Malignancy in Renal Transplantation

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An increased incidence of malignant tumors in transplant recipients was recognized as early as in the 1970s, and this effect was ascribed to the administration of immunosuppressive medication (1,2). In the early days of transplantation medicine, however, the clinician faced fulminant acute rejection episodes and severe infections; malignancy after transplantation represented only a minor problem. With longer graft survival and older donors (as well as recipients) and with the introduction of more potent immunosuppressive medication, malignancy represents a major burden in transplantation medicine. The overall incidence of malignancy after renal transplantation has been reported as being 3 to 5 times higher compared with the general population (3,4). However, an increased frequency is not found for all types of cancer (Figure 1). According to the Cincinnati Transplant Tumor Registry and other reports, the most frequent types of tumors are posttransplant lymphoproliferative disorder (PTLD) and squamous cell carcinoma (lip, cervix, vulva, skin) (5,6).

Epidemiology
Many retrospective analyses do not adequately reflect the magnitude of the problem (3,5). The cumulative prevalence of malignancy increases with the duration of follow-up. After 10 yr, the risk of cancer in transplant patients was recently reported as being 13.8-fold higher in transplant recipients than in the background population (7). When patients on hemodialysis were compared with transplanted patients, the risk of developing cancer was 10 times higher in the latter group (8,9). The progressive increase with time of observation is impressively illustrated by the Australian experience. In this high-risk setting of fair-skinned individuals with intense exposure to sunlight, the cumulative incidence of skin cancer, calculated by life-table analysis, increases progressively from 7% after 1 yr, to 45% after 11 yr, and 70% after 20 yr of immunosuppression (10). Among other factors, duration and intensity of immunosuppression emerged as a particularly powerful risk factor (10).

Incidence and type of cancer after renal transplantation vary between centers, countries, and time periods (11). Some of this variation is accounted for by the impact of competing causes of death. For instance, according to a report from the Glasgow transplant program, during the first 14 yr of the program (1969 to 1982), 40% of patient deaths were attributed to infection, 23% to cardiovascular disease, and 10% to malignancies. During the subsequent 14 yr, deaths resulting from infection decreased substantially, and the relative and absolute frequency of death from cardiovascular disease and malignancy increased concomitantly (9,11).

In single-center reports from Glasgow and Leiden, death due to malignancy was found in 15% and 14% of kidney graft recipients, respectively (9,12). In contrast, only 2.6% of renal allograft recipients in Japan were reported to have developed a malignancy between 1970 and 1995 (13).

Pathogenesis
Malignancy after transplantation can develop in three different ways:
• De novo occurrence in the recipient
• Recurrent malignancy in the recipient
• Transmission of malignancy from the donor

De Novo Occurrence of Malignancy in the Recipient
Immunosuppression and Malignant Transformation
In renal transplant recipients, the frequency of two types of malignancies stands out: skin cancer and lymphoproliferative disease. The spectrum for the latter ranges from benign PTLD to non-Hodgkin lymphoma (NHL). Evaluation of the literature on PTLD is complicated by the fact that reports commonly include cases with polyclonal proliferation as well as monoclonal lymphoproliferative disorders. According to the literature, malignancies of the lymphoproliferative system occur mostly within the first three yr after renal transplantation. The high overall risk of malignancy in heavily immunosuppressed patients is primarily due to the development of NHL. It has been claimed that the introduction of new and more potent immunosuppressive regimens is associated with an increased incidence of cancer after renal transplantation (14), but this
statement is not supported by solid epidemiologic evidence. There are conflicting reports on whether the introduction of cyclosporine was followed by a higher frequency of malignant tumors (15,16). It has also been reported that malignancies are more frequent in patients on triple drug regimens that include cyclosporine, azathioprine, and corticosteroids (17). There is little dispute that the development of lymphomas is particularly increased in patients receiving polyclonal or monoclonal antibodies for induction or rescue therapy. This is true for recipients of both renal and cardiac allografts (18). In an analysis of the United Network of Organ Sharing (UNOS), the risk of malignancy was particularly high in patients who received a combination of monoclonal antibodies, tacrolimus, and mycophenolate mofetil. In patients receiving this immunosuppressive regimen the overall risk of any type of cancer compared with the matched background population was increased by a factor of 5.11, and the risk of PTLD (with the above reservations) was higher by a factor of 27.2 (19).

