Nonmelanoma Skin Cancer in Solid Organ Transplant Recipients: Update on Epidemiology, Risk Factors, and Management

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BACKGROUND Nonmelanoma skin cancers (NMSC) are the most frequently observed cancers in solid organ transplant recipients (SOTR) and may have a significant disease burden.

OBJECTIVE To provide an update regarding the epidemiology and management of NMSC in SOTR.

RESULTS Ten-year incidence rates range from 10% in Italy to 20% in Northern Europe to 70% in Australia. More than 50% of NMSC are located on sun-exposed areas (head, dorsum of hands). Many risk factors have been identified, including age at transplantation, fair skin, type of immunosuppressive drugs, cumulative sun exposure, viral infections, and various genetic markers. Patients with a first NMSC have a 49 times higher risk of developing a subsequent NMSC. Skin self-examination and photoprotection should be encouraged in all transplanted patients. Long-term skin surveillance, early diagnosis and aggressive treatment of any suspicious lesion, reduction of immunosuppressive therapy, and conversion to m-TOR inhibitors can be also effective measures for reduction of NMSC incidence.

CONCLUSIONS NMSC is the most frequent cancer observed in SOTR. Early diagnosis, patient education, and modification of immunosuppression are effective measures for reduction of NMSC incidence.

The authors have indicated no significant interest with commercial supporters.

Nonmelanoma skin cancer (NMSC), namely basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common malignancies in humans.[1,2] BCC is a malignant neoplasm derived from hair follicle stem cells. Although metastases are rare, untreated BCC can invade locally and cause substantial tissue damage.[1] SCC is a malignant neoplasm deriving from epidermal keratinocytes and has a higher metastasizing potential. Although BCC is thought to arise de novo, SCC probably evolves in many cases through early lesions such as actinic keratoses (AKs).[2] AKs are cutaneous neoplasms consisting of proliferation of cytologically aberrant epidermal keratinocytes that develop in response to prolonged exposure to ultraviolet radiation.[3] These lesions are common in adults with fair skin and present as keratotic macules, papule, or plaques with superficial scale on a red base.[3] AKs have historically been considered precancerous or premalignant lesions, but in recent years, there has been an effort to redefine AKs as malignant neoplasms, because these lesions are essentially intraepidermal SCCs in evolution.[3] AKs are considered the initial lesion in a disease continuum that may progress to invasive SCC.[3] Although these lesions can spontaneously regress, up to 25% can evolve into SCC.[3]

Epidemiology of NMSC in Solid Organ Transplant Recipients

Solid organ transplantation recipients (SOTRs) are at risk for AK and NMSC, mostly SCC and BCC.[4–7] Incidence rates of posttransplantation NMSC differ

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ISSN: 1076-0512 • Dermatol Surg 2012;38:1622–1630 • DOI: 10.1111/j.1524-4725.2012.02520.x

according to geographic latitudes; in Italy the rate is approximately 5% after 5 years and 10% after 10 years.[8] Higher rates have been observed in Northern Europe (10% after 5 years and 40% after 20 years) and Australia (45% after 11 years and 70% after 20 years).[9,10] In the transplanted population, the BCC:SCC ratio is inverted (4:1 in nonimmunosuppressed people); the standardized morbidity ratio in comparison to nonimmunosuppressed people is 60–250 times for SCC and 10–40 times for BCC, with an excess risk in men.[6,11,12] AKs are common also in nonimmunosuppressed people, with approximately 25% of adults having at least one AK.[3,13] Organ transplanted patients have a risk of developing AK that is 250 times as high as in immunocompetent patients.[13] In transplanted patients with more than 50 AKs, the odds ratio of developing a SCC was 12.[7] The risk of developing a subsequent NMSC in transplanted patients with a previous NMSC is 49 times as high as in patients without NMSC.[11] The occurrence of NMSC in pediatric transplant recipients is rare during childhood.[14] NMSC is usually diagnosed in early adulthood, 12–15 years after transplantation, but limited data are available.[14] A summary of epidemiologic data and risk factors is reported in Table 1.

