Hepatocellular carcinoma at the University of Puerto Rico Liver Transplant Clinic

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The aim of this study was to determine the prevalence of hepatocellular carcinoma (HCC) in our liver transplant clinic, and describe the risk factors, predictors and treatment outcomes of primary liver cancer.

Methods: **459 of 469 records of patients attending the UPR Liver Transplant Clinic from September 1999 to January 2005 were reviewed. Frequency distributions were computed to describe the study group.**

Results: **35 patients (7%) were included. 33 patients were diagnosed during the pre-transplant evaluation and 2 were diagnosed in the explant. Mean age at diagnosis in males was 54.5 years and 61.3 years in females. The main cause of liver disease was hepatitis C plus ethanolism in 42.9% (15 cases). The frequency of HCC in patients with a BMI ^{3} 25 Kg/m^2 was more than twice that of patients with a BMI < 25 Kg/m^2. Predominant presenting symptoms were ascites (40%), abdominal pain and jaundice (25%). Normal alpha-fetoprotein was found in 25%. 76% had a MELD score < 20. Treatment modalities included trans-arterial embolization (TAE/TACE) (49%), conservative treatment (34%), liver transplant (OLT, 23%), partial resection (9%) and systemic chemotherapy (3%). Eight patients underwent OLT and one developed primary graft failure, needing a second transplant. Two had T1N0M0 score, with a 100% survival at 2 yrs, and 6 patients had a T2N0M0 score, 5 of which underwent TAE before OLT, with an overall survival of 67%. Partial resection had an overall survival of 66%.**

Conclusions: **The population of our clinic is similar in gender and age distribution, etiology of chronic liver disease, and clinical presentation of HCC to others previously described. Our treatment outcomes and mortality rates compare with those observed in the literature.**

Key words: Hepatocellular carcinoma, Liver transplant clinic, Chronic liver disease.

Hepatocellular carcinoma (HCC) is the most common malignant tumor arising from the liver, and is the fifth most common neoplasm in the world (1,2). HCC has been estimated to cause up to 1 million deaths per year worldwide (3,4). It carries a dismal prognosis and up to 70% of patients have unresectable disease at the time of diagnosis (5). The incidence has doubled in the past two decades in the United States, from 1.4 to 2.4 in 100,000, primarily due to the increasing rate of HCV in the population (2,6).

In 2000, a hundred and ninety-nine new cases of primary carcinoma of the liver in both females and males were reported in Puerto Rico for an adjusted incidence rate of 5.2 per 100,000 population per year (7). Primary liver carcinoma represents 3.9% of all the new cancer cases reported in Puerto Rico for the year 2000. This is a three–fold increase from the reported incidence in 1982, when the adjusted incidence rate was 1.8 per 100,000 population per year (8). This increase parallels that of the United States. Compared to the worldwide distribution of HCC, where high incidence regions have more than 15 cases per 100,000 population per year, PR is still considered a low incidence area. High incidence regions include Sub-Saharan Africa, Hong Kong, Taiwan, and the People's Republic of China, with an annual incidence of over 130,000 cases (9).

HCC usually develops in patients with chronic liver disease, with an annual incidence of 1-6% in patients with cirrhosis of different etiologies, and is the leading cause of death among them (1,10). Since studies have shown that treatment is more effective if HCC is diagnosed at an earlier stage, programs for screening and early diagnosis of HCC in patients with cirrhosis have been adopted,

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resulting in an increase in number of cases diagnosed (6). This surveillance has allowed up to 40% of patients to be treated by therapies that improve patient survival as much as 50% at 5 yrs in specialized centers (1). Periodic abdominal ultrasonography and serologic test for α-fetoprotein levels have been utilized for screening in many countries, including our Liver Transplant Evaluation Clinic, where it is performed every 6 months. Although still controversial, Yuen MF et al demonstrated that in areas in which facilities are available for performing both tests, HCC can be identified at an earlier stage, resulting in a higher chance of receiving treatment (11).