The hypothesis that the action of immunosuppressive drugs is responsible for the increased incidence of tumors in transplant recipients is supported by the observation that patients also develop tumors if they receive immunosuppressive therapy for conditions other than transplantation, e.g., rheumatoid arthritis, systemic lupus erythematoses (SLE), or dermatomyositis. An increased frequency of lymphoproliferative disease in these patients has been attributed to the administration of immunosuppressive agents, such as methotrexate, cyclosporine, or azathioprine (20–22).

A relationship between the intensity of immunosuppression and an increased incidence of tumors has been shown most convincingly for skin cancer. The established risk factors for basal cell and squamous cell cancer, such as exposure to sunlight, are also operative in transplanted individuals (23). Yet duration and intensity of immunosuppression emerged as an additional risk factor (24,25). A predisposition to squamous cell carcinoma may also be related to the increased prevalence of human papilloma virus (HPV) in transplant patients. Presumably because of immunosuppression, it is found in almost 90% of allograft recipients (26). Viral proteins E6 and E7 of HPV inhibit the tumor suppressor gene p53 and are thought to be involved in the induction of carcinoma in this high-risk population. In addition, exposure of the skin to ultraviolet radiation causes DNA mutations by formation of thymidine dimers, leading to inactivation of the tumor suppressor gene p53. Malignant proliferation is thought to be a result of the failure to repair such mutations.

The relationship between tumorigenesis and immunosuppression is not fully understood. The following points are of interest with respect to the pathogenesis of posttransplant malignancies. Natural killer cells play an important role in the host’s defense against malignancy (27). Depletion of natural killer cells (NK-1.1) in mice increased the implantation and growth of B16 melanoma cells or CT 38 colon carcinoma cells (28). After injecting colonic carcinoma cells into the superior mesenteric vein of syngenic mice, injection of natural killer cells together with interferon-γ reduced the tumor cell burden in the liver (29). The administration of anti-T cell antibodies, e.g., anti-Thy 1.2 or anti-asialo GM-1, was associated with increased tumor colonization (30). However, this was not true for all immunomodulatory antibodies. For instance, anti-CD4 monoclonal antibody (keliXimab) did not interfere with the immune response against malignant cells in mice (30). The recently introduced immunosuppressive agent rapamycin (Sirolimus) is believed to combine immunosuppressive action with antitumor effects (31).

These clinical and experimental observations are compatible with the notion that the increased frequency of malignancies in allograft recipients results mainly from immunosuppression. But this simple concept does not explain that the excess tumor incidence in kidney recipients is restricted to certain malignancies, such as skin tumors and lymphoma. It would therefore appear that immunosuppression alone is not sufficient for tumor development: additional risk factors, such as the patient’s genetic background, viral co-infection, or sun exposure apparently play also a role (Table 1).

### Conventional Risk Factors

Commonly known risk factors such as advanced age, cigarette smoking (32), and analgesic abuse (33) are risk factors for posttransplant malignancies as well. For instance, in patients with a history of phenacetin abuse, the risk of developing uroepithelial carcinoma is strikingly increased (34). This observation even led to the postulate that nephroureterectomy should be performed before transplantation.

