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Cutaneous Oncology in Organ Transplant Recipients: Meeting the Challenge of Squamous Cell Carcinoma

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Introduction

The incidence of nonmelanoma skin cancer continues to rise with over 1.3 million cases diagnosed in the United States in 2002.[1] Squamous cell carcinoma (SCC), the second most common human cancer, accounts for 250,000 cancers diagnosed in the U.S. annually. In the majority of cases, cure is achieved, however there are subsets of patients in whom SCCs behave aggressively and in whom SCC can be devastating.[2] This is particularly true in the case of organ transplant recipients (OTRs).[3]

There are over 100,000 OTRs currently living in the United States.[4] Over 25,000 transplants are performed in the U.S. annually with the large majority being renal transplants.[5] Transplant recipients are living longer with the half life of renal grafts reaching 20 years[6,7] and the 5 – year survival rate for heart transplant recipients approaching 80%.[8]

Epidemiology

OTRs are at significantly increased risk for developing skin cancers, particularly SCC.[4,9,10] OTRs are also at increased risk for Kaposi's sarcoma, Melanoma, and BCC.[4,9,10] Skin cancer is a cause of significant morbidity and even mortality in transplant patients. Seventy percent of transplant patients may eventually develop skin cancer with an increased SCC:BCC ratio.[10-17] In a study of 5356 consecutive patients transplanted between 1970 and 1994, NMSC other than BCC occurred in 172 patients.[18] Relative risk was ~109 for men and ~93 for women.

Kidney Transplantation and Skin Cancer

Jensen, et al, studied skin cancer in a Norwegian cohort that included over 2500 transplant recipients.[16] In this study, OTRs had increased risk for cutaneous SCC (65-fold), malignant melanoma (3-fold), and SCC of the lip (20-fold). Risk for skin cancer was higher (~20:1) in patients transplanted after age 60 and for those on triple immunosuppression. Kidney transplant patients were at lower risk for skin cancer than heart transplant patients. Kidney transplant recipients on cyclosporine, azathioprine, and prednisolone had a ~3 fold increased risk for developing cutaneous SCC relative to those receiving azathioprine and prednisolone without cyclosporine. Naldi, et al, reviewed 1062 kidney transplant recipients and showed a cumulative skin cancer incidence of nearly 6% at 5 years and over 10% at 10 years.[17] Older age at transplant and male sex favored development of skin cancer. In contrast to other studies, there was no difference in risk between kidney and heart transplant recipients. The SCC:BCC ratio was 1:2.6 for kidney transplant patients.

Euvrard, et al, reviewed skin cancer development in a series that included 580 kidney transplant patients.[11] Kidney transplant recipients were half as likely to develop skin cancer as heart transplant recipients. Kidney transplant patients were younger at transplant, received less intense immunosuppression, and had a longer interval between transplant and first skin cancer. The SCC:BCC ratio was 2.37:1 in kidney transplant recipients.

Heart Transplantation and Skin Cancer

In the study by Jensen, et al, heart transplant recipients were 3 times more likely to develop SCC than kidney transplant patients. Lampros, et al, reported on 248 heart transplant patients followed between 1985 and 1996.[13] Forty one patients (17%) developed 192 SCCs

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or BCCs. SCC accounted for ~90% of the skin malignancies (172) with the SCC:BCC ratio approaching 9:1. Two patients in this study developed metastases from primary cutaneous SCC. Skin cancer risk was associated with increased time after transplant, use of OKT3, male sex (~20:1), blue eyes, and fair skin.

In a study of heart transplant patients from Spain by Espana, et al, skin cancer was diagnosed in 14 of 92 patients between 1984 and 1993.[10] The risk for skin cancer rose from 4.8% in the first year after transplantation to 43.8% at seven years. Skin cancers occurred primarily in patients with skin types II and III. Interestingly the SCC:BCC ratio was 1.3:1. Four of the 14 patients developed SCC of the lip and 1 died of metastatic disease.

