

Liver Transplantation for Hepatocellular Carcinoma in Puerto Ricans: Underutilization of a Curative Therapy

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Objective: Hepatocellular carcinoma (HCC), the most common type of liver cancer, is becoming a healthcare burden for Puerto Rico and, in particular, for those clinics that specialize in liver disease. It is our hypothesis that liver transplantation, the most effective curative option for unresectable tumors, is underutilized. We describe in detail the outcomes of liver transplants for HCC in Puerto Ricans referred to a major liver transplant center in the USA.

Methods: Thirty-two Puerto Rican HCC patients receiving transplants (from January 1, 1997, through July of 2012) at Tampa General Hospital are described. Recurrence rates were calculated, and the Kaplan–Meier estimator was used for survival analysis.

Results: The proportion of transplants performed for HCC in our Puerto Rican patients was only 12% ($p = 0.05$). Disease-free survival at 1, 3, and 5 years was 93.7%, 83%, and 78.8%, respectively. Patient survival at 1, 3, and 5 years was 96.7%, 75%, and 67%, respectively. Sixty-nine percent of the 32 patients were alive at the mean follow-up of 56 months. The recurrence rate from 2002 to the present is 14%.

Conclusion: This study provides the most comprehensive report detailing the relative benefits of utilizing liver transplantation as a curative option for Puerto Ricans with hepatocellular carcinoma. It also incorporates the first comprehensive review of the available literature of liver cancer in Puerto Rico. Survival and recurrence rates were comparable to published results. In Puerto Rico, liver transplantation for HCC patients has been underutilized. In order to improve outcomes over the next 2 decades, it is imperative that the healthcare system in Puerto Rico handle the burden of this disease using liver transplantation, locoregional therapies, and newer treatments for hepatitis C and HCC. [*P R Health Sci J* 2014;33:170-176]

Key words: Liver transplants, Hepatocellular carcinoma, Liver cancer, Hispanics, Puerto Ricans, Transplant utilization

Hepatocellular carcinoma accounts for more than half a million deaths worldwide, annually (1). Evidence points towards hepatitis C and alcohol-related cirrhosis as the main causes of hepatocellular carcinoma in the Western hemisphere (2,3). In Puerto Rico, 2.3% of the general adult population is HCV seropositive (4). In those who develop chronic hepatitis C, it is estimated that nearly 30% will progress to cirrhosis (3). Furthermore, the obesity epidemic, together with the developments of non-alcoholic steatohepatitis (NASH), NASH-induced cirrhosis, and HCC, will impact Puerto Rico immensely in the following decades. Obesity, risks of cancer, and mortality are linked. A large percentage of the island's young people are overweight or obese, while estimates show this percentage to be lower in the corresponding population on the US mainland (5). Hepatocellular carcinoma was found to have the highest mortality rate in obese males than any other kind of cancer was found to have (6). In addition, it has the fastest growing mortality rate of all cancers (7).

The age-adjusted incidence rate in Puerto Rico for liver cancer in men was 9.1 per 100,000 population/yr and 3.7 per 100,000/yr in females from 1999 through 2003, per the Puerto

Rico Cancer Registry (8). There was an average annual increase of 2.4% per year in men and 1.0% in women, while the overall age-adjusted incidence rate was 6.1 per 100,000/year (9). This was a higher incidence rate than that which was previously reported in 2000 (5.2 per 100,000 population/yr) (9). These numbers are alarmingly higher than those that have been found in like populations in Puerto Rico's mainland counterpart, the United States, where the age-adjusted incidence rate was 2.4 per 100,000 in 2003 (3). In 2005, it was 4.9 per 100,000 (10). A thorough review of the data obtained from the Puerto Rico Cancer Registry and from the Surveillance, Epidemiology,

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and End Results (SEER) program concluded that liver cancer continues to be a public health priority in Puerto Rico. Health disparities were found, in which US whites, and non-Hispanic blacks in the US had significantly lower risks of death from liver cancer than Puerto Ricans did, with a reduction in risk ranging from 14% to 58% (11). The Puerto Rico Cancer Registry was last updated in 2008, and it can only be presumed that the figures of today would coincide in proportion with those found in the previous literature. With the current lack of surveillance and increasing incidence rates in Puerto Rico, HCC is and is projected to be an enormous burden for healthcare services as well as for specialized clinics and transplant centers (12).

