CME

# Skin cancer in immunosuppressed patients

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## ABSTRACT

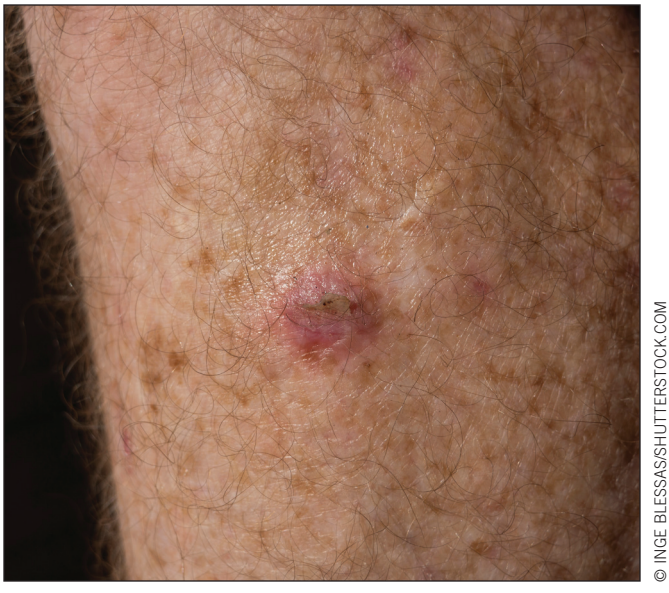
The number of people living with chronic immunosuppression is increasing in the United States. Patients with HIV, those who have had bone marrow or solid organ transplants, and patients taking biologics for autoimmune diseases are at increased risk for skin cancer. Skin cancer in these patients is more aggressive and more likely to metastasize and cause death. Medications and individual risk factors such as sex, age, and ethnicity are independent risk factors for the development of skin cancer. Routine screening and aggressive treatment of actinic keratoses and nonmelanoma skin cancers can reduce patients' skin cancer burden and improve patient outcomes.


**Keywords:** dermatology, skin cancer, immunosuppression, solid organ transplant, HIV, bone marrow transplant

## Learning objectives

- Identify rates of skin cancer in immunosuppressed patients, emphasizing their disproportionally increased mortality.
- Understand how medications can increase skin cancer risk and understand multidisciplinary approaches to modifying these medications.
- Review treatment and recent developments in the management of field cancerization and skin cancer.
- Describe screening recommendations for immunosuppressed patients.

Immunosuppression is becoming a common comorbidity in the United States. Advances in management of numerous conditions including HIV, hematologic malignancies such as chronic lymphocytic leukemia (CLL) and multiple myeloma, solid organ transplantation, and bone marrow transplantation have resulted in patients living longer with chronic immunosuppression.[1] Iatrogenic or medication-induced immunosuppression as a treatment for autoimmune conditions also is increasing.[2]



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A healthy immune system helps protect patients against skin cancer. Both branches of the immune system, innate and adaptive, identify and remove cancer cells.

Macrophages and natural killer (NK) cells are part of the innate or nonspecific immune system, and phagocytose cellular debris and foreign substances such as microbes or cancer cells. NK cells, a subset of white blood cells, are cytotoxic.[3] All cells in the body have major histocompatibility markers that identify cells as *self* rather than nonself or foreign. A cancer cell or a virus-infected cell loses its self marker. NK cells bind to these cells with no self marker and release cytotoxic granules into the cell to cause its death.[3]

Components of the acquired, adaptive, or specific immune system also protect against cancer. Cytotoxic T cells are a part of the adaptive immune system. When something goes awry within a cell, major histocompatibility 1 markers bind to these abnormal cancer proteins and bring them to the cell membrane. This is a signal to the cytotoxic T cells to come and destroy proteins that are cancerous or otherwise malformed.

