

Chapter 16: Cancer in Solid Organ Transplantation

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INTRODUCTION

Solid organ transplantation provides lifesaving therapy for patients with end-organ disease. The Scientific Registry of Transplant Recipients (SRTR) report announced that 17,654 kidney, 6455 liver, 1946 lung, 2554 heart, and 109 intestinal transplants were performed in 2013, superseding the number of transplants from prior years (1). It also reports continual improvement in death-censored graft survival (2,3). Success of field of transplantation is reflected in the rising number and longevity of the transplant organs. However, the same report also noted an increase in recipient death with graft function, primarily due to increased infections and cancers associated with chronic immunosuppression. Malignancy is the second leading cause of death with graft function (4). The risk of cancer is two- to four-fold higher in transplant recipients than age-, sex-, and race-matched individuals from similar geographic areas (5,6). Not only are cancers common, but they tend to be more aggressive and are associated with increased mortality among transplant recipients than in the general population. The relative risk varies by age. Children have the highest increase (15–30 times), and older individuals (*i.e.*, >65 years of age) experience a two-fold increase. The magnitude of increase in risk for all cancer types is similar across organ recipients; the incidence of specific cancer varies by transplanted organ. Knowledge of cancer types, including the magnitude of increased risk and its clinical course, can help develop prevention and early detection protocols and prompt management (including adjustment of immunosuppression) to minimize cancer related deaths.

COMMON CANCER TYPES IN TRANSPLANT RECIPIENTS

The incidence of cancer is highest for malignancies related to viral infections, including non-Hodgkin

lymphoma (NHL; Epstein-Barr virus [EBV]), Kaposi sarcoma (human herpes virus-8 [HHV8]), liver (hepatitis C virus [HCV] and hepatitis B virus [HBV]), and anogenital cancers (human papilloma virus [HPV]). The increased risk of these cancers is believed to be related to impaired immune control of these oncogenic viruses, which can be present in the recipient prior to transplant or transmitted at time of transplant via the donor organ. This notion is supported by similar amplified risks of these cancers in individuals with compromised immune systems, *i.e.*, HIV/AIDS, and reversal of this heightened risk on withdrawal of immunosuppression, *i.e.*, kidney graft failure and reinitiating of dialysis (7). Independent of immunosuppressive effects, the antirejection medications such as azathioprine and cyclosporine directly enhance the carcinogenic effects of ultraviolet (UV) radiation via inhibiting DNA repair and resulting in apoptosis of keratinocyte (8,9). Certain malignancies with no obvious infectious causes are also reported to be elevated, *i.e.*, colon, bladder, lip, kidney, and thyroid cancer. These cancers have been reported to occur at a greater frequency in patients with kidney disease prior to receiving a kidney transplant but do not occur frequently in people with HIV/AIDS, confirming the lack of a role of the immune system. Instead, they may be occurring due to underlying renal or bladder disease, loss of kidney function, and/or malignant transformation of acquired cystic kidney disease (common in individuals with renal failure) (6). Traditional risk factors such as smoking and alcohol intake leading to organ failure continue to play a role in development of cancer, *i.e.*, cancer in the native lung for those receiving a solitary lung transplant for chronic obstructive pulmonary disease, liver cancer in alcoholics, and colon cancer in

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patients with ulcerative colitis requiring a liver transplant due to primary sclerosing cholangitis. There are a few case reports of malignancy transmitted via donor organ. To summarize, both immunosuppression and host-related factors play an important role in the increased risk of cancer in transplant recipients. Table 1 lists the names of common malignancies with their incidence rates after transplantation.

Of note, the cancer risk of nasopharynx, cervix, prostate, breast, brain, and chronic lymphocytic leukemia are reported to be lower in transplant recipients than in the general population (5). Similar observations have been made in people with HIV infection, together suggesting that the immune system may not be primarily controlling the development and growth of these cancers (10). Alternatively, this observation can also be explained by aggressive screening for cervical, prostate, and breast cancer in the transplant population, leading to prompt treatment of precancerous lesions prior to or after transplant.