Ong, et al, (1999), reviewed skin cancers in 455 Australian heart transplant patients and found a cumulative incidence of 31% at 5 years and 43% at 10 years.[15] In this study, skin cancer accounted for 27% of 41 deaths after the fourth year following transplantation. SCCs were the most common cancers in this group outnumbering BCCs by a ratio of 3:1. Fair skin, increased age at transplant, and increased length of time after transplant were associated with greatest risk of developing skin cancer in this study.

The development of aggressive cutaneous malignancy after cardiothoracic transplant (CTT) was addressed by Venes, et al, in a study of 619 patients who received heart, lung, or heart –lung transplants between 1984 and 1995.[14] Aggressive skin cancer, including locally invasive SCC, recurrent SCC, poorly differentiated SCC, and regionally metastatic SCC, occurred in 27 of 66 (~ 41%) patients diagnosed with a malignancy. There were 10 deaths from metastatic disease.

Liver Transplantation and Skin Cancer

The incidence of skin cancer was 1.6% a series of liver transplant recipients by Levy[12] with a single case of metastases from primary skin cancer. In a study by Frezza, et al, 50 of 1657 liver transplant recipients developed tumors.[19] Skin cancers were most common with the SCC:BCC ratio approaching 1:1. A higher incidence of cancer was observed in patients treated with cyclosporine as opposed to tacrolimus.

Pathogenesis at the Molecular Level

P53 is key in epidermal cell apoptosis following UV radiation-mediated DNA damage.[20,21] Ultraviolet light (UVL) serves as an initiator as well as a tumor promoter [20,22] and p53 dependent apoptosis of sun-damaged cells is believed to protect against SCC. Mutations in p53 including formation of thymidine dimers are seen in AKs (70%) and SCC (90%).[22]

Mutant p53 tends to accumulate in the cytoplasm whereas wild type p53 tends to be degraded rapidly.[21] Some theorize that over expression of mutant p53 might contribute to tolerance.[23]

Ras GTPases regulate cell proliferation, angiogenesis, apoptosis, and cellular morphology.[23] Ras and Raf, a downstream effector molecule, stimulate cell division, inhibit differentiation, and enhance expression of integrins, all changes characteristic of SCC.[24] The cascade involving Ras and downstream effector molecules might be a viable target for attacking SCC on the molecular level.

The *NF-kB* family refers to conserved transcription factors implicated in regulation of apoptosis, differentiation and proliferation.[24] Blockade stimulates hyperproliferation in human epidermis in vitro. Mice with inhibited NF-kB show increased susceptibility to induction of SCC.[25] Blockade along with induction of oncogenic Ras can transform human epidermis to a highly aggressive neoplasia indistinguishable from SCC.[26]

The cDNK2A locus on 9p21 is widely mutated in a number of cancers.[23] It encodes a cyclin depenent kinase (CDK) inhibitor, p16[INK4A], and a p53 regulator that is translated by an alternative reading frame. The p16[INK4A] inhibits cell cycle progression in G1 by binding and inhibiting CDK4/6 kinases. CDK4/6 kinases phosphorylate retinoblastoma (Rb) proteins to remove the mid-G1 Rb block to cell cycle progression.[23] DNK4/6 is over expressed in SCC and is sufficient to induce SCC when co-expressed with oncogenic Ras.[27]

Gene Expression and Cancer

Microarray techniques allow for analysis of differential gene expression between diseased and normal tissue. With careful interpretation investigators may be able to identify key differences in gene expression that may lead to better risk stratification and novel points for therapeutic intervention. Preliminary unique gene expression patterns have been observed in head and neck squamous cell carcinoma (HNSCC).[28]

