De Novo Malignancies Following Liver Transplantation: Impact and Recommendations

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Key Points

1. De novo malignancy is one of the leading causes of late mortality after liver transplantation.

2. The risks of skin cancers and lymphoma are more than 10-fold greater than the risks in an age-matched and sex-matched general population.

3. Some types of neoplasia, such as lung, head and neck, and colorectal cancer, are more frequent in liver transplant recipients than in an age-matched and sex-matched population. The risks of other frequent malignancies, such as prostate and breast cancer, do not seem to be increased.

4. The most important risks for posttransplant malignancy are Epstein-Barr virus seronegativity (for lymphoma), sun exposure (for skin cancer), smoking, and increasing age.

5. Despite the absence of evidence, general recommendations (such as avoidance of overimmunosuppression, sunlight protection, and cessation of smoking) should be given. Screening protocols may help to detect neoplasia at an early stage of disease. ***Liver Transpl 15:S90-S94, 2009.***

Liver transplant recipients are at risk of developing de novo neoplasia through a variety of mechanisms. Immunosuppressive therapy decreases immune surveillance against malignant cells and against a variety of viruses that have oncogenic properties. Moreover, certain immunosuppressive drugs may have intrinsic oncogenic properties. As a result, liver transplant recipients have an increased risk of de novo neoplasia. For instance, in a recently published randomized trial, patients with alcoholic cirrhosis had a higher risk of nonhepatic neoplasia if they were transplanted than if they received standard care (5-year risk of neoplasia: 37% versus 6%).[1]

Overall, the risk of malignancy is 2 to 4 times higher in transplant recipients than in an age-matched and sex-matched population[2-6] (Table 1 and Fig. 1). This increased risk is especially high in neoplasia related to viral infections,[7] such as non-Hodgkin lymphoma, Kaposi's sarcoma, and uterine cervical cancer. The risk of skin cancer is also greatly increased.[3-6,8] The incidence of other common malignancies also seems to be increased, but this risk is not so high. Some series have shown that the risk of colorectal,[3,5] lung,[9] head and neck,[10] urological,[3] and hepatocellular carcinomas[11] are increased. In some cases, the cause of this increased risk may be a specific association between certain causes of liver disease and risk factors for the development of certain types of neoplasia in the general population. This is very important in 2 circumstances. First, there is the association between primary sclerosing cholangitis and ulcerative colitis, which markedly increases the risk of colorectal cancer. Second, patients with alcoholic liver disease may have an increased risk of neoplasia because a high intake of alcoholic beverages is associated with a higher risk of esophageal cancer and head and neck cancer and also because of the association between high alcohol intake and smoking, which is an important risk factor for some of the most frequently diagnosed tumors in transplant recipients. In fact, this increased risk has not been adjusted for well-known risk factors of neoplasia. Finally, the risk of other common neoplasia types such as prostate and

Abbreviations: EBV, Epstein-Barr virus; mTOR, mammalian target of rapamycin.

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TABLE 1. Relative Risks of Neoplasia in Liver Transplant Recipients in Comparison with a Sex-Matched and Age-Matched Population

Type of Neoplasia	Relative Risk
Overall	2–4
Squamous and basal cell skin cancer	20–70
Lymphoma	10–30
Head and neck cancer	4–7
In alcoholic liver disease	25
Lung cancer	1.7–2.5
Colorectal cancer	3–12
In ulcerative colitis	25–30
Prostate cancer	Not increased
Breast cancer	Not increased
Kidney cancer	5–30
Kaposi's sarcoma	100
Hepatocellular carcinoma	3.4

NOTE: The data in this table were taken from Herrero et al.,[2] Haagsma et al.,[3] Sheiner et al.,[4] Oo et al.,[5] Åberg et al.,[6] Fung et al.,[9] Herrero et al.,[10] and Hoffmann et al.[11] Tumors are listed in the order of frequency.