CLINICAL COURSE OF COMMON CANCERS

Non-melanoma skin cancer

Non-melanoma skin cancer is the most common malignancy in adult white solid organ transplant recipients. Squamous and basal cell carcinoma account for >90% of all skin cancers. Unlike the general population, squamous cell carcinoma is the most common skin cancer. It occurs 250 times as frequently as that seen in the general population, whereas the risk of basal cell cancer is increased by 10-fold. Thus, the ratio of squamous cell to basal cell cancer in patients without transplant (1:4) is reversed in transplant patients (4:1). A third of patients will have both types of skin cancer.

The risk factors for developing skin cancer are as follows: 1) recipient related: history of skin cancer prior to transplant, the presence of premalignant skin lesions (warts or keratosis), exposure to solar UV rays, location of residence (highest incidence in Australia), older age, male sex, and fair skin phenotype; 2) immunosuppression related: duration and type (mainly azathioprine and cyclosporine); and 3) infection related: keratinocytes of transplant recipients are more likely to be infected with HPV than nontransplant people. The

Table 1. Common malignancies and incidence rates after transplant in United States

Cancer type	Incidence/10,000 person-years	SIR (95% CI)
Skin cancer	23.7	13.85 (11.92–16.00)
Kaposi sarcoma	15.5	61.46 (50.95–73.49)
PTLD	194.0	7.54 (7.17–7.93)
Lung	173.4	1.97 (1.86–2.08)
Liver	120	11.56 (10.83–12.33)
Kidney	97	4.65 (4.32–4.99)

Data were obtained from reference 5. SIR, standardized incidence ratio (observed/expected cases).

appearance and distribution of cancer depends on recipient age. The older recipients are likely to have their first lesion within 3 years of transplant and it will typically develop on their head, whereas in younger folks, it occurs later (typically after 8 years), and lesions are located on dorsum of their hands. Squamous cell cancers in transplant recipients are also more aggressive, especially when poorly differentiated on histology. The treatment of skin cancers depends on the type of lesion and its extent. Superficial lesions can be managed with cryotherapy while deeper lesions require excision with clean margins. Last, changing immunosuppression to a mammalian target of rapamycin inhibitor (mTORi)-based regimen has been shown to decrease the risk of recurrent cancers (11).

Kaposi sarcoma

Kaposi sarcoma occurs 80–500 times more frequently in transplant recipients than in non-immunosuppressed populations. In addition, it tends to be more aggressive and multicentric with visceral involvement. Most cases occur due to infection with HHV-8, and therefore, are commonly seen in recipients from a high sero-prevalence area, *i.e.*, Mediterranean and African regions. It is also more common in men, with a male to female ratio of 3:1, and often occurs within the first year of transplant. Ninety percent of them present as cutaneous lesions on the legs or mucosal angiomatous lesions. Visceral involvement commonly occurs in heart and liver transplant recipients. The mainstay of treatment is reduction of immunosuppression, but this may lead to graft dysfunction (12).

Non-Hodgkin lymphoma

NHL, which is more commonly referred to as post-transplant lymphoproliferative disorders (PTLD), occurs seven to eight times more frequently than in the general population (standardized incidence ratio [SIR], 7.54; 95% CI, 7.17–7.93). It occurs more commonly in young (0–34 years) and older (≥ 50 years) male recipients. The incidence is highest in lung and heart recipients and lowest in kidney transplant recipients, possibly due to varying transfer of lymphoid tissue during organ transplant and intensity of immunosuppression. Its occurrence is associated with the use of T cell-depleting agents and a mycophenolic acid-based antirejection regimen. Data on the risk of PTLD with use of tacrolimus are equivocal. Use of cyclosporine and azathioprine is not associated with increased risk of lymphoma. It commonly presents within the first year of transplant or 5 years after transplant. Early-onset lymphoma is related to primary EBV infection, and late-onset lymphoma is independent of infection. Its pathology ranges from benign hyperplasia to lymphoid malignancy. PTLD differs from lymphoma in the general population not only in histopathologic findings, but it is also associated with increased extranodal involvement, predominant occurrence in the transplanted organ, an aggressive clinical course, and poor outcomes. The 5-year survival was 41% and did not vary based on time of presentation. The mortality was higher in heart transplant recipients than in kidney transplant recipients

due to inability to withdraw/cease immunosuppression. In addition to conventional therapy, the mainstay of treatment includes reduction in immunosuppression, especially antiproliferative agents, and use of antiviral agents in those with primary EBV infections (13,14).

