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Current Approaches to Skin Cancer Management in Organ Transplant Recipients

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Approximately 225,000 people are living with organ transplants in the United States. Organ transplant recipients have a greater risk of developing skin cancer, including basal cell carcinoma, squamous cell carcinoma, and malignant melanoma, with an approximately 250 times greater incidence of squamous cell carcinoma in certain transplant recipients, compared with the general population. Because skin cancers are the most common posttransplant malignancy, the resultant morbidity and mortality in these high-risk patients is quite significant.
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Approximately 225,000 people are living with organ transplants in the United States. Organ transplant recipients (OTRs) are at increased risk for both cutaneous and systemic malignancy. More than 1000 articles in the medical literature discuss cancer in the setting of organ transplantation, most of which focus on skin cancer.

Skin cancer is the most common human malignancy, with approximately 3.5 million skin cancers diagnosed annually in the United States.[1] Nonmelanoma skin cancer (NMSC) is the most common type, with approximately 2.8 million basal cell carcinomas and more than 700,000 squamous cell carcinomas (SCCs) diagnosed each year. In addition, more than 68,000 malignant melanomas (MMs) are diagnosed yearly in the United States, leading to more than 8600 deaths.[2]

Transplant recipients are at increased risk of developing skin cancer compared with the general population, with an approximately 250 times greater incidence of SCC in certain populations, depending on the type of transplant received.[1,3] Because skin cancers are the most common posttransplant malignancy, the resultant morbidity and mortality in these high-risk patients is quite significant.[4] This article reviews advances in managing skin cancer in these high-risk patients.

Pathogenesis

Exposure to ultraviolet radiation (UVR) is one of the primary causal factors in the development of NMSCs in OTRs.[5] Ultraviolet B radiation induces direct DNA damage and indirectly causes DNA damage through production of reactive oxygen species.[6] UVR also promotes the development of skin cancer through cutaneous immunosuppression.[7]

The immunosuppressive regimen required for graft survival in OTRs may lead to an impaired immune surveillance system, which may influence the development of skin cancers. Certain immunosuppressive agents may also promote malignancy through direct carcinogenesis.[8-10] Skin cancer in the setting of organ transplantation is also influenced by human papillomavirus carcinogenesis, cancer susceptibility genes, and skin type.[11-14] Additional risk factors for the development of skin cancer in OTRs include sun exposure history and presence of actinic keratoses (AKs).[15-23] The type of transplant, duration and type of immunosuppression, low CD4 count, and older age at time of transplantation may also be linked to skin cancer development in these patients.[24-28]

Epidemiology

Skin cancer occurs in more than 44% of light-skinned OTRs.[29] Overall, these patients have an approximately 100-fold increased risk of developing NMSC compared with the general population.[30] Specifically, there is a 65-fold increased risk of SCC, 10-fold increased risk of basal cell carcinoma (BCC), and an approximate 3.4-fold increased risk of MM.[3,10] In Queensland, Australia, in a retrospective follow-up study of 1098 renal transplant recipients, Bouwes Bavinck et al[14] reported that the cumulative incidence of skin cancer was approximately 70% after 20 years of immunosuppression.

Not only do skin cancers develop in OTRs, but in the setting of organ transplantation, these tumors can also behave more aggressively, with a greater risk for local recur-

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Table 1 Guidelines for Recommended Follow-Up Intervals by Risk Factors

Risk Factors	Follow-Up
Only risk factor is immunosuppression	Every 12-24 mo
Risk factors, such as sun exposure or fair skin, but no history of AK or NMSC	Every 6-12 mo
Early cutaneous carcinogenesis, ie, AKs or warts or 1-4 NMSCs/yr	Every 3-6 mo
Moderate cutaneous carcinogenesis, ie, 5-10 NMSCs/yr, high-risk SCC, MCC, or MM	Every 3 mo
Severe cutaneous carcinogenesis, ie, >10 NMSCs/yr, metastatic skin cancer	Every 1-3 mo

AK, actinic keratosis; MCC, Merkel cell carcinoma; MM, malignant melanoma; NMSC, nonmelanoma skin cancer; SCC, squamous cell carcinoma.

rence, metastasis, and mortality.[31,32] Ong et al,[33] who examined 455 patients with heart transplants in Australia, found a 27% mortality rate attributable to skin cancer. A retrospective analysis of 100 MMs in 95 OTRs also found that patients who had MMs with a Breslow thickness >2 mm had significantly decreased overall survival rates than patients with Breslow thicknesses of 2 mm or less, with a hazard ratio of 11.49.[34]

Management

Screening/Education

Education about skin cancer is important for OTRs and, when done properly, can improve skin cancer–related outcomes. According to guidelines published by the International Transplant Skin Cancer Collaborative in 2002, patients should be evaluated before transplantation for factors that may increase their risk of skin cancer and should also receive detailed education regarding sun protection, development of skin cancers, and how to perform self-examinations.[35] In addition, OTRs should be advised of the importance of frequent follow-up full skin examinations by a dermatologist. Follow-up examinations should occur anywhere from every 3 months to every 24 months, depending on the patient's risk factors (Table 1).[35,36]

Premalignant Lesions

Both AKs and SCCs in situ (SCCIS) occur in up to 40% of OTRs within 5 years after transplantation.[37] Because AKs are evidence of early cutaneous carcinogenesis and have a propensity to develop into invasive SCCs in OTRs,[38] these lesions should be treated promptly and aggressively to reduce the rate of SCC transformation. This is particularly important in younger transplant patients with severe actinic damage.

Localized destructive methods are excellent treatment options for isolated AKs. These modalities include cryosurgery, curettage with electrodesiccation (curettage with electrodesiccation; ED&C), CO_2 laser ablation, and curettage with cryotherapy (Fig. 1).

In patients with numerous AKs, regional field treatments should be considered. Regional treatment options include ablative skin resurfacing via laser, dermabrasion, chemical peels, topical 5-fluorouracil, topical imiquimod, and photodynamic therapy (PDT).

