Adjuvant radiotherapy in high-risk cutaneous squamous cell cancer of the head and neck in immunosuppressed patients

Shlomo A. Koyfman, MD, Nikhil Joshi, MD, and Allison Vidimos, MD
Cleveland, Ohio

INTRODUCTION

Head and neck cutaneous squamous cell carcinoma (HNCSCC) is a growing problem in the immunosuppressed population, and the behavior of these cancers can be unexpectedly aggressive. The role of adjuvant radiation therapy (RT) in the management of high-risk HNCSCC has been an area of much debate. We present a case of HNCSCC with perineural invasion (PNI) successfully treated with surgery and adjuvant RT to prevent recurrence.

CASE REPORT

A 39-year-old man with a history of cystic fibrosis underwent bilateral lung transplant in 2006 and was taking prednisone, 5 mg daily, and tacrolimus, 3 mg twice a day, for immunosuppression. He was treated previously with Mohs micrographic surgery (MMS) for multiple superficial head and neck skin cancers and topical 5-fluorouracil cream (5%) for field damage. He presented to the dermatology department with a 3.2- x 2.5-cm nodular mass in the right preauricular region composed of an erythematous boggy plaque with central hemorrhagic crusts and a posterior deeper nodular component slightly fixed to the underlying surface closer to the tragus (Fig 1, *A*). He denied any paresthesias or pain. No neck lymphadenopathy was found on examination. Computed tomography (CT) scan of the neck confirmed a 3.2- $\times$ 0.9- $\times$ 1.9-cm plaquelike soft tissue density of heterogeneous attenuation within the cutaneous and subcutaneous fat overlying and contiguous with the underlying parotid gland and masseter muscle without distinct invasion. No lymphadenopathy was seen (Fig 1, *B*).

The patient underwent radical resection of the lesion with MMS, parotidectomy, and ipsilateral supraomohyoid neck dissection with facial nerve preservation and an anterolateral thigh free flap reconstruction. The final histopathology found a 3-cm moderately differentiated primary cutaneous squamous cell carcinoma (SCC) with multifocal PNI. None of the 15 nodes sampled had disease (Fig 1, *C*).

Given the multifocal PNI and his immunosuppressed state, the patient was treated with adjuvant intensity-modulated RT (IMRT) to 58 Gy in 29 fractions (Fig 1, *D*). He had brisk radiation dermatitis and moderate moist desquamation as well as fatigue and taste changes. These symptoms resolved within several months, and he is disease free at 21 months of follow-up, with no significant late adverse effects. He continues to have multiple new superficial basal cell carcinomas and SCCs, which have been managed with MMS and topical 5-fluorouracil cream (5%). He was weaned off tacrolimus, which was replaced with sirolimus, 1.5 mg twice a day.

