REVIEW ARTICLE

Skin Changes Following Organ Transplantation

An Interdisciplinary Challenge

Claas Ulrich, Renate Arnold, Ulrich Frei, Roland Hetzer, Peter Neuhaus, Eggert Stockfleth

SUMMARY

Background: The immunosuppressants used in transplantation medicine significantly elevate the incidence of neoplasia, particularly in the skin. The cumulative incidence of non-melanocytic skin cancer (NMSC) in renal transplant recipients was 20.5% in a study carried out in German centers. Data on more than 35 000 renal transplant recipients in the USA document a cumulative NMSC incidence of over 7% after 3 years of immunosuppression.

Methods: The authors selectively review publications obtained by a PubMed search to discuss the incidence of, and major risk factors for, skin tumors and infectious diseases of the skin in immunosuppressed patients.

Results: The main risk factors for skin tumors are age at the time of transplantation, light skin color, previous and present exposure to sunlight, and the type and duration of immunosuppressive treatment. Squamous-cell carcinoma (SCC) is the most common kind of skin tumor in immunosuppressed patients. Human herpesvirus 8 and Merkel-cell polyoma virus also cause neoplasia more often in immunosuppressed patients than in the general population. Surgical excision is the treatment of choice. Actinic keratosis markedly elevates the risk that SCC will arise in the same skin area (odds ratio 18.36, 95% confidence interval 3.03–111). Patients with multiple actinic keratoses can be treated with photodynamic therapy or with acitretin. To lower the skin cancer risk, organ transplant recipients should apply medical screening agents with a sun protection factor of at least 50 to exposed skin areas every day. 55% to 97% of organ transplant recipients have skin infections; these are treated according to their respective types.

Conclusion: Squamous-cell carcinoma of the skin adds to the morbidity and mortality of transplant recipients and is therefore among the major oncological challenges in this patient group. Structured concepts for interdisciplinary care enable risk-adapted treatment.

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Outpatient Clinic for the Follow-up Care of Immunosuppressed Patients, Skin Tumor Center, Charité – Universitätsmedizin Berlin: Dr. med. Ulrich

Department of Hematology, Oncology, and Tumor Immunology Charité – Universitätsmedizin Berlin, Campus Virchow Klinikum: Prof. Dr. med. Arnold

Medical Director, Charité – Universitätsmedizin Berlin: Prof. Dr. med. Frei

Department of Cardiac, Cardiothoracic and Vascular Surgery, German Heart Institute Berlin: Prof. Dr. med. Dr. h.c. mult. Hetzer

Department of General, Visceral, and Transplant Surgery, Charité – Universitätsmedizin Berlin, Campus Virchow Klinikum: Prof. Dr. med. Neuhaus

Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin: Prof. Dr. med. Stockfleth

Cancer and infectious diseases arising as complications of treatment are now a major challenge in the interdisciplinary care of organ transplant recipients (1, e1–e4). The skin, with a surface area of roughly 2 m^2, is the body's largest interface with the outside world. Continuous immune surveillance enables it to maintain long-term control of extensive skin infections and even of certain types of skin cancer. Indeed, modern transplantation medicine only became possible when immunological research on the skin of burned patients by the British scientist (and, ultimately, Nobel laureate) Peter Medawar led to fundamental discoveries on the nature of tissue rejection. The development of ever more effective immunosuppressant drugs was a major reason why survival times after renal transplantation nearly doubled over the period 1988–1996, with a prolongation from 7.9 to 13.8 years after cadaveric transplants, and from 16.9 to 35.9 years after living-donor transplants (figures from the USA) (2). The long-term survival of persons taking drugs that inhibit cellular immune surveillance has created new, challenging problems in dermatology, with a higher incidence of skin infections (55–97%) (2) and of skin cancer as well (3, e3).

In this review article, we present the epidemiology, pathophysiology, clinical features, and treatment of the skin diseases that most commonly afflict transplant recipients. We consider data from national patient registries in the USA and Australia and the pathophysiologically relevant risk factors that they reveal (1, 2, 4, 5). We selectively review publications obtained by a search in the PubMed database with various combinations of key words ("skin cancer" AND "organ transplant," "infections" AND "organ transplant"). We also summarize the algorithms and treatments developed in 10 years of experience in the interdisciplinary care of transplant recipients at the Charité Hospital and the German Heart Center in Berlin.