Etiology and Pathogenesis

The pathogenesis of NMSC is multifactorial, with ultraviolet radiation, immunosuppression, genetic factors, and cutaneous infections due to human papillomavirus (HPV) as the most relevant factors.[15]

Ultraviolet Radiation

Ultraviolet radiation appears to be an important factor, with the highest incidence of NMSC observed in sunny countries such as Australia.[9,10,15] Also, more than 50% of NMSC are located on sun-exposed areas such as the head and dorsum of the hands.[6,11,15] Patients with fair skin, blue eyes, and red or blond hair have more NMSC than patients with a darker complexion.[10] The cumulative amount of sun exposure through the lifetime and especially before transplantation strongly predicted the risk of NMSC in two cohorts of Australian and Italian patients.[10,16] In a recent study, intense, long-lasting recreational sun exposure significantly increased the risk of developing NMSC.[17] Conversely, regular use of sunscreens and adequate clothing proved to be effective in reducing the number of AKs and new NMSC in a 24-month prospective follow-up study.[18]

Immunosuppressive Drugs

Drug-induced immunosuppression is the strongest risk factor for NMSC in SOTRs, but conflicting reports exist as to whether some immunosuppressive drugs favor the development of NMSC more than others.[19,20] Azathioprine has proven to be mutagenic

TABLE 1. Risk Factors for Nonmelanoma Skin Cancer (NMSC) in Solid Organ Transplant Recipients (SOTRs)

Age at transplantation
Mean time between transplantation and NMSC onset ranges from to 3 years in patients transplanted after the age of 50 to 8 years in patients transplanted at the age of 40.[6,12]
Type of transplanted organ
Ten-year incidence rate of NMSC in liver SOTRs is between 13% and 26%.[8–11]
Heart transplant patients and simultaneous pancreas and kidney transplant recipients seem to be at higher risk for NMSC than kidney transplant recipients because of more-intense immunosuppression and older age at transplantation and poor human leukocyte antigen matching but with no general agreement.[4,22,80–82]
Risk of subsequent NMSC
25% to 45% of patients with a first SCC will have a second lesion within 13 months, and 50% will have a second lesion within 3.5 years.[11,82–84]
Up to 100% of transplanted patients have subsequent NMSCs in the 5 years after the primary NMSC. Independent risk factors were the presence of multiple tumors at the first diagnosis, blue eyes, light-color hair and skin. Reduction of immunosuppression after the diagnosis of the first NMSC was protective.[84]

and to increase the sensitivity of DNA to ultraviolet radiation damage, but it is used more rarely than in the past.[15,21] Mycophenolate mofetil (MMF) has widely replaced azathioprine.[6,19] Patients receiving MMF seem to have a lower risk of NMSC than those treated with azathioprine.[4] Calcineurin inhibitors (cyclosporine and tacrolimus) have been shown to decrease DNA repair and apoptosis in human keratinocytes after ultraviolet B irradiation, leading to accumulation of DNA damage.[6,20] Addition of cyclosporine to a regimen containing azathioprine and prednisolone increased the risk of NMSC 2.8 times.[22] Supplemental immunosuppression due to acute rejection increased the risk of NMSC in a cohort of heart transplant recipients, and that risk directly correlated with the rejection score measured on cardiac biopsies.[16] Other studies found no relationship between type of immunosuppressive protocol and onset of NMSC, supporting the theory that NMSC occurrence is the consequence of the degree of immunosuppression rather than of a specific drug regimen.[8–11] Support for the role of total level of immunosuppression in the development of NMSC came from a prospective study in which patients were randomized to normal- or low-dose cyclosporine therapy.[23] The overall risk of cancer and the risk of skin cancers were significantly lower in the low-dose cyclosporine group.[23] Immunosuppressive therapy with m-TOR inhibitors has shown promising effects in reducing posttransplant cancer risk, including NMSC.[24] SCC experimentally induced with ultraviolet irradiation was markedly lower in frequency, number, size, vascularization, and progression in mice treated with m-TOR inhibitors than in those treated with calcineurin inhibitors or antimetabolites (azathioprine and MMF).[25,26] In the clinical setting, conversion from calcineurin inhibitors to m-TOR after the diagnosis of NMSC or AK delayed the development of new lesions, induced the regression of preexisting lesions, and reduced the recurrence of previously treated NMSC and the number of subsequent NMSC. This effect was evident even when the change in therapy was established many years after transplantation. These promising results need to be validated in larger populations and with longer follow-up.[27–30]