5-Fluorouracil is a chemotherapeutic agent that inhibits thymidylate synthetase, thus blocking DNA synthesis. Topi-

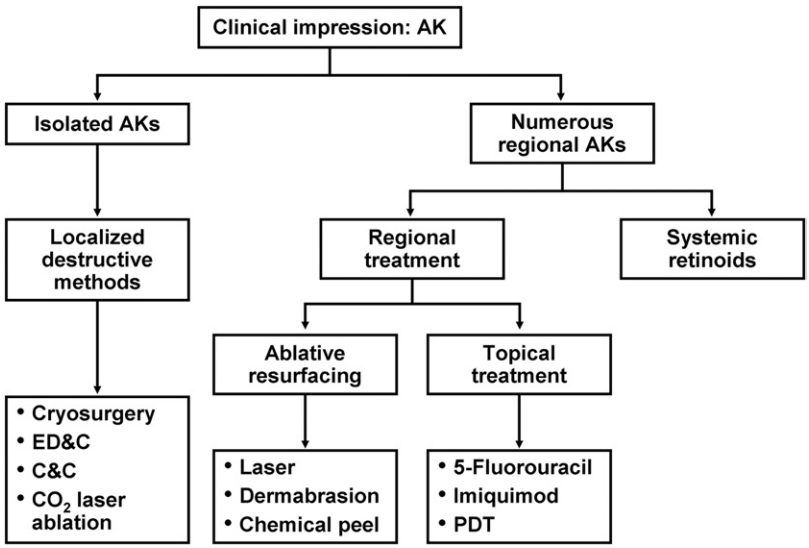

Figure 1 Guidelines for management of AKs in organ transplant recipients. C&C, curettage with cryotherapy; ED&C, curettage with electrodesiccation; PDT, photodynamic therapy.

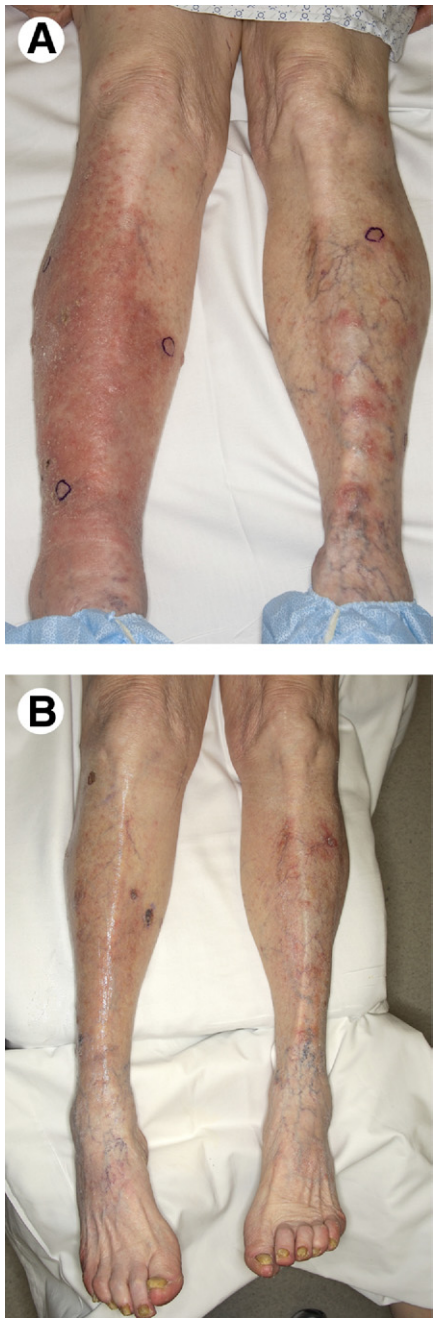

Figure 2 (A) Organ transplant recipient with extensive actinic damage of the legs. (B) After 2 weeks of chemowrap treatment with topical 5-fluorouracil under Unna boots.

cal 5-fluorouracil is widely used in the treatment of premalignant cutaneous lesions, with cure rates of up to 98%.[39] Topical 5-fluorouracil is even more effective under occlusion and is beneficial in treating extensive AKs in OTRs, especially on the lower extremities. One technique involves weekly chemowraps using topical 5-fluorouracil under occlusion with Unna boot wraps for 4-20 weeks (Fig. 2).[40]

Imiquimod is an immune-modulating agent that has proven effective in treating AKs as well. Randomized controlled studies have demonstrated its efficacy in transplant patients, with clearance rates of up to 62% compared with vehicle alone.[41] In a study of renal transplant recipients, 7 of 14 patients showed reduced skin atypia after topical imiquimod, 5% cream was applied 3 times weekly for 16 weeks. Adverse reactions primarily included local irritation.[42]

Topical PDT is another excellent way to treat large areas of precancerous changes in OTRs. PDT is a process that uses aminolevulinic acid or methyl aminolevulinate as photosensitizing agents, produce reactive oxygen species that selectively target proliferating cells after their activation by exposure to light. A recent study demonstrated that PDT offers a complete response rate of 71% for AKs in OTRs.[43]

Oral retinoids have been shown to inhibit tumor proliferation and differentiation in vivo and can reduce the number of keratotic lesions by 45%.[44,45] A recent systematic review suggested that systemic retinoids, specifically acitretin, decrease the incidence of NMSC in OTRs.[46] Certain considerations should be taken into account when deciding which oral retinoid to prescribe. Acitretin and isotretinoin can both be effective as chemopreventive agents. Unlike acitretin, isotretinoin has not been studied specifically in OTRs but has been used in patients with xeroderma pigmentosum and basal cell nevus syndrome.[47] Because isotretinoin has a shorter half-life than acitretin, it is the preferred choice in women of childbearing age. However, because of the iPledge program, isotretinoin is more cumbersome to prescribe. Isotretinoin may have more mucocutaneous and rheumatologic adverse effects than acitretin, and the dose is determined according to the patient's weight. Isotretinoin can be given at doses of 2 mg/kg per d; however, this is considered a high dose associated with many adverse effects. Low-dose isotretinoin may not be very effective in preventing certain forms of skin cancer, especially BCC.[48,49]

Some clinicians advocate starting at low doses of acitretin and increasing the dose while monitoring for adverse effects. The dosage of acitretin, however, can be initiated at 0.4 mg/kg per d.[50] Common adverse effects are headache, rash, and hyperlipidemia, in addition to the rebound phenomenon of development of multiple eruptive SCCs after cessation of acitretin.[51]

Management of BCCs in OTRs

Table 2 summarizes the management approaches to treatment of low- and high-risk BCCs in OTRs.