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**Key points**

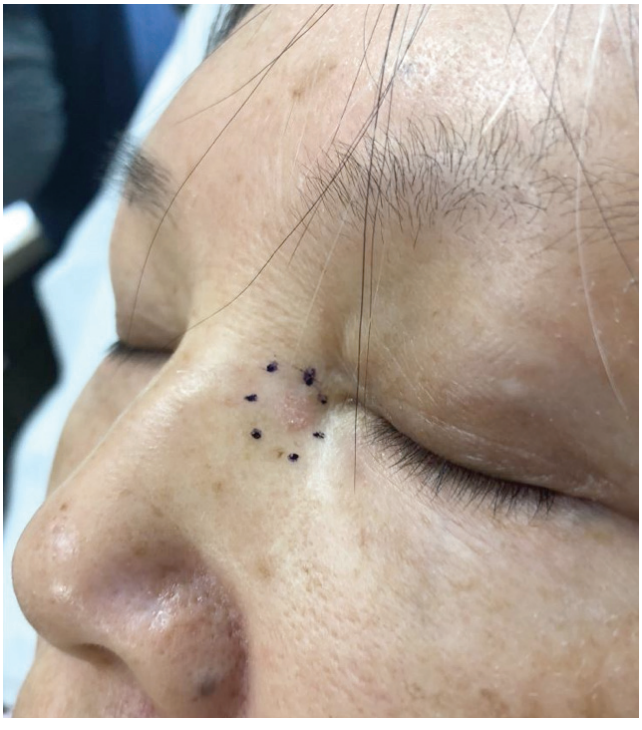
- Patients with immunosuppression are at increased risk for skin cancer.
- In these patients, skin cancer grows more quickly and is more likely to recur, metastasize, and cause death.
- Aggressive treatment of precancerous actinic keratosis is important to prevent high-risk squamous cell carcinoma.
- Oral vitamin B3 (nicotinamide) 500 mg twice daily reduces the rate of skin cancer and actinic keratosis by 23%.

## HOW IMMUNOSUPPRESSIVE MEDICATIONS ALLOW CANCER TO PROLIFERATE

Specific medications are associated with an increase in skin cancer risk. Medications that reduce the number of NK cells and cytotoxic T cells can be associated with increased cancer rates.

Prednisone in high doses impairs the immune system.[4] Doses greater than 1 mg/kg per day in children or more than 40 mg daily in adults can be considered high doses for the purpose of immune function.[5] Glucocorticoids move passively through the cell membrane into cells, where they bind to glucocorticoid receptors.[5] This complex moves to the nucleus, where it binds to and blocks proinflammatory genes and inhibits leukocytes (macrophages) from infiltrating a site of inflammation.[5]

**FIGURE 1.** Squamous cell carcinoma in situ on the left nasal sidewall of a kidney transplant recipient



Azathioprine, used in solid organ transplantation as well as for other indications in dermatology and rheumatology, inhibits purine synthesis necessary for components of DNA in leukocytes and lymphocytes (that is, NK cells, T cells, and B cells). Ultraviolet (UV) light interacts with the skin and causes cellular damage. Azathioprine inhibits the immune system's ability to repair this UV-induced cellular damage, increasing skin cancer risk. Patients who take azathioprine after receiving solid organ transplants are twice as likely to develop squamous cell carcinomas and 1.3 times more likely to develop melanoma than transplant recipients who did not take azathioprine as a maintenance therapy after transplant.[6,7]

Regardless of the particular solid organ transplanted, medications from three classes are an integral part of any post-transplant regime: antimetabolites (also called antiproliferative agents), specifically azathioprine or mycophenolate; calcineurin inhibitors such as tacrolimus or cyclosporine; and prednisone. Patients start with a high-dose corticosteroid and over 4 to 6 months are tapered to a lower dose of prednisone. During episodes of rejection, corticosteroids would likely be increased.

## AT-RISK GROUPS

**HIV** For the reasons outlined above and likely others that we do not understand well, patients with compromised immune systems have an increased occurrence of skin cancer: among patients with HIV, men develop skin cancer at a 3.6 times greater rate and women develop skin cancer at a 2.1 times increased rate than patients without HIV.[8] Interestingly, men and women on antiretroviral therapy have a lower rate of developing skin cancer.[8] This supports the idea that a functioning immune system protects against skin cancer development.