### Genetic Factors

Genetic factors are known to predispose to the development of malignancies, and this appears to apply also to transplanted patients. According to one study, patients who had an invasive

<table>
<thead>
<tr>
<th>Table 1. Malignancies after renal transplantation—risk factors</th>
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<tbody>
<tr>
<td>Imunosuppression</td>
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<tr>
<td>Conventional risk factors, i.e., age, smoking</td>
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<tr>
<td>Chronic viral infection</td>
</tr>
<tr>
<td>Genetic risk factors</td>
</tr>
<tr>
<td>History of treatment with cytotoxic agents, i.e., cyclophosphamide</td>
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</table>
carcinoma before transplantation had a much higher risk (RR 2.38) of developing a second invasive carcinoma de novo after transplantation (32). Some rare primary renal diseases (particularly von Hippel-Lindau disease) are associated with an intrinsically higher risk of developing renal cell carcinoma with an aggressive clinical course. When such patients receive a renal allograft, the frequency of renal cell carcinoma increases further (35). The risk of carcinoma is also markedly increased in patients with Wiskott-Aldrich syndrome or Drash syndrome. In transplant recipients with these rare syndromes, an excessive frequency of lymphoma and Wilms’ tumor was noted (36,37).

The hypothesis that genetic predisposition plays a role in the genesis of posttransplant malignancies is also supported by the observation that patients with malignancies after transplantation often have more than one type of tumor. Patients with as many as three different types of tumor have been reported (38). In patients with two malignancies, the most common secondary malignancy is a skin tumor. In a retrospective study by London et al. (39), skin tumors were found in 10 of 70 renal allograft recipients who had other types of malignancies.

### Chronic Viral Infections

Certain viral infections predispose transplant recipients to specific types of malignancies (Table 2). Epstein-Barr virus (EBV) is frequently associated with lymphoma, and human herpes virus 8 (HHV 8) is frequently associated with Kaposi sarcoma (40). NHL results from abnormal lymphoid cell proliferation after aggressive or prolonged immunosuppression. Some 98% of cases with PTLD are associated with latent EBV infection. EBV is a herpes virus that infects most adults and establishes an asymptomatic B cell infection via T cell–mediated suppression of viral growth (41). T-cell surveillance is impaired by cyclosporine, and it is even more disturbed by antibodies directed against T cells, e.g. OKT3 or ATG. In vitro studies showed that coinubcation of EBV-infected B cells with OKT3 or ATG resulted in increased B cell proliferation and immortalization (42). Such a mechanism is also likely to play a role in vivo. Schmidtko et al. (42) described EBV-associated PTLD after renal transplantation in primates, and this was particularly prominent in animals receiving an aggressive immunosuppressive conditioning regimen. The animal data are in good agreement with a large multicenter study of transplanted patients in which a higher rate of NHL was found in patients after the administration of antilymphocyte antibodies (18). Cathomas et al. (42) reported an association of Kaposi sarcoma with HHV 8 infection in a series of 18 renal transplant recipients. It is of note that almost all of these patients had received monoclonal or polyclonal antibodies as induction or rescue therapy for steroid-resistant rejection (43).

### Table 2. Viruses related to malignancies after transplantation

<table>
<thead>
<tr>
<th>Virus</th>
<th>Malignancy</th>
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<tbody>
<tr>
<td>EBV</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>HHV 8</td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>Human papillomaviruses (HPV)</td>
<td>Cervix cancer</td>
</tr>
<tr>
<td>HPV 58</td>
<td>Bowen disease</td>
</tr>
<tr>
<td>HPV 8, 19</td>
<td>Nonmelanoma skin cancer</td>
</tr>
<tr>
<td>HPV 16, 20</td>
<td>Skin and tonsillar carcinoma</td>
</tr>
<tr>
<td>HCV, HBV</td>
<td>Hepatocellular carcinoma</td>
</tr>
</tbody>
</table>

*a EBV, Epstein-Barr virus; HHV 8, human herpesvirus type 8; HCV, hepatitis-C virus; HBV, hepatitis-B virus.

Various types of papilloma virus are associated with skin, cervix, penis, or anogenital carcinomas (44).

