Development of malignancy following renal transplantation

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Spectrum of Cancer Risk among U.S. Solid Organ Transplant Recipients: The Transplant Cancer Match Study

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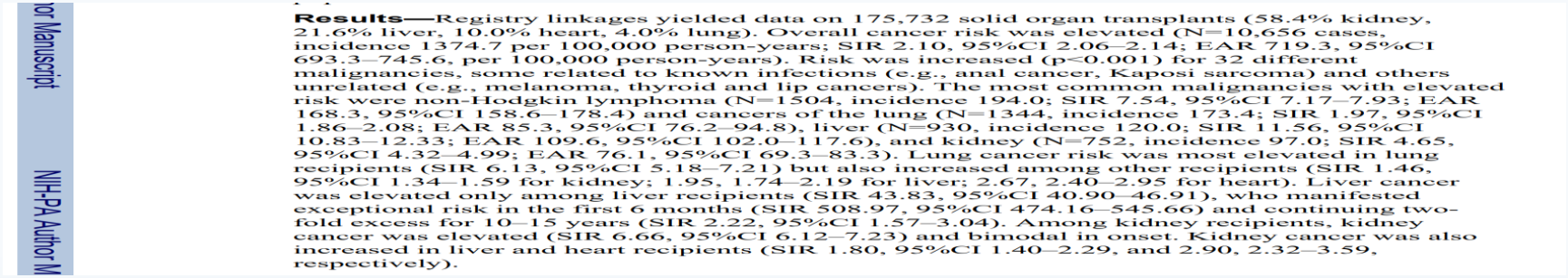
There is an increased risk of a wide range of cancers associated with solid organ transplantation.

The most extensive data come from a cohort study that analyzed the frequency of malignancy in over 175,000 solid organ transplant recipients during the period 1987 to 2008 .

The most common organs transplanted included kidney, liver, heart, and lung (in 58, 22, 10, and 4 percent of cases, respectively).

Overall, malignancy was identified in over 10,656 cases, which correlated with a standardized incidence ratio (SIR) of 2.10 (95% CI 2.06-2.14) compared with the general population and an excess absolute risk (EAR) of 719 cases per 100,000 person-years.

Engels EA, Pfeiter RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011; 306:1891.



Results—Registry linkages yielded data on 175,732 solid organ transplants (58.4% kidney, 21.6% liver, 10.0% heart, 4.0% lung). Overall cancer risk was elevated (N=10,656 cases, incidence 1374.7 per 100,000 person-years; SIR 2.10, 95%CI 2.06–2.14; EAR 719.3, 95%CI 693.3–745.6, per 100,000 person-years). Risk was increased ($p<0.001$) for 32 different malignancies, some related to known infections (e.g., anal cancer, Kaposi sarcoma) and others unrelated (e.g., melanoma, thyroid and lip cancers). The most common malignancies with elevated risk were non-Hodgkin lymphoma (N=1504, incidence 194.0; SIR 7.54, 95%CI 7.17–7.93; EAR 168.3, 95%CI 158.6–178.4) and cancers of the lung (N=1344, incidence 173.4; SIR 1.97, 95%CI 1.86–2.08; EAR 85.3, 95%CI 76.2–94.8), liver (N=930, incidence 120.0; SIR 11.56, 95%CI 10.83–12.33; EAR 109.6, 95%CI 102.0–117.6), and kidney (N=752, incidence 97.0; SIR 4.65, 95%CI 4.32–4.99; EAR 76.1, 95%CI 69.3–83.3). Lung cancer risk was most elevated in lung recipients (SIR 6.13, 95%CI 5.18–7.21) but also increased among other recipients (SIR 1.46, 95%CI 1.34–1.59 for kidney; 1.95, 1.74–2.19 for liver; 2.67, 2.40–2.95 for heart). Liver cancer was elevated only among liver recipients (SIR 43.83, 95%CI 40.90–46.91), who manifested exceptional risk in the first 6 months (SIR 508.97, 95%CI 474.16–545.66) and continuing two-fold excess for 10–15 years (SIR 2.22, 95%CI 1.57–3.04). Among kidney recipients, kidney cancer was elevated (SIR 6.66, 95%CI 6.12–7.23) and bimodal in onset. Kidney cancer was also increased in liver and heart recipients (SIR 1.80, 95%CI 1.40–2.29, and 2.90, 2.32–3.59, respectively).