Liver transplantation (OLT) is the most effective treatment for hepatocellular carcinoma in patients with cirrhosis and localized disease. The liver allocation system, using MELD (Model for End Stage Liver Disease) score since 2000 (12), assigns a priority score to patients with stage II tumors in an attempt to achieve transplantation before the tumor stage precludes its success (2,13).

The aim of this study was to describe the characteristics of HCC in the population with chronic liver disease seen in the University of Puerto Rico Liver Transplant Clinic.

Methodology

A retrospective review of the records of all patients seen in the UPR Liver Transplant Clinic from September 1999 to January 2005 was performed. Criteria for the diagnosis of HCC were α-fetoprotein levels (AFP) levels of more than 500 ng/mL, associated with a liver mass by US; a lesion on spiral CT or MRI with features consistent with HCC, with or without AFP ≥20ng/mL, liver biopsy showing HCC, or incidental HCC found in the explant of patients who underwent transplantation. 459 of 469 records were available and reviewed. Patients with equivocal laboratory data, an US lesion not documented on spiral CT scan or MRI, and all the remaining patients with end stage liver disease without a diagnosis of HCC were excluded.

A data collection worksheet was designed to review the medical records of patients that met the inclusion criteria. Demographic data, date of diagnosis, etiology of liver disease and symptoms were recorded. Body mass index was calculated whenever possible. All laboratory data at the first visit to the clinic and all imaging modalities as means for diagnosis were obtained for calculations of tumor staging and the MELD score. Tumor staging was based on the TNM score. Laboratory data included serological markers for hepatitis B (HBsAg, HBsAb, HBcAb), and hepatitis C (anti HCV), levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (Alk Phos), gamma glutamyltransferase (GGT), α-fetoprotein (AFP), coagulation profile and complete blood count. We analyzed the pattern of the most common laboratory findings related to the development of HCC as described in the literature. The elected treatment modality was recorded to monitor clinical outcomes. Mortality was recorded when available.

Frequency distributions were computed to describe the study group. The study was approved by the Medical Sciences Campus Institutional Review Board.

Results

459 records were available for review, 35 fulfilled the inclusion criteria for a diagnosis of HCC (7%); 2 out of 35 patients were diagnosed in the explant histology. The mean age at diagnosis was 57; 83% (29) of the patients with HCC were males.

Hepatitis C virus was an etiologic factor in 26 out of 35 patients (74%) (Figure 1). Twenty of twenty-nine (69%) had a BMI over 25 Kg/m^2 (overweight).

Initial presentation before diagnosis was ascites in 40% and abdominal pain and jaundice in 25%. Portosystemic encephalopathy was present in 22%. Weight loss, anorexia, and esophageal varices with and without evidence of bleeding were also found less frequently. Other symptoms included fever and diarrhea noted after the incidental finding of a liver mass. Several variables previously described as independent predictors for the development of HCC (14) are shown in Table 1.

Of the 424 patients without HCC, 187 had normal AFP

Figure 1. Distribution of Patients With HCC by Etiology of CLD

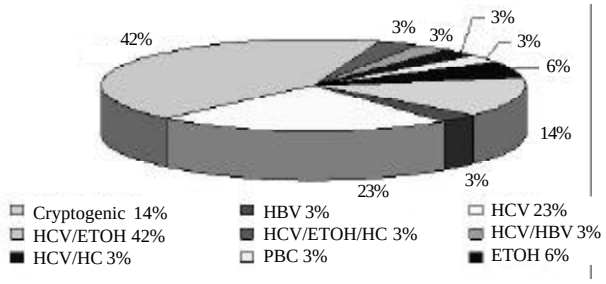


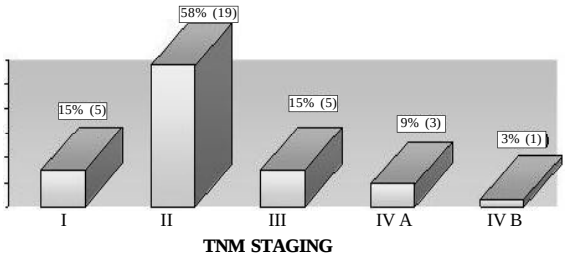
Table 1. Patients with laboratory variables described as independent predictors for HCC occurrence

PT activity < 75%	PLT < 75,000	HCV Ab
79 % 27/34	42% 13 /31	74% 26/35

levels (< 20 ng/mL), and 104 had levels above the upper limit of normal (≥ 20 ng/mL). Of 32 patients with HCC with AFP levels available, only 24 were above 20 ng/dL (range from 20 to 129,500 ng/dl), for a positive predictive value of only 19%.

