De Novo Malignancies After Liver Transplantation: A Major Cause of Late Death

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Key Points
1. Recurrent and de novo malignancies are the second leading causes of late death in liver transplant recipients, following age-related cardiovascular complications.
2. The increased incidence of de novo malignancies in liver transplant recipients compared with the general population reflects their demographic makeup, known preexistent risk factors for cancer, greater rate of chronic viral infection, and actions of exogenous immunosuppression.
3. The greatest incidence of de novo malignancies is seen in cancers associated with chronic viral infections, such as Epstein-Barr virus–associated posttransplant lymphoproliferative disease, and skin cancers, including squamous cell carcinoma and Kaposi’s sarcoma.
4. Although a greater incidence of such malignancies as oropharyngeal malignancy and colorectal cancer was noted, there did not appear to be an increased risk for liver transplant recipients matched for age, sex, and length of follow-up using modified life-table technique and Surveillance Epidemiology End Result data with a similar at-risk group. However, they may present with more advanced stages of disease.
5. An increased incidence of de novo cancers in chronically immunocompromised liver transplant recipients demands careful long-term screening protocols to help facilitate diagnosis at an earlier stage of disease. (Liver Transplant 2001;7:S109-S118.)

Although etiologic factors that determine the susceptibility of malignancy have not been fully defined, it is clear that complex interactions exist between environmental factors, genetic predisposition, oncological viral factors, and immune system status. The contribution of a dysfunctional immune system to the risk for developing malignancy was not appreciated until the advent of iatrogenic immunosuppression, developed for solid-organ transplantation. An increased incidence of de novo malignancies in immunosuppressed organ transplant recipients was first predicted by Starzl1 in 1968 and confirmed shortly thereafter.2,3 Several registry4-6 and single-center reports7-10 have clearly shown trends to increased incidences of certain types of posttransplantation de novo malignancies, principally those linked to a viral cause. Estimates of developing de novo malignancies range from 4.1% to 16%,5,11 depending on the type and demographics of the transplant population, length of follow-up, and the era in which transplantations were performed.

The purpose of this review is to examine the comparative frequency and types of both lymphoid and nonlymphoid malignancies in patients undergoing liver transplantation (LT). In addition, we speculate on the contribution of immunosuppression to the pathophysiological characteristics of cancer development in this population.

Incidence of De Novo Malignancies After LT

Much of the information on malignancies after LT comes from registry reports: the Israel Penn International Transplant Tumor Registry (IPITTR; formerly the Cincinnati Transplant Tumor Registry) and the Australian Combined Liver Transplant Registry. However, limitations of registry data include voluntary reporting, the total at-risk population usually is not specified, and all posttransplantation neoplasms are not reported uniformly. Thus, data from large single centers in which the at-risk population is defined may offer a better way to evaluate the true relative risk (RR) for cancer after LT. The reported incidence of de novo malignancies is listed in Table 1.

Penn12 summarized the IPITTR analysis of de novo cancers occurring after LT. Three hundred twenty-four liver transplant recipients developed 329 cancers. In contrast to de novo malignancies seen in renal allograft recipients, lymphomas were much more common in liver allograft recipients (57% vs 12% of all tumors), whereas skin cancers (39% vs 15%), cervical carcinomas (4% vs 1%), renal cancers (4% vs 1%), and vulvar carcinomas (3% vs 0.6%) were more common in renal allograft recipients. In addition, liver transplant recipients appeared to develop both lymphoid (15 vs 46 months)

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and nonlymphoid malignancies in a shorter time post-LT (27–72 months) compared with kidney transplant recipients. The longer follow-up of renal transplant recipients probably accounts for the greater incidence of other tumors, which tend to appear late after transplantation.

