Published in final edited form as:

Gastroenterology. 2009 December ; 137(6): 2010–2017. doi:10.1053/j.gastro.2009.08.070.

Long-term Probability of and Mortality from De-Novo Malignancy after Liver Transplantation

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Abstract

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 multi-center, 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's Liver Transplantation Database of 798 adults that 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 non-skin malignancies.

Results—The probability of developing any non-skin 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, $p=0.01$), a history of smoking (HR 1.6, $p=0.046$), PSC (HR 2.5, $p=0.001$), and ALD (HR 2.1, $p=0.01$) were associated with the 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 one 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

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No conflicts of interest for any of the authors

Author contribution: KDW; study concept and design; acquisition of data; KDW, GJG analysis and interpretation of data; drafting of the manuscript; KDW, RAP, WKK, JKH, WS, GJG critical revision of the manuscript for important intellectual content; RAP, WKK statistical analysis.

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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 followup and the era of transplantation^{3, 9–12}.

The majority of the 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, multi-centered long term outcomes database to identify the incidence, risk factors and mortality rates for post transplant de novo malignancies in adult liver transplant recipients.

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 was obtained on all patients up to January 2003 (median follow-up of 10 years, range of 0–12 years). The database contains 916 liver transplant recipients, of which 798 patients were ≥ 18 years of age 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, the University of Nebraska used cyclosporine and prednisone, and the University of California at San Francisco utilized 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 (ACR) were treated with three intravenous boluses of methylprednisolone (1000 mg). This study was approved by the National Institute of Health/National Institutes of Diabetes and Kidney Diseases (NIDDK) as well as Mayo Clinic IRB committee.

All patients with a diagnosis of malignancy post transplantation were determined and analyzed for patient demographics (age, gender, and race), pre-existing 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 previously reported¹⁴ were considered to have alcoholic liver disease regardless of their HCV status. Only 3 patients with HCV and ALD developed a non-skin malignancy, thus risk analysis could not be performed for this separate group. Patients who did not meet the criteria for excessive or unhealthy alcohol use were simply classified as HCV. For tobacco and alcohol use after transplant, subjective forms filled in by the patient were available and analyzed. At least one followup form was available in 81% of patients (generally within 0–2 years of transplant) and > 3 forms were available in 60% of patients. The 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 analysed. Data analysis on the use of anti-lymphocyte agents was

stratified by center, as UCSF used this agent for induction therapy, whereas the other centers did not. The analysis of data stratified by center was otherwise similar to unstratified data, and thus the remaining data presented is unstratified.

Analyses were performed only on de novo malignancies. Patients were analyzed separately for the outcomes of skin malignancy and non skin malignancy, with non-skin 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 pre-malignant 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 the 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 the probability of death after the diagnosis of malignancy. Time to diagnosis of malignancy post transplantation and time to death after the diagnosis of malignancy were also determined as well as risk factors for development of post transplant 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 risks¹⁵. 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 the 798 adult patients followed in this database, 55.5% were male with 80% of Caucasian race (10% Hispanic, 4% African American, and 3% Asian). The mean age at the time of transplant was 49.4 years (range 18.8 – 77.5). The underlying disease etiology at the time of transplant is depicted in Table 1. Of the study cohort, 115/798 (14%) were known to have concomitant inflammatory bowel disease (IBD) at the time of transplant. 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.

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 transplanted patients developed any de novo malignancy post transplantation, and 11% of patients developed a solid organ de novo malignancy within a median of 10 years followup. The probability of developing any de novo malignancy within 1, 5, and 10 years was 3.5%, 11.9%, and 21.7%, respectively.

Non-Skin Malignancies

The mean age at the time of diagnosis of non-skin malignancy was 55 years (range 26–76 years). Sixty percent (62/103) occurred in males, and 89% (92/103) occurred in Caucasians. Of all patients with de novo non-skin malignancies post transplant, 26% (27/103) had underlying primary sclerosing cholangitis (PSC) and another 25% (26/103) had any underlying alcohol related liver disease (ALD) (Figure 1). Three of these cases also had underlying HCV. The overall probability of developing a de novo non-skin malignancy was 3.0%, 6.7% and

