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Cutaneous Squamous Cell Carcinoma in the Organ Transplant Recipient

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Abstract

One in twenty solid organ transplant recipients (SOTRs) will develop a highly morbid or fatal cutaneous carcinoma after transplantation. The majority of these cases develop on the head and neck and may require intervention on the part of dermatology, dermatologic surgery, otolaryngology, transplant medicine, radiation oncology, and medical oncology. In this review, we discuss the problem of cutaneous squamous cell carcinoma (cSCC) in SOTRs as well as the prognostic factors and management strategies to care for this population.

Keywords

cutaneous head and neck cancer; transplant; squamous cell carcinoma; immunosuppression; immunotherapy

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INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is a malignancy of keratinocytes and is the second most common cancer with an annual incidence of 700,000 cases resulting in nearly 8800 deaths in the United States each year[1,2]. Unfortunately, the incidence of cSCC has continued to rise with an increase of 50 to 200% over the last 3 decades[1,3]. Given the role of the immune system in surveillance and removal of dysplasia, it is not surprising that immunosuppression leads to an increase in incidence of cSCC. Solid organ transplant recipients (SOTRs) have a 65–250 times increased incidence of cSCC and the risk is correlated with increased doses of immunosuppression, with increased risk with higher levels of immunosuppression, such as in lung transplant recipients [4–8]. Beyond just an increase in incidence, cSCC in SOTRs tends to recur more often and behave more aggressively with increased rates of metastasis and death. [9–11] The skin cancer specific mortality for transplant patients is nine-fold higher than those arising in immunocompetent patients. [12] Moreover, one in twenty SOTRs have a highly-morbid or fatal cSCC after transplant[13]. Therefore, there is a need for improvements in prevention, detection, and management of this disease in this patient population. In this review, we summarize the current data on keratinocyte carcinogenesis in SOTRs, review prognostic factors, and define the management of cSCC in SOTRs.

KERATINOCYTE CARCINOGENESIS IN SOTRs

The majority of cSCC occurs in sun-exposed locations and is driven by ultraviolet radiation (UVR) from sunlight and tanning beds. UVR functions as a carcinogen via two pathways leading to DNA mutagenesis: 1. direct DNA photoproduct formation and interaction with intracellular photosensitizers leading to the generation of reactive oxygen species and 2. Downregulation of the local immune response in the skin by decreasing antigen presentation capacity and increasing tolerance (reviewed in [14]). In SOTRs, immune surveillance is globally suppressed by drug therapy directed at T cells in an effort to prevent rejection. Therefore, the local environment is permissive for perpetuation of dysplasia and development of invasive carcinomas.

Chronic UVR exposure leads to mutations in known tumor suppressor genes (*TP53, NOTCH1, FAT1*) and known oncogenes (*HRAS, KRAS, NRAS*). In fact, the mutation rate in sun-exposed but otherwise normal appearing skin is estimated to be 5 mutations per megabase based on studies of upper eyelid skin which is close to the estimated mutational burden of oropharyngeal squamous cell carcinomas but about 10 fold lower than that reported for cSCCs [15]. Genome sequencing of cSCC has revealed nearly universal inactivating or non-synonymous mutations in *TP53* [16].

More recent work suggests that the immunosuppressive drugs given to SOTRs may also contribute to specific mutations leading to oncogenesis. Work by Inman and colleagues demonstrated a gene mutation signature seen in cSCC arising in patients on azathioprine [16]. The prevalence of this signature correlated with the time the patient had been on the drug. Interestingly, this gene signature was distinct from those attributed to UVR and was heavily biased to the transcriptional strand, therefore leading the authors to hypothesize that

it may influence transcription coupled nucleotide excision repair. In cell culture experiments, tacrolimus and mycophenolate were also shown to impair nucleotide excision repair pathways which are often used by keratinocytes to combat UVR-induced base substitution [17]

Furthermore, increasing evidence suggests that the drugs given to modulate T cell immunity may have a carcinogenic effect by modulation of transcription factors. Calcineurin inhibitors, the backbone of many immunosuppression regimens, can modulate ATF3 in keratinocytes leading to unchecked proliferation [18]. Therefore, these drugs also appear to be playing a role in cellular function in cells not involved in immunity. Continued investigation of the molecular changes of malignant keratinocytes from cSCC arising in the immunosuppressed patient is warranted.