MELD score was less than 20 in 26 of the 34 patients diagnosed with HCC (76%). 23 patients had an early stage of disease on diagnosis (73%, Stage I-II, Figure 2). Eight patients underwent OLT and one developed primary donor organ failure, needing a second transplant. Two of the 8 patients who underwent OLT had a T1N0M0 score, with 100% survival at 1.5 yrs. The remaining six patients who underwent OLT had a T2N0M0 score, 5 of which underwent TAE before OLT, with an overall survival of 67% at 1 yr. Of the 3 patients who underwent partial resection, one died, with survival at 1.5 yrs of 66%. The overall mortality for HCC was 45% (14 out of 30).

Figure 2. TNM Staging at Diagnosis of HCC



Treatment modalities for HCC included trans-arterial embolization (TAE) or chemoembolization (TACE) in 49%, OLT (23%), partial resection (9%), systemic chemotherapy (6%), or no treatment (34%). TAE(6) or TACE(11) was given to the patients for either shrinkage or liquefaction of the tumor. Five patients underwent OLT after TAE/TACE and 3 died after the transplant. One patient underwent a partial resection with survival of 11 months. Nine patients underwent embolization for unresectable disease and six died after a mean of 1.6 years. Other five patients were still alive at 12 months at the time the medical records were reviewed (Table 2). Of the 17 patients that underwent TAE, 5 patients suffered from post-embolization syndrome, 2 patients had bleeding, and one patient developed hemobilia, transient elevations in transaminases, and hepatic artery thrombosis. In the 3 patients that had partial resection of the liver, no immediate complications were reported, one died after 1.5 years. One patient underwent systemic chemotherapy.

Table 2. Treatment modalities according to TNM Stage at diagnosis

	TNM Stage at diagnosis				
Treatment	**T1N0M0**	**T2N0M0**	**T3N0M0**	**T4N0M0**	**M1**
OLT	2	1			
TAE/TACE		6	3	1	1
OLT		5			
PR		1			
Partial Resection	1	1			
Chemotherapy			1		
No treatment*	3*	5*	2*	2	

*Patients referred for alternative treatments who did not return to clinic.

OLT= orthotopic liver transplant
TAE= transarterial embolization
TACE= transarterial chemoembolization
PR= partial resection

Discussion

Velázquez et al. reported age as an independent predictive factor for hepatocellular carcinoma in a prospective randomized two- center study (14). Although gender and age of HCC vary in different countries, hepatocellular carcinoma is more common world-wide in males 50 to 60 yrs of age (14). Velázquez et al found that cirrhotic patients older than 54 years have a 4 time greater risk for developing HCC (14). In addition, obesity has been described as a significant independent predictor of the development of HCC (4). Patients with HCC in our clinic had the same age and gender distribution as previously reported, and increased BMI was present in the majority.

It has been suggested that 98.5% of patients with HCC have either cirrhosis of any cause or chronic active hepatitis (11). Other described risk factors include environmental toxins such as aflatoxins, which are common contaminants of corn, soybeans and peanuts (9). Exposure to this toxin is associated with mutations of the p53 tumor suppressor gene and has a potentiating effect when combined with HBV. Other toxins described as independent risk factors for the development of HCC include the blue-green algal toxin Microcystin found in pond-water and betel nut chewing, in China and Asia respectively (15). Benvegnù et al reported in a prospective surveillance study that an advanced stage of cirrhosis of any etiology was significantly associated with an increased risk of developing a nodular type of HCC (10). They also described that having chronic active hepatitis, specifically HBV as well as combined HBV and HCV was significantly associated with an infiltrating type of HCC. Hepatitis C infection was the main etiologic factor found in our population, with other causes of cirrhosis accounting for the rest. No patient had an HCC in the absence of chronic liver disease.