Polyoma virus, which has recently attracted considerable clinical attention, is a double-stranded DNA virus that induces acute interstitial nephritis in renal transplant recipients (45). It causes not only acute renal dysfunction, but is also tumorigenic by transforming cells mainly by the action of the middle T antigen (46,47).

At this point, some comments on the mechanism of virus-induced tumor formation may be appropriate. For any virus to induce uncontrolled cell proliferation in vivo, at least 3 processes must take place (48,49):

1. The virus must uncouple the mechanisms controlling progression of the cell cycle and cell division.
2. The virus must prevent the host cell from undergoing apoptosis.
3. The proliferating cell, bearing viral-derived antigens on its surface, must escape the attention of the host immune system.

Of particular interest is the escape from apoptosis, which is a requirement for sustained growth after transformation of the host cell by oncogenic viruses. A class of proteins, FLIPs (FADD-Like Interleukin 1B converting enzyme-like protease Inhibited Proteins), interfere with the initiation of apoptosis at the level of death receptors (50). Some FLIPs are encoded by class γ herpes viruses, e.g., herpes virus Saimiri (HVS) or HHV 8. So-called viral FLIPs (vFLIPs) inhibit apoptosis through several apoptosis-reducing receptors (CD95, TNF-R1, TRAMP/DR3, and TRAIL-R1) that presumably share common signaling pathways (51). All viruses encoding vFLIPs can transform cells in vitro and are associated with tumors in susceptible hosts. HVS causes lymphoma and leukemia in susceptible primates and induces stable growth transformation of human T cells in vitro. HHV 8 is associated with Kaposi sarcoma and multicentric Castleman disease.

Another important pathway for virus-induced malignancy is interference with the p53 tumor suppressor gene (52). P53 induces cell cycle arrest or apoptosis in response to DNA damage. Small DNA viruses use distinct mechanisms to counter p53. They either bind directly to p53 and inhibit p53-mediated transcriptional activation, or they promote the degradation of p53 via the ubiquitin pathway.

### Geographical Differences

A survey of the literature shows that the relative frequency of malignancy after renal transplantation varies widely between different geographical regions. In Japan, tumors of di-
gestive organs (50%)—liver, stomach, colon, rectum—are the most frequently observed posttransplant tumors, in good agreement with the generally high prevalence of GI cancers in this country. In contrast, the frequency of skin cancer and lymphoma is low in Japan (13). In the United Kingdom, the most frequent posttransplant malignancies are lymphoma, renal cell carcinoma, carcinoma of the digestive system, and bronchial carcinoma (39). In Saudi Arabia, the most frequent malignancies are Kaposi sarcoma, lymphoma (particularly in children), skin malignancy (with melanoma being more frequent in children than in adults), and anogenital cancers (53). In Australia, the risk of developing posttransplant skin cancer, particularly spinocellular carcinoma, is extremely high. The most favored explanation for this unique Australian experience is that a fair-skinned Caucasian population is exposed to excessive ultraviolet light (54). In South East Asia, where hepatitis B and C infections are endemic, the frequency of liver cancer after transplantation is high (55).

Transmission of Malignancy from the Donor

Transmission of a tumor via (micro)metastases of an undiagnosed malignancy in the donor is rare, but this possibility must also be considered in the differential diagnosis of malignancy after transplantation. According to data from the Organ Procurement and Transplantation Network/UNOS, a total of 21 donor-related malignancies was reported in 108,062 transplant recipients (56). Fifteen tumors were donor-transmitted (malignancies that existed in the donor at the time of transplantation), and six tumors were donor-derived (de novo tumors that develop in transplanted hematogenous or lymphoid cells of the donor). Donor-derived tumors have been reported in allografts obtained from donors with bronchial carcinoma, breast cancer, and malignant melanoma (6,57). In some patients, cessation of immunosuppression led to rejection of the donor-derived malignancy without further therapy. In most patients, however, specific anti-tumor therapy was necessary, i.e. surgery, chemotherapy, radiation, to induce remission.