Table 2 Management Approaches to Treat BCCs in OTRs

Low-Risk BCCs	High-Risk BCCs
Cryotherapy	Mohs micrographic surgery
ED&C	Definitive radiation therapy
Surgical excision	
Topical imiquimod	
Intralesional interferon	
Photodynamic therapy	

BCC, basal cell carcinoma; ED&C, curettage with electrodesiccation; OTR, organ transplant recipient.

Low-Risk BCCs

Cryotherapy is a method of localized destruction of tissue using liquid nitrogen to induce cellular injury through intra- and extracellular ice crystal formation. The success of this procedure depends on tumor selection, speed and duration of cooling, thaw time, and the number of freeze-thaw cycles. The goal is to achieve a temperature of –50°C to – 60°C at the base of the tumor with at least 3-mm margins and a freeze time of approximately 40-90 seconds.[52] This method has been described in the treatment of BCCs in immunocompetent patients. One study of 415 BCCs demonstrated a cure rate of 99.0% over 5 years.[52] Cryotherapy as a single modality has not been explored after transplantation.

When ED&C is performed, the surgeon destroys the cancerous lesion with electrocauterization and then scrapes the area with a sharp curette, a process generally repeated 2 or 3 times. This modality remains a popular treatment option in patients after transplantation because it can be used to treat multiple superficial cancerous lesions with cure rates demonstrated to be greater than 90% in immunocompetent hosts.[53]

Surgery is one of the modalities used most frequently to treat BCCs. Current guidelines for surgical excision of low-risk BCCs recommend at least a 4-mm margin. This has been shown to provide a 5-year cure rate of 90%-98% in the general population[54] and approximately 90% in the OTR population.[55]

Among immunocompetent individuals, imiquimod has demonstrated cure rates of 87% for superficial BCCs and 65% for nodular BCCs.[56] In 5 renal transplant patients, the use of topical imiquimod fully cleared only 40% of BCCs, demonstrating its greatest efficacy among patients with superficial BCCs.[57] In 1 survey, 4 of 25 dermatologists in the United States reported using imiquimod to treat superficial BCCs in OTRs.[58] The use of imiquimod is limited by adverse effects, cost, lower clearance rates, and whether the patient follows the prescribed treatment.

Interferon acts as both an antiproliferative agent and an immunomodulator. Its use has been investigated in chemoprophylaxis and treatment of premalignant lesions and skin cancers. Studies in which the authors used intralesional interferon injections for low-risk BCCs have demonstrated cure rates of up to 96%.[59] In patients with high-risk features, such as morpheaform subtypes or clinical recurrence, only 27% of those receiving interferon did not show any residual tumor.[60]

Topical PDT also has been used to treat BCCs. To optimize this treatment modality, lesions should be carefully selected as complete response rates are only approximately 62%, with a 33% response rate for nodular subtypes and an 82% response rate for superficial subtypes.[55] Nodular and infiltrative subtypes, ulcerated lesions, thicker tumors, and lesions located on the extremities demonstrated worse outcomes. Therefore, superficial BCCs on the trunk would be best for treatment with PDT.

High-Risk BCCs

Factors that lead to categorization of BCCs as high risk are listed in Table 3. BCCs at high risk for recurrence should be treated aggressively, particularly in OTRs. Mohs micrographic surgery (MMS) offers the highest cure rates for NMSCs, with cure rates as high as 99% for BCC.[61,62] When available, MMS should be the primary surgical treatment for BCCs located on the head and neck of OTRs.

Table 3 Clinical and Histologic Risk Factors for Local Recurrence and Metastasis of BCC

Low-Risk Features of BCCs	High-Risk Features of BCCs
Clinical features	Clinical features
Slow growth	Rapid growth
Low-risk location, such as extremity	High-risk site, such as mid face
Small lesion (<2-cm diameter)	Large size (≥2-cm diameter)
Well-defined borders	Poorly defined borders
	Incomplete excision
	Recurrent lesions
Histologic features	Histologic features
Superficial subtype	Infiltrative subtype
Nodular subtype	Morpheaform subtype
	Metatypical subtype

BCC, basal cell carcinoma.

If a patient cannot tolerate surgery, needs extensive surgery, or has an inoperable tumor, definitive radiation therapy may be an option. One study reported a cure rate of 95% in primary BCCs and an 86% cure rate for recurrent BCCs.[63] This modality should not be the primary option, particularly in OTRs, because radiation therapy may predispose the irradiated sites to the development of future NMSCs.

Clinical trials are underway to study a novel molecule in the treatment of advanced or metastatic BCC. GDC-0449 is a smoothened (SMO) protein inhibitor of the hedgehog pathway (implicated in the pathogenesis of BCCs). A phase 1 multicenter trial has demonstrated good responses with this agent in the treatment of metastatic BCCs.[64]

Management of SCCs in OTRs

SCCs in OTRs may show high-risk features, such as increased thickness, dermal invasion, and acantholysis, more frequently than in immunocompetent patients.[65] Furthermore, immunosuppressed patients with SCC are more than 4 times more likely to have local recurrence and metastasis than patients who are immunocompetent.[66] SCCs should therefore be treated promptly and aggressively, preferably with surgical modalities when appropriate.

