Curr Surg Rep (2019) 7:1
https://doi.org/10.1007/s40137-019-0223-3

Aggressive Cutaneous Malignancies: A New and Dangerous Phenomenon in Transplant Patients

Joseph Lopez[1] · Christine G. Gourin[2] · Anthony P. Tufaro[3]

Published online: 14 February 2019

Abstract
Purpose of Review In the general population, the incidence of cutaneous malignancies has been rising. However, a particular high-risk population—transplant recipients—suffer at an alarming rate from the incidence of aggressive cutaneous malignancies. The purpose of this review is to examine the latest literature on the epidemiology, risk factors, pathogenesis, prognosis, prevention, and management of highly aggressive cutaneous cancers in the transplant population.
Recent Findings With innovations in immunosuppression, surgical technique, and perioperative care, organ transplant recipients are now living longer but now suffer from increasing morbidity secondary to the rising incidence of these aggressive cutaneous cancers. Currently, the three most common causes of delayed mortality following organ transplantation are complications associated with infectious diseases, cardiovascular disease and malignancy.
Summary Cutaneous malignancies have now become the most common malignancy in this unique population.

Keywords Cutaneous Malignancies · Immunosuppression · Transplantation

Introduction

Since the first kidney transplantation was performed in 1954, significant strides have been made in the care of organ transplantation patients [1]. Life expectancies have dramatically risen with new innovations in surgical technique, perioperative care, and immunosuppression [2]. Recent reports show that five-year survival rates are as high as 85% and as low as 43% in kidney and lung transplantation recipients, respectively [3–6]. Although there continues to exist an organ donation shortage, over 100,000 organ transplantation recipients currently live in the United States with an estimated 30,000 additional organ transplantations performed annually. While, organ transplantation dramatically improves the survival of patients with organ failure, the survival benefits of organ transplantation are hampered by the morbidity and, at times, mortality from cancer [7].

Organ transplant recipients have a 3- to 4-fold higher risk of developing cancer than the general population (Fig. 1). The most common malignancy after organ transplantation is skin cancer [8]. In fact, approximately 50–70% of all organ transplantation patients are diagnosed with cutaneous malignancies. Although cutaneous malignancies are largely manageable, a subset of patients develop highly aggressive tumors that can cause substantial

This article is part of the Topical collection on *Surgical Oncology*.

✉ Joseph Lopez
jlopez37@jhmi.edu

Christine G. Gourin
cgourin1@jhmi.edu

Anthony P. Tufaro
anthony-tufaro@ouhsc.edu

[1] Department of Plastic & Reconstructive Surgery, Johns Hopkins Hospital, 1800 Orleans ST, Baltimore, MD 21287, USA

[2] Department of Otolaryngology-Head & Neck Surgery, Johns Hopkins University, 601 North Caroline Street, Baltimore, MD, USA

[3] Department of Surgery, Division of Plastic Surgery, Chief of Plastic Surgery, University of Oklahoma Health Sciences Center, 800 Stanton L. Young Blvd, Suite 8300, Oklahoma City, OK 73104, USA

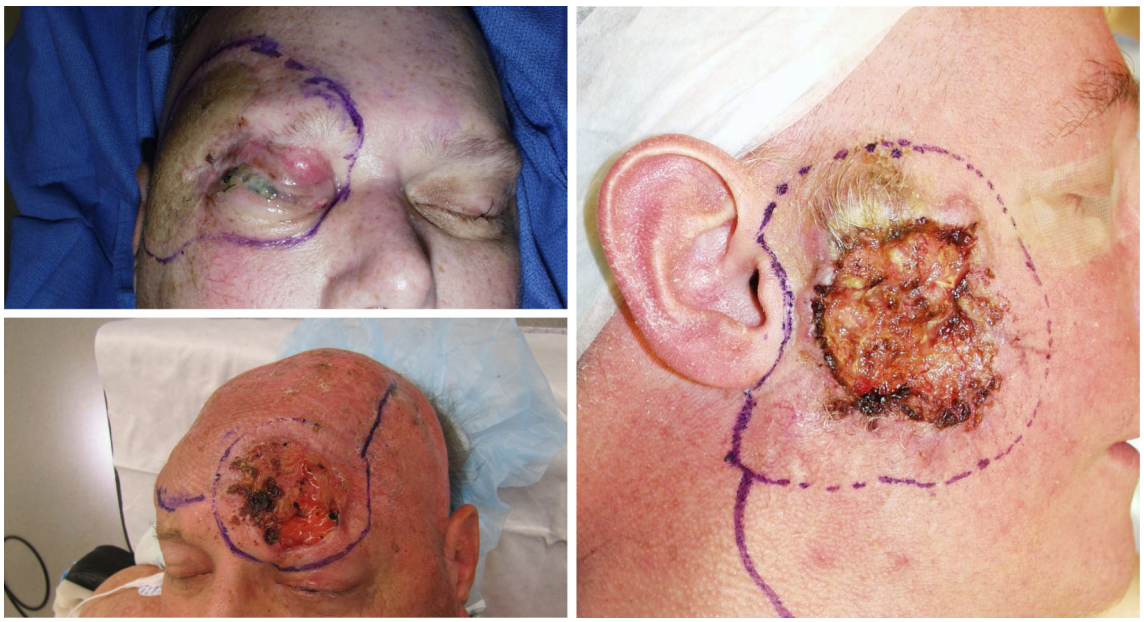

Fig. 1 Clinical examples of aggressive cutaneous malignancies in transplant patients. Complex case of a squamous cell carcinoma in the periorbital region in a liver transplant patient (top left). Complex case of squamous cell carcinoma that invaded frontal sinus, orbit, and dura in a kidney transplant patient (Bottom left). Complex case of a squamous cell carcinoma that invaded the parotid gland in a kidney transplant patient (far right)