Prothrombin activity <75% (4-6 s over normal), platelet

count less than 75 x 10^3 / mm^3 and anti- HCV antibodies, have been described as variables with independent predictive value for the development of HCC (14). Llovet et al. described that increasing trends in alkaline phosphatase and gamma glutamyltransferase levels were predictive of poor prognosis in patients with HCC (16). Of the available laboratory values in our patients, we found a Prothrombin time activity less than 75% in 79% and the presence of HCV Ab in 74% of the cases. Almost half of the patients with HCC had low platelet counts (less than 75,000).

The National Cancer Institute has no screening guidelines for HCC, but there is an increasing trend to screen high-risk populations using alpha-fetoprotein levels combined with ultrasound (US) or Computed Tomography (CT- scan)(17,18). Alpha-fetoprotein (AFP) is commonly used for surveillance as a serum marker for early detection of HCC. AFP levels of more than 400-500 ng/mL, associated with a liver mass by US; or AFP ≥20ng/mL and a lesion in spiral CT or MRI with features consistent with HCC are considered diagnostic of HCC. Levels may be normal in up to 40 % of cases with HCC, especially at an early stage, and may be elevated in patients with exacerbations of chronic hepatitis or in cirrhosis (19). Its use in the surveillance of HCC has reported sensitivity that ranges from 39% to 64%, specificity from 76% to 91% and positive predictive value of 9% to 32% (19). When combined with US the positive predictive value may improve, however its accuracy depends on the operator. Although a low positive predictive value was found for AFP alone in the present study, where forty percent of our cases had a normal AFP, combination with imaging studies increased the diagnostic sensitivity to 84%.

The staging of hepatocellular carcinoma is an important prognostic tool used to guide treatment and stratify patients according to their physical tolerance and life expectancy. Several staging systems have been proposed over the years but there is no consensus on which system is the best. We selected the TNM staging system because of the availability of imaging studies providing an objective evidence of size, nodal involvement and presence of metastases, and the limited information on biochemical data, which is used in other classifications, including the Okuda Classification, the Barcelona Clinic Liver Cancer (BCLC), and the Cancer of the Liver Italian Program (CLIP).

The tumor-node-metastasis (TNM) score has been widely used to establish whether a patient with HCC meets the inclusion criteria for transplantation. This score does not take into account underlying hepatic function, fails to predict survival in patients undergoing transplantation or resection (4,20), and does not distinguish patients with multifocal HCC. Patients with HCC stage T1 and T2 are generally considered to have good outcome after transplantation (21), although Mazzaferro et al have suggested that this system fails to demonstrate any prognostic value in the early stage of disease in a selected cohort evaluated prospectively after liver transplantation (21). The majority of our patients were found to have an early stage of disease at diagnosis, allowing several treatment modalities including liver transplantation, partial resection, and transarterial embolization with or without chemotherapeutic agents. Patients with advanced disease received systemic chemotherapy or only management of their end stage liver disease.

Allocation for liver transplantation in patients with HCC is based on MELD score and Milan criteria, which predict survival. The Milan criteria may be adapted to the TNM staging system as T1 HCC (single lesion <2 cm) and T2 HCC (one nodule >2cm; < 5 cm or two to three nodules no more than 3 cm). HCC patients Stage I do not receive any priority in MELD score, whereas those with stage II receive a priority score of 24 (2,15). Excellent survival rates are achieved after liver transplantation in patients with a unifocal tumor mass < 5 cm in diameter, or no more than 3 multifocal tumors each less than 3 cm in diameter, without tumor invasion of blood vessels or lymph nodes (3,4,21,22).

There is a 3-month pre-transplantation mortality of 8% for T1 HCC and 15% for T2 HCC (2,15). In our series, 76% of the patients diagnosed with HCC had a MELD score less than 20. The 8 patients who underwent OLT following the Milan criteria had an overall survival of 63% at 1.5 yrs in Stage I and Stage II disease, comparable with the survival rate described in the literature.