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- NHL incidence was highest in lung recipients, intermediate in liver and heart recipients, and lowest in kidney recipients

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- The tumor sites with a fivefold or greater increase, compared with the general population, included the following:
- Kaposi sarcoma (KS; SIR 61 and EAR 15)
- Skin (nonmelanoma, nonepithelial SIR 13.9 and EAR 22)
- Non-Hodgkin lymphoma (SIR 7.5 and EAR 168)
- Liver (SIR 11.6 and EAR 110)
- Anus (SIR 5.8 and EAR 9.6)
- Vulva (SIR 7.6 and EAR 6.5)
- Lip (SIR 16.8 and EAR 16)

- Other common malignancies with a statistically significant increase included the following:
- Lung (SIR 2.0 and EAR 85)
- Kidney (SIR 4.7 and EAR 76)
- Colon and rectum (SIR 1.2 and EAR 15.8)
- Pancreas (SIR 1.5 and EAR 6.4)
- Hodgkin lymphoma (SIR 3.6 and EAR 7.9)
- Melanoma (SIR 2.4 and EAR 29)

- Other primary malignancies that were significantly increased, but to a lesser extent, included stomach, oral cavity, larynx, pharynx, vulva, penis, thyroid, urinary bladder, lip, esophagus, salivary glands, soft tissue sarcomas, small intestine, testis, biliary tract, acute myeloid leukemia, plasma cell neoplasms, and chronic myeloid leukemia.

- By contrast, the incidence of breast cancer was significantly decreased (SIR 0.85 with an EAR of -11.2), as was the risk of prostate cancer (SIR 0.92 with an EAR of -11.3).

CLINICAL CHARACTERISTICS

- When all cancers are considered, the average age at diagnosis is approximately 40 years, and the average latency is approximately three to five years after transplantation .

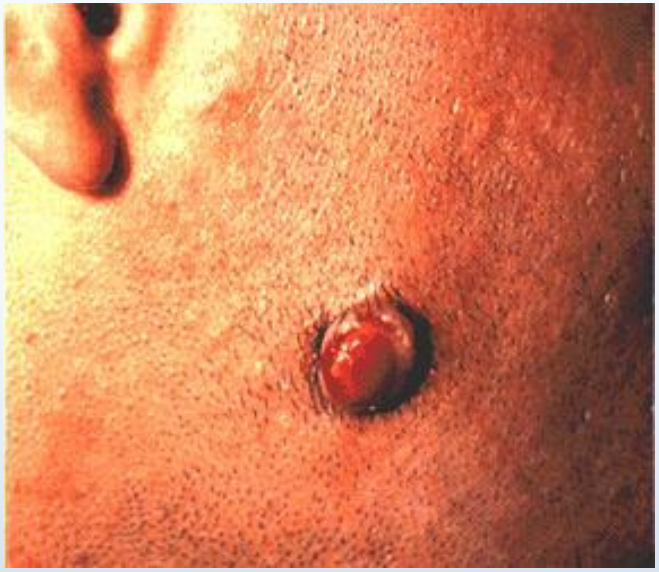
- However, the average time to presentation of particular neoplasms occurs at distinct time intervals following transplantation:

- Kaposi sarcoma (KS) – 13 to 21 months
- Lymphomas – 32 months, although the incidence is highest during the first year when the risk of primary viral infection and the level of immunosuppression are most intense .
- Epithelial (including skin) cancers – 69 months.
- Cancers involving the anogenital region – 84 to 112 months .

- The latency is even longer among patients who received allografts as **children**, in whom the lesions often develop during adulthood (mean interval after transplantation was **142 months** for carcinomas of the vulva and perineum in one series.

Kaposi sarcoma

- Most cases of post-transplant KS occur in individuals of Mediterranean, Jewish, Arabic, Caribbean, or African descent .
- This is a function of the geographic distribution of human herpesvirus 8 (HHV-8, also known as KS-associated herpesvirus [KSHV])
- There is a male predilection (male to female ratio 3.3:1), and the average age at diagnosis is 43 years, younger than for patients with classic KS .