The epidemiology and incidence of skin cancer

In the absence of nationwide tumor databases, the incidence of malignant skin tumors in organ transplant recipients in Germany can only be estimated on the basis of data from local centers. The transplantation medicine team at a major university hospital in Munich (Großhadern) reported a 20.5% cumulative incidence of non-melanocytic skin cancer among 2419 patients who received a transplant in the period 1978–2005, corresponding to a 52.7-fold elevation of the relative risk (95% confidence interval [CI]: 44.79–61.76) (5). An

analysis of health insurance data from more than 35 000 renal transplant recipients in the USA showed that the cumulative incidence of non-melanocytic skin cancer after 3 years of immunosuppression was above 7%, corresponding to a 20-fold elevation of the skin cancer risk compared to the immunocompetent general population (1). In an Australian cohort study of cancer-related mortality after hepatic, renal, and cardiac transplantation, non-melanocytic skin cancer took first place, as it was found to elevate the standardized mortality rate (SMR) to 49.6 (95% CI: 31.5–74.5) (6).

It is characteristic that non-melanocytic skin cancers such as basal-cell carcinoma (BCC) and invasive squamous-cell carcinoma (SCC), along with actinic keratosis (AK), the in situ precursor of SCC, rise in incidence among transplant recipients to a far greater degree than other cancers do (5). It remains unclear why epithelial skin cancers appear to be the main beneficiaries of immune suppression. Moreover, the incidence ratio of SCC to BCC among transplant recipients is about 4:1, while BCC predominates in immunocompetent persons (7). The magnitude of this shift in the incidence ratio toward invasive SCC has been found to correlate with the dose of immunosuppression among transplant recipients (heart > kidney > liver) and with its duration, as well as with the amount of cumulative UV exposure that they receive (southern Europe > northern Europe) (8).

Multiple verrucous skin changes are a clinical warning sign of a markedly increased risk for SCC. A European multicenter study revealed a highly significant association between verrucous keratoses and SCC arising in the same skin area (odds ratio [OR] 18.36, 95% CI 3.03–111) (9).

Aside from SCC, two further tumor types that are clearly associated with viruses arise more frequently in immunosuppressed transplant recipients. Iatrogenic Kaposi's sarcoma, associated with human herpesvirus 8 (HHV-8), arises with a latency of 2 to 5 years; its incidence in immunosuppressed transplant recipients is 84 times higher than that of classic Kaposi's sarcoma in immunocompetent persons from the same geographic region (7, e1). Merkel-cell carcinoma, which is associated with oncogenic Merkel-cell polyomavirus, is also more common in immunosuppressed patients (9, e1, e2).

Although immunosuppressed persons often develop a greater number of melanocytic nevi, the incidence of malignant melanoma among transplant recipients is only relatively mildly increased, by a factor of 3 to 4 (10). Primary cutaneous lymphomas, such as B- or T-cell lymphoma, are rare, as are angiosarcoma, leiomyosarcoma, and atypical fibroxanthoma. More precise data on the incidence of these entities are not available (11).

The management of skin tumors in transplant recipients

Among all the types of skin tumor that can arise after organ transplantation, squamous cell carcinoma is of special importance (1, 6, 7). Not only does immunosuppression disproportionately increase the incidence of SCC, it also makes these tumors more aggressive. They grow more rapidly, are more likely to metastasize, and tend to infiltrate blood vessel walls and to invade perineurial sheaths (e1). Furthermore, in immunosuppressed patients, SCC tends to arise multifocally in skin areas that are exposed to sunlight *(Figure 1)* (e2). With very few exceptions, all invasive skin tumors in transplant recipients must be surgically excised. For particularly aggressive ones, sentinel lymph node biopsy is indicated as well (12).

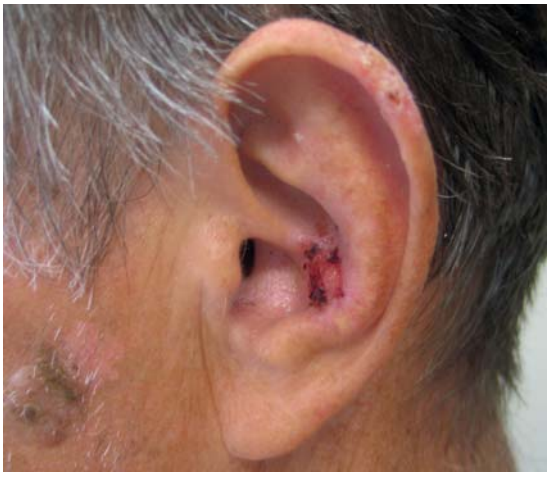


Figure 1
Multiple actinic keratoses and squamous cell carcinomas in an organ transplant recipient