13.6% within 1, 5 and 10 years of transplant. The cumulative incidence of hematologic malignancy was 1.5%, 1.9% and 3.2% at 1, 5 and 10 years post transplant. The cumulative incidence of a solid organ cancer was 1.5%, 4.8% and 10.5% at 1, 5 and 10 years. PSC patients had the highest cumulative incidence of non-skin cancers of 5.5%, 10.4% and 21.9% at 1, 5 and 10 years. ALD patients had cumulative incidence for non-skin cancer of 5.2%, 8.4% and 18.1% at 1, 5 and 10 years. All other patients in the study group (without PSC or ALD) had a 1.7%, 5.3% and 10.2% cumulative incidence of non-skin malignancy post transplant. The difference in the probability of developing a malignancy between PSC and ALD patients is due to the increased cumulative incidence of hematologic malignancy in the PSC patients (Figure 2a). PSC patients had a 1, 5 and 10 year probability for developing a hematologic malignancy of 2.4%, 2.4% and 5.6%, respectively, compared to a 1.3%, 1.8% and 2.8% for all other diagnoses (including ALD). For solid organ malignancy the 1, 5 and 10 year cumulative incidences were: PSC 3.1%, 8.0% and 17.0%, ALD 3.2%, 6.5% and 15.4%, and all other diagnoses 0.6%, 3.5% and 7.4% (Figure 2b).

Anatomic site and recipient risk factors for developing de novo non-skin 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 frequently encountered (Table 2). High grade dysplasia or low grade dysplasia in the setting of polyps that prompted colectomy were included in frequency data (n=6) as they were considered significant precancerous lesions requiring intervention but not included in any further 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 (HR=1.9, p=0.12). Patients with underlying IBD at the time of transplant were at increased risk for developing a GI malignancy (HR 2.34 (1.02 – 5.38), p=0.045). Patients with PSC and IBD (with intact colons) were at further risk (HR 3.51 (1.48–8.36), p=0.005). Forty three (5%) patients had a colectomy prior to liver transplant (27 had PSC). With correcting for colectomies prior to transplant, the risk of GI malignancy at 1, 5, and 10 year was 2.0%, 4.1%, and 8.2%, respectively in PSC patients, compared to 0%, 0%, and 2.6% respectively in non-PSC patients. The 1, 5, and 10 year incidence rates of GI malignancy in the PSC and IBD population (corrected for colectomy prior to transplant) were as follows: PSC without IBD (n=39): 0, 0, 2.8%; PSC with IBD (n=60): 3.3%, 6.7%, 11.8%; IBD without PSC (n=21): 0, 0, 5.2%; and patients without PSC or IBD (n=594): 0.16%, 1.0%, 3.1%. For ALD recipients the risk of GI malignancy at 1, 5 and 10 years was 0%, 1.3% and 5.0%. 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%.

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

Risk factors for developing denovo non-skin malignancy

Univariate analysis revealed no significant predictor of increased risk of hematologic malignancy after liver transplant. Specifically, neither male gender (HR 2.2 (0.92–5.28), p=0.08), PSC (HR 1.88 (0.78–4.50), p=0.16), nor exposure to antilymphocyte agents (1 exposure: HR 0.761 (0.43–1.35), p=0.347, ≥2 exposures HR: 1.652 (0.43–6.30), p=0.4622) demonstrated a statistically significant relationship.

Univariate analysis for risk factors relating to solid organ malignancy revealed age in decades (HR 1.26 (1.02–1.55), $p=0.03$), a history (prior to transplant) of smoking (HR=1.67 (1.07–2.63), $p=0.025$), inflammatory bowel disease (IBD) (HR= 1.84 (1.09–3.01), $p=0.018$), PSC (HR=1.72, $p=0.03$), ALD (HR=1.81, $p=0.012$), and viral hepatitis (HR=0.33, $p=0.01$) to be significant. Neither acute cellular rejection (HR 0.83, $p=0.42$), nor the use of anti-lymphocyte agents (stratified by center) (1 exposure HR=0.92 (0.63–1.35), $p=0.68$, 2 or more exposures HR=1.00 (0.55–1.81), $p=0.99$) were associated with increased solid organ malignancy. The use of alcohol and smoking after transplantation may well be risk factors for the development of malignancy following liver transplantation. Unfortunately, the information in the data base on these behaviors was insufficient for a clinically relevant statistical analysis. Multivariate analysis (Table 3) shows age, smoking prior to transplant, ALD and PSC remain significant predictors of solid organ malignancy.

Survival subsequent to diagnosis of non-skin malignancy

The probability of death after diagnosis of all non-skin malignancy was 40% at one year, and 55% at 5 years, respectively. The probability of death after the 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 were: GI 33% and 48%, lung 59% and 84%, oropharyngeal/laryngeal 22% and 44% and female genitourinary 21% and 29% respectively.

