Malignancy: An Adverse Effect of Immunosuppression

Mrudula Munagala and Anita Phancao

Contents

M. Munagala (✉) · A. Phancao
MTI – University of Miami, Miami, FL, USA
e-mail: mrm410@med.miami.edu

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Abstract

Benefits of solid organ transplantation in end stage organ diseases are indisputable. Malignancy is a feared complication of solid organ transplantation and is a leading cause of mortality in patients with organ transplantation. Iatrogenic immunosuppression to prevent graft rejection plays a crucial role in the cancer development in solid organ transplant recipients. Chronic exposure to immunosuppression increases the malignancy burden through deregulation of host immune defense mechanisms and unchecked proliferation of oncogenic viruses and malignancies associated with these viruses. Vigorous screening of candidates undergoing transplant evaluation for malignancies, careful assessment of donors, and vigilant monitoring of transplant recipients are necessary to prevent, detect, and manage this life-threatening complication.

Keywords

Immunosuppression · Malignancy · Solid organ transplant

1 Introduction

Over the past decades, life expectancy of solid organ transplant recipients (SOTRs) has improved significantly due to the tremendous progress made in surgical techniques, immunology, and refinement of medical management including modern immunosuppression. Short-term outcomes of graft and patient survival have changed notably with improved screening for rejection and advances in histopathology. There has not been a significant change in the long-term survival of SOTRs over the past decade, predominantly due to mortality from cardiovascular diseases, infection, and malignancy (Lamb et al. 2011; Meier-Kriesche et al. 2004; Rana et al. 2019). Mortality of SOTRs secondary to infection and cardiovascular diseases improved after implementation of antimicrobial prophylaxis and identification and screening for cardiovascular risk factors along with optimal management of modifiable risk factors (Pilmore et al. 2010). However, malignancy in transplant recipients remains a great challenge and engenders increased mortality burden, reduced quality of life and survival of SOTRs. Risk of cancer is substantially higher in organ transplant recipients compared to the general population. This increased risk is attributed to long-term exposure to immunosuppression and impaired immune surveillance mechanisms associated with chronic immunosuppression. Immunocompromised patients are a heterogeneous group of patients including SOTRs, patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), congenital immunodeficiencies, patients on dialysis and patients receiving chemotherapy and/or radiation (Gatti and Good 1971; Grulich et al. 2007; Maisonneuve et al. 1999; Serraino et al. 2007). These groups of patients share a similar cancer risk profile elucidating a broader understanding of the role of immunosuppression in carcinogenesis (Gatti and Good 1971; Grulich et al. 2007;

Maisonneuve et al. 1999; Serraino et al. 2007). In this chapter, we summarize the adverse effects of immunosuppression and its association with malignancies with a focus on SOTRs who are exposed to chronic pharmacologic immunosuppression to prevent graft rejection.

2 Epidemiology of Malignancy in Immunocompromised Patients

Increased risk of malignant neoplasms in primary immunodeficiency syndromes has been described in the literature decades ago suggesting the role of the immune system in oncogenesis. In kidney transplant recipients (KTRs), the risk of de novo malignancy reverts to pre-transplant level after graft failure suggesting the role of immunosuppression in malignancy and need for adjustment of immunosuppression to reduce those risks (KDIGO 2009; Vajdic et al. 2006; Van Leeuwen et al. 2010). The risk of malignancy in SOTRs is comparable to patients infected with HIV/AIDS after excluding Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL) inferring an association between immunodeficiency and carcinogenesis (Grulich et al. 2007; Serraino et al. 2007). Although increased susceptibility for cancers is noted in SOTRs and patients with HIV/AIDS, SOTRs are more prone to develop colorectal cancers, thyroid and lip cancers as opposed to HIV infected populations (Grulich et al. 2007).

Solid organ transplantation (SOT) has been recognized as the gold standard treatment option for patients with end stage organ failure and survival advantage outweighs the adverse effects of immunosuppression in these patients (Rana et al. 2015). Choice of immunosuppressive regimens in SOTRs requires careful consideration of various factors such as risk of rejection, infection, and malignancy. There is a reported two-to-four-fold greater risk of malignancy in SOTRs compared to the general population matched for age, gender, and race. The magnitude of malignancy risk is variable based on type of malignancy and the transplanted organ. Nonetheless, the increased risk is persistent in all SOTRs regardless of the transplanted organ and despite the exclusion of patients with preexisting neoplasms prior to organ transplantation (Acuna et al. 2016; Chapman et al. 2013; Collett et al. 2010; Engels et al. 2011). Analysis of a large cohort of SOTRs derived from linking between population-based transplant and cancer registries in the United States (US) between the years of 1987 and 2008 demonstrated a clear increased risk of malignancies in SOTRs. Data was analyzed in 175, 732 SOTRs with a cohort comprised of 58.4% KTRs, 21.6% liver transplant recipients, 10% heart transplant recipients and 4% of lung transplant recipients. The incidence of malignancy per 100,000 person years was 1,375 with an excess absolute risk (EAR) of 719.3 per 100,000 person years and a standardized incidence ratio (SIR) of 2.10 [95% CI, 2.06-2.14] suggestive of an exaggerated risk compared to the general population. The increased burden is noted for both cancers of infectious and noninfectious etiology (Engels et al. 2011).

Non-melanoma skin cancer (NMSC) and lip cancers, post-transplant lymphoproliferative diseases (PTLD), and KS and anogenital cancers are frequently seen in SOTRs. In addition, an elevated risk for other cancers such as urogenital cancers, cancers of kidney and thyroid gland have been reported in organ transplant recipients (Acuna et al. 2016; Agraharkar et al. 2004; Buell et al. 2005; Chapman et al. 2013; Collett et al. 2010; Engels et al. 2011; Wimmer et al. 2007). Life expectancy of SOTRs is expected to be compromised by malignancy rather than cardiovascular events in the upcoming years due to the improvements in management of cardiovascular risk factors. Furthermore, cancers in SOTRs are biologically more aggressive and are associated with worse outcomes (Ajithkumar et al. 2007; Campistol et al. 2012; Hall et al. 2013; Vegso et al. 2007).

3 Pathogenesis of Malignancy in Solid Organ Transplant Recipients

Carcinogenesis in SOTRS is a result of complex and dynamic interplay of multiple factors including genetic, host, and environmental factors. Increased incidence of cancers in SOTRs is driven by altered dynamics of host immune surveillance, oncogenic viral infections, and direct carcinogenic effects of immunosuppressive agents (Ajithkumar et al. 2007; Campistol et al. 2012; Hall et al. 2013; Vegso et al. 2007). In addition, underlying chronic disease that prompted the transplantation and associated risk factors may predispose SOTRs to higher risk of malignancies. Natural immune defense mechanisms minimize the risk of neoplastic transformation by elimination of tumor cells, prevention of inflammation, and cell protection. Dysregulation of immune systems by pharmacologic immunosuppression promotes neoplastic transformation and growth by altering mechanisms of early detection and eradication of subclinical tumor cells, immune evasion of tumor cells, bolsters inflammation and proliferation of oncogenic viruses (Sherston et al. 2014). Tumorigenesis is a multistep process and is characterized by sustained proliferative signaling, insensitivity to growth suppressor signals, neo-angiogenesis, evasion of immune mediated destruction, resistance to apoptosis, invasion of tissue and metastasis and metabolic rewiring (Fouad and Aanei 2017; Hanahan and Weinberg 2011). Carcinogenesis in transplant is dominated by impaired immune modulation including reduced ability to eradicate the tumor cells, escape and evasion of neoplastic cells fostering a “tumor microenvironment” (Fouad and Aanei 2017; Hanahan and Weinberg 2011).

