Malignancy after lung transplantation

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Abstract: Lung transplantation is an established therapeutic option for selected patients with advanced lung diseases. As early outcomes after lung transplantation have improved, chronic medical illnesses have emerged as significant obstacles to long-term survival. Among them is post-transplant malignancy, currently representing the 2nd most common cause of death 5–10 years after transplantation. Chronic immunosuppressive therapy and resulting impairment of anti-tumor immune surveillance is thought to have a central role in cancer development after solid organ transplantation (SOT). Lung transplant recipients receive more immunosuppression than other SOT populations, likely contributing to even higher risk of cancer among this group. The most common cancers in lung transplant recipients are non-melanoma skin cancers, followed by lung cancer and post-transplant lymphoproliferative disorder (PTLD). The purpose of this review is to outline the common malignancies following lung transplant, their risk factors, prognosis and current means for both prevention and treatment.

Keywords: Lung transplant; malignancy; immunosuppression; risk factors

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Introduction

Outcomes after lung transplantation have steadily improved since Dr. Hardy’s first attempt more than 50-years ago (1). While initially considered to be a rare, extreme surgical intervention, lung transplantation is now an established therapeutic option for selected patients with advanced lung diseases. It is a procedure after which short and intermediate-term survival is now commonplace with increasing numbers of patients achieving long-term survival with median survival approaching 7-year in the current era (2). As outcomes have improved, chronic lung allograft dysfunction (CLAD) and chronic medical illnesses have emerged as a major obstacle to long-term survival. The focus of this review is on one of these major medical illnesses: malignancy after lung transplantation.

Transplant recipients have significantly higher rates for developing cancer than the general population (3). When cancers are found, treatment is often difficult and prognosis may be worse. In fact, in the most recent report of the International Society for Heart and Lung Transplantation (ISHLT), cancer represented the 2nd most common cause of death in lung transplant recipients five to ten years out from transplant (17.3%) and for patients who were more than 10-year after the procedure (17.9%) (2).

The necessary requirement for post-transplant chronic immunosuppressive therapy and resulting impairment of anti-tumor immune surveillance and anti-viral activity is thought to have a central role in cancer development (4). Induction agents that deplete T-lymphocytes in particular
have been associated with increased risk of cancer after solid organ transplantation (SOT) (5). In the setting of impaired cell-mediated immunity, oncogenic viruses such as Epstein-Barr virus (EBV), human papilloma virus (HPV) and others have emerged as major risk factors for cancer development (4,6). Various immunosuppressive agents/regimens may also directly impact cancer risk that is independent of their effects on the overall level of immunosuppression. For example, reports suggest that azathioprine is associated with increased risk for skin cancer, while mycophenolate mofetil (MMF) is not. A recent study showed that switching azathioprine to MMF resulted in a reduced risk of squamous cell skin carcinoma (7). While the mechanism is not well understood, azathioprine appears to have photosensitizing properties that have direct mutagenic effects (8). In contrast, mammalian target of rapamycin (mTOR) inhibitors may interfere with cancer cell proliferation and angiogenesis and have been associated with lower incidence of certain cancers such as Kaposi’s sarcoma, mantle cell lymphoma and nonmelanoma skin cancer (9,10). Calcineurin inhibitors (CNI) such as cyclosporine and tacrolimus appear to independently promote cancer progression/aggressive behavior by increasing levels of the cytokine transforming growth factor-beta (TGF-β) (11). CNIs may also interfere with the body’s DNA repair processes thereby promoting tumor development (12).

In general, lung transplant recipients receive more immunosuppression than other SOT populations, likely contributing to the observed higher rates of cancer in this population. Other environmental risk factors such as extent of sun exposure and pre-transplant tobacco exposure also increase cancer risk (13,14). Compared to the general population, SOT recipients have significantly higher risk of developing Kaposi’s sarcoma, nonmelanoma skin cancers, non-Hodgkin’s lymphoma, liver, oral, vulvar, vaginal, anal, renal, bowel, bladder, thyroid, pancreatic and lung cancers (6). In contrast, there does not appear to be excess risk of breast or prostate cancer in the SOT population (15-17). Among recipients of lung transplants, the most common cancers are non-melanoma skin cancers, followed by lung cancer and post-transplant lymphoproliferative disorder (PTLD) (15).

Cancers after SOT most commonly develop de novo in the recipient. Tumors may also represent recurrent cancer from a pre-transplant malignancy. Rarely, tumors are donor related. Donor related disease may arise as a result of tumor transmission from a previously known or unknown malignancy in the donor, or as malignant transformation of donor cells within the recipient without a previous malignancy (18,19).