Such a molecular fingerprint has yet to be established for cutaneous SCC however this is the subject of ongoing collaborative efforts involving the Laboratory of Investigative Dermatology at the Rockefeller University and the Section of Mohs Micrographic and Dermatologic Surgery at the Weill Medical College of Cornell. Presently, several studies support the importance of differential expression of key genes in SCC and SCC cell lines. In one pilot study, p16[INK4A] was 85% sensitive and 96% specific in distinguishing Bowen's disease from AK.[29] Dazard, et al, studied the response of normal keratinocytes and SCC to UVB and found up-regulation of CXC/CC chemokines, growth factors, pro-inflammatory mediators including S100A9, DNA repair genes, and proteases including MMP1 and MMP 10.[30] They found that Delta Np63 and PUMILIO, potential markers for maintenance of keratinocytes stem cells, were down-regulated. Gariboldi, et al, found that the serpin like SCCA2 was associated with younger onset in 2 series of patients with cutaneous SCC.[31]

Environmental and Inherited Factors Involved in Pathogenesis

The pathogenesis of skin cancer in the general population and in organ transplant recipients involves

ultraviolet light (UVL).[32] Tumor initiation occurs through UV induced genetic changes in keratinocytes DNA.[20,32] In addition, UV specific changes take place in tumor suppressor p53. Thus UVL acts as both tumor initiator and tumor promoter.[20,32]

HPV is involved in the pathogenesis of SCC.[33] HPV types 6, 11, 16 and 18 have been associated with cervical cancers.[34] HPV types 5 and 8 are associated with epidermodysplasia verruciformis.[35] HPV 16 has been implicated in SCC occurring on the digits.[36] HPV 16 and 18 have associated E6 and E7 proteins that inhibit tumor suppressor p53.[37] In addition it has been shown that E6 may inhibit UV induced apoptosis by a p53 independent mechanism thus acting as a p53 independent tumor promoter by allowing propagation of atypical keratinocytes. Furthermore it has been shown that EDV associated HPV types are found in SCCs from OTRs.[38] This is in agreement with Stockfleth, et al, who recently showed that HPV DNA was detected more frequently in SCCs from OTRs compared to non-OTRs (75% vs 37%) and that HPV 5 and 8 were detected most frequently in SCCs from transplant recipients.[39] Euvrard, et al, examined warts, actinic keratoses and SCCs from renal transplant recipients for the presence of HPV types 1a, 2a, 5, 16, and 18.[40] HPV DNA was detected in 44 of 86 specimens overall including 14 of 17 warts, 4 of 17 actinic keratoses, and 14 of 30 SCC. Benign types 1 and 2 were detected in 5 SCC.

Opinion differs as to whether certain HLA types confer protection or risk.[10,15,16] There was no association with haplotypes HLA-A3, HLA-A11, HLA-DR and mismatches for HLA-B in the study of heart transplant patients by Espana, et, al. In contrast, HLA-DR homozygosity was associated with skin cancer and HLA-DR7, HLA-A1 and HLA-A11 seemed to be protective in a study by Ong. Major factors associated with increased risk for skin cancer are summarized in **Table 1**.

Table 1 Factors Associated with SCC in Organ Transplant Recipients

Risk Factor	Reference
Sun Exposure	Lindelof, et al. (18)
HPV 5 and 8	Euvrard, et al., (40) Stockfelth, et al. (39)
Fair skin	Lampros, et al., (10) Espana, et al. (13)
Heart transplant	Jensen, et al., (16) Euvrard, et al. (11)
Intense immunosuppression	Preciado, et al. (69) Euvrard, et al. (11)
Older age at transplant	Jensen, et al., (16) Euvrard, et al. (11)
Male sex	Naldi, et al., (17) Lampros, et al. (13)

Immunosuppression and Skin Cancer

Immunosuppression is key to preventing graft rejection and optimizing graft survival. However, immunosuppressive regimens have been associated with increased rates of skin cancer. Studies suggest that both azathioprine and cyclosporine contribute to increased risk for skin cancer through direct carcinogenic effects as well as decreased immunosurveillance.[4,41-44] Intensity and duration of immune suppression appear to correlate with risk of aggressive SCC.[4]

