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

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See related article, Murthy SK et al, on page 1367 in CGH.

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 18% at 10 years; all other diagnoses had a 10% probability. 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.5,6–8 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.
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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis C alone</td>
<td>130 (16.3)</td>
</tr>
<tr>
<td>Hepatitis C/alcohol</td>
<td>53 (6.6)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>101 (12.7)</td>
</tr>
<tr>
<td>Hepatitis B or B+D</td>
<td>37 (4.6)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>46 (5.8)</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>127 (15.9)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>100 (12.5)</td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td>81 (10.1)</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>44 (5.5)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>22 (2.8)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>22 (2.8)</td>
</tr>
<tr>
<td>Other</td>
<td>35 (4.4)</td>
</tr>
</tbody>
</table>
During the 12.6-year study period, 171 patients developed 271 de novo malignancies. Of these, 124 were non-skin-related malignancies and 147 were skin-related (Table 2). Overall (adjusted for competing risk of death), 22% of transplant recipients developed any de novo malignancy posttransplantation, and 11% of patients developed a solid organ de novo malignancy within a median of 10 years’ follow-up. Probability of developing any de novo malignancy within 1, 5, and 10 years was 3.5%, 11.9%, and 21.7%, respectively.

### Nonskin Malignancies

Mean age at time of diagnosis of nonskin malignancy was 55 years (range, 26–76 years). Sixty percent (62 of 103) occurred in males, and 89% (92 of 103) occurred in Caucasians. Of all patients with de novo nonskin malignancies posttransplantation, 26% (27 of 103) had underlying primary sclerosing cholangitis (PSC) and another 25% (26 of 103) had any underlying ALD (Figure 1). Three of these cases also had underlying HCV. The overall probability of developing a de novo nonskin malignancy within a median of 10 years’ follow-up. Probability of developing any de novo malignancy within 1, 5, and 10 years was 3.5%, 11.9%, and 21.7%, respectively.

#### Anatomic Site and Recipient Risk Factors for Developing De Novo Nonskin Malignancy

Gastrointestinal malignancies were the most common solid organ malignancy, with lung, female genitourinary (which includes uterine, ovarian, cervical, and vulvar malignancies), and oropharyngeal/laryngeal malignancies encountered frequently (Table 2). High-grade dysplasia or low-grade dysplasia in the setting of polyps that prompted colectomy were included in frequency data but not in outcomes analysis. The probability of developing malignancy at a specific site is shown in Figure 3. The 10-year probability of developing a gastrointestinal (GI) malignancy was 3.6%, lung cancer 2.0%, female genitourinary malignancy 1.8%, and oropharyngeal/laryngeal cancer 1.1%.

PSC alone was not a statistically significant risk factor for GI malignancy (hazard ratio [HR] 1.9, P = .12). Patients with underlying IBD at the time of transplantation were at increased risk for developing a GI malignancy.

#### Table 2. Nonskin Malignancies by Site

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic (n = 29)</td>
<td></td>
</tr>
<tr>
<td>PTLD/lymphoma</td>
<td>24</td>
</tr>
<tr>
<td>Leukemia/MM</td>
<td>4/1</td>
</tr>
<tr>
<td>Solid organ (n = 96)</td>
<td></td>
</tr>
<tr>
<td>Bowel</td>
<td>25</td>
</tr>
<tr>
<td>Dysplasia and adenoma</td>
<td>6a</td>
</tr>
<tr>
<td>GU</td>
<td>15b</td>
</tr>
<tr>
<td>Lung</td>
<td>14</td>
</tr>
<tr>
<td>Oroph/larynx</td>
<td>10</td>
</tr>
<tr>
<td>Kidney</td>
<td>4</td>
</tr>
<tr>
<td>Breast</td>
<td>4</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
</tr>
<tr>
<td>Liver</td>
<td>2</td>
</tr>
<tr>
<td>Prostate</td>
<td>1</td>
</tr>
<tr>
<td>Bone</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>Metastatic</td>
<td>4c</td>
</tr>
</tbody>
</table>

GU, female genitourinary; MM, multiple myeloma; oroph, oropharyngeal; PTLD, posttransplantation lymphoproliferative disorder.

-a Adenoma with high-grade dysplasia requiring colectomy included in frequency data but not in outcomes analysis.

-b Includes 11 patients with cervical or vulvar dysplasia or carcinoma in situ.

-c Includes 2 peritoneal carcinomatosis.

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(HR = 2.34 [95% confidence interval [CI], 1.02–5.38], P = .045). Patients with PSC and IBD (with intact colons) were at further risk (HR = 3.51 [95% CI, 1.48–8.36], P = .005). Forty-three (5%) patients had a colectomy prior to liver transplantation (27 had PSC). With correcting for colectomies prior to transplantation, risk of GI malignancy at 1, 5, and 10 years was 0, 1.3%, and 5.0%, respectively. For patients without PSC or ALD, the risk of GI malignancy at 1, 5, and 10 years was 0.2%, 0.8%, and 2.4%, respectively.

