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Retrospective Analysis Of Screening Patterns In Cirrhotic Patients With Heptocellular Carcinoma

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RETROSPECTIVE ANALYSIS OF SCREENING PATTERNS IN CIRRHOTIC PATIENTS WITH HEPTOCELLULAR CARCINOMA

by

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ABSTRACT

The incidence of hepatocellular carcinoma (HCC) in cirrhotic patients is increasing worldwide. Cirrhotic patients are recommended by the American Association for the Study of Liver Disease (AASLD) to receive HCC screening and surveillance every 6 months to a year. The purpose of this study was to identify the current screening and surveillance patterns for cirrhotic patients with HCC in clinical practice. Hepatocellular carcinoma can be detected by radiological studies in addition to laboratory testing. It is important to implement the AASLD screening guidelines, as early identification might decrease the mortality rate of patients with cirrhosis and HCC. The research question guiding this study was: What are the screening patterns of cirrhotic patients diagnosed with cirrhosis and HCC that have been referred to the Hepatology Division? A retrospective, descriptive, cross-sectional design was used for this study. Data were collected from subjects who were referred to a Specialty Hepatology Division for evaluation and treatment. Approval was obtained from the IRB. Cirrhotic patients diagnosed with HCC meeting the inclusion and exclusion criteria were used in this study. The aim of the study was to identify the clinical patterns of practitioners screening for HCC in cirrhotic patients. Validity and reliability for the data collection tool was not established. Variables that were studied included demographic data, etiology of cirrhosis, type of HCC screening, time increments of screening, and size of tumor at the time of diagnosis. The data were analyzed with the use of crosstabs, frequency, and correlation statistics. Despite the recommended HCC screening and surveillance guidelines cirrhotic patients were not screened. The different screening patterns that were identified were

none, *sporadic*, and *annual* (every 6 months to 1 year). The patterns differed by the practitioner managing the patient. Also, cirrhosis was diagnosed late in the disease process, although many of the patients are followed by gastroenterologists. It can be assumed that the late diagnosis of cirrhosis was another factor that was preventing the implementation of HCC screening and surveillance. Implications for practice were identified. Practitioners are responsible for performing HCC screening and surveillance of cirrhotic patients based on the recommended guidelines of the AASLD for the management of cirrhotic patients and the detection of small lesions. Only 33% of the patients were screened with the use of ultrasound, and 43% were screened with alpha-fetoprotein. The lesions that were diagnosed were larger in the non-screened patients than the screened patients. The Hepatology Division was the only setting that was screening the patients' based on the recommended guidelines. The recommendation based on the results of this study is for all cirrhotic patients to be managed by hepatology services if one is available.

This thesis is dedicated to my mother and father. Dad, although you have left this Earth, you still live in my heart. Although you were taken from us, we cherish all of the moments that we shared with you, and we reminisce about our childhood memories frequently. You were a wonderful father, and as children, we could not ask for more than that. Mom, thank you for instilling determination in me and for encouraging education from childhood. You always wanted me to "be something." I have purposely gone out of my way to show you that all of your hard work did not go to waste. To my children, obtaining an education is important and will take you far in life. Anything is possible, if you just put your mind to it. No dream is impossible. If you can dream it, you can do it.

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CHAPTER 1: INTRODUCTION

Problem/Significance

Hepatocellular carcinoma (HCC) is increasing in incidence worldwide (Albrecht, 2008). More than 500,000 new cases of HCC are diagnosed yearly (Nouso et al., 2008). The significance of HCC in cirrhotic patients is overwhelming; the annual rate of HCC is between 3 to 7% in cirrhosis patients (Trevisani et al., 2004). The increase of HCC incidence has been attributed to the increasing rate of cirrhosis and the lack of HCC screening in cirrhotic patients (Trevisani et al., 2004). The annual incidence of HCC increases from less than 1% to more than 6% (Daniele, Bencivenga, Megna, & Tinessa, 2004). Hepatocellular carcinoma is one of the most common neoplasm's in the world and is an important health concern (Pascual et al., 2008).

Cirrhosis is a premalignant condition. Approximately10% to 30% of patients with cirrhosis is eventually diagnosed with HCC (Chang & Chuang, 1988). Although all cirrhotic patients have a higher incidence of HCC than the general population, the hepatitis C virus (HCV) population is at the greatest risk (Trevisani et al., 2004). Patients with HCV account for 55% of patients diagnosed with cirrhosis, with hepatitis B virus (HBV) accounting for 17% of cirrhosis, and 9% of cirrhosis is related to alcohol, and 19% being caused by other causes of cirrhosis (Snowberger et al., 2007). Of the 55% of patients diagnosed with HCV cirrhosis, approximately 85% of them will be diagnosed with cirrhosis in the first one to two decades after the initial infection (Rahbin et al.,

2008). Other causes of cirrhosis include non-alcohol steatohepatitis (NASH), autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis (Bisceglie, 2004).

A large population of patients is undiagnosed with cirrhosis until the late stages of the disease process or until they become symptomatic, according to the American Association for the Study of Liver Disease (AASLD, 2008). It is estimated that over 50% of patients infected with HCV are unaware of their hepatitis status until they display symptoms (Nguyen, Gildengorin, Truong, & McPhee 2007). The unknown status of the liver disease allows the virus to damage the liver without the knowledge of the practitioner or the patient. Symptoms of decompensation for patients with cirrhosis include, among others, variceal bleeding due to portal hypertension, ascites, and hepatic encephalopathy.

Recommended Screening

The AASLD (2008) guidelines recommend HCC surveillance and screening for cirrhotic patients with the use of ultrasound of the liver every 6 months to a year. Alpha fetoprotein (AFP) is also commonly used for HCC surveillance and screening. AFP has been used in clinical practice as a serum marker for HCC in humans since 1968 (Yu, Chie, & Chen, 2004). According to Yu, Chie, and Chen (2004), levels of AFP levels greater than 15ng/mL are indicative of HCC. Ultrasound became available for identifying liver lesions in the early 1980s (Chang & Chuang, 1988; Yu et al., 2004), and is able to detect small HCC lesions. Ultrasound and AFP are the two most common tests used in clinical practice for surveillance and screening cirrhotic patients for HCC. These tests

increase the potential for early diagnosis of HCC, and decrease the mortality and morbidity that occurs with late diagnosis of HCC.

Early diagnosis of HCC is vital to improved outcome of cirrhotic patients. Diagnosing HCC early encourages a more favorable outcome for the cirrhotic patient, with curative treatment instead of palliative treatment options (Patel, Terrault, Yao, Bass, & Ladabaum, 2005). The 5-year survival rate for cirrhosis patients without signs of decompensation with early HCC diagnosis may reach up to 70 to 80% (Pascual et al., 2008).

A wide variety of physicians manage patients with cirrhosis. Practitioners that manage cirrhosis include general practitioners, gastroenterologists, and hepatologists. The recommended treatment guidelines per evidence-based medicine are not always followed due to the lack of awareness of guidelines (Nguyen et al., 2007). The lack of HCC surveillance and screening in cirrhotic patients is indicated in the increasing mortality rate of HCC due to late diagnosis.

Background of HCC

According to Albrecht (2008), the incidence of HCC in cirrhotic patients is increasing worldwide. In the early 1990s, the incidence of HCC was 2.4 per 100,000 patients in comparison to the late 1970s when the incidence rate was 1.4 per 100,000 patients (Davila, Petersena, Nelson, & Serag, 2002). Cirrhotic patients are prone to HCC due to the nature of their liver disease, which cause damage to the hepatocytes that are the functioning cells of the liver. The liver has a massive blood supply, providing nutrients for the atypical cells to grow. These atypical cells then manifest themselves by

becoming dysplastic and eventually cancerous. HCC is a hypervascular tumor, and the massive blood supply feeds the tumor (Trinchet, 1995).

Treatment Options

Early diagnosis of HCC decreases the cirrhotic patients' mortality rate. The decrease in mortality rate is due to the multiple treatment options available to the patient with early diagnosis. The options of liver transplantation, partial hepatectomy, and trans-arterial chemoembolization (TACE) are some of the treatment options that are available for small lesions. In patients with late diagnosis of HCC, treatment options are limited.

The treatment options for HCC differ depending on the size and the characteristics of the lesion. Treatment options become limited once the lesion has grown beyond sizes that have been determined to be treatable by the recommended guidelines of professional organizations. Different treatment regimens can be offered depending on the practitioner and the facility. Patients with large liver lesions do not have the treatment options of TACE, liver transplant, or liver resection. The American Cancer Society does not recommend chemoembolization in patients with large tumors. Chemoembolization is limited to small tumors with a curative success rate in early diagnosis and with well-preserved synthetic function (Trinchet, 1995). Evidence-based medicine has concluded that the risks of chemoembolization in large tumors outweigh the benefits when attempting to chemoembolize large tumors.

According to Mazzaferro et al. (1996), liver transplants are not recommended in patients outside the Milan criteria or those with metastatic HCC. The Milan criteria states that patients with one lesion 2-5 cm or those with up to three lesions with a maximum diameter each of 3 cm are transplant candidates. The findings of Mazzaferro are

supported by the United Network for Organ Sharing (UNOS; 2008) organization, which is the governing body that originates the guidelines for liver transplantation.

Lastly, liver resection is also not recommended for patients with tumors that are proximal to large vessels or HCC or who have metastatic disease, according to the American cancer society (Sarasin, Giostra, Hadengue, 1996; Stuart, 2003). Bleeding complications are possible with resection of tumors close to big vessels. For these reasons, HCC screening and surveillance so that small tumors can be detected is vital in the management of cirrhotic patients.

In an urban setting in the southeastern United States, hepatocellular carcinoma patients are referred to the Specialty Hepatology Division routinely. Many of whom are beyond the optimal treatment phase for curative treatment. With suboptimal surveillance and screening of cirrhotic patients, small lesions are not detected. These patients have limited treatment options due to the Milan criteria. Patients outside the Milan criteria are limited to palliative treatment options.

A number of patients who are referred to the Hepatology Division are within the Milan criteria for orthotopic liver transplant (OLT). These patients that meet the UNOS (2008) transplant guidelines are screened and are listed for transplant if they are cleared during pre-transplant evaluation. Cirrhotic patients with HCC that are referred and still have the option of chemoembolization of the tumor are treated as recommended along with interventional radiology. Patients with large lesions are managed by the Hepatology Division and an oncologist. They receive oral chemotherapy and other treatment regimens based on the recommendations of the oncologist.

Patterns of Screening

Surveillance programs increase the diagnosis of small HCC lesions (Nouso et al., 2008). Some of the recommended surveillance methods for HCC are AFP, US, or spiral computed tomography (CT) or magnetic resonance imaging (MRI) every 3-6 months. Since diagnosing small lesions increases the treatment options for HCC patients, the decisions to utilize HCC surveillance in cirrhosis patients are critical.

Practitioners that choose not to screen cirrhotic patient for HCC make their decision based on many different factors. Some of the factors that have been identified in the review of the literature as the causes of late diagnosis of HCC in cirrhotic patients are the lack of access to care or management of cirrhotic patients, the lack of following the recommended guidelines, fragmented care, practitioner preferences, and the increased risk of HCC, specifically related to HCV patients (Rahbin et al., 2008). One of the most common reasons identified for the lack of transplant or other curative treatment options in cirrhotic patients with HCC is late diagnosis (Mazzaferro et al., 1996; Yu et al., 2004).