Sheil13 reported for the Australian and New Zealand Liver Transplant Registry that of 434 patients who survived a mean of 2 years after LT, there was a 2% incidence of de novo cancer. Thirteen malignancies were detected in 12 transplant recipients: 6 patients, non-Hodgkin’s lymphoma; 3 patients, Kaposi’s sarcoma; 1 patient, leukemia; 1 patient, testicular cancer; 1 patient, bladder cancer; and 1 patient, thyroid cancer. In an updated analysis of this registry presented at the Seventh Congress of the International Liver Transplantation Society,14 of 1,170 of 1,540 LT survivors, de novo cancers were noted in 184 patients. One hundred thirty-eight patients developed skin cancers (including 4 patients with Kaposi’s sarcoma); 19 patients, post-transplant lymphoproliferative disorder (PTLD); 11 patients, digestive cancers; 6 patients, genitourinary cancers; 5 patients, endocrine tumors; and 7 patients, other cancers. By 10 years post-LT, 30% of patients had developed de novo cancers.

Kelly et al15 at Mt Sinai Medical Center noted that of 888 liver transplant recipients, 4.3% developed de novo cancers. They noted that alcoholic patients had a significantly greater incidence of de novo malignancies, but these tumors were no more aggressive than reported for the general population. However, in a follow-up report of long-term LT survivors (≥5 years), there was a significant increase in the incidence of de novo malignancies, with a standardized incidence ratio (SIR) of 3.94 for nonskin cancers and 3.14 for nonmelanoma skin cancers.16 The SIR is used to provide a comparative incidence of the observed number of malignancy cases to the expected number of cases. Thus, a SIR value greater than 1.00 indicates excess risk, whereas a value less than 1.00 is a decreased risk.

The Barcelona group reviewed 340 liver transplant recipients surviving more than 2 months and noted a 4.7% incidence of de novo tumors; the mean time to appearance was 28 months.17 Twenty-five percent of these tumors were PTLD; 12.5%, colon, bladder, breast, skin, and oropharyngeal cancers; and 6%, cervical cancer and small-bowel adenocarcinoma.

The Groningen group noted that 21 of 174 LT survivors developed de novo malignancies at 1-year.18 Although skin cancers accounted for the majority of these cancers, surprisingly, only 1 patient developed PTLD. Cumulative risks for de novo malignancy were 6%, 20%, and 55% at 5, 10, and 15 years after LT, respectively. The overall RR compared with the general population was 4.3 (95% confidence interval, 2.4 to 7.1). Significantly increased RRs were observed for nonmelanoma skin cancer (RR, 70.0), nonskin solid cancer (RR, 2.7), renal cell cancer (RR, 30.0), and colon cancer (RR, 12.5). Multivariate analysis showed that age older than 40 years and pre-LT use of immunosuppression were significant risk factors.

The Baylor group reported on 556 liver transplant recipients, of whom 25 patients (4.5%) developed de novo tumors.19 Of these, skin cancers and PTLD were represented equally, with a single case each of colon, breast, prostate, pancreas, and liver cancer.

Recently, at the Seventh Congress of the International Liver Transplantation Society, the Berlin group reported a 6% incidence of malignancy at 5 years post-LT.20 With a median follow-up of 6 years, de novo neoplasms were detected in 62 of 1,007 liver transplant recipients and included PTLD, 13 patients; skin cancers, 17 patients; cervical cancers, 9 patients; lung cancers, 6 patients; breast cancers, 5 patients; oropharyngeal cancers, 4 patients; and miscellaneous cancers, 8 patients.