Alongside the reactive strategy of excising invasive SCC, it is also very important proactively to eradicate preinvasive SCC in the form of actinic keratoses (AK). The latter progress to invasive SCC in only about 10% of immunocompetent hosts, but in more than 30% of transplant recipients (7). Typically, AK develop on skin areas that are chronically exposed to light, such as the forehead, the ears, the bald scalp, and the forearm, in what is called cutaneous carcinomatosis.

Nonspecific destructive methods, such as cryosurgery with liquid nitrogen, are suitable for isolated AK; for multiple AK, modern topical treatments are available (13, e5) *(Table 1)*. There have been only a few controlled clinical trials to date of topical therapy for actinic keratosis in transplant recipients (e6–e16). Photodynamic therapy (PDT) is by far the most extensively studied treatment with respect to efficacy and safety (e8–e16). In one randomized controlled trial (RCT), PDT brought about a complete remission in 13 of 17 patients and a partial remission in a further 3, while no patient in the placebo group experienced any improvement of AK during the 16-week period of observation (e12). In an American trial of cyclically repeated application of PDT for 12 transplant recipients who had already had multiple prior SCCs, the incidence of new SCC during two years of PDT treatment was 95% lower than in the period before the study (e13).

Many alternative treatments would theoretically be suitable for AK in transplant recipients but have not been approved for this purpose.

Patients with severe AK or multiple SCCs are treated with systemic retinoids. Renal transplant recipients treated

TABLE 1

The management of non-melanocytic skin tumors in organ transplant recipients

Aktinic keratoses (AK)	Treatment	Squamous cell carcinoma	Treatment	Basal cell carcinoma (BCC)	Treatment
Mild (<5 AK)	– sunlight protection – lesion-adapted treatment of individual lesions (cryotherapy, laser, curettage) – potential combination with topical treatment	**clinically not aggressive:** – small lesions – slow growth – well-demarcated edges – not ulcerated	– sunlight protection – treatment of cutaneous carcinosis (AK) – micrographically guided excision – modification of immunosuppression	**superficial BCC**	– sunlight protection – excision (with histological confirmation of margins) – PDT if indicated
Moderate (<10 AK/100 cm^2)	**as above, and:** – topical PDT treatment – diclofenac in hyaluronic acid gel (for small areas) – potential modification of immunosuppression	**clinically aggressive growth:** – extensive lesions – rapid growth – poorly demarcated edges – ulceration	**as above, and:** – potential sentinel lymph node biopsy – systemic retinoids, if indicated	**nodular and other BCC**	– as above – potential modification of immunosuppression
Severe (>10 AK/100 cm^2)	**as above, and:** – modification of immunosuppression – systemic retinoids, if indicated	**histologically aggressive growth:** – poorly differentiated – invasion of subcutaneous fat – perineurial invasion	**as above, and:** – potential sentinel lymph node biopsy – systemic retinoids		

AK, actinic keratosis; BCC,basal cell carcinoma; PDT, photodynamic therapy

with acitretin 30 mg/d for 6 months had a significantly lower incidence of de novo SCC. Two of 19 patients in the acitretin group (11%) and 9 of 19 in the control group (47%) developed SCC (p = 0.1) (14). Effective long-term treatment of skin tumors in organ transplant recipients usually consists of an individually tailored combination of different treatment methods *(Table 1)*. Basal cell carcinoma, the most common kind of skin cancer in immunocompetent persons, is 10 times more common among transplant recipients, but this is still a much smaller increase than that of SCC (13). Unlike SCC, BCC developing under immunosuppression is generally no more aggressive than in immunocompetent persons and should be treated surgically (15).