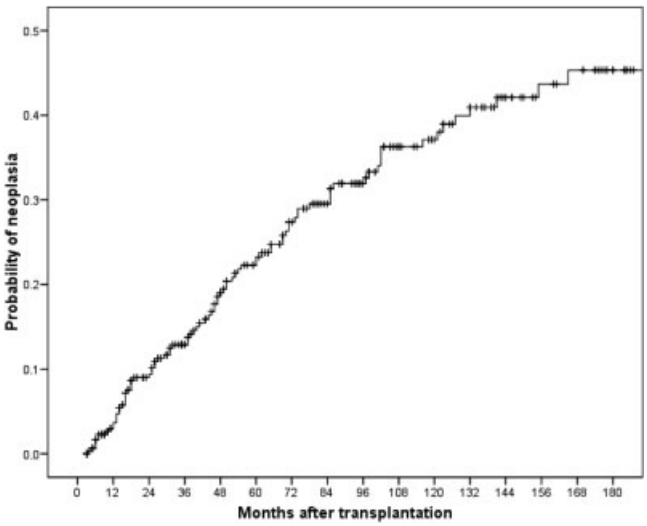

Figure 1. Risk of de novo malignancy after liver transplantation in 322 liver transplant recipients with survival greater than 3 months after transplantation (April 1990 to January 2009).

breast cancer does not seem to be increased in liver transplant recipients.[9] As a result, the risk of mortality due to neoplasia is significantly higher than that in the general population,[2,3] and de novo neoplasia is one of the most common causes of mortality after transplantation, mainly in the long term.[12] In our experience (Fig. 2), more than 30% of late deaths are caused by de novo malignancy, and de novo malignancy is the single most frequent cause of death after liver transplantation.

The outcomes after the diagnosis of malignancy in liver transplant recipients seem to be worse than the outcomes in the general population. Unfortunately, there have been no studies that have confirmed whether this is true and whether it results from a more advanced stage at diagnosis, from more aggressive behavior of neoplasia in transplant recipients, or from the presence of comorbidities.

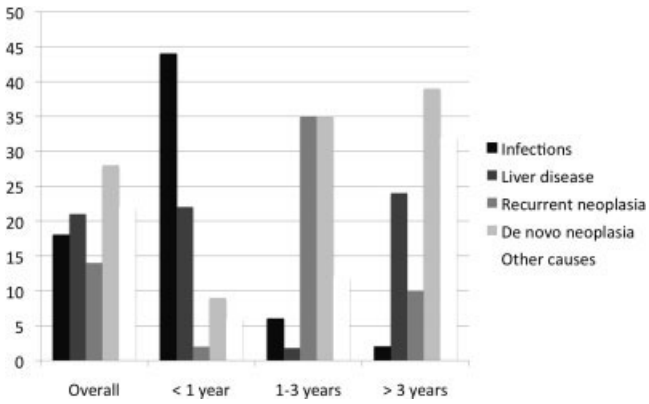

Figure 2. Causes of death after liver transplantation at Clinica Universidad de Navarra (April 1990 to April 2009; 90 deaths/340 transplanted patients).

RISK FACTORS OF NEOPLASIA

Immunosuppression

The intensity of immunosuppressive treatment has been related to the development of neoplasia. For instance, antilymphocyte antiglobulin therapy increases the risk of lymphoproliferative disorders,[13] and azathioprine may be related to the development of cutaneous neoplasia.[14] In relation to the use of calcineurin inhibitors, cyclosporine has been related to a greater risk of cutaneous neoplasia,[14] but tacrolimus has been related to a higher incidence of internal neoplasia.[15] The antiproliferative effect of mammalian target of rapamycin (mTOR) inhibitors may be associated with a protective effect against neoplasia. In fact, several retrospective analyses have shown that renal transplant recipients receiving sirolimus-based immunosuppressive therapy have a lower incidence of cutaneous malignancies.[16]

Age

The incidence of neoplasia according to age has a U shape. In children and young adults, the incidence of neoplasia is high because of the high incidence of lymphoma at these ages. This is because their Epstein-Barr virus (EBV) status before transplantation is frequently negative, and EBV-seronegative patients have the highest risk of lymphoma.[13] In young adults, the risk of malignancies is lower, and this risk increases with age, just as in the general population. In fact, the increased risk of malignancy is one of the most important causes of lower survival after the transplantation of older re-