Identifying cirrhosis appears to be a factor in the lack of screening for HCC. Practitioners should be educated on the importance of diagnosing HCC early with the use of HCC screening and surveillance in cirrhotic patients. Late diagnosis of HCC affects treatment options. Treatment options become very limited in the latter stages due to the recommendations of the Milan criteria. The UNOS (2008), which establishes guidelines for potential liver transplant listing, agrees with the findings of the Milan criteria.

Objective/Aims

The AASLD (2008) has recommended guidelines for surveillance and screening cirrhotic patients for HCC to promote early diagnosis of smaller lesions. A review of the

literature emphasized the importance of screening cirrhotic patients for HCC. The literature has also indicated that the mortality of cirrhotic patients with HCC is increasing worldwide (Albrecht, 2008). This is due to the lack of screening, resulting from late detection of HCC. Promoting the early diagnosis of HCC is the primary objective of the AASLD (2008).

The diagnosis of HCC can be optimized with screening cirrhotic patients per the AASLD guidelines. The objective of this study was to assess the current screening patterns of practitioners screening and surveillance methods of cirrhotic patients. This was accomplished through chart reviews of patients that were diagnosed with HCC and cirrhosis among patients referred to the specialty Hepatology Division.

Other potential goals of this project were to identify variables that would encourage early diagnosis of HCC in cirrhotic patients. Since early diagnosis of HCC increases the treatment options available for patients, optimal treatment options are expected to improve the expected outcomes and decrease mortality rates as well.

Definition of Terms

Identifying conceptual and operational definitions are important in a research project. According to the ACS, a lesion can be defined as a tumor, mass, or a carcinoma (American Cancer Society, 2008). These terms were used interchangeably in this project when referring to HCC. The conceptual definition of HCC is a cancer tumor of the liver. The operational definition in this research project did concur with the conceptual definition. Small tumors are considered to be less than 2 cm in size. Large tumors are tumors greater than 2 cm in size as documented in the medical record at the Hepatology Division.

The model for end stage liver disease (MELD) score measures the severity of the disease process of cirrhosis and also predicts the mortality rates in cirrhosis patients in a 3-month time period. MELD score ranges is a logarithm calculation using the bilirubin, creatinine, and international normalized ratio (INR). Milan criteria are a predictor of favorable outcomes in HCC patients. Lesions within the Milan criteria are one lesion less than 5 cm and three lesions less than 3 cm.

Assumptions

1. The quality of the data in the records is accurate.

2. The Hepatology Division has a sufficient amount of subjects to perform this research.

Importance of Proposed Research

The proposed research contributes to nursing knowledge and clinical practice by informing practitioners of the importance of HCC screening in cirrhotic patients for early diagnosis of small lesions. The first objective is to assess the current practices of providers for HCC screening methods in cirrhotic patients. Promoting early diagnosis of HCC in cirrhotic patients managed by transplant centers, gastroenterologists, and primary care practitioners is another objective. A desired accomplishment is to allow patients with cirrhosis and HCC the expanded treatment options of early diagnosis. These treatment options are curative treatments, liver resection, TACE, and the potential for liver transplantation. Lastly, the most important goal of this research is to promote practice change in HCC surveillance and screening in cirrhotic patients.

The following chapters further discuss HCC screening in cirrhotic patients following the plan above. Chapter 2 synthesizes the research evidence. Chapter 3 describes the implementation of the project thesis. Chapter 4 discusses the findings of the research. The final chapter offers recommendations for practice based on the findings of the study.

CHAPTER 2: LITERATURE REVIEW

The Importance of HCC Screening

This chapter further elaborates on the review of the literature of HCC screening and surveillance in cirrhotic patients. The consistencies and inconsistencies of HCC screening and surveillance in cirrhotic patients are discussed along with what is known and unknown about screening. The current clinical practice interventions are explored. This chapter justifies the need for research on HCC screening in cirrhotic patients.

Purpose

The purpose of this literature review is to discuss the suggestions and the findings of the literature regarding HCC screening and surveillance in cirrhotic patients. The review of the literature indicates that HCC is increasing in cirrhotic patients worldwide, and that screening and surveillance practices may be ineffective despite the guidelines that have been recommended by the AASLD (Bisceglie, 2004; Chen et al., 2006). The increasing incidence of the diagnosis of HCC has increased the awareness of HCC screening in cirrhotic patients.

Background

Hepatocellular carcinoma is the fifth most common neoplasm in the world, and it is easily diagnosed with the use of laboratory and radiological studies. The AASLD (2008) has recommended HCC screening in cirrhotic patients due to their high-risk of

developing HCC. Ultrasound is the recommended screening by AASLD (2008) for early HCC detection in cirrhotic patients. Screening for HCC is a vital part of the HCC surveillance and management of cirrhotic patients. The most common screening tools used to detect and diagnosis HCC are AFP and ultrasound (Pascual et al., 2008; Patel et al., 2005; Yu et al., 2004).

Cirrhosis is considered to be a premalignant condition for liver carcinoma. The mortality rate of HCC is high in cirrhotic patients, with the mortality rate worsening with later diagnosis. The survival rate of a cirrhotic patient with late diagnosis of HCC is less than five years after diagnosis. However, the survival rate of a cirrhotic patient with early diagnosis of HCC is variable, usually over five years, with reports of survival rates of up to decades. Early diagnosis and treatment of HCC is essential for improved outcomes in cirrhotic patients. Cirrhotic patients that are screened for HCC are diagnosed early and have better treatment options (Altekruse, McGlynn, and Reichman, 2009).

The increasing rate of late HCC diagnosis and its high mortality rate over the past two decades indicate that there is a lack of HCC screening in cirrhotic patients in general. The literature notes that patients that too many patients are diagnosed with HCC are being diagnosed late with the detection of liver lesions that are greater than 5 cm. Late diagnosis of HCC increases the mortality rate of cirrhotic patients. The later the diagnosis, the more negative the consequences are: increased mortality rate, reduced likelihood of curative procedures, higher cost of healthcare, and no option of liver transplantation as treatment (Altekruse et al., 2009; Mazzaferro et al., 1996; Yu et al., 2004).

Hepatitis C infected patients have a higher rate of HCC diagnosis than any of the other causes of cirrhosis. Hepatitis C virus is recognized as a major public health problem worldwide affecting mostly low economic countries (Rahbin et al., 2008). The incidence of HCC is increasing in the Western Countries of the world, including the United States (Pascual et al., 2008). The most common causes of HCV are intravenous drug use, blood transfusions, and other high-risk behaviors including multiple sex partners. The increasing rate of infection of HCV might be contributing to the increasing in HCC diagnoses (El-Serag, Gish, & Marrero, 2009).

Increasing in Incidence

The incidence of HCC is increasing worldwide (Maruyama, Yoshikawa, & Yokosuka, 2008). Hepatocellular carcinoma is known as the fifth most common neoplasm in the world (Kulkarni, Barcak, El-Serag, & Goodgame, 2004). In Asia, HCC is one of the most common cancers (Maruyama et al., 2008). In Taiwan, HCC is the leading cause of death and the second cause of death in females over the past decade (Yu et al., 2004). Hepatocellular carcinoma has also been reported to be the third leading cause of cancer-related death in Japan (Takayasu et al., 2006).

Historically, the lowest reported incidence of HCC rates were in the United States; however, in recent decades, HCC incidence has doubled (Altekruse et al., 2009; Pascual et al., 2008; Peterson, Baron, Marsh, Oliver III, Conger Hunt, 2000). One million new cases of HCC are diagnosed annually worldwide (Kulkarni et al., 2004). According to Baron and Peterson (2001), HCC is the most common abdominal malignancy worldwide and occurs most often in patients with chronic liver disease and cirrhotic patients.

Over the past two decades particularly in the younger age groups of Asian and African Americans, the incidence of HCC has increased from 1.4 per 100,000 between 1976 and 1980 to 2.4 per 100,000 during the 1990s (Davila et al., 2002). Davila et al. (2002) also noted a significant increase in HCC diagnosis among individuals between the ages of 40 and 60 years of age in the 1990s compared to the late 1970s. These researchers analyzed the trends in the incidence of mortality from HCC. Participants were obtained from the Surveillance, Epidemiology, and End Result Registries (SEER) and Behavior Risk Factor Surveillance System (BRFSS), with all participants residing in the United States. The SEER and BRFSS are population- based cancer registries that account for more than 14% of the United States population. Patient information is entered into the database, with their diagnosis codes. There were a total of 11,547 patients with HCC diagnosis confirmed with histological studies. The majority of the participants were men at 73%, with the women accounting for the other 27%. The cities in the reporting group with the greatest number of cases were San Francisco, California, Detroit, and Michigan. Across the nine geographic regions in the U.S., whites had the lowest age-adjusted incidence rate of 1.5 per 100,000, followed by African Americans of 3.2 per 100,000, and other races of 7.0 per 100,000. The findings concluded that the mean age of patients with cirrhosis is 65 years old, with a large subset of patients being greater than 55 years old (Davila et al., 2002). These findings indicate that HCC is prevalent in the United States, reinforcing the need for surveillance programs for cirrhosis patients.

Indication for Surveillance

The indication for HCC screening and surveillance programs in cirrhotic patients is evident, with the increasing prevalence of HCC worldwide. Controversy about the

roles of screening and surveillance was examined by Bisceglie (2004). He recommended that screening with AFP blood test and ultrasound is adequate to detect HCC, with high sensitivity and reliability. AFP can be elevated for reasons not affiliated with HCC. The sensitivity and specificity of AFP is dependent on the amount detected in the blood (Maruyama et al., 2008). The sensitivity and specificity of AFP over 200 is 13.8% and the specificity of AFP is 97.4%. However, when elevated over 20ng/mL, the sensitivity of AFP is 62%, and the specificity is 78%.

The cost of AFP testing is approximately $75. AFP is sensitive to HCC. An elevated AFP may be related to other etiologies other than HCC. Pregnancy is one of the most common causes of elevated AFP, other than HCC. Ultrasonography is another common tool used to screening for HCC in cirrhotic patients. Ultrasonography is relatively inexpensive and non-invasive and detects small and large lesions. Ultrasounds allow the individual reading the film to visualize lesions, describe lesions based on their characteristics, determine the location of the lesions, and size the lesions. The detection of a lesion will prompt a complete work up of the lesion and define the lesion as malignant or non malignant, is priority. In cirrhotic patients, the likelihood of malignancy in an identified lesion is greater than the likelihood of a non-malignancy. The median doubling of lesions has been estimated to be four months. This rate of doubling of HCC is the reason for the AASLD (2008) guidelines recommending ultrasound every 6 to12 months for persons diagnosed with cirrhosis for early detection of small lesions. This time period gives the practitioner the option to use judgment to determine the time increments to screen each patient, based on the each individual case (Koteish & Thuluvath, 2002). This judgment allows the practitioner to meet the needs of the

individual patient and the recommended guidelines of the AASLD for HCC screening and surveillance. The practitioner can order screening every 6 months or every year, still meeting the guidelines of the AASLD and remaining within the limits of insurance guidelines in relation to the amount of tests that was covered.