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Pittsburgh2,21</th>
<th>ANZ13</th>
<th>Mt Sinai15,16</th>
<th>Berlin20</th>
<th>Dallas19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up (mo)</td>
<td>93</td>
<td>24</td>
<td>65</td>
<td>60</td>
<td>35</td>
</tr>
<tr>
<td>Overall (%)</td>
<td>12.5</td>
<td>2.3</td>
<td>12.9</td>
<td>6.1</td>
<td>4.5</td>
</tr>
<tr>
<td>PTLD (%)</td>
<td>4.4</td>
<td>1.0</td>
<td>2.9</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Skin (%)</td>
<td>3.5</td>
<td>0.5</td>
<td>4.3</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Gastrointestinal (%)</td>
<td>1.0</td>
<td>0</td>
<td>0.7</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Genitourinary (%)</td>
<td>0.9</td>
<td>0.3</td>
<td>2.2</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Lung (%)</td>
<td>0.8</td>
<td>0</td>
<td>0.7</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Oropharyngeal (%)</td>
<td>0.8</td>
<td>0</td>
<td>0.7</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous (%)</td>
<td>1.2</td>
<td>0.3</td>
<td>2.1</td>
<td>2.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>
The University of Pittsburgh Experience

In the most detailed and comprehensive analysis of the nature and comparative frequency of de novo malignancies, 1,000 consecutive adult and pediatric primary liver transplant recipients were followed up for a mean of 93.3 ± 11.0 months on a prospective basis (Fig. 1).\(^8,21\) Forty-four patients developed PTLD. Eighty-one patients developed de novo nonlymphoid malignancies, 35 of which were skin cancers, including 2 melanomas and 2 Kaposi’s sarcomas; 11 gastrointestinal cancers, 9 genitourinary cancers, 8 pulmonary cancers, 7 oropharyngeal cancers, 3 breast cancers, 2 metastatic cancers of unknown primary tumors, 2 leukemias, 2 thyroid cancer, 1 brain cancer, 1 de novo hepatocellular carcinoma, and 1 ophthalmic malignancy.

Compared with SIRs from the Surveillance Epidemiologic End Results (SEER) data,\(^22\) the incidence of oropharyngeal cancer was found to be 7.6 times greater \((P < .01)\) and that of respiratory malignancies, 1.7 times greater \((P \leq .05)\) than predicted. Conversely, the incidence of breast cancer was 1.9 times less \((P > .05)\) and that of genitourinary malignancy was 1.5 times less \((P > 0.05)\) than in their matched cohorts. No difference was observed in risk for gastrointestinal malignancies.

In a subanalysis of a high-risk group for PTLD, 353 pediatric primary liver transplant recipients were studied to determine the incidence of PTLD.\(^23\) The incidence of PTLD was 13.7% with tacrolimus immunosuppression versus 8.3% with cyclosporine (CyA), in part related to more sensitive detection methods in the former group. In the tacrolimus group, the diagnosis of PTLD presented at a mean age of 5.5 ± 0.7 years (range, 0.6 to 15 years), with an average time from LT to PTLD of 10.1 ± 2.1 months.

Figure 1. Inverse relationship between the incidence of PTLD and nonlymphoid malignancies in various age populations.

Figure 2. Kaplan-Meier survival after de novo malignancies for different types of cancers after the time of diagnosis.
Survival Statistics

Survival with de novo malignancies is generally poor, but is dependent on tumor type. In addition, the impact of these malignancies on patient survival is evolving. In our experience, survival in patients with PTLD has improved over time. Survival after the diagnosis of PTLD was significantly better for tacrolimus-treated patients with PTLD at 81.2% than for CyA-treated patients with PTLD at 50% after 5 years, also in part related to improved strategies for management of this complication. This also compares favorably with other reports on PTLD, in which mortality rates were approximately 60%. Nevertheless, the development of de novo malignancies significantly compromises long-term survival. Sheil reported that the 10-year survival rate in all patients with de novo malignancy was only 27%.

We reported that 1-year survival rates for skin cancer, oropharyngeal cancer, and lung cancer were 90.9%, 34.3%, and 37.5%, respectively. The 1-year survival rate for genitourinary and gastrointestinal cancer was 100%; however, at 2 years, it had decreased to 60% and 40%, respectively (Fig. 2). All patients with metastatic disease of unknown primary tumor, Kaposi’s sarcoma, brain tumor, and cancer of conjunctiva died within the first year from the time of diagnosis ($P = .015$).

