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"Will all liver transplantation patients eventually die from cancer?"

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Cancer occurring after transplantation, either recurrent or de novo malignancy, is a serious complication of liver transplantation and of great concern to transplant physicians and patients. Liver transplant (LT) recipients are at risk of developing cancer after transplantation from a variety of mechanisms. Prior to transplantation, long-term exposure to known carcinogens such as alcohol and tobacco or infection with oncogenic viruses such as HBV and HCV place many patients with advanced liver disease at increased risk. After transplantation, immunosuppressive medications result in decreased immune surveillance against malignant cells and increases the risk of malignancies mediated by viruses such as human papilloma virus, Epstein–Barr virus and human herpes virus-6. With the rising incidence of hepatocellular carcinoma (HCC), an increasing number of liver transplantations are being performed for the treatment of hepatic malignancies, which may recur after LT (OPTN Data 2004). Finally, given the demographic shift toward an older population, the majority of patients undergoing LT in the USA are now over the age of 50 (OPTN Data 2004). Given these facts, the question is raised: "Will all liver transplant patients eventually die from cancer?"

Recipients of LT can develop cancer either as the recurrence of a pre-transplantation malignancy (e.g. post-transplantation recurrence of HCC), or a de novo malignancy developing after LT. De novo malignancies include sporadic cancers, malignancies associated with the immunocompromised state (e.g. post-transplantation lymphoproliferative disorder) as well as those cancers associated with the patient's pre-transplantation disease state (e.g. colorectal carcinoma complicating inflammatory bowel disease in patients with primary sclerosing cholangitis). While the transmission of tumors of donor origin to organ transplant recipients can occur, the incidence is very low. Among a cohort of over 100,000 cadaveric organ transplant recipients from the Organ Procurement and Transplantation Network/United Network for Organ Sharing, the donor-related tumor rate was 0.017% [1].

In order to ascertain whether LT recipients are more likely to die from cancer we need to understand whether LT recipients are at a higher risk of developing cancer and whether they have increased cancer-related mortality than non-LT patients with cancer.

1. Cancer incidence after liver transplantation

Solid organ transplantation and subsequent chronic immunosuppression has been long associated with an increased risk for the development of cancer. Patients are at increased risk for hematologic malignancies as well as solid cancers. Concerning solid malignancies, several studies have demonstrated a higher incidence of both cutaneous and non-cutaneous solid malignancies in LT recipients compared with the general population. The reported rates in various studies range from 3 to 17%. The reported neoplasia rates are likely to be elevated due to the presence of screening bias among this population of patients where close medical surveillance is routine. These studies are also limited due to heterogeneity in terms of many important variables such as cohort size, patient population, indication for LT, era of transplantation, immunosuppressive regimen and length of follow-up. Many of these studies are further limited by inadequate control groups [2–18].

Among the larger published series, Galve et al. reported the cancer prevalence in 1827 Spanish LT recipients. Seventy patients (3.8%) were diagnosed with de novo malignancies after transplantation, including 17 skin

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Abbreviations: HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; LT, liver transplant; PTLD, post-transplant lymphoproliferative disorder; PSC, primary sclerosing cholangitis.

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cancers, 17 hematologic malignancies and 29 solid tumors including eight upper aerodigestive tract tumors (head, neck and esophageal cancers). Cancer occurred in patients at an average age of 53.5 years. Cancer tended to occur early after transplantation with the mean time to occurrence of 30.7 months. Fifty percent of cancers developed within 2 years of LT [7]. In a series of 1421 US LT recipients, 125 (8.8%) developed de novo malignancies including 41 skin cancers and 35 lymphomas. Fifty-nine patients with de novo malignancies died from tumor related deaths resulting in a 60% mortality for patients with non-cutaneous neoplasms (16).