Liver transplantation (LTx) offers the best strategy for long-term survival for HCC patients with underlying cirrhosis that is unresectable. Fewer than 15% of patients with HCC are candidates for resection. Although hepatic resection is widely available, it should be offered early and limited to patients without portal hypertension, to avoid post-operative hepatic failure (13). For these patients, the likelihood of disease-free survival is greatest when liver transplantation is undertaken. To that end, dealing with the hepatocellular carcinoma health crisis is being made feasible by Puerto Rico's newly created liver transplant program and because, as well, of the local organ procurement agency's access to the majority of Puerto Rican donors.

After more than a decade of our taking part in University of Puerto Rico liver transplant evaluation clinics and working at the Tampa General Hospital liver transplant center, we, the authors, are of the opinion that liver transplantation as a viable treatment strategy for HCC patients is not being utilized to its fullest extent (14). As a result of our review of the literature of HCC in Puerto Rico, which literature consists of 6 reports published over the last 47 years, we discovered that only 2 of these reports mentioned liver transplants as an available treatment option. According to the literature we reviewed, 10 patients from Puerto Rico received transplants in the past 47 years.

It is our hypothesis that, in our program, liver transplantation for Puerto Ricans with HCC is underutilized. This manuscript will provide the evidence of overall underutilization, doing so by taking into account the proportion of HCC patients from Puerto Rico who received transplants at the transplant center (the greatest number of said transplants having taken place in the last decade) and the results of our literature review. Our aim is to describe in detail the outcomes of LTx for HCC in Puerto Ricans referred to a major liver transplant center in the USA. Based on our experience with LTx in Puerto Ricans, we expect the results to be excellent (15). To our knowledge, this is the only article that describes the outcomes for a consecutive series of patients from PR who were offered LTx for their hepatocellular carcinoma.

Methods

Approval for the study was obtained from the Institutional Review Board of the University of South Florida. Patients

were identified consecutively from the time of Tampa General Hospital's program's inception. Data on all patients were complete, having been obtained from the Electronic Privacy Information Center (EPIC), the Organ Transplant Care Platform (via Organ Transplant Tracking Record, OTTR), and transplant flowcharts. In addition, the United Network for Organ Sharing database containing our institution's transplant data was also accessed. From a consecutive series of LTx patients at Tampa General Hospital from January 1, 1997, through July of 2012, 1,420 LTx recipients were identified. Of these, 263 patients were Puerto Ricans. Thirty-two HCC patients from Puerto Rico were referred to our center for LTx and received transplants (6 of these patients had incidental tumors at the time of explanting and were included). These 32 patients comprised the study group. Patients of Puerto Rican descent residing on the US mainland or in Florida who received a transplant at our center were excluded. The Barcelona Clinic for Liver Cancer (BCLC) classification was used for cancer stage (16). All liver transplants were carried out in an orthotopic fashion, with either a venovenous bypass or caval preservation. Immunosuppression consisted of tacrolimus with mycophenolate mofetil and corticosteroids. Attempts were made to withdraw corticosteroids at 3 to 6 months post-LTx and to minimize MMF or tacrolimus, as needed. In cases of renal insufficiency, basiliximab was administered. Statistical analysis consisted of Kaplan-Meier analysis to calculate survival and disease-free survival; a log-rank test was used to calculate differences between the curves. Patient survival was obtained from transplant-dedicated databases at Tampa General Hospital. Patients who died within 60 days were excluded from the recurrence analysis to avoid a bias from underreporting recurrences. The statistical analysis was as follows: The difference between 2 groups was determined by Fisher's 2-tailed t-test. A 2-tailed p-value less than or equal to 0.05 was considered significant. Data were entered into Microsoft Excel for Windows (Microsoft Corporation, Redmond, WA). Statistical analysis was done using SAS 9.2 (Cary, NC; SAS Institute Inc.).