3.1 Immune Surveillance

Immune surveillance is an essential host defense mechanism against the development of cancers and for the maintenance of cellular homeostasis. Paul Ehrlich introduced the concept of repression of neoplastic cells by the host immune system in 1909 which generated impassioned debate for the decades to follow. He proposed

that a normally functioning host immune system destroys the subclinical tumor in its latency prior to clinical manifestation. The theory of "immunological surveillance of neoplasia" was reappraised by Lewis Thomas and Sir Frank Macfarlane Burnet in the late 1950s. Thymus dependent immunologic response was theorized to offer defense against tumor development by early detection and elimination at incipient stage. The central theme of this theory was that an immunocompetent host would be less susceptible to cancer development compared to an immunodeficient host. However, mice experiments by Carlos Martinez demonstrated reduced incidence of mammary tumors in mice that had undergone thymectomy compared to the group with intact thymus (Burnet 1970; Martinez 1964). Prospective role of immunosurveillance in carcinogenesis was summarized by Keast based on high incidence of tumors during extremes of age when immune system is nascent or senescent, with use of immunosuppressant medications, after thymectomy in animal experiments and in patients with disorders of cell mediated immunity. The association between immunological disorders and development of reticuloendothelial cancer without implying any causal effect was presented by Doll et al. (Doll and Kinlen 1970). The theory of "immunological surveillance" encountered strong criticism following the nude mice experiments by Stutman et al. and argued against carcinogenic potential of immunosuppressed state (Stutman 1979). Nonetheless, the advances in immunobiology and mice genetics rekindled the interest in the mystic role of the immune system in recognizing and destroying the tumorigenic cells. Pioneering work of Shakaran et al. validated the paradoxical role of the immune system in carcinogenesis and engendered the conceptualization of immunoediting. Over the past two decades, the theory of immunosurveillance evolved into a broader and more widely accepted concept of immunoediting that addresses not only the prevention of tumors, but also the immunogenicity of tumor cells. Immunoediting is a dynamic process characterized by three phases including elimination by immunosurveillance, equilibrium, and immune evasion leading to the escape phase (Shankaran et al. 2001). Chronic pharmacologic immunosuppression in SOTR leads to uninterrupted proliferation of tumor cells due to reduced threshold of surveillance leading to escape from immune elimination. Emanation of previously cured malignancies of donors in SOTRs has been appertained to potential lack of tumor equilibrium in the transplant recipient due to immunosuppression that may have otherwise existed in the immunocompetent donor (Teng et al. 2008).

3.2 Role of Viral Infections in Carcinogenesis

Majority of cancers in SOTRs are driven by oncogenic viruses as SOTRs are more vulnerable to reactivation of latent infections as well as acquisition of new viral infections. Oncogenic viruses can trigger genomic instability, impair DNA (deoxyribonucleic acid) repair mechanism, disrupt cellular homeostasis, and alter cell signaling pathways abetting neoplastic transformation. The association between Human Papillomavirus (HPV) in anogenital cancers, Human Herpesvirus 8 (HHV8) in KS, and Epstein–Barr virus (EBV) in NHL and Hodgkin lymphomas (HL),

Merkel cell polyomavirus (MCPyV) in Merkel Cell Cancer of the skin, Hepatitis B virus (HBV) and Hepatitis C (HCV) viral infections in hepatocellular carcinoma has been well established. The International Agency for Research on Cancer (IARC) has in fact identified these viruses as biological human carcinogens (Bouvard et al. 2009). Innate and adaptive immune responses combat viral infections in an immunocompetent host and eliminate or minimize the severity of infections. Some infections may attain a latent state by restriction of gene expression and cessation of replication by subverting cell signaling pathways. Infections with oncogenic viruses in SOTRs could be transmitted from donor or may have new onset infection if not immune from prior exposure or vaccination and/or activated from dormancy after transplantation due to immunocompromised state. Oncogenicity of viral infections is mediated through direct or indirect carcinogenic mechanisms. Direct carcinogenic mechanisms include activation of proto-oncogenes, expression of viral oncogenes along with impairing tumor-suppressor genes leading to proliferation, angiogenesis, and resistance to apoptosis. Indirect mechanisms include promoting chronic inflammation and oxidative stress with production of mutagenic molecules leading to local inflammation and tissue damage, immunosuppression, chronic antigenic stimulation, and tumor growth modulation (Krump and You 2018; Saha et al. 2010).

3.3 Direct Effect of Immunosuppressive Agents in Carcinogenesis

Immunosuppressive drugs used in SOTRs are described to have carcinogenic potential independent of their effects on host immunity and exert direct carcinogenic effects. IARC has labeled immunosuppression drugs as human carcinogens and declared azathioprine and cyclosporine to be human carcinogens (IARC 1990, 2012). Cyclosporine promotes carcinogenesis independent of immunosuppression effects by various mechanisms including increased transcription and expression of the transforming growth factor-β (TGF-β) gene, which in turn promotes invasion and metastasis of tumor cells. In addition, cyclosporine also impairs response to DNA damage, inhibits apoptosis, and promotes vascularization of tumors by inducing vascular endothelial growth factor (VEGF) production (Barle et al. 2014; Hojo et al. 1999; Maluccio et al. 2003; Olshan et al. 1994; Yarosh et al. 2005). Azathioprine has direct carcinogenic effects and serves as a causative factor for development of premalignant dysplastic keratotic lesions. Among SOTRs on azathioprine regimen, higher levels of active metabolites of azathioprine were noted in red blood cells of transplant recipients with skin cancer compared to those without skin cancer. Metabolic derivatives of azathioprine can cause DNA damage and promote tumor growth in SOTRs and azathioprine is also reported to sensitize the skin to UV radiation (Lennard et al. 1985; Taylor and Shuster 1992).

4 Carcinogenesis in Immunocompromised Patients: Risk Factors

Israel Penn International Transplant Tumor Registry (IPITTR) is a SOTR tumor registry that is originally conceptualized by Dr. Israel Penn and was initially started at University of Colorado. This registry maintains a comprehensive repository of information on recipients of organ transplantation with cancers. This registry was previously known as Cincinnati Transplant Tumor Registry (CTTR) and was renamed to be IPITTR after Dr. Penn as a tribute to him. He was first to report high incidence of malignancies in SOTRs and his registry paved path for future research in this area (Israel Penn International Transplant Tumor Registry n.d.). Multiple studies based on this registry data and other population-based studies have reported several risk factors associated with the development of malignancy in SOTRs (Israel Penn International Transplant Tumor Registry n.d.; Acuna et al. 2016; Agraharkar et al. 2004; Chapman et al. 2013; Collett et al. 2010; Engels et al. 2011; Sherston et al. 2014; Wimmer et al. 2007). These risk factors can be primarily classified into patient related factors, transplant related factors, environmental factors, and management factors.