All lesions clinically suspicious for SCC should be biopsied. Selection of appropriate therapy is made by evaluation of clinical and histologic features, the presence of lymphadenopathy, evidence of metastasis, and the patient's co-morbid conditions. Classification of a patient's SCC as low or high risk is essential for proper management. The clinical and histologic risk factors for local recurrence and metastasis are summarized in Table 4.[65] Table 5 summarizes treatment modalities for SCCs in OTRs and Fig. 3 outlines a treatment algorithm.

Table 4 Clinical and Histologic Risk Factors for Local Recurrence and Metastasis in SCCs

Low-Risk Features of SCCs	High-Risk Features of SCCs
Clinical features	Clinical features
Primary tumor	Recurrent lesion
Well-defined borders	Poorly defined borders
Diameter <2 cm on the trunk and extremities	Diameter ≥2 cm on the trunk and extremities
Diameter <1 cm on the cheeks, forehead, neck, and scalp	Diameter ≥1 cm on cheeks, forehead, neck, and scalp
Diameter <0.6 cm on the "mask areas" of the face, genitalia, hands, and feet	Diameter ≥0.6 cm on the "mask areas" of the face, genitalia, hands, and feet
Slow growth	Rapid growth
Lack of neurologic symptoms	Neurologic symptoms
	Ulceration
	Lesion within scar, chronic inflammation, or previous radiation therapy
	Satellite lesions
	Immunocompromised patient
Histologic features	Histologic features
Depth <4 mm	Depth ≥4 mm
In situ or keratoacanthoma type	Acantholysis
Well-differentiated histology	Moderate or poor differentiation
Restriction to papillary dermis	Extension into deeper dermis/subcutaneous fat
No evidence of perineural or vascular invasion	Perineural or vascular invasion

SCC, squamous cell carcinoma.

Adapted from Kovach BT and Stasko T: Squamous cell carcinoma in organ transplant recipients, in Otley CC, Stasko T (eds): Skin Disease in Organ Transplantation. Cambridge: Cambridge University Press; 2008, pp 172-181.Used with permission.

Low-Risk SCCs

For early, superficial SCCs that demonstrate low-risk clinical and pathologic features, superficial ablative techniques may be used. These include cryotherapy, ED&C, curettage with cryotherapy, and topical regimens, such as 5-fluorouracil and imiquimod.

Excellent cure rates have been reported with cryotherapy for treatment of properly selected superficial SCCs.[52,67] Advantages of cryotherapy include good cure rates, acceptable cosmesis, low morbidity, low cost, and ability to treat multiple lesions at the same time. One major disadvantage of cryotherapy is the highly user-dependent nature of therapeutic success.

In low-risk SCCs, ED&C can have cure rates of 96.8%-98.9%.[68] Advantages of ED&C include low cost and effectiveness. It is important to note, however, that excisional surgery may be a better option for small tumors in hair-bearing areas because tumor cells extending down follicular structures may not be completely eradicated with ED&C.

Topical therapies may be considered in patients who are not good candidates for the above-mentioned treatments or who have a considerable tumor burden. A systematic review found clearance rates of 73% to 88% in SCCIS and 71% for invasive SCC with use of topical imiquimod, 5% cream. The same study reported clearance rates of 27% to 85% for SCCIS with use of topical 5-fluorouracil[69]; however, OTRs were not included in this study population. Thus, because of the risk of progression and increased aggressiveness of NMSCs in OTRs, the ablative therapies discussed previously are more often recommended, largely because of their greater efficacy in completely treating small low-risk tumors.

The workhorse for treating skin cancer in OTRs is surgery. Surgical excision of low-risk SCCs with 4-6-mm margins offers a 95% cure rate.[70] This technique provides histologic evaluation of tumor margins and rapid healing with often favorable cosmesis. Surgical excision has similar cure rates to ED&C[71]; therefore, potential disadvantages compared with ED&C include a greater risk of complications, such as hematoma and wound dehiscence, increased cost, and increased procedure time in patients with multiple low-risk SCCs.

High-Risk SCCs

Excisional surgery is recommended for high-risk SCCs under certain circumstances, specifically when MMS is unavailable. For high-risk SCCs, a 6-mm to 1-cm margin is recommended and cure rates may reach 95%.[70] Prophylactic irradiation of the surgical site as an adjunctive modality may be considered in aggressive, high-risk tumors after surgical excision.

MMS offers the advantage of complete margin visualization and tissue conservation, with cure rates ranging from 96% to 97% in primary SCCs and 90% to 94% in recurrent SCCs.[71] It sometimes happens that an SCC that is clinically small may in fact exhibit perineural invasion or other aggressive histopathologic features, such that a large final defect is ultimately required to clear the cancer (Fig. 4). Complete margin control is particularly important in OTRs because of their increased risk of developing subclinical tumor extension and spread. MMS should therefore be the surgical modality of choice for the management of high-risk SCC in OTRs.

If an OTR is not a surgical candidate, radiation therapy may be considered for the treatment of high-risk NMSCs.

Table 5 Treatment Options for SCCs in OTRs

Treatment	Pros	Cons
Topical regimens		
5-Fluorouracil cream	Field treatment for low-risk SCCs	Not as effective as imiquimod; significant irritation; depends on patient compliance; no margin control; not good for invasive SCC
Imiquimod cream	Effective field treatment for low-risk SCC; excellent cosmesis	Local irritation; depends on patient compliance; no margin control; not good for invasive SCC
Superficial ablative techniques		
Cryotherapy	Low cost, rapid, can treat multiple lesions	Pain, scarring, blistering; less margin control; no field control; only for in situ and minimally invasive SCC
Photodynamic therapy	Effective field treatment, 1-3 sessions, rapid recovery, can treat multiple lesions	Pain during session, need to avoid sun exposure for 48 h after treatment, only good for superficial tumors
ED&C or C&C	Highly effective on properly selected low-risk SCCs	Less margin control; less favorable cosmesis; not good for high-risk SCC
Surgical excision		
Excision with postoperative evaluation of margins	Some margin control; can remove larger tumors	More prone to incomplete excision; higher recurrence rates
Mohs micrographic surgery	Treatment of choice for high-risk SCC; excellent margin control; tissue sparing	High cost; difficult with multiple tumors; need for specialist
Adjuvant treatment		
Radiotherapy	Option with incompletely excised tumors and higher-risk SCCs; may decrease tumor burden and risk of metastases	Recurrences in radiation field may be difficult to treat; risk of radiation dermatitis and radiation-induced carcinogenesis
Chemoradiotherapy	Better cure rates than radiation therapy alone	Still mostly investigational; severe toxic effects
Nonsurgical definitive therapies		
Radiation therapy	Good option for inoperable tumors, poor surgical candidates, in-transit metastases	No margin control; recurrences in radiation field may be difficult to treat; risk of radiation dermatitis and radiation-induced carcinogenesis
Sentinel lymph node dissection	May help stage patients with previously undiagnosed metastatic disease	Unclear survival benefit; morbidity from surgery
Systemic treatments		
Oral retinoids	May decrease tumor burden in advanced SCCs	Serious adverse effects; rebound phenomenon
Chemotherapy	Option for inoperable tumors	Limited experience