Lung cancer

Risk of lung cancer in transplant recipients is moderately increased compared with that in the general population (SIR, 6.13; 95% CI, 5.18–7.21). It is common in older male transplant recipients. It is more common in lung transplant recipients, with the highest risk occurring in the first 6 months of transplant (SIR, 11.17; 95% CI, 7.48–16.04) and falling to a five-fold greater risk thereafter. The elevated early risk of cancer may be due to cancer in the explanted lung (15). A novel study of single-lung versus bilateral-lung transplant recipients matched for underlying disease, smoking history, and age reported a five-fold increase in cancer among those with single-lung transplants, where the primary cancer was noted in the lung of the recipient (16). In addition to smoking and chronic immunosuppression, chronic inflammation and repeated infections may be playing a role in development of lung cancer in native lung (17). Recipients of other organs had smaller elevations in their risk, and its occurrence increased with time.

Liver cancer

Risk of liver cancer was strongly elevated in liver transplant recipients compared with the general population (SIR, 43.83; 95% CI, 40.90–46.91). Ninety-five percent of liver cancers were diagnosed within the first 6 months after transplant. Like the lung, the increased incidence of cancer within 6 months of transplant may be due to delayed recognition of cancer in the explanted liver. Thereafter, the risk of liver cancer was two-fold higher than the general population. These late-onset liver cancers may be due to recurrent disease related to HCV or HBV. Liver cancer risk is not increased among other organ recipients (5).

Kidney cancer

The risk of kidney cancer was highest in kidney transplant recipients (SIR, 6.66; 95% CI, 1.57–3.04), but was also elevated in liver and heart recipients. Among all recipients, kidney cancer occurs mainly in older men and had a bimodal pattern of presentation. It occurred within the first 6 months, and a second peak was seen 4–15 years after transplant. Some of the early cases can be explained by malignant transformation of the cysts that develop in patients with ESRD prior to transplant (6). As mentioned previously, the risk of renal cancer is already high among patients with CKD and continues to remain high after transplant (18).

SURVEILLANCE AND MANAGEMENT

In view of the higher cancer incidence and poorer prognosis, prevention and screening play an important role. Surveillance

for routine age-appropriate screening, as that in general population, is recommended for all (Table 2). Annual instead of biannual pap testing is recommended to detect precancerous lesions that may progress faster to cancer under influence of immunosuppression. There are no data on vaccinating transplant recipients who are HPV naïve. Annual mammograms are also recommended for all women over age 50. The patients should be counseled about higher incidence of false-positive findings (calcification and increased density of breast with chronic steroid use), resulting in increased interventions. In addition, recipients should also be screened for colorectal cancers with yearly fecal occult blood testing and flex sigmoidoscopy or colonoscopy every 5 years. Of note, most of these practices have not been validated in a transplant cohort (19). In the absence of evidence, an individualized approach to screening should be used based on the individual's cancer risk, existing comorbidities, overall life expectancy, and preference for screening.

Skin cancer may be prevented by using sunscreen (SPF + 15) and sun hats, avoiding sun peak hours, and covering up the exposed skin with long sleeves. Annual follow-up with an experienced dermatologist for total body skin examination is also advocated for those at high risk. Systemic retinoid should be avoided, and topical retinoid treatments can be tried to treat dysplastic lesions but with caution due to fear of increased risk of rejection. Those with repeated precancerous skin lesions can be counseled to switch to an mTOR inhibitor-based immunosuppressive regimen. Routine screening for renal cancer is not recommended (19).

In addition to traditional therapy, reduction in immunosuppression is often recommended. The underlying idea is that this allows immune reconstitution and control of the malignancy by the recipient's recovering immune system. If

Table 2. Common cancers and recommendations for screening

Cancer type	Recommendations for screening
Breast	Annual or biennial mammography for all women older than 50 years; for women between 40 and 49 years, no evidence for or against screening
Colorectal	Annual fecal occult blood testing and/or 5-year flexible sigmoidoscopy or colonoscopy for individuals >50 years
Cervical	Annual pap and pelvic examination once sexually active
Prostate	Annual digital rectal examination and PSA in all males after age 50 years
Liver	α -Fetoprotein and liver ultrasound every 6 months in high-risk individuals, <i>i.e.</i> , HBV or HCV infection, but no firm data
Skin	Monthly self-examination and total body skin examination every 6–12 months by an expert skin physician
Kidney	No firm recommendation, but some have suggested regular ultrasound of native kidneys