**Transplant** More than 826,000 solid organ transplants were performed in the United States between 1988 and 2020.[9] Patients who have received transplants are at greater risk for skin cancer than their age- and sex-matched peers; the risk for squamous cell carcinoma is increased 65 to 200 times (**Figure 1**).[10] A population-based study integrating an Irish national cancer registry and the national renal transplant database of Ireland found a 16 times increased risk of basal cell carcinoma development in this population.[11] A study of transplant patients from 1987 to 2010 showed melanoma risk was two to three times greater than the general population.[7] However, a cohort of renal transplant recipients from 2004 to 2012 found a fivefold increased risk of melanoma in these patients.[12] The incidence of post-transplant melanoma, although still less than squamous cell or basal cell carcinoma, appears to be increasing over the past decade.

**Chronic lymphocytic leukemia** Long-term survivors of chronic lymphocytic leukemia have nearly a fourfold increased risk of melanoma.[13] Patients who have received hematopoietic cell transplants have a relative risk of

developing melanoma that is 3.5 to 8 times greater than that of the general population.[14] Patients with chronic lymphocytic leukemia and those who have received hematopoietic cell transplants also have an increased risk for development of nonmelanoma skin cancer. Nonmelanoma skin cancer is the most common second primary malignancy in patients with chronic lymphocytic leukemia.[13] These patients had a 20-year cumulative incidence of 6.5% for basal cell carcinoma and 3.4% for squamous cell carcinoma.[14]

**Tumor necrosis factor (TNF)-alpha inhibitors for autoimmune disease** Patients on TNF-alpha inhibitors for autoimmune diseases such as inflammatory bowel disease, psoriasis, rheumatoid arthritis, and ankylosing spondylitis are at increased risk for nonmelanoma skin cancer, but no data have supported that these patients are at increased risk for melanoma.[15,16] More data are needed to assess skin cancer development in this population. Because quieting an overactive immune system is a goal of treatment for these patients, perhaps increased immune system activity reduces their skin cancer risk at baseline.

## INCREASE IN SKIN CANCER MORTALITY

In patients with immunosuppression, skin cancer is more aggressive, grows at a more rapid rate, metastasizes more frequently, and causes death more often. A study of patients with chronic lymphocytic leukemia found a 17-fold increased mortality from nonmelanoma skin cancer over the general population.[17] Patients with chronic lymphocytic leukemia and squamous cell carcinoma or melanoma have poor outcomes because of an increase in local recurrence, nodal metastases, and distant metastases.[18] A survey of deaths from nonmelanoma skin cancer in Australia found that about 17% of patients who died from squamous cell carcinoma of the skin had a concurrent diagnosis of chronic lymphocytic leukemia.[19] These studies from Australia illustrate that skin cancer is not only more prevalent but also more deadly in patients with immunosuppression. Nonmelanoma skin cancer is tracked in Australia; however, in the United States it is not a reportable cancer, which limits similar studies for mortality. Of note, the UV index in Australia is higher than in the United States, which may influence incidence rates. A study of patients from the northeastern United States found that patients with chronic lymphocytic leukemia had an equal risk of dying from that disease as they did of dying from skin cancer.[20]

Patients who have had solid organ transplants also have an increased rate of death from skin cancer. A recent review of all US organ transplant recipients between 1987 and 2013 calculated that mortality from skin cancer in the cohort was nine times higher than that reported by the CDC for the general population.[21] Though the incidence of squamous cell carcinoma is higher than that of melanoma, melanoma still results in more deaths in this population, particularly in patients who are White, male, over age 50 years, or have had heart or lung transplants.[21]

## RISK FACTORS

Race, age, and personal history of sun exposure are all independent risk factors that contribute to skin cancer risk. White men over age 50 years with heart or lung transplants are at the highest risk of dying from skin cancer post-transplantation.[21] Heart and lung transplant recipients are at increased risk for skin cancer mortality over liver and kidney recipients because they need higher doses and longer durations of immunosuppression to combat organ rejection.[21,22] Cumulative sun exposure increases rates of nonmelanoma skin cancer to sun-exposed sites like the arms and face; a history of nonmelanoma skin cancer before transplant also is associated with increased rates of nonmelanoma skin cancer after transplant.[23]

A study of non-White organ transplant recipients found distinct ethnic differences in risk factors for development of post-transplant skin cancer.[24] The squamous cell carcinomas diagnosed in Black patients developed in sun-protected areas and occurred in patients whose lesions tested positive for human papillomavirus (HPV) and/or who endorsed a history of viral warts.[24] Skin cancer in patients of Asian ancestry was located on sun-exposed areas and occurred in patients who immigrated to the United States from equatorial locations.[24] Immigration history and history of warts or HPV are important risk factors in patients of these ethnicities.[24]