### Donor transmitted malignancies

Donor transmitted malignancies are extremely rare due to the rigorous donor selection criteria but remain a concern as the severe shortage of organs and high waitlist mortality has led many transplant centers to consider organs from extended-criteria donors (20-22). The incidence of donor transmitted tumors appears to be low and reported to be between 0.01–0.05% (21,23,24). In 2008, the United States Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) established a subcommittee to review the impact and risk of donor-related malignancy transmission. Their report was published in 2011 (25). Although they found that high level evidence was not available to precisely determine cancer transmission risks, estimates could be determined. The reports suggested that certain cancers (e.g., basal cell skin carcinoma, in situ cervical carcinoma, solitary papillary thyroid cancer) posed minimal risk (<0.1%) for transmission while other tumors had high risk (>10%) for transmission to the organ recipient. High risk tumors include: malignant melanoma, breast cancer > stage 0, colon cancer > stage 0, choriocarcinoma, certain criteria for CNS tumors, renal cell carcinoma >7 cm, any metastatic cancer and prior history of melanoma, leukemia, lymphoma, small cell lung/ neuroendocrine tumors. Other cancers were designated as low or intermediate risk (25). Ultimately, the decision to accept a donor with a known or possible history of cancer depends on the potential transplant candidate’s severity of illness, likelihood of survival until another donor is identified, individual transplant center’s assessment of risk and patient willingness to consider these types of donors.

### Common malignancies after lung transplant:

#### Skin cancer

Nonmelanoma skin cancers are the most common malignancies in SOT recipients including after lung transplantation (14,26). They account for up to 50% of all cancers reported in the post-transplant population. Squamous cell carcinoma (SCC), is the most common with a 100–200-fold increased risk compared to the general population (14). The incidence of basal cell carcinoma (BCC) is comparatively low with reports showing a 4–10-fold increased risk thus the BCC to SCC ratio which is
approximately 4:1 in immunocompetent populations, is reversed in SOT recipients. Recent studies have reported an incidence of 11.4% for BCC and 26.5% for SCC at ten years’ post-transplant (27,28). Merkel cell carcinoma is a rare, aggressive nonmelanoma skin cancer of neuroendocrine origin that is 24-fold more common in transplant recipients (29). Compared to the general population, non-melanoma skin cancers develop at a younger age, behave more aggressively, often developing at multiple sites with frequent local recurrences and higher rates of metastatic disease and mortality (17,28).

SOT recipients are also at increased risk for malignant melanoma. A recent analysis reported a relative risk of 2.7 compared to non-transplant patients (27). Although donor transmission of cancer is rare, melanoma is one of the more commonly reported donor-derived malignancies. In fact, presentation many years after transplantation has been described with one case report describing donor transmitted melanoma presenting in a lung transplant recipient more than 30-years after resection in the donor (18,30,31).

### Risk factors
The increased risk for non-melanoma skin cancer in SOT recipients is primarily attributed to immunosuppression. Among SOT recipients, lung transplant patients generally require treatment with the highest level of immunosuppression. Thus, it’s not surprising that rates of nonmelanoma skin cancer and death from this malignancy are highest after lung transplantation (14). Infections with oncogenic viruses likely play an important role as well with some studies reporting that the majority of squamous skin cancers in the transplant population are associated with HPV infection (32). Other reported risk factors for both melanoma and nonmelanoma skin cancers include male sex and increased age at transplantation (14,27,28,33). High sun exposure and fair skin are known risk factors for non-melanoma skin cancers in the transplant population (29). Compared to the general population, non-melanoma skin cancers develop at a very high ratio of 9:1 in immunocompetent populations, is reversed in SOT recipients. Recent studies have reported an incidence of 11.4% for BCC and 26.5% for SCC at ten years’ post-transplant (27,28). Merkel cell carcinoma is a rare, aggressive nonmelanoma skin cancer of neuroendocrine origin that is 24-fold more common in transplant recipients (29). Compared to the general population, non-melanoma skin cancers develop at a younger age, behave more aggressively, often developing at multiple sites with frequent local recurrences and higher rates of metastatic disease and mortality (17,28).

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### Treatment
Treatment for skin cancer in lung transplant recipients is similar to non-transplant populations and centers on excision of the cancer, typically employing the Mohs micrographic surgical approach to preserve uninvolved tissue. Wide surgical excision may also be considered. Immunosuppressed recipients have increased risk of complications after excision including surgical site infections.
and wound dehiscence (43). If possible, immunosuppression should be reduced to diminish risk for cancer recurrence and surgical complications. As some studies report that an immunosuppression regimen employing mTOR inhibitors (e.g., sirolimus) with a dose reduction of CNIs is associated with lower rates of skin cancer, this approach should also be contemplated, yet balanced with possible adverse effects, including impaired wound healing (28).