Voriconazole, the triazole antifungal, used to prevent *Aspergillus* infection after lung transplant, has been implicated in phototoxic drug reactions and as an agent leading to increase in cSCC[19]. In a retrospective cohort study encompassing 20 years of lung transplantation at a single center, there was a 73% increase in the risk of cSCC in patients who received voriconazole [20]. The mechanism for voriconazole genotoxicity is likely due to increased oxidative damage[21,22].

Unlike oropharyngeal squamous cell carcinoma where HPV has a defined role in oncogenesis, there is conflicting data on the role of human papilloma virus (HPV) in cSCC carcinogenesis with the exception of lesions of the genitalia [23]. The skin has the highest prevalence of HPV when compared to other organ systems, however the subtypes of alpha HPVs found in the skin tend to be of low-oncogenic risk and often lead to verruca vulgaris (common wart) formation. Members of the skin-tropic beta genus of HPV which rarely integrate in the host genome have been found in verruca plana (flat warts) and are hypothesized to cause progression to carcinoma as patients with epidermodysplasia verruciformis are particularly susceptible to HPV beta infection and develop cSCCs early in adulthood. With an abundance of subtypes of beta HPV, high rate of colonization, and no clear mechanism of carcinogenesis it remains unclear what role beta HPVs cause in cSCC. A recent paper implicates CD8 T cell response to beta HPVs in protection from carcinogenesis and notes loss of that response in immunosuppressed individuals[24]. Unlike oropharyngeal squamous cell carcinoma, p16 is not a reliable marker for HPV etiology in cSCC as 100% of the invasive cSCCs tested showed staining for p16 in a retrospective analysis [25]. Therefore, the role of HPV in cSCC carcinogenesis remains unclear in immunosuppressed patients.

PROGNOSTIC FACTORS

Staging

The expert consensus-based American Joint Committee on Cancer staging system 7th edition (AJCC7) did not optimally stratify patients, as patients with poor outcomes were enriched in stage T2, whereas few patients were classified as T3 or T4 [1]. A study in heart and lung transplant patients showed an increase in risk of recurrence with increasing stage when using the AJCC7 [26] however no patients met criteria for T3 or T4 in this cohort.

Subsequently, the Brigham and Women's Hospital Tumor (BWT) Staging of cSCC was introduced to better stratify the T2 of the AJCC7 [27]. Out of the 84 patients upstaged from T2 in AJCC7 to T2b in BWT, 18 (21%) had a local recurrence, 18 (21%) a nodal metastasis and 9 (11%) disease specific death [28], reflecting the high-risk nature of T2b by BWT criteria. Consequently, the AJCC 8th edition aimed to shift higher risk patients from T2 to T3 [29], while merging the highest risk patients from the former AJCC7 T3 and T4 stages in a new T4a and T4b stage. The clinical and pathological factors used for tumor staging are summarized in Table 1. A recent study has confirmed, that the AJCC8 is more distinctive, monotonous as well as homogeneous than the AJCC7, while being comparable to the BWT [30]. Blechman and colleagues demonstrated similar distinctiveness, homogeneity, and monotonicity in AJCC8 and BWH staging when assessing cSCCs from 58 immunosuppressed patients [31]

A comprehensive meta-analysis of 17,248 patients has validated the relevance for many of the AJCC8 factors in predicting local recurrence, metastasis or disease-specific death, yet some criteria shown to be independently and strongly correlated with outcome measures, such as immunosuppression and location (lip, temple, ear), are not included in either the BWH or the AJCC8 system [2]. This observation suggests that immunosuppression may lead to biologically aggressive cancer behavior that is not currently captured by pathologic staging factors (perineural invasion, depth of invasion, grade of differentiation). An obstacle to including immunosuppression as a factor in staging is the heterogeneity of suppression, both in terms of underlying cause of immunosuppression (organ transplantation, HIV infection, chronic lymphocytic leukemia) and treatment (specific drug, dose, duration of treatment) [2,29]. We recommend considering all invasive cSCCs with a high-risk pathologic feature in SOTRs to be at elevated risk for recurrence and metastasis and therefore advocate for an intensified workup, treatment, and surveillance.