Results

The fraction of transplants performed on our Puerto Rican HCC patients was low (32/263 or 12%). The fraction of HCC patients from Florida and the US mainland who received transplants was higher (220/1,167 or 17%). The difference did not achieve significance but suggests a trend ($p = 0.05$; Fisher 2-tailed test). Hepatitis C accounted for the etiology of liver disease in 24/32 patients (76%). The average Child-Pugh score at referral was 9.7. The average donor was 43 years old. The median waiting time was only 28 days. Table 1 depicts the demographics of the 30 HCC patients who received transplants. Table 2 depicts the characteristics of the excised tumors. Patient survival by pathologic stage (BCLC) at 1, 3, and 5 years was 100%, 87%, and 87%, respectively, for patients at stage A, and

89%, 67%, and 55%, respectively, for patients at stage B. There were only 2 stage C patients, both of whom expired within 42 months post-transplant after their cancer recurred. Patient survival by pathologic stage was significant (log-rank = 0.02). Disease-free survival rates for stage A patients at 1, 3, and 5 years were 100%, 94%, and 94%, respectively; said rates for stage B patients were 80%, 8%, and 68%, respectively. Disease-free survival by pathologic stage was also significant (log-rank = 0.01). Figures 1 and 2 depict disease-free survival and patient survival (as derived by the Kaplan-Meier method), respectively. Disease-free survival at 1, 3, and 5 years was 93.7%, 83%, and

78.8%, respectively. Patient survival at 1, 3, and 5 years was 96.7%, 75%, and 67%, respectively. Currently, 22/32 (69%) of the patients are alive. The mean follow-up time for all the patients was 56 months.

Six patients saw their cancer recur (6/30), a rate of 20%. In the MELD era (from Feb. 2002), the recurrence rate was 14%. No patients were excluded because of early death, as none died

Table 1. Patient Demographics

Recipient age	55
Donor age	43
BMI	28
Waitlist Time, Median	28 days
Sex: Male/Female	90%/10%
incidental	16.60%
<i>Etiology</i>	
HCV	14 (44%)
HCV+ETOH	10 (32%)
ETOH	4 (12%)
cryptogenic/NASH	3 (9%)
HBV	1 (3%)
<i>Locoregional Therapy</i>	
MELD @ Tx	22
Cold Time (min)	466
Warm Time (min)	43.6

Table 2. Tumor Characteristics

<i>Radiological Stage (BCLC)</i>	
A	78%
B	22%
Radiol. Tumor Burden (cm)	3.24
Size of Largest Tumor (cm)	3
Average Number of Nodules	1.3
Average TACE Treatment	1.3
<i>Pathology Stage (BCLC)</i>	
A	18 (58.6%)
B	10 (34.4%)
C	2 (6.8%)
Number of HCCs, Path	2.14 cm
Size of 1st Tumor	3.34 cm
<i>Results of Locoreg Therapy</i>	
Partial Necrosis	11 (40.7%)
Full Necrosis	16 (59.2%)
AFP, Median	31.2

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; TACE, trans-arterial chemoembolization; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein

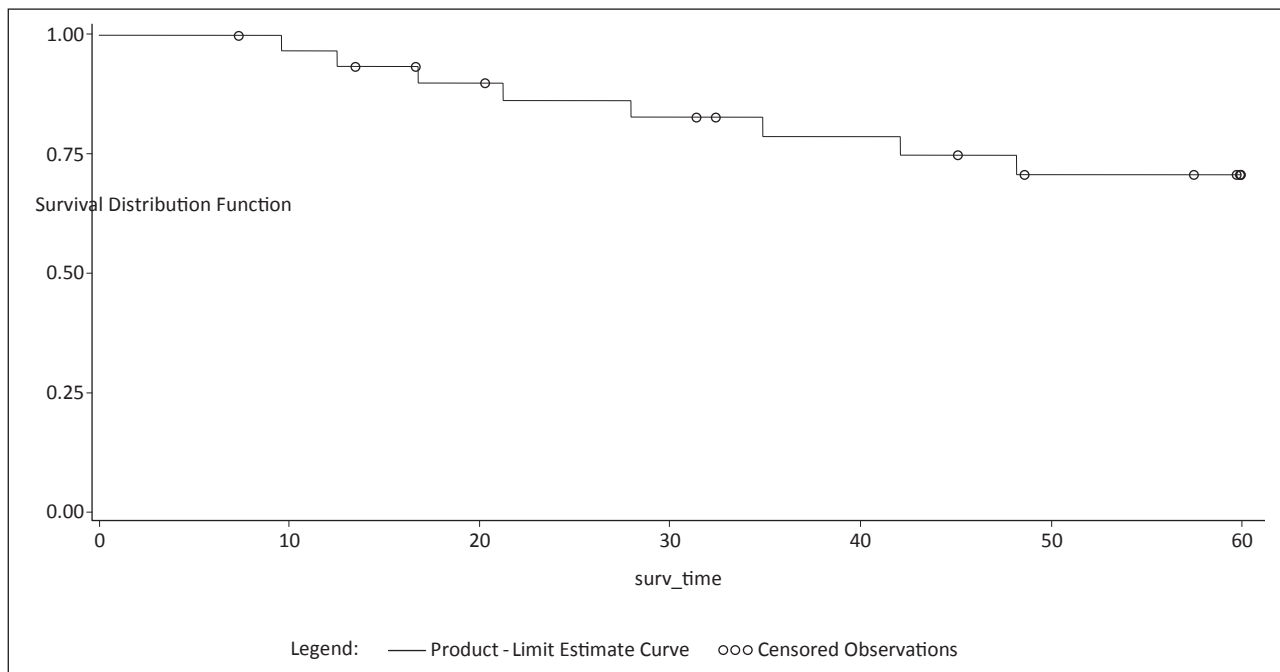


Figure 1. Patient Survival

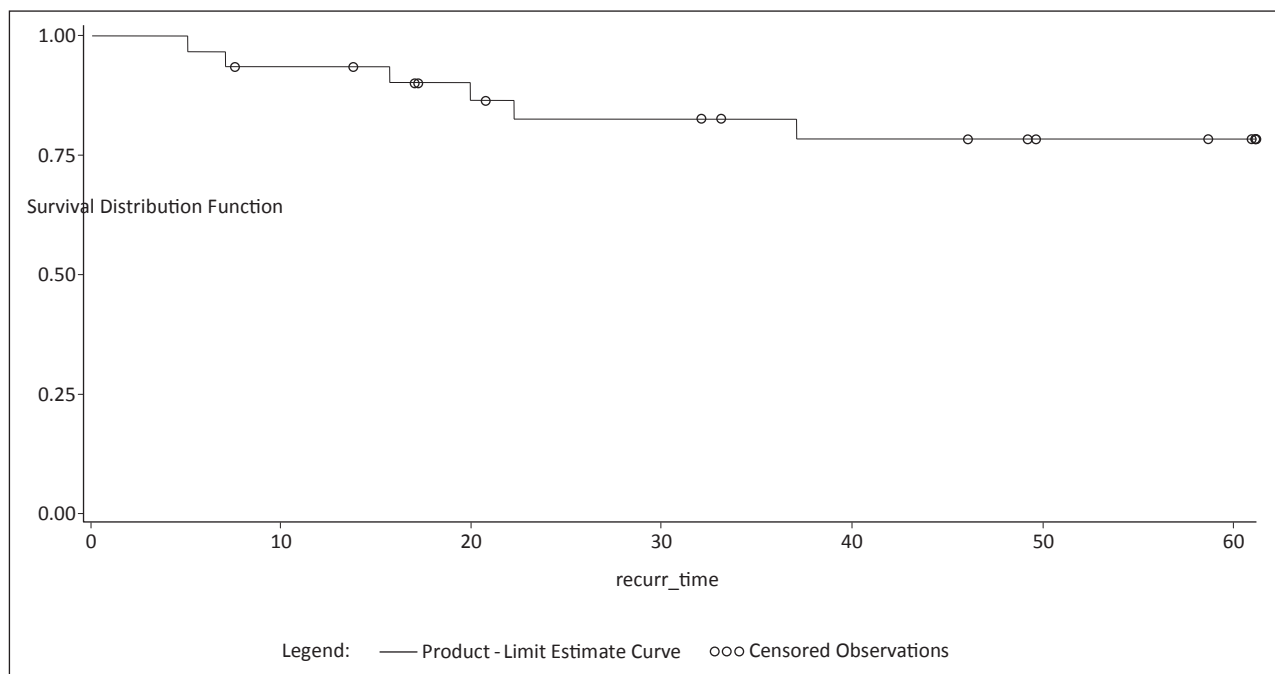


Figure 2. Disease-free Survival

Table 3. Causes of Death

(n = 10)	
Disease Recurrence	5
Renal Failure	1
Subdural Hematoma	1
Graft Failure and Rejection	1
Anoxia	1

within 60 days of having received their transplant. The median time to recurrence was 17.4 months. Of the 10 deceased patients, 5 (50%) died of cancer recurrence. Causes of death are depicted in Table 3. Whether or not a given patient was treated with transarterial chemoembolization (TACE)—and if so, the type used—and the size of that patient’s tumor were found not to be predictors of survival in this small series of patients.

Discussion

To our knowledge, this is the first comprehensive report examining liver transplantation as a curative option for hepatocellular carcinoma in Puerto Ricans referred to the US mainland, and the study that this report describes contained the largest number of patients receiving transplants, to date. It provides insight into the infrequent number of transplants performed for HCC over a 15-year period at a large liver transplant center with a long-time association with Puerto Rican patients. Our study demonstrates that there is acceptable long-term survival with a recurrence rate, post-transplant, of 14% at a median follow-up of 56 months. We believe this article

will be of great value to specialists in liver disease, insurers, the Department of Health, and the recently created liver transplant program at Auxilio Mutuo Hospital in San Juan, Puerto Rico.

A total of 32 HCC patients from Puerto Rico received transplants and were followed on a long-term basis. Not surprisingly, 73% of them had chronic hepatitis C as the etiology of their liver disease. The 3-year patient survival rate was 75%, and the 5-year patient survival rate was 67%. The recurrence rate at nearly 5 years of follow-up in the recent transplant era (MELD), in which HCC patients were prioritized for liver transplantation, was 14%. The survival of the patients in this Puerto Rican series is similar to what we have seen in our overall experience with hepatocellular carcinoma at Tampa General Hospital