Management of the Allograft Recipient with a Preexisting Malignancy

When a patient is considered for the transplant waiting list, the question arises whether a history of malignant disease is a contraindication to renal transplantation. One retrospective analysis comprised 913 renal allograft recipients with a total of 939 preexisting cancers (58), illustrating that more often than not the nephrologist must deal with this problem in today’s aging dialysis population. There is consensus that a 2-yr waiting period should be interposed between the successful treatment of cancer and transplantation. A waiting period is not required for the following tumors: incidentally discovered renal cell carcinoma, any type of in situ carcinoma, and basal cell carcinoma of the skin. Because of a high likelihood of recurrence even beyond the second year after treatment, a waiting period of more than 2 yr is advisable in patients with a history of malignant melanoma, breast cancer, and colorectal carcinoma. The issue of recurrence was addressed in a retrospective study of 1297 renal allograft recipients with a history of malignancy (59). For tumors diagnosed and treated before transplantation, the frequency of recurrence after transplantation was 21%. For tumors diagnosed and treated after transplantation the respective figure was 33%. Among tumors diagnosed and treated before transplantation, the frequency of recurrence after transplantation was highest for breast cancer, symptomatic renal cell cancer, sarcoma, bladder cancer, and multiple myeloma (59).

Management of the Allograft Recipient with De Novo Malignancy after Transplantation

When a patient develops a malignancy de novo after renal transplantation, the question arises whether it is useful to reduce or stop immunosuppression. The underlying idea is that this move might allow rejection of the malignancy by the recipient’s recovering immune system. If immunosuppression is stopped, particularly early after transplantation, graft monitoring at short intervals is necessary; otherwise fulminant rejection may be discovered too late, with the potential consequence of graft rupture. Removal of the graft is often advisable.

Successful reduction or cessation of immunosuppression was reported in transplanted patients who developed NHL and Kaposi sarcoma (60). Despite this the rate of death remained high in patients with posttransplant lymphoma. Therapeutic strategies targeting B cells (61), including local or systemic administration of specific anti-CD20-, anti-CD21-, and anti-CD20- (rituximab) B cell antibodies, were successful with a follow-up of several months (62,63). There are also reports of successful antiviral treatment with acyclovir, valacyclovir, or ganciclovir in EBV-induced lymphoproliferative disease (64). In patients who do not respond to these therapies or in severe disease, a treatment regimen including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is recommended (65).

Transplant recipients with premalignant skin lesions should be referred to a dermatologist for active treatment and close follow-up. Skin cancers should be completely removed. Secondary prevention includes the use of topical or systemic retinoids in patients with actinic keratoses and squamous-cell carcinoma and reduction of immunosuppression when possible.

Posttransplant Kaposi sarcoma is particularly interesting because it is the tumor with the highest relative risk compared with the background population (53). The clinical course is often aggressive, with a mortality rate of 34% within 3 yr of diagnosis. Involvement of visceral organs is an indicator of severe disease. Aggressive forms of gastrointestinal involvement may be diagnosed during endoscopy. Reduction of immunosuppression leads to complete remission in 30% of the patients. Localized lesions may be treated surgically or by local radiation (66).