Risk of developing a lung cancer was highest in ALD patients, with 5- and 10-year risks 2.0% and 4.8%, respectively, compared to non-ALD patients with 0.15% and 1.3%, respectively. The 5- and 10-year risk of oropharyngeal/laryngeal malignancy was 3.2% and 4.6%, respectively, for ALD patients and 0.16% and 0.32%, respectively, for non-ALD patients. The 5- and 10-year risks of genital/urinary malignancy were 1.1% and 1.8%, respectively.

**Risk Factors for Developing De Novo Nonskin Malignancy**

Univariate analysis revealed no significant predictor of increased risk of hematologic malignancy after liver transplantation. Specifically, neither male gender (HR = 2.2 [95% CI, 0.92–5.28], P = .08), PSC (HR = 1.88 [95% CI, 0.78–4.50], P = .16), nor exposure to antilymphocyte agents (1 exposure: HR = 0.761 [95% CI, 0.43–1.35], P = .347, ≥2 exposures HR = 1.652 [95% CI, 0.43–6.30], P = .4622) demonstrated a statistically significant relationship.

Univariate analysis for risk factors relating to solid organ malignancy revealed age in decades (HR = 1.26 [95% CI, 1.02–1.55], P = .03), a history (prior to transplantation) of smoking (HR = 1.67 [95% CI, 1.07–2.63], P = .025), IBD (HR = 1.84 [95% CI, 1.09–3.01], P = .018), PSC (HR = 1.72, P = .03), ALD (HR = 1.81, P = .012), and viral hepatitis (HR = 0.33, P = .01) to be
significant. Neither acute cellular rejection (HR = 0.83, \(P = .42\)), nor use of antilymphocyte agents (stratified by center) (1 exposure HR = 0.92 [95% CI, 0.63–1.35], \(P = .68\); 2 or more exposures HR = 1.00 [95% CI, 0.55–1.81], \(P = .99\)) was associated with increased solid organ malignancy. Use of alcohol and smoking after transplantation may well be risk factors for development of malignancy following liver transplantation. Unfortunately, the information in the database on these behaviors was insufficient for a clinically relevant statistical analysis. Multivariate analysis (Table 3) shows age, smoking prior to transplantation, ALD, and PSC remain significant predictors of solid organ malignancy.

**Survival Subsequent to Diagnosis of Nonskin Malignancy**

Probability of death after diagnosis of all nonskin malignancy was 40% at 1 year, and 55% at 5 years, respectively. The probability of death after diagnosis of solid organ de novo malignancy was 38% at 1 year and 53% at 5 years. Once diagnosed with a hematologic or solid organ malignancy, the median time to death for patients was 35 months and 56 months, respectively. The probability of death at 1 and 5 years once diagnosed with site-specific malignancies was GI 33% and 48%, lung 59% and 84%, oropharyngeal/laryngeal 22% and 44%, and female genitourinary 21% and 29%, respectively.

**Skin Malignancies**

Mean age at time of diagnosis was 59 years (range, 27–79 years). Sixty-seven percent occurred in male patients and 98% of the skin malignancies occurred in Caucasians. Twenty-nine percent of skin malignancies occurred in patients with PSC, with the remaining cases evenly distributed among other underlying disease etiologies (data not shown). All but 1 of the cases had nonmelanoma skin cancers, while 31 patients had multiple skin malignancies. The 1-, 3-, 5-, and 10-year probability of developing a first skin malignancy was 0.5%, 3.8%, 5.9%, and 10.8%, respectively. Univariate analysis shows risk factors to be male gender (HR = 1.83 [95% CI, 1.16–2.88], \(P = .009\)), age (HR = 1.81 [95% CI, 1.44–2.26], \(P < .001\)), IBD (HR = 2.18 [95% CI, 1.34–3.52], \(P = .002\)), PSC (HR = 1.90 [95% CI, 1.18–3.05], \(P = .008\)), autoimmune hepatitis (HR = 0.16 [95% CI, 0.02–1.12], \(P = .009\)). In a multivariate model, PSC (HR = 1.90, \(P = .008\)), male gender (HR = 1.78, \(P = .013\)), and age (HR = 1.85, \(P < .001\)) were significant. Acute cellular rejection, previous (prior to transplantation) or current smoking or alcohol use was not associated with skin malignancy.