morbidity and mortality. For example, it is not uncommon for high-risk transplant patients to develop over several dozen cutaneous malignancies in a single year with resulting high risk of metastasis and death [9]. While the vast majority of these malignancies are squamous cell cancers, we also see an alarming increase in Merkel cell carcinoma, melanoma and cutaneous lymphoma [10]. Interestingly, we also see squamous cell cancers appear more commonly than basal cell carcinomas, which is the opposite of what we normally see in the general population. Additionally, the incidence of cutaneous squamous cell carcinoma is 250 times higher in transplant recipients as compared to non-transplant patients. This review discusses the rising incidence of these aggressive cutaneous malignancies in the transplantation population. Furthermore, we include an in-depth discussion of the pathogenesis, epidemiology, prevention and management of these malignancies.

Epidemiology

Classically, two population based cohort studies out of Norway and Australia provided much of the current knowledge regarding the incidences of cutaneous malignancies in organ transplantation recipients [11, 12]. In the Australian study, Ong et al. documented a 45% incidence of skin cancers within 10 years of transplantation [11]. In the Norwegian study of heart and kidney transplant recipients, the incidence was estimated to be 65 times greater in transplant recipients when compared to the general population [12]. A smaller but similar study out of Oregon documented a 35% incidence rate after 10 years in patients with heart transplants [13]. Other more recent population-based studies performed over the last decade have found a 2- to 4-fold increase risk of skin cancers [14, 15]. Because of these and other cohort studies, the high risk of skin cancer after solid organ transplantation is now well documented and accepted.

More recent studies have focused on examining whether the risk of cutaneous malignancies has changed during the last few decades [16, 17]. A recent Norwegian study examined a large cohort of over 8000 organ transplantation recipients with long-term follow-up (over 6.5 years) and underwent transplantation in the 1970s–2010s. This study suggested that the rate of cutaneous malignancies was actually declining in Norway due to more individualized immunosuppression therapy. However, another recent large study from the Netherlands found contradicting results [16]. Krynitz et al. examined the incidence of all skin cancers in over 10,000 kidney, liver, heart, and lung transplant recipients from 1970s to 2000s, and found that the rate of squamous cell carcinoma increased 100-fold, overall during that period, while the risk of other cancers only doubled. Interestingly, the risk for patients with kidney and lung transplantation after 10–20 years was 200-fold. The authors argued that this finding was largely explained by the accelerating rate of squamous cell carcinoma in a smaller, high-risk group of patients. For

example, in patients who had developed a fifth squamous cell carcinoma, the rate of developing another squamous cell increased to over 80%. This study also found an extremely high relative risk for a number of rare, aggressive cutaneous cancers including Merkel cell carcinoma and Kaposi's sarcoma. Engels et al. similarly found a 61-fold increase in the risk of Kaposi's sarcoma in the United States [17]. Lastly, it is estimated that transplant recipients have a 2- to 4-fold increase risk of developing melanoma [18, 19]. The Oxford—United Kingdom transplant center found that melanomas were diagnosed in transplant recipients at 8 times the rate than that of the general population [20]. Even though many of these cutaneous malignancies are widely considered benign, some studies have found a 50-fold increase mortality rate when compared to the general non-transplanted population [21]. Overall, these results suggest that vigilance is necessary in this unique and vulnerable population.

Risk Factors

A recent nationwide multicenter cohort study examined the risk factors associated with the development of post-transplant skin cancer including SCC, MM, and Merkel cell carcinoma (MCC) [22]. As one of the most comprehensive studies to date, Garrett et al. found that increasing age, white race, male gender, and thoracic organ transplantation elevated the risk of post-transplantation skin cancer. More specifically, the rate of skin cancer was 1.5 times higher in male versus females, ~ 8 times higher in whites versus non-whites, and 1.5 times higher in those with thoracic versus the abdominal transplants. In addition, congruent to the results previously discussed above by Krynitz et al., Garrett et al. found that those receiving transplants after 2008 had 1.5 times higher risk for cutaneous malignancies [16, 22]. Other studies have found that both older age at transplantation and a longer time interval following transplantation increases the risk for cutaneous malignancies. The bimodal distribution in the incidence of skin cancers in transplant patients seems to provide evidence for this (Fig. 2) [17, 23]. Patients over the age of 50 experience a steady increase in risk after just 2 years post transplantation. While younger patients, experience a significant increase in their relative risk for skin cancers at 10–12 years post-transplant. On average, this occurs typically at 26–28 years of age. Similarly, patients over the age of 40 tend to present with lesions on the head and neck region, while patients younger than 40 years of age mainly present with lesions on the upper extremities or trunk.