4.1 Patient Related Factors

Patient related factors including genetic predisposition, age, race, gender, comorbid medical conditions, underlying chronic pathology that necessitated the organ transplantation and prior history of infections with oncogenic viruses influence the risk of malignancy in SOTRs (Agraharkar et al. 2004; Buell et al. 2005; Chapman et al. 2013; Collett et al. 2010; Engels et al. 2011; Grulich et al. 2007; Krump and You 2018; Serraino et al. 2007; Vajdic et al. 2006; Wimmer et al. 2007). There is twofold increased risk of cancer for recipients >65 years of age, while children who receive organ transplantation carry a 15–30 times increased risk of cancer. There is an increase in the risk of cancer by 40% in SOTRs with prior history of cancer compared to those who do not have prior history of cancer. Caucasian race and male sex are associated with higher incidence of cancers. It was initially assumed that this increased risk may be related to higher rates of skin cancer due to inherent predisposition for skin cancers. Nonetheless, skin cancers alone could not validate the heightened risk that was observed. ESRD secondary to diabetic nephropathy pre-transplant are noted to have less cancer burden compared to other etiologies (Webster et al. 2007).

A retrospective study of large cohort of KTRs by Agraharkar et al., with a mean follow-up of 6.1 years with more than 10-year follow-up in 21% of the patients demonstrated high frequency of skin (40%), gastrointestinal (13%), urologic (11%) malignancies, and lymphomas (9%) compared to the general population. KTRs who developed malignancies seem to be older (43.5 years) at the time of transplant with a mean age of 50 ± 12 years at the time of cancer diagnosis (Agraharkar et al. 2004). In this study, incidence of breast and lung cancers was found to be lower in KTRs

than the general population with a SIR of 0.7. There is significant elevation in the incidence of lymphomas with a SIR of 4.9, renal cell cancers with a SIR of 7.2, and colorectal cancers with a SIR of 1.5. Although the risk of cancer development is higher in patients >60 years after transplantation with a relative risk (RR) of 6.2 compared to KTRs of age < 40 years, younger patients at the time of transplant were observed to have the highest relative risk for developing malignancies compared to age matched general population (Agraharkar et al. 2004). The similar risk profile for cancers had been reflected in patients with ESRD receiving dialysis therapy in a study by Maisonneuve et al. suggesting the importance of underlying disease contributing to the risk of cancers in transplant recipients (Agraharkar et al. 2004; Maisonneuve et al. 1999). EBV seronegative status at the time of transplant posed high risk for malignancy in SOTRs (Shahinian et al. 2003). There is notably high risk of gastric cancer related to Helicobacter pylori in Asian populations suggestive of genetic predisposition in the cancer manifestation (Engels et al. 2011).

4.2 Environmental Factors

Geographical and environmental factors play an important role in carcinogenesis. There is an exponential increase in risk of skin cancer in patients with high skin exposure compared to the regions with limited exposure to sun. This high risk is attributed to increased ultraviolet (UV) radiation associated with excess exposure to sunlight (Birkelans et al. 1995; Euvrard et al. 1997, 2003; Hartevelt et al. 1990; Kullavanijaya and Kim 2005; Vink et al. 1996). There are geographical differences in the spectrum of cancers in SOTRs as noted by a study that assesses cancer incidence in SOTRs in Taiwan. The skin cancer risk was noted to be significantly higher in western countries compared to the studies reported from Asian countries including Japan and Taiwan (Birkelans et al. 1995; Hartevelt et al. 1990; Hoshida and Aozasa 2004; Lee et al. 2016). Gastric and hepatocellular cancers are more common among SOTRs in Japan compared to western countries (Birkelans et al. 1995; Hartevelt et al. 1990; Hoshida and Aozasa 2004; Lee et al. 2016).

4.3 Transplant Related Factors

The role of transplant related factors such as type of organ transplant, time since transplantation, living versus deceased donor status and history of malignancy or oncogenic viral infections in carcinogenesis in SOTRs needs to be considered. There is an elevated risk of liver cancer among liver transplant recipients and this risk is more pronounced in the first 6 months after the transplant. There is substantially elevated risk of kidney cancers in KTRs with SIR of 6.6 [95% CI 6.12–7.32] and recipients of liver and heart transplant with SIR of 1.80 [95% CI 1.40–2.29] and 2.90 [95% CI 2.32–3.59], respectively (Engels et al. 2011). Cardiothoracic transplantation carries a higher burden of malignancy following transplant compared to other organs and may likely be related to higher intensity of immunosuppression used in

heart and lung transplant recipients (Collett et al. 2010; Engels et al. 2011; Na et al. 2013; Taylor et al. 2005a).

4.4 Management Related Factors

In SOTRs, time since transplantation, induction at the time of transplant, duration and intensity of immunosuppression are important factors that are well known to be associated with carcinogenesis. An increase in frequency of PTLD is noted in patients who received induction with antithymocyte globulin (ATG) or monoclonal anti-T cell antibody, muromonab-CD-3 (OKT3) (Cherikh et al. 2003). Agraharkar et al. reported a cumulative incidence of 19% for NMSC and 36% for all malignancies was reported in KTRs at 25 years after the transplant. Despite using a stringent p value of 0.002, post-transplant duration of >10 years had remained a significant risk factor in this study owing to the risk of prolonged exposure to immunosuppression therapy in development of cancers (Agraharkar et al. 2004). The high incidence of cancers in recipients who are of younger age at the time of transplantation compared to age matched controls could potentially be attributed to longer cumulative exposure to immunosuppressive therapy and likelihood of exposure to primary infections with oncogenic viruses after transplant compared to older counterparts who may have been exposed and achieved seronegative status prior to transplant (Saha et al. 2010).

5 Classification of Malignancies in SOTRs

Malignancy in SOTRs is a well-known complication and can be categorized into three broad groups: 1) Recurrence of cancers that were present before transplant and/or activation of dormant neoplasms, otherwise described as pre-transplant malignancy (PTM), 2) Cancers that are transmitted inadvertently from donors with prior history of malignancy or undiagnosed or occult malignancies at the time of transplant described as donor derived malignancy (DDM), and 3) Cancers arising de novo after the transplant reported as de novo malignancies (DNMs). In addition, latent infection with oncogenic viruses can predispose SOTRs to malignancy development after transplant in the setting of immunosuppression.

5.1 Recurrence of Pre-Transplant Malignancy in Solid Organ Transplant Recipients

Pre-transplant malignancy (PTM) is considered to be a significant risk factor for development of cancer in SOTRs. Analysis of IPITTR data suggested a recurrence rate of 21% with high frequency of recurrence in those who had been transplanted with a time interval <2 years since the diagnosis of cancer or receiving therapy for cancer (Penn 1997a). Contrary to data reported by Penn, a more recent meta-analysis

by Acuna et al. identified the risk of cancer recurrence to be lower in SOTRs with PTM than previously reported with a pooled recurrence rate of 1.6 [95% CI 1.0–2.6] per 100-person year. Recurrence rate of 1.1 per 100-person year was noted in liver transplant recipients compared to 2.4 in patients with KTRs (Acuna et al. 2017). A thorough evaluation including the risk of recurrent cancer is warranted in patients who are undergoing transplant assessment with prior history of malignancy. Cancer remission intervals and permissible wait times prior to considering for transplantation in these patients are variable based on the type of malignancy and survival expectancy from the neoplasm (Acuna et al. 2017). Multidisciplinary assessment with input from oncology colleagues is essential in the decision-making process. American Joint Committee on Cancer (AJCC) and American Society of Transplantation (AST) issued a consensus statement delineating the general recommendations to assist evaluation of patients undergoing evaluation for SOT with a history of PTM (Al-Adra et al. 2021). Nevertheless, the decision to either consider for transplant or defer the transplant may need to be tailored to each patient based on careful assessment of risk-benefit profile. Examination of various risk factors including tumor biology, response to treatment, cancer free interval, recurrent risk estimates, genetic and epigenetic risk factors, organ in consideration, potential effect of immunosuppression on recurrence of tumor, life expectancy and alterate therapy options is essential in analyzing the risk-benefit ratio (Al-Adra et al. 2021; Penn 1993).