Azathioprine inhibits T and B cell proliferation by inhibiting nucleotide synthesis.[45] It is a mutagen, a photosensitizer and an immunosuppressant. A metabolite of azathioprine, 6-thioguanine has been found in higher concentrations in red blood cells from renal transplant recipients with skin cancer.[46] Azathioprine has been associated with high numbers of UV induced tumors in animals.[47]

Cyclosporine inhibits IL-2 transcription, enhances TGF-β expression and thus inhibits T cell function.[48] Animal studies support direct carcinogenesis by cyclosporine.[49] Cyclosporine has been associated with tumor growth in SCID mice.[50] Cyclosporine induced carcinogenesis was blocked by antibody to TGF-β implicating TGF-β in cyclosporine induced carcinogenesis. Cyclosporine has been shown to enhance invasive tumors in vitro and to promote the growth of transplanted UV induced tumors in mice.[51]

Penn and First[52] reviewed development of cancer following cyclosporine therapy compared with other immunosuppressive regimens and found fewer skin cancers in the cyclosporine group.

In a recent study by Lerut, et al,[53] of 70 liver transplant patients treated with cyclosporine monotherapy, 2 patients (2.8%) developed skin cancer over a 3 year follow up period.

Corticosteroids inhibit proliferation of T cells.[5] Steroids are often included in multi-drug immunosuppressive regimens. Karagas, et al,[54] reviewed chronic use of oral steroids in non-OTRs and found that it was associated with increased risk of SCC.

Mycophenolate mofetil (MMF) inhibits nucleotide synthesis thus blocking T and B cell proliferation.[55] Triemer, et al,[56] report one BCC in 106 renal transplant patients treated with MMF, cyclosporine and corticosteroids compared with 1 SCC in 106 patients treated with azathioprine, cyclosporine and steroids over a 6 month period.

OKT3 is an antithymocyte antibody used in the induction phase of immunosuppression and for steroid resistant rejection episodes.[57] Stempfle, et al, report rapid growth of merkel cell carcinoma during treatment of acute cardiac allograft rejection with OKT3.[58] Similarly, Lampros, et al,[13] reported increased risk of development of skin cancers in heart transplant recipients treated with OKT3. In contrast, Oechslin, et al,[59] reported no association between OKT3 induction and malignancy following heart transplant.

Tacrolimus (FK 506), a metabolite of the fungus Streptomyces tsukubaensis, suppresses T-lymphocytes by inhibiting the production of IL-2, IL-3, IL-4, TNFa, and GM-CSF.[45,60] Jain, et al, report a 2% incidence of skin cancer over 6.5 years in patients treated with tacrolimus.[61] Frezza, et al, reported lower incidence of all tumors in liver transplant patients treated with tacrolimus vs cyclosporine.[19] This is consistent with a report that tacrolimus had antiproliferative effects in murine tumor studies.[62]

The macrolide rapamycin acts by inhibiting Target of Rapamycin (mTOR), a key signaling protein that controls activation of a number of other proteins that direct progression of the cell cycle in response to pro-inflammatory cytokines.[63] Some studies suggest rapamycin inhibits tumor growth while being immunosuppressive. Furthermore, rapamycin was shown to inhibit several UV-induced mechanisms involved in skin carcinogenesis. Preliminary clinical studies have reported a lower incidence of skin malignancy in patients treated with rapamycin compared to CsA from the time of transplantation.[64]

Catastrophic Skin Cancer in Transplant Recipients

Local Disease Skin cancer is not only more common in OTRs but also more serious. In some cases, skin cancer in OTRs can be devastating in terms of quality of life, lost productivity and threatened mortality. Berg and Otley diagnosed catastrophic cutaneous carcinomatosis in patients with more than 10 NMSCs per year or evidence of metastatic disease.[4] In addition, OTRs with widespread severe actinic field damage, suffering from hundreds of actinic keratoses mixed in with their cancers might be best classified in this category **(Figure 1)**.[4,65]