Surveillance for HCC is not recommended for the general population because the risk of developing HCC is low (Bisceglie, 2004). Bisceglie (2004) indicated that the cost to screen the general population is considered to be unacceptable due to the low incidence in the general population. In fact, Bisceglie concluded that although the current surveillance tests for HCC screenings are sub optimal in relation to sensitivity and specificity, the current screening methods are better than not screening.

Maruyama et al. (2008) evaluated the role of both ultrasound and AFP for screening for HCC. Since the sensitivity and specificity of AFP has respectively been established, the use of AFP for screening and surveillance of HCC is accepted in clinical practice. Although false positives may result in a screening, AFP is commonly used to screen for HCC. However, a positive AFP should be correlated with the use of ultrasound for early HCC detection. Maruyama et al., (2008) emphasized against the use of single method screening with AFP for HCC screening and surveillance. Instead, the use of AFP and ultrasound was recommended for HCC screening and surveillance due to their synergistic effect of early diagnosing small lesions in cirrhotic patients. The specificity of ultrasound is noted to be 93.8%. Meanwhile, the sensitivity of ultrasound is 71.4%. Ultrasound for HCC detection has been identified to have a higher sensitivity than MRI. Magnetic resonance imaging has a sensitivity of 56% and CT has a documented sensitivity of 67%, so the relatively less expensive test seems superior. The authors

concluded that advancements in the ultrasound field have led to optimal HCC diagnosis and management.

Cirrhotic patients may need different types and methods of screening and surveillance based on their individual presentation or history and physical. The physical size of the patient is one of the major problems that have been identified in detecting lesions, along with the radiologist interpreting the ultrasound. Different methods of screening may differ based on the different individual needs of the patient or other factors (Koteish & Thuluvath, 2002).

In summary, HCC is increasing worldwide. The indications for screening cirrhotic patients for HCC are undeniable in relation to the use of radiological and laboratory studies for early detection of small lesions. Screening and surveillance promote early diagnosis and curative treatment instead of palliative treatment. As stated in the literature review, the most recommended screening methods identified were the use of AFP and ultrasound. The sensitivity and specificity of AFP and ultrasound are sufficient enough to increase early diagnosis of HCC and decrease the mortality rate of HCC patients. The usefulness of screening has been indicated by the reviewed articles.

Usefulness of Surveillance

Pascual et al. (2008) evaluated the usefulness of surveillance programs for early diagnosis of HCC in clinical practice. They compared the survival of patients with HCC diagnosed in surveillance programs to patients diagnosed with HCC that were not in surveillance programs. Two hundred and ninety patients were included in the clinical study. Of the 290 patients, 117 patients were diagnosed during regular surveillance programs, and 173 were not in surveillance programs. The patients were obtained from

the hospital as referrals to the liver unit. The surveillance program entailed ultrasound and AFP every 6 months. If a tumor was suspected, histological evaluation of the tumor was used to diagnose HCC. The patients were divided into three groups. The first group comprised patients diagnosed with HCC during regular surveillance program. The second group comprised patients with known liver disease but who were not included in a surveillance program but who were later diagnosed with HCC due to displaying symptoms. The third group consisted of patients simultaneously diagnosed with HCC and cirrhosis. Preliminary data analysis did not show any statistical difference in the prognosis between the second and the third group. Due to the three groups showing no statistical difference, the research groups reanalyzed the data using two groups. Group 1 comprised of patients diagnosed with HCC during surveillance. Group 2 included patients that were not participants of a surveillance group but who were diagnosed with HCC. Small tumors were considered as tumors less than 5 cm. Patients' mean survival for those in the surveillance and those not in surveillance programs were very similar at 15 to 16 months. Evidence such as this results in uncertainty for many physicians managing cirrhosis patients. The article concluded that surveillance programs are purposeful for diagnosing small tumors for potential curative treatment regimens. Surveillance programs increase survival in patients with cirrhosis diagnosed with HCC. These programs are more useful in patients with less advanced stages of liver disease.

The usefulness of HCC screening to diagnose HCC with ultrasound was evaluated by Yu et al. (2004). The participants were obtained from the National Taiwan University Hospital Cancer Registry from January 1996 to December 1997. Data were also obtained from the Taiwan mortality database and were linked to the participants by an

identification number to ascertain death from HCC. A total of 680 participants were included in this retrospective chart review. Hepatocellular carcinoma was confirmed by proven pathology, angiography or CT, and clinical presentation or history. The chart reviewers were all qualified and well trained in research. Participants were between the age of 20 years old and 70 years old. They were divided into three groups: surveillance, opportunistic, and symptomatic. A significant difference was noted between patients receiving ultrasound screening, whether incidental of routine. These individuals had a reduction in mortality rate from HCC. The adjusted odds ratios for surveillance versus non-surveillance were 56%, after following them for three years. They concluded that the usefulness of screening is suggested to improve the prognosis of patients with HCC.

The usefulness of screening for HCC has shown to be essential for early diagnosis. Early diagnosis is correlated with decreasing the mortality rate of HCC. Late diagnosis limits treatment options and excludes liver transplantation as a treatment option.

Accuracy of Surveillance

Snowberger et al. (2007) assessed the accuracy of screening for HCC in patients with cirrhosis. Hepatocellular carcinoma screening was done with AFP, ultrasound, CT, and MRI imaging to screen for HCC in cirrhosis patients. The study was a retrospective study conducted at a Transplant Center. Two hundred and thirty nine participants were enrolled in the research study. The participants of the research were confirmed with HCC in the explanted liver at the time of liver transplant. Screening intervals varied from 3, 6, and 12 months determined by the practitioners risk assessment. AFP and radiological imaging were used with the cutoff of 8.9 ng/mL. The majority of the patients (148/239)

had an elevated AFP. Ultrasound screening was utilized in 199/239 participants. HCC was detected in 115 or 57.8% of the participants. The size of the tumors that were detected was 3.4± 2.0 cm. The average tumor that was detected by ultrasound was 1.5 to 2.4 cm. CT was used in 164 patients with HCC, with tumor identification in 113/239 patients. The lesions detected were less than or equal to 2 cm. MRI was utilized to screen 197 of the 239 patients. Tumors were identified in 153 of the cases. MRI appeared to be more sensitive than ultrasound or CT for small lesions. The article concluded that early diagnosis is critical for optimal management of HCC and that although serum AFP and ultrasound every 6 to 12 months have been recommended by the AASLD for screening, the optimal methods are debatable. MRI was found to be the most sensitive for HCC imaging for smaller lesions. Prognostic value was evident when the AFP was extremely elevated. Although the accuracy of HCC screening and surveillance has been proven, the different types of screening tests are still a very debatable topic.

Factors Influencing Screening

Nguyen et al. (2007) investigated factors influencing physicians' screening behavior for liver cancer among high-risk patients. They evaluated the behaviors affecting screening for HCC in high-risk patients by surveying gastroenterologists, primary care physicians, and nephrologists. The total number of participants that responded to the survey was 459 of the 743 physicians that received surveys. The participants were drawn from the American Medical Association master file. Screening practices were not defined separately; they included AFP and radiological imaging. Screening was determined by a yes, no answer. The Asian-American population was oversampled due to the high prevalence of HBV and cirrhosis in Asia. The variables that

were identified as factors affecting screening were socio-demographic measures, medical training, specialty, years in practice, number of patients seen daily, and the type of health insurance that the patient presented at the time of visit. Nguyen et al. (2007) hypothesized that gastroenterologists were more likely to screen for liver cancer that primary care physicians, and study findings supported this hypothesis. Gastroenterologists were excluded from the analysis due to their 100% rate of screening cirrhosis patients for HCC. The findings noted that Gastroenterologists were more likely to screen for liver cancer than PCPs and nephrologists. The authors also concluded that despite the lack of clear evidence of effectiveness of HCC screening in cirrhotic patients, many PCPs and general practitioners (GP) screen high risk patients for HCC to detect small lesions. The fact that many physicians screen for HCC will indirectly affect the survival of high-risk patients, with early diagnosis of HCC and detection of smaller lesions.

The impact of survival of patients who received surveillance for HCC in the management of cirrhotic patients was investigated by Trevisani et al. (2004). They retrospectively evaluated 742 patients with HCC detected during semiannual or annual surveillance. Eighty-seven of the patients had HBV, with 461 patients diagnosed with HCV; alcohol (ETOH) cirrhosis affected 59 patients, with 135 patients diagnosed with multi-etiologic etiology for liver disease, and 78 patients co-infected with HCV and HBV. The participants' diagnosis of cirrhosis was confirmed by histology, laparotomy, portal hypertension, or the severity of liver dysfunction. The diagnosis of HCC along with staging was verified with CT and AFP greater than 200ng/mL. Patients within the Milan criteria were recommendation for OLT, per UNOS (2008) transplant recommendations.

The Milan criterion is a world-renowned study that is utilized by UNOS to guide transplant centers of patients that are safe to be transplanted with low risk of metastasis (Mazaferro et al., 1996). The Milan criterion recommends HCC patients with liver tumors for transplant based on the size and the number of tumors. Participants that were included were patients with one lesion less than 5 cm or three lesions less than 2 cm each. Four groups of patients were compared: HBV, HCV, ETOH, and multi-etiology. Most of the participants in all groups diagnosed with HCC were noted to have a unifocal lesion in all groups. Lesions less than 3 cm were found in more than 60% of the patients, and large tumors greater than 5 cm were uncommon and found in only 3% to 8% of the patients. Infiltrative HCC was more common in HBV and multi-etiologic patients. Two hundred out of the 742 patients met the Milan criteria for possible OLT listing. Among the demographics and the clinical features, the only one of significance was age. Age was a factor in transplanting patients, due to life expectancy based on previous studies done in Italy. Screened patients 65 years and older revealed a significance in the diagnosis of unifocal lesion 52% of the participants, with 50% of them undergoing OLT.

The article summarized that prognosis for patients with HCC detected during surveillance is independent of etiology, that prognosis of patients depends on liver function, oncologic features, and treatment, and that single nodules were found to be less common in multi-etiologic patients. An unexpected finding was that liver disease etiology does not affect the life expectancy of a patient if HCC is detected during surveillance. The results of the study were that liver disease etiology does not affect the life expectancy of a patient if HCC is detected during surveillance. Lastly, the surveillance interval did not influence survival despite the fact that HCC detected during

the more stringent screening program were diagnosed early with small lesions (Trevisani et al., 2004).

Cost-Effectiveness of HCC Surveillance

The cost of HCC surveillance is a major burden to the cost of health care in managing cirrhotic patients. Although the AASLD have recommended HCC surveillance and screening in cirrhotic patients, the cost of managing these high-risk patients can be overwhelming to the cost of health care. Patel et al. (2005) researched the cost effectiveness of HCC surveillance in patients with HCV cirrhosis. Although the cost to the patient of the laboratory and radiological studies differ depending on the type of insurance coverage, the cost of the screening tests are expensive overall. The cost of AFP is approximately $75, with the cost of ultrasound approximately $900. Lastly, the cost of CT is approximately $7,000.