For inoperable tumors and patients deemed to be at prohibitively high risk for surgery, radiation therapy may be recommended (44). Therapeutic options for locally advanced or metastatic disease are limited. Systemic treatment with epidermal growth factor receptor (EGFR) inhibitors may be appropriate for select patients. Recently, treatment with cemiplimab, a high-affinity, highly potent human monoclonal antibody directed against programmed death 1 (PD-1) was approved for the treatment of advanced cutaneous squamous cell cancer (45). However, this approach has not been studied in transplant recipients and there is significant concern that immunotherapeutic approaches that inhibit PD-1 will increase risk of graft rejection.

**Lung cancer**

Lung cancer is more commonly seen in SOT recipients than the general population, with the greatest risk in lung transplantation followed by heart, liver and kidney transplantation (15,46). Lung transplant recipients appear to have up to a 5-fold increased risk of lung cancer compared to the general population, with reported incidence ranging from 1–9% (47,48). Chronic obstructive pulmonary disease (COPD) and interstitial lung disease are the leading indications for lung transplant, both conditions are independently associated with lung cancer (2). Similar to the general population, significant pre-transplant exposure to carcinogenic toxins (e.g., cigarette smoke), older age and male gender have been reported to increase risk of lung cancer after transplantation. Single lung recipients appear to be at highest risk for lung cancer as this procedure necessarily leaves behind a native lung exposed to these conditions (15,47-51). While early stage lung cancer has a better prognosis than presentation at later stages, a recent report from the US Scientific Registry for Transplant (SRTR) found that outcomes in lung transplant recipients is generally poorer than lung cancer treated in the general population even though detection at earlier stages and surgical resection is more common (48). Poorer outcomes in the transplant population likely reflect the deleterious effects of immunosuppression on promoting aggressive tumor behavior and metastasis.

**Clinical presentation**

Lung cancer may be seen in four distinct clinical situations after lung transplantation: (I) lung cancer in the native lung after single lung transplantation; (II) incidental detection of lung cancer in the explanted diseased lung; (III) lung cancer development in the allograft (donor transmitted or *de novo* malignancy); and (IV) recurrence in a patient transplanted for the primary indication of lung cancer.

As mentioned previously, most cases of lung cancer in lung transplant recipients arise in the native lung of single lung transplant recipients. The recent SRTR report indicates a 13-fold higher rate in this group compared to the general population (15,48). Prevalence rates ranging from 1.5–8.9% have been reported (52,53). In contrast, lung cancer in the allograft after single or bilateral lung transplantation is very uncommon (49). This is likely due to the careful donor selection process. However, as the extreme shortage of donor organs persists, transplant centers are increasingly utilizing extended-donors who may be older and have a more extensive smoking history. It remains to be seen if this will impact the future incidence of lung cancer in the allograft (20,48,49,54,55).

Recipient pre-transplant screening with chest CT scan has made tumor detection in the explanted lungs an unusual finding. Incidence ranges from 0.8–2% in various studies (56,57) with adenocarcinoma being the most frequent histologic type (52). Prognosis in these patients is stage dependent. Early stage I cancer has a more favorable prognosis, while most patients diagnosed with nodal involvement, stage II or III disease, experience recurrence and die within a year (33,52,56,57). Recent history of malignancy is generally considered an absolute contraindication to lung transplantation, with a 2- to 5-year disease free interval recommended for many types of cancers prior to listing (58). At present, there are no consensus guidelines for lung cancer screening for candidates on the wait list with many centers employing an approach similar to what is recommended in the general population with annual Chest CT scans in high risk populations (59,60). Detecting lung cancer before transplantation can be challenging as many abnormalities on CT imaging may represent inflammatory or infectious processes rather than malignancy. Lung cancer arising in the background of interstitial changes may be difficult to recognize. Furthermore, imaging modalities such as
Development of de novo lung cancer in the allograft is relatively uncommon. Prevalence ranges from 0.3–1.8% (52,56). Lung cancer in the allograft often raises concern about donor transmission, especially if it occurs in the months immediately following transplantation. De novo tumors, however, may be of either donor or recipient origin and seen even after bilateral lung transplantation (61,62).

