Epidemiogic aspects of skin cancer in organ-transplant recipients

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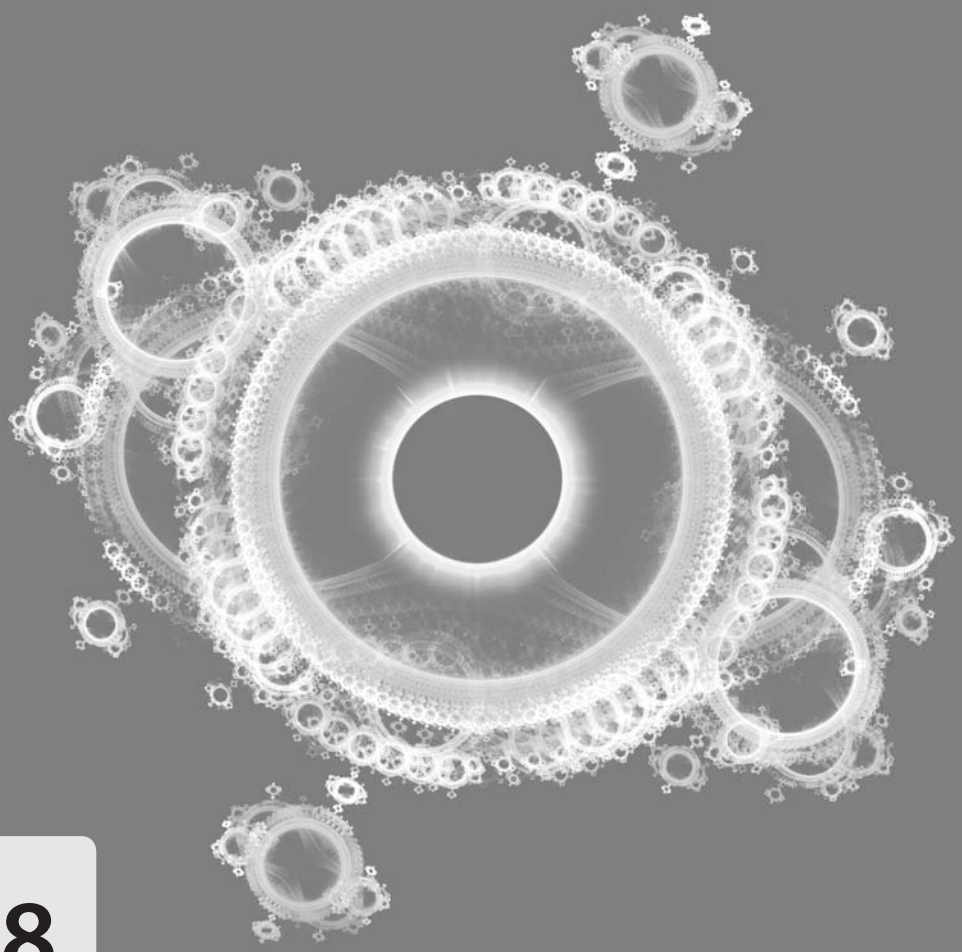

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Summary and discussion

Introduction

The risk of (skin) cancer and other skin diseases is highly increased in organ transplant recipients (OTR) who are kept on immune suppressive drugs to prevent graft rejection (Table 1). This thesis dealt with the epidemiologic aspects and risk factors for cancer, focused on cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) and other skin diseases in this group of patients. The studies presented in **Chapter 2-4 and 6** focused on *descriptive epidemiology*, to characterize and report both the pattern and frequency of cancer and skin diseases in OTR. **Chapter 5 and 7** were mainly based on *analytic epidemiology*, where we searched for new risk factors for cancer in OTR. Both descriptive and analytic components together contribute to increasing our understanding of this problem in OTR and may be of benefit in the design of a more rational clinical follow up of these patients.

In this concluding chapter, the descriptive as well as analytic epidemiological aspects of cancer and skin diseases in OTR are discussed in view of new evidence and recent findings by others. In addition, suggestions for future research are provided.