MANAGEMENT

Screening

Due to the increased risk of cSCCs in SOTRs, clinical skin surveillance is an integral part of management of these patients. Patients with Fitzpatrick skin phototype I (always burn with exposure to sunlight) and II (often burn, rarely tan with exposure to sunlight) are at the highest risk for cSCC development. Further, patients who are male, over 50 at the time of the transplant, and have a heart or lung transplant are at the highest risk of cSCC [8]. Currently, there is no validated risk stratification system available for stratifying patients pre- or post-transplant. Rather, an expert consensus panel has formulated recommendations for screening in the post-transplant setting. Patients without lesions should have skin screening every 12 months while patients with one skin cancer should have skin exam every 3–6 months. In patients with multiple nonmelanoma skin cancers or lesions at high risk for recurrence or metastasis, screening should be done every 3 months [32].

Primary and Secondary Prevention

As UV light is the major driver of cSCC, UV protection is of utmost importance for prevention of cancer in this population. All fair-skinned transplant recipients should be

counseled on sunscreen use, sun protective clothing, and avoidance of midday sun. Numerous studies have looked at sun safety education for solid organ transplant recipients. Collectively, these studies have shown improvement in patient understanding and compliance with sun protection with all modalities of teaching [33,34]. A study on sunscreen use and malignancy revealed fewer precancers as well as cSCC in SOTRs who used sunscreen on a regular basis [35].

Taking advantage of the march to carcinogenesis which starts as normal skin progresses to actinic keratosis (AK), followed by cSCC *in situ*, and finally invasive cSCC, patients can be treated with field therapy for field disease. Field disease is characterized by a large plaque of AK in a sun exposed area and typically has ill-defined borders[36]. Given the pathophysiology of carcinogenesis, it is not surprising that these patients would have significant field disease burden as adjacent skin is typically exposed to the same amount of UV radiation. Topical therapies to ameliorate field cancerization have been recommended. The most common of these is topical 5-fluorouracil. This drug blocks DNA synthesis and has shown improvement in field disease in SOTRs with 98% AK clearance rate at 8 weeks post therapy [37,38]. Capecitabine, the oral pro-drug for 5-fluorouracil has been used with some success for treatment of field disease and secondary prevention. In two case observation studies of SOTRs, a decrease from one cSCC every two months, to one every six months was seen when the patient was placed on capecitabine at 1g/m2 divided into two daily doses, given for 14 days followed by a 7 day drug holiday. [39,40]. However, in both reports, 60% of patients required a break from the medication regimen due to toxicity. Additionally, imiquimod, a Toll-like receptor agonist, has been used in transplant recipients to illicit a local immune response to clear actinic damage. Initially there were concerns of inciting a systemic immune response with use of this medication, however two RCTs in renal transplant recipients showed efficacy without adverse effect to the graft [41,42]. One treatment session lead to 49% AK clearance in SOTRs at one month post treatment [43].

Photodynamic Therapy (PDT) utilizes the photosensitizing products of the heme pathway to cause cell death after application of wavelength restricted visible light. Recent work has shown that this treatment can normalize aberrant cancer-associated gene expression pathways [44]. PDT was found to be more effective at clearing field disease than topical chemotherapy [37] and imiquimod [43] in SOTRs. Some studies have suggested primary and secondary prevention of both field disease and cSCC with PDT for SOTRs, whereas others have not shown significant benefit [43,45–48].

A commonly prescribed medication in the dermatology clinic is the systemic retinoid, acitretin. While topical retinoid (tretinoin cream) was unable to improve field disease and prevent cSCC development in the Veteran’s Study, systemic retinoid has been used successfully to slow down development of cSCC in the high risk population [49,50]. However, many report side effects from the medication and a rebound effect when the medication is removed. With known teratogenicity, this medication should not be used in women of child-bearing potential. More recently, work in Australia suggested the addition of niacinamide to the diet (500mg twice a day) for secondary prevention of skin cancer in all-comers [51]. However, a study of nicotinamide in patients who had undergone renal

transplant did not show an improvement, perhaps due to the study being underpowered due to lack of enrollment [52].

Modification of Immunosuppression Regimen

Expert consensus guidelines suggest reducing immunosuppression in transplant patients who develop multiple skin cancers per year and in individuals with high risk lesions [53]. For patients on an immunosuppression regimen containing a cell cycle inhibitor, such as azathioprine or mycophenolate, removal of the cell cycle inhibitor is paramount. A meta-analysis revealed a 56% increase in risk for cSCC in patients exposed to azathioprine [54].

