# Inferior outcomes in immunosuppressed patients with high-risk cutaneous squamous cell carcinoma of the head and neck treated with surgery and radiation therapy

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***Background:*** Immunosuppressed patients have higher rates of cutaneous squamous cell carcinoma of the head and neck.

***Objective:*** This study reviews the effect of immune status on disease characteristics and treatment outcomes.

***Methods:*** Patients with cutaneous squamous cell carcinoma of the head and neck treated with surgery and postoperative radiotherapy between 2000 and 2011 were included. Immunosuppressed patients underwent prior organ transplantation or chemotherapy. Baseline variables were compared using $\chi^2$ and unpaired *t* tests. Overall survival and disease-free survival were calculated using the Kaplan-Meier method.

***Results:*** In this study of 59 patients, 38 (64%) were immunocompetent and 21 (36%) were immunosuppressed. Most patients had recurrent tumors (63%) and node-positive disease (61%), which were well balanced between the groups. Poorly differentiated tumors (62% vs 21%; $P = .009$), lymphovascular invasion (29% vs 11%; $P = .08$), and extracapsular extension (57% vs 41%; $P = .09$) were more frequent in the immunosuppressed group. Two-year disease-free survival (45% vs 62%) and 2-year overall survival (36% vs 67%) were inferior for immunosuppressed patients.

***Limitations:*** Limitations include single institution, retrospective study with small sample size, and potential referral bias.

***Conclusions:*** Immunosuppressed patients with cutaneous squamous cell carcinoma of the head and neck more frequently present with high-risk pathologic features and inferior outcomes. Early multidisciplinary assessment and alternate management strategies merit prospective investigation. (J Am Acad Dermatol 2015;73:221-7.)

***Key words:*** cutaneous squamous cell carcinoma; head and neck; high-risk skin cancer; immunosuppressed; radiation; transplantation.

Chronic immune suppression is associated with a higher incidence of cutaneous squamous cell carcinoma (cSCC).[1-3] Organ transplant recipients (OTR) on chronic immunosuppressive therapy demonstrate up to a 65- to 100-fold increase in incidence of cSCC compared with the immunocompetent population.[4] This increased risk for cSCC has also been observed in patients chronically exposed to cytotoxic chemotherapy, such as patients with chronic lymphocytic leukemia or who

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have undergone bone-marrow transplantation.[5-7] With the emergence of more potent and efficacious modern immunosuppressive therapy, posttransplantation survival time is longer, and the incidence of cSCC has subsequently increased.[1,8] Data suggest a more aggressive phenotype of this disease in immunosuppressed patients. Some studies of cSCC in the immunosuppressed population have reported high locoregional recurrence (LRR) rates and distant metastatic rates of 13% to 41% and 7% to 16%, respectively. LRR and distant metastasis is rare in immunocompetent patients, with rates less than 5%.[9-12]

There are numerous case reports of cSCC of the head and neck (cSCC-HN) with virulent clinical courses, and studies have shown that immunosuppressed patients with cSCC-HN more frequently exhibit high-risk pathologic features.[9,10,13-18] However, there is a paucity of data addressing comparative outcomes in this particular patient population. Whether recurrence risks are higher in immunosuppressed patients with cSCC-HN compared with immunocompetent patients is unclear. Many patients with high-risk cSCC-HN also receive postoperative radiation therapy (RT) to reduce the incidence of locoregional failure.[19] However, published data comparing outcomes between the immunosuppressed and immunocompetent populations treated with resection and postoperative RT are scarce. This study seeks to address these questions by comparing patterns of failure, survival, and toxicity outcomes in patients with high-risk cSCC-HN treated with surgical resection and postoperative RT, focusing on a possible association between immune status and outcomes.

**CAPSULE SUMMARY**

- Cutaneous squamous cell carcinoma of the head and neck is more common in immunosuppressed patients.
- This study demonstrated that immunosuppressed patients with cutaneous squamous cell carcinoma of the head and neck have more aggressive pathology and exhibit inferior outcomes after treatment with surgery and adjuvant radiation therapy.
- Early multidisciplinary assessment and prospective investigation regarding alternate management is merited in this population.

## METHODS

This institutional review board–approved retrospective study included patients with cSCC-HN who received surgical resection and postoperative RT between 2000 and 2011. Patients were 18 years of age or older and had histologically confirmed cSCC-HN. Patients who had metastatic disease, had squamous cell carcinoma in situ only, received palliative doses of RT, or had inadequate medical records (lack of record of tumor pathology or record of follow-up after completion of RT) were excluded. Patients with primary or recurrent stage I to IV disease were included. All patients were restaged according to the American Joint Committee on Cancer 7th edition system. All patients received surgical resection by wide local excision or Mohs micrographic surgery. The type of surgical resection was at the discretion of the treating surgeon.

The immunosuppressed population included patients on chronic immunosuppressive therapy at the time of the primary tumor diagnosis, mostly in the setting of OTR, and in a minority, in the setting of chronic hematologic malignancies or Crohn's disease. Immunosuppressive agents included prednisone, cyclosporine, azathioprine, sirolimus, tacrolimus, and mycophenolate mofetil. OTR included those receiving kidney, heart, lung, or liver, or who underwent bone-marrow transplantation.

Postoperative RT was typically delivered with conventional electron beam therapy and 3-dimensional-conformal RT during the earlier years of the study, until around 2003, whereas intensity-modulated RT was used in more recent years of the study, routinely after 2004. Doses of 54 to 70 Gy were typically used. RT targets typically included the tumor bed with generous clinical target volume margins. For patients with significant perineural invasion (PNI), nerve roots were targeted to their origin at the skull base. For patients with positive nodal disease, ipsilateral lymphatics were included as well. Some patients received 2 to 3 cycles of concurrent cisplatin chemotherapy along with RT, most often in the setting of positive margins or extracapsular extension (ECE).

Toxicity was scored according to the Common Terminology Criteria for Adverse Events v4.0. Acute toxicity was defined as toxicity developing within 90 days of the end of RT, whereas late toxicity was defined as that developing more than 90 days after the completion of RT. We examined acute toxicities including diet changes, the need for feeding tube, radiation dermatitis, mucositis, and pain. We examined chronic toxicities including xerostomia, taste changes, dysphagia, osteonecrosis, trismus, neuropathy, and pain.

All patients were followed up with postoperative treatment imaging with either computed

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