Descriptive epidemiology

Cancer

There is abundant evidence that the incidence of cancer is increased in OTR compared with the general population [1-9]. We confirmed the high burden of non-melanocytic skin cancer (NMSC), melanocytic skin cancer and non-cutaneous malignancies (NCM) in kidney transplant recipients (KTR) (**Chapter 2**) and simultaneous pancreas kidney transplant recipients (SPKTR) (**Chapter 5**). Cancers of the oral cavity, stomach, female genital organs, kidney, thyroid gland, but also leukemias and lymphomas, occurred 2 to 10 times more often compared with the general population. For SCC the standardized morbidity ratio even was as high as 40 (**Chapter 2)**. Many of the cancers that occurred at increased rates were those with a known or suspected infectious cause. Rates of stomach carcinomas were more than doubled and H. Pylori is estimated to cause over 60% of all stomach cancer [10]. Infection with human papillomavirus type 16 and 18 are causing cervical cancer [11, 12] and may also play a role in the etiology of a part of cancers of the oral cavity [13]. Lymphomas are related to Epstein - Barr virus infection [14, 15]. Several studies have suggested a possible causal role of beta- and maybe gamma-papillomavirus infections in the pathogenesis of cutaneous SCC, either directly, or in conjunction with sun exposure [16-21]. Since the immune system

may be crucial in protection from these infection related malignancies, these types op cancers may develop predominantly in immunocompromised OTR. Therefore, prevention and treatment of infections in OTR may reduce the incidence of malignancies.

We also confirmed the findings of previous studies [22-24] that there is a very high risk of subsequent NMSC after the first one (**Chapter 3**) and we found an increased risk of SCC in patients with a prior BCC and vice versa (**Chapter 6**). Furthermore, we have shown that OTR with SCC mainly developed new SCC and those with BCC mainly developed BCC (**Chapter 3**). Possibly, this could be explained by genetic predisposition or by different lifestyle factors of the patients, since the risk of SCC is considered to be associated with chronic sun exposure, whereas BCCs are more associated with intermittent, intense sun exposure [25]. Another explanation could be of immunologic nature. We hypothesize that a state of immune unresponsiveness may have been induced by the occurrence of the first skin cancer with immunologic tolerance to subsequent skin cancers with the same antigenic profile as the possible result.

We have also found an increased risk of NCM in OTR who developed SCC and BCC, but not the other way around (**Chapter 6**). The increased risks of NCM after the development of a prior SCC or BCC are in line with findings in the general population [26-28]. An inherited predisposition of cancer, a suboptimal immune response or lifestyle factors (smoking, sun exposure) are all possible explanations for the increased risk of NCM in patients with a prior SCC or BCC. Future research may provide insights in shared mechanisms of immunity against these types of cancer. We did not demonstrate an increased risk of SCC or BCC after the development of NCM, which is in contrast to findings in the general population [29]. Firstly, this difference may be explained by a lack of power due to the smaller population in our study compared with the 760 000 patients studied by Hemminki et al. Secondly, due to surveillance bias it is difficult to prove the association, since patients with NCM have a high probability of death soon after the NCM has been diagnosed, which has been shown in **Chapter 2**. A higher mortality rate is not observed in patients with SCC or BCC (**Chapter 2**). So far, cardiovascular diseases are the leading cause of death in OTR (30-50%), followed by infection (17-30%), but as a consequence of longer patient survival and older recipient age, malignancies have appeared as the third highest cause of mortality (8-18%) [30] and some authors believe that it will surpass cardiovascular diseases as the main cause of death in the coming years [31]. Therefore, it is very important that future research focuses on the prevention of malignancies.

Skin diseases

Compared with the large number of studies focusing on the development of skin cancer in OTR, infectious and inflammatory skin diseases have been studied less frequently [16, 19, 32-37]. Despite different methods however, all of these studies concluded that the prevalence of skin infections is very high with frequencies varying from 55-97% (Table 1) [33-37]. In **Chapter 4** we confirmed the high burden of skin diseases, and many patients developed multiple or recurrent skin diseases. The spectrum of skin diseases changed considerably with increasing time after transplantation and confirmed earlier publications that skin infections (e.g. herpes and candida) already occur early after transplantation [33, 34, 38], while most skin cancers increase exponentially with increasing time after transplantation [9, 39-42]. Although little is known about vascular skin problems after organ transplantation, there are some studies describing both arterial and venous vascular complications in KTR [43, 44]. In our cohort a significant proportion (8%) of the OTR does have some type of skin condition related to vascular diseases (**Chapter 4**). These data indicate that dermatologic care in OTR should not only be focused on skin malignancies, but also on skin infections and vascular skin diseases.