and similar to what has been characterized in the recent literature (see below). However, only in the last 4 years, have we seen a trend towards better survival in our center (3-year patient survival of 82%), despite no change in the recurrence rates (17). This may be attributed to hepatitis C care and available systemic therapy with sorafenib. Recent studies of HCC recurrence with liver transplantation in the MELD era are limited. Levy et al, in a series of 244 patients, included 44 with incidental tumors. The recurrence rate was, as expected (because of a large number of incidental tumors), that is, lower, being only 10.7%, with a mean follow-up of only 27 months (18). Recurrence-free survival at 5 years was 83.5%, and patient survival was 61.7%. Nissen et al reported on 122 patients who had a recurrence-free survival rate at 3 years of 89%, with an overall recurrence rate of 10.6% (19). Finally, Sharma et al, reporting on 94 patients, observed a recurrence rate of 18% at a median follow-up of 2.1 years (20). Our study did not confine transplants to the standard Milan

criteria, tumors less than or equal to 5 cm or 3 tumors, each less than or equal to 3 cm, as 21% of the patients presented with a radiologic stage above that determined by the Milan criteria. Furthermore, 34% of the patients had a pathologic stage beyond that determined by the Milan criteria. The short time spent on a liver transplant waiting list was an advantage to these patients but does not reflect more important parameters, such as the timing of a diagnosis of HCC, the time it takes to treat patients with locoregional therapy prior to referral to a transplant, the process resulting in any given patient's referral to a liver transplant center, and the types of locoregional therapies available. These 4 factors have affected many Puerto Rican hepatocellular cancer patients who could have benefited from liver transplantation. Despite our excellent results, we want to convey the message that many patients were never referred, for many reasons, including age, cancer stage, disease progression during the referral process, the fact of his or her being an alcoholic, and, most frequently, insurance (21).