…Kaposi sarcoma

The clinical presentation is similar to that of classic KS, manifested as angiomatous lesions predominantly affecting the legs and causing lymphedema.

…Kaposi sarcoma

- Approximately 90 percent of patients have cutaneous and/or mucosal lesions, while 10 percent have disease that is limited to the viscera .
- For unclear reasons, visceral involvement is less common in patients with kidney as compared with liver or heart allografts (25 to 30 versus 50 percent).
- At least partly because of this, patients who develop KS after a liver or heart transplant have shorter survival than those who have undergone kidney transplantation .

PATHOGENESIS

- ❖ Several factors have been linked to the increased incidence of secondary malignancies among transplant recipients, including:

- Sun exposure
- Extent and duration of immunosuppression
- Concomitant viral infection
- In patients undergoing kidney transplantation pre-transplantation dialysis.
- In rare cases, malignancy has been transplanted from the donor.

- **Episodes of graft rejection in the first year** after transplantation increase the likelihood of developing a secondary malignancy, possibly because of the greater level of immunosuppression that is required .

Type, extent, and duration of immunosuppressive therapy

- Antibody therapy directed against T lymphocytes (as with OKT3 or antilymphocyte serum) specifically predisposes to posttransplant lymphoproliferative disorders (PTLD) induced by Epstein-Barr virus (EBV).

- By contrast, antibody therapy targeting B lymphocytes (as with rituximab) may reduce the incidence of lymphoproliferative disorders and is regarded by many as appropriate first-line therapy for these disorders.

Calcineurin inhibitors

- cyclosporine itself may promote cancer progression, principally via the production of transforming growth factor-beta (TGF-beta).

- Another notable cytokine with increased levels is interleukin-6 (IL-6), which may help EBV - induced B-cell growth .

- Data from one series suggest that the use of tacrolimus increases the risk of malignancy following kidney transplantation .

- In a prospective trial, 231 kidney allograft recipients were randomly assigned after 12 months of standard immunosuppressive therapy to receive cyclosporine doses adjusted to yield trough blood concentrations between 75 to 125 ng/mL (low-dose group) or doses that yielded trough concentrations between 150 to 250 ng/mL (normal-dose group) .
- At a median follow-up of 66 months, patients receiving the low-dose cyclosporine regimen had a significantly lower incidence of all secondary cancers (23 versus 37 cancers), particularly skin cancers (17 versus 26 cancers).

Dantal J, Hourmant M, Cantarovich D, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. Lancet 1998; 351:623.

Azathioprine

- The use of azathioprine has been associated with neoplastic development post-transplantation, particularly an increased risk of cutaneous squamous cell carcinomas (SCCs) .

Sirolimus

- Some data suggest that sirolimus, suppresses the growth and proliferation of tumors in various animal models .
- Possible mechanisms of actions include inhibition of p70 S6K (thereby decreasing cell proliferation), interleukin-10 (IL-10, decreasing tumor cell Jak/STATs activity), and cyclins (blocking cell cycle activity).

- In humans, evidence also suggests that sirolimus may confer a decreased risk of malignancy compared with other immunosuppressive medications .

- A systematic review and meta-analysis of randomized trials that compared immunosuppressive regimens with and without sirolimus using patient-level data from kidney and kidney-pancreas transplant recipients .

- Compared with controls, sirolimus was associated with a 40 percent decrease in the overall risk of malignancy (adjusted hazard ratio [HR] 0.60, 95% CI 0.39-0.93) and a 56 percent decrease in the risk of non-melanoma skin cancer (HR 0.44, 95% CI 0.30-0.63).
- This result was most striking among patients who converted to sirolimus from another immunosuppressive regimen with an overall decrease in malignancy risk (HR 0.34, 95% CI 0.28-0.41), nonmelanoma skin cancer (HR 0.32, 95% CI 0.24-0.42), and other cancers (HR 0.52, 95% CI 0.38-0.69).
- By contrast, analysis of de novo sirolimus trials revealed no difference in malignancy risk between sirolimus and controls.
- However, sirolimus was associated with an increased mortality risk in this meta-analysis (HR 1.43, 95% CI 1.21-1.71).
- The increased mortality was driven by increased cardiovascular and infection-related deaths in the sirolimus group.