Skin Malignancies

The mean age at the time of diagnosis was 59 years (range 27–79 years). Sixty-seven percent occurred in males and 98% of the skin malignancies occurred in Caucasians. 29% of skin malignancies occurred in patients with PSC, with the remaining cases evenly distributed amongst other underlying disease etiologies (data not shown). All but one of the cases had non-melanoma 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 (1.16–2.88), $p=0.009$), age (HR 1.81 (1.44–2.26), $p<0.001$), IBD (HR=2.18 (1.34–3.52), $p=0.002$), PSC (HR=1.90 (1.18–3.05), $p=0.008$), autoimmune hepatitis (HR=0.16 (0.02–1.12), $p=0.009$). In a Multivariate model, PSC (HR=1.90, $p=0.008$), male gender (HR=1.78, $p=0.013$), and age (HR=1.85, $p<0.001$) were significant. Acute cellular rejection, previous (prior to transplant) or current smoking or alcohol use were not associated with skin malignancy.

De novo non-skin 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). 87/127 (69%) had co-morbid IBD. Within 12 years of transplant, 24 (19%) developed a skin malignancy, 27(22%) developed a first non-skin 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 post transplant ($p=0.6$). There is no relationship between PSC diagnosis and risk of rejection post-transplant (HR=1.11 (0.88 – 1.41), $p=0.37$).

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

DISCUSSION

Malignancy was the leading cause of non-hepatic death in the NIDDK long database, and accounted for 1/3 of the non-hepatic deaths in this patient population¹⁶. In this multi-centered study, de novo malignancy occurred in 22% of patients within 12 years of transplant, 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 followup and more thorough documentation of malignancies. The advantage of this data is that it was prospectively obtained from multiple centers and therefore would be more closely reflective of the general transplant population. A limitation however, is lack of ethnic diversity in this cohort. The probability of developing these malignancies increases after 5 years of followup (Figure. 3); thus, any study with less than 5 year followup will underestimate the incidence of malignancies.

Approximately 1/2 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 pretransplant exposure to immunosuppression for IBD. This would have to be a dose effect as autoimmune hepatitis patients are also often treated with immunosuppression before transplant, albeit at lower doses, and did not have as high of a risk for skin malignancy. The degree of immunosuppression in this pre transplant setting cannot be ascertained in this database. Thus, multiple factors may be involved in this increased risk. Vitamin D is known to have antiproliferative properties²², and deficiency of vitamin D has been shown to increase the risk of malignancies²³. Thus, these patients with vitamin D deficiency and chronic immunosuppression may be at a higher baseline risk, but unless they have chronic cholestasis after transplant, it is unclear how long this risk would remain elevated.

PTLD is the second most commonly reported de novo malignancy and accounts for as high as 35% of non-skin related malignancies in other studies, which included pediatric patients¹². The current study only included adult patients and PTLD accounted for 9% of all de novo malignancies, and 19% of all non-skin malignancies. Of all the patients in the cohort, 3% developed PTLD, which is consistent with the reported literature for adult patients^{1, 10, 12}. 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 the development of these malignancies. The numbers were quite small and the lack of significance may be a type 2 error. The use of antilymphocyte agents are well known risk factors associated with PTLD, but these were not found to be a risk factor for denovo malignancy of any cause (including hematologic) in this study.

The probability of solid organ and hematologic malignancies is more than doubled in the post liver transplant population compared to the general population. The National Cancer Institute - Surveillance Epidemiology and End Results data (SEER data) suggests that a person without malignancy at the age of 50 has a 6.5% probability of developing any invasive malignancy in the following 10 years²⁴. In this transplant population (mean age 49) the overall probability for non-skin malignancy at 10 years was 13.6%. Prior to transplant, patients with cirrhosis have been shown to have not only an increased risk of hepatic malignancies, but also increased incidence of other cancers²⁵. 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 post-transplant setting. Immunosuppression is thought to facilitate post-transplant 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 the development of de novo malignancy in the general population²⁴ and prior to liver transplantation²⁵, 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

transplant and generally (with some exceptions) remain abstinent after a transplant. Wiesner et al, determined 16% of ALD patients in this NIDDK cohort drank alcohol (defined as “any alcohol”) after transplant, compared to 14% in the rest of the cohort population.¹⁴ Our analysis suggests that drinking alcohol after transplant did not confer an increased risk of malignancy (data not shown), but this must be taken into context. Patients with a history of alcohol excess prior to transplant, that drank alcohol after transplant 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 transplant and the likelihood of capturing accurate and complete data on all recipients, in particular the high risk ALD population, makes 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 transplant²⁶. Our data confirms that a history of smoking prior to transplant (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 transplant was unable to prove an increased risk in post transplant 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 no they continue to smoke) require diligent ongoing monitoring and surveillance for malignancy (particularly oropharyngeal/laryngeal and lung) in the post transplant setting.