5.2 Donor Derived Malignancy in Solid Organ Transplant Recipients

Transmission of cancers from donors with a history of previously treated cancer or undiagnosed cancer is an infrequent cause of cancer in SOTRs (Feng et al. 2002; Kauffman et al. 2000; Ma et al. 2014; Penn 1995). The estimates of risk are variable with significantly higher rates in IPTRR registry compared to Organ Procurement and Transplantation (OPTN) reports. Magnitude of risk varies based on the type of cancer and transplanted organ. Donors with a history of primary central nervous system tumors, renal cell carcinoma, malignant melanoma, and choriocarcinoma are at high risk for transmission compared to colon and breast cancers (Penn 1995). The persistent disparity between organ donation and end stage organ failure patients awaiting organs leads to evolution of extended criteria for organ donation. The expansion of donor pool by including older age donors renders high risk for donor derived malignancy (DDM) as advanced age is associated with a high rate of premalignant or occult lesions. Primary central nervous system malignancies are reported to be a common source of DDM. Careful assessment of donors with unusual presentations and prior history of malignancies is essential to minimize the risk of transmission. United States Donor Transmitted Assessment Committee (DTAC) provides guidance to physicians and patients regarding risk of donor transmitted diseases including malignancy from potential donors. Risk categorization of transmission risk of malignancies is a helpful aid in assessing the potential risk of transmission (Ison and Nalesnik 2011; Kauffman et al. 2002; Penn 1995).

Intra-operative assessment of all visible organs and prompt biopsy and histological assessment of any suspected masses and/or lymph nodes must be considered. Once a DDM is identified in an organ recipient, notification of other organ recipients from the donor is crucial.

5.3 De Novo Malignancies in Solid Organ Transplant Recipients

De novo malignancy is a well-recognized complication following organ transplantation due to inherent need for immunosuppression to prevent graft rejection and has emerged as a major cause of mortality and morbidity in these patients. De novo malignancies in SOTRs are primarily driven by immunocompromised state due to pharmacologic immunosuppression, oncogenic viral infections, direct oncogenic effects of immunosuppression, genetic and environmental risk factors. A 10-year incidence of de novo cancers in SOTRs is twice that of an age- and sex- matched general population cohort with marked elevation in the incidence of NMSC (Collett et al. 2010). A retrospective analysis of data from cardiothoracic and liver transplant recipients between 1984 and 2006 in Australia demonstrated excess risk of death secondary to de novo malignancy compared to the general population (Na et al. 2013). This risk was consistently elevated in both sexes, pediatric and adult populations and in all transplanted organ groups. Most common malignancy that resulted in death of transplant recipient was NHL in this cohort. Pediatric transplant recipients were noted to have the highest risk of death from de novo malignancy with 80% of deaths in pediatric SOTRs were related to NHL (Na et al. 2013). Age is an important risk factor in estimating the excess cancer risk. Like in the general population, advanced age is a risk factor for cancer development in SOTRs. While the absolute risk of cancer is significantly elevated in older transplant recipients, excess rate of cancer risk compared to the general population, defined by the relative risk (RR) is much greater in youngest recipients of organ transplant (Chapman et al. 2013; Engels et al. 2011; Na et al. 2013; Webster et al. 2007). This may be secondary to increased vulnerability of young transplant recipients to primary infections in the setting of chronic employment of immunosuppression. Heart and lung transplant recipients are at the higher risk for de novo malignancy after transplantation compared to kidney and liver transplant recipients owing to the risk of more intense immunosuppression required in cardiothoracic transplantation (Na et al. 2013).

Most common post-transplant malignancies in SOTRs include NMSC, lymphoproliferative disorders, KS, and HPV related anogenital cancers (Acuna et al. 2016; Chapman et al. 2013; Collett et al. 2010; Engels et al. 2011; Na et al. 2013; Webster et al. 2007). Although overall cancer burden is increased in SOTRs, the incidence of breast, prostate, ovarian, and testicular cancers in SOTRs is not elevated in comparison with the general population (Wong et al. 2017). Population-based studies in patients with HIV/AIDS noted that the incidence of breast, prostate, and ovarian cancers is observed at a relatively low or comparable rate to that of the general population, suggesting that an immunocompromised state in itself may not predispose to the increased number of these cancers. Nonetheless, breast cancers are

associated with poor prognosis in SOTRs compared to the general population, despite similar incidence rates (Grulich et al. 2007; Na et al. 2013; Serraino et al. 2007).

The risk of death from de novo malignancies is elevated in all SOTRs compared to the general population. The magnitude of cancer risk differed among SOTRs based on the transplanted organ with excess risk greatest for lung transplant recipients (Acuna et al. 2016; Chapman et al. 2013; Engels et al. 2011; Na et al. 2013). Compared to the general population, prognosis of cancers in SOTRs is poor and is associated with excess mortality. Cancers are more advanced at the time of diagnosis in SOTRs with more poorly differentiated tumors and respond poorly to the treatment (Acuna et al. 2017; Ajithkumar et al. 2007). Interactions between immunosuppressants and antineoplastic agents need to be considered in designing treatment strategies. A multidisciplinary approach may need to be pursued to address these cancers in SOTRs.

5.3.1 Skin Cancers

The most common cancer in SOTRs is NMSC with predominance of squamous cell carcinoma (SCC) of the skin with >50-fold increased risk compared to that of the general population (Euvrard et al. 1997, 2003; Hartevelt et al. 1990; Krynitz et al. 2013; Na et al. 2013; Penn 1997b). Although keratinocyte carcinomas including SCC and basal cell carcinoma (BCC) account to >90% of skin cancers in SOTRs, KS, Merkel cell carcinoma, and malignant melanoma are reported to occur more commonly in SOTRs compared to the general population. There is reported 65–250-fold increase in the incidence of SCC and 10–16-fold increased incidence of BCC in SOTRs. In contrast to the general population, the ratio of SCC to BCC is reversed in SOTRs (Euvrard et al. 2003; Penn 1997b). SCCs of SOTRs are noted to have histologic features suggestive of epithelial to mesenchymal transition that is ascribed to the use of immunosuppression (Euvrard et al. 2003).