Analytic epidemiology

Immunosuppressive therapy

So far, there is no convincing epidemiological evidence for differences in oncogenic potential between the specific immunosuppressive agents. Comparison of incidence rate by type of immunosuppressive drug is difficult, because the regimen of immunosuppressive agents is strongly associated with the time period in which the patient is transplanted and the time period of transplantation has a profound effect on the risk of cancer. A recent study showed that treatment with azathioprine (Aza) was associated with a significant increased risk for SCC [45]. On the other hand, a randomized controlled trial in which patients were randomly allocated to one of three different treatment groups (Aza and prednisolone vs. long-term cyclosporine vs. short-term cyclosporine with a switch to Aza) from Australia, suggest that Aza and cyclosporine-based regimens are associated with similar overall long-term skin cancer risk after a follow up of 20 years, suggesting that the risk may be mediated by the total burden of immunosuppression rather than the agent [46]. Our studies provided additional evidence that Aza compared with other immunosuppressive drugs may increase the risk of both first and subsequent SCC (**Chapter 3 and 5**). Aza has been recognized to

Table 1 Skin diseases and (skin) cancer with increased risk in OTR based on the literature and this thesis.

Generally starting < 1 year after transplantation	Generally starting > 1 year after transplantation
Skin infections	**Skin infections**
Herpes	Human papilloma virus (warts)
Folliculitis	Erysipelas
Tinea versicolor	Dermatomycosis
Candidiasis	Onychomycosis
Skin inflammation	**Skin inflammation**
Acne	Dermatitis
Alopecia	
Skin miscellaneous	**Skin miscellaneous**
Oedema	Vascular problems
Hypertrichosis (Cyclosporin)	
Drug reactions	
Benign skin tumours	**Benign skin tumours**
Mollusca (poxvirus)	Warts (human papillomavirus)
	Seborrheic keratosis
	Cysts
	Lipoma
(Pre)malignant skin tumours	**(Pre)malignant skin tumours**
Kaposi sarcoma	Actinic keratoses
	Bowen's disease
	Keratoacanthoma
	Squamous cell carcinoma
	Basal cell carcinoma
	Malignant melanoma
	Merkel cell carcinoma
	Other adnex tumors
	Cutaneous lymphoma
Non skin cancer	**Non skin cancer**
Post-transplant Lymphoproliferative disorder	Lymphoma
	Leukemia
	Internal

increase photosensitivity of the skin and also enables UVA to directly damage DNA [47]. These characteristics of Aza may increase the risk of both first as well as subsequent SCC in patients who are chronically using this drug. Because most modern transplant regimens use combinations of mycofenolatemofetil, the calcineurin antagonist

tacrolimus and mTOR-inhibitors sirolimus and everolimus, future research should focus on these novel immunosuppressive agents. There is evidence to suggest that sirolimus compared with other immunosuppressive medications may confer a decreased risk of skin cancer [48, 49] due to its antiangiogenic effect, resulting in impaired tumor development. This is currently studied at our institute in both animal and human experimental studies (RESCUE trial).

Patients who are rejecting their grafts are treated with high doses of immunosuppressive therapy, including treatments with methylprednisolone, anti-thymocyte globulin (ATG) and muronomab-CD3 (OKT3) [50, 51]. One could speculate that these high doses of immunosuppressive rejection therapy lead to a state of severe immune deficiency and an increased risk of malignancies. However, there is only one study showing that rejection treatments are associated with a higher risk of SCC [52]. Using high serum creatinine levels at 1 year after transplantation as a measure of graft rejection, Bordea et al showed that patients with high serum creatinine levels had a higher risk of developing skin cancer [53]. They postulated that patients with a high serum creatinine level had maintained higher levels of immunosuppression to prevent rejection, which may have led to a higher risk of skin cancer [53]. However, Bordea et al, did not observe an increased incidence of skin cancer in patients receiving additional immunosuppression in the form of rejection treatments with ATG and OKT3, which is in line with several other studies [53-56]. We provided additional evidence that rejection therapy is not associated with an increased risk of malignancies. First, in **Chapter 5** we have shown that impending graft rejection, and the subsequent rejection therapies were not associated with SCC or BCC. In addition, **Chapter 7** showed that an increased number of transplantations are associated with a decreased risk of both SCC and NCM. Patients with multiple transplantations have rejected previous grafts, and are therefore treated with high levels of immunosuppression, including OKT3 and/or ATG to prevent final rejection, during short periods.

