CANCER AFTER TRANSPLANTATION

In the general population, there is strong evidence that cancer risk is reduced for patients who have undergone kidney transplantation. The incidence of lung cancer is reduced, but for other solid cancers, and for cancers associated with viral infections (e.g. herpesvirus), the data are inconclusive.

In KTRs, the risk of second primary cancers is considered. The lifetime risk for any second primary cancer is approximately 5-10%.

Cancer Incidence and Survival

Cancer Categories by SIR for Kidney Transplant Recipients and Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Cancer Category</th>
<th>SIR Category</th>
<th>Transplant Population</th>
<th>Rare Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>High SIR</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Moderate SIR</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Low SIR</td>
<td>Very low</td>
<td>Very low</td>
<td>Very low</td>
</tr>
</tbody>
</table>

The risk of cancer is higher in transplant recipients than in the general population. This is likely due to the immunosuppressive therapies used to prevent rejection.

Overview of Other Complications in KTRs

As with any medical procedure, kidney transplantation is associated with a number of potential complications. These complications can be categorized into different types, including:

- Infections
- Infection-related issues
- Immunosuppressive therapy
- Graft failure
- Infectious diseases
- Malignancies
- Chronic kidney disease
- Cardiovascular disease
- Hypertension
- Hypothyroidism
- Diabetes mellitus
- Hyperlipidemia
- Anemia
- Bone disease
- Osteodystrophy
- Anemia
- Erythropoietin therapy
- Hyperparathyroidism
- Hypocalcemia
- Hypertension
- Cardiovascular disease
- Hypertension
- Diabetes mellitus
- Hyperlipidemia
- Anemia
- Bone disease
- Osteodystrophy
- Anemia
- Erythropoietin therapy
- Hyperparathyroidism
- Hypocalcemia
- Hypertension
- Cardiovascular disease
- Hypertension
- Diabetes mellitus
- Hyperlipidemia
- Anemia
- Bone disease
- Osteodystrophy
- Anemia
- Erythropoietin therapy
- Hyperparathyroidism
- Hypocalcemia
- Hypertension
- Cardiovascular disease

These complications can arise during the initial period immediately following transplantation and in the long-term follow-up period.

CANCER INCIDENCE AND SURVIVAL

In KTRs, the risk of second primary cancers is considered. The lifetime risk for any second primary cancer is approximately 5-10%.

The risk of cancer is higher in transplant recipients than in the general population. This is likely due to the immunosuppressive therapies used to prevent rejection.

The malignancies that are most common in KTRs are:

- Skin cancer
- Bladder cancer
- Gastrointestinal cancer
- Lung cancer
- Breast cancer
- Lymphoma
- Multiple myeloma

These malignancies are more common in KTRs than in the general population, and the risks are higher for some specific subtypes.

The incidence of cancer in KTRs is generally lower than in the general population, but the risk is still significant.

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Monitoring kidney allograft function

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>A measure of kidney function</td>
</tr>
<tr>
<td>Urine protein and/or urine albumin</td>
<td>Used to detect proteinuria</td>
</tr>
<tr>
<td>Creatinine and eGFR</td>
<td>Used to monitor kidney function and track allograft function</td>
</tr>
</tbody>
</table>

Managing immunosuppressive medications

- **A** = mild side effect (likely not important). "M" = moderate side effect (high risk). "S" = severe side effect (potentially life-threatening).
- **A** = minimal adverse impact. "M" = moderate adverse impact and trend toward nonadherence. "S" = severe adverse impact and clinically significant nonadherence.
- **A** = minimal treatment impact. "M" = moderate treatment impact and trend toward nonadherence. "S" = severe treatment impact and clinically significant nonadherence.

COMMON SOURCES OF PROBLEMS IN KIDNEY ALLOGRAFT DYSFUNCTION

- **Acute rejection**
- **Thrombotic microangiopathy (TMA)**
- **Hemolytic-uraemic syndrome (HUS)**
- **Graft-versus-host disease (GVHD)**
- **Infection**
- **Drug toxicity**
- **Hypertension**
- **Polyglandular autoimmune syndrome**
- **Lupus**
- **Immunodeficiency**
- **Uremic toxins**
- **Anemia**
- **Glucose intolerance**
- **Hyperlipidemia**
- **Hypertension**
- **Cardiovascular disease (CVD)**
- **Osteoporosis**
- **New-onset diabetes mellitus**
- **Hepatitis**
- **HIV**
- **Other infections**
- **Thrombosis**
- **Thrombotic microangiopathy**
- **Post-transplant lymphoproliferative disorder**
- **Amyloidosis**
- **Systemic lupus erythematosus**
- **Post-infectious glomerulonephritis**
- **IgA nephropathy**
- **Minimal change disease**
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STAGING SEVERITY OF KIDNEY DISEASE WITH TRANSPLANT