Knoll GA, Kokolo MB, Mallick R, et al. Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. BMJ 2014; 349:g6679.

- The substitution of sirolimus for cyclosporine in kidney transplant recipients has been associated with complete regression of Kaposi sarcoma (KS) .

- Sirolimus was substituted for cyclosporine in one study of 15 kidney transplant patients with KS .

- This resulted in the disappearance of lesions in all patients by three months, but acute rejection episodes and decreases in kidney function were not observed.

- Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med 2005; 352:1317.

- In a retrospective review of Medicare claims data for transplant recipients who underwent transplant from January 2000 to September 2006, **de novo use of sirolimus was associated with a 22 percent increased risk of PTLD**

- Nee R, Hurst FP, Dharnidharka VR, et al. Racial variation in the development of posttransplant lymphoproliferative disorders after renal transplantation. Transplantation 2011; 92:190.

- In one study of 45,164 Medicare-insured kidney transplant recipients from the United States Renal Data System (USRDS), compared with a regimen that included rabbit anti-thymocyte globulin induction and maintenance tacrolimus, mycophenolate, and glucocorticoids, a sirolimus-based regimen was associated with significantly higher three-year risks of pneumonia ,sepsis, diabetes ,acute rejection, graft failure ,and patient death ,but reduced skin cancer risk.

- The use of sirolimus in this study was not associated with a reduction in any other malignancy.

- Dharnidharka VR, Schnitzler MA, Chen J, et al. Differential risks for adverse outcomes 3 years after kidney transplantation based on initial immunosuppression regimen: a national study. Transpl Int 2016; 29:1226.

- Some clinicians use the combination of sirolimus (goal levels of 5 to 8 ng/mL) plus glucocorticoids in kidney transplant recipients with malignancy, either in remission or being actively treated .

- However, the use of sirolimus for transplant recipients with non-melanoma skin cancer may not be justified, given the overall increase in associated mortality .

Mycophenolate mofetil

- Mycophenolate mofetil impairs lymphocyte function by blocking purine biosynthesis via inhibition of the enzyme, inosine monophosphate dehydrogenase.
- Some malignancies, including some solid tumors, have dramatic elevations of this enzyme, suggesting that this agent may have some anti-proliferative activity .
- Some population studies also suggest that the risk of developing a malignancy is not higher with mycophenolate mofetil and may actually be associated with a decreased risk .
- In a study using data from two large registries, there was a nonsignificant trend to a decreased risk with mycophenolate- versus non-mycophenolate-based therapy .*
- A principal mechanism of a lower malignancy risk with mycophenolate mofetil, to the degree that it occurs, may be due to the decreased incidence of acute rejection.

*Robson R, Cecka JM, Opelz G, et al. Prospective registry-based observational cohort study of the long-term risk of malignancies in renal transplant patients treated with mycophenolate mofetil. Am J Transplant 2005; 5:2954.

Coexisting viral infection

- At least four viruses may be cocarcinogenic in transplanted patients:

- EBV : Lymphomas
- Human herpesvirus 8 (HHV-8) : Kaposi sarcoma
- Human papillomavirus (HPV) :Squamous skin cancers
- Merkel cell polyomavirus (MCV) : post-transplant lymphoproliferative disorders

Kaposi sarcoma and human herpesvirus 8

- The presence of HHV-8 in tumor tissue has been recognized in all forms of KS: classic KS, endemic KS, acquired immune deficiency syndrome (AIDS) KS, and posttransplant KS, with serologic evidence of infection also being common .

- HHV-8 infection is necessary but not sufficient for the development of KS.

- Pre-transplant antibody screening would appear to be useful for identifying high-risk patients.

- Donor testing is warranted as well, particularly in areas with high sero-prevalence.

Squamous skin cancers and human papillomavirus

- The role of human papillomavirus (HPV) in the development of cSCC remains uncertain.