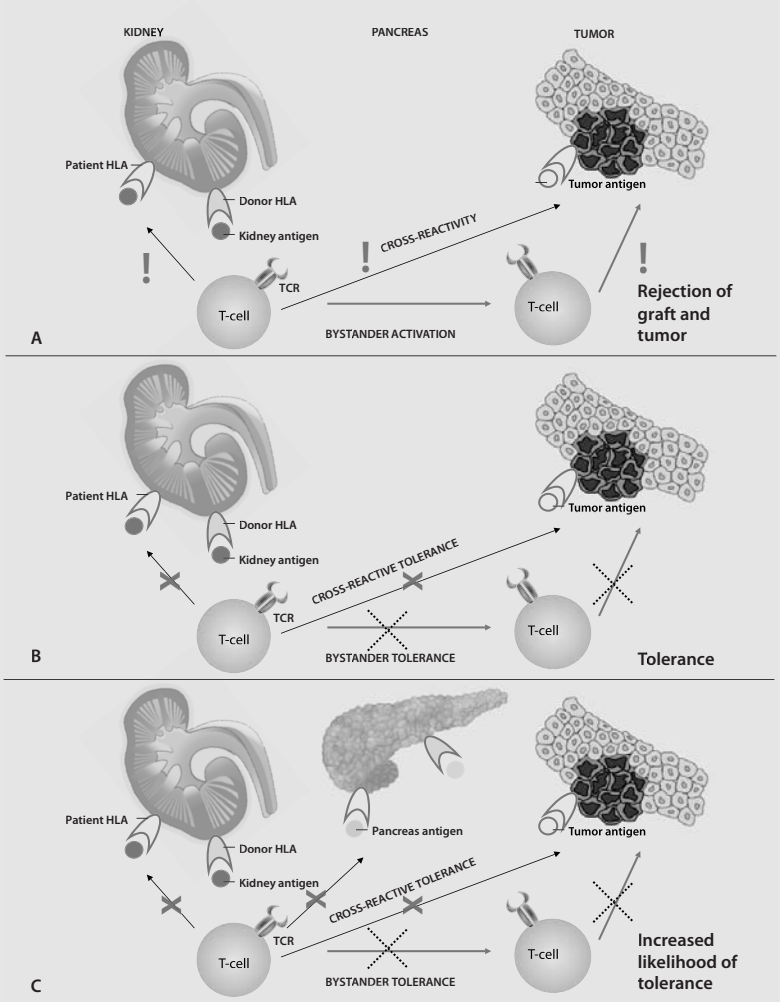
From 1991 until 1993, SPKTR are routinely treated with OKT3 as induction therapy and since 1998, SPKTR are routinely treated with high dose of induction therapy with ATG or daclizumab or in exceptional cases with basiliximab to prevent later rejection. In **Chapter 5** we have shown that induction treatments, similarly as rejection treatments, are also not associated with cancer. Apparently, the high levels of immunosuppression in induction and rejection treatments with the expected lower activated immune response during these periods do not lead to an increased risk of malignancies.

Shared immunity against organs and tumors

In **Chapter 7** we have shown that the rejection rate is associated with a decreased risk of cancer. Patients with three and more transplantations had a 1.6 respectively 3.6-times decreased risk of both NCM and SCC. A mechanism which may explain the prevention of malignancies in OTR is heterologous immunity, which is partial immunity that can occur in response to an antigen if the host has been previously immunized with an unrelated antigen [57]. This can be due to bystander activation or cross-reactivity, which is a reaction of a T-cell against more than one antigen. For example, some human virus-specific T-cells have been shown to recognize antigens in other HLA molecules [58]. We speculate that in patients with multiple transplantations bystander activation or cross-reactivity between donor grafts and malignancy-associated antigens result in protection from development of malignancies (Figure 1 A).