Direct effects of immunosuppression agents, type and duration of immunosuppression, and exposure to UV radiation play a central role in development of skin cancers (Han et al. 2012; Krynitz et al. 2013; Penn 1997b; Vink et al. 1996; Yarosh et al. 2005). Caucasian race, older age at the time of transplant, exposure to HPV infections, and history of prior skin cancers contribute to the risk of skin cancer in SOTRs. Genetic factors such as human leukocyte antigen (HLA) and polymorphisms in glutathione *S*-transferase may also influence development of cutaneous neoplastic lesions. SOTRs with cutaneous carcinomas have significantly lower CD4 counts than patients without skin cancer (Banvinck et al. 1993; Euvrard et al. 2003; Harwood et al. 2000; Krynitz et al. 2013; Ramsay et al. 2001). Higher incidence of skin cancers is noted in heart transplant recipients compared to KTRs and liver transplant recipients. However, this differential risk is attributed to higher intensity of immunosuppression used in heart transplant recipients. Skin cancers are more prevalent in geographical areas with high sun exposure and cancers are seen more often in sun exposed body parts in SOTRs. UV light has direct carcinogenic effect and causes local immunosuppression by mutagenic effects on *p*53 tumor-suppressor gene (Banvinck et al. 1993; Euvrard et al. 2003; Vink et al.

1996; Yarosh et al. 2005). UV light also induces histologic changes locally, promotes local inflammation, and has synergistic effect with HPV and immunosuppression agents (Harwood et al. 2000; Krynitz et al. 2013). There is also a significant association between SCC and HPV infection. HPV is postulated to be cocarcinogenic and HPV DNA has been isolated in approximately 65-90% of SCC lesions in SOTRs (Euvrard et al. 2003; Harwood et al. 2000; Krynitz et al. 2013). SCC in SOTRs appears to be more aggressive with high metastatic potential compared to the general population. Presence of multiple tumors, extracutaneous manifestation of tumors, cephalic location, older age, and high exposure to UV radiation are associated with unfavorable prognosis (Euvrard et al. 2003; Krynitz et al. 2013).

5.3.2 Lip Cancer

SOTRs are at greater risk for lip cancer with 13–66-fold increase in risk compared to the general population with poorly understood reasons for this excess risk (Acuna et al. 2016; Chapman et al. 2013; Collett et al. 2010; Engels et al. 2011; Krynitz et al. 2013). A 15-fold increase in the incidence of lip cancer is observed in SOTRs compared to the general population (Laprise et al. 2019). While elevated risk of lip cancer is noted both in SOTRs and patients with HIV/AIDS, the magnitude of risk is higher in SOTRs compared to patients with HIV/AIDS (Grulich et al. 2007; Laprise et al. 2019). Lip cancers are predominantly SCCs and can be external lip cancers or mucosal lip cancers. Tobacco use and alcohol consumption predisposes to mucosal lip cancers and exposure to UV radiation plays an important role in development of cancers of the external lip (Euvrard et al. 2003; Grulich et al. 2007; Laprise et al. 2019). Prior diagnosis of SCC, Caucasian race, immunosuppressive therapy particularly with cyclosporine and/or azathioprine have been strongly associated with lip cancer (Laprise et al. 2019).

5.3.3 Kaposi Sarcoma

KS is an angioproliferative disorder of vascular endothelium driven by oncogenic virus HHV-8. Although most cases of KS in SOTRs are secondary to HHV-8 reactivation in organ recipients, cases of donor transmission have been described in the literature. The incidence of KS in SOTRs is profoundly increased and is 400–500-fold greater in SOTRs compared to the general population with a preponderance for male sex (Acuna et al. 2016; Chapman et al. 2013; Collett et al. 2010; Engels et al. 2011; Krynitz et al. 2013). It can manifest as a cutaneous sarcoma or visceral sarcoma or can present with mixed features in SOTRs. The most common presentation of cutaneous KS is angiomatous lesions on legs similar to classic KS and gastrointestinal tract, lymph nodes, and lung are affected in visceral form of KS. The incidence of KS is greatly elevated in SOTRs compared to the general population and predominantly seen in patients of Mediterranean, Jewish, Arabic, Caribbean, and African descent. KS manifests at an earlier age in SOTRs compared to patients with classic KS with a mean age of 43 at the time of diagnosis in SOTRs (Euvrard et al. 2003). KS is known to respond well to reduction in immunosuppression and especially reduction of CNIs to the minimal safe dose is associated with regression of lesions.

5.3.4 Anogenital Cancers

Immunocompromised patients are at increased risk for anogenital cancers, and the risk increases by approximately 20-fold in these patients compared to the general population. HPV infection, multiple sexual partners, smoking, prior history of genital herpes, presence of extragenital skin cancers, and high intensity immunosuppression are all risk factors associated with development of anogenital cancer (Euvrard et al. 2003). Anogenital HPV is highly prevalent in female transplant recipients who are sexually active (Euvrard et al. 2003).

5.3.5 Post-Transplant Lymphoproliferative Disorders

Post-transplant lymphoproliferative diseases (PTLD) is used to describe a spectrum of lymphoproliferative disorders ranging from benign hyperplasia to aggressive lymphomas in SOTRs. PTLD is the most common cause of cancer related death in both adult and pediatric organ transplant recipients (Campistol et al. 2012; Vegso et al. 2007). Although proliferation of any cell lines B cells, T cells, natural killer cells, and plasma cells could cause PTLD, vast majority of PTLDs are of B cell lymphomas and a strong association with EBV infection has been noted. PTLDs in SOTRs are more aggressive in nature and respond poorly to conventional treatment measures compared to lymphoproliferative malignancies in the general population. Vast majority of PTLDs (90%) are associated with EBV infection (Opelz and Dohler 2004; Shahinian et al. 2003; Taylor et al. 2005a; Yarosh et al. 2005). Normally functioning T cell plays a critical role in immune control of EBV infection and inhibition of T cell function secondary to immunosuppression in SOTRs and impaired T cell function in primary immunodeficiency disorders and patients with HIV/AIDs leads to loss of immune control of EBV infection. Risk of NHL is elevated in these conditions due to loss of immune modulation of EBV mediated lymphoproliferation (Opelz and Dohler 2004).

NHL usually demonstrates bimodal incidence pattern with early onset PTLD developing within the first year of the transplant and late onset PTLD developing later in the post-transplant course with a median time of 4 years (Opelz and Dohler 2004; Shahinian et al. 2003). Recipients of heart and lung transplants are at a higher risk of PTLD than KTRs and liver transplant recipients owing to the need of heavy immunosuppression in the former group. SOTRs who are induced with T cell depleting agents such as antithymocyte globulin (ATG) or muromonab-CD-3 (OKT3) were observed to have higher risk of developing PTLD (Gao et al. 2003; Opelz and Dohler 2004). Heightened incidence of PTLD is noted in cardiothoracic transplant recipients compared to KTRs and liver transplant recipients (Cherikh et al. 2003; Gao et al. 2003). Tacrolimus is associated with higher risk of PTLD than cyclosporine and patients treated with mycophenolate mofetil (MMF) are reported to have less risk of PTLD compared to patients treated with azathioprine.

The risk of Hodgkin's lymphoma (HL) is also elevated in SOTRs as well as those with HIV infection when compared to the general population, indicating the role of impaired immune regulation in the inception of this cancer. Analysis of SRTR data by Quinlan et al. demonstrated a twofold increase in risk of developing HL in SOTRs compared to general population with a SIR of 2.2 [95% CI 1.7–2.7] with

greatest risk in children and adolescents. EBV seronegative status at the time of the transplant was associated with elevated risk with SIR of 4.7 [95% CI 1.9–9.6]. Cardiothoracic transplant recipients were noted to be at higher risk for HL development than abdominal organ recipients (Quinlan et al. 2010).