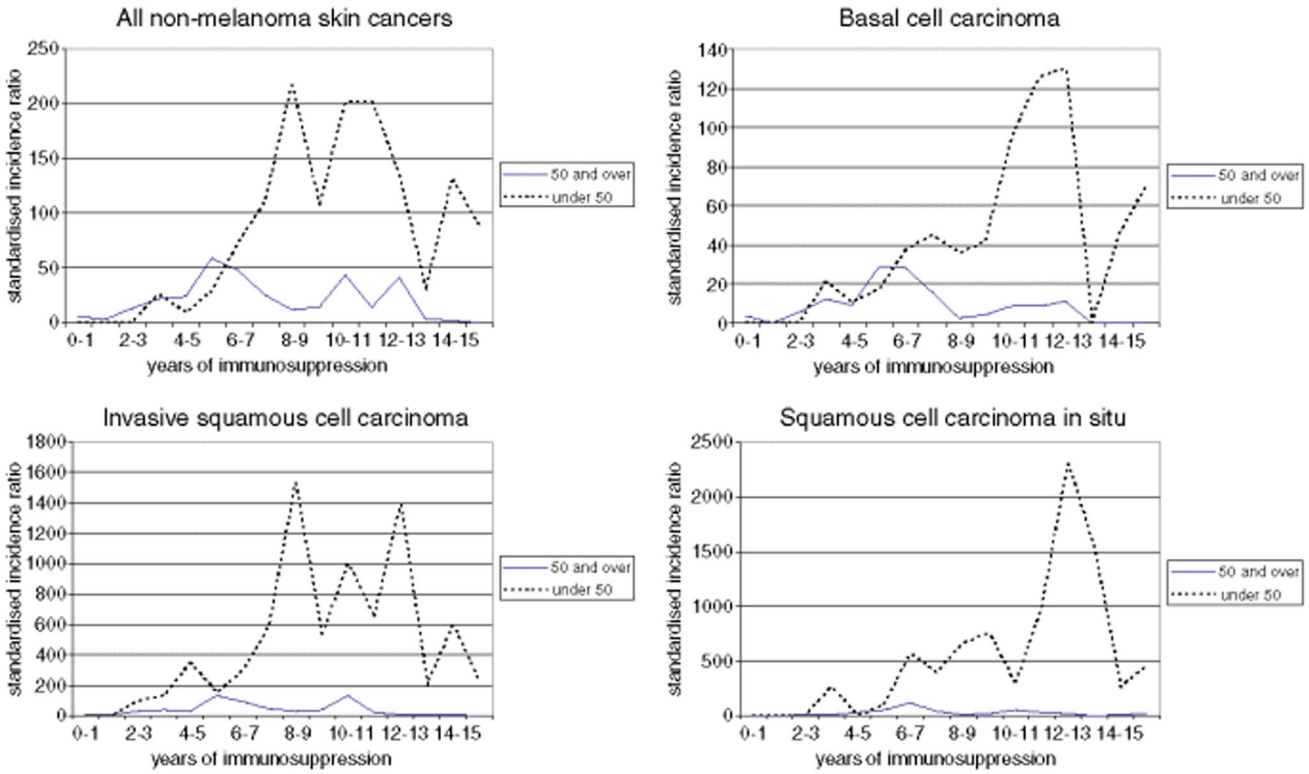

Fig. 2 Bimodal incidence rate of skin cancers by duration of immunosuppression therapy.* The incidence of non-melanoma skin cancer increases 2–6 years post-transplantation and then 10–12 years post-transplantation (bimodal distribution) (top left graph). *Obtained by permission from Moloney et al. [23]

Table 1 Mechanisms of action for commonly used immunosuppression medications

Immunosuppression medication	Mechanism of action
Cyclosporin A	Inhibits transcription of IL-2
Sirolimus	Binds to immunophilins and inhibits cytokine activation;
Tacrolimus	Inhibits transcription of IL-2
Mycophenolate mofetil	Inhibits nucleotide synthesis of both T and B cells
Azathioprine	Inhibits nucleotide synthesis of both T and B cells
Prednisone	Inhibits proliferation of T cells
Muromonab	Anti-T cell immunoglobulin

Immunosuppresion Therapy

In the post-transplantation period, immunosuppression therapy is administered to prevent acute and chronic allograft rejection. Multiple immunosuppressive regimens are utilized (Table 1). The selection of which immunosuppression therapy to use is based on allograft type and transplant center preferences. Early protocols in the 1970s and 1980s mainly used steroids, azathioprine, and cyclophosphamide. However, more recently, agents such as tacrolimus (FK-506, Prograf), sirolimus, and mycophenolate mofetil (Cellcept) are used [24].

Sirolimus has recently received considerable interest, not only for its immunosuppressive effects, but also for its anti-neoplastic capabilities [25]. Through inhibition of the mTOR (mammalian target of rapamycin) pathway, sirolimus prevents B and T cell activation through IL-2 release, impaired VEGF production, and inhibition of IL-10. Additionally, sirolimus enhances E-Cadherin inhibition of mesenchymal–epithelial transformation, therefore, preventing metastasis. Several recent studies have examined the anti-neoplastic effects of sirolimus. Sago et al. examined the rate of skin cancer in transplant recipients who were switched from standard therapy to sirolimus and found that sirolimus significantly regressed pre-existing lesions and reduced the rate of skin cancers at 12 months [26]. Others have similarly found that conversion from calcineurin inhibitors (e.g., cyclosporine) to mTOR drugs, such as sirolimus, reduced the rate of new cutaneous malignancies (Fig. 3) [27–29]. Overall, the results of these studies suggest that sirolimus may be a more optimal immunosuppressive agent that could be utilized in high-risk organ transplant patients.

