Special Concern About Squamous Cell Carcinoma of the Scalp in Organ Transplant Recipients

Jennifer Z. Cooper, MD; Marc D. Brown, MD

Background: Several risk factors are generally accepted to portend more aggressive behavior of cutaneous squamous cell carcinoma. These include tumor size, tumor depth, histologic subtype, location on the lip or ear, tumor arising in scar, recurrent tumor, and tumor demonstrating perineural invasion. Organ transplant recipients can have significant morbidity and mortality from squamous cell carcinoma.

Observations: Four organ transplant recipients developed metastatic disease from squamous cell carcinoma of the scalp.

Conclusions: Squamous cell carcinoma of the scalp in organ transplant recipients should be considered a high-risk tumor because of its anatomic location. Margin-controlled tumor extirpation, sentinel lymph node biopsy, and adjuvant radiation therapy should all be considered in the organ transplant recipient population.

Arch Dermatol. 2006;142:755-758

There are more than 140,000 organ transplant recipients (OTRs) alive in the United States, with 20,000 more new transplants being performed each year. Survival of these recipients of solid organ transplants has been increasing secondary to improvements in immunosuppressive regimens, treatment of infectious disease, and tissue matching.1 Nonmelanoma skin cancer causes significant morbidity and mortality in the OTR population. The relative risk for the development of squamous cell carcinoma (SCC) in a population cohort of 5356 patients in Sweden was 108.6 in males and 92.8 in females.2 Australian studies3-5 have shown the risk of nonmelanoma skin cancer in renal and heart transplant recipients to be in the range of 18.8% to 29% at less than 5 years after transplantation to 47% to more than 70% of patients at 20 years. The risk of metastatic SCC in OTRs is estimated to range from 7% to 13% compared with 1% to 3% in nonimmunosuppressed patients (based on multiple risk factors).

There are generally accepted clinical and histologic criteria that raise concern for possible development of metastatic disease based on tumor type and behavior. These criteria include tumor size greater than 2 cm, tumor depth greater than 4 mm, poorly differentiated histologic subtype, location on the lip or ear, SCC arising in scar, recurrent tumor, and tumor demonstrating perineural invasion.

Aggressive behavior of SCC of the scalp in different clinical settings has been previously described. In a retrospective study of 2927 patients with SCC in Finland, male patients with SCC of the scalp and neck region had the worst prognosis.6 A case of severe exacerbation of SCC of the scalp was observed in a patient with chronic lymphocytic leukemia who was receiving fludarabine phosphate. The authors of that report hypothesized that the depression of the T-lymphocyte population was causal in the proliferation of the patient’s scalp SCC. Many of the immunosuppressive agents used in OTRs to prevent organ rejection have direct or indirect suppression of T-cell function.7

Carucci et al8 suggested that in-transit metastases tend to occur after high-risk SCC more frequently in OTRs than in patients who have not received transplants. They also noted that these in-transit metastases tended to occur after high-risk tumors of the forehead or scalp and were associated with a poor prognosis in OTRs. On the basis of our experience, we propose that the scalp may be an area of special anatomic concern for SCCs in OTRs. Herein we...
describe 4 cases of metastatic SCC with primary lesions of the scalp.

**REPORT OF CASES**

**CASE 1**

A 68-year-old man underwent double lung transplantation in 1993 for emphysema. Four years after his transplantation he began to develop multiple cutaneous carcinomas. From 1997 until 2000 these were primarily in situ SCCs. In August and December 1999, 2 SCCs of the scalp (parietal and vertex) were treated with curettage and electrodesiccation in the setting of multiple background actinic keratoses. Approximately 6 months later, the patient underwent a 2-stage Mohs procedure for an SCC of the scalp. In July 2000, a biopsy specimen of a scalp nodule showed poorly differentiated SCC filling the dermis and subcutis. There was no connection from an adjacent site.

Within 1 month, the patient developed 8 metastatic cutaneous scalp lesions (Figure). He was referred for radiation therapy (XRT) and received 7000 rad (70 Gy) fractionated daily over 40 days. Despite the XRT, within 6 weeks the patient began to develop more dermal scalp nodules consistent with metastatic SCC. The dosages of his immunosuppressive drugs (cyclosporine, prednisone) were decreased by 50% at that time. The patient subsequently underwent multiple wide excisions, a radical neck dissection, and additional XRT with capecitabine sensitization, with minimal response. Intralesional methotrexate was used successfully for palliative local control; however, there was rapid onset of successive new lesions. The patient had neck dissection with a positive node but never developed clinical lymphadenopathy. Computed tomography of the chest never showed disease involvement. The patient began to experience constitutional symptoms in 2002. He also developed a facial nerve palsy, indicating involvement of the seventh cranial nerve. The patient died of metastatic disease in October 2002.