Genetic Factors

The effect of genetic factors in the pathogenesis of NMSC in SOTRs has been recently reviewed.[31] Polymorphisms in the methylenetetrahydrofolate reductase may alter the pattern of DNA ethylation and increase the risk of SCC; they may also increase the sensitivity of DNA to damage induced by ultraviolet irradiation.[32] Genetic variations in human pigmentation genes change the synthesis of melanin and thus may contribute to ultraviolet-induced skin damage.[33–35] Alteration of P53 tumor protein may enhance the development of HPV-induced anogenital SCC, but its role in the pathogenesis of NMSC in SOTRs is controversial.[36–38] Polymorphisms of the glutathione-S-transferase family reduce the ability to metabolize the products of oxidative stress, leading to greater DNA damage and subsequent development of NMSC in SOTRs after adjusting for age at transplantation.[39] Interleukin-10 and the retinoblastoma gene are also implicated in the pathogenesis of NMSC.[40–42] In a recent study, polymorphisms reducing the activity of the cyclooxigenase-2 were protective for NMSC in SOTRs through impairment of prostaglandin synthesis.[43] The effect of some human leukocyte antigens (B27, A11, DR1) and of HLA-A and -B mismatching has also been studied but with conflicting results and no definitive conclusion, possibly depending on the different populations examined.[9,44,45]

HPV Infection

The first evidence that HPV may play a role in SCC came from observations of patients with epidermodysplasia verruciformis (EV), who are genetically predisposed to HPV infection and develop SCC harboring specific beta-PV types (notably HPV5, HPV8, HPV20) on sites exposed to ultraviolet radiation.[46,47] BetaPV DNA has been detected in SCC from transplanted patients and immunocompetent people, together with the expression of specific betaPV genes.[48–51] Functional data support a potential role for betaPV as a cocarcinogen with ultraviolet radiation. BetaPV abrogation of ultraviolet radiation–induced apoptosis[52,53] and

interference with DNA repair and cell-cycle arrest may contribute to skin carcinogenesis.[54–57] Detection of HPV DNA has been associated with SCC and AK in case–control studies.[58–60] In a recent case–control study, the association between betaPV infection and SCC was demonstrated with the detection of DNA in the eyebrows and of antibodies against HPV in the peripheral blood, further supporting the role of this virus in the pathogenesis of NMSC.[61,62]

Approach to SOTRs with NMSC

General measures such as photoprotection with adequate clothing and sunscreens, prohibition of sun bed use, and regular self-skin examination should be encouraged in all patients. Proactive surveillance (regular skin examination) should be performed at least annually in all patients, even if they do not complain of any signs or symptoms of NMSC.[63,64] The frequency of follow-up visits may vary according to the risk associated with the specific skin cancer (Table 2).[63,64] Patients with low risk NMSC should be checked every 6 months, those with multiple AKs or a previous NMSC every 3–6 months, and those with high-risk SCC every 3 months.[63,64] Patients with a suspected skin lesion should be promptly referred to a dermatologist, and if necessary, suspected lesions should be biopsied or removed. Regular and aggressive treatment of all AKs with cryosurgery, topical therapies, or photodynamic therapy (PDT) is strongly recommended.[63]

TABLE 2. Approach to the Transplanted Patient with Nonmelanoma Skin Cancer (NMSC)[26–30,63,64,69,77–79]