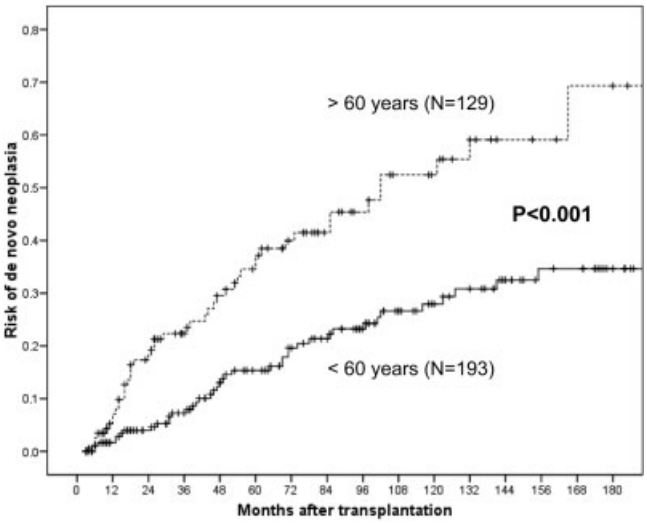

Figure 3. Risk of de novo malignancy after liver transplantation in 322 liver transplant recipients with survival greater than 3 months after transplantation (April 1990 to January 2009) according to their age at transplantation (older or younger than 60 years; $P < 0.001$).

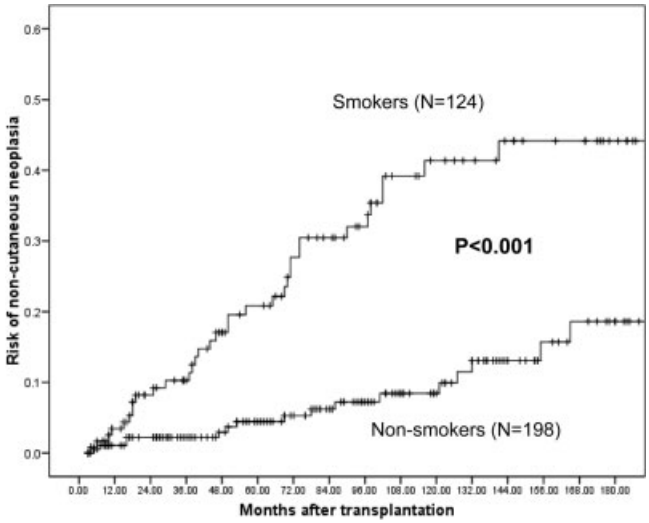

Figure 4. Risk of de novo malignancy after liver transplantation in 322 liver transplant recipients with survival greater than 3 months after transplantation (April 1990 to January 2009) according to smoking status ($P < 0.001$).

cipients.[17] Figure 3 shows the risk of de novo malignancy according to age in our series.

Risk Factors Specific for Different Types of Neoplasia

Lymphoma

As previously mentioned, the most important risk factor for lymphoproliferative disease is EBV infection (more frequently when the recipient is EBV-negative). Other potential risk factors are the use of OKT3 and antithymocyte globulins, hepatitis C virus infection, and cytomegalovirus infection.

Cutaneous Neoplasia

Kaposi's sarcoma is closely associated with human herpesvirus 8 infection. The main risk factors for squamous cell and basal cell carcinomas are skin type and sun radiation[8]; other potential risk factors are infection by human papillomavirus, hepatocellular carcinoma, primary sclerosing cholangitis, and the immunosuppression received,[14] but the role of these factors is less clear.

Upper Aerodigestive Tract and Lung Cancer

As in the general population, smoking is associated with a higher risk of esophageal, head and neck, and lung cancer. It is also probably associated with a higher risk of urological (other than prostate) neoplasia. In fact, smoking is an independent risk factor for noncutaneous malignancy after liver transplantation[2] (Fig. 4). Alcohol seems to also be an important risk factor for the development of head and neck cancer and esophageal cancer.[18]

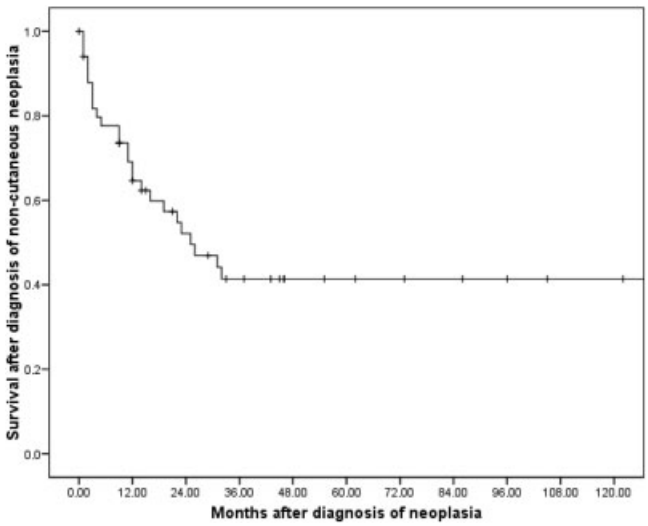

Figure 5. Survival after the diagnosis of de novo malignancy in 51 liver transplant recipients who were diagnosed with a noncutaneous malignancy (from a total population of 322 patients with a follow-up greater than 3 months).