Risk factors for skin cancer in organ transplant recipients

The following risk factors for the appearance of actinic keratoses, squamous cell carcinoma, and basal cell carcinoma under immunosuppression are of central importance:

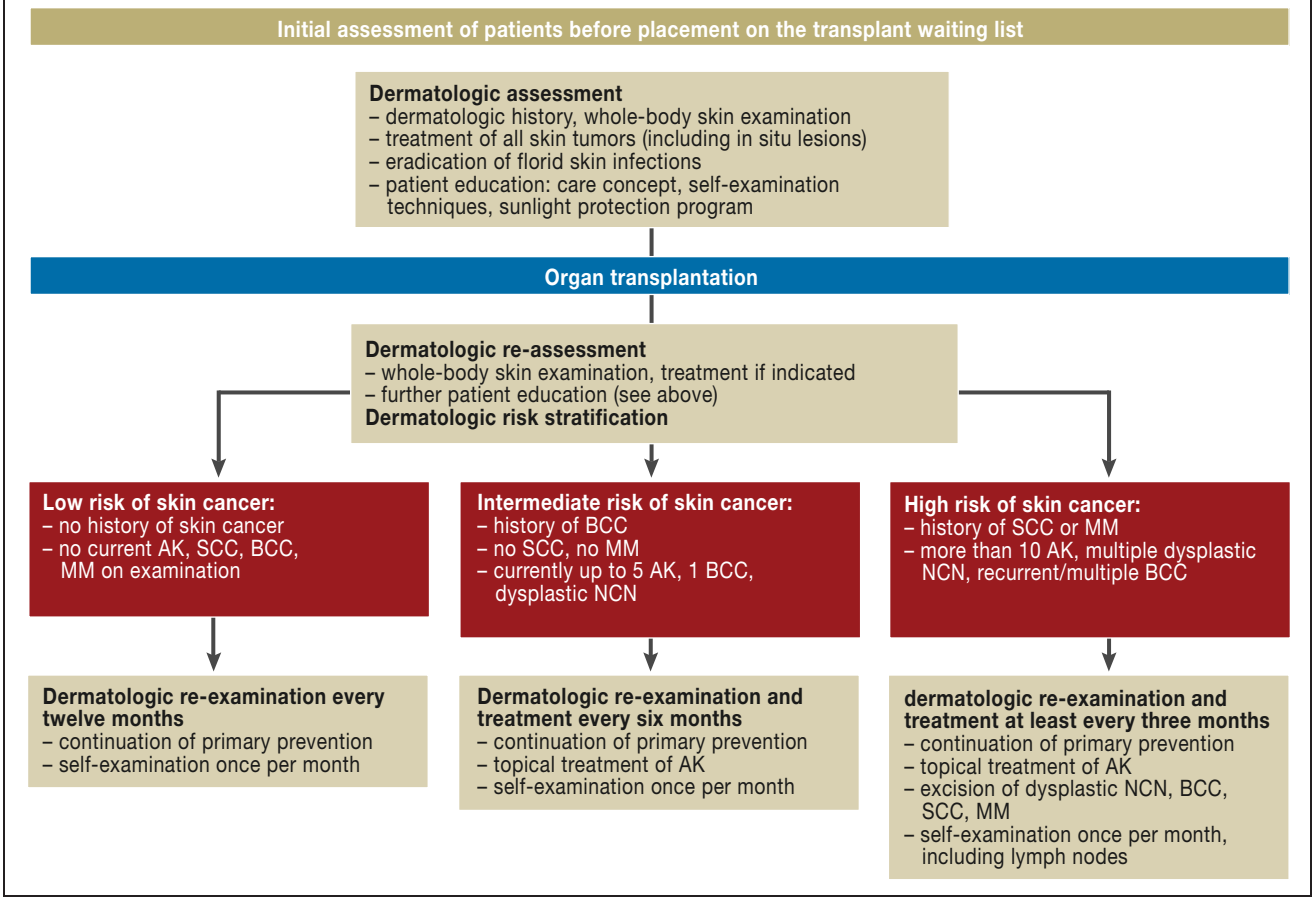
- UV radiation, including both present and past occupational and leisure-time exposure (cumulative exposure to sunlight), in association with individual susceptibility (light skin);
- immunosuppression, depending on the drug used and its duration and dosage.

Risk-factor modification—protecting the patient from sunlight and individualized selection and dosing of immunosuppressive drugs—is the mainstay of the primary prevention of skin tumors and other skin diseases in organ transplant recipients.