**CASE 2**

A 43-year-old man initially underwent renal transplantation in 1978 and had a second transplantation in 1997. He was followed up closely every 1 to 2 months by a dermatologist and during the past 15 years had more than 250 SCCs. In November 1996, the patient had a poorly differentiated SCC with perineural invasion of the right parietal area of the scalp. This was treated with excision with 6-mm margins, and the margins were clear. One year later, the patient underwent 2-stage Mohs surgery for a rapidly enlarging SCC of the right frontal part of the scalp, with resultant 3.5 × 2.5-cm defect. Approximately 18 months later the patient experienced swelling in the right cheek. A highly anaplastic parotid metastasis was discovered. Neck dissection showed 2 of 20 nodes positive for SCC. The patient underwent 4 cycles of adjuvant chemotherapy. The patient continued to be closely observed, without evidence of recurrent metastatic disease.

**CASE 3**

A 52-year-old white woman, with Fitzpatrick skin type II, underwent renal transplantation in 1994. Since that time she had had fewer than 10 skin cancers. In January 2000 an actinic keratosis of the vertex scalp was subjected to biopsy and treated with electrodesiccation and curettage. The area never fully healed. In May 2000 a biopsy specimen from the nonhealing area showed moderately differentiated SCC. Treatment consisted of a 2-stage Mohs procedure with deep permanent sections confirmed negative by dermatopathology. Approximately 6 months later, the patient developed a 6-mm papule of the left parietal area of the scalp consistent with cutaneous metastatic SCC. During the next 2 years the patient developed 5 additional metastatic cutaneous nodules of the scalp that were treated with excision, grafting, and XRT. The patient was then monitored closely, with nodes remaining clinically negative. Routine computed tomography of the chest showed normal results as well. A possible node with increased uptake was identified by positron emission tomography in the supraclavicular region. This finding was being further evaluated.

**CASE 4**

A 54-year-old white man, with Fitzpatrick skin type II, underwent his first renal transplantation in the 1980s and a second transplantation in 1997. He was followed up every 1 to 2 months by a dermatologist and had more than 150 SCCs, mostly in situ. In December 1998 the patient developed a recurrent SCC of the scalp after previous curettage and electrodesiccation. The recurrent SCC was treated with a 2-stage Mohs procedure that was closed in a primary fashion. Almost 2 years later the patient developed a dermal nodule at the edge of the scar. Pathologic examination showed a poorly differentiated adenocarcinoma, probably SCC. This tumor was treated with a 2-stage Mohs procedure, with the peristeum being positive for tumor. Radiation was given as adjuvant treatment. In July 2004, a pea-sized mobile lymph node in the left cervical chain was noted. During a 1-month pe-
Period this rapidly increased to larger than 1 cm. The patient was examined by the head and neck surgery department, and a fine-needle aspirate disclosed a possible adenocarcinoma. Computed tomographic surveillance showed a possible mass in the colon, which was believed to be a possible source of the patient's metastatic disease to the lymph node. Laparotomy and superficial parotidectomy—supraomohyoid neck dissection were performed simultaneously. Pathologic examination of the colon lesion demonstrated a benign villous adenoma. Neck dissection showed poorly differentiated SCC of 3 lymph nodes with extracapsular spread. The patient completed a course of postoperative XRT to the left parotid bed and neck.

**COMMENT**

Squamous cell carcinoma is a significant cause of morbidity and mortality in OTRs. Not only are they at higher risk for developing cutaneous disease, they also have greater potential to develop diffuse field disease and metastatic spread. Patients who develop metastatic SCC have a poor prognosis. In the organ transplant population, this development is a significant cause of mortality. The 5-year survival for metastatic SCC has been reported to be as low as 26% for the general population.