5.3.6 Thyroid Cancer

SOTRs are at elevated risk for thyroid cancer and a 2.5-fold higher incidence rate is noted in SOTRs compared to the general population. Risk was amplified in KTRs with an incidence rate ratio (IRR) of 1.26 [95% CI 1.03–1.53]. The risk is more pronounced in patients who underwent kidney transplant secondary to hypertensive nephrosclerosis with an IRR of 1.41 [95% CI 1.03–1.94] and liver transplant secondary to cholestatic liver disease/cirrhosis with an IRR of 1.69 [95% CI 1.09–2.63]. In addition, longer duration of dialysis prior to kidney transplant is strongly associated with higher incidence of thyroid cancer. Majority of thyroid cancers in SOTRs were identified to be papillary thyroid cancers (91%) followed by follicular cancers (5%). Increased risk of death with a Hazard Ratio (HR) of 1.33 [95% CI 1.02–1.73] is noted among patients diagnosed with thyroid cancer following the organ transplantation (Kitahara et al. 2017).

5.3.7 Lung Cancer

Lung transplant recipients are at highest risk for lung cancers among SOTRs. Despite lower incidence of lung cancer in kidney, liver, and heart transplant recipients compared to lung transplant recipients, the overall risk of all SOTRs is higher than general population. The risk of developing lung cancer is sixfold higher in lung transplant recipients compared to two- to threefold increased risk noted in the recipients of other organs. Smoking is a major risk-factor in the development of lung cancer. The risk of lung cancer is higher in single lung transplant recipients compared to bilateral lung transplant recipients (Collett et al. 2010; Engels et al. 2011). This may be attributed to the presence of native lung in single lung transplant recipient that continues to carry the burden of underlying disease process, and the exposure to the risk factors that may have been contributed to the pathogenesis of underlying disease process that prompted the transplant.

6 Immunosuppression in Organ Transplantation

Immunosuppressive medications used in organ transplantation are associated with a wide spectrum of adverse effects including malignancy and can contribute to decreased life expectancy or quality of life in these patients. First successful life prolonging kidney transplantation was performed in 1954 between identical twins at Peter Bent Brigham Hospital, Massachusetts. The genetic matching of recipient and donor ushered the graft and recipient survival despite no use of immunosuppression. Sublethal total body irradiation (TBI) by Murray et al. demonstrated that immunologic barrier of transplantation could be vanquished by immunosuppression. Nonetheless, cytoablative radiation has proven to be an undesirable modality of

immunosuppression due to high mortality (>90%) associated with TBI. Scientific work of Sir Peter Medawar laid the foundations of transplant immunology with discovery of acquired immunological tolerance and received Nobel Prize for his pioneering work. Pharmacologic immunosuppression gained momentum in the 1960s with emergence of therapeutic agents for leukemia such as 6-mercaptoprurine, cyclophosphamide, and methotrexate. George Hutching and Gertrude Elion introduced azathioprine, a more clinically permissible congener of 6-mercaptopurine. Sir Roy Clane's work resulted in the emergence of azathioprine as a successful immunosuppression therapy and a viable therapeutic option for organ transplant recipients. A significant survival advantage was noted with combination immunosuppressive regimens comprising of azathioprine and corticosteroids. Continued evolution of science in the field of transplant led to the discovery of cyclosporine compared to single agent regimens. Dramatic graft and patient survivals were noted following the use of cyclosporine and brought transformational change in field of organ transplantation.

Immunosuppressive regimens are essential in preventing rejection and for the survival of allograft in SOTRs. Most organ transplant recipients receive a combination of two or three pharmacologic agents for immunosuppression. Although some immunosuppressant medications are described to be more carcinogenic than others, it is the overall intensity and duration of immunosuppression that profess the risk of cancer development in SOTRs (Cherikh et al. 2003; Herman et al. 2001; Martinez and de Gruijl 2008; Taylor et al. 2005b). Corticosteroids are used as first-line agents during the transplantation and immediately after transplantation. Corticosteroids are anti-inflammatory and decrease the production of cytokines and circulating CD4 cells. Corticosteroids promote carcinogenesis predominantly through immune modulation. Steroids reduce the immune surveillance of tumor cells resulting in evasion and escape of tumorigenic cells (Taylor et al. 2005b). Corticosteroids also increase the risk of infection and thus cancers related to oncogenic viruses.

MMF and azathioprine are antimetabolites that are used in organ transplantation. Azathioprine has been recognized as a carcinogen and is implicated in the development of skin cancers and NHL in SOTRs. The use of azathioprine in modern era of organ transplantation is sparse. Synergistic effects of azathioprine and UV radiation result in mutagenic oxidative damage of DNA and impaired repaired response leading to carcinogenesis. Despite the pro-oncogenicity seen in in vitro studies with impaired DNA damage response and inflated invasion of tumor cells, clinical studies failed to demonstrate any substantial increased risk of malignancy with MMF. In fact, MMF based immunosuppressive regimens demonstrated lower risk of PTLD compared to immunosuppressive regimens based on azathioprine (Cherikh et al. 2003).

Cyclosporine and Tacrolimus are the two common CNIs used in the management of SOTRs and CNIs remain cornerstone of immunosuppression in SOTRs. CNIs based maintenance immunosuppressive regimens are associated with reduced graft rejection and improved survival. However, unfavorable nephrotoxic and metabolic side effect profile of CNIs led to investigations toward CNI free immunosuppressive regimens. CNIs based immunosuppressive regimens are also implicated in increased

malignancy risk in SOTRs. CNIs can promote carcinogenesis through immunosuppression as well as direct carcinogenic effects by inducing TGF-β production that aids in evasion of host immune defenses and stimulating the secretion of vascular endothelial cell growth factor (VEGF) that facilitates tumor angiogenesis (Han et al. 2012; Hojo et al. 1999; Olshan et al. 1994). Tacrolimus has a dose-dependent effect on TGF-β expression and thus permits the idea of potential modulation of carcinogenic effect with therapeutic level monitoring.

Mammalian Target of Rapamycin (mTOR) is a conserved protein kinase that plays an important role in cell growth, proliferation, survival, metabolism, and autophagy through various signaling pathways. The mTOR signaling pathway modulates protein synthesis, gene transcription, and translation and thus controls cellular homeostasis, angiogenesis, cytoskeletal remodeling, stress response, and activity of immune cells. It plays a key role in activation, differentiation, and function of immune cells by regulating the expression of various inflammatory mediators, cytokines, chemokines, membrane receptors, and apoptosis (Koehl et al. 2004; Martinez and de Gruijl 2008). Dysregulation of various elements of this pathway could lead to disease states such as neoplastic transformation, insulin resistance, obesity, and neurodegeneration. mTOR inhibitors piqued interest in transplant field as these agents offer immunosuppression and tumor growth suppression. There are several clinical trials that demonstrated reduced incidence of cancers in patients treated with sirolimus in kidney transplant recipients (Alberu et al. 2011; Gatault and Lebranchu 2013; Lebranchu et al. 2009; Schena et al. 2009). CONCEPT study demonstrated less incidence of cancers in patients whose immunosuppression was switched from Cyclosporine to Sirolimus 3 months after kidney transplantation compared to the cohort that continued to receive CNI-based immunosuppressive therapy (Lebranchu et al. 2009).