C&C, curettage with cryotherapy; ED&C, curettage with electrodesiccation; OTR, organ transplant recipient; SCC, squamous cell carcinoma.
Adapted from Kovach BT and Stasko T: Squamous cell carcinoma in organ transplant recipients, in Otley CC, Stasko T (eds): Skin Disease in Organ Transplantation. Cambridge: Cambridge University Press; 2008, pp 172-181.Used with permission.

Radiation therapy can be extremely effective for properly selected tumors, taking into account the facts that tumor control and cosmesis tend to be related to lesion size and that radiation is less effective in recurrent lesions. In general, smaller primary lesions and BCCs have better outcomes with radiation as monotherapy than larger tumors or SCCs.[63]

Adjuvant postsurgical radiation therapy may be an option for incompletely excised tumors as well as aggressive high-

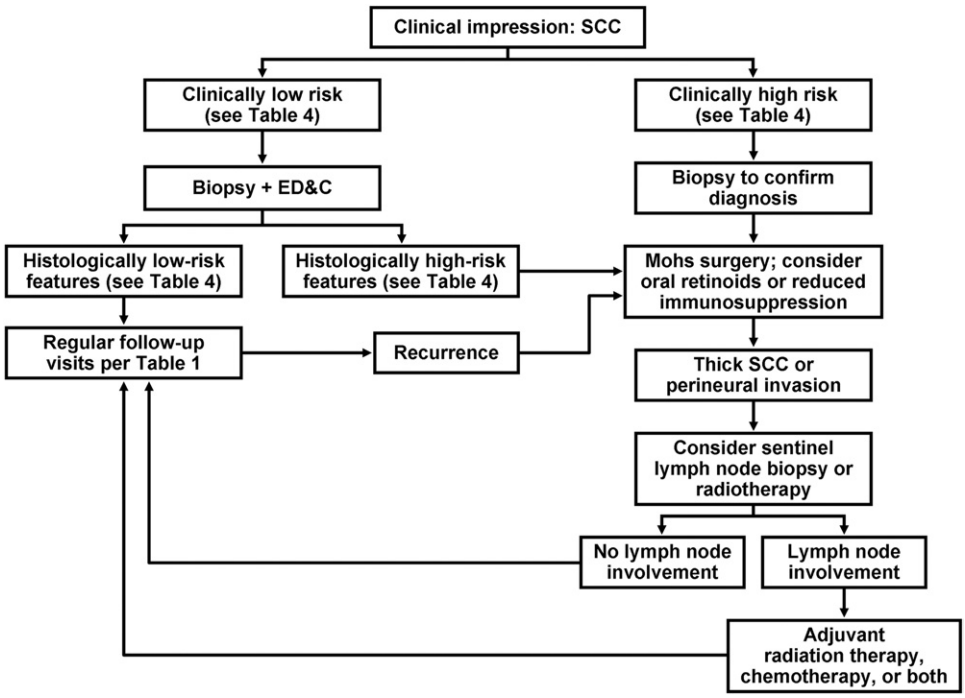

Figure 3 Guidelines for management of SCCs in organ transplant recipients. ED&C, curettage with electrodesiccation. (Adapted from Kovach BT and Stasko T: Squamous cell carcinoma in organ transplant recipients, in Otley CC, Stasko T (eds): Skin Disease in Organ Transplantation. Cambridge: Cambridge University Press; 2008, pp 172-181. Used with permission.)

risk NMSC. Incompletely excised tumors have a recurrence rate of 33% to 50% in OTRs, and additional treatment is therefore essential.[72] The goal of adjuvant radiation therapy is to treat any residual tumor and to prevent recurrence.

Adjuvant chemotherapy and chemoradiotherapy are treatment modalities used after surgical excision or MMS, particularly for high-risk lesions, patients with positive lymph nodes, or SCCs with vascular or perineural involvement. Several authors[73-76] have demonstrated a decreased risk of recurrence and metastasis as well as increased survival for patients with head and neck SCC when postsurgical adjuvant chemotherapy and chemoradiotherapy were used rather than adjuvant radiation alone. However, the utility of adjuvant chemoradiotherapy is still being investigated, and it is unclear whether these treatments will be beneficial in OTRs.

Particularly in unresectable lesions, newer nonsurgical interventions are being investigated. The epidermal growth factor receptor (*EGFR*) gene has been found to be overexpressed in SCCs of the head and neck.[77] Several agents have been developed that block the EGFR, including gefitinib and erlotinib, as well as agents that act as anti-EGFR monoclonal antibodies, such as cetuximab and panitumumab. Recently, recommendations were made by the Head and Neck Cancer Disease Site Group regarding the use of EGFR-targeted therapy in stage III and IV head and neck cancers.[78] The consensus was that platinum-based chemoradiation should remain the treatment of choice for locally advanced tumors. However, in patients who are over the age of 70 years or with locally advanced tumors who cannot medically tolerate chemotherapy, radiotherapy plus cetuximab is recommended to improve overall survival.