Immunotherapy of melanoma (67), colorectal cancer (68), and renal cell carcinoma (69) is currently under investigation in nontransplant patients. Whether these treatment modalities will be useful in organ transplantation awaits further studies.
Table 3. Protocol for screening of patients after transplantation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>History and physical examination</td>
<td>to exclude disseminated or localized organ involvement by PTLD (every 3 mo during the first year after transplantation, subsequently at yearly intervals)</td>
</tr>
<tr>
<td>Skin examination by dermatologist</td>
<td>(every 6 mo in high-risk patients, otherwise yearly)</td>
</tr>
<tr>
<td>Ultrasonography or CT scan of the native kidney</td>
<td>(at yearly intervals)</td>
</tr>
<tr>
<td>Gynecologic examination, including PAP smear</td>
<td>(and ultrasonography of female reproductive organs (at yearly intervals)</td>
</tr>
<tr>
<td></td>
<td>In selected cases</td>
</tr>
<tr>
<td>PSA and digital rectal examination</td>
<td>(male &gt; 50 yr, at yearly intervals)</td>
</tr>
<tr>
<td>Fecal occult blood testing</td>
<td>(age &gt; 50 yr, at yearly intervals)</td>
</tr>
<tr>
<td>Abdominal ultrasound and serum alpha-fetoprotein levels</td>
<td>(in carriers of hepatitis B or C virus)</td>
</tr>
<tr>
<td>Cystoscopy (de novo)</td>
<td>(when history of cyclophosphamide treatment)</td>
</tr>
</tbody>
</table>

* According to Kasiske et al. (75) and others.

Screening of the Allograft Recipient for Malignancy

Regular tumor screening is advisable when a patient is considered for renal transplantation and especially after transplantation (Table 3) (75). The rising age of patients on the waiting list in conjunction with the increasing length of time patients spend on the waiting list enhances the risk that malignancy will escape detection so that recipients with preexisting tumors will receive transplants.

History and physical examination, with attention to symptoms suggesting organ involvement by PTLD, should be performed every 3 mo during the first year after transplantation and at least yearly thereafter.

Screening to detect skin tumors is most important. Periodic inspection of the entire skin, with emphasis on sun-exposed areas, by a dermatologist is mandatory (at least at yearly intervals). In high-risk patients (e.g., those who have previously been diagnosed with squamous cell carcinoma), more frequent controls are indicated (at least every 6 mo). Primary prevention of skin cancers includes avoidance of sun exposure, use of protective clothing, and use of effective sunscreen by the patient, according to the European Best Practice Guidelines (70). Compliance is a universal problem. According to a study from Leeds, only 54% of patients remembered that they had received any advice concerning cancer prevention, and only 30% of patients knew why extra precautions against sunlight were necessary (71).

Yearly gynecologic examinations are mandatory to exclude vulvar, perineal, and uterine malignancies. In women without hysterectomy, transvaginal ultrasonography is recommended.

Multicystic transformation of contracted kidneys in patients with primary renal disease is a precancerous condition. Ultrasonographic examination of the recipient’s kidney should be performed at least at yearly intervals. Urologic examination is indicated in patients with a history of analgesic nephropathy who develop microhemia. Another high-risk group includes those patients who received cyclophosphamide for treatment of vasculitis, especially in those patients where the cumulative dose exceeds 20 g (72). Some authors also recommend urologic examination in patients who have been treated with azathioprine for more than 10 yr (73).

Periodic screening of feces for occult blood is advisable because colonic carcinoma is more frequent after renal transplantation. Patients with a history of ureterosigmoidostomy should undergo colonoscopy at least 10 yr after renal transplantation because of the risk of late colonic carcinoma (74).

For other solid organ cancers (prostate, breast), guidelines published for screening and prevention of solid organ cancers in the general population should be strictly applied to transplant recipients.

Outlook

Early diagnosis and treatment of posttransplant malignancies is an important challenge in transplantation medicine. An even greater challenge is the prevention of malignancies. Documentation of tumors arising de novo after transplantation as well as elucidation of their relationship with particular immunosuppressive treatment regimens is a first step in this direction.

This overview attempted to summarize the available evidence in this area. As even more potent immunosuppressive drugs enter the transplant field, it will be important to monitor their tumor-inducing potential. Reduction of life-threatening infection had been a goal in the past decades. In the future, the reduction of posttransplant malignancies must be another target in the effort to improve immunosuppression in graft recipients.

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References


