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Transplant dermatology

By Lauren D. Crow, MD, MPH

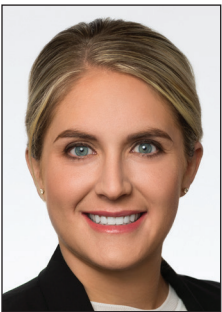
Epidemiology	
	Increase in incidence of skin cancer after transplant
Squamous cell carcinoma	65-fold ¹
Basal cell carcinoma	10-fold ¹
Melanoma	3.4-fold ³
Merkel cell carcinoma	24.6-fold ²
Kaposi sarcoma	84-fold ²
Adnexal carcinomas	9.8-34.3 fold ²

Risk factors for post-transplant skin cancer ⁵	
	Hazard Ratio
White race	7.79 (5.34-11.37)
History of skin cancer	4.69 (3.61-6.09)
Age over 50 at transplant	2.65 (2.12-3.21)
Male gender	1.61 (1.34-1.89)
Thoracic organ (heart or lung)	1.51 (1.26-1.82)

Post-transplant skin cancer screening recommendations by SUNTRAC ⁴ risk group			
Cumulative incidence of skin cancer			
	Average 5-year risk	Average 10-year risk	Screen within:
Low risk*	1.01%	2.33%	10 years of transplant
Medium risk*	6.15%	13.73%	2 years of transplant
High risk*	15.14%	31.75%	1 year of transplant
Urgent risk*	44.75%	74.85%	6 months of transplant

*Risk group calculator available via SUNTRAC app in iOS or Android format

Medications that influence keratinocyte carcinoma risk	
Medication	Proposed mechanism of action
Tacrolimus	↑ KC risk through ultraviolet (UV)-mediated damage of DNA repair pathways
Cyclosporine	↑ KC risk through activation of oncogene ATF3 ↓ apoptosis following UVB damage
Azathioprine, MMF	↑ KC risk through photocarcinogenesis
Everolimus, Sirolimus	↓ KC risk through promotion of autophagy and apoptosis of UV-damaged KCs
Thiazide diuretics	↑ KC risk through photosensitization/phototoxicity
Adalimumab, infliximab, etanercept	↑ KC risk through ↓ tumor surveillance via CD8/natural killer cells ↓ KC risk through inhibition of tumor growth and development
Fluoroquinolones, tetracyclines	↑ KC risk through photosensitization/phototoxicity
Simeprevir, sofosbuvir, efavirenz	↑ photosensitivity, no current evidence of ↑ KC risk
Voriconazole	↑ KC risk through photosensitization/phototoxicity
Vemurafenib, dabrafenib	↑ KC risk through promotion of KC proliferation
Vismodegib	↑ KC risk through promotion of KC proliferation



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Treating field cancerization in SOTR		
Treatment	Mechanism of action	Considerations
Photodynamic therapy + topical 5-aminolevulinic acid (ALA) or methyl-esterified ALA (MAL)	Topical ALA or MAL are precursors of protoporphyrin IX, a photosensitizer that accumulates in dysplastic cells. Light exposure causes production of reactive oxygen species and death of dysplastic and cancerous cells.	Erythema, edema, desquamation, pain, and crusting in the application area; consider frequent cycling
5-FU (topical)	Pyrimidine analog that inhibits thymidylate synthase, DNA replication, cell proliferation	Local inflammatory reactions, repeated treatments necessary for efficacy; consider use of chemowraps
Imiquimod (topical)	Toll-like receptor agonist that enhances anti-tumor immune response	Adverse events include local erythema, scabbing, crusting, flaking, erosion, edema, and weeping; cytokine release syndrome, enhancing immune response may lead to organ rejection
Diclofenac sodium (topical)	Cyclooxygenase inhibitor	Irritant contact dermatitis
Ingenol mebutate (topical)	Macrocyclic diterpene ester found naturally in the sap of <i>Euphorbia peplus</i> ; causes cell death and pro-inflammatory response through protein kinase C delta	Edema, pain, and pruritis in the application area
Oral chemoprophylaxis in SOTR		
Nicotinamide	Vitamin B3 analog	Limited evidence in SOTRs/immunosuppressed population; one very small randomized control trial showing non-significant reduction in NMSC and AK with 500 mg nicotinamide twice daily.
Acitretin	Retinoid; activates nuclear retinoid receptors	Avoid in pts with kidney dysfunction, pregnant women/women planning on becoming pregnant within 3 years; retinoid related side effects limit tolerability (mucocutaneous xerosis, hair loss, pruritis, arthralgia), must be used long term for an effect and discontinuation may lead to cSCC rebound.
Capecitabine	Oral prodrug converted to fluorouracil through a 3 step enzymatic process	Low tolerability; adverse events include fatigue, hand-foot syndrome, diarrhea, nausea/vomiting, mucositis, anemia, hyperuricemia/gout; studies of capecitabine in SOTRs have been small
Immunomodulators associated with decreased risk of NMSC		
Belatacept	CTLA-4 fusion protein; binds to CD86/CD80 to suppress T-cell function	Data limited to renal transplant patients that switched from calcineurin inhibitors to belatacept
Sirolimus	mTOR inhibitor, inhibits lymphocyte growth and proliferation	Data limited to renal transplants