Risk factors for high-risk lesions that appear most likely to recur or metastasize were summarized as a consensus opinion from the International Transplant Skin Cancer Collaborative (ITSCC) in 2016.[25] These included size greater than 2 cm and high-risk location, with mucous membranes (mouth, penis, anus, and vulva) being the highest-risk locations followed by lip, ear, and temple.[25] Depth greater than 2 mm and perineural invasion also were risk factors for recurrence or metastasis.[25]

## APPROACH TO MANAGEMENT

When possible, perform a baseline examination for skin cancer for any patient before starting immunosuppression treatment. If the patient has skin cancer before solid organ transplantation, identify and treat it before organ transplantation and immunosuppression. See the ITSCC guidelines for wait times before transplantation for patients with a history of a high-risk malignancy (**Table 1**).

A baseline skin examination also is recommended before starting a high-risk medication, such as:

- Prednisone more than 10 mg/kg for more than 3 weeks
- Azathioprine[6]
- Hydrochlorothiazide (emerging data on this)[26]
- Calcineurin inhibitors (questionable data)[6]
- TNF-alpha inhibitors (questionable data)[16]
- Ruxolitinib.[27]

After a baseline skin examination, all patients with immunosuppression should have regular full-body skin examinations by a dermatologist or dermatology PA every 6 to 12 months to monitor for skin cancer.[23] See **Figure 2** for the ITSCC follow-up recommendations for organ transplant patients. No guidelines exist for patients with chronic lymphocytic leukemia or for other patients with immunosuppression, so the ITSCC figure may be used as a guideline for follow-up.

Clinicians in dermatology who monitor these patients should document when skin cancers develop, to determine if skin cancer development is increasing over time. Another factor that can increase skin cancer development is a reduction in baseline immune function. Patients who have had solid organ transplant receive increased immunosuppression when they are rejecting their transplanted organ, which can result in increase in skin cancer development.[28]

## TREATING ACTINIC KERATOSES AND SKIN CANCER

Aggressive treatment of precancerous lesions (actinic keratoses) is integral to managing squamous cell carcinoma in immunocompromised patients. Nicotinamide, also known as niacinamide or vitamin B3, given 500 mg twice daily reduces nonmelanoma skin cancer development by 23% in patients with a history of nonmelanoma skin cancer.[29] This vitamin is well tolerated and beneficial for all patients with a history of nonmelanoma skin cancer.

In patients with clinical evidence of chronic sun exposure, including poikiloderma of Civatte and numerous actinic keratoses, the goal should be to keep the patient's actinic burden as low as possible. Areas such as the face, dorsum

**TABLE 1.** Recommended wait times before transplantation for patients with a history of skin cancer

| Skin malignancy | Appropriate treatment before transplantation | Wait time after treatment and before transplantation |
|---|---|---|
| ***Cutaneous squamous cell carcinoma*** | | |
| No history but at risk for squamous cell carcinoma | Treatment of field disease | No delay necessary |
| Low risk | Surgical excision with clear margins or Mohs micrographic surgery | No delay necessary |
| High risk (not including perineural invasion) | Surgical excision with clear margins or Mohs micrographic surgery | 2 years |
| High risk with perineural invasion or two or more risk factors | Surgical excision with clear margins or Mohs micrographic surgery | 2 to 3 years |
| High risk with local nodal metastatic disease | Surgical excision with appropriate lymph node dissection, with or without adjuvant radiation therapy | 5 years |
| Distant metastasis | Refer for oncology opinion | Not eligible for transplantation |
| ***Merkel cell carcinoma*** | | |
| Local with negative sentinel lymph node biopsy | Wide local excision with or without adjuvant radiation therapy | 2 years |
| Local with nodal metastasis | Wide local excision, lymph node dissection, adjuvant radiation therapy | 3 to 5 years |
| Distant metastasis | Refer for oncology opinion | Not eligible for transplantation |
| ***Malignant melanoma*** | | |
| *In situ* | Wide local excision | No wait necessary; follow up at 3 months post-transplantation |
| Stage Ia | Wide local excision | 2 years |
| Stage Ib/IIa | Wide local excision with or without sentinel lymph node biopsy | 2 to 5 years |
| Stage IIb/IIc | Wide local excision with sentinel lymph node biopsy | 5 years |
| Any stage III or IV | Refer for oncology opinion | Not eligible for transplantation |