7 Conclusions

Optimal immunosuppression is key to the success of organ transplant. However, chronic exposure to immunosuppression in SOTRs is unfortunately associated with higher incidence of various hematologic and non-hematologic malignancies. Complex interplay of various factors including immune, non-immune, infectious, environmental, and genetic factors leads to carcinogenesis in SOTRs. While advances in transplant medicine, histopathology, and surgery have helped in expanding the donor pool and willingness to take more risk, they come with the cost of increased risk of cancers, thus suggesting the need for enhanced vigilance in screening, patient and donor selection, early recognition and management of malignancies, as well as individualization of appropriate immunosuppressive regimens in this high-risk population.

References

Acuna SA, Fernandes KA, Daly C et al (2016) Cancer mortality among recipients of solid-organ transplantation in Ontario, Canada. JAMA Oncol 2(4):463–469

Acuna SA, Huang JW, Dossa F et al (2017) Cancer recurrence after solid organ transplantation: a systemic review and metanalysis. Transplant Rev 31(4):240–248

Agraharkar ML, Cinclair RD, Kuo YF et al (2004) Risk of malignancy with long-term immunosuppression in renal transplant recipients. Kidney Int 66:383–389

Ajithkumar TV, Parkinson CA, Butler A (2007) Management of solid tumors in organ-transplant recipients. Lancet Oncol 8(10):921–932

Al-Adra DP, Hammel L, Roberts J et al (2021) Pretransplant solid organ transplant malignancy and organ transplant candidacy: a consensus expert opinion. Am J Transplant 21(2):460–474

Alberu J, Pascoe M, Campistol J et al (2011) Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. Transplantation 92(3):303–310

Banvinck JN, De Boer A, Vermeer BJ, Hartevelt MM et al (1993) Sunlight, keratotic skin lesions and skin cancer in renal transplant recipients. Br J Dermatol 129(3):242–249

Barle EL, Winkler GC, Ulrich P et al (2014) Cancer risk of immunosuppressants in manufacturing. Regul Toxicol Pharmacol 70(1):122–124

Birkelans SA, Storm HH, Lamm LU et al (1995) Cancer risk after renal transplantation in the Nordic countries, 1964-1986. Int J Cancer 60(2):183–189

Bouvard V, Baan R, Straif K et al (2009) A review of human carcinogens. Part B: biological agents. Lancet Oncol 10(4):321–322

Buell JF, Gross TG, Woodle ES (2005) Malignancy after transplantation. Transplantation 80 (2 Suppl):S254–S264

Burnet FM (1970) The concept of immunological surveillance. Prog Exp Tumor Res 13:1–27

Campistol JM, Cuervas-Mons V, Manito N et al (2012) New concepts and best practices for management of pre- and post-transplantation cancer. Transplant Rev (Orlando) 26(4):261–279

Chapman JR, Webster AC, Wong G (2013) Cancer in the transplant recipient. Cold Spring Harb Perspect Med 3(7):a015677

Cherikh WS, Kauffman HM, McBride M et al (2003) Association of the type of induction immunosuppression with posttransplant lymphoproliferative disorder, graft survival, and patient survival after primary kidney transplantation. Transplantation 76(9):1289–1293

Collett D, Mumford L, Banner NR et al (2010) Comparison of the incidence of malignancy in recipients of different types of organ: a UK registry audit. Am J Transplant 10(8):1889–1896

Doll R, Kinlen L (1970) Immunosurveillance and cancer: epidemiological evidence. Br Med J 4:420–422

Engels E, Pfeiffer R, Fraumeni J et al (2011) Spectrum of cancer risk among US solid organ transplant recipients. JAMA 306(17):1891–1901

Euvrard S, Kanitakis J, Pouteil-Noble C et al (1997) Skin cancers in organ transplant recipients. Ann Transplant 2(4):28–32

Euvrard S, Kanitakis J, Claudy A (2003) Skin cancers after organ transplantation. N Engl J Med 348 (17):1681–1691

Feng S, Buell JF, Cherikh WS et al (2002) Organ donors with positive viral serology or malignancy: risk of disease transmission by transplantation. Transplantation 74(12):1657–1663

Fouad YA, Aanei C (2017) Revisiting the hallmarks of cancer. Am J Cancer Res 7(5):1016–1036

Gao SZ, Chaparro SV, Perlroth M et al (2003) Post-transplantation lymphoproliferative diseases in heart and heart-lung transplant recipients: 30-year experience at Stanford university. J Heart Lung Transplant 22(5):505–514

Gatault P, Lebranchu Y (2013) Conversion to mTOR-inhibitor based immunosuppression: which patients and when? Transplant Res 2(Suppl. 1):S3

Gatti RA, Good RA (1971) Occurrence of malignancy in immunodeficiency diseases. A literature review. Cancer 28(1):89–98

Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM (2007) Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 370(9581):59–67

Hall EC, Pfeiffer RM, Segev DL, Engels EA (2013) Cumulative incidence of cancer after solid organ transplantation. Cancer 119(12):2300–2308

Han W, Soltani K, Ming M, He YY (2012) Deregulation of XPC and CypA by cyclosporin A: an immunosuppression-independent mechanism of skin carcinogenesis. Cancer Prev Res 5 (9):1155–1162

Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–674

Hartevelt MM, Bouwes-Bavinck JN, Koote AM et al (1990) Incidence of skin cancer after renal transplantation in the Netherlands. Transplantation 49(3):506–509

Harwood CA, Surentheran T, McGregor JM et al (2000) Human papillomavirus infection and non-melanoma skin cancer in immunosuppressed and immunocompetent individuals. J Med Virol 61(3):289–297

Herman M, Weinstein T, Korzets A et al (2001) Effect of cyclosporin A on DNA repair and cancer incidence in kidney transplant recipients. J Lab Clin Med 137(1):14–20

Hojo M, Morimoto T, Maluccio M et al (1999) Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature 397(6719):530–534

Hoshida Y, Aozasa K (2004) Malignancies in organ transplant recipients. Pathol Int 54(9):649–658

IARC (1990) IARC monographs on the evaluation of carcinogenic risks to humans, vol 50. Pharmaceutical drugs. International Agency for Research on Cancer, Lyon

IARC (2012) A review of human carcinogens: pharmaceuticals. IARC monogr. eval. carcinog. risks hum. 100A–22. International Agency for Research on Cancer, Lyon

Ison MG, Nalesnik MA (2011) An update on donor-derived disease transmission in organ transplantation. Am J Transplant 11(6):1123–1130

Israel Penn International Transplant Tumor Registry (n.d.). https://ipittr.uc.edu

Kauffman HM, McBride MA, Delmonico FL et al (2000) First report of the united network for organ sharing transplant tumor registry: donors with a history of cancer. Transplantation 70 (12):1747–1751

Kauffman HM, McBride MA, Cherikh WS, Spain PS, Marks WH, Roza AM (2002) Transplant tumor registry: donor related malignancies. Transplantation 74:358–362

KDIGO (2009) KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 9(suppl 3) https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2009-Transplant-Recipient-Guideline-English.pdf

Kitahara CM, Yanik EL, Ladenson PW et al (2017) Risk of thyroid cancer among solid organ transplant recipients. Am J Transplant 17(11):2911–2921

Koehl GE, Andrassy J, Guba M et al (2004) Rapamycin protects allografts from rejection while simultaneously attacking tumors in immunosuppressed mice. Transplantation 77(9):1319–1326

