Long-term Probability of and Mortality From De Novo Malignancy After Liver Transplantation

KYMBERLY D. S. WATT,* RACHEL A. PEDERSEN,‡ WALTER K. KREMERS,‡ JULIE K. HEIMBACH,§ WILLIAM SANCHEZ,* and GREGORY J. GORES*

*Division of Gastroenterology and Hepatology, ‡Department of Health Sciences Research, §Department of Surgery, William J. von Liebig Transplant Center, Mayo Clinic and Foundation, Rochester, Minnesota

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BACKGROUND & AIMS: Information about malignancies that arise in patients after liver transplantation comes from volunteer registry databases and single-center retrospective studies. We analyzed a multicenter, prospectively obtained database to assess the probabilities of and risk factors for de novo malignancies in patients after liver transplantation. **METHODS:** We analyzed the National Institute of Diabetes and Digestive and Kidney Diseases' liver transplantation database of 798 adults who received transplants from April 1990 to June 1994 and long-term follow-up data through January 2003. In this patient population, 171 adult patients developed 271 de novo malignancies. Of these malignancies, 147 were skin-related, 29 were hematologic, and 95 were solid organ cancers; we focused on nonskin malignancies. **RESULTS:** The probability of developing any nonskin malignancy was highest in patients with primary sclerosing cholangitis (PSC; 22% at 10 years) or alcohol-related liver disease (ALD; 18% at 10 years); all other diagnoses had a 10% probability. Multivariate analysis indicated that increased age by decade (hazard ratio [HR] = 1.33, $P = .01$), a history of smoking (HR = 1.6, $P = .046$), PSC (HR = 2.5, $P = .001$), and ALD (HR = 2.1, $P = .01$) were associated with development of solid malignancies after liver transplantation. The probabilities of death after diagnosis of hematologic and solid malignancy were 44.0% and 38.0% at 1 year and 57.6% and 53.1% at 5 years, respectively. **CONCLUSIONS: De novo malignancy primarily affects patients with PSC or ALD, compared to other transplant recipients, with a significant impact on long-term survival.**

De novo malignancy occurs more commonly after liver transplantation than in the general population.[1,2] Despite the fact that many of the malignancies described are skin cancers with an excellent prognosis, the overall mortality rate from de novo malignancy in this patient population is high.[1,3–5] Indeed, de novo malignancy is one of the leading causes of late mortality in liver transplant recipients.[4,6–8] Variable incidence rates for de novo malignancy (2%−16%) have been reported in the literature, but vary depending on the length of follow-up and era of transplantation.[3,9–12]

The majority of information regarding the incidence of de novo malignancy in liver transplant recipients is based on registry databases or single-center retrospective studies. These large registries are vulnerable to reporting bias and an unclear denominator for the at-risk population. Many of the single-center retrospective studies include both adult and pediatric patients, which is complicated by the vastly different risk profiles for these patient populations. Limited data exist on risk factors associated with malignancies after liver transplantation.

We have analyzed a prospectively obtained, multicentered long-term outcomes database to identify the incidence, risk factors, and mortality rates for posttransplantation de novo malignancies in adult liver transplant recipients.

Materials and Methods

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Liver Transplantation Database was established to prospectively collect data regarding patients undergoing liver transplantation. Data collection occurred at three clinical centers: Mayo Clinic, Rochester, MN; University of Nebraska, Omaha, NE; and University of California at San Francisco, with coordination through the University of Pittsburgh.[13] All liver transplant recipients at these institutions were enrolled in the database from April 15, 1990 to June 30, 1994, and followed in the original study until January 1998. Subsequent long-term follow-up data were obtained on all patients up to January 2003 (median follow-up of 10 years; range, 0−12 years). The database contains 916 liver transplant recipients, of which 798 patients were 18 years

Abbreviations used in this paper: ALD, alcohol-related liver disease; CI, confidence interval; GI, gastrointestinal; HCV, hepatitis C virus; HR, hazard ratio; IBD, inflammatory bowel disease; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; PSC, primary sclerosing cholangitis; PTLD, posttransplantation lymphoproliferative disorder.

