Liver Transplantation in Patients With Nonalcoholic Steatohepatitis-Related Hepatocellular Carcinoma

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See related article, Marrero JA et al, on page 110 in *Gastroenterology*.

BACKGROUND & AIMS: The increasing incidence of hepatocellular carcinoma in the United States is only partially accounted for by hepatitis C virus (HCV) infections. The prevalence of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis (NASH) is not known; guidelines from the American Association for the Study of Liver Diseases do not recommend surveillance imaging. We sought to determine the prevalence of hepatocellular carcinoma among patients undergoing liver transplantation for NASH-related cirrhosis and their outcome after surgery, compared with controls. **METHODS:** We reviewed the records of adult patients with NASH cirrhosis who underwent liver transplantation by using a prospectively collected database from a single center. Data from patients with NASH cirrhosis were compared with matched controls who received transplantation for primary biliary cirrhosis/primary sclerosing cholangitis, alcoholic liver disease, or HCV. **RESULTS:** Seventeen of 98 patients (17%) with NASH cirrhosis were diagnosed with hepatocellular carcinoma. The mean age was 63 years, and 70% were male. Six patients were diagnosed with hepatocellular carcinoma incidentally on explant. Survival after liver transplantation was 88% after mean follow-up of 2.5 years. The number of NASH patients known to have hepatocellular carcinoma before liver transplantation was greater than the number of patients with primary biliary cirrhosis/primary sclerosing cholangitis and comparable to the number of patients with alcoholic liver disease and HCV. **CONCLUSIONS: Patients with NASH cirrhosis are at risk for developing hepatocellular carcinoma; patients with NASH cirrhosis, especially men older than 50 years, should undergo surveillance imaging. Patients with NASH and hepatocellular carcinoma have good outcomes after liver transplantation.**

To view this article's video abstract, go to the AGA's YouTube Channel.

There are approximately 1 million new cases of primary hepatocellular carcinoma (HCC) diagnosed annually worldwide. Liver cancer is the sixth most common cancer and the third most common cause of death from cancer. The majority of cases of HCC develop in patients with chronic liver disease or cirrhosis. The major risk factor for the development of HCC worldwide is infection with hepatitis B virus (HBV).[1]

HCC complicating cirrhosis has a high mortality rate, unless it is detected in its early stages. Most cases do not survive a year.[2] HCC is now a leading cause of death in patients with cirrhosis.[3–5]

The incidence of HCC in the United States has doubled during the last 30 years.[6] The cause of this increase is incompletely understood. The increasing incidence in the United States has been partially attributed to hepatitis C virus (HCV)-associated cirrhosis, with HBV and alcoholic liver disease (ALD) playing a smaller role.[7] Up to one half of HCC cases in the United States, however, are idiopathic, suggesting that other risk factors are responsible for this increase.[8]

Recent studies have suggested that the epidemic rise in obesity and diabetes mellitus (DM) could account for at least a portion of these idiopathic cases.[8–10] Although it is unproved, some experts hypothesize that the relationship of obesity and DM to HCC is mediated through the development of nonalcoholic steatohepatitis (NASH).[11]

As the incidence of obesity, DM, and other features of metabolic syndrome increases, so too does the incidence of NASH. It is estimated that nearly 10 million Americans have NASH, making it the most common cause of chronic liver disease in the United States.[12] NASH cirrhosis is likely to become a leading indication for liver transplantation (LT) in the near future.[13] Although NASH is known to progress to end-stage liver disease, little is known about the incidence of HCC in patients with NASH cirrhosis. There is growing evidence, however, indicating that HCC should be considered in the natural history of progressive NASH. The first reported case of NASH-related HCC was published in 1990.[14] Since then, several case reports and case series have documented the occurrence of HCC in patients with NASH.[15–20]

The American Association for the Study of Liver Disease (AASLD) currently recommends screening and surveillance for HCC in high-risk groups, including hepatitis B carriers and

Abbreviations used in this paper: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; ALD, alcoholic liver disease; BMI, body mass index; CIT, cold ischemic time; CTP, Child-Turcotte-Pugh; CT, computed tomography; DM, diabetes mellitus; FAL, fractional allelic loss; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HTN, hypertension; LOH, loss of heterozygosity; LOS, length of stay; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; US, ultrasound; WIT, warm ischemic time.

1542-3565/09/$36.00
doi:10.1016/j.cgh.2009.02.025

cirrhosis caused by hepatitis C, alcohol, hemochromatosis, and primary biliary cirrhosis (PBC). Although the guidelines acknowledge that cirrhosis from other diseases (NASH, alpha$_1$-antitrypsin deficiency, and autoimmune hepatitis) puts patients at an increased risk for the development of HCC, they state that in these patients "no recommendations for or against surveillance can be made because of a lack of data (that) precludes an assessment of whether surveillance would be beneficial."[21]

The aims of this study were 2-fold: (1) to determine the incidence of HCC in patients who underwent LT for a diagnosis of NASH cirrhosis compared with the other most common indications for LT in the United States and (2) to determine the outcome of patients with HCC and NASH cirrhosis undergoing LT.

Materials and Methods

We retrospectively reviewed the records of all adult patients undergoing LT for a diagnosis of NASH cirrhosis by using a prospectively collected database at a single center.

