independent board certified radiologists. The radiologic reports as well as the AFP level will be reported back to the study site investigator as well as the subject's primary provider.

Subjects with no evidence of disease will continue to be followed. Subjects with suspicious lesions on CT or US in the absence of a diagnostic AFP level will be worked up as follows:

- If lesion < 1 cm will continue to follow
- If lesion 1-2 cm, tissue biopsy will be performed

- If lesion > 2 cm will treat as HCC in the absence of any known non-liver malignancy unless radiology studies are equivocal in which case tissue biopsy might be performed.

Further imaging for HCC (i.e. MRI or repeat non-scheduled CT and/orUS) will be left to the discretion of the subject's primary caregiver. The choice of treatment modality in confirmed cases of HCC will be left to the discretion of the subject's primary caregiver. Biopsies will not be performed unless clearly clinically indicated, as there is a low risk of seeding the needle track as well as the standard risk associated with any invasive procedure.

Once subjects have been screened for 5 years they will go back to receiving standard care. As this will likely continue to involve standard screening for HCC these subjects will continue to be followed for an additional year to see if any HCC lesions are detected as part of their standard screening. Any lesions so detected will be considered 'misses' for the last screening session done during the study. Additionally, for any subjects transplanted in the year following the end of the study the explant will be studied to determine the presence or absence of HCC.

D. Study Drugs

N/A

E. Medical Device

US: will be performed using wide-angle convex probes of 3.5MHz, pulsed waves and power Doppler module. All images will be read independently by an experienced radiologist.

CT: high resolution helical CT with iodinated intravenous contrast will be performed with cuts of the entire hepatic bed. An arterial as well as a delayed phase portal scan will be performed so as to view contrast in each vascular bed. All images will be read independently by an experienced radiologist.

F. Study Questionnaires

N/A

G. Study Subjects

Subjects will be recruited primarily from GI and Liver clinics at participating centers

Inclusion criteria

- 45-75 years of age
- Cirrhosis of the following etiologies. Child's A or Child's B
  - HCV, HBV, EtOH, HH, PBC, PSC
- No serologic or radiologic evidence of HCC at study onset

Exclusion criteria

- Renal insufficiency
- DM
- Hx of iodinated contrast allergy

H. Recruitment of Subjects

Recruitment of subjects will occur in Gastroenterology and Liver Transplant Clinics at participating medical centers. Patients in these clinics are very likely to be currently undergoing screening of HCC if they are in a high-risk group. Therefore, entry into this study will not impose an undue burden on this group. The only change in their management will be the addition of the CT scan to their screening protocol.

I. Confidentiality of Study Data

All patient records will be stripped of personal identifiers and coded. The data will be stored in a secure location available only to the study's principal investigators.

J. Potential Conflict of Interest

N/A

K. Location of the Study

The study will be performed in the GI and Liver clinics at CPMC and four other participating medical centers in New York City.

L. Potential Risks

Patients will have to undergo CT scans at 6-month intervals exposing them to radiation they might not have to undergo as part of a standard screening protocol. Each CT scan will expose the patient to approximately 10mSv of radiation. There is no known carcinogenic effect of being exposed to multiple CT scans but there may be a potential risk associated with this level of radiation exposure. IV contrast given with the CT scan carries a low risk of allergic reaction or acute renal failure. The risk of renal failure is approximately 0.1% with renal insufficiency being the primary risk factor for the development of contrast –induce nephropathy (CIN). DM may also be a risk factor for CIN, although it is not clear that this relationship exists in the absence of established renal insufficiency. For these reasons patients with chronic renal insufficiency or Diabetes mellitus will be excluded fro the study. There may also be an unknown risk of higher false positive tests associated with screening for HCC with CT scan as opposed to US. If so, a patient could theoretically undergo an unnecessary MRI or biopsy as part of a work-up for a falsely diagnosed HCC lesion.

M. Potential Benefits

Patients will be monitored more carefully for HCC than they would by any standard screening protocol. Therefore, there is a potential benefit that HCC could be caught in a research subject that would not have been caught during a standard screening protocol.

N. Alternative Therapies

If a patient does not wish to enroll in the study they will still be offered conventional screening for HCC as practiced by the GI/Liver clinic in which the patient is followed.

O. Compensation to Subjects

There will be no compensation offered to subjects.

P. Costs to Subjects

The costs of the helical CT scans will be covered by the study grant. The costs of AFP tests and US will also be covered by the study grant if the subject was not being screened for HCC prior to enrolling in the study.

Q. Minors as Research Subjects

N/A

R. Radiation or Radioactive Substances

Subjects will undergo up to 10 helical CT scans. Each scan will expose the subject to a small amount of radiation, approximately 10 mSv per scan.

S. References

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