Supporting the hypothesis of cross-reactivity between donor graft and malignancy, we have found evidence that the opposite mechanism may also occur by induction of cross-reactive tolerance. Besides immunosuppressive therapy and other risk factors induction of immunologic tolerance may play a role in the development of malignancies in OTR (**Chapter 5 en 7**). Immunologic tolerance is a state of immune unresponsiveness to specific antigens induced by previous exposure to these antigens. Tolerance may result from T cells recognizing their antigen in a tolerizing environment, such as in the presence of immunosuppressive drugs, which may cause suppression, functional inactivity or apoptosis of the T cells [59]. Cross-reactive tolerance against antigens derived from donor organs has been demonstrated in animal models. Rats who received a heart in combination with a lung or spleen were more tolerant for the transplanted heart, since a reduced rejection rate of the transplanted heart was observed [60]. We have shown that SPKTR have an increased risk of SCC compared with KTR (**Chapter 5**). We speculate that the transplanted pancreas may have induced more tolerance against donor antigens presented in patient or donor HLA molecules. An increased cross-reactive tolerance against SCC-associated antigens in the host could then lead to an increased risk of SCC in SPKTRs (Figure 1 B and C). This could potentially affect SCC more severely than BCC, as SCCs are more antigenic cancers than are BCCs [61]. Similarly, tolerance may develop towards antigenic NCM. Induction of tolerance is a major goal in graft transplantation but these data suggest that the induction of tolerance could lead to unwanted side effects, such as an increased risk of infections and malignancies. Animal studies which should point out whether this hypothesis is true should be performed, so that we can learn more about the underlying mechanism and the role of different immunosuppressive agents, modulating this process.

Figure 1 Mechanism of shared immunity against organs and tumors.



A. The T cell is activated after recognition of its specific kidney antigen in a patient or donor HLA molecule, and after recognition of its specific tumor antigen in a patient HLA molecule due to cross-reactivity, which may result in rejection of both kidney and tumor. Alternatively, another T cell recognizing the tumor antigen is activated due to bystander activation, which may result in rejection of the tumor. **B**. The T cell does not respond to recognition of its specific kidney antigen in a patient or donor HLA molecule, and neither to its specific tumor antigen in a patient HLA molecule due to cross-reactive tolerance. Alternatively, another T cell recognizing the tumor antigen does not respond due to bystander tolerance. **C**. Similar to B., but the presence of an increased number of donor antigens derived from the additional transplanted organ increases the likelihood of occurrence of cross-reactive tolerance or bystander tolerance.

TCR: T cell receptor, HLA: human leukocyte antigen

Guidelines for dermatologists

In Table 2 we summarize clinical predictors for SCC in OTR to distinguish high risk and low risk patients for the development of SCC. The risk factors hatched in grey were studied in this thesis. The others are known risk factors from literature [18, 39, 53, 62, 63]. To reduce the tumor burden in OTR, the management of these patients requires an interdisciplinary approach including education about photoprotection, revision of immunosuppression and adequate dermatological treatments. Prevention of skin cancer in OTR will depend on better patient education. Awareness about skin cancer risk, and compliance with photoprotective measures, have indeed improved with proper dissemination of information to OTR in specialized dermatology clinics [64]. Therefore, we recommend that all candidates for transplantation should receive oral and written information about dermatological complications after transplantation and advice on sun-protective clothing and the use of sunscreen to avoid these complications. There is a high need for developing guidelines of dermatological care for OTR as these patients represent a significant and increasing challenge to dermatologists. In Table 3 we provide a schematic proposal for dermatological evaluation and aftercare in OTR based on the results of this thesis and the literature [65]. Early diagnosis through regular and appropriate follow up preferably in specialized dermatology clinics for OTR is strongly recommended. We therefore advise to check each OTR at least every two years. Since time after transplantation, resulting in more years on maintenance immunosuppression, and older age were risk factors for SCC (**Chapter 2-7**) we advise to check patients using immunosuppression for more than 10 years or being older than 50 years of age once a year. In these non sun damaged patients the focus should be on sun protective measures. Independent on age and time on immunosuppression, when patients have signs of severe or moderate sun damage, we recommend to checking them twice a year. Individual primary actinic keratoses (AK) can be treated with cryosurgery or topical application of imiquimod or 5-fluorouracil. However, this does not prevent the occurrence of new AK, since the areas of 'field cancerisation', where a discrete area of tissue is at increased risk of developing skin cancer, are not cured. Systemic retinoids can be used for chemo-prevention since there are studies suggesting that these drugs reduce the number of preexisting AK and slow down the development of new lesions [66-68]. Tolerability of the drug, however, is a major factor limiting its use [67]. In addition, it seems reasonable to consider revision of immunosuppression in patients with AK, both by reduction of the immunosuppressive dose [22] or conversion to sirolimus [48, 49], although more studies are needed to determine the potentially beneficial effect of these measures. Since we

Table 2 Risk factors for squamous cell carcinoma in organ transplant recipients. Risk factors studied in this thesis are hatched in grey.