Role of Immunosuppression

It is tempting to speculate on the pathophysiological process in which exogenously administered immunosuppressive agents potentiate the development of or enhance the aggressive nature of de novo malignancies. Antirejection medications induce a state of iatrogenic depression of immune surveillance, suggested to be a condition permissive for the development of malignancy. However, it also was suggested that such immunosuppressive agents as azathioprine and CyA have intrinsic properties that favor the establishment of de novo malignancies. Potential mechanisms range from inherent carcinogenic properties of antiproliferative agents to alterations in the cytokine milieu associated with CyA (and perhaps tacrolimus) to an independent effect on cell-adhesive properties.

It is well known that antiproliferative and alkylating agents can initiate and/or potentiate DNA damage and act synergistically with other carcinogens. Azathioprine has been suggested to have a role in skin cancer development; a study by Lennard et al showed that renal transplant recipients on azathioprine therapy who developed skin cancer had greater levels of the metabolite 6-thioguanine than those who did not develop skin cancer. However, large-animal models have not shown excessive cancer rates when chronically administered either cyclophosphamide or azathioprine. CyA has been suggested to heighten the risk for carcinogenesis in an autonomous fashion. Hojo et al showed that CyA induces phenotypic changes in cells, including nontransformed cells, with increased membrane ruffling, cell locomotion, and extracellular matrix–independent growth. This effect appears to be mediated by transforming growth factor-β (TGF-β) because monoclonal antibodies to TGF-β prevent metastasis in an experimental model. It is known that TGF-β is a potent cell-growth modulator and affects cell-extracellular matrix interactions in a dose-dependent manner. Although both CyA and tacrolimus increase TGF-β transcription rates in humans in vivo, comparative studies suggest that this may be more prevalent with CyA.

Discussion

Several regional registries of posttransplantation malignancies in organ transplant recipients have been maintained. In the United States, this was initially created at the University of Colorado, but currently resides at the IPITTR at the University of Cincinnati. In Australia, the Transplant Society of Australia and New Zealand has a long running registry, whereas in Europe, the Collaborative Transplant Study is maintained at the University of Heidelberg. The reported incidence of de novo malignancies after LT has ranged from 4% to 16%, depending on the length of follow-up, age distribution of patients who underwent LT, and nature of the immunosuppressive regimen used. It is clear that a point incidence for the risk for de novo malignancies will not be accurate because the longer a transplant recipient survives, the greater the cumulative risk. This was highlighted by Flattery, who noted that the actuarial risk for de novo cancer among cardiac transplant recipients increased from 2.7% ± 1.9% at 1 year to 25.6% ± 11% at 5 years. In our own series, as expected, we noted that the overall frequency of de novo nonlymphoid cancers increased as further follow-up accrued.

Most studies addressing the development of de novo malignancies in liver transplant recipients recognized that a significant proportion of patients have PTLD. PTLD encompasses a spectrum of abnormal conditions of lymphocyte proliferation that occur in the setting of iatrogenically induced immunodeficiency after organ transplantation. The susceptibility of transplant recipi-
ments to the development of lymphomas was first described in 1968. The relationship of these lesions to a viral cause was confirmed when Epstein-Barr virus (EBV) was found to be associated with the majority of PTLD (reviewed in 41). Most PTLDs arise within the first 1 to 2 years after transplantation. However, recent evidence shows that the proportion of EBV-negative PTLDs increases in late presentations. The actuarial 1-year incidence of PTLD is approximately 2%, although the incidence is up to 10 times greater in children aged younger than 5 years (more likely to be EBV seronegative) compared with adults (usually EBV seropositive). Of note to this discussion are recent reports of an increased incidence of PTLD in patients with hepatitis C virus coinfection, not only in liver transplant recipients, but in heart transplant recipients, as well.