**De Novo Nonskin Malignancy in PSC and ALD Transplant Recipients**

One-hundred and twenty-seven patients were transplanted for PSC, of which 60% were male with a mean age of 48 years (range, 20–72 years), and 87 of 127 (69%) had comorbid IBD. Within 12 years of transplantation, 24 (19%) developed a skin malignancy, 27 (22%) developed a first nonskin malignancy (8 GI, 6 hematologic, 3 lung, 3 breast, 2 kidney, 2 other/metastatic malignancy). PSC patients with IBD were not statistically more likely than PSC patients without IBD to develop any de novo malignancy posttransplantation (\(P = .6\)). There is no relationship between PSC diagnosis and risk of rejection posttransplantation (HR = 1.11 [95% CI, 0.88–1.41], \(P = .37\)).

Of 154 patients with ALD, 79% were male, 74% with a history of smoking, and a mean age 50 years (range, 33–69 years). Within 12 years of transplantation, 18 (12%) developed skin malignancies, and 26 (17%) developed nonskin malignancies (4 lung malignancies, 7 oropharyngeal/laryngeal malignancies, 7 GI malignancies [including 2 esophagus], 4 hematologic malignancies). Of the patients with solid organ malignancies, 19 of 22 had a history of smoking.

**Discussion**

Malignancy was the leading cause of nonhepatic death in the NIDDK long database, and accounted for one-third of nonhepatic deaths in this patient population.\(^{16}\) In this multicentered study, de novo malignancy occurred in 22% of patients within 12 years of transplantation, which is higher than previously noted in single-centered retrospective studies, during the same era of transplantation.\(^{9,11,17–21}\) This likely reflects duration of follow-up and more thorough documentation of malignancies. The advantage of these data is that they were prospectively obtained from multiple centers and therefore would be more closely reflective of the general transplantation population. A limitation, however, is lack of ethnic diversity in this cohort. The probability of developing these malignancies increases after 5 years of follow-up (Figure 3); thus, any study with <5-year follow-up will underestimate the incidence of malignancies.

Approximately one-half of our study malignancies were skin-related, and the cumulative incidence was 10.8% at 10 years. Patients with PSC had a higher risk of skin malignancy, which may be related to pretransplantation exposure to immunosuppression for IBD. This would have to be a dose effect, as autoimmune hepatitis patients are also often treated with immunosuppression.
before transplantation, albeit at lower doses, and did not have as high a risk for skin malignancy. Degree of immunosuppression in this pretransplantation setting cannot be ascertained in this database. Thus, multiple factors might be involved in this increased risk. Vitamin D is known to have antiproliferative properties, and deficiency of vitamin D has been shown to increase risk of malignancies. Thus, these patients with vitamin D deficiency and chronic immunosuppression may be at a higher baseline risk, but unless they have chronic cholestasis after transplantation, it is unclear how long this risk would remain elevated.

Posttransplantation lymphoproliferative disorder (PTLD) is the second most commonly reported de novo malignancy and accounts for as much as 35% of nonskin-related malignancies in other studies, which included pediatric patients. The current study only included adult patients, and PTLD accounted for 9% of all de novo malignancies and 19% of all nonskin malignancies. Of all patients in the cohort, 3% developed PTLD, which is consistent with the reported literature for adult patients. Although PSC patients accounted for the highest fraction of hematologic malignancies (most of which were PTLD), PSC itself was not a statistically significant risk factor for development of these malignancies. The numbers were quite small and the lack of significance may be a type II error. Use of antilymphocyte agents is a well-known risk factor associated with PTLD, but this was not found to be a risk factor for de novo malignancy of any cause (including hematologic) in this study.

The probability of solid organ and hematologic malignancies has more than doubled in the post—liver transplantation population compared to the general population. The National Cancer Institute’s Surveillance Epidemiology and End Results data suggest that a person without malignancy at the age of 50 has a 6.5% probability of developing any invasive malignancy in the following 10 years. In this transplantation population (mean age, 49 years) the overall probability for nonskin malignancy at 10 years was 13.6%. Prior to transplantation, patients with cirrhosis have been shown to have not only an increased risk of hepatic malignancies, but also increased incidence of other cancers. It is not surprising that this same patient population, now with an extended life expectancy and exposure to chronic immunosuppression, would also be at higher risk of developing a malignancy in the posttransplantation setting. Immunosuppression is thought to facilitate posttransplantation malignancy by impairing cancer surveillance mechanisms and creating an environment for oncogenic viruses to thrive. Alcohol, cigarette smoking, and age are common risk factors associated with development of de novo malignancy in the general population and prior to liver transplantation; thus it is also expected that these risk factors are associated with de novo malignancy after transplantation. In order to receive a liver transplant, however, patients are generally abstinent from alcohol for months to years prior to transplantation and generally (with some exceptions) remain abstinent after transplantation. Wiesner and colleagues determined 16% of ALD patients in this NIDDK cohort drank alcohol (defined as “any alcohol”) after transplantation, compared to 14% in the rest of the cohort population. Our analysis suggests that drinking alcohol after transplantation did not confer an increased risk of malignancy (data not shown), but this must be taken in context. Patients with a history of alcohol excess prior to transplantation who drank alcohol after transplantation did have an increased risk of malignancy, but it is unclear if this risk is over and above the risk associated with the prior alcohol use. The definition of any use of alcohol catches infrequent users as well as excessive users, making it less likely to discern a significant difference. Unfortunately, there is no definable threshold of intake above which an increased risk may occur. The bias of subjective patient-reported data collection in this patient population and the effect on any analysis of risk cannot be ignored. The stigma of admitted alcohol use after transplantation and the likelihood of capturing accurate and complete data on all recipients, in particular the high-risk ALD population, make interpretation of this component of the analysis very difficult. Previous exposure to excessive alcohol with an increased baseline risk of malignancy in the ALD cirrhotic patient appears to translate into a more influential risk in the immunosuppressed setting. As important is the likelihood of ongoing tobacco smoking in this patient population. A recent study has shown a higher rate of de novo malignancy in active smokers after a liver transplantation.