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of the hands, lips, scalp, and ears may have actinic keratoses and invasive squamous cell carcinoma in the same field (**Figures 3** and **4**).[30,31] A lesion that clinically appears to be an actinic keratosis in an immunocompetent patient can be diagnosed by histopathologic appearance as a squamous cell *in situ* or an invasive squamous cell carcinoma. This results in patients often having lesions that should be biopsied and excised, treated with cryotherapy or with watchful waiting, even though such lesions are more invasive than they appear clinically.

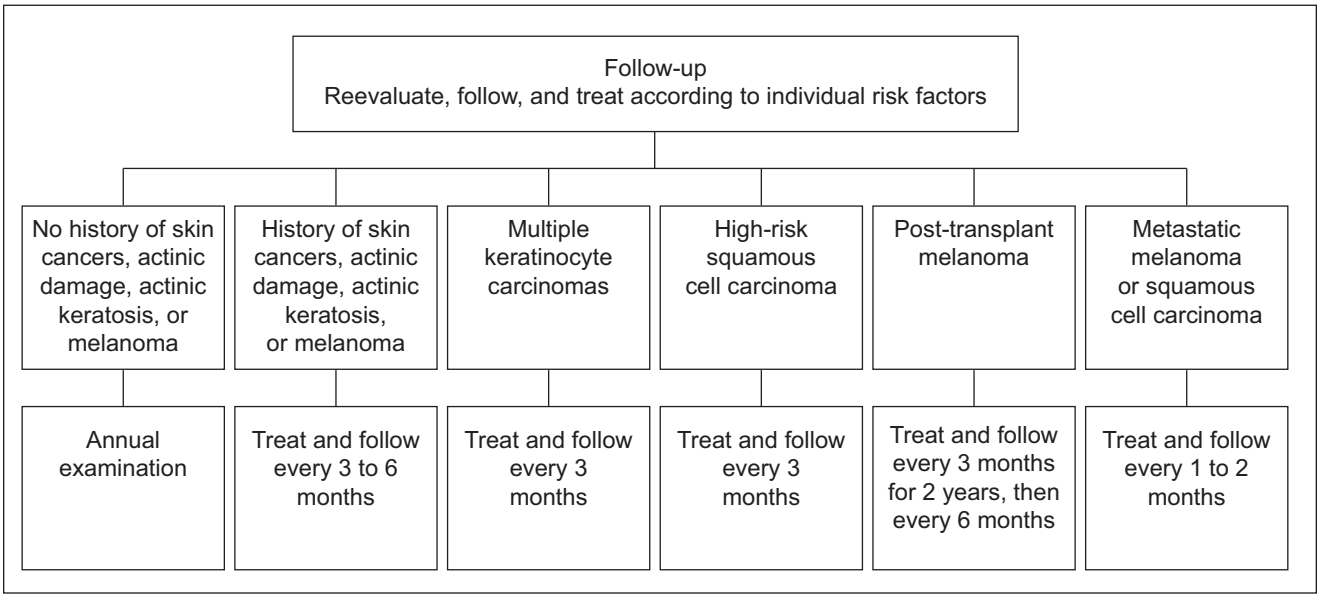
Precancerous lesions can be treated in a variety of ways. Cryotherapy with liquid nitrogen can treat solitary actinic keratoses.[32] Patients with numerous actinic keratosis require field treatment with topical chemotherapy—specifically 5-fluorouracil, 5-fluorouracil in combination with calcipotriene, or photodynamic therapy.[23,32,33] Typically, areas with more actinic keratoses are areas that receive cumulative daily sun exposure, including the face, lips, ears, scalp, forehead, dorsum of the hands, and forearms. Extremities with extensive hyperkeratotic actinic keratoses can be managed with chemowraps, in which 5-fluorouracil is applied to the area and then occluded with petrolatum-impregnated gauze, zinc oxide, and self-adherent bandages.[34] These are changed weekly in the office so that the patient can be monitored for response and for adverse reactions including pain or secondary infection. Of note, this use of 5-fluorouracil is off label.[34]