Type of Posttransplantation NMSC	
Low-Risk NMSC	*High-Risk NMSC*
Size <0.6 cm, in the "mask" areas of the face (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular areas, temple, and ear), genitalia, hands, and feet. <1.0 cm, cheeks, forehead, neck, and scalp. <2.0 cm, trunk and extremities. Well-defined clinical margins, nonulcerated, slow growing. Histology: well differentiated, invasion limited to papillary dermis, absence of neurotropism, perivascular or intravascular invasion	Size >0.6 cm, in the "mask" areas of the face (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular areas, temple, and ear), genitalia, hands, and feet. >1.0 cm, cheeks, forehead, neck, and scalp. >2.0 cm, trunk and extremities. Multiple and/or recurrent cancers Indistinct clinical borders/ Rapid growth/Ulcerated Histology: Deep extension of tumor into the subcutaneous fat and poor differentiation, with perivascular or intravascular invasion
Therapy and Follow-up	
Surgical therapy with clear margins (Mohs surgery if available) Follow-up every 6 months	Surgical therapy with clear margins (Mohs surgery if available), lymph-node dissection if necessary Adjuvant radiation therapy if surgical excision is not curative. Limited evidence of SNLB Ultrasound examination of all local lymph-nodes, chest X-ray, and follow-up every 3 months. Reduction of immunosuppressive therapy or conversion in m-TOR inhibitors Chemoprevention with retinoids or capecitabine Follow-up every 3 months

Revision of immunosuppressive therapy (Reduction of posology or conversion in m-TOR inhibitors) or chemoprevention with retinoids should be negotiated with transplant physicians, when the patient present more than five NMSC per year.[26–30,63,64,69,77–79]

Topical imiquimod (three times per week for 16 weeks) applied on skin areas up to 60 cm^2 has been proven to be safe and effective in reducing the number and the size of AKs, and the number of SCCs, and no effects on systemic immunity was reported.[65,66] Electrodesiccation and curettage may be used when there are multiple lesions, because patients tolerate this procedure better than multiple surgical procedures. Aggressive electrodesiccation and curettage can be safe therapy for appropriately selected low-risk (small and superficial) SCCs and has an acceptable cure rate.[64] PDT may be used in SOTRs for the treatment of AKs not responsive to conventional treatments (cryotherapy, topical 5-fluorouracil (5-FU), carbon dioxide laser, curettage, and electrosurgery), and superficial NMSC.[63,64] A response rate of 72% for scalp and facial lesions and 40% for acral lesions has been observed, and PDT is more effective than 5-FU in achieving complete resolution of lesions, with a better cosmetic outcome.[67] It has been proposed that repeated cycles of PDT prevent the development of NMSC, but there is no general agreement.[64,67,68] Any lesion that does not respond to these treatments should be excised.[62–64,67,68] Surgical therapy for NMSC should be performed according to current guidelines, and clear margins on histologic examination should be obtained.[69,70] Mohs micrographic surgery is recommended as the optimum surgical approach, especially for high-risk lesions on the ears, lips, and perioral and periorbital areas, where tissue conservation is desired.[69,70] Radiation therapy is helpful if surgical excision is not curative.[70] Patients with a previous NMSC should undergo periodic examinations to exclude the risk of a subsequent NMSC.[11] The utility of sentinel lymph node biopsy (SLNB) in SOTRs with invasive or multiple SCC is still being debated; the majority of studies have been performed in patients with oral and anogenital SCCs, with limited data on cutaneous carcinomas.[71–73] In a cohort of patients with oral SCC, SLNB had a negative predictive value of 96% and a false negative rate of 9.8%.[71] In two recent reviews, SLNB was positive in 24% of anogenital cancers and in 14% to 21% of cutaneous SCCs. Lower rates were observed in cancers of the head and neck (10.1%) than in cancers of the trunk and extremities (18.6%). False negatives were 0% for anogenital cancers and cutaneous cancers of the head and neck and 22% for SCCs of the trunk and extremities. None of these studies were randomized controlled studies comparing patients undergoing SLNB with controls undergoing nodal observations. No uniform criteria for enrolling patients (e.g., size and thickness of the tumor, skin site, type of surgical procedure, adjuvant therapy, histologic differentiation of the tumors) were used.[71–73] For these reasons, the benefits of SLNB for disease progression and survival with SCC remain unclear, and close monitoring of patients is needed.[69,71–73] In patients developing from five to 10 SCC per year, systemic chemoprevention with retinoids or oral capecitabine should be considered.[64,74–76] Acitretin is effective at a dosage of 20–25 mg/d, and a low initial dose of 10 mg, increasing by 10-mg increments at 2- to 4-week intervals, minimizes side effects and improves patient adherence.[64,74–76] A baseline fasting lipid panel, liver function tests, serum creatinine, and complete blood cell count should be performed before beginning therapy. These values are rechecked at 2–4 weeks, monthly thereafter for the first 3 months, and every 3 months if the dosage is not modified. Blood examinations may be rechecked 2 weeks after every dose increase. Chemoprevention with oral retinoids must continue as long as possible, and drug discontinuation is recommended only in case of liver toxicity or high fasting plasma levels of lipids.[64,74–76] After discontinuation, a rebound effect occurs[64,74–76] Acitretin is a known teratogen and is contraindicated in women of childbearing potential. These patients can benefit from isotretinoin because it is rapidly eliminated after discontinuation of therapy.[64,74–76] Oral capecitabine is a prodrug of 5′-deoxy-5-fluororidine that has been successfully employed in metastatic breast cancer and colon adenocarcinoma.[77,78] Two open-label studies reported that oral capecitabine (1,000–1,500 mg/m^2 per day for 14 days, 7 days off, with cycles repeated every 3 weeks) decreases incidence rates of NMSC and AKs from 40% to 100% after a median