Our data confirm that a history of smoking prior to transplantation (74% in the ALD population) increased the risk of solid organ de novo malignancies, but the limited analysis we were able to perform on ongoing smoking after transplantation was unable to prove an increased risk in posttransplantation smokers. This is most likely reflective of the data biases described previously. The 10-year probability of lung cancer or oropharyngeal/laryngeal cancers is only increased in the ALD patient (4.8% and 4.6%, respectively) compared to the non-ALD patient. Thus, all patients with ALD, particularly those with a history of smoking (whether or not they continue to smoke) require diligent ongoing monitoring and surveillance for malignancy (particularly oropharyngeal/laryngeal and lung) in the posttransplantation setting.

It is not unexpected to have an increased risk of associated GI malignancy in PSC patients because of the association with IBD, but it is unexpected that hematologic malignancies and skin malignancies were more frequently encountered in PSC patients than in any other diagnoses. Rejection is thought to occur more frequently in PSC patients and thus these patients may be exposed
to more intense immunosuppression therapy, potentially increasing their risk for malignancy. However, patients with PSC did not experience higher rates of rejection in this study cohort. PSC patients with IBD are at higher risk for colon cancer, and this risk increases after transplantation. In this population, patients with PSC alone did not have statistically significant (HR = 1.9, P = .12) increased risk for GI malignancy, but IBD increases this risk 2.3-fold (HR = 2.3, P = .045). The lack of significant risk in the PSC-alone population is possibly due to dysplasia screening in this group of patients. It should be emphasized that more than one-half of the solid organ malignancies experienced in the PSC population were not GI malignancies. As already stated, vitamin D deficiency may be an additional contributor to cancer risk in these patients. Most PSC and IBD patients are already monitored for colon cancer with surveillance colonoscopy on an annual basis, but these data suggest that they should be monitored for all malignancies very closely after transplantation.

When PSC and ALD patients were removed from our cohort, all other patients (mean age, 50 years) had a 10-year probability of nonskin malignancy of 10%, thus showing the rest of the transplantation population is at a modestly higher risk of malignancy than the general population (6.5%; Surveillance Epidemiology and End Results). This population would likely benefit from diligent cancer screening programs similar to the general public, whereas PSC and ALD patients may benefit from more extensive screening surveillance.

Mortality after a diagnosis of malignancy is also higher, despite the likelihood of earlier cancer detection in the highly monitored setting with posttransplantation screening protocols. Surveillance Epidemiology and End Results data (from the late 1990s, when these cancers were diagnosed) suggested the probability of dying from any invasive cancer after diagnosis in the general population was 21% at 1 year and 36% at 5 years. This cohort of patients had a 40% 1-year and 55% 5-year probability of death from the time of diagnosis, with the majority dying as a consequence of their malignancy. Reasons for such an increase in mortality after transplantation are unclear, but it is generally thought that aggressive immunosuppression may result in increased proliferation and spread of the tumor and that this results in more advanced stages of disease at presentation, precluding surgical or chemotherapeutic options. The current era of lower immunosuppression dosing and different immunosuppressant choices may impact the incidence and mortality of de novo malignancy.

In summary, de novo malignancy affects more than one-fifth of transplantation patients, and the probability of invasive malignancy after liver transplantation is twice that of the general population overall. Solid organ malignancies occur in 11% of transplantation patients and have a worse prognosis than similar cancers in the non-transplantation population. Increased age, history of smoking, PSC, or ALD increases the probability of developing any solid organ de novo malignancy after liver transplantation. Results of this study suggest that rigorous screening protocols for malignancy detection are warranted. Further study into the impact of screening protocols on long-term outcomes is warranted.

References