As shown by Pollard et al\textsuperscript{10} in their analysis of 1069 cardiothoracic transplant recipients, 11.2% developed nonlymphoid malignancy. Half of these malignancies were of the head and neck, with 96% being of cutaneous origin. The most common site of cutaneous head and neck malignancies was the scalp (>15%). Of patients with a cutaneous malignancy in their study, 32.5% had 1 skin cancer that was aggressive. Although it was not delineated in their study how many scalp lesions metastasized, it can be extrapolated from these data that some did display aggressive behavior.

We suggest that the scalp be viewed as an anatomic location of high concern for aggressive behavior of SCC, akin to the ear and lip, especially in this subset of patients. Possible explanations for higher metastatic potential in the scalp include the scalp's highly vascular nature, the diffuse field disease present in many of these patients, and the complex lymphatic drainage pattern. Despite the diffuse scalp disease that these patients may develop, it may be prudent to attempt margin control early in the course of the patients' cutaneous disease, even for superficial or well-differentiated disease.

The seemingly more aggressive nature of these tumors presents a difficult management dilemma. Of the 4 patients described, 3 had severe background disease. The concept of field cancerization is highly applicable in OTRs. Field cancerization is the presence of genetically altered cells that, while not possessing the hallmark behavior of cancer (invasive growth and metastatic potential), are present in tumor-adjacent “normal” skin.\textsuperscript{11} Diffuse field disease containing the genetically altered surrounding skin gives ample opportunity for the development of additional cutaneous SCC. Tumor burden and management in this setting can be extremely challenging. This problem leads to the conclusion that there is a need for further trials in the use of more widespread field treatments, such as immune response modifiers or photodynamic therapy, in this subset of patients.

If the scalp tumors are now to be considered at higher risk for aggressive behavior, some questions arise. Should adjuvant XRT be considered for SCC of the scalp in OTRs? What is the utility of sentinel node biopsy in this subset of patients?

The use of XRT for all SCCs of the scalp is impractical in these patients. However, it should be thoughtfully considered as early adjuvant treatment of a tumor of the scalp that has any of the features of more aggressive behavior previously described.

Sentinel node biopsy is an emerging modality in the evaluation of nonmelanoma skin cancer. Sentinel node biopsy of the head and neck has long been thought of as a technically challenging procedure because of the complex lymphatic drainage patterns in that anatomic region.\textsuperscript{12} In a series reported by Reschly et al\textsuperscript{13} of 9 patients with high-risk SCC, 4 patients had a positive sentinel lymph node. Three of the 9 patients had head and neck SCCs. Although 2 of the latter patients had negative sentinel lymph nodes, 1 had a positive node. This finding highlights the potential utility of sentinel lymph node biopsy in the head and neck because 3 nodal basins were identified. With only 1 node in the right side of the neck, XRT was pursued in the appropriate field.\textsuperscript{13} Sentinel lymph node biopsy is a relatively low-risk procedure. Optimal management of high-risk SCC may be a combination of local tumor clearance (via Mohs surgery or wide local excision) and sentinel lymph node biopsy in the case of clinically negative results of nodal examination.\textsuperscript{14}

The patients described in this study represent an unfortunate reality in the care of OTRs. This small case series exemplifies the need for more rigorous reporting and perhaps multicenter pooling of data to see whether this observation holds true, as well as to identify other potential anatomic sites of concern in this subset of patients.

Perhaps the lesson of utmost importance is that proactive dermatologic care should be provided to OTRs. Close follow-up provided in a multidisciplinary, comprehensive setting is ideal. Considerations of margin control for all scalp tumors, adjuvant XRT for histologically aggressive tumors, and the emergence of sentinel node biopsy as a useful technique for nonmelanoma skin cancers of the head and neck may lower the chance of development of catastrophic metastatic disease.

Accepted for Publication: July 15, 2005.
Correspondence: Jennifer Z. Cooper, MD, Department of Dermatology, University of Maryland, 405 Redwood St, 6th Floor, Baltimore, MD 21201 (jzcooper@som.umaryland.edu).

Author Contributions: Study concept and design: Cooper and Brown. Acquisition of data: Cooper. Analysis and interpretation of data: Cooper and Brown. Drafting of the manuscript: Cooper and Brown. Critical revision of the manuscript: Cooper and Brown. Administrative, technical, and material support: Cooper. Study supervision: Cooper and Brown.
leading role in the development and publication of the manuscript: Cooper. Critical revision of the manuscript for important intellectual content: Brown. Study supervision: Brown.

Financial Disclosure: None.

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