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Immunosuppressive medications and their related cutaneous toxicities		
Medication	Mechanism of action	Associated cutaneous toxicities
Cyclosporine A	Calcineurin inhibitor; inhibits IL-2 transcription	Hypertrichosis, sebaceous hyperplasia, nodulocystic acne, folliculitis, epidermal cysts, gingival hyperplasia, pilar keratosis, pseudofolliculitis barbae
Azathioprine	Metabolized to 6-mercaptopurine, which inhibits de novo purine synthesis	Hypersensitivity reactions, alopecia, increased photosensitivity
Prednisone	Inhibits T-cell proliferation	Acne/acneiform eruptions, skin fragility, purpura, striae distensae
Muromonab	Anti-CD3; inhibits T-cells	Cytokine release syndrome
Mycophenolate mofetil	Inhibits inosine-5'-monophosphate dehydrogenase and de novo purine synthesis	Aphthous ulcers, acne, peripheral edema, worsening of eczema
Tacrolimus	Calcineurin inhibitor; inhibits transcription of IL-2	Telogen effluvium alopecia
Rapamycin (sirolimus)	Binds immunophilin FKBP12 to create a complex that inhibits mTOR signaling; prevents cell proliferation	Aphthous ulcers, palmoplantar peeling, impaired wound healing, acneiform eruptions, pilosebaceous inflammation, peripheral edema
Deoxyspergualin	Inhibits T and B cell differentiation	Unknown
Leflunomide	Inhibits dihydroorotate dehydrogenase, which prevents ribonucleotide synthesis and cell proliferation	Toxic epidermal necrolysis, alopecia, allergic skin reactions
Mizoribine	Inhibits de novo purine synthesis via inosine monophosphate synthetase and guanosine monophosphate synthetase inhibition	Unknown
Brequinar sodium	Inhibits dihydroorotate dehydrogenase, which prevents ribonucleotide synthesis and cell proliferation	Stomatitis/mucositis, dose dependent skin rash, photosensitivity, hyperpigmentation reactions

Common cutaneous infections in SOTR	
Bacterial	
Organism	Typical presentation
Staphylococcus aureus	Cellulitis, recurrent furuncles, abscesses, ecthyma, necrotizing fasciitis
Nocardia	Cellulitis, abscesses, subcutaneous nodules; often precedes disseminated disease
Pseudomonas aeruginosa	Ecthyma gangrenosum, otitis externa, necrotizing fasciitis
Mycobacterium tuberculosis	Subcutaneous nodules, verrucous lesions, or large caseating abscesses

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Common cutaneous infections in SOTR	
Viral	
Organism	Typical presentation
Herpesvirus family	Painful vesicles and ulcers (HSV-1, HSV-2), erythematous papules and vesicles in different stages of healing (VZV), morbilliform rash, ulcers, purpura, necrotic papules, vesiculobullous eruptions, and petechiae (CMV), oral hairy leukoplakia, diffuse maculopapular rash, and post-transplant lymphoproliferative disorder such as B cell lymphomas and primary cutaneous T cell lymphomas (EBV), red and violaceous macules (HHV-8).
Human Papilloma Virus	Warts and condylomas; associated with ↑risk of squamous cell carcinomas
Molluscum contagiosum	Small papules with central umbilication
Trichodysplasia spinulosa polyoma virus	Pruritic papules with central white spicules distributed over the central face and associated with loss of eyebrows and eyelashes
Fungal	
Cryptococcus neoformans	May precede meningitis; papules, pustules, cutaneous or subcutaneous nodules, ulcers, and cellulitis
Histoplasma capsulatum	Erythematous rash, subcutaneous nodules, cellulitis
Aspergillus fumigatus	Papules, nodules, pustules with signs of disseminated aspergillosis
Aspergillus flavus	Ecthyma and necrotic lesions
Candida	Oral thrush, onychomycosis, erythematous skin lesions
Trichosporon	Papules and nodules with central necrosis or ulceration
Blastomycosis dermatitidis	Verrucous lesions, ulcers, pustules, nodules, and plaques
Mucormycosis	Tissue necrosis and ulceration
Dermatophytes	Majocchi's granuloma presents as a perifollicular papules, abscesses, plaques, or nodules; onychomycosis
Parasites	
Demodex family	Acne rosacea

Abbreviations:

- SUNTRAC: Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator
- KC: keratinocyte carcinoma
- UV: ultraviolet
- SOTR: solid organ transplant recipient
- ALA: 5-aminolevulinic acid
- MAL: methyl-esterified aminolevulinic acid
- 5-FU: 5-Fluorouracil
- NMSC: non-melanoma skin cancer
- AK: actinic keratosis
- cSCC: cutaneous squamous cell carcinoma
- HSV-1,2: Herpes simplex virus 1,2
- VZV: varicella zoster virus
- CMV: cytomegalovirus
- EBV: Epstein-Barr virus
- HHV-8: Human Herpesvirus 8

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