It is not unexpected to have an increased risk of associated GI malignancy in PSC patients, due to the association with inflammatory bowel disease 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 patients²⁷ 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 inflammatory bowel disease (IBD) are at higher risk of colon cancer and this risk increases after transplant²⁸. In this population, patients with PSC alone did not have statistically significant (HR=1.9, p=0.12) increased risk for GI malignancy but IBD increases this risk 2.3 fold (HR=2.3, p=0.045). 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 over 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 patients²³. Most PSC and IBD patients are already monitored for colon cancer with surveillance colonoscopy on an annual basis, but this data suggests that they should be monitored for all malignancy very closely after transplant.

When PSC and ALD patients were removed from our cohort, all other patients (mean age 50 years) had a 10 year probability of non-skin malignancy of 10%, thus showing the rest of the transplant population is at a modestly higher risk of malignancy than the general population (6.5%. SEER data²⁴). 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 post transplant screening protocols. SEER data (from the late 1990's, when these cancers were diagnosed) suggested the probability of dying from any invasive cancer after diagnosis in the general population was 21% at one year and 36% at five years²⁴. This cohort of patients had a 40% one year and 55% five 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 transplant is unclear, but 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 denovo malignancy.

In summary, de novo malignancy affects over 1/5 of transplant 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 transplant patients and have a worse prognosis than similar cancers in the non-transplant population. Increased age, a history of smoking, primary sclerosing cholangitis or alcohol related liver disease increase the probability of developing any solid organ de novo malignancy after a liver transplant. The 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 merits further study.

Acknowledgments

This study is supported by the National Institutes of Diabetes and Kidney Diseases (NIDDK). This manuscript was not prepared in collaboration with the investigators of this study and does not reflect the opinions or views of the NIDDK.

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Figure 1.

Non-Skin Malignancy by Underlying Liver Disease Diagnosis. (PSC= primary sclerosing cholangitis, ALD= alcoholic liver disease, PBC= primary biliary cirrhosis, HCV= hepatitis C, Crypt= cryptogenic cirrhosis, AIH= autoimmune hepatitis, FHF, fulminant hepatic failure, Malig= malignancy, HBV= hepatitis B, Metab= metabolic disease.)

* 3 cases with ALD and HCV included in ALD category.

Figure 2.

Figure 2a and 2b. Probability of developing de novo non-skin malignancy by underlying disease. 1a = hematologic malignancy, 1b = solid organ malignancy

Figure 3.
Probability of Site Specific Malignancies.
GI = gastrointestinal, GU= female genito-urinary, OP = oropharyngeal/laryngeal.

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%)

Table 2**Non-Skin Malignancies by Site**

Hematologic (n=29)	
PTLD/lymphoma	24
Leukemia/MM	4/1
Solid Organ (n=96)	
Bowel	25
Dysplasia&adenoma	6 [^]
GU	15 [*]
Lung	14
Oroph/larynx	10
Kidney	4
Breast	4
Esophagus	3
Pancreas	3
Liver	2
Prostate	1
Bone	1
Other	3
Metastatic	4 ^{**}

PTLD = post-transplant lymphoproliferative disorder, MM= multiple myeloma, GU = female genitourinary, oroph= oropharyngeal,

* includes 11 patients with cervical or vulvar dysplasia or carcinoma in situ,

** includes 2 peritoneal carcinomatosis,

[^] adenoma w high grade dysplasia requiring colectomy included in frequency data but not in outcomes analysis

Table 3

Risk Factors for Solid Organ Malignancy: Multivariate Analysis

Risk Factor	HR (CI)	P value
Age by decade	1.33 (1.05 – 1.66)	0.014
Smoking history	1.72 (1.06 – 2.79)	0.029
ALD	2.14 (1.22 – 3.73)	0.007
PSC	2.62 (1.50 – 4.56)	0.001

PSC= primary sclerosing cholangitis, ALD= alcoholic liver disease