The projected rate of HCC in cirrhotic patients is expected to peak in 2015, due to the increasing rate of HCV infections. It is estimated that 1.1% of the population will have been infected with HCV for 20 or more years. This percentage was calculated based on the population, the rate of infected individuals, and the time of infection.

Physicians that argue against screening programs believe that the cost of surveillance is too costly. In these participants, the screening methods consisted of AFP and ultrasound every 6 months and CT was performed after any positive screening test of AFP >20. The cost of surveillance per year for the average cirrhotic patient in a screening program is $6,000. The total cost of managing patients with cirrhosis is estimated at over $50,000/year. The cost of management of cirrhosis and treatment of HCC if indicated is estimated at over $170,000/year. This cost includes liver surveillance and liver

transplantation. Although from an economic standpoint, HCC screening is costly, it is much less than treating HCC for the estimated five-year survival rate that has been estimated. Over a five-year period, the cost of managing cirrhosis and treating HCC would cost over $800,000 per patient.

Nouso et al. (2008) researched the cost effectiveness of the HCC surveillance programs in relation to Child-Pugh class A. Child-Pugh is the classification of symptoms of cirrhosis to determine the severity of the disease process (Pascual et al., 2008). The identified symptoms utilized by Child-Pugh are encephalopathy, ascites, bilirubin, albumin, and prothrombin time. Each of these symptoms has a score from 1 to 3. The score for each symptom is given based on the severity of the symptom. Three classes of categories have been identified to define the severity of cirrhosis patients. Class A is the total score of 4 to 6. Class B is the total score of 7 to 9. Class C is the total score of 10 to 15. Participants of this cost-effectiveness research began at the age of 45.

Two groups of patients were identified; the first group received no surveillance for HCC, and the second group received surveillance every 6 months. The surveillance used was liver ultrasound. Patients that were screened and diagnosed with HCC received confirmatory diagnosis with the use of AFP, spiral CT, and fine needle biopsy. The patients that were diagnosed were divided into two categories, curable and incurable. All costs were calculated from the perspective of the health care system current cost. The annual incidence of HCC was 4%, resulting in an increase in incremental cost-effectiveness ratio (ICER). The ICER decreased as the incidence of HCC increased. The gain in quality-adjusted life years (QALYs) increased as the incidence increased. The

comparison of small HCC lesions to large HCC lesions strongly influenced the gain in QALYs and ICER with screening.

Nouso et al. (2008) concluded that although the annual incidence of HCC increased from 1% to 8%, the increase in the gain of QALYs increased from 0.15 to 0.81. When no small HCC was detected incidentally and transplantation was not selected for therapy of HCC, the difference was $US30 600/QALY, when transplantation was selected for therapy of HCC or due to decompensation the cost of the ultrasound was 17 900/QALY. The cost of treatment overall still was lower in the case of transplantation and the estimated life of the individual exceeds the five years mortality rate of late diagnosed HCC. Factors identified that affected the QALY were the starting age of surveillance and HCV type cirrhosis. In conclusion, the gain in QALYs and ICER by the surveillance of HCC varied among different patient subgroups and depends critically on the rate of small HCC detected incidentally in no-surveillance group and also depends on the annual incidence of HCC and the choice of liver transplantation as a treatment option.

Lin, Keeffe, Sanders, and Owens (2004) researched the cost-effectiveness of screening for HCC in patients with HCV. The participants of this research study consisted of 40-year-old patients with no risk factors for HCC except for HCV cirrhosis. Ultrasound and AFP was used to screen for HCC. Three different types of screening methods were used. Ultrasound and AFP every 6 months, AFP and ultrasound every 12 months, and AFP every 6 months with ultrasound every 12 months were used to screen the patients. According to a national survey, AFP every 6 months and ultrasound every 12 months is the most commonly used methods used to screen for HCC (Chalasani, Said, Ness, Hoen, & Lumeng, 1999). The true costs of laboratory and radiologic tests,

outpatient follow-up, and surgical procedures were obtained using the hospital cost accounting system. Since 25% of Gastroenterologists report using CT instead of ultrasound to screen for HCC, the analysis was modeled to account for these 25% of specialists' preference in screening. One-, two-, and three-way sensitivity analyses were performed. For the most commonly used screening, AFP every 6 months and ultrasound every 12 months, the QALYs was .048 and the LYs gained was 6 months. The most efficacious strategy that was identified was the biannual method of screening. The use of ultrasound and AFP every 6 months was costly and increased QALY by 0.033 and had a LY of 0.036. The use of CT increased the cost of the screening without increasing the QALY or the LY. In conclusion, the most cost-effective screening methods identified were the use of biannual AFP and ultrasound, with a cost-effective ratio of <$50,000/QALY.

The cost-effectiveness of HCC screening has been identified to be efficacious. Hepatocellular carcinoma screening increases the detection of small lesions. Although the cost of HCC screening is high, the cost of not screening increases mortality and higher costs of care for disease detected late in its course. The cost of health care increases without early detection. Late diagnosis of HCC increases the cost of treatment. Patients that are diagnosed late become more critically ill, potentially requiring hospitalizations, procedures, and possibly surgery depending on the stage of diagnosis.

Hepatitis B

Hepatocellular carcinoma is also very common among HBV infected patients (Bruno et al., 1997). Hepatitis B virus is known to have multiple mutations. These mutations cause HBV to be resistant to treatment. This resistance to treatment is the

groundwork for cirrhosis. The continuous damage that takes place in the liver causes fibrosis.

Non-Alcoholic Fatty Liver Disease

Although these viruses are commonly the cause of cirrhosis, multi-etiology is another cause of cirrhosis. Multi-etiology includes alcohol cirrhosis, biliary cirrhosis, non-alcoholic fatty liver disease (NAFLD), and co-infection with multiple viruses. Each of these conditions causes serious health concerns on their own. Multiple viruses cause fibrosis at a faster rate with co-infection than with a single virus infection. This is due to the rapid deterioration of the liver by the different strains of viruses. Multi-etiologic patients and co-infected individuals are at more increased risk for cirrhosis than single etiology causes (Trevisani et al., 2004). American Association for the Study of Liver Disease recommends screening all high-risk patients for HCC.

Iannaccone et al. (2007) retrospectively evaluated 22 men with tissue diagnosis of HCC in NAFLD cirrhosis patients. Twelve of the patients were incidental findings of HCC during ultrasound for unrelated reasons. The other 10 patients had abdominal pain, abnormal liver enzymes, or a palpable mass. The mean age of the men that participated in the research was 64.5 years of age. All 22 patients underwent a partial hepatectomy. Fourteen patients underwent both helical multiphasic CT and MRI, six underwent CT alone, and two underwent MRI only. Helical CT and MRI images were reviewed by two radiologists. The radiologists were aware of the diagnosis of HCC but unaware of cirrhosis. The details of the lesion were elicited from the radiologists. For example the size, location, and lesion surfaces were some of the questions that were asked to be described by the radiologists. Obesity was identified in 55% of participants, diabetes in

64%, and hypertension in 59% of the participants. Liver enzymes were elevated in 55% of the patients. Serum AFP was elevated in 36% of the patients. It was over 400ng/mL in 18% of the patients. In conclusion, NAFLD patients were more likely to present with large solitary or dominant mass, that was encapsulated, necrosed, and hypervascular. The average size of the tumors was 7.6 cm. A delay in the diagnosis of cirrhosis was evident in NAFLD patients. These patients are less likely to be screened for HCC than viral hepatitis patients due to unknown cirrhosis.

Conclusion

The review of the literature emphasized the importance of the early diagnosis of HCC in cirrhotic patients. Early diagnosis of HCC to detect small lesions is imperative to reducing the mortality rate of cirrhotic patients. The mortality rate of late diagnosis shortens the life span of cirrhotic patients and late diagnosis increases the total cost of managing HCC in cirrhotic patients. The use of radiological and laboratory studies can diagnose HCC early to detect smaller lesions; however, the relative advantage of screening programs is still not clearly demonstrated in the literature. Further study is necessary to determine the impact of HCC surveillance and screening practices on case and quality of cirrhotic patients' care outcomes.

CHAPTER 3: METHODOLOGY

The purpose of Chapter 3 is to define the research design and identify the purpose of the research design of this study. The participant sample is identified along with the reason for the sample population. Legal and ethical issues are addressed in this chapter. Validity and reliability are also discussed. Lastly the data collection tool and the methods are explained along with the analysis of the findings.

Design

A level I descriptive, cross-sectional design was used to conduct the research study analyzing the screening and surveillance of cirrhotic patients referred to the Hepatology Division for HCC. The rationale for choosing a descriptive design is due to the ability of this design to observe, describe, and document aspects of the current screening patterns of cirrhotic patients for HCC in clinical practice.

Descriptive research provides important information to the research about the population being studied. In this research study, the end point explained what is common, prevalent, and what exists in the screening and surveillance of cirrhotic patients diagnosed with HCC. Advantages of descriptive research are the revealed relationships between variables, the large amount of data that is gathered, and its ability to help to simplify large amounts of data in a more understandable way (Swatzell & Jennings, 2007).

Descriptive research also answers the who, what, when, where, and how questions. Disadvantages of descriptive research are that the researcher does not attempt to predict or manipulate an outcome, the information generated is broad in nature, and the potential for research bias exist (Oman, Krugman, & Fink, 2003).

Setting

The Hepatology Division was chosen for the site of this research study due to most cirrhotic patients being referred to the transplant center as a last resort for evaluation and treatment. Cirrhotic patients are managed by many different types of practitioners, ranging from primary care practitioners to gastroenterologists. The wide varieties of practitioners that manage cirrhotic patients alter the type of disease management of these patients, and sometimes lead to suboptimal care based on the recommended guidelines. The referring practitioners refer based on many different reasons. Some of them refer to the Hepatology Division for the cirrhotic patient to be established with a hepatologist, for disease management for HCC, or for transplant evaluation and workup. Since cirrhosis is a premalignant condition, guidelines have been outlined by the AASLD for screening and surveillance of cirrhotic patients for HCC.

In clinical practice, after observing consistent late diagnosing of HCC in cirrhotic patients that were referred to the Hepatology Division, the decision was made to study cirrhotic patients with HCC to evaluate current screening and surveillance in clinical practice. Many of these patients were not being screened per the recommended AASLD guidelines. The Hepatology Division performs HCC screening and surveillance for all cirrhotic patients, as per the AASLD guidelines. The Hepatology Division is equipped with an expert hepatology services, employing three hepatologists along with fellows,

and Transplant Surgeons. The hepatologists manage cirrhotic patients, HCC, end stage liver disease, and many other types of liver diseases.

Definitions

The conceptual definition of HCC based on the American Cancer Society (2008) is a cancerous lesion that begins in a hepatocyte cell in the liver. Many different growth patterns exist, some of which are slow growing and others fast. The operational definition for HCC is any lesion in the liver that has histological confirmation of malignancy as documented in the patient's medical record.