Ultraviolet (UV) light exposure

The fact that more than 90% of skin tumors in organ transplant recipients arise in skin areas exposed to UV light points to the key role of UV radiation as the main carcinogen among immunosuppressed persons, just as in the general population (16). UV radiation exerts a direct mutagenic effect on the DNA of keratinocyte stem cells as well as an indirect tumor-promoting effect by additionally weakening cutaneous and systemic immune surveillance (17). An Australian study demonstrated the protective effect of sunscreen against AK, SCC, and malignant melanoma, and the daily application of sunscreen is now a standard recommendation for immunosuppressed persons (17–20, e17–e20). Additional support for this practice comes from the findings of a case-control study of 120 organ transplant recipients whom the authors have followed as outpatients: 60 recipients of liver, kidney, and heart transplants (20 of each) used a medical screening agent with a sun protection factor (SPF) of at least 50 for 24 months. Persons in a control group matched for age, type of transplant, and time since transplantation were given only the standard advice about sun protection and were told to use commercially available sunscreens of their own choice. Persons in the sun protection group had a partial remission of actinic keratoses (−120 lesions vs. +82 in the control group, $p<0.01$) and less commonly developed SCC [0 vs. 8, $p<0.01$]) and BCC (2 vs. 9, not statistically significant) (18). The typical commercially available sunscreens used in most studies were generally underdosed below the concentration of 2 mg/cm^2 for which the reported SPF is applicable; when sunscreens are used to prevent skin cancer, their use in the proper dosage

FIGURE 2



Dermatologic evaluation and continuing care concept for organ transplant recipients

AK, actinic keratosis; BCC, basal cell carcinoma; MM, malignant melanoma; NCN, nevus-cell nevus; SCC, squamous-cell carcinoma

should be assured by the provision of instructions on proper use as well as dosing dispensers and instructions on how to use them. It seems inexplicable that the statutory health insurance carriers in Germany have declined until now to reimburse effective, medically advised protection against ultraviolet light in this high-risk patient group, except for rare, individual cases.

Immunosuppression

One of the main contributions of transplantation medicine to the prevention of long-term complications of chronic immunosuppression, including skin tumors, has been the ongoing readjustment of immunosuppressant doses to the lowest possible maintenance dose for the individual patient. A trial of high- versus low-dose cyclosporine in organ transplant recipients resulted in a lower incidence of tumors in the low-dose group over 66 months of follow-up (19% vs. 32%, $p<0.034$) (19).

Some immunosuppressant drugs can themselves directly induce skin tumors. It has been shown in cell culture, for example, that azathioprine (Aza), through its metabolite 6-thioguanine, specifically sensitizes keratinocyte DNA to long-wave UVA radiation, while also inducing T-dimers in the affected skin cells by way of oxygen radicals (20). Moreover, clinical studies have shown that Aza is associated with the appearance of multiple SCCs as well as of warts. Therefore, from the dermatological point of view, Aza should be replaced in modern immunosuppressive protocols by mycophenolic acid drugs or mTOR inhibitors (mTORi) (21). It should be pointed out explicitly here that modern, less oncogenic immunosuppressants than Aza are not only recommended for de novo immunosuppression; there is also a recommendation that Aza should be switched to one of these drugs even in patients who received their transplants long ago (22). On the other hand, combining cyclosporine A (CyA) with an mTOR inhibitor such as sirolimus or everolimus significantly lowers the incidence of skin tumors in comparison with CyA monotherapy (22% vs. 39%; mean latency of SCC, 15 vs. 7 months; $p = 0.02$) (23). Multiple retrospective and prospective studies have shown that the mTOR inhibitors, through their antiproliferative effect on tumor cells and their inhibitory effect on tumor angiogenesis, significantly lower the incidence of both AK ($p<0.0001$) and SCC ($p = 0.0176$) . The mTOR inhibitors are particularly well known for the excellent results seen in

TABLE 2

Dermato-oncologic criteria for patient evaluation before transplantation

Skin tumor	Transplantation possible without special concern	Dermatologic assessment recommended	Criterion of exclusion for transplantation	Interval to dermatologic reassessment after diagnosis of skin cancer (if transplantation was not possible at first)
Basal cell carcinoma				
primary	X			5 years
metastatic, in remission			X	not applicable
metastatic, not in remission			X	
Squamous cell carcinoma				
primary, low risk	X			
primary, high risk*[1]		X		3 years
metastatic, in remission			X	3–5 years
metastatic, not in remission			X	not applicable
Melanoma				
stage 0*[2] (in situ)	X			
stage I*[2]		X		2–3 years
stage II*[2]			X	3–5 years
stage III*[2]			X	not applicable
stage IV*[2]			X	not applicable
Merkel- cell carcinoma				
primary		X		2–3 years
metastatic, in remission			X	3–5 years
metastatic, not in remission			X	not applicable
Kaposi's sarcoma		X		3 years
Dermatofibrosarcoma protuberans	X			
Rare malignant skin tumors*[3]		X		3 years