**Basal and squamous cell carcinomas** can be treated with topical chemotherapy, electrodessication and curettage, wide local excision, or Mohs microsurgery. National Comprehensive Cancer Network (NCCN) guidelines recommend choosing a treatment based on specific traits of the skin cancer, including depth of invasion into skin and nerves, size, and tumor location.[35,36] NCCN recognizes that patients on immunosuppression have an increased risk of skin cancer recurrence and recommend that all nonmelanoma skin cancers in these patients be treated with wide local excision or Mohs microsurgery, as indicated by location and size.[35,36]

High-risk lesions that should be treated with Mohs microsurgery include lesions greater than 2 cm, those in high-risk locations (ear, lip, scalp, temple), lesions more than 2 mm deep, poorly differentiated lesions, those with perineural invasion, and lesions in patients with a history of lesion recurrence.[25]

Patients with more than five squamous cell carcinomas in 2 to 3 years or field cancerization not controlled on topical 5-fluorouracil, 5-fluorouracil/calcipotriene, or photodynamic therapy should be started on oral soriatane, a drug traditionally used in dermatology to treat psoriasis.[37] Soriatane is a vitamin A derivative that reduces the rate at which patients make actinic keratoses and squamous cell carcinomas.[38] However, the effects of soriatane take 6 to 8 weeks to see clinically and only last while the medication is being taken. If the medication is stopped because of adverse reactions, which are common, the patient's rate of squamous cell carcinoma development rebounds within about 8 weeks.[32,38] Adverse reactions to soriatane include inflammatory nail paronychias, hair and eyelash loss, skin stickiness, ectropions (everting of the eyelids), dyslipidemia, and photosensitivity.[38] This medication is contraindicated in pregnancy.[38]

**FIGURE 2.** Screening algorithm for follow-up in patients after solid organ transplantation



If the patient has had more than six invasive squamous cell carcinomas in a year, consider referral to a medical oncologist for evaluation of the risks and benefits of starting capecitabine, an oral medication also used to treat metastatic breast and colorectal cancers.[30,39,40] Capecitabine is a prodrug that is enzymatically converted to the antimetabolite fluorouracil in the tumor, where it inhibits DNA synthesis and slows tumor growth. The drug typically is given in pulse doses of 1 to 2 weeks followed by a week off.[39] Data are unclear on whether the drug's benefit is sustained after termination of therapy or whether it has the rebound effect seen in soriatane.[39] Adverse reactions to capecitabine include fatigue, diarrhea, oral ulcers, and hand and foot syndrome.[30] More research is warranted.

Immune checkpoint inhibitors such as pembrolizumab and nivolumab treat metastatic squamous cell carcinoma. However, these medications have not been used for treatment for metastatic cancer in patients who have had solid organ transplants because of early case reports that these drugs caused organ rejection, allograft loss, and death.[41] This is an area of emerging study and research. Therefore, early and aggressive intervention for treatment and prevention of skin cancer is vital for these patients.

## WORKING AS AN INTERDISCIPLINARY TEAM

When a patient develops skin cancers at increasing frequency, primary care providers should contact the prescriber of the immunosuppressive drugs to discuss the risks and benefits of reducing the patient's dosage of immunosuppressants.[42] In patients who have had solid organ transplants, reducing immunosuppressant dosages can result in organ rejection, organ loss, and patient death; dosage changes must be weighed against these risks. However, certain transplant organs are more amenable to modification of immunosuppression than others. For example, immunosuppression can be reduced in a patient who had a kidney transplant and develops metastatic skin cancer because graft rejection would not be fatal; hemodialysis provides a life-sustaining treatment. The liver also has an amazing regenerative ability; thus, a transplanted liver can withstand a small amount of rejection.[42] Heart and lung transplants are not as amenable to modification.