> *Abbreviations used:*
>
> | | |
> |---|---|
> | CT: | computed tomography |
> | HNCSCC: | head and neck cutaneous squamous cell carcinoma |
> | IMRT: | intensity-modulated radiation therapy |
> | MMS: | Mohs micrographic surgery |
> | PNI: | perineural invasion |
> | RT: | radiation therapy |
> | SCC: | squamous cell carcinoma |
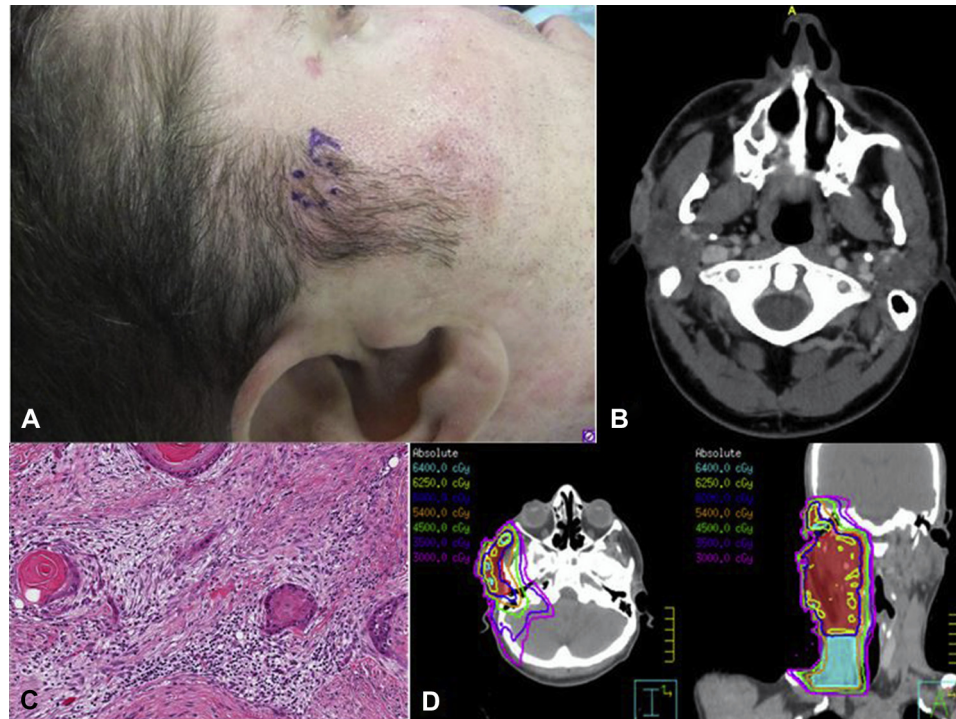
Fig 1. A, Pre-auricular mass with overlying erythema. **B**, Axial section on contrast CT scan shows a 3.2- × 0.9- × 1.9-cm plaquelike soft tissue density of heterogeneous attenuation within the cutaneous and subcutaneous fat overlying and contiguous with the underlying right parotid gland and masseter muscle without distinct invasion. No lymphadenopathy was seen. **C**, Photomicrograph shows several peripheral nerve trunks with perineural carcinoma. An associated lymphocytic inflammatory infiltrate surrounding the perineurium is present. **D**, Axial (left panel) and coronal (right panel) sections on radiation planning CT scan show the high-dose planning target volume (in red) and low-dose planning target volume in blue. Isodose lines are depicted with 6000 cGy prescription line covering the high-dose target and the 5400 cGy line covering the elective nodal target. The high-dose target includes branches of the facial nerve as they track back toward the stylomastoid foramen. There is excellent sparing of intracranial and midline organs at risk. (**C**, Hematoxylin-eosin stain; original magnification: ×12.)

DISCUSSION

Immunosuppression from organ transplant is a well-recognized risk factor and suspected prognostic factor for skin cancer development.[1] Several other poor prognostic factors have been identified including location (ear, lip, anogenital region), size greater than 2 cm, greater than 4 mm depth of invasion, PNI, poor differentiation, infiltrative/desmoplastic growth pattern, local recurrence, and prior radiation exposure.[2] Surgery remains the primary therapy for this disease. Radiation is an important treatment modality either as adjuvant after surgery or for unresectable or cosmetically challenging areas and is often indicated in patients with these high-risk features.

PNI occurs in 5% to 10% of patients with HNCSCC and is a common indication for postoperative radiotherapy.[3] The extent of PNI is relevant, as focal PNI has been associated with more favorable outcomes. Although variably defined, patients with isolated unifocal involvement of a small (<0.1 mm) unnamed nerve may be safely observed. In a series comprising predominantly patients treated with resection and adjuvant RT, Lin et al[3] found that focal PNI was associated with improved relapse-free survival compared with extensive PNI (86% vs 74%; $P = .1$). In addition to being associated with a 15% to 25% risk of local recurrence, some studies suggest that the presence of PNI predicts for a higher likelihood of nodal metastases as well, ranging from 5% to 17% in varying studies, and serves as a rationale for elective nodal irradiation in these patients.[4] In an Australian series, patients with recurrent disease that had PNI at the time of recurrence are at significantly higher risk of recurrence both locally (40% vs 19%; $P < .01$) and regionally (29% vs 5%; $P = .02$), and strong consideration should be given to elective nodal irradiation

in this setting.[3] In one study, almost half the recurrences in patients with clinically occult, pathologically determined microscopic PNI occurred in the first-echelon lymph nodes.[5] Patients with clinically evident PNI, either owing to neurologic symptoms such as numbness, pain, or facial weakness or radiographic evidence of nerve enhancement, have inferior outcomes with locoregional control rates of 50% and cancer-related mortality rates as high as 40%.[6] Radiographic evaluation of PNI should be performed using magnetic resonance imaging when clinical symptoms of PNI such as pain or paresthesias are present. Review of imaging with a neuroradiologist is crucial, as radiographic detection of PNI can be easily overlooked.