Criteria

The exclusion and inclusion criteria are the guidelines for the participants of the study that outline the target population. The inclusion criteria include:

1. Patients must be above the age of 18 years.

2. Patients must have confirmed diagnosis of cirrhosis by symptomology or histological analysis.

3. Patients must be a patient of the Hepatology Division.

4. Patient must have a diagnosis of HCC.

Subjects

Subjects selected for this study were chosen to represent the entire population of cirrhotic patients with HCC referred to hepatology. The patients in this study were conveniently available to the researcher due to the clinical setting of the study. The participants were patients of a Southeastern Hepatology Division managed by

hepatologists. All subjects in this research study had documented cirrhosis and HCC. Some of the subjects had biopsy confirmed HCC; others did not. The histories of the cirrhotic process of the patients were available in their extensive chart and dictations. The participants were receiving treatment regimens that have been ordered by the Hepatologist pertinent to their health condition.

Variables

Several variables were collected during this descriptive study. Demographic data were collected to describe the sample, including the type of HCC screening and surveillance, the years the patients was diagnosed with cirrhosis, the etiology of cirrhosis, and the mode of diagnosis. Other variables included the intervals of screening, the instruments used to screen, and size of the lesion at the time of diagnosis. These variables are all important in the identification of small lesions in cirrhotic patients due to possible relationships that may exist between them.

Procedure

A retrospective review of medical records of subjects meeting inclusion criteria was performed by the Principal Investigator (PI), a nurse practitioner. The PI used the eligibility guidelines to determine the charts to be reviewed for inclusion and analysis. Access to the subjects' charts was gained after the IRB process, and approval was received from University of Central Florida (UCF; see Appendix A) and Florida Hospital (see Appendix B). Performance standards were maintained, as outlined by Health Insurance Portability and Accountability Act (HIPAA), and standing policies and procedures of the teaching hospital and the Hepatology Division.

The patients' charts were reviewed by the PI for the variables outlined on the data collection tool. The variables for the study were collected from the chart review on the data collection tool and placed in an Excel spreadsheet and exported to a statistical software package (SPSS Version 18.0) for analysis.

Procedures used for data collection meet HIPAA regulations. The patient's entire medical record since the time of diagnosis of cirrhosis was evaluated for the pertinent information related to HCC screening and surveillance. Each subject was issued a unique identification code and no information which could personally identify the subject was collected. The code list and data files were secured in separate locations. The computer that was used to conduct this study was secured with a required password for access.

The steps of the research project after IRB approval were:

1. Identify the participants.
2. Code the participants.
3. Collect the data.
4. Analyze the data.
5. Report the findings.

Human Subjects

Human subject considerations are pertinent to completing the research project to assess the screening and surveillance of HCC in cirrhotic patients referred to the Hepatology Division. HIPAA guidelines were followed. Since this was a retrospective analysis of records, a consent waiver was requested and granted.

All data were collected by the PI. Because this was a retrospective chart review and no identifiers were recorded, no risks were involved. Treatment of the participants

was not affected. The participants did not benefit from this project. A potential benefit to future cirrhotic patients is possible depending on the findings, due to potential policy change for the screening of cirrhosis patients and increasing awareness of the importance of HCC screening and surveillance. Participants were not denied care nor received less optimal care if their chart was not reviewed.

A confidentiality pledge was included in the presentation to IRB. The IRB was assured that the privacy of the participants was maintained; HIPAA guidelines were followed with strict confidentiality of the patients' medical information. Records were locked in the Specialty Hepatology Division and available only to the research investigator.

Instrument

For this descriptive study, a cross-sectional research approach of retrospectively analyzing the HCC screening and surveillance in cirrhotic patients was performed utilizing the researcher-designed data collection tool for data collection (Appendix C). No previously used data collection tool was located that would provide that data variables to meet the aims and objectives of this research study. Reliability and validity of the data collection tool was not documented. The data collection tool was used to gather pertinent information that described screening history for cirrhotic patients and general information about HCC and the etiology of the cirrhosis.

The purpose of the tool was to allow the researcher to gather the necessary information of the subjects' cirrhosis, HCC, and the environment of the diagnosis. This includes the time of diagnosis, the method to diagnosis, the location of the tumor, and the stage of the cancer at the time of diagnosis.

A limitation of the data collection tool was its lack of reliability. The reliability of the tool is that it had not been demonstrated as a reliable tool due to perfectionist newness. The data collection tool was tested, with inter-rater reliability. Adjustments to the tool were made based on the results of the pilot study.

Data Analysis

Analysis of the data was performed once the data on the data collection tool was retrieved from the charts. The preliminary steps involve data cleaning and assessing the reliability of measures. The PI recorded the data directly on the data collection tool, and then inputted the information into the computer that was used to analyze the data. Missing data were coded as needed. Outliers were placed in a subgroup of the sample and analyzed separately. Distribution of scores on the variables and normalizing distributions before running statistics was done. Assumptions were met. Measurement error was assessed to inform the researcher of the extent of measurement error.

Frequencies and descriptive statistics were used for data analysis. Descriptive analysis included mean, mode, median, ranges, and standard deviations. Descriptive analysis included mean, mode, median, ranges, and standard deviations. Correlation was used to identify relationships between variables. Also, comparisons among groups were calculated.

CHAPTER 4: RESULTS

The purpose of this chapter is to present the results of the Retrospective Analysis of Cirrhotic Patients with HCC referred to the Hepatology Division. This study enrolled 37 participants from the Hepatology Division meeting the inclusion and exclusion criteria outlined in Chapter 3.

Sample

Table 1 describes the participants and the findings of the variables. Seventy-eight percent of the participants were male. The median age of the participants was 60 years of age. The youngest patient was 34 and the oldest patient was 74. The mean age was 58.6 with a standard deviation of 9. European Americans dominated the sample totaling 59% of the participants; Hispanic Americans totaled 19%, with 8% of the participant of Asian descent. Almost 60% of the subjects were married. Sixty-eight percent of the subjects completed high school. More than 61% of the participants spoke English as their primary language, with 84% of them with non-immigrant status.

Table 1

Demographic Characteristics of Participants

Characteristic	*n*	%
Gender		
Male	29	78
Female	8	22
Age		
18-59	17	46
Over 59	20	54
Ethnicity		
European	22	59
African American	0	0
Hispanic American	7	19
Asian American	3	8
Caribbean	1	3
Other	4	11
Marital Status		
Married	18	58
Life partner	3	10
Single	9	29
Divorced	1	3
Education		
Did not complete high school	2	7
High school diploma	17	68
Associate's degree	0	0
Bachelor's degree	6	21
Graduate degree	1	4
Language		
Spanish	9	24
English	22	62
Asian Country	3	8
Other	2	6

Note. $N = 37$.

Etiology of Cirrhosis

Table 2 describes the etiology of cirrhosis. The majority of the sample participants were infected with HCV accounting for 58% of the sample. Alcohol accounted for 11%, with ETOH and HCV accounting for 8%. Non-alcohol fatty liver disease accounted for 3% along with ETOH and NAFLD. One patient had autoimmune induced cirrhosis; one patient had hemochromatosis, one patient with HBV.

Table 2

Summary of Types of Cirrhosis of Patients

Types of Cirrhosis	*n*	%
Autoimmune	1	3
HBV	1	3
HCV	21	58
HBV and HCV	3	8
NAFLD	1	3
NAFLD and ETOH	1	3
ETOH	4	11
ETOH and HCV	3	8
Hemochromatosis	1	3

Note. $N = 37$.

Length of Time Diagnosed with Cirrhosis

Figure 1 indicates that the length of time from diagnosis of cirrhosis to HCC, with 53% the patients in this study diagnosed with cirrhosis was within zero to five years prior to their HCC diagnosis. Twenty percent of the patients were diagnosed with cirrhosis over 15 years before their diagnosis of HCC. Eighteen percent of the participants were diagnosed with HCC within 6 to 10 years of being diagnosed with cirrhosis. Lastly, only

8% of the patients were diagnosed with cirrhosis for 11 to 15 years prior to their diagnosis of HCC.

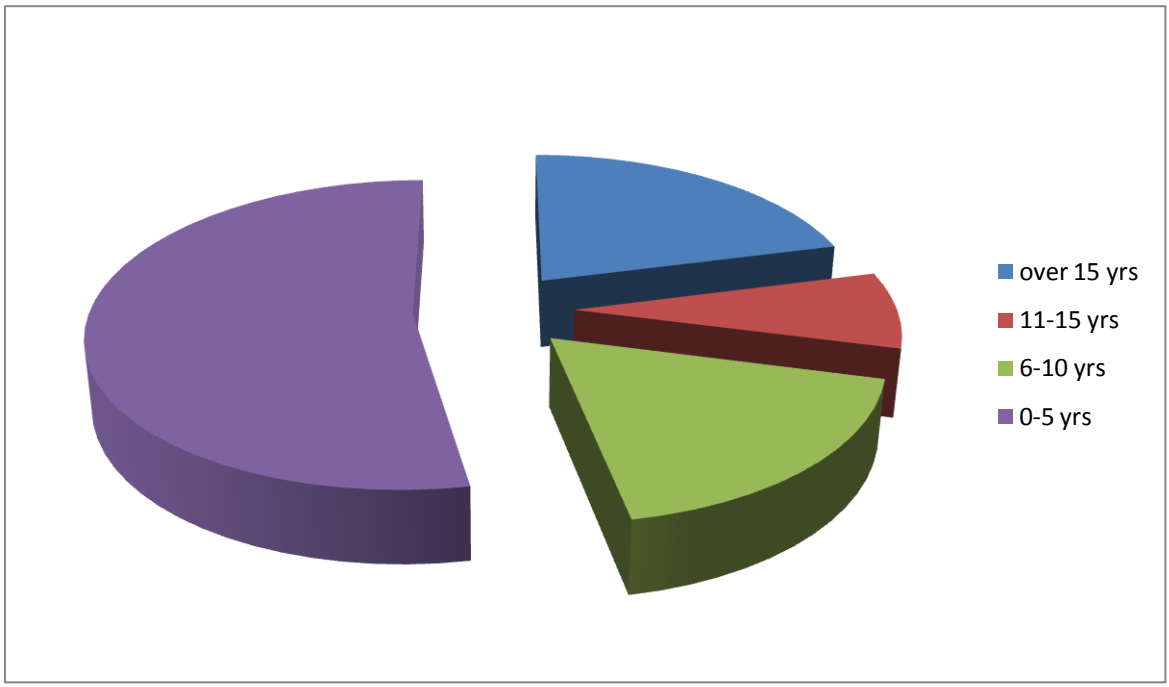

Figure 1. Years diagnosed with cirrhosis.

Co-Morbidities

Table 3 describes the co-morbidities of the patients in this study. Diabetes was the highest co-morbidity measuring 41%. Hypertension was present in 35% of the patients. Dyslipidemia followed HTN, with 11% of the patients. Lastly 6% of the patients of this study were diagnosed with renal failure.

Table 3

Summary of Co-Morbidities of Participants

Co-morbidities	*n*	%
Hypertension	13	35
Diabetes	15	41
Hyperlipidemia	4	11
Renal Failure	2	6

Note. N = 37.