TABLE 3. Top Recent Findings for Nonmelanoma Skin Cancer (NMSC) in Organ Transplant Patients

Incidence rates of posttransplantation NMSC differ according to geographic latitudes, with higher risk in Northern Europe and Australia. The risk of developing a subsequent NMSC in transplanted patients with a previous NMSC is 49 times higher if compared to transplanted patients without previous NMSC.
Pathogenesis of NMSC is multifactorial, with ultraviolet radiation, drug-induced immunosuppression, genetic factors, and human papillomavirus the most relevant factors.
m-Tor inhibitors seem to reduce the incidence of de novo NMSC and the number of recurrences and of subsequent NMSC.
Photoprotection, regular self-skin examination and periodical examination by a physician should be performed in all the patients, irrespective of whether they have NMSCs or not.
Early and aggressive treatment of all lesions is necessary. For patients with multiple NMSCs, with recurring or subsequent cancers, reduction of immunosuppressive therapy, administration of m-Tor inhibitors, or chemoprevention with retinoids or oral capecitabine should be considered.

duration of treatments of 12 months, but it had no effects on metastatic SCC.[77,78] Adverse events (e.g., mucositis, hand-foot syndrome, muscular aches) were mild, but further studies are needed to validate these promising results.[77,78] Patients with recurring NMSC or multiple NMSC at the first consultation may benefit from decreasing immunosuppressive therapy or changing the current immunosuppressive regimen into an m-TOR-based immunosuppressive regimen.[24,27–30,79] This approach is effective even when the change in therapy is made many years after transplantation.[27–30] Table 3 summarizes the top recent findings about NMSC in organ transplant patients.

Conclusions

NMSC is the most frequent cancer observed in SOTRs. Although it rarely metastasize, it may have a significant disease burden. Because these lesions are easily visible they may be diagnosed and treated early. The key to managing this patient population lies in a multidisciplinary approach encompassing patient education regarding risk factors (sun exposure) and skin self-examination and dermatologic screening before transplantation, in the immediate posttransplantation period, and at regular intervals during follow-up. Rapid referral to a dermatologist is mandatory once lesions suspicious for skin cancer are diagnosed. The management of patients with high-risk cutaneous cancers must be multidisciplinary and requires negotiation with transplant physicians to reduce immunosuppressive therapy to the minimum dosage allowing graft survival; shifting to an m-TOR inhibitor; and cooperation between the dermatologic surgeon, plastic surgeon, radiotherapist, and oncologist.[64,69]

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