2. Recurrent malignancies

Liver transplantation is considered to be the treatment of choice for patients with hepatocellular carcinoma (HCC) and decompensated cirrhosis [19]. Despite the use of established criteria for selecting LT candidates with the lowest risk of HCC recurrence, HCC has been reported to recur after LT in approximately 10% of patients [20–22]. After the adoption of the model for end-stage liver disease (MELD) score for organ allocation among LT candidates in the USA, the number of patients undergoing LT for HCC tripled during the first year. Subsequently, a number of patients were identified whose diagnosis of HCC could not be rigorously verified and thus a reduction in assigned MELD score was performed. Nonetheless, the proportion of patients undergoing LT who have HCC continues to rise, the number of patients with recurrent HCC is expected to increase (OPTN Data 2004) [21].

The natural history of recurrent HCC is not well established, although given concomitant immunosuppression, recurrent cancer may run a more aggressive course. In a series of 132 LT recipients from three Italian transplant centers, Regalia et al. reported a 15.9% HCC recurrence rate. Ninety percent of patients developed recurrence within 2 years of transplantation. The authors identified tumors greater than 3 cm in diameter, the presence of a peri-tumoral capsule and tumors, which exceeded the Milan criteria for LT as independent risk factors for post-transplantation recurrence. TNM (American Joint Committee on Cancer Tumor, Nodal Involvement and Metastatis classification system) stage, vascular invasion, pre-transplantation chemoembolization and serum alpha-fetoprotein level did not independently predict HCC recurrence in this study [23]. More recently, among a cohort of 67 patients with undergoing LT for HCC complicating HCV-related liver disease at a single US center, 11 patients (16.4%) developed cancer recurrence. Subsequently, eight deaths occurred from recurrent HCC. The majority of patients (81%) had cancer recurrence within 1 year of transplantation. Both patients who had late (>3 years after LT) recurrence presented with lung metastases. TNM staging, vascular invasion and pre-operative tumor diagnosis (as opposed to incidentally discovered tumors) predicted post-operative recurrence of HCC. Survival after transplantation was predicted by lower TMN staging and pre-LT chemoembolization [24]. Roayaie and colleagues reported the outcomes of 311 patients who had HCC at time of LT from a single US center. Recurrent HCC occurred in 57 patients (18.3%) at a median time of 12.3 months after LT. The prognosis of recurrent HCC was poor, with a median survival of only 8.7 months after recurrence. Multivariate analysis identified larger tumor size (greater than 5 cm in diameter), poorly differentiated histology and bony metastases (irrespective of other metastases) as predictors of decreased survival from time of LT. Early recurrence (less than one year after LT) and bony metastases predicted shortened survival from the time of recurrence, while surgical management of recurrent tumors was shown to increase survival from time of recurrence [21]. Together, these studies suggest that the recurrence rate of HCC after LT may be higher than previously reported.

While the majority of patients with cancer recurrences have presented early after LT, a minority patients present with cancer recurrence several years after transplantation. Two of the 11 patients in the Shimoda series developed recurrence of HCC more 3 years after transplantation and approximately 10% of patients in the Roayaie series developed recurrence 4 or more years after LT [21,24]. Patients with recurrent liver disease after LT, such as HCV infection, continue to have an oncogenic stimulus which may, in part, account for late recurrence. While patients who developed a HCC early after LT should be considered to have true recurrence, one could speculate that the development of HCC late after LT represents tumors with a different biology or possibly a de novo primary tumor.

3. De novo malignancies

3.1. Skin cancer

Cutaneous malignancies are the most commonly occurring cancers after LT. The prevalence of cutaneous malignancies is increased in transplant recipients and varies with the degree of immunosuppression. The majority of cutaneous malignancies are non-melanoma skin cancers such as squamous cell carcinoma and basal cell carcinoma. While basal cell carcinomas are the most common cutaneous malignancy in the general population, squamous cell skin cancer is more common among transplant recipients. The rate of developing squamous cell skin cancer is estimated to be increased over 60-fold in LT recipients compared to the general population. Fortunately, mortality rates from skin cancer in LT recipients are low with melanoma as the major cause of death [9,25]. While the transmission of donor-related tumors is rare, malignant melanoma is the most commonly transmitted tumor. Transplant recipient mortality due to the transmission of