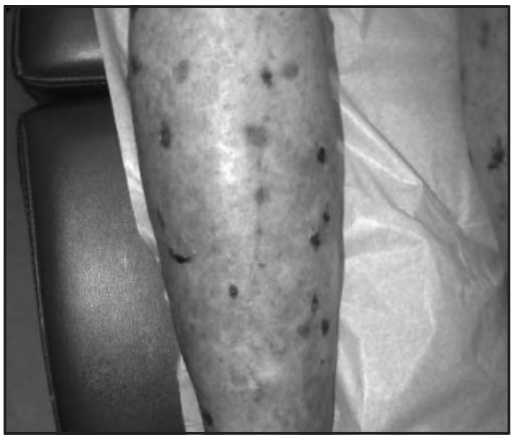

Figure 1. In cases of extensive field damage, it is difficult to distinguish between pre-malignant lesions and superficial carcinomas.

Metastatic Disease Skin cancers metastasize more frequently in OTRs.[66] In transit metastatic SCC lesions are usually nondescript gray to flesh colored subcutaneous papules that are not contiguous with the primary lesion.[67] They are likely to represent spread along lymphatic vessels and nerves, are a poor prognostic indicator and represent a therapeutic challenge. In a recent study, development of in transit metastases from primary cutaneous SCC in OTRs was associated with 33% mortality at 2 years.

Regional lymph nodes are the most common site of metastases from primary skin cancer in transplant patients. Euvard, et al, reported a series of 50 OTRs with at least 1 SCC among whom 5 (10%) had an aggressive course defined as multiple local recurrences with or without lymph node metastasis.[68] In this series, all aggressive tumors were located on the head with 3 in kidney transplant recipients and 2 in heart transplant recipients. Three patients (60%) developed nodal metastases and died.

Distant metastases from skin cancers in OTRs are associated with a 29% relapse rate at 1 year and a disease specific survival rate of 56% at 3 years.[66] Preciado, et al, reviewed aggressive head and neck cancers in OTRs.[69] There were 8 cases of primary cutaneous SCC metastatic to parotid. Two were well differentiated SCC, 5 were moderately differentiated and 1 was poorly differentiated SCC. In all cases primary tumors were treated by surgical excision.

Medical and Surgical Management of SCC in OTRs

While it is tempting to consider potential points of intervention revealed by molecular studies in the future, clinicians must contend with the growing number of transplant recipients with skin cancer today. Currently, our best approach relies on early detection through thorough and sometimes frequent evaluation depending on the extent of disease. Medical and surgical management of skin cancer, particularly SCC in OTRs is a significant challenge for dermatologists. Members of the Guidelines Committee of the International Transplant Skin Cancer Collaborative reviewed ~300 articles relevant to management of SCC in OTRs and combined this review along with their collective experience in management of SCC in OTRs to develop the first set of guidelines of care for SCC in OTRs.[70] One of the key points in managing SCC in OTRs is differentiating between higher risk and lower risk lesions.

Lower Risk Lesions Less aggressive lesions were characterized as those that were smaller size, static or slowly growing, well demarcated and well differentiated histologically. It was recommended that all less aggressive SCC in OTRs should be managed by destructive or excisional modalities depending on anatomic site.[70] It was recommended that histologic analysis be performed on all SCC in OTRs. Biopsy may be performed before or at the time of treatment. Tangential excision for histologic analysis followed by immediate destruction may be used and may be useful inpatients with multiple lesions on the trunk and extremities.[70] Topical therapy with imiquimod[71] or 5-fluorouracil[72] can be used on superficial lesions and actinic keratoses[73-75]. In one study, SCC in situ in 5 OTRs was effectively managed by using these agents in combination.[76]