- HPV has been detected at a greater frequency in lesional versus non-lesional skin in organ transplant recipients with SCC (90 versus 11 to 32 percent of specimens positive for HPV) .

- Beta-HPV subtypes, such as HPV 5, HPV 8, and HPV 9 (which are considered to be non-pathogenic to the general population), can induce pre-neoplastic and neoplastic skin lesions in immunocompromised patients and may play a causal role in post-transplant cSCCs .

Transmission from the donor

- Unintended transmission of malignant cells from a donor is rare but may result in metastatic cancer in the immunosuppressed transplant recipient .

- In a survey of a single kidney transplant center's experience, the risks of having a donor with an undetected malignancy and of transmitting the cancer were 1.3 and 0.2 percent, respectively .

- Almost all of these tumors were believed to have occurred because of the presence of occult malignant cells in the transplanted organ.

- No malignancy transmission was noted with central nervous system (CNS) tumors, with the exception of one medulloblastoma.

- By contrast, a history of melanoma or choriocarcinoma was associated with high rates of transmission, with early and almost universal death.

- A variety of donor-transmitted malignancies have been documented including :cancers of the lung, breast, colon, rectum, and kidney, KS, and glioblastoma multiforme.

Kidney tumors in kidney transplant recipients

- Kidney transplant recipients are at increased risk of developing carcinoma of the native kidneys, particularly if they have undergone prolonged periods of dialysis .

- Kidney tumors are rare in transplanted kidneys.

CANCER SCREENING

- The Clinical Practice Guidelines Committee of the American Society of Transplantation has published recommended guidelines for cancer screening in kidney transplant patients .

Cancer type	Recommendation
Breast	Women 50 to 69 years: annual screening mammography with or without clinical breast examination; age 40 to 49 years: the benefit of screening is less certain and should be left to the decision of the clinician and patient; ≥70 years of age: annual screening is appropriate as long as estimated life exectancy is ≥8 years.
Skin	Monthly self-examination; clinician examination annually, with early referral for suspected lesions.
cervical	All women ≥18 years old and sexually active girls <18 years old should undergo an annual pelvic examination and Pap smear.
Anogenital	Yearly physical examination of the anogenital area, including pelvic examination and cytologic studies for women. Insufficient evidence to recommend for or against screening anoscopy and biopsies of anal epithelium
KS/other sarcomas	Examination of skin, conjunctivae, and oropharyngeal mucosa annually; patients at higher risk (ethnicity, geographic area of residence or serologic positivity for HHV) may benefit from more frequent screening.
Prostate	Annual screening with digital rectal examination and PSA recommended for men ≥age 50 years if their estimated life expectancy is at least 10 years. If positive family history or African-American race, may start annual screening earlier (eg, age 45 years).
Colorectal	Starting at age 50 years: annual FOBT and either sigmoidoscopy every five years or colonoscopy every 10 years*. At some institutions, screening is started at age 40 years or five years after transplant, whichever comes First.
PTLD	Complete history and physical examination every three months, particularly in the first post-transplant year; patients at increased risk of PTLND may benefit from more frequent screening.
Lung	Not recommended
HCC	For patients with chronic hepatitis B or C and cirrhosis, serum AFP and liver ultrasound every 6 to 12 months
Renal cell	Screening via cytologic or radiographic means is not recommended, except possibly for patients with a history of analgesic abuse

Renal carcinoma

- The development of renal cell carcinoma (RCC) is of principal concern in the kidney transplant patient, with most cancers arising in the native kidneys and not the kidney allograft.

- Since urine cytology is unreliable for nonfunctioning native kidneys, surveillance ultrasonography or computed tomography (CT) scanning has been suggested for routine monitoring.

- Suggested yearly imaging screening examinations, particularly in those with acquired cystic kidney disease (ACKD).

- In a prospective study, ultrasound screening of the native kidneys was performed in 561 patients, of whom 129 had ACKD .

- Newly diagnosed RCC was found in eight patients (1.5 percent), seven having ACKD.

- Thus, the prevalence of kidney cancer was 4.8 percent in the whole group and 19.4 percent among those with ACKD.