Previous studies have shown that sirolimus, a macrolide that inhibits mTOR therefore blocking central cell growth and proliferation signaling pathways, has anti-tumor properties, particularly in patients with renal transplants with history of cSCC [55,56]. A switch from tacrolimus to sirolimus was found to prevent cSCC development, if done after the patient has one cSCC, regardless of whether that one tumor was considered high risk [56]. The addition of sirolimus lead to a reduction in the incidence of skin cancer and lower risk of recurrence with no increased risk of overall mortality [57]. Although adverse effects are common in patients on sirolimus, serious consideration should be given to transitioning transplant patients with cSCC patients off calcineurin inhibitors which have been associated with increased incidence of cSCC and recurrent lesions [58].

Surgical Resection

Local recurrence and nodal metastasis are the main determinants of morbidity and mortality both in the immunocompetent and immunosuppressed population, therefore locoregional control is of paramount importance. Surgical management of advanced cSCC in the head and neck region in immunocompromised patients can be challenging. Surgeons must balance extent of surgery (margins, regional nodal dissection) with potential cosmetic and functional morbidity. Tumors often encroach upon or involve key facial and cervical structures including the eye, nose, lips, and ears. Moreover, the primary tumor or pathologic regional disease may invade into deeper structures such as facial muscles, parotid gland, bone, and facial nerve. Surgical excision techniques which allow for complete circumferential peripheral and deep margin assessment (CCPDMA) should be utilized in immunosuppressed patients.

Mohs micrographic surgery provides complete margin assessment. However, when Mohs surgery is unavailable or unfeasible, traditional excision with CCPDMA by frozen sections in place of the breadloaf technique is an alternative [59–61]. A combined procedure where peripheral margins are cleared by a Mohs surgeon and deep margin is cleared by an otolaryngologist, surgical oncologist, or plastic surgeon, may also be considered for more extensive cases. Additionally, a staged-procedure with en face grossing, fixing, and paraffin embedding of the sample such that all margins are examined to ensure complete margin assessment may suffice. In many cases, surgical resection is necessary to complete tumor staging. In a recent report from a single institution, over 70% of T3 tumors were only appropriately staged after information gained from pathologic analysis during Mohs surgery [62]. Therefore, surgeons should consider sending the debulked section of the tumor for

fixation and histopathologic analysis for appropriate staging. There is encouraging evidence that the complete margin assessment offered by Mohs or CCPDMA indeed ensures local control with recurrence rates between 1–5% in the immunocompetent patient [63,64]. In a single center cohort of 215 patients, 20% of which were immunosuppressed, the recurrence rates of high-risk cSCC after Mohs surgery was 1.5% [65]. The immunosuppressed patients were not individually analyzed from this cohort.

Though it is well known that there is increased risk of regional metastases in the immunocompromised patient (5–12%) with cSCC, there is no clear consensus for surgical management of regional nodal basins in the clinically node-negative patient[66]. In this situation, surgeons often consider regional basin dissection when there are multiple risk factors including advanced primary disease(>2 cm in size), deep tumor invasion (beyond subcutaneous fat, bone invasion), concerning histologic features (poorly differentiated, perineural invasion), or in cSCC involving high-risk areas such as the external ear or lip [67]. Alternatively, high risk patients have also been stratified by AJCC 8th edition staging and Brigham and Women's Tumor staging system. Interrogating the sentinel node might be especially useful in the AJCC8 T3 stage where 30% of patients with poor histological differentiation show lymph node metastasis [30]. A meta-analysis of 23 studies showed, that 7.9% of patients present with a positive sentinel lymph node (SLN), while at the same time acknowledging that the underlying primary studies might have been limited by a unclear definition of high risk patients by the respective staging systems [68]. More data, utilizing an updated staging system, is needed to show the clinical benefit of sentinel lymph node biopsies in the high-risk population. We recommend close clinical and sonographic surveillance of the regional lymph node basin for all immunosuppressed patients until the benefit of SLN biopsy has been shown more clearly [69]. Future investigations may reveal which patients would be best suited for observation, SLNB, or elective regional basin dissection in immunocompromised patients.