Lung adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) with predominant or pure lepidic patterns, entities previously known as bronchoalveolar carcinoma (BAC), are a subset of lung adenocarcinoma without evidence of stromal, pleural or lymphatic invasion. Select patients with this diagnosis may be considered for lung transplantation (58,63). Several studies that specifically evaluated transplantation outcomes of patients with BAC demonstrated that while post-transplant recurrence rates were high for diffuse disease, impact on long-term survival was mixed (64,65). However, these studies utilized now outdated nomenclature that lumped together all patients with BAC. The recent re-classification of BAC into subtypes by histology and molecular criteria has identified distinct subgroups with different outcomes (57,58). Thus, it's possible that outcomes after lung transplantation could be better for certain subtypes (e.g., AIS) but additional studies are needed to confirm this hypothesis (57).

Treatment

Regardless of tumor origin, treatment of lung cancer after transplantation is challenging. Immunosuppression is typically reduced if deemed to be safe. Use of an immunosuppression regimen that includes an mTOR inhibitor may be considered as this class of immunosuppressive drugs has potential antineoplastic effects. Their impact in treatment of non-small cell lung cancer (NSCLC), however, is not clear (66,67). Unfortunately, many transplant recipients have significant co-morbidities or poor pulmonary reserve that limits consideration of definitive therapy with surgical resection or treatment with chemotherapy and/or radiation (56). Over the last few years, treatment with immune checkpoint inhibitors, have emerged as an important therapeutic option for advanced NSCLC with recent data showing improved overall survival (68). Unfortunately, these drugs have not been well studied in the post-transplant setting and the limited available data raises significant concern that the primary mechanism of action of these medications to enhance anti-tumor immune effects may have the unintended consequence of increasing alloreactivity and promote accelerated graft loss (69-71). Further study is needed to determine safety and efficacy before definitive recommendations regarding these medications can be established.

The best preventative measures for lung cancer are related to risk factor modification. Smoking cessation is mandatory for lung transplant candidacy and treatment groups should confirm abstinence post-transplant. High rates of cancer in the native lung in single lung transplant have led some authors to favor double vs. single lung transplant (52). However, this approach should be considered carefully as unintended consequences may cause greater harm by limiting organ availability and increased waiting times resulting in greater likelihood of clinical decline and mortality for the overall waitlisted patient population (72).

PTLD

The term PTLD represents a heterogeneous group of lymphoid disorders that includes benign polyclonal B-cell proliferation and monoclonal malignancies such as diffuse large-B cell lymphoma. It is one of the most common cancers seen in organ transplant recipients with intestinal and lung transplant recipients reported to be at greatest risk (15,73). Most cases of PTLD are associated with EBV-infection with higher risk in the lung transplant population likely related to the large amount of passenger lymphoid tissue in the allograft containing latent EBV infected donor B-lymphocytes and the relative increased intensity of the post-transplant immunosuppression regimen. Post-transplant immunosuppression impairs T-cell-specific immunity against EBV and increases the likelihood of developing lymphoma. Notably, multiple studies have shown an association between lymphoma onset and induction with OKT3 (humanized anti CD3) which is no longer used (13). Anti-thymocyte globulin (ATG) and alemtuzumab (anti CD52) which are also lymphocyte depleting agents, have been shown in some studies to be associated with lymphoma development. Non depleting agents such as basiliximab and daclizumab (IL-2 receptor antagonists) have not been associated with increased risk for PTLD (73-77).

The incidence of PTLD after lung transplantation has been reported to be between 3–9% and is associated with worse long-term survival and high mortality (78,79).
Transplant recipients without prior exposure to EBV who receive an organ from a donor with history of EBV infection are more likely to develop PTLD and have severe disease. Thus, it’s not surprising that pediatric patients are at greatest risk (13,80). While PTLD most commonly arises from EBV infected B cells (85%), it may develop from T-cells, natural killer cells and plasma cells (81). EBV-negative PTLD is also increasingly recognized. Its pathogenesis is not well understood (82).

Clinical presentation
PTLD can develop at any time point after transplantation. The majority of cases (~60%) develop “early” or in the first post-transplant year with the remaining cases designated as “late-onset” PTLD (81). Early onset PTLD is typically seen in children and adults who have not had prior EBV infection and acquire the infection from the donor. Thus, early PTLD is seen to develop more commonly in the allograft. Studies suggest that this type of PTLD is more likely to respond to reduction in immunosuppression (83). In contrast, late onset PTLD, is seen more commonly in extrathoracic locations (e.g., intestinal tract and lymph node tissue) is disseminated and more likely to be an EBV negative tumor. Late-onset PTLD is generally associated with worse prognosis (73,78,79,84).