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Glomerular filtration rate (GFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>&gt;90 mL/min/1.73 m²</td>
</tr>
<tr>
<td>1</td>
<td>Mild decline</td>
<td>60–89 mL/min/1.73 m²</td>
</tr>
<tr>
<td>2</td>
<td>Moderate decline</td>
<td>30–59 mL/min/1.73 m²</td>
</tr>
<tr>
<td>3</td>
<td>Severe decline</td>
<td>15–29 mL/min/1.73 m²</td>
</tr>
<tr>
<td>4</td>
<td>Dialysis</td>
<td>&lt;15 mL/min/1.73 m²</td>
</tr>
</tbody>
</table>

Sodium levels should be maintained within normal range to prevent fluid overload and suppression of renin-angiotensin system (RAS).
Detecting kidney allograft dysfunction as soon as possible will aid timely diagnosis and treatment. Serum creatinine and urine protein measurement are widely used to screen for and monitor allograft dysfunction. Evidence is accruing that monitoring urine albumin excretion, as determined by denaturant, albuminuria; direct, high-grade albuminuria is an early marker of apparent cause in most likely to be an arrhythmia or cardiovascular event, not acute rejection, chronic allograft injury (CAI), drug toxicity, severe or acute kidney disease, obstruction or RVT. Renal biopsy is often necessary for diagnosing indistinguishable or non-diagnostic circumstances. If CAI is very likely, it is advisable to avoid repeated provocative testing and to avoid allograft biopsies in CAI.

Corticosteroids for Acute Rejection

Corticosteroids are the mainstay of immunosuppressive therapy for the treatment of acute rejection. They are effective in reducing the frequency and severity of acute rejection and improving allograft survival. The use of corticosteroids is based on the severity of the rejection episode, with higher doses of steroids being used for more severe rejection.

Managing Immunosuppressive Medications

Immunosuppressive medications are used to prevent organ transplantation. These medications are intended to prevent and treat allograft rejection and drug toxicity.

Monitor Kidney Transplant Recipients

Monitoring kidney transplant recipients (TTRs) is considered to be based on:
- Damage to native kidneys
- Allograft rejection
- Chronic kidney disease (CKD)
- Decreased GFR

Some tests need to be performed routinely to detect abnormalities that may lead to treatment or prophylaxis of complications that are common in TTRs.

Monitoring Allograft Function

Screening tests may be performed after transplantation:
- Blood pressure, pulse, height, BMI, weight
- Urea, creatinine, albumin
- Complete blood count
- Fasting plasma glucose, GTT or HbA1c
- Lipid profile (fasting)
- Complete urine screen for drug and alcohol abuse
- Screening of KTRs for possible infections

Defining Prophylaxis and Allograft Injury

Defining prophylaxis and allograft injury is important for the appropriate use of immunosuppressive medications. Prophylaxis is defined as the administration of medications to prevent a specific condition, while allograft injury is defined as the presence of a specific condition that has been induced by the use of immunosuppressive medications.

Screening for Infection

Screening for infection is important to identify patients who are at risk for infection and to initiate appropriate treatment.

Managing Infections

Managing infections in TTRs is important to prevent infection-related complications and to improve allograft survival. Infections are a common cause of morbidity and mortality in TTRs.

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Managing infections in TTRs is important to prevent infection-related complications and to improve allograft survival. Infections are a common cause of morbidity and mortality in TTRs.
Primary care management of KTRs: Need for lifelong care caused by complications of prior CKD and chronic allograft nephropathy. Damage to native kidneys (or dialysis) may be strongly encouraged to follow a regimen to prevent acute rejection and risk for adverse effects) is considered standard practice.

Some patients need to be followed periodically to detect abnormal values that may lead to treatment or prophylaxis of complications that are common in KTRs.

Risk factors for medication nonadherence

Secondary care management of KTRs: Consider providing periodic polyclonal gammopathy of unknown significance,

Defining and addressing cell rejection during the early post-transplantation period to prevent calculi and recurrent glomerular diseases

Screening tests for urine protein excretion for acute rejection and risk for adverse effects) is considered standard practice.