When regional metastatic disease is present, surgical excision via neck dissection and/or parotidectomy remain the standard of care. When parotid metastases are present, incidence of occult disease in the neck is high (22.5– 42%) in all patients with head and neck cSCC [70,71]. Therefore, neck dissection should be strongly considered in these cases. Due to high prevalence of extracapsular extension in parotid metastases from cSCC, patients should be aware of possible need to perform total, rather than superficial, parotidectomy and the possibility of sacrifice of the main trunk or branches of the facial nerve. At present, surgical management of regional metastatic disease does not change when treating an immunocompromised patient.

Radiation Therapy

In many cases of locally advanced cSCC, radiation therapy is utilized as part of a curative regimen in either the adjuvant setting, in the case of resectable disease, or definitively, in cases where the tumor is unresectable due to local invasion, location or if the patient is not an operable candidate due to comorbidities. The addition of adjuvant radiation may be considered in the immunocompromised population where it could otherwise be safely omitted. However, even with aggressive combined modality therapy, rates of loco-regional

recurrence (LRR) in immunocompromised patients are significantly worse than immunocompetent patients. In a single institution case series of 59 patients, outcomes were dramatically worse in immunocompromised versus immunocompetent cSCC treated with surgery and post-operative radiation therapy (PORT)[72]. In a follow-up study examining a similar question, but with over 200 patients from several institutions, similar results were observed, with dramatically higher rates of LRR following surgery and PORT in immunosuppressed patients (54%) versus immunocompetent patients (17%)($p<0.001$) [73]. In both studies tumor characteristics were more unfavorable in immunosuppressed patients, with higher rates of poor differentiation and extracapsular extension (ECE). However, on multivariate analysis, immunosuppression remained a significantly associated with worse LRR. Moreover, the risk of distant metastasis was also significantly higher in immunosuppressed patients (25% vs. 10%).

These retrospective findings would argue for the intensification of adjuvant radiation with cytotoxic chemotherapy, and this is commonly performed off-trial, usually in the context of close or positive margins or ECE, extrapolating from clinical trials of head and neck squamous cell carcinoma [74]. For example, in the aforementioned retrospective study, approximately 14% of patients were treated with concurrent chemoradiation [73]. However, the benefit to adjuvant chemoradiation in cSCC has been called into question by the results of TROG 05.01, a phase III randomized trial, examining loco-regional control in cSCC completely resected followed by PORT or PORT plus weekly carboplatin [75]. In this study, no significant difference was found in freedom from LRR at 2 years between arms (88% vs 89%), nor in Disease Free Survival (DFS) or Overall Survival (OS), although the trial was not powered for the latter two endpoints. However, this study excluded immunosuppressed patients, and used carboplatin instead of cisplatin. The role of adjuvant concurrent chemoradiation specifically in cSCC in SOTRs has not been evaluated.

In patients for whom surgery is not possible or feasible, definitive radiation therapy may be utilized, sometimes with concurrent chemotherapy. The loco-regional recurrence rates following radiation therapy vary between 4% in favorable settings and 30% in the setting of large tumors or other negative prognostic factors (rev. in [76]). In the latter setting, concurrent chemotherapy may be added based on data extrapolated from other disease sites. One small prospective trial of 20 immunocompetent patients and one immunosuppressed patient with locally advanced cSCC on the head and neck treated with weekly platinum and radiation therapy achieved a complete clinical response in slightly over 50% of patients, with an 80% 1 year OS [77]. In the absence of additional prospective data, our bias is to add concurrent chemotherapy to definitive radiation in the locally advanced setting.

Radiation toxicity may be affected by the type of immunosuppressive medication used in SOTRs. Sirolimus, or rapamycin, is part of the post-transplant regimen for many patients. The target of this drug, the mammalian target of rapamycin (mTOR), has been heavily studied as a potential target for radiosensitization in head and neck cancer [78,79]. While a case report demonstrates a dramatic response to a comparatively low dose of radiation in a laryngeal squamous cell carcinoma in a patient on an mTOR inhibitor [80], this patient and two others have suffered toxicities significantly greater than expected [81,82]. In a phase I study of an mTOR inhibitor combined with chemoradiation in head and neck cancer, 5mg

day was associated with dose limiting mucositis in 1 of 6 patients, with grade 3 mucositis developing very early on during radiation [83]. Thus, while not definitive data by any means, close monitoring of toxicity is needed when treating with radiotherapy in patients currently on mTOR inhibitors such as everolimus and sirolimus.