Pathogenesis

Organ transplantation patients develop cutaneous malignancies due to immunosuppression therapy. In fact, the incidence of skin cancer is directly associated with the

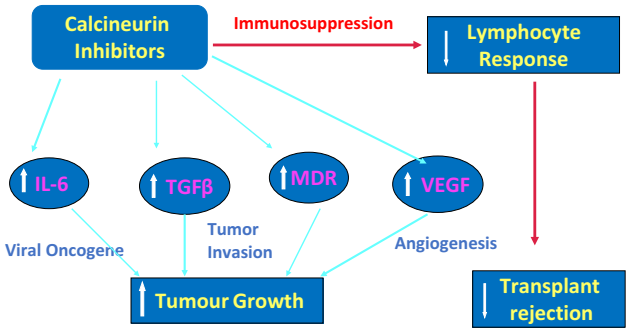

Fig. 3 Induction of skin cancers by calcineurin-based immunosuppressant medications. Enhanced TGFβ-effects on tumor growth. Induced invasiveness via a *direct & cell autonomous* mechanism

level of immunosuppression [30]. Organ transplant patients with cutaneous malignancies have been found to have significantly lower CD4 + T cell counts than organ transplant recipients without skin cancer [17, 21]. It is hypothesized that immunosuppression agents augment the risk of skin cancer through three mechanisms: (1) impaired immune surveillance; (2) impaired immunity against co-pathogenic viruses; and (3) direct carcinogenesis.

Immune surveillance is largely mediated by both the innate and adaptive immune system—more specifically, dendritic cells, T cells, and macrophages [31]. Since most immunosuppressive drugs work by inhibiting the proliferation of highly metabolic immune cells, surveillance of malignant cells is impaired. One such affected immune cell type is the CD1 + Langerhans cell. A type of dendritic antigen presenting cell (APC), Langerhans cells exist in high numbers in the epidermis. These APCs migrate to draining lymph nodes and facilitate the induction and presentation of antigen to T cells—the primary cell involved in tumor suppression. Unfortunately, immunosuppression therapy impairs dendritic cell function via the regulation of cytokine pathways, such as IL-10 and TGF-β. When upregulated, these cytokines decrease T cell-mediated cytotoxicity and augment tumor-permissive activity.

Immunosuppressive agents also suppress the activation of T cells directly [32]. T cells play an instrumental role in tumor rejection through T cell-mediated apoptosis of tumor cells. T cells infiltrate tumors after proper antigen presentation, and thereafter engage tumor cells via the Fas ligand initiating tumor cell destruction [33]. However, the majority of immunosuppression agents target T cells and inhibit their function, and hindering their usual anti-tumor activities. For example, Muromonab is an anti-T-cell immunoglobulin that works as an antagonist of CD3, a co-receptor essential for T cell proliferation and activation.

Macrophages have also been shown to play a central role in regulating tumor proliferation. Previous studies have shown M1 macrophages promote tumor elimination through production of IL-12 and nitric oxide synthase [34].

While tumors have been shown to skew tumor-associated macrophages to a more M2 phenotype (i.e., tumor-favorable type of macrophage), immunosuppression can dramatically alter the effectiveness and capabilities of all macrophages, altering their effectiveness and anti-tumor capabilities. To further compound the issue, macrophages have been shown to be deleteriously affected by UVB radiation. In response to UV radiation, neutrophils secrete IL-4 and IL-10 and convert macrophages towards a more tumor-favorable phenotype [35].

Immunosuppression can also impair the immune system's ability to fight off pathogenic viruses. Recently, there has been great interest in exploring the role of human papilloma virus (HPV) in cutaneous malignancies. HPV E6 and E7 are both potent oncoproteins associated with the malignant transformation of virally infected cells [36]. The E6 oncoprotein inhibits UV-induced apoptosis of cells. Although the exact mechanisms delineating HPV carcinogenesis in immunocompromised individuals is still being studied, the higher incidence of HPV DNA in skin cancers (up to 90%) from transplant recipients than in immunocompetent individuals suggests that HPV may play a key role.

Lastly, immunosuppression agents may be directly carcinogenic. Studies performed in rodents have demonstrated that one agent, cyclosporine, can enhance tumor progression independent of its immunosuppressive effects [37, 38]. Using severe combined immunodeficiency (SCID) mice as a model, these investigators found that cyclosporine's carcinogenic effects were TGF-β mediated. Additionally, cancer cells were found to develop invasive characteristics when exposed to cyclosporine [37]. Similarly, other researchers have found that another agent, azathioprine, can act as a mutagen and photosensitizer [39–41]. Previous clinical studies have attempted to quantify the relative risk of various immunosuppression agents on the incidence of skin cancers [42–44]. Unfortunately, there exists conflicting evidence on whether some agents are more deleterious than others. Furthermore, many of the studies are retrospective in nature and provide low level-of-evidence support. Several more well-designed studies have found that dual or mono-therapy immunosuppression decreases the risk of cutaneous malignancies when compared to triple immunosuppression [45, 46]. As a result, some transplant centers today try to utilize low-dose immunosuppressive protocols or newer therapies (i.e., sirolimus) to reduce the incidence of skin cancers. Abou Ayache et al. published their results using a calcineurin inhibitor monotherapy after kidney transplantation and found similar rates of graft survival when compared to standard triple therapy [47]. But equally important, these investigators found that monotherapy reduced the risk of squamous cell carcinoma [47]. Despite the results of these studies and others, triple therapy remains the most commonly utilized immunosuppression regimen globally.