Some CausEs of proteinuria after Kidney transplantation

Specimen collection methods

ToxINs proFIlEs of IMMunosuppressives

Infections

• Oral polio

• HbA1c

• Epistem-Barr virus

• Hepatitis B virus

• Hepatitis C virus

• Varicella zoster virus

• BK polyoma virus

• Epstein-Barr virus

• HUS

• Thrombotic thrombocytopenic purpura

• Membranous glomerulonephritis

• Amyloidosis

• Systemic lupus erythematosus

• Diabetic nephropathy

• Vasculitis

• IgA glomerulonephritis

• Minimal change disease

• Cirrhosis

• Diabetes mellitus

• Hypertension

• Prednisone

• Azathioprine

• Mycophenolate mofetil

• Tacrolimus

• Cyclosporine A

• Influenza types A and B (administer annually)

• Inactivated polio

• Pneumovax

• Hepatitis A*

• Hepatitis B, inactivated

• Varicella zoster virus

• Epstein-Barr virus

• BK polyoma virus

• Human immunodeficiency virus

• Candida

• Hemolytic-uremic syndrome

• HUS

• Typhoid Vi

• Oral polio

• Hepatitis A

• Aseptic meningitis

• HbA1c

• HUS

• Varicella zoster virus

• Epstein-Barr virus

• BK polyoma virus

• Human immunodeficiency virus

• Hepatitis A virus

• Hepatitis B virus

• Hepatitis C virus

• Influenza

• Oral polio

• Varicella zoster virus

• Epstein-Barr virus

• BK polyoma virus

• Human immunodeficiency virus

• Hepatitis A virus

• Hepatitis B virus

• Hepatitis C virus

• Influenza

• Varicella zoster virus

• Epstein-Barr virus

• BK polyoma virus

• Human immunodeficiency virus

• Hepatitis A virus

• Hepatitis B virus

• Hepatitis C virus

• Influenza
Detecting kidney allograft dysfunction as soon as possible will allow timely diagnosis and treatment to prevent graft loss. Serum creatinine and urine protein measures are the gold standard for diagnosing allograft dysfunction. Serum creatinine is a reliable marker of renal allograft function, and urine protein excretion accurately reflects the presence of proteinuria. In general, proteinuria is a valuable indicator of glomerular dysfunction because it is consistent with damage to the allograft. As such, it is recommended to screen and monitor patients for increased proteinuria on an annual basis for the first year, and subsequently at each clinical visit. 

Several conditions may contribute to elevated proteinuria levels, including infection, acute rejection, chronic allograft injury (CAI), drug toxicity, exogenous or autoimmune disease kidney injury, or de novo kidney disease. 

**CAI**

- Acute rejection
- Thrombotic microangiopathy
- Transplant glomerulopathy

**Acute rejection**

- Acute antibody-mediated rejection
- Acute cellular rejection

**Diagnosis**

- Presence of anti-HLA antibodies
- Increase in serum creatinine
- Increase in urine protein

**Management**

- Steroids
- Anti-thymocyte globulin
- Thymoglobulin

**Cellular rejection**

- Increased serum creatinine
- Increased urine protein
- Tissue damage

**Diagnosis**

- Presence of anti-HLA antibodies
- Decrease in glomerular filtration rate

**Management**

- Steroids
- Azathioprine
- Anti-thymocyte globulin

**Antibody-mediated rejection**

- Increased serum creatinine
- Increased urine protein
- Tissue damage

**Diagnosis**

- Presence of anti-HLA antibodies
- Decrease in glomerular filtration rate

**Management**

- Steroids
- Anti-thymocyte globulin
- Plasma exchange

MANAGING IMMUNOSUPPRESSIVE MEDICATIONS

**Toxicity Profile of Immunosuppressive Medications**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Steroids</th>
<th>CNI</th>
<th>Tac</th>
<th>mTOR</th>
<th>B/CZA</th>
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CANCER AFTER TRANSPLANTATION

Kaposi’s sarcoma

Very low: The estimate of effect is very uncertain,
Moderate: The true effect is likely to be close to 1.0 (1C)
Low: The true effect may be substantially different

Kaposi’s sarcoma is a tumor associated with viral infection (infection with human herpes virus-8, HHV-8) and is a common complication following solid organ transplantation. The risk of developing Kaposi sarcoma increases in recipients of an organ from a donor with Kaposi sarcoma. Kaposi’s sarcoma can also be found in patients who have had an organ transplant from a non-HIV donor who has Kaposi’s sarcoma. Treatment of Kaposi’s sarcoma is usually successful and may include surgery, chemotherapy, radiation therapy or a combination of these modalities. In general, the mortality rate is low (1C). Recurrence is common and is a function of the primary lesion number, size and location, and the response to therapy (1C). Cancer in transplant recipients is often recurrent or first diagnosed during the first year after transplantation (1C). The risk of Kaposi’s sarcoma is increased in transplant recipients who are male, black, HIV-positive, and recipients of liver or kidney transplants (1C).