The pathophysiological course of PTLD is not completely understood. The majority of PTLDs are of B cell origin (>90%), whereas the remainder is of T cell origin, and only rarely of null cell, i.e., without identifiable T- or B-cell markers. EBV is believed to have a role in the development of the majority of PTLDs, presumably by binding to the EBV-specific receptor found on B cells and providing a growth signal to the infected B cell. Expression of viral proteins can lead to a number of immune consequences. For instance, the viral product bcl-2 protects EBV-infected B cells from programmed cell death. The underlying commonality in the development of PTLD is the role of exogenous immunosuppression, believed to be related to suppression of host defenses (primarily T cells, which normally provide surveillance and protection from outgrowth of viral-infected cells). This supports the finding that reduction or withdrawal of immunosuppression leads to regression of PTLD in many cases.

Treatment of PTLD has been controversial. For patients with disease that fails to respond to a reduction in immunosuppression, a variety of systemic therapies have been used as a second step of treatment. These include interferon alfa, chemotherapy regimens, anti-B-cell monoclonal antibodies, and cell-based therapies. No clinical trial has delineated which therapeutic approach is best. The potential for exacerbation of rejection with interferon, toxicity with chemotherapy, and logistic problems with cell-based therapy make antibody therapy attractive. With the unavailability of anti-CD21 and anti-CD24 monoclonal antibodies, anti-CD20 monoclonal antibody therapy has been used instead and recently was reported to be of some benefit in post-LT PTLD. Chemotherapy may be necessary for refractory PTLD.

It was of interest that LT for alcohol-related liver disease was associated with a greater incidence of de novo cancers than in patients who did not undergo LT for alcoholic liver disease (ALD). In our series at 5 years post-LT, overall patient survival rates for the ALD and non-ALD groups were similar (72.0% vs 66.5%). However, after 5 years, patient survival for the ALD group was significantly less (P = .001) compared with the non-ALD group. Although rates of PTLD in the ALD (3.2%) and non-ALD groups (2.6%) were similar, surprisingly, mortality in the ALD group with PTLD was significantly greater (83%) compared with the non-ALD group (17.6%; P = .002). Although there are many reports of PTLD in LT populations, there are no reports of increased mortality caused by PTLD in liver transplant recipients with ALD. Ethanol has been reported to increase karyotypic chromosomal aberrations; expression of TGF-β in a variety of cells, including macrophages and liver cells; and suppression of immunity toward cancer and infections in experimental models.

This potential enhancement of cancer susceptibility in patients with ALD who underwent LT was also noted in other de novo cancers, with rates of oropharyngeal and lung cancers 25.5 and 3.7 times greater in the ALD group compared with the general population matched for age, sex, and length of follow-up using SEER data, respectively. The incidence of de novo cancer for the non-ALD group was similar to that in the general population. Rates of genitourinary cancers also were 2.2 times greater in the alcoholic population, but not in the nonalcoholic group; however, this did not reach statistical significance. The increased incidence of oral, esophageal, pharyngeal, laryngeal, and hepatic malignancies has been documented in nonimmunosuppressed middle-aged and elderly individuals with moderate to large amounts of alcohol consumption. In our experience, 70% of patients who developed oropharyngeal, lung, and gastrointestinal cancers in the study had an alcoholic history before LT. Most of these patients were fully rehabilitated and free from alcohol consumption before LT and have been believed to remain sober after LT. Whether abstinence from alcohol and tobacco use can reverse this susceptibility is unclear, although reports suggest this in the nontransplantation population.

Skin cancers represent the single largest nonlymphoid class of de novo malignancies. The pathophysio-
logical cause of skin cancer development is multifactorial, with sun exposure, age, race, and viral causes implicated. Human papillomavirus is a large class of DNA viruses shown to have a critical role in the development of cervical intraepithelial neoplasms and cervical cancer. Human papillomavirus, specifically types 5 and 8, has been implicated as a cofactor in the development of skin cancers (primarily squamous cell carcinoma) in immunosuppressed patients.  