Transplant patients on new regimens that include mycophenolate rather than azathioprine have a lower risk of

**FIGURE 3.** Moderately differentiated squamous cell carcinoma (circled) on the left cheek in a field of actinic damage including actinic keratoses, squamous cell carcinoma in situ, and squamous cell carcinoma. The patient's left ear was removed as part of squamous cell carcinoma treatment.

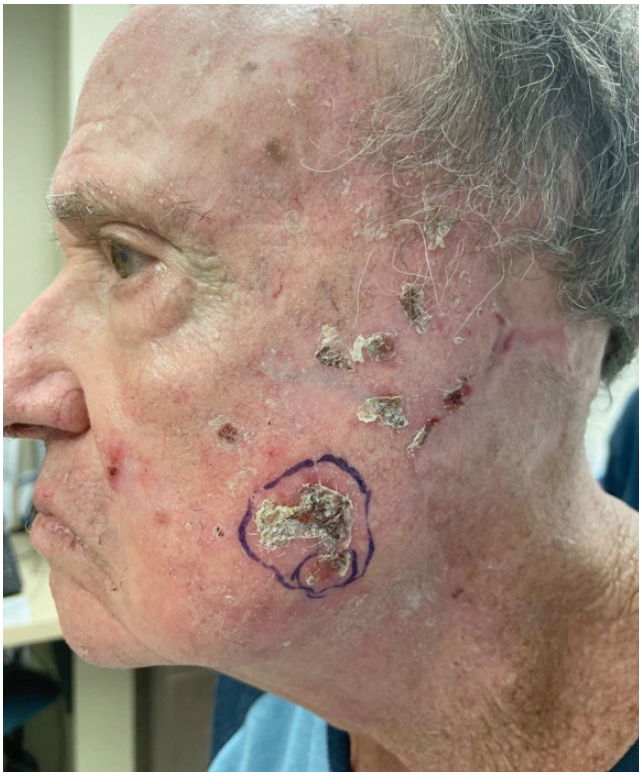
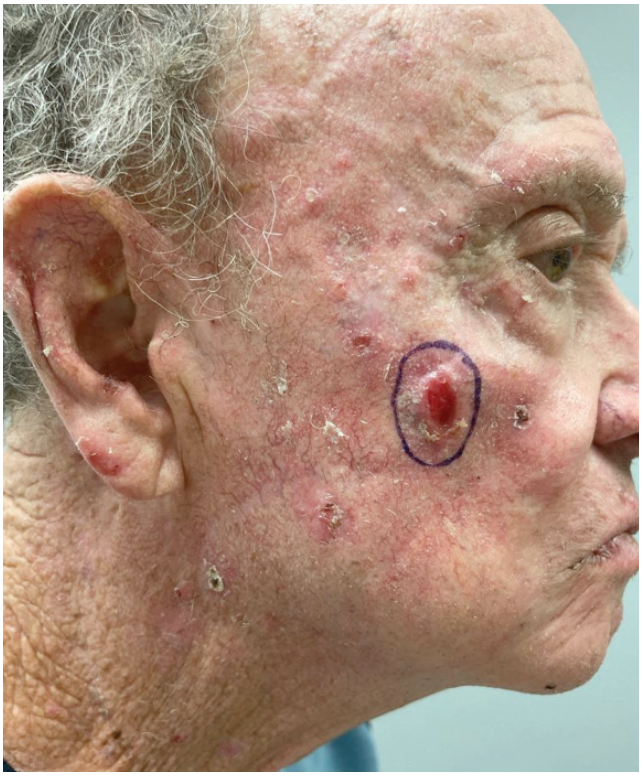


**FIGURE 4.** Well-differentiated squamous cell carcinoma on the right cheek (circled) in a field of actinic damage including actinic keratoses, squamous cell carcinoma in situ, and squamous cell carcinoma



developing squamous cell carcinoma.[6] However, patients who received a transplant before 1995, the year mycophenolate was approved, may have a history of azathioprine exposure. Discontinuing azathioprine does not lower the risk of developing skin cancer to zero, but switching to mycophenolate has been shown to reduce patients' risk for squamous cell carcinoma.[6] If a patient is on azathioprine and is developing squamous cell carcinomas, discuss the risks and benefits of switching to mycophenolate.