PSA, prostate-specific antigen. Adapted from reference 24.

immunosuppression is stopped or lowered, particularly early after transplantation, graft monitoring at short intervals is necessary. Successful reduction or cessation of immunosuppression was reported in transplanted patients who developed NHL and Kaposi sarcoma (20). Use of mTORi has been shown to reduce risk of new squamous cell cancer in patients with a prior history of skin cancer (11,21) and are also very effective in treating Kaposi sarcoma (22). However, tolerability of mTORi is poor and is associated with a 35% discontinuation rate. Although there are strong data favoring the use of an mTORi-based regimen in those with skin cancers and Kaposi sarcoma, there are insufficient data for solid organ cancers (23).

In summary, cancer remains a leading cause of morbidity and mortality in transplant recipients. Routine surveillance and early detection with prompt intervention directed at cancer and immunosuppression are recommended to improve the life of the recipient and their transplant organ.

TAKE HOME POINTS

- Cancer risk is increased by two- to four-fold in transplant recipients and tends to be more aggressive than age-, sex-, and race-matched individuals from the general population.
- Skin cancer is the most common cancer, followed by PTLD and cancer of the transplanted organ.
- Emphasis should be placed on adherence to recommended cancer surveillance protocols for early detection and prompt management.
- Management of cancer developing after transplant includes reduction of immunosuppression and switching to an mTOR inhibitor–based regimen for those with skin cancers.

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REVIEW QUESTIONS

1. A 50-year-old white woman, status post–kidney transplant 10 years ago, was recently diagnosed with squamous cell skin cancer on her nose. What should you advise her?
 - a. Continue regular follow-up with dermatology
 - b. Discontinue calcineurin inhibitor and switch to mTOR inhibitor–based regimen
 - c. Apply sun screen
 - d. Avoid peak hours of sun exposure
 - e. All of the above

Answer: e is correct. The patient should follow-up with dermatology for a complete skin examination as the risk of a second skin cancer is high. Exposure to UV light is one of the main risk factors for development of cancer, and therefore, avoiding sunlight and applying sunscreen may prevent development of new skin cancers. Last, studies have shown that switching to an mTOR inhibitor–based regimen reduces the risk of additional skin cancers.

2. Which of these factors lead to increased risk of cancer in the transplant recipient?
 - a. Viral infections
 - b. Immunosuppression
 - c. Chronic Infections
 - d. Smoking
 - e. All of the above

Answer: e is correct. The majority of the cancers in transplant recipients are due to viral infections such as HPV, HCV, HBV, EBV, and HHV-8. However, smoking, chronic infections, and certain immunosuppressants are also reported to increase risk of cancer.

3. A 12-year-old boy underwent kidney transplant 6 months ago. He received thymoglobulin for induction and was maintained on a triple immunosuppressive regimen including mycophenolic acid derivatives. He was EBV negative at the time of transplant. He now presents with low-grade fever and pain over the allograft. The biopsy reveals dense lymphocytic infiltrate with minimal tubulitis. The lymphocytes stained positive for CD3 and CD20. SV-40 stain is negative. What is the most likely diagnosis in this patient?
 - a. Rejection
 - b. Acute interstitial nephritis
 - c. Post-transplant lymphoproliferative disorder (PTLD)
 - d. BK virus nephropathy

Answer: c is correct. The boy has developed PTLN as suggested by a mixed lymphocytic population in the biopsy. CD3⁺ indicates the presence of T cells, and CD20⁺ indicates the presence of B cells. Rejection will have only CD3⁺ or T-lymphocytes. Lack of SV-40 staining rules out BK virus nephropathy. The presence of abundant polymorphic lymphocytes with minimal tubulitis should be a clue for PTLN. He had several risk factors for development of PTLN including young age, EBV naïve, use of a T cell–depleting agent for induction, and use of mycophenolic acid derivatives.

4. How will you manage this patient?
 - a. Increase immunosuppression
 - b. Decrease immunosuppression
 - c. Discontinue bactrim
 - d. Start cidofovir

Answer: a is correct. Treatment includes reduction of immunosuppression in this patient. Increasing immunosuppression to treat possible rejection may be harmful.