*[1] Criteria for high risk of metastasis of squamous cell carcinoma (e22): recurrence, deep invasion (>4–6mm), large size (diameter >2mm), perineurial invasion, poorly differentiated lesion (Broders 3 or 4), rapid growth, localization on the temple, scalp, ear, or lip, origin in scar tissue

*[2] American Joint Comittee on Cancer (AJCC) 2002

*[3] e.g., atypical fibroxanthoma, microcystic adnexal carcinoma, malignant hidradenoma, extramammary Paget's disease (33)

Kaposi's sarcoma, up to complete remission (e21), when the treatment is changed to include a drug of this type (23–25). In cases with very advanced metastatic disease, discontinuation of the immunosuppressive treatment is recommended, even for renal transplant recipients. This usually leads to loss of the transplant (26).

Skin infections in organ transplant recipients

55% to 97 % of organ transplant recipients suffer from skin infections (27). Attenuation of the T-cell-mediated immune response by immunosuppression favors not only the development of tumors (as discussed above), but also the invasion and dissemination of atypical, unusually severe clinical variants of skin infection. In immunosuppressed patients, infections with rare pathogens play a larger role in the differential diagnosis of skin infections (28).

Bacterial infections that arise in transplant patients resemble those of immunocompetent persons. Temporary increases in the steroid dose to treat rejection reactions, or in the early phase after transplantation, commonly give rise to acneiform folliculitis and pustules in the first few months of immunosuppression (29).

In addition to the common fungal infections of the nails and the soles of the feet that are also seen in immunocompetent persons, transplant patients often suffer from pityriasis versicolor—a harmless condition in itself—and mucocutaneous candidiasis (29). The latter most often arises in the first year after transplantation or after treatment for tissue rejection (28). Systemic mycoses are an important clinical complication of immunosuppression, and primary pulmonary infections with *Aspergillus spp*. or *Candida albicans* can have secondary dermatological manifestations (29). Skin eruptions can be a challenging problem in differential diagnosis; they range from maculopapular exanthems and single ulcerated plaques to painful erythematous nodules scattered all over the limbs and trunk. The examination of such cutaneous manifestations by an experienced dermatologist, in combination with

cytology and histology, enables the timely and specific diagnosis of many types of fungal pneumonia (29). Immunosuppressed patients are also characterized by the more common occurrence of otherwise rare mycoses, including infections wtih *Mucor spp.*, *Alternaria spp.*, and pheohyphomycetes, and even disseminated cryptococcosis (28). It should be borne in mind that drugs given systemically to combat dermatomycoses may interact with immunosuppressant drugs (28).

The main types of viral infections with cutaneous manifestations that are of particular importance for organ-transplant recipients are due to herpesviruses and human papillomaviruses (HPV). Among transplant patients who are not taking vala-/ganciclovir for cytomegalovirus (CMV) prophylaxis, reactivation of herpes simplex viruses (HSV) and varicella-zoster virus (VZV) occurs in 0–30% of patients within 6 months (29). Clinical episodes of HSV and VZV reactivation closely resemble those seen in immunocompetent persons if the transplantation took place long ago, but reactivations in the setting of high-dose immunosuppression—in the first few weeks after transplantation, or during treatment for rejection reactions—tend to produce larger, sometimes necrotizing lesions (28, 29). VZV or HSV infection, especially primary infection, may spread systemically to cause potentially fatal pneumonia, vasculitis, hepatitis, or encephalitis; this danger can be lessened by timely and appropriate virostatic treatment (29).

Common warts due to HPV are among the more frequent types of skin infection after renal transplantation, with a prevalence of 50% at one year and over 90% at five years (30). They are often multiple and tend to resist treatment and to recur. They can be treated with physical destruction (cryotherapy, laser, curettage), topical drugs (salicylic acid–5-FU ointment, cidofovir, imiquimod), or systemic drugs (retinoids, switch to an mTOR inhibitor) (31). In routine clinical practice, it is often advisable to use multiple types of treatment in combination. Note that many of the available treatments have a restricted approval status (31).