It is our opinion that intense screening for HCC, based on the presence of chronic liver disease (cirrhosis), having a positive family history of liver disease, and infectious hepatitis, among other risk factors, will be needed to increase this malady's cure rate. Educational programs aimed at medical societies and specialists dealing with chronic liver disease will be needed to accomplish this goal. Guidelines for the screening, diagnosis, and treatment of hepatocellular carcinoma come from published reports, most recently updated in July 2010, and endorsed by the American Association for the Study of Liver Diseases (AASLD) (22). Patients at risk for HCC need to be entered into surveillance programs. It is very likely that intense screening could detect more liver cancers and at earlier stages. Epidemiologic studies in Florida performed at our center suggested that HCC cases were concentrated in areas near liver transplant centers (Alsina, unpublished data).

To date, there are 6 articles pertaining to liver cancer in Puerto Rico. The first article, by Manuel Martinez Maldonado, consists solely of HCC cases identified from 1946 through 1963 at the UPR Medical Center and the then-named San Juan Veterans Administration Hospital (today known as the VA Caribbean Healthcare System). Twenty-six cases were identified, all of which patients represented had a median survival of 7 months (23). The study ruled out *Schistosoma mansoni* as an etiologic factor of HCC in Puerto Rico, as none of the cases in this study was associated with this parasite. Torres and Bravo-Fernandez, in 1985, reviewed 78 patients with liver cancer at the University Hospital in San Juan. Only 8% of the patients were alive within 1 year of the study's initiation (24). A study by Lopez-Garcia et al from the Veterans Administration Caribbean Healthcare System (taking place from 1992 through 2002) contained 114 cases of HCC, all of which patients were of Hispanic ethnicity (25). Forty-two percent of these patients were treated according to current standards of care, 2 (1.7%) received liver transplants,

and the majority, 58%, received palliative treatment. The mean survival rate in this series was 10.3 months. Rivera-Resto did a retrospective study (covering from 1999 through 2005) of 459 patients with advanced liver disease, the cases of which were obtained from a specialized liver transplant evaluation clinic at the University of Puerto Rico (2). In this study, 35 (7%) of the patients fulfilled the criteria for HCC, and 8 with HCC (23%) underwent transplantation. It should be noted that this population of patients was a selective one; most of them were already scheduled to receive transplants, and our study does not intend to address the overall utilization of liver transplantation for HCC. The overall 18-month survival rate of the patients in this study who underwent transplant surgery was 67%. A second study, this one at the VA Administration and undertaken by Narvaez-Lugo et al, included 33 patients treated with transarterial chemoembolization or percutaneous ethanol injection from 2000 through 2005 (1). This was a select population of HCC patients who were able to receive locoregional therapy, as 93% of them were either Child-Pugh A or B cirrhotics. Median survival for this select group was 2 years. The study does not mention whether or not liver transplantation was utilized in these patients. Finally, a study by Romero et al compared the survival distribution of HCC in Puerto Rico during the periods of 1988 to 1992 and 1998 to 2002. This retrospective study from the PR Central Cancer Registry database noted a high incidence rate of HCC, 6.1 per 100,000 (1999–2003)—which is a very high incidence, considering the time period studied (9). Median survival in the first period of time was 1.8 months and in the second, 3 months, both of which are dismal. The 1-year patient-survival rates for the first and second time periods were 22% and 16%, respectively. The 3-year survival rates for the first and second time periods were 9% and 6.7%, respectively, which are both much lower than the average that has been determined for the US population.