Sirolimus and everolimus are mammalian target of rapamycin (mTOR) inhibitors that block B- and T-cell activation and prevent cell cycle proliferation.[43] The mechanism of action of these drugs makes them less oncogenic.[44,45] Sirolimus or everolimus can be substituted for calcineurin inhibitors in transplant regimens to reduce cancer risk.[44] However, the benefit is greatest if the switch from calcineurin inhibitor to mTOR inhibitor is made after the first incidence of nonmelanoma skin cancer.[44] Also, a systematic review and meta-analysis of 5,000 patients found increased risk of mortality from heart disease and infection after patients were switched to an mTOR inhibitor; although these findings have not been replicated, risks and benefits of mTOR therapy need to be weighed and timing is important.[45]

## PATIENT MONITORING

Patients who have had solid organ transplants appear to have increased risk for noncutaneous cancers, including colorectal cancer, lung cancer, and anogenital cancer.[46,47] A Dutch study of kidney transplant recipients found that median survival after a cancer diagnosis was only 2.7 years, compared with 8.3 years for kidney transplant recipients who did not have cancer.[48] As with skin cancer, malignancies in transplant recipients often were more aggressive and developed at a much later stage than cancers in patients who did not have transplants.[46] Encourage patients to keep up with all age-appropriate cancer screenings. The American Society of Transplantation recommends all patients have occult blood testing or flexible sigmoidoscopy every 5 years to screen for colon cancer, and annual or biennial mammograms after age 50 years for women.[21,46,49,50]

## SKIN CANCER PREVENTION EDUCATION

A systematic review of cutaneous malignant neoplasms in patients who received hematopoietic cell transplants found that the time for melanoma to develop was 1 to 4 years from time of cell transplantation, 2 to 7 years for squamous cell carcinoma, and 7 to 9 years for basal cell carcinoma.[14] Clinicians should tell patients that their risk of skin cancer increases as the time after their transplant increases, and they should consequently increase the frequency of their dermatology follow-ups to monitor for development of skin cancer.

At every visit, talk to patients about lifestyle modifications that can reduce their modifiable risk factors. Counsel patients on aggressive sun protection, specifically on wearing long-sleeved shirts and wide-brimmed hats, avoiding the midday sun, and using SPF 30 to 50 sunscreen daily on the face, lips, ears, scalp (if bald or with thinning or thin hair), neck, upper chest, forearms, and hands. A recent study found that skin cancer education early in the transplant timeline increased patients' knowledge as well as improved sun-protective behaviors, specifically regular sunscreen use and avoiding the midday sun.[49]

Patients with a past or present history of working outdoors (such as ranchers, park rangers, lifeguards, landscapers, and construction workers) or who have outdoor hobbies such as gardening, sailing, marathon running, or swimming are at greater skin cancer risk because of their increased cumulative UV light exposure.[7,12,19] Instead of limiting these activities, patients can use sunscreen daily and wear sun-protective clothing.

## HPV

HPV is associated with cervical, vaginal, anal, penile, and certain head and neck cancers in the general population, specifically the tonsils and base of the tongue.[51] Patients who have had solid organ transplants are at increased risk of these malignancies compared with the general population.[52]

The link between HPV and cutaneous squamous cell carcinoma is less well established. A meta-analysis of 12 articles showed that tumors in immunosuppressed patients were three times more likely to contain HPV than a tumor in an immunocompetent patient.[53]

Emerging research has focused on whether the HPV vaccine can be used to strengthen the immune system's ability to fight off viral causes of squamous cell carcinoma. Transplant patients can mount a significant immune response to the vaccine.[54] A recent case report of two patients found that patients developed no basal cell carcinomas and about two-thirds fewer squamous cell carcinomas in the year following the vaccine compared with the year before vaccination.[55] More robust research is needed in this area, but HPV vaccination may be beneficial to patients who are chronically immunosuppressed.

## CONCLUSION

Skin cancer in patients who are immunosuppressed is more aggressive, more likely to recur, and more likely to cause death. Medications such as azathioprine or ruxolitinib as well as individual risk factors such as sex, age, and ethnicity are independent risk factors for the development of skin cancer. Routine screening and aggressive treatment of actinic keratoses and nonmelanoma skin cancers can reduce patients' skin cancer burden and improve patient outcomes. **JAAPA**

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