Furthermore, although OTRs are at increased risk of developing recurrence or metastasis, there is still no consensus on the use of sentinel lymph node biopsy to aid in the evaluation and staging of a patient with possible subclinical metastasis to the local lymph node basins. The authors of one study found that SCCs near the parotid gland had the highest risk of metastases, especially SCCs that were more than 4 mm thick. The risk of occult nodal disease has been reported as 20%-40% in adjacent nodal regions, making sentinel lymph node biopsy an attractive option to help stage properly selected high risk patients.[79] For patients with aggressive forms of SCC near the parotid gland, a parotidectomy with lymph node dissection may be considered to prophylactically decrease the risk of metastases.

Management of Multiple NMSCs in OTRs

Once multiple NMSCs or isolated high-risk SCCs begin to develop in an OTR, prophylactic treatment and reduction in immunosuppression should be considered. Systemic agents used for prophylactic chemoprevention and recommendations for reduction in immunosuppression will be discussed here; however, ablative resurfacing techniques, such as CO_2 laser, dermabrasion, or chemical peels, may also be considered in areas with a considerable tumor burden primarily consisting of small or superficial NMSC.

Most of the agents described are investigational but may offer options for chemoprophylaxis or adjuvant therapy in

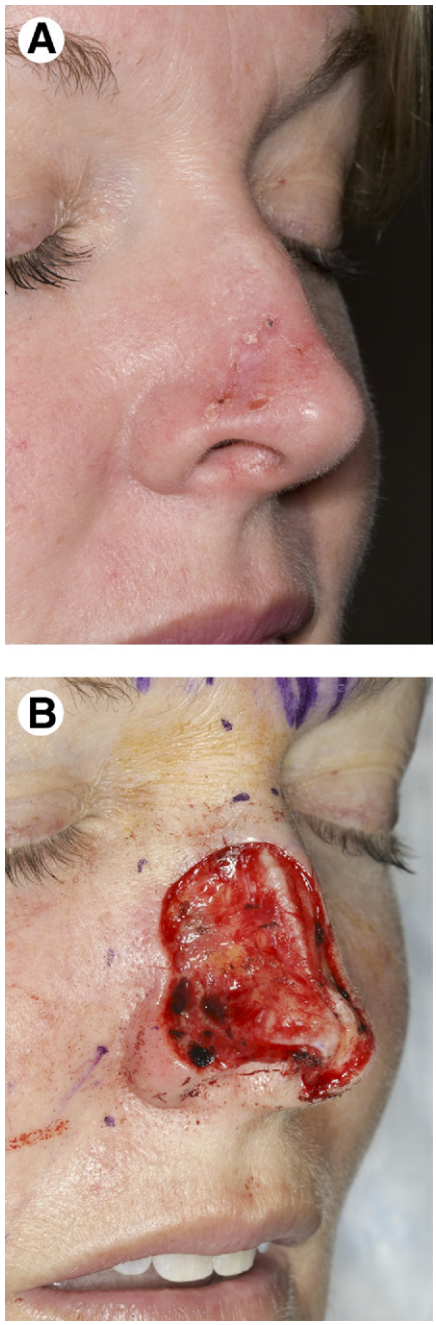

Figure 4 (A) Renal transplant recipient with infiltrating basal cell carcinoma. (B) Post–Mohs micrographic surgery defect demonstrating significant subclinical extension of this tumor.

OTRs with aggressive skin cancers. Oral retinoids, as discussed previously, may be an option for chemoprophylaxis, with a recent review suggesting that acitretin may decrease the incidence of NMSCs in OTRs.[46] Capecitabine is an oral prodrug of 5-fluorouracil. It has been approved by the U.S. Food and Drug Administration for treatment of breast and colorectal cancer. Capecitabine has also demonstrated notable improvements in NMSC in the setting of organ transplantation.[80]

Resiquimod is a Toll-like receptor 7 and 8 agonist. The mechanism of action in resiquimod is similar to that of imiquimod; however, resiquimod is about 10-100 times more potent, with clearance rates of AKs reported from 77% to 90%.[81]

Reduction in immunosuppression is an additional management option when deemed safe. Reducing immunosuppressive medications should be considered in patients with considerable tumor burden and high-risk skin cancers. Decreasing immunosuppression may place these patients at increased risk of graft rejection. Thus, a consensus on a safe level of immunosuppression for the NMSC tumor burden has been recently developed.[82] Dose reduction was stratified into mild, moderate, and severe by risk of permanent allograft function and death. With one NMSC, mild reduction in immunosuppression should be considered in both kidney and liver transplant recipients. With 2 or more NMSCs, a decrease in immunosuppression should be considered in heart allograft patients. The consensus group also recommended moderate reduction in immunosuppression in kidney and liver allograft recipients once these patients begin experiencing more than 25 NMSCs per year or high-risk skin cancers, such as high-risk SCC, Merkel cell carcinoma (MCC), or stage II or greater MM. Severe reduction in immunosuppression is recommended only in patients with skin cancers known to have mortality of approximately 90% over 3 years, including untreatable metastatic SCC, stage IV MM, or metastatic MCC.[82]

In addition, several investigators have shown that the use of mammalian target of rapamycin inhibitors for immunosuppression, as opposed to calcineurin inhibitors, may reduce the risk of malignancy associated with immunosuppression in OTRs.[83-85] MTOR inhibitors, such as sirolimus and everolimus, have a negative growth effect on cancer cells.[84,85] In addition, therapy with sirolimus alone or sirolimus maintenance after cyclosporine withdrawal has shown lower rates of malignancy 2 years after renal transplantation and should be considered in OTRs in whom skin cancer begins to develop.[82]

Management of MM

Several clinical scenarios are considered in the treatment of MM in OTRs. These include (1) a personal history of MM before transplantation, (2) donor transmission of MM, and (3) posttransplant development of MM. In general, patients found to have numerous dysplastic nevi on pretransplant examination should be followed closely, with a low threshold for biopsy. Patients with a history of a dysplastic nevus or MM in situ are considered low risk for metastasis and should not be prevented from receiving a transplant by this information alone.[86]