The study has several limitations, including the small number of patients with cancer over such a broad time period. On the other hand, our study has done the most comprehensive literature review of HCC in Puerto Rico.

Our vast literature review reinforces how underutilized liver transplantation has been. Our 32 cases, spread over such a long time period despite the long-standing affiliation with the university, specialized clinics, and educational programs for gastroenterology fellows and specialists, reinforce the underutilization of liver transplantation as a therapeutic option for HCC. This experience has to be placed in the context of the upcoming liver-disease epidemic, which epidemic will be further complicated by hepatitis C, obesity and subsequent non-alcoholic hepatitis, and hepatocellular carcinoma. With the creation of a local liver transplant program in Puerto Rico, will the utilization increase? Will patients have more access to all available therapies? Those questions remain. Is it possibly time for Puerto Rico to step up the care of hepatocellular carcinoma

with specialized, complex, multidisciplinary, and expensive curative care that only liver transplantation can provide?

Conclusion

Liver transplantation is the treatment of choice for unresectable hepatocellular carcinoma at select stages. Our study provides the most comprehensive report regarding utilizing liver transplantation as a curative option for hepatocellular carcinoma in Puerto Ricans referred to the mainland and also contains the largest number of transplant patients. It is apparent from our study that survival was as expected; however, room for improvement exists. Both the findings of our program and the existing literature make apparent the fact that transplantation is an underutilized treatment option for HCC in Puerto Rican patients. The rate of transplants for patients with HCC should have been higher. The progression of the disease across stages that tend to be responsive to transplant and the logistics of performing transplants on patients on the mainland (as opposed to in PR) are the main impediments to using liver transplantation as a curative option for HCC. Whether new hepatitis C therapies and adjuvant cancer therapies can improve post-transplantation survival remains to be seen. We expect to see improvements in long term-survival in the near future but we are uncertain at this time, on the improvement of cancer recurrence. The creation of multidisciplinary liver cancer programs with appropriate support, including those offering liver transplantation, are imperative if Puerto Rico is to be able to handle the burden of this disease expected in the upcoming 2 decades.

Resumen

Objetivo: El carcinoma hepatocelular, el cáncer hepático más común, está resultando en una carga al sistema de salud de Puerto Rico, particularmente en clínicas especializadas en enfermedades hepáticas. Es nuestra hipótesis que el tratamiento mediante trasplante de hígado en el carcinoma hepatocelular está poco utilizado. Se describe aquí en detalle los resultados de trasplante de hígado en puertorriqueños con carcinoma hepatocelular trasplantados en un centro de trasplantes de hígado en Estados Unidos con afiliación a Puerto Rico. **Métodos:** Treinta y dos pacientes con carcinoma hepatocelular y originándose de Puerto Rico fueron trasplantados. Tasas de recurrencia de cáncer fueron calculadas y Kaplan-Meier se utilizó para sobrevivencia. **Resultados:** La proporción de trasplantes en pacientes de Puerto Rico con carcinoma hepatocelular representó solo un 12% de los pacientes trasplantados de Puerto Rico. La sobrevivencia del paciente a 12, 36 y 60 meses fue 97%, 75% y 67%, respectivamente. La tasa de recurrencia de cáncer desde 2002 fue de 14%. **Conclusión:** Este estudio provee el reporte más completo de tratamiento de cáncer hepatocelular con trasplante de hígado como tratamiento curativo e incorpora el primer

resumen de la literatura en cáncer de hígado en Puerto Rico. Las tasas de sobrevivencia y cura a por cáncer en esta población fueron comparables a experiencias obtenidas en Estados Unidos. Se demostró que el trasplante de hígado es poco utilizado en puertorriqueños con carcinoma hepatocelular en nuestro centro. Para poder aumentar la sobrevivencia y cura de esta enfermedad, es imprescindible que Puerto Rico se prepare para el aumento en la carga de esta enfermedad en las próximas dos décadas, ofreciendo trasplante de hígado y tratamientos locoregionales.

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