Patients were considered to have a diagnosis of NASH cirrhosis on the basis of histopathologic findings and if they fulfilled the following criteria: absence of alcohol history, exclusion of other forms of chronic liver disease, on the basis of history, laboratory testing, histology, and absence of potential exposures to hepatotoxins or medications associated with hepatic steatosis.

All patients underwent extensive serologic testing, including testing for hepatitis B (hepatitis B surface antibody, surface antigen, and core antibody), hepatitis C (hepatitis C second-generation enzyme-linked immunosorbent assay, HCV RNA), hemochromatosis (serum iron, % saturation, total iron binding capacity, ferritin, and HFE genetic testing if indicated), Wilson disease (ceruloplasmin levels), alpha$_1$-antitrypsin deficiency (alpha$_1$-antitrypsin levels and phenotype), autoimmune hepatitis (antinuclear antibody titers, anti–smooth muscle antibody titers, anti–liver kidney microsomal antibody titers, and quantitative immunoglobulin levels), and PBC (antimitochondrial antibody titers).

All pre-LT imaging (ultrasound [US] and either triphasic computed tomography [CT] scan or magnetic resonance imaging [MRI]) reports were reviewed.

All explants were examined by experienced hepatopathologists. All explant biopsy reports and available biopsy reports before transplant were reviewed to ensure findings consistent with NASH or NASH cirrhosis. Histologic criteria for NASH included macrovesicular hepatic steatosis, Mallory's hyaline, ballooning degeneration, scattered predominantly neutrophilic inflammation, and pericentral and perisinusoidal fibrosis.[22]

Demographic data collected included recipient characteristics (age, sex, race, body mass index [BMI], history of alcohol or illicit drug use, medical history, laboratory data, Model for End-Stage Liver Disease [MELD] score, Child-Turcotte-Pugh [CTP] score, and the number of patients on dialysis or intubated before transplant), patient survival in days, retransplantation, and cause of death. Donor characteristics included age, sex, race, BMI, cause of death, and percent steatosis on biopsy (when available). Surgical cold ischemia times (CITs) and warm ischemia times (WITs), length of operation, and total transfusion requirement during the operation were also noted.

Outcome after LT was determined by (1) patient survival, defined as short-term (30 days) and long-term (1, 3, and 5 years), and (2) length of stay (LOS) after transplant, defined as number of hospital days (intensive care unit or otherwise) in patients who were eventually discharged from the hospital to home, rehabilitation, or nursing facility.

Incidental HCC was defined as a cancer found only on pathologic evaluation of the explanted native liver, without evidence on pre-LT imaging. Although pretransplant alpha-fetoprotein (AFP) was reviewed on all patients, elevated levels were not considered diagnostic of HCC before transplant. This is in concordance with previously published data on the definition of incidental HCC.[23,24]

Explant reports from all patients with HCC were reviewed. The number of tumors, largest tumor size, tumor differentiation, evidence of microscopic vascular invasion, pathologic TNM classification, pathologic staging, and genetic analysis/loss of heterozygosity (LOH) were noted.

HCC for topographic genotyping was performed on 9 of 17 (52.9%) patients. In these patients, microdissected targets were performed on HCC lesions to determine allelic imbalance or LOH. The fractional allelic loss (FAL) rate was defined as the fraction of mutated markers divided by the total number of informative markers. On the basis of previously published data, an FAL of $\leq$0.3 was supportive of indolent behavior, and an FAL $>$0.3 indicated the capacity for aggressive behavior.[25]

Patients with HCC (both known and incidental) are followed at our institution for recurrence with either CT or MRI of the chest, abdomen, and pelvis every 3 months for the first year, every 6 months for the next year, and then annually.

Comparison Groups

Patients with NASH cirrhosis were compared in a 1:2 ratio with patients in each of 3 control groups (total 588 patients) who were transplanted for cholestatic liver disease (PBC/primary sclerosing cholangitis [PSC]), ALD, or HCV. The control groups were matched (in order of priority) for age, sex, MELD score, and year of transplant.

Patients with NASH-related HCC were also compared with all patients transplanted at our center with a diagnosis of HCC during the last 15 years with etiologies other than NASH.

Statistical Analysis

Continuous variables were compared by using Student t test. Categorical variables were compared by using χ^2 test. Survival after LT was calculated by using the Kaplan–Meier method and compared by using the log-rank test. Data are expressed as means. All analyses were performed by using Stata 8.0 (Statacorp, College Station, TX).

The study was approved by the University of Pittsburgh Institutional Review Board.

Results

Of 2012 adult patients who underwent LT at our center from July 6, 1997 to June 31, 2008, we identified 143 patients with a diagnosis of NASH cirrhosis. After review, 45 patients were eliminated for the following reasons: cryptogenic cirrhosis (n = 12), evidence of alpha$_1$-antitrypsin deficiency (n = 7), autoimmune hepatitis (n = 5), alcohol use (n = 5), hemochromatosis (n = 4), HCV (n = 3), HCV/ALD (n = 2), Wilson disease (n = 2), methotrexate-induced liver injury (n = 2), possible acetaminophen toxicity (n = 1), fulminant hepatic failure (n = 1), and HBV/ALD (n = 1), leaving 98 patients (4.8%