Krump NA, You J (2018) Molecular mechanisms of viral oncogenesis in humans. Nat Rev Microbiol 16(11):684–698

Krynitz B, Edgren G, Lindelof B, Baecklund E, Brattstrom C, Wilczek H et al (2013) Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008 – a Swedish population-based study. Int J Cancer 132(6):1429–1438

Kullavanijaya P, Kim HW (2005) Photoprotection. J Am Acad Dermatol 52(6):937–958

Lamb KE, Lodhi S, Meier-Kriesche HU (2011) Long-term renal allograft survival in the United States: a critical reappraisal. Am J Transplant 11(3):450–462

Laprise C, Cahoon EK, Lynch CF et al (2019) Risk of lip cancer after solid organ transplantation in the unites states. Am J Transplant 19(1):227–237

Lebranchu Y, Thierry A, Toupance O et al (2009) Efficacy on renal function of early conversion from cyclosporine to sirolimus 3 months after renal transplantation: concept study. Am J Transplant 9(5):115–1123

Lee K-F, Tsai Y-T, Lin C-Y, Hsieh C-B et al (2016) Cancer incidence among heart, kidney, and liver transplant recipients in Taiwan. PLoS One 11(5):e0155602

Lennard L, Thomas S, Harington CI et al (1985) Skin cancer in renal transplant recipients is associated with increased concentrations of 6-thioguanine nucleotide in red blood cells. Br J Dermatol 113(6):723–729

Ma MK, Lim WH, Turner RM et al (2014) The risk of cancer in recipients of living-donor, standard and expanded criteria deceased donor kidney transplants: a registry analysis. Transplantation 98 (2):1286–1293

Maisonneuve P, Agodoa L, Gellert R (1999) Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 354(9173):93–99

Maluccio M, Sharma V, Lagman M et al (2003) Tacrolimus enhances transforming growth factor-beta1 expression and promotes tumor progression. Transplantation 76(3):597–602

Martinez C (1964) Effect of early thymectomy on development of mammary tumors in mice. Nature 203:1188

Martinez OM, de Gruijl FR (2008) Molecular and immunologic mechanisms of cancer pathogenesis in solid organ transplant recipients. Am J Transplant 8(11):2205–2211

Meier-Kriesche HU, Schold JD, Srinivas TR et al (2004) Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 4(3):378–383

Na R, Grulich AE, Meagher NS et al (2013) De novo cancer-related death in Australian liver and cardiothoracic transplant recipients. Am J Transplant 13(5):1296–1304

Olshan AF, Mattison DR, Zwanenburg TSB (1994) Cyclosporine A: review of genotoxicity and potential for adverse human reproductive and developmental effects. Mutat Res 317(2):163–173

Opelz G, Dohler B (2004) Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 4(2):222–230

Penn I (1993) The effect of immunosuppression on pre-existing cancers. Transplantation 55 (4):742–747

Penn I (1995) De novo cancers in organ allograft recipients. Curr Opin Organ Transplant 3:188–196

Penn I (1997a) Evaluation of transplant candidates with pre-existing malignancies. Ann Transplant 2:14–17

Penn I (1997b) Skin disorders in organ transplant recipients. Arch Dermatol 133:221–223

Pilmore H, Dent H, Chang S, McDonald SP, Chadban SJ (2010) Reduction in cardiovascular death after kidney transplantation. Transplantation 89(7):851–857

Quinlan S, Landgren O, Mortann L et al (2010) Hodgkin lymphoma among U.S. solid organ transplant recipients. Transplantation 90(9):1011–1015

Ramsay HM, Harden PN, Reece S et al (2001) Polymorphisms in glutathione S-transferase are associated with altered risk on nonmelanoma skin cancer in renal transplant recipients: a preliminary analysis. J Invest Dermatol 117(2):251–255

Rana A, Gruessner A, Agopian VG et al (2015) Survival benefit of solid-organ transplant in the United States. JAMA Surg 150(3):252–259

Rana A, Ackah AL, Webb GJ et al (2019) No gains in long-term survival after liver transplantation over the past three decades. Ann Surg 269(1):20–27

Saha A, Kaul R, Murakami M et al (2010) Tumor viruses and cancer biology: modulating signaling pathways for therapeutic intervention. Cancer Biol Ther 10(10):961–978

Schena FP, Pascoe MD, Alberu J et al (2009) Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. Transplantation 87(2):233–242

Serraino D, Piselli P, Busnach G et al (2007) Risk of cancer following immunosuppression in organ transplant recipients and in HIV-positive individuals in southern Europe. Eur J Cancer 43 (14):2117–2123

Shahinian VB, Muirhead N, Jevnikar AM et al (2003) Epstein-Barr virus seronegativity is a risk factor for late-onset posttransplant lymphoproliferative disorder in adult renal allograft recipients. Transplantation 75(6):851–856

Shankaran V, Ikeda H, Bruce AT et al (2001) IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature 410(6832):1107–1111

Sherston SN, Carroll RP, Harden PN et al (2014) Predictors of cancer risk in the long-term solid organ transplant recipient. Transplantation 97(6):605–611

Stutman O (1979) Chemical carcinogenesis in nude mice: comparison between nude mice from homozygous matings and heterzygous matings and effect of age and carcinogen dose. J Natl Cancer Inst 62(2):353–358

Taylor A, Shuster S (1992) Skin cancer after renal transplantation: the casual role of azathioprine. Acta Dermatol Venerol 72(2):115–119

Taylor AL, Marcus R, Bradley JA (2005a) Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. Crit Rev Oncol Hematol 56(1):155–167

Taylor AL, Watson CJ, Bradley JA (2005b) Immunosuppressive agents in sold organ transplantation: mechanisms of action and therapeutic efficacy. Crit Rev Oncol Hematol 56(1):23–46

Teng MW, Swann JB, Koebel CM et al (2008) Immune-mediated dormancy: an equilibrium with cancer. J Leukoc Biol 84(4):988–993

Vajdic CM, McDonald SP, McCredie MR (2006) Cancer incidence before and after kidney transplantation. JAMA 296(23):2823–2831

Van Leeuwen MT, Webster AC, McCredie MR et al (2010) Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study. BMJ 340:c570

Vegso G, Toth M, Hidvegi M et al (2007) Malignancies after renal transplantation during 33 years at a single center. Pathol Oncol Res 13(1):63–69

Vink AA, Strickland FM, Bucana C et al (1996) Localization of DNA damage and its role in altered antigen-presenting cell function in ultraviolet-irradiated mice. J Exp Med 183(4):1491–1500

Webster AC, Craig JC, Simpson JM et al (2007) Identifying high risk groups and quantifying absolute risk of cancer after kidney transplantation: a cohort study of 15183 recipients. Am J Transplant 7(9):2140–2151

Wimmer CD, Rentsch M, Crispin A et al (2007) The janus face of immunosuppression – de novo malignancy after renal transplantation: the experience of the transplantation center Munich. Kidney Int 71(12):1271–1278

Wong G, Au E, Badve SV et al (2017) Breast cancer and transplantation. Am J Transplant 17 (9):2243–2253

Yarosh DB, Pena AV, Nay SL et al (2005) Calcineurin inhibitors decrease DNA repair and apoptosis in human keratinocytes following ultraviolet B irradiation. J Invest Dermatol 125 (5):1020–1025