Symptoms of Decompensation and Laboratory Values

A summary of symptoms and lab results of participants is provided in Table 4. Symptoms of liver decompensation included bleeding, jaundice, encephalopathy, and ascites. The most common symptom of decompensation was bleeding noted in 29% of the participants. Encephalopathy and ascites occurred in 27% of the participants. Eleven percent of the participants had jaundice. Abnormal INR was experienced in 60% of subjects. The mean INR was 1.24 with a minimum INR of .93 and a maximum INR of 1.85. Sixty percent of subjects experienced hypoalbunemia. Hyperbilirubinemia occurred in 47% of subjects. The median bilirubin was 3.07 units, with a maximum bilirubin of 30 units. Lastly, 15% of individuals displayed laboratory results of elevated creatinine above 1.12.

MELD Score

Figure 2 displays the MELD scores of the participant in the study. The average MELD score was 8, with a mode MELD score of 7. The highest reported MELD was 22, with the lowest reported MELD of 6. The standard deviation of the MELD score was 10.06. The MELD is important describes the severity of the disease process.

Table 4

Summary of Symptoms and Labs of Participants

Characteristics	*n*	%
Decompensation		
Bleeding	10	29
Jaundice	4	11
Encephalopathy	9	27
Ascites	9	27
Abnormal laboratory value		
Albumin	21	60
INR	14	54
Creatinine	5	15
Bilirubin	13	47

Note. N = 37.

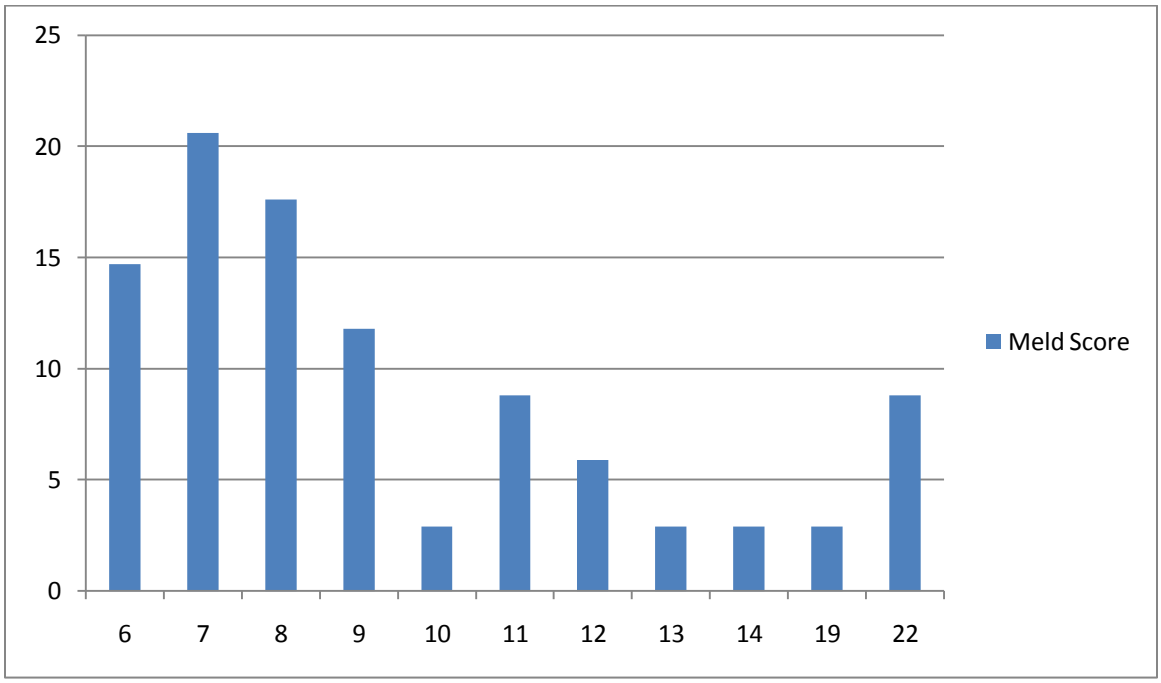

Figure 2. Histogram of participants' MELD scores.

Summary of Lesions

Table 5 describes the summary of HCC diagnosis lesions at the time of diagnosis, the referring physicians of the patients managing physicians, and HCC screening as per recommendations. A large percentage of the subjects were diagnosed with one lesion, with the average lesion measuring 2.5 cm. The mean size of the lesions was 2.97 cm. The largest lesion was 11.83 cm, with the smallest lesion measuring 1.10 cm. The median size of the screened patients lesions were 1.49 cm, with the unscreened patients lesions measuring 2.5 cm. Of the participants in this study, 64% were diagnosed with lesions between 2-5 cm. Lastly, 27% of the patients were diagnosed with lesions less than 2 cm, with only 8% of the patients diagnosed with lesions that were greater than 5cm.

The referring physicians of the subjects in this study to the Division of Hepatology were 70% gastroenterologists and 30% PCP. Seventy percent of the patients were referred for HCC. In this study the HCC diagnosis was made by a gastroenterologist 32% of the times, 12% by a PCP, and 27% by the Hepatology Division. The Hepatology division screened the patients according to the AASLD guidelines. The lesions that were identified by the Hepatology Division were identified early. Twenty four percent of the participants were diagnosed with HCC in the hospital. One patient was an incidental finding that was diagnosed during explantation of the liver during the liver transplant. This patient had received multiple USs, CTs, and MRIs. All of the radiological studies were negative. It should also be noted that over 50% of the subjects in this study received OLT since their referral. Ultrasound detected 40% of the lesions. CT 33% of lesions, with MRI mostly used as a confirmatory test.

Table 5

Summary of HCC Lesions

Characteristic	*n*	%
Number of lesion		
One lesion	24	68
Two lesions	8	23
Three lesions	3	9
Size of the lesion		
Less than 2.0 cm	9	27
2.5-5 cm	20	64
Over 5 cm	3	8
Referred for HCC		
No	26	70
Yes	11	30
Lesion diagnosed with		
Ultrasound	13	40
Computerized tomography (CT)	11	33
Magnetic resonance Imaging (MRI)	9	27

Note. N = 37.

In summary of Table 6, the recommended ultrasound screening of every 6 months to a year was not performed in 67% of the subjects in this study. Only 33% of the participants were screened according to the guidelines, and the screening was performed by the Hepatology Division. AFP screening was performed every 6 months to a year in only 43% of the participants. More than 55% of the patients were not screened routinely with AFP.

Of the patients referred to the Division of Hepatology, 32% were diagnosed with HCC by a gastroenterologist. The Hepatology Division detected 26% of the HCC.

Twenty four percent of the patients were diagnosed with HCC during a hospital stay. Lastly, 3% of the patients were diagnosed with HCC in surgery.

Table 6

HCC Screening, Referring, and Diagnosing Practitioners

Characteristic	*n*	%
Ultrasound screening per protocol		
Yes	12	33
No	23	67
AFP screening per protocol		
Yes	15	43
No	20	57
Referred for HCC		
Yes	26	70
No	11	30
Who diagnosed HCC		
Gastroenterologist	11	32
Hepatology	9	26
PCP	4	12
Hospital	8	24
During surgery	1	3
Other	1	3

Note. N = 37.

Screening Patterns of HCC

The recommended AASLD guidelines for HCC screening and surveillance were not indicated in the screening patterns of the subjects in this study. More than half of the patients were not screened with ultrasound and AFP every 6 months a year. Of the patients, 67% were not screened with ultrasound. Only 43% of the patients were screened with AFP screening.

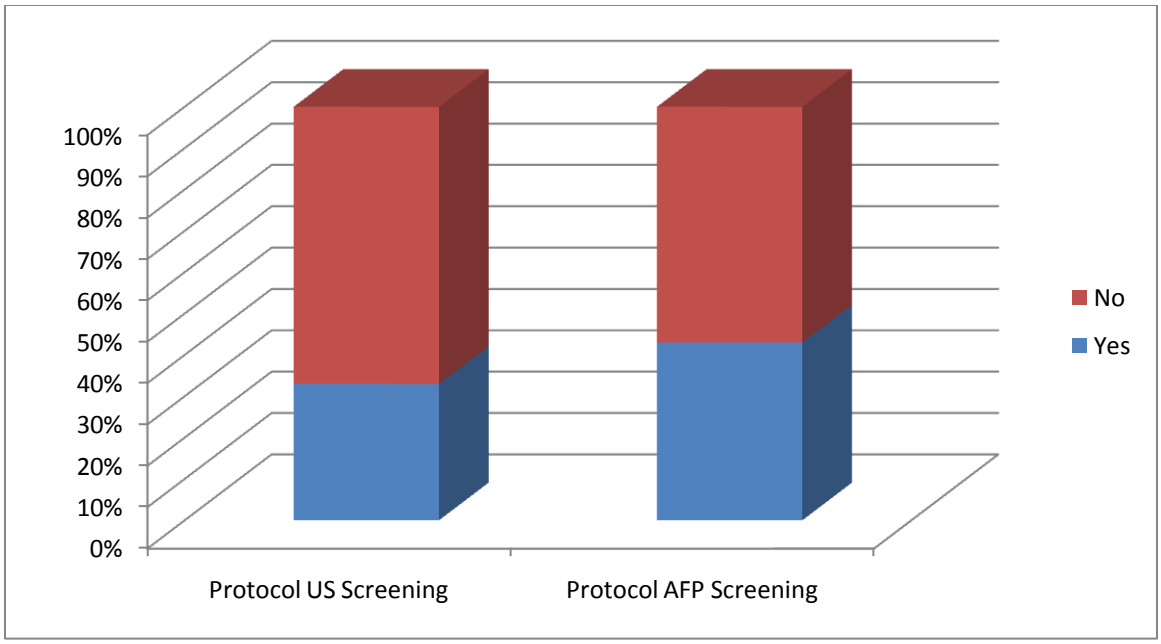

Figure 3. Comparison of ultrasound and AFP HCC screening protocols.

Table 7 discusses the screening patterns of HCC screening in cirrhotic patients. The screening patterns of cirrhotic patients referred to the Hepatology Division were not in accordance to the AASLD guidelines. The screening patterns of PCPs were 25% with gastroenterologist following at 27%. The Hepatology Division performed the highest percentage of HCC screening. They screened 90% of their patients.

The mean number of lesions detected in patients who received HCC screening was 1.4. The patients who were screened were detected earlier and had smaller lesions. Although ultrasound screening was indicated to be higher in sensitivity in detecting HCC, AFP was significant also. Using AFP and HCC in combination indicated to detect small treatable lesions.