Prognosis/Survival

Previous studies have attempted to examine the aggressiveness of skin cancer in the organ transplantation population. As defined by several previous studies, aggressive cutaneous malignancies associated with solid organ transplant recipients have a higher rate of recurrence, regional and distant metastasis and mortality [48, 49]. For example, melanomas in transplant patients have been shown to be of higher pathologic grade, more invasive, and of higher mortality risk when controlling for confounding factors [50]. In the general population, mortality risk from melanoma is approximately 15% at 5 years but among transplant recipients, it reaches 30% [19]. Similarly, transplant patients with Merkel cell carcinoma may have a more aggressive disease with 68% having lymph node metastasis and associated with a 56% mortality [51]. Other studies have documented that metastatic skin cancer in organ transplant recipients can have a poor 3-year disease-free survival of only 50% [52, 53]. Overall, disease-related mortality from cutaneous malignancies in the transplanted population is much higher than the general population [54].

In the pediatric population, patients who received organs before 18 years of age, have a higher rate of melanoma and squamous cell carcinoma than adult transplant recipients [55]. More alarming, these studies have documented a higher metastatic and mortality rate for children with organ transplants [56]. Since the pediatric population will need life-long immunosuppression, the risk of morbidity and mortality from aggressive cutaneous lesions in this population is disturbing.

Prevention and Surveillance

Patient education regarding the importance of avoiding UV light exposure and smoking cessation is extremely important to reduce the risk of developing cutaneous malignancies. Regular sunscreen use has been found to reduce the incidence of pre-invasive cutaneous lesions in organ transplant recipients [57]. Unfortunately, previous studies have raised concerns regarding the education that transplant patients receive regarding their higher risk for skin cancer [58]. For example, studies have shown that transplant recipients demonstrate poor compliance with sun protection and sunscreen use techniques even though they are provided educational instruction [59, 60]. Educational initiatives that are innovative and aimed at improving patient compliance are still necessary and warrant

exploration to reduce the hazard associated with these modifiable risk factors. Until these initiatives are fully incorporated into the clinical care of all transplant patients, we advocate for close follow-up of transplant patients with a dermatologist for an annual full body skin examination.

Early skin cancer detection is also important in all organ transplant recipients. Regular screening examinations also play a crucial role in decreasing the morbidity and mortality secondary to cutaneous malignancies [61]. Currently, the American Cancer Society and American Society of Transplantation recommend monthly self-examinations for all transplant recipients [62]. Most transplant centers also advocate that transplant recipients be evaluated regularly in inter-disciplinary clinics that include dermatologist, plastic surgeons, surgical oncologist, medical oncologist, and radiation oncologist [63]. Some of these centers have built skin cancer screening protocols for prevention purposes. For the first time, a nationwide skin cancer screening program was initiated in Germany recently [64–66]. Although the efficacy of this national screening program is still being evaluated, the results of this initiative will be closely monitored by international transplant programs to determine whether screening methods are essential to combat post-transplant skin cancer.

Management

The management of suspicious cutaneous lesions begins with an early, skin biopsy. Tumor pathology and biology dictates treatment. However, the treatment of cutaneous malignancies almost always necessitates surgical treatment.

Surgical management of melanoma and non-melanoma cutaneous cancers is managed similarly to traditional principles. Surgical excision with 4–7 mm margins is recommended for primary and recurrent non-melanoma skin malignancies [67]. In the case of aggressive squamous cell carcinoma, emerging data suggest that sentinel lymph node biopsy (SLNB) may be warranted [68, 69]. Most of the current evidence stems from several case series and lower level-of-evidence studies which argue that SLNB may improve discovery of latent lymphatic metastasis and prognosis. Takahashi et al. recently found in a series of 26 patients that the 3-year survival of SLNB-negative and -positive cases was 100% and 20%, respectively [70]. Although another recent study out of Japan has found similar results, a large-scale multicenter, prospective study has not yet been conducted, and will be necessary to fully explore the benefit of SLNBs in setting of high-risk squamous cell carcinoma, especially in the setting of immunosuppresion [71].

Other adjuvant therapies may also be necessary for high-risk non-melanoma skin cancers such as chemotherapy or radiotherapy. Radiotherapy has been used as an adjuvant therapy after incomplete resection and nodal/perineural involvement. The role of radiotherapy in eliminating all residual microscopic tumor cells to prevent recurrence is well documented. For example, Veness et al. demonstrated in the largest series to date that surgical therapy followed by radiotherapy lowered the rate of recurrence and improved 5-year survival in metastatic squamous cell carcinoma when compared to surgery alone [49].

Melanoma and Merkel cell carcinoma is similarly managed as compared to immunocompetent patients. Surgical margins for melanoma are determined by Breslow thickness. In Merkel cell carcinoma, wide local excision with 1–2 cm margins is recommended [72]. Additionally, SLNBs should be performed for staging in both melanoma and Merkel cell carcinoma. Similar to metastatic squamous cell carcinoma, adjuvant radiotherapy offers a decrease recurrence benefit in Merkel cell carcinoma and melanoma [65].