Higher Risk Lesions It is key to remember that SCC in an OTR is considered to be a high-risk lesion as defined by Rowe, et al.[2] When managing SCC in an OTR it is important to differentiate those lesions that are highest risk for recurrence or metastasis. Increased risk may be associated with factors including rapid growth, large diameter, location on ear, lip, or scalp, aggressive histology, and recurrent SCC **(Figure 2)**.[2,4,70] Careful inspection of the surrounding skin to exclude the presence of satellite lesions is necessary as is examination of the draining lymph nodes.[2,67,70] Aggressive SCC confined to skin and soft tissue in OTRs should be

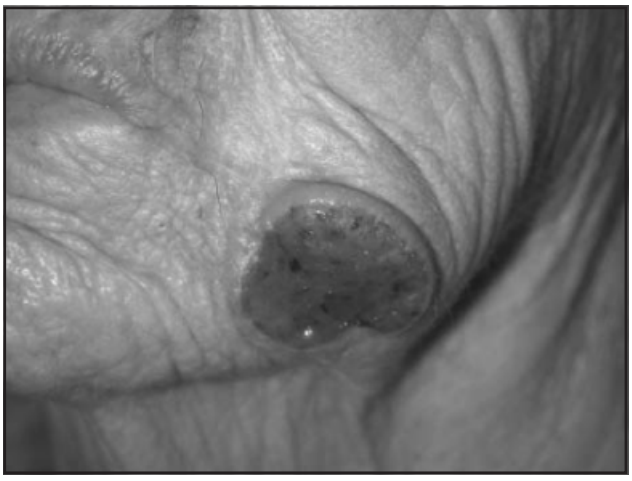

Figure 2. A large, rapidly growing, recurrent SCC falls into the category of highest risk for metastasis.

managed by Mohs micrographic surgery or standard surgical excision.[70] Every attempt should be made to achieve clear margins. Management of selected high-risk lesions is summarized in **Table 2**.

Table 2 Management of Highest Risk SCC in OTRs

Tumor Characteristic	Management
Invasive SCC	MMS or Excision
Aggressive histology	MMS or Excision
Perineural SCC	MMS or Excision followed by XRT
High risk anatomic site	MMS or Excision
Large tumor	MMS or Excision
Recurrent cancer	MMS or Excision
In transit metastases	Excision, XRT, Retinoids, Decrease immunosuppression

Vandeghinste, et al, first reported the cessation of new dysplastic skin lesions during acitretin treatment.[77] Other studies have followed including one by McNamara, et al, where five of 15 patients showed reduction of new skin lesions on acitretin.[78] Bavinck, et al, enrolled 44 renal transplant recipients in a randomized, double-blind, placebo-controlled trial to evaluate chemoprevention with acitretin (30 mg/d).[79] Patients in the treatment group developed significantly fewer new SCCs (11% vs 47%) Yuan, et al, treated 15 renal transplant recipients with progressive AKs, widespread warts or recurrent skin cancers with acitretin (10-50 mg/day).[80] Fewer warts and AKs were noted in all patients and fewer SCCs were seen in some patients treated for longer than one year. Side effects in these studies included dry mouth and dry eyes, mild hair loss, elevated cholesterol and serum triglycerides, however no effect on kidney function was observed.[78-80] A recent study suggests that acitretin has no effect wound healing after surgery.[81] Topical retinoids have the potential for fewer side effects. In one study, a significant decrease in the number of AKs was noted in patients treated with adapalene.[82]

Reduction of immunosuppressive therapy may be considered in cases of severe, life threatening skin cancer.[4] In a recent series of 6 patients in whom skin immunosuppressive therapy was discontinued, 4 patients experienced decreased development of skin cancers.[83] Maintenance vs reduction of immunosuppression was addressed in a study of 9 renal transplant recipients with aggressive cutaneous SCC invading deep subcutis or muscle or with in transit or nodal metastases.[84] A significant decrease in development of metastases was noted in the group in whom immunosuppression was withdrawn. The authors postulate that the degree of immunosuppression may act to switch a locally growing SCC into a tumor with metastatic potential. In contrast, no conclusions regarding reduction of immunosuppression could be drawn from a study of OTRs with in transit metastases.[67] It must be remembered that reducing immunosuppression may predispose to rejection and therefore any decisions regarding alteration of immunosuppression must be reached in cooperation with the primary transplant physician.