Hematological Complications

Leukemia

There are no increased risks for leukemia in KTRs. Others are rare, with Nutcracker’s syndrome and myelofibrosis being the most frequently reported. The incidence rates of leukemia in KTRs are up to 1.5 times the incidence in the general population, but the absolute risk is low. Acute leukemia has been described in KTRs in the setting of lymphoproliferative disorders. Other hematological malignancies include multiple myeloma and Waldenstrom’s macroglobulinemia. Although rare, there have been occasional reports of Kaposi’s sarcoma developing in the bone marrow of KTRs (1C).

Melanoma

Melanoma is a rare tumor that occurs in the skin. Melanoma is common in skin of dark pigmentation and is a recognized complication in KTRs with dark skin pigmentation. Annual skin and lip examinations are recommended in the general population. This is especially true for KTRs (1C). Skin cancer is a leading cause of cancer deaths in the United States. KTRs with dark skin pigmentation should have annual skin and lip examinations by a skin professional, with experience in diagnosing skin cancers, for a lifetime, or at least until the age of 60 years (1C). Annual skin examinations are recommended for KTRs who have had a skin cancer, regardless of skin color (1C).

Other Complications

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Cancer after transplantation (KTRs) is a term used when cancer develops in patients who have received a kidney transplant. The risk of cancer after transplantation is higher than in the general population, and the types of cancer that occur can be different from those in the general population. The risk of cancer is highest in the first year after transplantation, but it can occur at any time after the transplant. The cumulative incidence of cancer in KTRs is estimated to be 5-15% at 10 years, and the incidence continues to increase over time.

Factors that increase the risk of cancer after transplantation include:
- Immunosuppressive medications used after transplantation
- Age at transplantation
- Gender (women have a higher risk than men)
- Race (African Americans have a higher risk than other races)
- Previous history of cancer
- Smoking
- Obesity
- Diabetes

Symptoms of cancer after transplantation may include:
- Unusual or persistent changes in the body
- Changes in stool or urine
- Changes in appetite or weight
- Changes in skin color or texture
- Persistent fatigue or joint pain

Diagnosis of cancer after transplantation often involves a combination of imaging tests, laboratory tests, and biopsies. Treatment options may include surgery, chemotherapy, radiation therapy, or a combination of these. The treatment plan will depend on the type of cancer, the stage of the disease, and the overall health of the patient.

Cancer after transplantation can be serious, and it is important for KTRs to be aware of the signs and symptoms of cancer and to report them to their healthcare providers promptly. Regular follow-up care after transplantation is important to detect and treat any potential cancer early.
CANCER AFTER TRANSPLANTATION

Transplantation of Bone Disease

The National Kidney Foundation Kidney Disease: Improving Global Outcomes (KDIGO) Bone Disease Work Group developed evidence-based guidelines for diagnosis, prevention, and treatment of bone disease in patients with chronic kidney disease (CKD) in the general population, including patients with renal transplant recipients (KTRs). These guidelines have been developed following a systematic literature review and expert panel consensus. The background for this review is briefly described below.

In the general population, there is strong evidence that bone disease is secondary to CKD. More specifically, as the GFR decreases, the risk for osteoporosis increases. This is believed to occur as a result of a combination of decreased parathyroid hormone (PTH) production and calcium absorption, as well as increased bone resorption.

Hypertension

The Cardiometabolic Risk Management guidelines of the National Kidney Foundation (NKF) are designed to provide information and recommendations for clinicians and patient care teams to promote the care of people with CKD and at risk for CKD.

The KDIGO Bone Disease Work Group recommends that all KTRs receive bone disease prevention and treatment in accordance with the KDIGO Clinical Practice Guidelines for CKD-MBD in the general population (KDIGO 2009). These guidelines are based on a systematic evidence-based literature review and expert panel consensus.

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### CARDIOVASCULAR DISEASE

#### Risks of Cardiovascular Disease

- **Very low:** The estimate of effect is very uncertain.
- **Moderate:** The true effect is likely to be close to the point estimate.
- **Low:** The true effect may be substantially different from the point estimate, but occurs at a substantially higher rate in the KDIGO group.