Chemoprophylaxis and management of precancerous lesions is equally important in organ transplant recipients. Imiquimod, 5-fluorouracil (5-FU), and PDT (photodynamic therapy) are all non-surgical treatment options. In fact, it is recommended to treat warts, actinic keratoses, and papillomas aggressively as possible with either excision or topical agents [73]. Imiquimod is a topical immunomodulator that has been approved for the treatment of warts, actinic keratoses, and basal cell carcinoma [74]. A recent study by Brown et al. found that it was a safe and efficacious agent for recipients of organ transplantation [75]. Photodynamic therapy has also been investigated in the organ recipient population [76]. PDT involves the use of exogenously administered precursor of photosentizer proporphyrin IX synthesis which upon activation by light, can destroy tumor cells. It has been previously shown to be effective for actinic keratoses [76]. In a study by Piaserico et al., PDT was found to be highly efficacious in treating actinic keratoses in organ transplant recipients, especially in the scalp and face (72% response) [77]. Lastly, systemic retinoic acid therapy should be considered in organ transplant recipients with a history of multiple cutaneous malignancies or aggressive squamous cell carcinoma since it has been shown to be an effective chemoprevention modality [78, 79]. In summary, chemoprevention of precancerous skin lesions should be optimized in the immunosuppressed population. Although it should never be considered a replacement for surgical management, optimal prevention protocols should be offered to reduce the risk of significant mortality or morbidity from aggressive skin cancers. Prevention protocols complemented with low-dose immunosuppressive protocols or newer therapies

(i.e., sirolimus) may assist in hampering the aggressiveness of cutaneous malignant lesions that are highly deleterious in the transplant population.

Conclusion

Aggressive skin cancers can be debilitating and cause significant morbidity and mortality in patients on immunosuppression. It is the most common malignancy in the organ transplantation population and can negatively impact the quality of life of organ transplantation recipients. Vigilance and routine surveillance is necessary after transplantation to prevent mortality. Furthermore, proper patient education is important to raise awareness of the risk associated with immunosuppression use. Prospective studies are still warranted to determine the optimal management and risk stratification of this vulnerable population.

Compliance with Ethical Guidelines

Conflict of interest Anthony P. Tufaro reports other from Polarity TE, outside the submitted work. Joseph Lopez and Christine G. Gourin declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Murray JE. The first successful organ transplants in man. J Am Coll Surg. 2005;200:5–9.
2. Carpenter CB. Improving the success of organ transplantation. N Engl J Med. 2000;342:647–8.
3. Colvin M, Smith JM, Hadley N, et al. OPTN/SRTR 2016 annual data report: Heart. Am J Transplant. 2018;18(Suppl 1):291–362.
4. Smith JM, Weaver T, Skeans MA, et al. OPTN/SRTR 2016 annual data report: Intestine. Am J Transplant. 2018;18(Suppl 1):254–90.
5. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2016 annual data report: Kidney. Am J Transplant. 2018;18(Suppl 1):18–113.
6. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2016 annual data report: Liver. Am J Transplant. 2018;18(Suppl 1):172–253.
7. Garrett GL, Lowenstein SE, Singer JP, He SY, Arron ST. Trends of skin cancer mortality after transplantation in the united states: 1987 to 2013. J Am Acad Dermatol. 2016;75:106–12.
8. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: Advances in therapy and management: Part I. epidemiology of skin cancer in solid organ transplant recipients. J Am Acad Dermatol. 2011;65:253–61; **quiz 262**.
9. Berg D, Otley CC. Skin cancer in organ transplant recipients: Epidemiology, pathogenesis, and management. J Am Acad Dermatol. 2002;47:1–17; **quiz 18–20**.
10. Otley CC, Pittelkow MR. Skin cancer in liver transplant recipients. Liver Transpl. 2000;6:253–62.
11. Ong CS, Keogh AM, Kossard S, Macdonald PS, Spratt PM. Skin cancer in australian heart transplant recipients. J Am Acad Dermatol. 1999;40:27–34.
12. Bouwes Bavinck JN, Hardie DR, Green A, et al. The risk of skin cancer in renal transplant recipients in queensland, australia. A follow-up study. Transplantation. 1996;61:715–21.
13. Lampros TD, Cobanoglu A, Parker F, Ratkovec R, Norman DJ, Hershberger R. Squamous and basal cell carcinoma in heart transplant recipients. J Heart Lung Transplant. 1998;17:586–91.
14. Pritchett EN, Doyle A, Shaver CM, et al. Nonmelanoma skin cancer in nonwhite organ transplant recipients. JAMA Dermatol. 2016;152:1348–53.
15. Tessari G, Naldi L, Boschiero L, et al. Incidence and clinical predictors of a subsequent nonmelanoma skin cancer in solid organ transplant recipients with a first nonmelanoma skin cancer: A multicenter cohort study. Arch Dermatol. 2010;146:294–9.
16. Krynitz B, Edgren G, Lindelof B, et al. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008–a swedish population-based study. Int J Cancer. 2013;132:1429–38.
17. Engels EA, Pfeiffer RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011;306:1891–901.
18. Hollenbeak CS, Todd MM, Billingsley EM, Harper G, Dyer AM, Lengerich EJ. Increased incidence of melanoma in renal transplantation recipients. Cancer. 2005;104:1962–7.
19. Penn I. Malignant melanoma in organ allograft recipients. Transplantation. 1996;61:274–8.
20. Le Mire L, Hollowood K, Gray D, Bordea C, Wojnarowska F. Melanomas in renal transplant recipients. Br J Dermatol. 2006;154:472–7.
21. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med. 2003;348:1681–91.
22. •• Garrett GL, Blanc PD, Boscardin J et al. Incidence of and risk factors for skin cancer in organ transplant recipients in the united states. JAMA Dermatol. 2017;153:296–303. *This study found that increased age, white race, male sex, and thoracic organ transplantation were risk factors for development of post-transplant skin cancer.*
23. Moloney FJ, Comber H, O'Lorcain P, O'Kelly P, Conlon PJ, Murphy GM. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. Br J Dermatol. 2006;154:498–504.
24. Holt CD. Overview of immunosuppressive therapy in solid organ transplantation. Anesthesiol Clin. 2017;35:365–80.
25. Kahan BD. Sirolimus: a comprehensive review. Expert Opin Pharmacother. 2001;2:1903–17.
26. Salgo R, Gossmann J, Schofer H, et al. Switch to a sirolimus-based immunosuppression in long-term renal transplant recipients: Reduced rate of (pre-)malignancies and nonmelanoma skin cancer in a prospective, randomized, assessor-blinded, controlled clinical trial. Am J Transplant. 2010;10:1385–93.
27. Campbell SB, Walker R, Tai SS, Jiang Q, Russ GR. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. Am J Transplant. 2012;12:1146–56.
28. •• Euvrard S, Morelon E, Rostaing L et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med. 2012;367:329–339. *This level I study provided evidence that switching from calcineurin inhibitors to sirolimus had an*