Table 7

Summary Table of Pattern of HCC Screening

Characteristic	Screened per protocol	Not screened
Who diagnosed lesion		
Hepatology	90%	10%
Gastroenterology	27%	73%
PCP	25%	75%
Number of lesions with AFP		
1 lesion	54%	46%
2 lesion	0%	100%
3 lesion	67%	33%
Number of lesions with ultrasound		
1 lesion	42%	58%
2 lesion	0%	100%
3 lesion	66%	33%
Number of lesions		
Mean number of nodules	1.40	2.5
Size		
Means size of lesion with ultrasound	3.18	3.00
Mean size of lesion with AFP	2.67	3.20
Largest tumor size	2.97 cm	11.83 cm
Size of lesion with AFP		
Less than 2cm	29%	26%
2-5 cm	64%	58%
Greater than 5 cm	7%	16%
Size of lesion with ultrasound		
Less than 2 cm	18%	32%
2-5 cm	72%	54%
Greater than 5 cm	10%	14%

CHAPTER 5: DISCUSSION

Major Findings

The systematic retrospective analysis of patients referred to the Division of Hepatology indicated that cirrhotic patients were not screening according to the AASLD guidelines prior to referral to the Hepatology Divisions. The records that were reviewed in this retrospective chart analysis demonstrated that cirrhotic patients were screening sporadically by gastroenterologist and PCPs; patients were diagnosed with large lesions indicating that no HCC screening or surveillance was performed; patients were not referred to the Hepatology Division until HCC was diagnosed, and cirrhosis was diagnosed late in the disease process.

Importantly 53 % of the patients were diagnosed with HCC within 5 years of their cirrhosis diagnosis. This indicates that the initial diagnosis of cirrhosis was undiagnosed, since Rahbin, et al 2008 noted that cirrhosis is likely to occur within the first two decades of HCV infection. Several of the patients were not diagnosed with cirrhosis, until the HCC was detected and after further work-up of their symptoms. Therefore, screening for cirrhosis itself is also deficient and may be the reason for the lack of HCC screening and surveillance. According to Chang and Chuang 1988, cirrhosis is a premalignant condition with approximately 10-30% of patients with cirrhosis resulting in the diagnosis of HCC. It is obvious that making the diagnosis of cirrhosis is essential to incorporating the

recommended AASLD guidelines for HCC screening and surveillance in cirrhotic patients.

Another major finding that was identified indicated that in clinical practice, patients that have been diagnosed with cirrhosis were also not screened according to the AASLD guidelines. The AASLD guidelines recommend HCC screening and surveillance of cirrhotic patients with ultrasound to every 6 months to a year for early HCC detection. The review of literature indicated that ultrasound and AFP are the two most common imaging and laboratory tests used for HCC screening and surveillance in cirrhotic patients (Maruyama et al., 2008). The utilization of ultrasound for HCC screening increases the diagnosis of smaller lesions for improved outcomes and decreases the mortality rate. The findings of this study revealed that ultrasound diagnosed 40% of HCC lesions in the subjects. Computerized tomography was used to diagnose 33% of the HCC in this study. Magnetic resonance imaging was used more as a verification of the lesion when making the diagnosis of HCC than as a screening tool. Once a lesion was identified, CT was used widely for biopsying the lesion in almost 50% of the cases. With the records revealing that HCC screening was sporadic and not according to the recommended AASLD guidelines, this explains the increasing in late diagnosis of HCC and the high mortality rate of these patients. In this study, although the majority of the lesions were diagnosed late with the lesions measuring 2.5 cm, over 50% of the participants received OLT which is curative treatment.

AFP screening was also performed sub-optimally in almost 70% of the patients in this study. According to Yu et al. (2004) AFP is commonly used in clinical practice as serum markers for HCC. Four of the patients that were not screening in accordance with

the guidelines were noncompliant and again some of the patients had cirrhosis that was undiagnosed. Only 4 of the 37 patients were noncompliant. Ten percent of the patients presented with elevated AFP prior to the diagnosis of the lesion, and the elevation in AFP prompt more intense investigation by the practitioner with the use of MRI or specialized CT imaging. Another small amount of patients maintained a normal AFP, although they did have a lesion that was identified on imaging.

Symptoms of decompensation occurred in the majority of the patients in this study, with the most frequent experienced symptom of bleeding due to portal hypertension occurring in 29% of the patients. The next most common symptom was encephalopathy and ascites. Twenty seven percent of the patients displayed both of these symptoms. Lastly jaundice was only documented in11% of patients. According to Pascual et al. (2008), some of the most common clinical manifestations symptoms in decompensated cirrhotic patients were ascites, weakness, abdominal pain, variceal bleeding, encephalopathy, diarrhea, jaundice, and fever. In their study 40% of the patients showed evidence of ascites, 19% of variceal bleeding, 7% encephalopathy, and 3% jaundice.

The most common co-morbidity that was documented in the participants of this study was diabetes. Diabetes was documented in over 41% of the patients. Hypertension was documented in 35% of the patients, with dyslipidemia next at 11%. Renal failure occurred in only 6% of the patients in this study. This was surprising due to the high risk of renal failure that is common in end stage liver disease patients. Hepato-renal syndrome is common, due to the failing liver and the decreased blood flow to the kidneys. This syndrome resolved in OLT.

The results of this study in relation to diagnosing smaller lesions with HCC screening were supported by the review of literature. It was interesting to note that 70% of the subjects were referred to the Division of Hepatology stat for HCC. Although most of the referrals were for single lesions, the lesions were considered large lesions according to the standards of the ACS. Twenty-three percent of the subjects' records indicated them having 2 lesions at the time of diagnosis, with 9% of the patients having 3 lesions at the time of diagnosis. The maximum amount of lesions that was reflected in the records was 3.

Diagnosing smaller lesions improves treatment outcomes and decreases mortality rates (Pascual et al., 2008). In this study the majority of the lesions that were diagnosed were diagnosed were not small. Twenty seven percent of the patients were diagnosed with lesions measuring less than 2 cm. The majority of the lesions were 2-5 cm totaling 64%. Only 8% of the records indicated lesions measuring over 5 cm. The median size of the lesions that were diagnosed measured 2.5 cm. The mean size of the lesions was 2.97 cm. The range of the lesions measured 1.10-11.83cm.

Lesions larger than 2 cm are considered large according to the ACS. The larger the lesion is, the larger the opportunity for metastasis and for limited treatment options. According to the Milan criteria, most of the patients in this study were still optimal for liver transplantation; however, the goal for HCC surveillance and screening is to identify smaller lesions that are less than 2 cm. Smaller lesions decrease the risk of metastatic disease, the risk of decompensation, and the risk of ineligibility for OLT. Practitioners should screen cirrhotic patients utilizing the recommended guidelines, to optimize the diagnosis of smaller lesions for better patient outcomes.

Similar to previous studies, this study demonstrated that HCV patients were more likely to be diagnosed with cirrhosis and HCC than other etiologies of cirrhosis. The HCV accounts for 55% of patients diagnosed with cirrhosis (Snowberger et al., 2007). In this study Hepatitis C accounted for 58% of the cirrhotic patients with HCC. Following HCV was ETOH was the etiology of 11% of the patients. Alcohol and HCV was the etiology of 8% of the sample. The other participants in this study were diagnosed with autoimmune cirrhosis, hemochromatosis, NAFLD, or HBV. Since the literature notes that HCV in on the rise, is can be assumed the incidence for HCC is also on the rise. In all cirrhotic patients, HCC screening is a vital part of their management, since this study indicated that HCC can affect all cirrhotic patients.

The effectiveness of HCC screening and surveillance was identified in this study. Since the goal of HCC screening and surveillance is to identify smaller lesions for improved outcomes, the effectiveness of the tools used to screen in clinical practice are of importance. In this study, although the majority of the participants were diagnosed with HCC with the detection of the lesion by ultrasound imaging, a notable number of them were diagnosed with CT imaging. Approximately 33% of the HCC in this study was detected by CT. Although CT is not recommended for HCC screening and surveillance by the AASLD, this study has shown that CT is capable of detecting small liver lesions as well as ultrasound. In fact, many patients were sent for CT after the detection of the lesion by ultrasound, for confirmation or possibly for more information related to the tumor and other structures that could be identified with the use of CT imaging. The AASLD guidelines recommend HCC screening and surveillance with ultrasound. This study has shown that either ultrasound or CT imaging has the ability to diagnose small

lesions. However, from a cost standpoint ultrasound would be used for screening and surveillance instead to CT.

It is important to note that over70% of the patients in this study was managed by a gastroenterologist prior to them being referred to the Hepatology Division. This indicates that gastroenterologists were not screening their cirrhotic patients as recommended by the AASLD guidelines. Gastroenterologists are our first line in diagnosing cirrhosis and in the early detection of smaller lesions, since they are the primary referral for practitioners with patients with abnormal liver enzymes, hepatitis, or liver disease. Since a large sum of patients referred to the Hepatology Division was referred from gastroenterologists, if gastroenterologists implemented HCC screening and surveillance in their cirrhotic patients, the potential to diagnose smaller lesions would be beneficial.

One patient was noted to have a PCP and a gastroenterologist. This patient was referred to the gastroenterologist by the PCP for a HCC lesion measuring 5-6 cm on a MRI that was done sporadically. This patient was not routinely for HCC. The patient was evaluated by the gastroenterologist first and then referred to the Hepatology Division for further management. The ideal care for this patient should have been, to first perform HCC screening and surveillance since the patient was cirrhotic, then refer the patient directly to the Hepatology Division once a lesion is detected, instead of to the gastroenterologist.

All patients with HCC should be referred to a Hepatology Division for evaluation and treatment. The Hepatology Division is highly specialized in managing and treating HCC patients. In these settings all cirrhotic patients are screened for HCC according to

the AASLD guidelines. Hepatology has the capabilities of making decisions that can change the predicted outcome of the patients' outcome.

Diagnosing Cirrhosis

The review of literature suggests that many patients with cirrhosis are unaware of their liver function status. This can occur for many reasons. One of the most common reasons is that cirrhosis is typically asymptomatic for up to decades. Another common reason is due to the practitioners ignoring elevated liver function test (LFT).

Hepatocytes are the working cells of the liver. These cells are regenerating cells that work to carry out the many functions of the liver. Inflammation of hepatocytes is displayed in laboratory testing as the transaminases or LFT. Elevated LFT is an indication that hepatocytes are inflamed. Continuous inflammation of the hepatocytes has the ability to damage the liver, resulting in fibrosis and finally ending in cirrhosis of the liver.

The signs of inflammation of the liver that are displayed as a result of the destruction of hepatocytes are elevated LFT. Elevated LFT should be investigated, when elevated during laboratory testing for annual physicals, or for any reasons. The workup for elevated LFT should include a detailed review of the current medications as the cause, acute hepatitis panel laboratory testing, and lastly ultrasound imaging if the no cause can be identified. If the acute hepatitis panel is negative, medications are not the source of the elevated LFT, and the ultrasound is within normal limits, other tests should be performed to evaluate for fibrosis or cirrhosis. A nuclear scan of the liver has the capability of evaluating the hepatocellular cells for dysfunction, with the use of a radioactive tracer that is injected into the venous circulation. This tracer is up taken from the circulation by

the hepatocytes. The hepatocytes that are functioning will take up the tracer, meanwhile the hepatocytes that and not functioning will not uptake the tracer. The results of the nuclear scan will inform the practitioners of the function of the liver. A more invasive evaluation of the liver cells is a liver biopsy for tissue sampling. The liver biopsy has the capabilities to inform the practitioner with more detailed information about the hepatocytes. Some details that are available with a liver biopsy is the amount of inflammation of the hepatocytes, evidence of fibrosis or bridging, patterns of disease processes (autoimmune, chronic active hepatitis, or hemochromatosis) to name a few. Since early diagnosis of cirrhosis is the precursor to knowing which patients need to be screening for HCC for early detection of smaller lesions, elevated LFT should be investigated, and cirrhosis should be ruled out in patients with elevated LFT (Aragon and Younossi, 2010; Skelly, James, & Ryder, 2001).