#### Implications for Your Adult Kidney Transplant Recipients and Chronic Kidney Disease

- **New-onset diabetes after transplantation (NODAT)**: The incidence of NODAT is highest in the first year following transplantation. NODAT is defined by the World Health Organization (WHO) guidelines for the management of diabetes.
- **Cardiovascular disease risk reduction**: Patients with atherosclerotic cardiovascular disease (CVD) risk factors should be identified and appropriate therapy initiated.
- **Cancer incidence**:
  - **Common cancers** in kidney transplant recipients: Breast, colon, prostate, and skin cancer (e.g., myeloma and renal cell carcinoma).
  - **Rare cancers** associated with viral infections (e.g., EBV-associated lymphomas). Others are rare, such as cancers associated with hepatitis C.
  - **Risk of developing cancer, compared to the general population**: Kidney transplant recipients from around the world are at greater risk of developing cancer.

#### Hypertension and Dyslipidemias

- **Hypertension**: Blood pressure should be measured at each clinic visit. Target systolic blood pressure is <140 mm Hg and target diastolic blood pressure is <90 mm Hg.
- **Dyslipidemias**: LDL cholesterol should be <70 mg/dL. Non-HDL cholesterol should be <130 mg/dL. Triglycerides should be <150 mg/dL. Consider LDL apheresis for patients with very high triglyceride levels (>1000 mg/dL).

#### Hyperuricemia

- **Suggest treating hyperuricemia in KTRs when there are complications, particularly gout**: Hyperuricemia is a risk factor for CVD and bone disease. The risk of fractures following kidney transplantation is high.

#### Anemia

- **Assess and treat anemia by removing underlying causes whenever possible**: Hyperbaric oxygen therapy can be considered for patients with dialysis-dependent anemia and iron deficiency.

#### Bone Disease

- **Bone disease is multifactorial, and most KTRs have preexisting CKD-MBD. The risk of fractures following kidney transplantation is high.**

#### Sexual Dysfunction

- **Sexual dysfunction is common in male and female KTRs, and many patients will not spontaneously report it.**

#### Continuity in Care

- **Clinical practice guidelines are general and do not imply a specific protocol. This document is updated annually and information may not be applicable to all situations or settings at any particular time. This document is generalized approval and not a substitute for good clinical judgment.**

### CANCER AFTER TRANSPLANTATION

#### Overview of Other Complications in KTRs

- **New-onset diabetes after transplantation (NODAT):** The incidence of NODAT is highest in the first year following transplantation. NODAT is defined by the World Health Organization (WHO) guidelines for the management of diabetes.
- **Cardiovascular disease risk reduction:** Patients with atherosclerotic cardiovascular disease (CVD) risk factors should be identified and appropriate therapy initiated.
- **Cancer incidence:**
  - **Common cancers** in kidney transplant recipients: Breast, colon, prostate, and skin cancer (e.g., myeloma and renal cell carcinoma).
  - **Rare cancers** associated with viral infections (e.g., EBV-associated lymphomas). Others are rare, such as cancers associated with hepatitis C.
  - **Risk of developing cancer, compared to the general population:** Kidney transplant recipients from around the world are at greater risk of developing cancer. [Adapted from Table 29]

#### Clinical Practice Guidelines

The KDIGO Clinical Practice Guidelines document is based on extensive review of the literature. In 2009, KDIGO was designated to provide information and guidance for professionals with the goal of improving care for patients with kidney disease. KDIGO, an international collaboration of guideline development organizations, is the world’s largest undertaking in the field of chronic kidney disease. The KDIGO clinical practice guidelines are a global effort, and this document is intended to be widely available and comprehensible to healthcare professionals around the world.

#### Acknowledgments

This document is available at

**KDIGO disclaimer**

KDIGO makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise when clinicians take into account the implications of the estimate of the effect. Variations in practice will inevitably and appropriately occur when clinicians take into account the setting of any particular clinical situation. The recommendations in this document are general and do not imply a specific protocol.

**Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients.**


**Strength of Recommendation Taxonomy**

- **A:** Strongly recommended
- **B:** Recommended
- **C:** Suggest
- **S:** Standardized indicator ratio—the ratio of the observed to the expected new cases of cancer (adapted from Table 29)

**KIDNEY TRANSPLANT**

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**Implications for Primary Care in:**

- **Kidney Transplant Recipients and Chronic Kidney Disease**

**References**

- **Managing Your Adult Kidney Transplant Recipients and Chronic Kidney Disease**

**Appendices**

- **Managing Adults Affected by Transplantation**
- **Adult Infections and Kidney Wound Dysfunction**
- **Nephrogenic Diuretic After Transplantation**
- **Cancer**

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