In some cases, sun exposed areas on transplant patients are overrun with pre-malignant and malignant skin lesions.[4,65] This is sometimes referred to as “transplant hand”. It is not uncommon for hands, arms and legs to be involved with overwhelming numbers of lesions. In these cases, topical therapies, destructive modalities, and excision may be used in combination or rotated in an attempt to achieve and maintain control. In extreme cases, large areas can be removed and resurfaced by split thickness skin grafts. Physical therapy may be required to optimize postoperative function.

Although not considered standard of care, sentinel lymph node dissection (SLND) may be considered in selected high risk SCC in the appropriate setting. Reschly, et al, reviewed the utility of sentinel lymph node dissection in patients with high risk SCC on the trunk or extremities.[85] Histologically positive nodes were found in four of nine patients (44%) without clinical lymphadenopathy. Two of the four patients with positive sentinel nodes died of metastatic disease within 2 years. All five patients with negative sentinel lymph nodes were alive without disease at a median follow-up of 8 months. Altinyollar, et al, reported on SLND in 20 patients with SCCs greater than 2 cm on the lip without clinically appreciable lymph nodes.[86] Nodal disease was identified in three patients (16.6%).

In transit metastases from primary cutaneous SCC present a significant challenge.[67] The presence of in transit metastatic disease is a poor prognostic indicator. In a recent study, OTRs with in transit metastases had worse prognosis than non-OTRs. At 2 years follow up, 33% of OTRs showed no evidence of disease (NED), 33% were dead from disease and 33% were alive with disease. All patients alive with disease had progressed to nodal or distant metastases. Eighty percent of the non-OTRs were NED at 2 years with 20% alive with local

recurrence. No non-OTRs were dead from disease and none had progressed to nodal or distant metastases. Patients were managed with varying combinations of surgery and XRT. Immunosuppression was reduced in some transplant patients. No conclusions could be drawn with respect to optimal management however it was clear that a multidisciplinary approach with careful coordination between dermatologists, dermatopathologists, dermatologic surgeons, surgical and medical oncologists and transplant physicians is necessary to optimize outcome.

Martinez reviewed the literature regarding the use of chemotherapy in HNSCC and proposed adaptation of key management concepts in cases of advanced locoregional and metastatic SCC in OTRs.[87] In one phase 2 study, 39 patients were treated with IFN-α, retinoic acid, and cisplatin.[88] The complete response rate was 17% with patients having locally advanced disease responding better than patients with metastatic disease (67% vs 17%).

Longitudinal Dermatologic Care in Transplant Recipients

Christensen et al, described the advantages and disadvantages of various approaches of addressing the needs of transplant recipients.[89] The utility of a multidisciplinary transplant clinic that includes transplant surgeons, nephrologists, hepatologists, cardiologists, endocrinologists, hypertension specialists, psychiatrists and dermatologists was discussed. Some physicians set aside practice sessions specifically for transplant patients while others simply integrate their transplant patients into their daily practice routine. Regardless of the model used, key issues include enhancement of communication between various members of the health care team, insuring access to dermatologists for timely evaluation of suspicious lesions and development of educational programs directed towards patients and colleagues, particularly transplant physicians and nurse coordinators.[89] There are advantages and disadvantages to each model based on the special needs and frequent follow up usually required.[4] Patients with multiple or severe life threatening cancers may need to be followed as frequently as every 1-2 months while those with skin type greater than III or patients with no history of actinic keratoses or skin cancers may be evaluated annually. Follow up should include evaluation of previously treated areas for signs of recurrence and careful examination of draining lymph nodes to exclude regional disease.

As the number of solid organ transplants continues to rise so too will the number of skin cancers in OTRs. Dermatologists will be called upon to manage their skin cancers and to develop novel therapeutic and preventative strategies.

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