Another viral-associated skin cancer is Kaposi’s sarcoma, which is significantly greater in the transplantation population than in the general population. The reported incidence of Kaposi’s sarcoma in the transplant population ranges from 0.18% to 6%, with a latency of 20 to 24 months.  

The SEER age-adjusted incidence rate (adjusted to the 1970 US population) for 1993 for men of all races was 5.8 cases/100,000 population per year. It has been suggested that human herpesvirus 8 is involved in the cause of this disorder. Afflicted patients tend to be men of Mediterranean descent, in whom the prevalence of human herpesvirus 8 is greatest. Although instances of regression of even visceral disease have been reported with cessation or reduction in immunosuppressive drugs, our experience with Kaposi’s sarcoma has been poor, with high mortality.

Some liver transplant recipients were at risk for the development of cancer irrespective of immunosuppression and LT. Certain conditions are associated with a greater risk for the development of cancer, such as the association between ulcerative colitis (UC) and colorectal cancer. In the first report on the risk for colon cancer after LT in patients with primary sclerosing cholangitis (PSC), 31 patients at the University of Pittsburgh with UC and PSC had an incidence of colon cancer of 6.5%. In our more recent series, 2 patients out of 35 with UC and PSC developed de novo colon cancer after LT; however, compared with SEER estimates, this risk was not considered to be greater than that in the general population compared with the entire transplant population at risk.

The postoperative course of patients with inflammatory bowel disease (IBD) who underwent LT for PSC was analyzed for the incidence of colorectal cancer. Bleday et al. noted that colorectal cancer occurred in 3 of 27 patients (11%), and these patients developed their cancer rapidly, within 9 to 13 months after LT. In a retrospective study of 1,085 liver transplant recipients, the incidence of colon cancer was found to be 8% in patients with IBD versus 0.1% in transplant recipients without IBD. Among 57 patients with intact colons who underwent LT for PSC with coexistent UC, the risk for colon cancer was increased fourfold, but this difference was not statistically significant. The IPITTR conducted a retrospective review to define the risks of immunosuppression for colon cancer in liver transplant recipients with UC and PSC. They reported on 21 patients with de novo colon cancer, of whom 10 patients (48%) had a diagnosis of PSC and 10 patients had metastatic lesions at the time of diagnosis. As expected, survival was better in patients who had localized disease than among those with metastatic disease.

Vera et al. at the Queen Elizabeth Hospital (Birmingham, UK) studied 152 patients with PSC who underwent LT. Patients with more than a 10-year history of UC pre-LT had a 30% risk for developing cancer by 6 years post-LT. Ten patients underwent colectomy post-LT; 17 patients had a colectomy performed either before or during LT. Patients who underwent prophylactic colectomy before or during LT had a superior 10-year survival rate (87%) versus 60% in patients with an intact colon, although the difference was not statistically significant. The 5-year survival rate was 55% in patients with colon cancer versus 75% in patients without colon cancer. They concluded that risk factors for an increased incidence of de novo colon cancers were age older than 45 years, diagnosis of PSC, length of time with UC, and presence of colon polyps.

One of the limitations of these studies is the common assumption that the risk for liver transplant recipients with UC and PSC to develop colon cancer is distributed uniformly over time. However, this is unlikely to be true for most premalignant conditions in that the risk increases exponentially over time. As shown in Figure 3, the risk for colorectal cancer in the setting of IBD in patients with PSC increases dramatically after 20 years from the onset of IBD symptoms, but does not differ from the risk for colon cancer in patients with IBD who did not undergo LT. Thus, the incidence of colorectal cancer will always be greater after LT than before simply because of the longer duration of IBD in liver transplant recipients.
Whether this risk is increased in liver transplant recipients has not been shown, but our experience, as well as that of others, suggests that this risk is greater than in the general population.