Schwarz A, Vatandaslar S, Merkel S, Haller H. Renal cell carcinoma in transplant recipients with acquired cystic kidney disease. Clin J Am Soc Nephrol 2007; 2:750.

- Based upon these findings, the authors recommend the following screening approach, which varies with the presence of ACKD and radiologic characteristics of cysts in the native kidney.

- Independent of ACKD, all transplant patients should, at minimum, undergo ultrasonography of the native kidneys once a year.

- Patients with ACKD plus Bosniak category I or II cysts should undergo kidney ultrasonography twice a year and CT scan for progressive lesions.

- Patients with ACKD plus Bosniak category IIF cysts should undergo kidney ultrasonography four times per year and yearly CT scan or magnetic resonance imaging (MRI).

- Nephrectomy and CT scan for progressive lesions should be performed if progression is observed.

- Patients with ACKD plus Bosniak category III or IV cysts should undergo nephrectomy.

Schwarz A, Vatandaslar S, Merkel S, Haller H. Renal cell carcinoma in transplant recipients with acquired cystic kidney disease. Clin J Am Soc Nephrol 2007; 2:750.

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- Given the markedly increased risk of renal carcinoma, our approach is to monitor for microscopic or gross hematuria post-transplant using urinalysis every three to six months, with scheduled follow-up clinic visits.

- If this is positive, we obtain a urine culture; a morning urine cytology (that is repeated three times); an ultrasonography of the native kidney, transplant kidney, and bladder; a urine polymerase chain reaction (PCR) for BK (polyomavirus); and a prostate specific antigen (PSA, in male patients).

- The sensitivity and specificity of urinalysis for hematuria to detect renal cell is unknown.

PREVENTION AND TREATMENT

- The approach to post-transplant malignancies begins with general preventive measures.

- In particular, excess immunosuppression, especially with calcineurin inhibitors, or repeated exposure to agents that selectively target T lymphocytes such as OKT3 should be avoided.

- Careful screening of the patient and donor prior to transplantation to help detect an underlying pre-existing malignancy should also be performed.

Reduction of immunosuppressive therapy

- Reduction or cessation of immunosuppressive therapy is useful primarily for patients who have undergone kidney transplantation since loss of the graft to rejection is not a fatal event in these patients.

- Such measures may result in tumor regression in some cases of lymphoma; some skin cancers; Kaposi sarcoma (KS), in which reducing the calcineurin inhibitor exposure may be particularly important ; and donor-derived malignancies.

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- Despite the association of the calcineurin inhibitors with increased transforming growth factor-beta (TGF-beta) levels and the risk of malignancy, our first approach when serious malignancy occurs post-transplantation is to discontinue the antimetabolite.

- This is because rejection is less likely to occur with double therapy with a calcineurin inhibitor and prednisone than the combination of an antimetabolite with prednisone.

- Some clinicians would substitute sirolimus for the calcineurin inhibitor and antimetabolite

TRANSPLANTATION IN PATIENTS WITH PRE-EXISTING MALIGNANCY

- There is a marked variability in the likelihood of recurrence according to tumor type that determines the recommendations for patients with pre-existing tumors :

- Recurrence rates of 0 to 10 percent were noted among patients with localized renal cell carcinoma (RCC); testicular, cervical, and thyroid cancers; and lymphomas (including Hodgkin and non-Hodgkin lymphoma).
- A higher recurrence rate (11 to 25 percent) was reported for patients with Wilms tumor and for carcinomas of the uterus, colon, prostate, and breast.
- The highest recurrence rate (over 25 percent) was recorded in patients with bladder carcinoma, advanced RCC, sarcomas, myelomas, and both melanoma and non-melanoma skin cancers.

- **No waiting period for transplantation** is necessary with low-risk tumors, such as an incidentally discovered renal carcinoma, in situ carcinoma, primary basal cell skin carcinoma , and low-grade bladder cancer .

- **Transplantation should be delayed for at least five years** with tumors that carry a high risk of recurrence following transplantation: melanoma (some recommend 10 years), breast, and colorectal cancer .

- Transplantation should be delayed for approximately two years with most other tumors

Thank You