Patient guidance & care structures in Germany

Once transplantation medicine has accomplished its primary task of transplanting an organ and preventing rejection, the further management of transplant recipients becomes an interdisciplinary challenge, particularly with respect to the prevention and treatment of infectious diseases and cancer. A key element in the reduction of mortality from immunosuppression is the interdisciplinary diagnosis, prevention, and treatment of cancers arising after transplantation. A scheme for the continuing dermatological care of transplant recipients was initiated in 2002 at the Charité Hospital and the German Heart Center in Berlin *(Figure 2),* and, since then, analogous special outpatient clinics have been established at other German transplantation centers (32). Ideally, an individual dermatological risk profile and a plan for continuing care after transplantation should be established at the patient's initial visit to the dermatologist, before he or she is put on the transplant waiting list. As in the past, patients should continue to be educated about how to protect themselves from sunlight and about simple self-examination methods. Any florid cutaneous infections or pre-invasive skin tumors that are already present should be treated at this point and regularly rechecked until transplantation. For patients who have already had a skin tumor before transplantation, an aid to the critical assessment of the indication for transplantation has been developed *(Table 2)* (33).

The work of special dermatological outpatient clinics for organ transplant recipients in Germany is coordinated by the Committee for the Care of Immunosuppresssed Patients of the Dermatologic Oncology Working Group (Arbeitsgemeinschaft Dermatologische Onkologie, ADO). Analogously specialized care is provided in private dermatological practices with an emphasis on dermatologic oncology. An "interdisciplinary care passport" for organ transplant recipients will be introduced in 2014 to facilitate the documentation of interdisciplinary care.

Dedication
The authors dedicate this article to Prof. Dr. med. Wolfram Sterry on the occasion of his becoming Professor Emeritus.

Conflict of interest statement
Dr. Ulrich has received payment for serving on Advisory Boards for the Calderma, Novartis, Pfizer, and Meda companies, reimbursement of scientific meeting participation fees and travel costs from Pfizer, and research support (third-party funding) from Calderma and Wyeth.

Prof. Stockfleth has beem paid for serving on Advisory Boards for the Meda, Spirig, and Almirall companies,

Prof. Arnold, Prof. Frei, Prof. Hetzer, and Prof. Neuhaus state that they have no conflicts of interest.

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KEY MESSAGES

- The high rate of cutaneous complications in the ever-larger group of patients treated with chronic immunosuppression implies a pressing need for interdisciplinary follow-up care, with the participation of specialized dermatologists.
- Skin tumors, particularly squamous cell carcinoma, are of special oncological relevance because of their more aggressive behavior, multifocal appearance, and relatively high lethality.
- Proactive prevention (i.e., use of suncreens, individually adapted immunosuppressant medication) and the timely treatment of actinic keratoses can significantly lower the risk of squamous cell carcinoma in organ transplant recipients.
- 55% to 97% of organ transplant recipients have skin infections. Under immunosuppressive treatment, these can be atypical and unusually severe. Infections caused by rare pathogens must be considered in the differential diagnosis.

Further information can be found at the following Internet addresses:

– Committee for the Care of Immunosuppressed Patients of the Dermatologic Oncology Working Group: www.ado-homepage.de

– German Transplantation Society (Deutsche Transplantationsgesellschaft e.V., DTG): www.d-t-g-online.de

– Skin tumor centers certified by the DKG: www.onkozert.de/hauttumor_zentren.htm

– German network of dermatologists in private practice specializing in the care of organ-transplant recipients (the ONKODERM e.V. network): www.onkoderm.de

– German Dialysis and Renal Transplantation Board (Kuratorium für Dialyse und Nierentransplantation e.V., KfH): www.kfh-dialyse.de/kfh/index.html

– German Association of Organ-Transplant Recipients (Bundesverband der Organtransplantierten e.V., BDO): www.bdo-ev.de

– German Working Group for Nursing Care in Transplantation (Arbeitskreis AKTX-Pflege e.V.): www.aktxpflege.de

– Skin Care in Organ Transplant Patients Network, Europe: www.SCOPEnetwork.org

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Corresponding author
Dr. med. Claas Ulrich
Hauttumorcentrum der Charité
Charitéplatz 1
10117 Berlin, Germany
claas.ulrich@charite.de

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REVIEW ARTICLE

Skin Changes Following Organ Transplantation

An Interdisciplinary Challenge

Claas Ulrich, Renate Arnold, Ulrich Frei, Roland Hetzer, Peter Neuhaus, Eggert Stockfleth

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