Another coexistent premalignant condition as an indication for LT is myeloproliferative disorder (MPD), which contributes as a leading cause of Budd-Chiari syndrome, frequently resulting in end-stage liver failure necessitating LT. It was reported that up to 10% of patients with MPDs progress to acute leukemia. There is concern that immunosuppression after LT may increase this risk. Dousset et al reported on two patients with MPD and Budd-Chiari syndrome who underwent LT and developed leukemia relatively late after LT (29 and 31 months). The King’s College group reported that of six patients with MPD, one patient developed acute leukemia 6 years after LT. This suggests that leukemic transformation follows the natural history of the disease, rather than an effect of immunosuppression.

Last, although not truly de novo malignancies, donor-transmitted malignancies should be considered in the differential diagnosis and have been reported. Inadvertent cancer transmission through organ transplantation has been documented by correlation of donor autopsy findings or medical history with the subsequent development of a malignancy in the transplant recipient. In our experience, one patient in this LT population apparently developed carcinosarcoma in the liver as a result of donor transmission. Penn noted that 117 of 270 recipients of organs from donors with malignancies developed cancer. Jonas et al reported the transmission of a single glioblastoma multiforme of 49 organs transplanted from donors with central nervous system malignancies.

Measures for prevention and early detection are critical to reduce the impact of de novo malignancies after LT. Risks can be reduced by cessation of risk factors, such as alcohol consumption, smoking, and photodamage. Early detection with routine colonoscopy for high-risk individuals, such as those with IBD, and follow-up endoscopy for those with Barrett’s metaplasia of the esophagus, will allow early intervention. On our study, only 20% of nonskin malignancies were discovered on routine screening. Almost one half the patients with nonskin nonlymphoid de novo cancers presented with advanced disease at the time of diagnosis; rapid dissemination of the cancer in a setting of reduced immune surveillance could account for presentation at an advanced stage, as well as accelerated malignant progression. A tendency toward aggressive behavior has been noted in malignancies in renal transplant recipients. Although instances of tumor regression with cessation or reduction in the immunosuppressant regimen have been noted in PTLD, most nonlymphoid de novo nonskin cancers follow a virulent course unchecked by return to normal immune surveillance.

Conclusions

In conclusion, PTLD remains the most common type of de novo malignancy in the post-LT patient. Of nonlymphoid malignancies, skin cancers were the most common type of cancer observed with the best long-term survival, although there are significant proportions of skin cancers that lead to death. In liver transplant recipients compared with the general population matched for age, sex, and length of follow-up, the RR for developing oropharyngeal cancer was 7.6 times greater, and for lung cancer, 1.7 times greater. Interestingly, rates of female (breast, ovary, uterus, and cervix) cancers were 1.9 times less (SIR, 0.53) and may reflect a diligent policy of pre-LT and post-LT mammography and gynecological evaluation. However, the lower incidence of de novo breast cancer was also noted in the Collaborative Transplant Study registry. The rate of genitourinary malignancy was 1.5 times less (SIR, 0.68) than expected, in contrast to the greater incidence of anogenital malignancies detected in renal transplant recipients. Despite an apparent increased risk for colon cancer in liver transplant recipients with IBD, the rate for gastrointestinal malignancy was not significantly greater than that in the general population (SIR, 1.06).

However, the rapid progression of de novo malig-
nancies in chronically immunocompromised transplant recipients warrants careful attention to the early evaluation and treatment of suspicious lesions, particularly in high-risk patients. Based on data presented, we strongly recommend screening in adult liver transplant recipients aged older than 45 years with indirect laryngoscopy (for smokers), chest radiograph, prostate-specific antigen level in men, mammography plus continuation of cervical smears in women, and colonoscopy in high-risk patients at regular intervals during follow-up examinations. These screening procedures may facilitate diagnosis of these cancers at an early and (hopefully) curable stage of disease.

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