antitumor effect among kidney-transplant recipients with previous history of cutaneous malignancy.
29. Hoogendijk-van den Akker JM, Harden PN, Hoitsma AJ et al. Two-year randomized controlled prospective trial converting treatment of stable renal transplant recipients with cutaneous invasive squamous cell carcinomas to sirolimus. J Clin Oncol. 2013;31:1317–1323.
30. Ulrich C, Kanitakis J, Stockfleth E, Euvrard S. Skin cancer in organ transplant recipients–where do we stand today? Am J Transplant. 2008;8:2192–8.
31. Rangwala S, Tsai KY. Roles of the immune system in skin cancer. Br J Dermatol. 2011;165:953–65.
32. Yu SH, Bordeaux JS, Baron ED. The immune system and skin cancer. Adv Exp Med Biol. 2014;810:182–91.
33. Hill LL, Ouhtit A, Loughlin SM, Kripke ML, Ananthaswamy HN, Owen-Schaub LB. Fas ligand: A sensor for DNA damage critical in skin cancer etiology. Science. 1999;285:898–900.
34. Tjiu JW, Chen JS, Shun CT, et al. Tumor-associated macrophage-induced invasion and angiogenesis of human basal cell carcinoma cells by cyclooxygenase-2 induction. J Invest Dermatol. 2009;129:1016–25.
35. Kang K, Gilliam AC, Chen G, Tootell E, Cooper KD. In human skin, UVB initiates early induction of IL-10 over IL-12 preferentially in the expanding dermal monocytic/macrophagic population. J Invest Dermatol. 1998;111:31–8.
36. McLaughlin-Drubin ME, Munger K. The human papillomavirus E7 oncoprotein. Virology. 2009;384:335–44.
37. Hojo M, Morimoto T, Maluccio M, et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature. 1999;397:530–4.
38. Kelly GE, Meikle W, Sheil AG. Effects of immunosuppressive therapy on the induction of skin tumors by ultraviolet irradiation in hairless mice. Transplantation. 1987;44:429–34.
39. Moore DE, Sik RH, Bilski P, Chignell CF, Reszka KJ. Photochemical sensitization by azathioprine and its metabolites. Part 3. A direct EPR and spin-trapping study of light-induced free radicals from 6-mercaptopurine and its oxidation products. Photochem Photobiol. 1994;60:574–81.
40. Lennard L, Thomas S, Harrington CI, Maddocks JL. Skin cancer in renal transplant recipients is associated with increased concentrations of 6-thioguanine nucleotide in red blood cells. Br J Dermatol. 1985;113:723–9.
41. Perrett CM, Walker SL, O'Donovan P, et al. Azathioprine treatment photosensitizes human skin to ultraviolet A radiation. Br J Dermatol. 2008;159:198–204.
42. Jonas S, Rayes N, Neumann U, et al. De novo malignancies after liver transplantation using tacrolimus-based protocols or cyclosporine-based quadruple immunosuppression with an interleukin-2 receptor antibody or antithymocyte globulin. Cancer. 1997;80:1141–50.
43. Glover MT, Deeks JJ, Raftery MJ, Cunningham J, Leigh IM. Immunosuppression and risk of non-melanoma skin cancer in renal transplant recipients. Lancet. 1997;349:398.
44. Geusau A, Dunkler D, Messeritsch E, et al. Non-melanoma skin cancer and its risk factors in an austrian population of heart transplant recipients receiving induction therapy. Int J Dermatol. 2008;47:918–25.
45. Campistol JM, Eris J, Oberbauer R, et al. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. J Am Soc Nephrol. 2006;17:581–9.
46. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. Transplantation. 2005;80:883–9.
47. Abou Ayache R, Thierry A, Bridoux F, et al. Long-term maintenance of calcineurin inhibitor monotherapy reduces the risk for squamous cell carcinomas after kidney transplantation compared with bi- or tritherapy. Transplant Proc. 2007;39:2592–4.
48. Adamson R, Obispo E, Dychter S, et al. Long-term outcome with the use of OKT3 induction therapy in heart transplant patients: a single-center experience. Transplant Proc. 1998;30:1107–9.
49. Veness MJ, Quinn DI, Ong CS, et al. Aggressive cutaneous malignancies following cardiothoracic transplantation: the australian experience. Cancer. 1999;85:1758–64.
50. Vajdic CM, Chong AH, Kelly PJ, et al. Survival after cutaneous melanoma in kidney transplant recipients: a population-based matched cohort study. Am J Transplant. 2014;14:1368–75.
51. Penn I, First MR. Merkel's cell carcinoma in organ recipients: Report of 41 cases. Transplantation. 1999;68:1717–21.
52. Martinez JC, Otley CC, Stasko T, et al. Defining the clinical course of metastatic skin cancer in organ transplant recipients: A multicenter collaborative study. Arch Dermatol. 2003;139:301–6.
53. Wong G, Chapman JR, Craig JC. Death from cancer: a sobering truth for patients with kidney transplants. Kidney Int. 2014;85:1262–4.
54. Penn I. Neoplastic complications of transplantation. Semin Respir Infect. 1993;8:233–9.
55. Yanik EL, Smith JM, Shiels MS, et al. Cancer risk after pediatric solid organ transplantation. Pediatrics. 2017. https://doi.org/10.1542/peds.2016-3893.
56. Penn I. Posttransplant malignancies in pediatric organ transplant recipients. Transplant Proc. 1994;26:2763–5.
57. Jurgensen JS, Degen A, et al. Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: A 24 months, prospective, case-control study. Br J Dermatol. 2009;161(Suppl 3):78–84.
58. Cowen EW, Billingsley EM. Awareness of skin cancer by kidney transplant patients. J Am Acad Dermatol. 1999;40:697–701.
59. Butt A, Roberts DL. Renal transplant recipients and protection from sun: Need for education. Lancet. 1997;349:179–80.
60. Seukeran DC, Newstead CG, Cunliffe WJ. The compliance of renal transplant recipients with advice about sun protection measures. Br J Dermatol. 1998;138:301–3.
61. Finkenstedt A, Graziadei IW, Oberaigner W, et al. Extensive surveillance promotes early diagnosis and improved survival of de novo malignancies in liver transplant recipients. Am J Transplant. 2009;9:2355–61.
62. Kasiske BL, Vazquez MA, Harmon WE, et al. Recommendations for the outpatient surveillance of renal transplant recipients. American society of transplantation. J Am Soc Nephrol. 2000;11(Suppl 15):S1–86.
63. Harwood CA, Mesher D, McGregor JM, et al. A surveillance model for skin cancer in organ transplant recipients: a 22-year prospective study in an ethnically diverse population. Am J Transplant. 2013;13:119–29.
64. Choudhury K, Volkmer B, Greinert R, Christophers E, Breitbart EW. Effectiveness of skin cancer screening programmes. Br J Dermatol. 2012;167(Suppl 2):94–8.
65. Arron ST, Canavan T, Yu SS. Organ transplant recipients with merkel cell carcinoma have reduced progression-free, overall, and disease-specific survival independent of stage at presentation. J Am Acad Dermatol. 2014;71:684–90.
66. Stang A, Jockel KH. Does skin cancer screening save lives? A detailed analysis of mortality time trends in schleswig-holstein and germany. Cancer. 2016;122:432–7.
67. •• Mittal A, Colegio OR. Skin cancers in organ transplant recipients. *Am J Transplant*. 2017;17:2509-2530. *This study performed a systematic review and meta-analysis to determine the effect of azathioprine on skin cancer risk. It found that azathioprine is associated with an increased risk of squamous cell carcinoma in organ transplant patients*.