Risk factors	No apparent risk factor	Protective factors
Chronic sun exposure	Donor type (living/ cadaver)	Multiple kidney transplantations
Painful sunburns	Rejection therapy	Sirolimus versus other maintenance immunosuppression
Fitzpatrick skin type I and II	Induction therapy	Fitzpatrick skin type V and VI
High number of keratotic skin lesions (risk indicator)	HLA mismatching	
Human papillomavirus infection		
Smoking		
Male		
Older age (at transplantation)		
Azathioprine versus other maintenance immunosuppression		
Simultaneous pancreas kidney transplantation		
Previous diagnosis of SCC/BCC/NCM		
Longer time since transplantation / years on immunosuppression		

have shown that the first SCC serves as a predictive marker for multifocal tumor development (**Chapter 3**), patients with a previous SCC, but also patients with previous BCC or NCM, should be considered as a high risk group and should therefore be checked at least 4 times a year (Table 3). All OTR with rapidly growing (and often

painful) lesions should be seen within 1 to 2 weeks. In OTR with suspected or biopsy-proven SCC, surgery with histology-controlled margins is the gold-standard therapy. In patients with multiple SCC, curettage and electrodessication can be used for lesions on the trunk and extremities, since it has been shown that this is an effective treatment for SCC in OTR [69, 70] with a low recurrence rate [69]. However, strict follow-up in specialized dermatology clinics in OTR with multiple SCC is necessary.

Summary and concluding remarks

Descriptive epidemiologic data in this thesis demonstrated and confirmed the major morbidity of NCM, NMSC and other skin diseases in OTR. Analytic epidemiologic data in this thesis showed that Aza as maintenance immunosuppressive drug is a risk factor for first and subsequent SCC. Furthermore, SPKTR have a highly increased risk to develop SCC compared with KTR and the rejection rate was shown to be associated with a decreased risk of cancer. To our knowledge, these are the first data suggesting that besides immunosuppressive therapy, induction of immunologic tolerance may play a role in the development of malignancies.

Since many malignancies and skin diseases were related to an infectious cause, future studies should point out whether prevention and treatment of infections will reduce the incidence of both (skin) malignancies and (skin) infections. Considering the harmful effects of the classical immunosuppressive agent Aza and the promising anticarcinogenic effects of mTOR inhibitors, future studies should aim to study the effect of this novel drug class on the risk of malignancies. Since induction of tolerance, which is a major goal in graft transplantation, could possibly result in unwanted side effects, such as an increased risk of infections and malignancies, it is very important that future animal studies should be performed to learn more about the underlying mechanisms.

As far as the mechanisms of tolerance are not clarified yet, the frequent occurrence of malignancies in OTR due to immunosuppression should be managed adequately by well educated physicians in near future. A proper guideline is needed to provide optimal management of OTR, to prevent and reduce morbidity and mortality due to infections and malignancies in these patients.

Table 3 Schematic proposal for dermatological evaluation and aftercare in organ-transplant recipients.

Number of recommended visits to dermatology outpatient clinic	Patient characteristics	Management
Once in two years	No keratotic skin lesions/ no sun damage No history of cutaneous malignancies Fitzpatrick skin type V-VI Less than 10 years after transplantation < 50 years of age	Sun protective measures
Once a year	No keratotic skin lesions/ no sun damage No history of cutaneous malignancies More than 10 years after transplantation OR > 50 years of age	Sun protective measures
Two times a year	Low number (less then 10) keratotic skin lesions/ Severe to moderate sun damage No history of cutaneous malignancies	Sun protective measures Consider systemic retinoids Revision of immunosuppression Cryosurgery/topical imiquimod/ 5-fluorouracil
Four times a year	Patients with more then 10 keratotic skin lesions/severe sun damage Patients with a history of one SCC/BCC	See above plus Complete surgical removal
Five and more times a year	Multiple previous SCC/BCC	See above plus Complete surgical removal Consider curettage and coagulation

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