Patients with superficial spreading melanomas with a Breslow thickness of <1 mm are counseled to wait 2 years from diagnosis before receiving a transplant. Transplant candidates with thicker melanomas and negative lymph node involvement must wait 5 years from diagnosis until transplant. In general, patients with lymph node involvement or metastasis are not considered good candidates for organ transplants.[87]

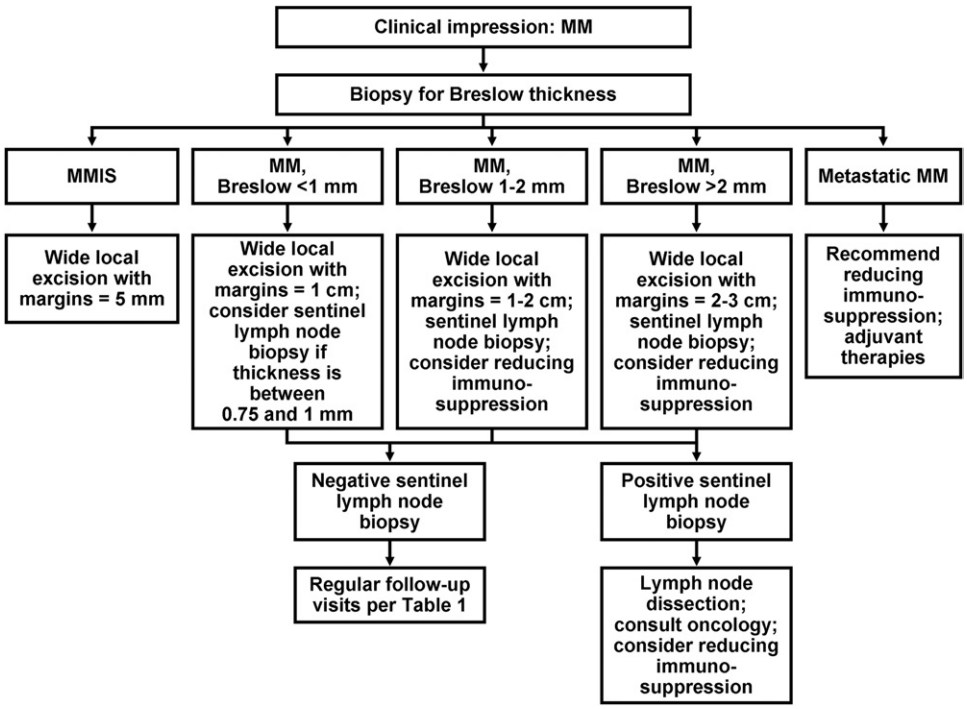

Figure 5 Guidelines for management of MMs in organ transplant recipients. MMIS indicates malignant melanoma in situ.

Treatment recommendations for OTRs found to have de novo MM after organ transplantation are based on guidelines for the immunocompetent population (Fig. 5). Although large population-based studies are lacking, poorer outcomes have been reported in the recent literature in OTRs in whom MM develops.[34] Therefore, in addition to standard recommendations for wide local excision, consideration of a sentinel lymph node biopsy, particularly in MM with a Breslow thickness of 0.75-1.0 mm, is more frequently warranted. Adjuvant chemotherapy and more frequent follow-up examinations with a low threshold for biopsy may also be considered for OTRs in whom MM subsequently develops.

Special Scenarios

Perineural Invasion

Perineural invasion is a particularly worrisome feature, linked to an increased risk of metastasis (Fig. 6).[71] SCCs with perineural invasion should be treated with MMS when it is available.[71,88] Deep, aggressive SCCs with perineural invasion near the parotid gland may be candidates for parotidectomy and neck dissection in addition to MMS. Finally, aggressive SCCs with perineural invasion warrant consideration of postoperative radiation, even when they have already been completely treated with MMS.[89]

Metastatic SCC

OTRs with metastatic SCC are generally assessed on an individual basis. In general, however, these patients should be considered candidates for adjuvant postoperative radiation therapy, retinoid chemoprophylaxis, systemic chemotherapy, and decreased immunosuppression.[35] As mentioned above, capecitabine may be a systemic chemotherapy option for these patients. In addition, in patients with recurrent or metastatic head and neck SCCs, cetuximab plus platinum-based chemotherapy showed improved response rates, as well as better overall and progression-free survival.[78]

In-Transit Metastases

Dermal or satellite metastases can occur with all the common forms of skin cancer but are seen most often with SCC, MCC, and MM, clinically presenting as growing subcutaneous nodules adjacent to previously treated sites. These in-transit metastases are most commonly diagnosed on the forehead and scalp and are seen more frequently in OTRs than in nontransplant patients. Disease-specific mortality at 24 months has been shown to be 33% in OTRs with in-transit metastases.[90] Thus, OTRs with in-transit metastases should be treated with aggressive surgery when containment of the tumor is considered possible, in addition to adjuvant radiation therapy and systemic chemotherapy.

Metastases to Regional Lymph Nodes

With metastatic head and neck SCCs, prolongation of survival and palliation are the main treatment goals because 50% of untreated patients survive only 4 months.[91] SCCs demonstrating in-transit metastasis and positive lymph node involvement should be treated with a combination of lymph node dissection and adjuvant radiation therapy, chemotherapy, or both.