Colorectal Cancer

Patients with ulcerative colitis associated with primary sclerosing cholangitis have a high risk of developing colorectal cancer[5] if they have an intact colon. It is not clear whether this risk is due only to long-term ulcerative colitis or also to immunosuppressive therapy.

PREVENTION AND EARLY DIAGNOSIS

Survival after the diagnosis of de novo malignancy is low. If skin cancers are excluded, median survival after neoplasia diagnosis is lower than 3 years (Fig. 5). Therefore, a program of neoplasia surveillance could have a positive impact on survival.

Some of the neoplasia screening programs in general populations have insufficient evidence to be recommended.[19] Similarly, none of the recommendations for the prevention and early detection of malignancy after liver transplantation are based on scientific evidence.

The first recommendation is to avoid overimmunosuppression, as it has been suggested that intense regimens of immunosuppression are associated with a higher frequency of malignancy.[15] The use of mTOR inhibitors could be associated with a lower incidence of neoplasia, but this benefit has been shown only in retrospective studies in renal transplant patients, and it is nearly restricted to skin cancer, which infrequently leads to death.[16] Other potential measures are related to specific types of neoplasia.

Lymphoproliferative Disease

It has been shown that patients who develop posttransplant lymphoproliferative disease have higher levels of EBV DNA than those who do not develop it.[13] Thus, monitoring of the EBV DNA load has been suggested to be of value in the early diagnosis of lymphoma. Unfortunately, there is no clear threshold value predictive for lymphoproliferative disease. Therefore, it has been proposed that the evolution of the EBV viral load or the combination of the EBV DNA load and EBV-specific cytotoxic T lymphocyte responses may be more useful. Two approaches have been suggested for patients with a high risk of posttransplant lymphoproliferative disease according to the EBV DNA load: antiviral therapy[20] and a gradual decrease in immunosuppressive therapy.[21]

Skin Cancer

As skin cancer is the most frequent cancer after transplantation, some authors have suggested that transplant recipients should be evaluated every year by a dermatology specialist. With this approach, skin cancer can be diagnosed during early stages, and this would allow curative resections in all cases[8] (in transplant recipients, skin cancer with an aggressive course and metastatic spread has been reported). Protection against sunlight seems a logical recommendation for transplant recipients, mainly for patients with a fair skin type. Unfortunately, it is possible that the decades of cumulative sun exposure before transplantation are more important than the few years of exposure after it. Finally, in patients with recurrent skin malignancies, conversion to mTOR inhibitors may have a protective effect against the development of new skin cancers.[16]

Smoking-Related Neoplasia

As smoking is a very significant risk factor for the development of neoplasia, smoking cessation should be recommended to avoid the development of de novo malignancies. Once again, it is possible that cumulative lifelong smoking is more important than active smoking. In fact, active smokers did not have a higher risk of malignancy than exsmokers.[22] The relevance of avoiding risk factors must be stressed in patients transplanted for alcoholic liver disease, not only because of the association between alcohol and smoking but also because alcohol consumption is a risk factor for neoplasia in the general population.[23]

As de novo neoplasia is one of the most frequent causes of long-term mortality in liver transplant recipients, some authors have suggested different surveillance protocols. In our experience, the use of a strict protocol has allowed us to diagnose neoplasia in some patients at an early and potentially curative stage.[10] This protocol has evolved over the years and includes yearly urinanalysis, abdominal ultrasound, chest X-ray film, prostate specific antigen determination (for elderly males), and ear-nose-throat examination and low-radiation chest computed tomography scan (for smokers); it also includes mammography every 2 years and colonoscopy every 7 to 10 years (or more frequently in the case of previous colonic adenomas and every year for patients with long-term ulcerative colitis).

CONCLUSIONS

De novo neoplasia is a frequent complication in liver transplant recipients. It is one of the most frequent causes of death in the long term. The main risk factors for its development are EBV seronegativity (for lymphoma), ulcerative colitis (for colorectal cancer), sun radiation (for skin cancer), smoking (for lung, head and neck, and urological cancer), and increasing age. The role of each immunosuppressive protocol in the risk of cancer remains controversial. Unfortunately, preventive measures and programs for the early diagnosis of neoplasia cannot be widely recommended until the evidence of their usefulness become stronger.

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