The liver is responsible for many functions in the body. Some of the important functions of the liver are the production of clotting factors, manufacturing proteins, storing fats and carbohydrates, detoxifying the blood, and forming and secreting bile. The liver is vital to the survival of human beings. Unlike the kidneys or the heart, no machine has the capabilities of reproducing the functions of the liver such as a dialysis machine or a balloon pump. Once the liver is unable to function according to the demands of the body, decompensation may occur. The symptoms of decompensation include but are not limited to, elevated bilirubin, elevated clotting factors, elevated creatinine due to the hepato-renal syndrome, hypoalbunemia, and or encephalopathy. The complex functions of the liver are vital to survival.

Conclusion

The findings of this preliminary study suggest that HCC screening in cirrhotic patients is indicated, effective, and useful in diagnosing small lesions. Screening for HCC with ultrasound, AFP, or CT has shown to be beneficial, to diagnosis HCC early and allow the individual curative treatment options. Early HCC diagnosis increases treatment options, decreases mortality rates, and therefore is cost effective. The diagnosis of small lesions is imperative to improving the mortality rate of cirrhotic patients, and decreasing the cost of care that will occur with late diagnosis. This study reiterated the importance of HCC screening cirrhotic patients as per the AASLD guidelines. It also indicated that cirrhosis is under diagnosed, which is likely due to its asymptomatic nature. The review of literature reported that late diagnosis of HCC has a five-year mortality rate of over 70% (Pascual et al., 2008). Decreasing the mortality rate of HCC in cirrhotic patients should be an expected goal of all practitioners caring for cirrhotic patients. This can be accomplished by HCC surveillance and screening based on the existing recommended AASLD guidelines.

Limitations

Limitations were identified in this study. Over 70% of the participants of the study were transplant patients, a convenience sampling method was used to select the patients, and one center was utilized for data collection. The sample size was small, yet still indicated those cirrhotic patients were not screened according to the AASLD. These limitations have been acknowledged.

Strengths

There were numerous strengths that were identified in this preliminary descriptive study. The knowledge of the practitioners conducting the study, the facility used to retrieve the data, the piloting of the data collection tool, and the richness of the documentation from the Division of Hepatology were a few strengths that were identified. The practitioners affiliated with this study are knowledgeable in gastroenterology and hepatology. The hepatologist on the committee of this research study is the chief hepatologist of the Hepatology Division. The Division of Hepatology was equipped with detailed documentation and rich data that was available for data collection. The data were collected directly on the tool by the primary investigator and re-verified while inputting the data into the computer. These strengths increase the validity of this study and the findings.

Implications for Nursing

The effectiveness of HCC screening and surveillance was evident in this descriptive study. Due to the increasing rate of HCC worldwide (Albrecht, 2008) and the fact that HCC is reported as the fifth-leading cause of cancers deaths in the world (Kulkarni et al., 2004) HCC screening and surveillance in cirrhotic patients is supported and recommended in clinical practice. The early identification of cirrhosis and the implementation of HCC screening and surveillance in cirrhotic patients are crucial in their management. Practitioners should be aware of the AASLD guidelines for the proper management of cirrhotic patients. The implementation of these guidelines has the potential for practitioners to detect smaller lesions, decrease the mortality rate of the patients, and provide curative treatment options in cirrhotic patients. Thus, implementing

HCC screening in cirrhotic patients has the potential to change projected patient outcomes.

Implications for Future Research

Future research is recommended in HCC screening and surveillance of cirrhotic patients for early detection of smaller lesions. Adapting the current AASLD guidelines for HCC screening is sufficient and effective when caring for cirrhotic patients. Ultrasound and AFP is effective in diagnosing small HCC lesions. To ensure proper HCC screening and surveillance in cirrhotic patients, they should be referred to hepatology divisions. The increasing rate of HCC worldwide and the increased mortality rate of HCC in cirrhotic patients escalate the indications for further research in HCC screening. Research has the potential to enlighten researchers and others of the effectiveness, usefulness, and other benefits of the HCC screening for small lesion detection. Research is the gatekeeper for evidence-based practice.

Impact of Project

The outcomes of this project are relevant to the management of cirrhotic patients and the importance of HCC screening and surveillance for early identification of smaller lesions. Individuals that were affected by the outcomes of this study includes practicing practitioners caring for cirrhotic patients, practitioners unaware of the recommended AASLD HCC screening and surveillance guidelines, and could affect the treatment guidelines for HCC screening and surveillance. The outcomes were expected to reveal descriptive information surrounding HCC screening in cirrhotic patients. Some of the information that was revealed in the endpoint of the study was the screening and

surveillance practices of practitioners, the type of imaging tools used to diagnose HCC, when HCC is diagnosed, and who made the diagnosis. These findings can be used as the foundation for future research projects with cirrhotic patients and HCC.

APPENDIX A: IRB APPROVAL (UCF)

University of Central Florida Institutional Review Board
Office of Research & Commercialization
12201 Research Parkway, Suite 501
Orlando, Florida 32826-3246
Telephone: 407-823-2901 or 407-882-2276
www.research.ucf.edu/compliance/irb.html

Approval of Exempt Human Research

From: **UCF Institutional Review Board #1**
FWA00000351, IRB00001138

To: **Shelly Ann Scott-Castell**

Date: **April 01, 2010**

Dear Researcher:

On 4/1/2010, the IRB approved the following activity as human participant research that is exempt from regulation:

Type of Review:	Exempt Determination
Project Title:	Retrospective Analysis of Screening Patternsin Cirrhotic Patients with Hepatocellular Carcinoma
Investigator:	Shelly Ann Scott-Castell
IRB Number:	SBE-10-06868
Funding Agency:	
Grant Title:	
Research ID:	N/A

This determination applies only to the activities described in the IRB submission and does not apply should any changes be made. If changes are made and there are questions about whether these changes affect the exempt status of the human research, please contact the IRB. When you have completed your research, please submit a Study Closure request in iRIS so that IRB records will be accurate.

In the conduct of this research, you are responsible to follow the requirements of the Investigator Manual.

On behalf of Joseph Bielitzki, DVM, UCF IRB Chair, this letter is signed by:

Signature applied by Joanne Muratori on 04/01/2010 11:19:59 AM EST

IRB Coordinator

APPENDIX B: IRB APPROVAL (FLORIDA HOSPITAL)

Florida Hospital
Institutional Review Board
212 E. Winter Park Street
Orlando, FL 32804
Telephone: (407) 303-5581
Fax: (407) 303-3638
FWA: 00002060

May 11, 2010

Shelly Scott-Castell ARNP
601 E. Rollins Street
Orlando FL 32804

Dear Ms. Scott-Castell:

FH #: 2459-7492; Sponsor #: n/a

Title: Retrospective Analysis of Cirrhotic Patients with Hepatocellular Carcinoma

Florida Hospital IRB Expedited Initial Approval Date: 05/11/10
FH IRB Expiration Date: 05/10/11
Waiver from Informed Consent Granted under: 45 CFR 46.116(d)
HIPAA Authorization: Waived
Meeting Date for FH IRB Notification: 06/08/10

NOTE: This study may not be initiated without approval of the Florida Hospital Office of Research Administration.

In response to your request and on behalf of the Florida Hospital IRB, the IRB granted expedited approval to the study as noted above, based on categories approved in 45 CFR 46.110. Unless the informed consent requirement was waived, you are required to use the IRB approved informed consent.

Prior to the expiration dated noted above, the IRB must be made aware of the status of your project(s). A progress report will be required. [45 CFR 46.109 (e)] If the project has not been completed, you may request renewed approval.

It is your responsibility to remain in compliance with all applicable state and federal regulations regarding research as well as adhering to the Florida Hospital IRB ***Handbook for the Protection of Human Research Subjects***.

You are reminded that a change in the study requires resubmission and approval of the IRB prior to initiation of the change in the study or informed consent.

It is the responsibility of the principal investigator to report to the Chair of the Institutional Review Board within 10 days, and in writing, any related unanticipated problems involving risks to subjects or others, such as adverse reactions to biological drugs, radio-isotopes or to medical devices.

Florida Hospital Institutional Review Board complies with federal and state regulations and GCP guidelines. Failure of the principal investigator or members of his/her research team to abide by the Florida Hospital IRB *Handbook for the Protection of Human Research Subjects* or failure to abide by FDA/OHRP Regulations governing this research may result in suspension and/or termination of this study.

Florida Hospital Institutional Review Board has the authority to review all documentation and the informed consent process for studies approved through the Florida Hospital IRB.

Laura Orem

Laura Orem, CIP, CIM
IRB Administrator
IRB Member
Florida Hospital IRB

APPENDIX C: DATA COLLECTION TOOL

Hepatocellular Carcinoma in Cirrhotic Patients
Data Collection Tool/Form

Assigned Subject # ____

Age _____

First clinic appointment date _____

Date of Referral _____

Demographic Data:

Race	Ethnicity	Gender	Immigrant	Marital
(1) Caucasian	(1) Hispanic	(1) Male	(1) Yes	(1) Married
(2) African American	(2) Non Hispanic	(2) Female	(2) No	(2) Single
(3) Hispanic				(3) Separated
(4) Asian				(4) Widowed
(5) American Indian				(5) Never Married
(6) Caribbean				(6) Partner

Level of Education	Primary Language	Length of Time in US
(1) Middle School	(1) English	(1) Date of Arrival in the US
(2) High School	(2) Spanish	
(3) Bachelor's	(3) French	
(4) Graduate	(4) Asian	
(5) Doctoral	(5) Other than above	

Cirrhosis Data: Rate of Cirrhosis Diagnosis:

Cause	Year of Diagnosis	Health when Diagnosed with HCC
(1) HCV		(1) Bleeding Yes/No
(2) HBV		(2) Jaundiced Yes/No
(3) Fatty Liver		(3) Encephalopathy Yes/No
(4) ETOH Cirrhosis		(4) Ascites Yes/No
(5) Co-Infected		
(6) Unknown		

Co-morbidity
(1) Diabetes Yes/No
(2) HTN Yes/No
(3) Renal Failure Yes/No

Date of Diagnosis	How Diagnosed Cirrhosis	History on Noncompliance with Labs, Tests, Meds, Appointments
		(1) Yes
		(2) No

Hepatocellular Carcinoma Screening Data:

Ultrasound Dates	AFP Dates	Ultrasound Dates	C.T. Date	MRI Date

Hepatocellular Carcinoma Data:

Date of Diagnosis	Who Diagnosed HCC	Number of Nodules	Tumor Size

Provider Info:

Total Number of Providers	Type of Provider	Location of Provider
	(1) Hepatologist	
	(2) Gastroenterologist	
	(3) General Practitioner	
	(4) Nurse Practitioner	
	(5) Physician Assistant	
	(6) Other	

Clinical Data at Time of Diagnosis:

Bilirubin	INR	Creatinine	Albumin

MELD Score_____

Child Pugh _____

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