Adjuvant radiation therapy can be used to decrease local nodal recurrence in most cases. In a retrospective study of patients with metastatic head and neck SCC, patients undergoing surgery plus adjuvant radiation therapy had a lower recurrence rate (20% vs 43%) and an improved 5-year dis-

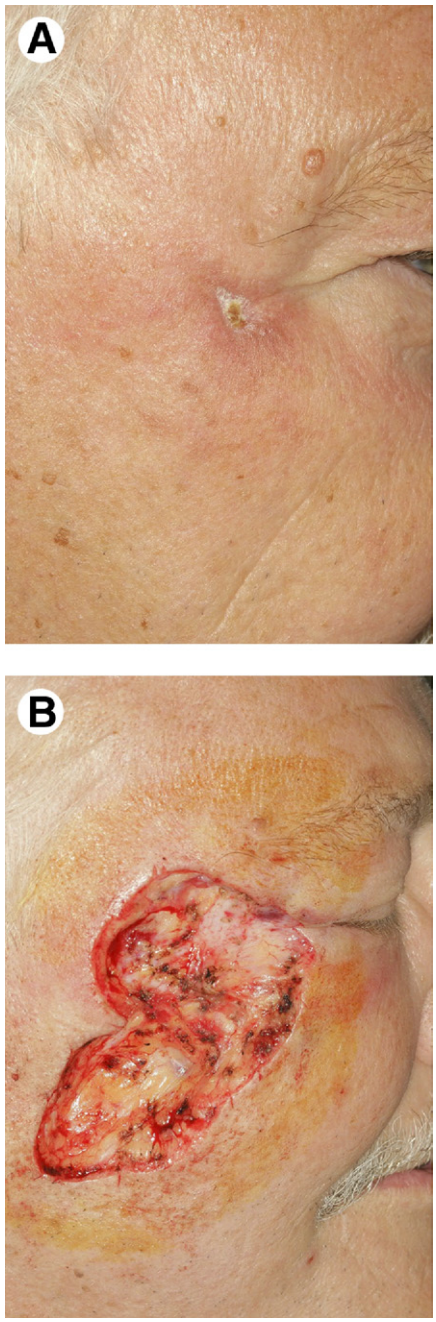

Figure 6 (A) Liver transplant patient with a small SCC showing perineural invasion. (B) Large post–Mohs micrographic surgery defect demonstrating extensive subclinical disease in a high-risk SCC.

ease-free survival rate (73% vs 54%; $P = 0.004$) compared with those who had surgery alone.[92] One study of metastatic SCC in OTRs specifically reported the disease-specific survival at 1 year as 39% in patients with distant or systemic metastases and 89% in OTRs with in-transit or regional nodal metastases, with a mean time from primary to metastatic tumor of 17 months. The overall 3-year disease-specific survival was 56%.[32]

Historically, chemotherapy in the setting of metastatic skin cancer has been used mostly for palliation. Palliative chemotherapy tends to improve quality of life temporarily, with 1 study demonstrating an extension of 10 weeks of life when cisplatin was used.[93]

Induction chemotherapy is used before definitive surgery or radiation therapy to decrease the initial tumor size, to treat subclinical metastases, or both. Because there are conflicting data regarding the efficacy of these regimens in reducing metastases and survival, with some investigators failing to demonstrate improvement in these outcomes,[73,94-97] this modality is now used mainly with concurrent chemoradiotherapy along with combinations of 5-fluorouracil and platinum-based chemotherapy to reduce rates of distant metastatic recurrences. It has been suggested that in OTRs with cutaneous SCCs involving the facial nerve, induction chemoradiotherapy may be used to avoid facial nerve resection.[98]

Definitive chemoradiotherapy is an alternative treatment modality in patients for whom surgery is not an option. This combination regimen is thought to control regional and systemic metastases with the synergistic benefits of tumor radiosensitization and chemotherapy.[99] In a meta-analysis of 63 randomized controlled studies, a 4% increased survival at 5 years was demonstrated with the addition of chemotherapy; however, survival increased 8% at 5 years when chemoradiotherapy was compared directly with radiotherapy alone.[96] More recently, numerous studies in which the authors used either combination chemotherapy or monotherapy with various radiation therapy regimens have demonstrated that concurrent chemoradiotherapy is superior to radiation therapy alone in unresectable head and neck tumors.[100-103] Guidelines for the ideal chemoradiotherapy regimen have not yet been determined. Patient selection is important given the increased toxicities, such as mucositis and weight loss.[104] Therefore, this modality should be used in OTRs with advanced or metastatic SCCs if the benefits outweigh the potential toxicities.

Extensive Scalp Disease

Many older male OTRs may exhibit extensive actinic damage of the scalp, which may be more difficult to treat secondary to follicular extension. In addition, field involvement may further enhance the difficulty of treating subclinical disease. A low threshold for biopsy of lesions suspicious for invasive SCC and aggressive treatment of actinic damage are necessary to decrease local disease and prevent SCC development and progression. Repetitive treatment with topical 5-fluorouracil for extensive actinic damage is recommended. In addition, wide excision and closure with skin grafting are recommended to control local disease and aid in easier observation for possible recurrence in patients with multiple carcinomas on the scalp.

Actinic Cheilitis and SCC of the Lip

In situ and invasive SCC of the lip tends to be more aggressive than SCC on other glabrous skin sites. In addition, OTRs are 20 times more likely to develop lip SCC compared with the general population.[10] Because actinic cheilitis, the precursor to lip SCC, is generally diffuse in OTRs, complete vermilionectomy, whether excisional or with CO_2 laser, may be used to eradicate the premalignant damage,[105] whereas any invasive component should be treated with MMS.

Conclusions

Because OTRs are at increased risk for aggressive skin cancers associated with worse outcomes, early and aggressive treatment of patients exhibiting signs of cutaneous carcinogenesis is necessary. UVR is the most controllable risk factor for skin cancers in OTRs, and education regarding sun protection has proven beneficial in these patients. Skin self-examinations and regular follow-up examinations with a dermatologist are also important in OTRs.

Generally, treatment is determined for each patient by risk factors, individual patient characteristics, and tumor burden. In addition to traditional treatments, such as cryotherapy, ED&C, surgical excision, and MMS, other treatment modalities can be used to treat skin cancer in OTRs. Patients with considerable tumor burden may benefit from prophylactic regimens as well as a reduction in immunosuppression. A multidisciplinary, team-based approach with specialists in the areas of transplant medicine, otorhinolaryngology, dermatology, surgical oncology, radiation oncology, and hematology is ideal when treating this unique group of patients. Through education and management, dermatologists can play an important role in the overall health and outcomes these patients experience because of skin cancer.

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