The use of pre-transplant adjuvant therapy for HCC has been suggested to improve tumor free survival after transplantation (3,4,22). Almost half of our patients received trans-arterial embolization or chemoembolization (TAE/TACE). In five, the goal was shrinkage or liquefaction of the tumor prior to OLT; only 2 of these patients with unresectable disease achieved good results. The number of patients receiving other treatment modalities, such as tumor resection and systemic chemotherapy, was too small to reach any conclusions.

A review of a population with chronic liver disease in Puerto Rico showed a prevalence of hepatocellular carcinoma of 7%. Half of these were associated to hepatitis C, a disease that has shown a high prevalence in San Juan (23). Characteristics of the population and outcome were similar to that reported in other groups. The rising incidence in hepatocellular carcinoma in Puerto Rico is likely related to the large number of patients infected with chronic hepatitis C, a statistic that raises the specter of a serious public health problem in the next decade. Awareness about this complication of hepatitis C and cirrhosis could result

in earlier diagnosis and better chance of effective treatment and survival.

Resumen

Trasfondo: El cáncer hepatocelular (CHC) es el quinto cáncer más común en el mundo. En el año 2000 en Puerto Rico se reportaron 199 casos nuevos de cáncer primario de hígado, con una incidencia ajustada de 5.2 por cada 100,000 habitantes al año. La meta de este estudio es determinar la prevalencia de CHC en nuestra clinica de transplante de hígado y describir los factores de riesgo, predictores y resultados de los tratamientos ofrecidos a estos pacientes. ***Métodos:*** Se revisaron los expedientes médicos de todos los pacientes que se atendieron el la Clínica de Transplante de Hígado de la Universidad de Puerto Rico desde septiembre de 1999 hasta enero de 2005. De 469 expedientes, 459 estuvieron disponibles para ser evaluados. ***Resultados:*** Un total de 35 pacientes (7%) cumplieron los criterios de inclusión para CHC. Treinta y tres de éstos fueron diagnosticados durante la evaluación pre-transplante y 2 se diagnosticaron en la patología del hígado removido. La edad promedio a la cual se hizo el diagnóstico en hombres fue 54.5 años y 61.3 en las mujeres. La razón principal de enfermedad crónica de hígado en pacientes con CHC fue en pacientes con etanolismo crónico que al mismo tiempo estaban infectados con el virus de hepatitis C (42.9%). La frecuencia de CHC en pacientes con un índice de masa corporal mayor de 25 era más de dos veces la frecuencia que en pacientes con un índice de masa corporal menor de 25 Kg/m^2. El síntoma predominante al momento de la presentación clínica fue acsitis (40%), dolor abdominal e ictericia (25%). Se encontraron valores normales de alfa-fetoproteína en 25% de los pacientes. Un total de 26 de los 34 pacientes diagnosticados con CHC (76%) tuvieron una puntuación de MELD de menos 20. Las modalidades de tratamiento incluyen embolización trans-arterial con y sin agentes quimoterapéuticos (49%), tratamiento conservador (34%), transplante de hígado (23%), reselección parcial (9%) y quimioterapia sistémica (3%). Un total de 8 pacientes fueron transplantados y uno desarrollo rechazo primario del órgano transplantado requiriendo un segundo transplante. Dos pacientes tuvieron un puntuación de T1N0M0 con un 100% de sobrevida de 2 años y seis pacientes tuvieron una puntuación de T2N0M0, cinco de los cuales fueron sometidos a embolización trans-arterial antes del transplante con una sobrevida total de 67%. Los pacientes que recibieron resección parcial tuvieron una sobrevida de 66%. ***Conclusiones:*** La población de nuestra clínica es similar a otras poblaciones estudiadas en términos de género, distribución por edad, etiología de enfermedad crónica de hígado y presentación clínica de CHC. Nuestros resultados de tratamiento e índices de mortalidad se comparan con otros observados en la literatura. La incidencia ascendente de CHC en Puerto Rico debe crear conciencia y promover el diagnóstico y manejo adecuado con el fin de mejorar la sobrevida de estos pacientes.

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