Treatment/prognosis
Treatment approaches generally involve reduction of immunosuppression to enhance cell-mediated immune response against EBV-infected cells, administration of anti-B-cell agents such as rituximab and/or cytotoxic chemotherapeutic drugs, consideration of surgical resection or radiation therapy for localized disease and perhaps immunotherapeutic approaches such as the infusion EBV-specific cytotoxic T-lymphocytes for disease refractory to other approaches (81).

Immunosuppression reduction alone has a response rate of up to 45% in SOT (85). Unfortunately, this approach is associated with significant risk for rejection and graft loss (78,85). In fact, in some reports, CLAD rather than PTLD related death, was the leading cause of mortality in lung recipients with PTLD (74).

In practice, immunosuppression reduction usually involves discontinuing the cell cycle inhibitor (e.g., MMF, azathioprine), lowering CNI target serum trough levels and decreasing corticosteroid dosing while monitoring graft function closely (77,86). The next line of therapy after immunosuppression reduction is treatment with the chimeric anti-CD20 monoclonal antibody rituximab. CD20 is present on the surface of both normal and malignant B-cells. Rituximab binding to these cells induces cell death. Response rates have ranged between 44–66% in various studies and rituximab may be used in isolation, in conjunction with immunosuppression reduction or in combination with more traditional cytotoxic chemotherapeutic agents (73,79,87). More recently, there has been interest in developing targeted immunotherapies to treat PTLD. Approaches that are currently being explored include ex vivo expansion and adoptive transfer of autologous EBV-specific cytotoxic T-lymphocytes into the transplant recipient. Further study is needed to determine the safety and efficacy of these approaches (88-90).

PTLD is associated with a worse overall and CLAD free survival compared to thoracic organ transplant recipients without PTLD. Poorer prognosis is associated with reduced performance status, disseminated disease and disease location. EBV-negative tumors and late-onset disease generally has worse outcomes (73,78,91-93). A recent meta-analysis of PTLD in lung transplant recipients demonstrated a significantly lower risk of death in double lung transplant recipients compared to single-lung recipients. However, confounding factors such as age, indication for transplantation, severity of pre-transplant illness, frailty, intensity of immunosuppression could not be adjusted for. Thus, further study is needed to determine if double lung transplantation is independently associated with a survival advantage in patients with PTLD (79).

Prevention
Strategies to prevent PTLD are limited and center on early detection of EBV viremia in high risk (e.g., EBV-naive) patients. Low levels of viremia can be identified through polymerase chain reaction (PCR)-based approaches. Several reports have shown that high or increasing EBV viral loads often precede the development of PTLD (94-96). If detected, pre-emptive reduction in immunosuppression could be considered to potentially avert PTLD development (97). For transplant recipients deemed to be at high risk for graft rejection, empiric treatment for possible PTLD with rituximab in the setting of persistent EBV viremia has been considered with reports suggesting safety and benefit (98,99). While initial studies raised hope that high-risk patients treated with anti-viral prophylaxis (e.g., ganciclovir) would have lower risk of PTLD development, a recent meta-analysis reported that there was no difference in rates of PTLD development between those who received
anti-viral prophylaxis and those that did not (100-102).

**Other malignancies**

An analysis of the United States Scientific Registry of Transplant Recipients (SRTR) showed lower rates of breast and prostate cancer compared to the general population. This somewhat unexpected finding is likely due to the intensive screening for malignancies transplant candidates are required to undergo before transplantation with detection of cancer excluding patients from transplantation or necessitating treatment and extended cancer-free survival before transplantation (15). Other contemporary reports did not find lower rates highlighting the importance of maintaining rigorous screening after transplantation (103,104). As survival after transplantation increases, the rates of these cancers are expected to increase further. Once these cancers develop, there is concern that they may behave more aggressively and have poorer outcome (103,105).

Solid organ transplant recipients are at increased risk for colorectal cancer (15,106). In particular, lung transplant recipients with cystic fibrosis (CF) appear to be at especially high risk. Specific guidelines for colorectal screening among CF patients have been developed and should be followed during the transplant evaluation and post-transplant phases of care (15,106,107). At present, there is no consensus regarding malignancy screening for solid-organ transplant recipients. The American Society of Transplantation recently reviewed the recommendations from different societies for various cancers (108).

**Conclusions**

Post-transplant immunosuppression increases the risk of many different types of cancer. As early outcomes have continued to improve, malignancy has emerged as an important obstacle to long term survival and quality of life. Patient education about these risks, adherence to general screening protocols and closer attention to certain high-risk cancers is essential. In the future, enhanced understanding of how immunosuppression increases malignancy risk, development of novel diagnostic tools that allow for early detection and targeted treatments may improve malignancy related outcomes.

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