Systemic therapy

Systemic therapy remains the primary treatment option for patients with locoregional recurrence without surgical or radiation options and/or metastatic cSCC. Systemic agents evaluated in immunocompetent advanced cSCC include traditional cytotoxic agents (platinum, 5FU, taxane), drugs targeting the Epidermal Growth Factor Receptor (EGFR), and immunotherapy. There is a paucity of data on the efficacy of systemic therapy specifically in SOTRs and to date these systemic therapies have not been studied specifically in this patient population.

Targeted therapy against the epidermal growth factor receptor (EGFR) has been evaluated in advanced cSCC, where EGFR is frequently overexpressed [84]. Cetuximab, an IgG1 monoclonal antibody that targets EGFR, was evaluated in a phase II trial that included 36 patients and it showed a response rate (RR) of 27% and disease control rate (DCR) of 70%, however the duration of activity was short with a median progression free survival (PFS) and OS of 4 and 8 months respectively[84]. Panitumumab, an IgG2 monoclonal antibody against EGFR, was also evaluated prospectively with a RR of 31% in 16 patients[85]. Gefitinib, an oral small molecule inhibitor of EGFR, was tested in advanced disease with zero responses and DCR of 27%[86]. These aforementioned studies were in immunocompetent patients, and only case reports have been published with some response in kidney and heart transplant patients with advanced cSCC. In terms of other potential molecular targets, while certain mutations are shared between HNSCC and cSCC, no direct comparison of the mutational profile in immunocompetent vs. SOTRs cSCCs by whole exome sequencing have been conducted and the question remains as to whether there are any unique mutations in SOTRs that could be targeted.

Immunotherapy has been evaluated in prospective trials in immunocompetent cSCC patients. Interferon alpha in combination with 13-cis-retinoic acid yielded a RR of 68% with 25% achieving a complete response (CR). In combination with cisplatin the overall response rate was 34% with 17% of patients having a CR and those that had a CR had a median duration of response of 34 months. Response rates in patients with locally advanced disease were an impressive 67%[87]. However, due to toxicity, these regimens were never fully integrated into standard practice. More recently, anti-PD-1 monoclonal antibody (mAb) cemiplimab was evaluated in immunocompetent patients with advanced cSCC The RR was an impressive 47% with an estimated one year PFS and OS of 53% and 81% respectively[88]. These results lead to the FDA approval of cemiplimab for advanced cSCC in September 2018.

While efficacious in immunocompetent cSCC patients, risk of organ rejection in SOTRs with checkpoint inhibitors has led to these patients being excluded from trials. Numerous case reports have been published and are summarized in Table 2[89,90,99–108,91,109–112,92–98]. Work done at MD Anderson resulted in a comprehensive review pooling data

from 29 patients from published case reports with 10 patients treated locally [113]. In this analysis the majority of patients had melanoma (62%) and had undergone kidney transplant (59%). The analysis included 5 cSCC patients. Forty one percent of patients had graft rejection with 81% of those patients losing their graft despite medical intervention. Graft rejection occurred early after treatment with a median time of 21 days (95% CI 19.3 – 22.8 days) and the majority of tested patients showed acute rejection, T cell-mediated, with 4 out of the 5 patients analyzed for PD-1/PD-L1 showing expression of these co-signaling molecules in the allograft immune microenvironment. While 6 patients received Ipilimumab and Nivolumab (5 Ipilimumab followed by nivolumab and 1 combination therapy) 41% of patients treated with single agent anti-PD-1 and 37% of those just treated with Ipilimumab rejected their graft. This observation differs from initial impressions that the risk was much higher with anti-PD-1/PD-L1 mAb which was based on case reports. Importantly, response rates were comparable to those reported in immunocompetent patients (all 5 cutaneous SCC patients had a response) and did not show a clear correlation with allograft rejection. In regards to immunosuppressive medications, in the MD Anderson series a numerically higher response rate was observed in those that were on single agent prednisone compared to single agent calcineurin or mTOR inhibitors, calcineurin, or combination therapy, 63% vs. 42% respectively, albeit those receiving single agent prednisone had a higher rate of rejection[113]. In our analysis of published case reports, all patients that had their immunosuppression held had allograft rejection.