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of age or older at the time of transplantation and were included in our analysis. Thirty percent of patients (n = 241) were from Mayo Clinic, 27% (n = 216) from University of Nebraska, and 43% (n = 341) from University of California at San Francisco. Immunosuppression protocols varied slightly at each center, with Mayo Clinic using cyclosporine, prednisone, and azathioprine; University of Nebraska using cyclosporine and prednisone; and University of California at San Francisco using antilymphocyte globulin followed by cyclosporine, prednisone, and azathioprine. All centers participated in the FK506 Primary Immunosuppression Trial, resulting in a subgroup of 92 recipients receiving a tacrolimus-based regimen. Patients who developed biopsy-proven acute cellular rejection were treated with 3 intravenous boluses of methylprednisolone (1000 mg). This study was approved by the NIDDK as well as Mayo Clinic Institutional Review Board committee.

All patients with a diagnosis of malignancy posttransplantation were determined and analyzed for patient demographics (ie, age, gender, and race), preexisting malignancy, etiology of underlying liver disease, documented alcohol abuse history, smoking history, comorbid illnesses, and type of malignancy. All patients who met the criteria for excessive alcohol use, as reported previously,[14] were considered to have alcoholic liver disease regardless of their hepatitis C virus (HCV) status. Only 3 patients with HCV and alcohol-related liver disease (ALD) developed a nonskin malignancy; thus risk analysis could not be performed for this separate group. Patients who did not meet criteria for excessive or unhealthy alcohol use were simply classified as HCV. For tobacco and alcohol use after transplantation, subjective forms filled in by the patient were available and analyzed. At least 1 follow-up form was available for 81% of patients (generally within 0 to 2 years of transplantation) and >3 forms were available for 60% of patients. Data used from these forms were a simple yes/no answer to "do you currently smoke?" or "do you currently drink alcohol?" Frequency or quantity of alcohol use was not captured and, therefore, these parameters could not be analyzed. Data analysis on use of antilymphocyte agents was stratified by center, as University of California at San Francisco used this agent for induction therapy and the other centers did not. Analysis of data stratified by center was otherwise similar to unstratified data, and thus the remaining data presented are unstratified.

Analyses were performed only on de novo malignancies. Patients were analyzed separately for the outcomes of skin malignancy and nonskin malignancy, with nonskin malignancies categorized as hematologic versus solid organ malignancies. For frequency analysis, we included colonic high-grade dysplasia or low-grade dysplasia associated with adenoma with subsequent colectomy as a significant premalignant finding, but excluded these patients from further outcomes analysis. Cervical and vulvar high-grade dysplasia/carcinoma in situ were included in the female genitourinary malignancy data analysis. Risk factors were analyzed for development of de novo malignancy. Malignancy sites with ≥9 patients were further studied with competing risk analyses. Outcomes analyzed included probability of developing a de novo malignancy and probability of death after diagnosis of malignancy. Time to diagnosis of malignancy posttransplantation and time to death after diagnosis of malignancy were also determined, as well as risk factors for development of posttransplantation de novo malignancies.

Statistical Analysis

Numerical variables are summarized by means, standard deviations, and ranges, and categorical variables by counts and percents. Incidence of cancer adjusting for the competing risk of death was determined for the entire follow-up period using an extension of the Kaplan–Meier method accounting for these competing risks.[15] Risk factors relating to incidence of cancers were determined using Cox regression analysis. Two-sided 95% confidence intervals are described, and tests were performed at the 5% level, again using a two-sided approach.

Results

Demographics of the Patient Population

Of 798 adult patients followed in this database, 55.5% were male and 80% were Caucasian (10% Hispanic, 4% African American, and 3% Asian). Mean age at the time of transplantation was 49.4 years (range, 18.8−77.5 years). Underlying disease etiologies at the time of transplantation are provided in Table 1. Of the study cohort, 115 of 798 (14%) were known to have concomitant inflammatory bowel disease (IBD) at the time of transplantation. Twenty-two of the 798 patients were transplanted with underlying malignancy (16 with hepatocellular carcinoma, 3 with cholangiocarcinoma, 1 fibrolamellar carcinoma, and 2 with other malignancies). Eleven patients had recurrent malignancy documented. These malignancies were not further analyzed.

Table 1. Underlying Liver Disease at the Time of Transplantation

Disease	Frequency (%)
Hepatitis C alone	130 (16.3)
Hepatitis C/alcohol	53 (6.6)
Alcohol	101 (12.7)
Hepatitis B or B+D	37 (4.6)
Autoimmune hepatitis	46 (5.8)
Primary sclerosing cholangitis	127 (15.9)
Primary biliary cirrhosis	100 (12.5)
Cryptogenic cirrhosis	81 (10.1)
Acute liver failure	44 (5.5)
Metabolic	22 (2.8)
Malignancy	22 (2.8)
Other	35 (4.4)