68. Kwon S, Dong ZM, Wu PC. Sentinel lymph node biopsy for high-risk cutaneous squamous cell carcinoma: Clinical experience and review of literature. World J Surg Oncol. 2011;9:80.
69. Ross AS, Schmults CD. Sentinel lymph node biopsy in cutaneous squamous cell carcinoma: A systematic review of the english literature. Dermatol Surg. 2006;32:1309–21.
70. Takahashi A, Imafuku S, Nakayama J, Nakaura J, Ito K, Shibayama Y. Sentinel node biopsy for high-risk cutaneous squamous cell carcinoma. Eur J Surg Oncol. 2014;40:1256–62.
71. Fukushima S, Masuguchi S, Igata T, et al. Evaluation of sentinel node biopsy for cutaneous squamous cell carcinoma. J Dermatol. 2014;41:539–41.
72. Schadendorf D, Long GV, Stroiakovski D, et al. Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomised trials. Eur J Cancer. 2017;82:45–55.
73. Kovach BT, Stasko T. Use of topical immunomodulators in organ transplant recipients. Dermatol Ther. 2005;18:19–27.
74. Ulrich C, Busch JO, Meyer T, et al. Successful treatment of multiple actinic keratoses in organ transplant patients with topical 5% imiquimod: A report of six cases. Br J Dermatol. 2006;155:451–4.
75. Brown VL, Atkins CL, Ghali L, Cerio R, Harwood CA, Proby CM. Safety and efficacy of 5% imiquimod cream for the treatment of skin dysplasia in high-risk renal transplant recipients: Randomized, double-blind, placebo-controlled trial. Arch Dermatol. 2005;141:985–93.
76. Dragieva G, Prinz BM, Hafner J, et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. Br J Dermatol. 2004;151:196–200.
77. Piaserico S, Belloni Fortina A, Rigotti P, et al. Topical photodynamic therapy of actinic keratosis in renal transplant recipients. Transplant Proc. 2007;39:1847–50.
78. McKenna DB, Murphy GM. Skin cancer chemoprophylaxis in renal transplant recipients: 5 years of experience using low-dose acitretin. Br J Dermatol. 1999;140:656–60.
79. Bavinck JN, Tieben LM, Van der Woude FJ, et al. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. J Clin Oncol. 1995;13:1933–8.