While interesting observations have been made, firm conclusions in SOTRs cannot be made solely based on case reports. Further research is needed for example to better define whether alteration of immunosuppression can modulate response and risk of rejection in these patients. While dialysis can serve as a life-sustaining option for kidney transplant patients, rejection of a lung, heart, or liver is not tenable. Given the significant morbidity and mortality caused by cSCC in SOTRs and impressive efficacy of anti-PD-1/PD-L1 monoclonal antibodies in advanced immunocompetent cSCC, there is a great need for a better understanding of the tumor and graft immune microenvironment and to determine management strategies to maximize efficacy in this patient population while minimizing the risk to the graft. A prospective trial is planned evaluating nivolumab and ipilimumab in kidney transplant patients with malignancy utilizing tacrolimus and prednisone as immunosuppression (NCT03816332). In addition to targeting PD-1:PD-L1, other more tumor specific immune targets may have potential as well as immunotherapies that are injected directly into the tumor. For example, B7-H3 expression has been observed on tumor but not in the immune cell population of the graft in SOTR with cSCC[114].

Conclusion

SOTRs are at an increased risk for cSCC. These tumors are not only more frequent but also at higher risk for LRR and distant metastases in this patient population. Here, we have reviewed the factors contributing to this increase in incidence as well as prevention and management of this disease. The head and neck region is the most common site for this disease and cosmetic and functional considerations make treatment especially challenging. Given the unique nature of these patients, multidisciplinary care is paramount. Further research specifically in this patient population is needed to improve outcomes.

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- Cutaneous SCCs are more common and more aggressive in transplant recipients
- Primary and secondary prevention and patient education can decrease tumor burden
- Solid organ transplant patients often require multidisciplinary cancer care

Table 1.

Tumor staging systems

Staging System	Stage	High Risk Clinical Features	High Risk Pathological Features
AJCC (8th Edition)	Tis= in situ disease T1=no high risk features T2=moderate size T3=large size *or* one high risk pathological feature T4a=cortical bone/marrow invasion T4b=skull base invasion and/or skull base foramen involvement	Moderate size (2–4cm) Large size >4cm	Perineural invasion (nerves deeper than dermis, >=0.1mm in caliber, or with radiological or clinical evidence of involvement) Deep Invasion (beyond subcutaneous fat or >6mm from granular layer)
BWH	Tis= in situ disease T1= no high risk features T2a= one high risk feature T2b= 2–3 high risk features T3= 4 high risk features or bone involvement	Size >= 2cm	Poor differentiation PNI of nerves >= 0.1mm in caliber Invasion beyond subcutaneous fat

Table 2.

Outcome based on immunotherapy target in published reports of solid organ transplant recipients receiving immunotherapy

Agent	# Cases	Tumor Type	Tumor ORR	Continued Immunosuppression?	Number of immunosuppressants	Graft Rejection	Median time to Rejection	Mean time to Rejection	Range Time to Rejection
All	30	Melanoma - 15 HCC - 5 SCC - 5 NSCLC - 4 Duodenal adeno −1	CR - 3 PR - 9 SD - 5 PD −10 Unknown - 4	Continued Regimen −7 Decreased Regimen −15 Changed Agents −5 Held −3	Three - 2 Two - 12 One - 14 Zero - 2	14/30 (47%)	17.5 days	28 days	5 days - 4 months
PD-1	18	Melanoma - 6 HCC - 6 SCC - 2 NSCLC - 3 Duodenal adeno −1	CR - 2 PR - 3 SD - 4 PD −4 Unknown - 5	Continued Regimen −6 Decreased Regimen −10 Changed Agents −2 Held −0	Three - 2 Two - 9 One - 6 Zero - 1	9/18 (50%)	30 days	33 days	5 days - 4 months
CTLA-4	7	Melanoma - 7	PR - 3 SD - 1 PD −3	Continued Regimen −1 Decreased Regimen - 6	Two - 1 One - 6	2/7 (27%)	26 days	26 days	22 days - 1 month
Both	5	Melanoma - 3 SCC - 2	CR - 1 PR - 2 PD −2	Continued Regimen −1 Decreased Regimen - 2 Held - 2	Two - 2 One - 1 Zero - 2	3/5 (60%)	8 days	12 days	8 – 21 days