When treating patients with PNI using radiation, we recommend targeting the local tumor bed, cranial nerve pathways to the skull base, and nodal basins, as PNI portends higher risks of failure in each of these locations, especially in immunosuppressed patients. Highly conformal radiation techniques including IMRT with image-guided radiotherapy are warranted to maximize coverage of the targets of interest and minimize dose to surrounding organs at risk.

Clinically involved lymph nodes carry higher risks of failure, and multimodality therapy including surgery (for primary and nodal basins) and adjuvant radiation, is indicated. In another study from Australia, improved 5-year disease-free survival (74% vs 34%; P = .001) and 5-year overall survival (66% vs 27%; P = .003) was seen in patients treated with resection of the primary tumor and neck dissection followed by postoperative RT compared with those treated with surgery alone.[7]

Emerging data suggest that some HNCSCCs behave quite aggressively in immunosuppressed patients. These cancers are more likely to demonstrate multifocality, PNI, and deep infiltration than in immunocompetent patients, and some investigators recognize inferior outcomes in these patients, even with aggressive multimodality treatment.[8,9] We found a 2-year recurrence-free survival rate of 48% in the immunosuppressed population compared with 73% in the nonimmunosuppressed population for patients with locally advanced HNCSCC treated with resection and adjuvant radiotherapy.[10] As such, we often favor comprehensive treatment for these patients, including targeting nodal levels at risk and the course of the involved nerve, as we did in this patient.

In our practice, we recommend adjuvant radiation for immunosuppressed patients with resected SCC if they have de novo T3 or T4 disease, node-positive disease, or any T1 to T2N0 disease with PNI (aside from unifocal involvement of a small unnamed nerve), or any recurrent disease. A combination of other high-risk features, such as size greater than 2 cm, poorly differentiated or spindle cell histology, or ear or lip primary tumor, can also play a role in favoring adjuvant RT, especially in these higher-risk patients.

This case highlights the importance of a multidisciplinary approach to the immunosuppressed patient with HNCSCC. Radiotherapy plays an important part in treating these high-risk patients. Further work is needed to better risk stratify patients for intensified adjuvant therapies.

REFERENCES

1. Gordon Spratt EA, Carucci JA. Skin cancer in immunosuppressed patients. *Facial Plast Surg*. 2013;29:402-410.
2. National Comprehensive Cancer Network (NCCN). Basal Cell and Squamous Cell Skin Cancers, Version 2. 2014. NCCN Clinical Practice Guidelines in Oncology 2014.
3. Lin C, Tripcony L, Keller J, et al. Perineural infiltration of cutaneous squamous carcinoma and basal cell carcinoma without clinical features. *Int J Radiat Oncol Biol Phys*. 2012;82: 334-340.
4. Mendenhall WM, Amdur RJ, Hinerman RW, Cognetta AB, Mendenhall NP. Radiotherapy for cutaneous squamous and basal cell carcinomas of the head and neck. *Laryngoscope*. 2009;119:1994-1999.
5. Garcia-Serra A, Hinerman RW, Mendenhall WM, et al. Carcinoma of the skin with perineural invasion. *Head Neck*. 2003;25: 1027-1033.
6. Jackson JE, Dickie GJ, Wiltshire KL, et al. Radiotherapy for perineural invasion in cutaneous head and neck carcinomas: toward a risk-adapted treatment approach. *Head Neck*. 2009; 31:604-610.
7. Wang JT, Palme CE, Morgan GJ, Gebski V, Wang AY, Veness MJ. Predictors of outcome in patients with metastatic cutaneous head and neck squamous cell carcinoma involving cervical lymph nodes: Improved survival with the addition of adjuvant radiotherapy. *Head Neck*. 2012;34:1524-1528.
8. Lott DG, Manz R, Koch C, Lorenz RR. Aggressive behavior of nonmelanotic skin cancers in solid organ transplant recipients. *Transplantation*. 2010;90:683-687.
9. Oddone N, Morgan GJ, Palme CE, et al. Metastatic cutaneous squamous cell carcinoma of the head and neck: the Immunosuppression, Treatment, Extranodal spread, and Margin status (ITEM) prognostic score to predict outcome and the need to improve survival. *Cancer*. 2009;115:1883-1891.
10. Manyam B, Gastman B, Reddy CA, et al. Inferior outcomes in immunosuppressed patients with high-risk cutaneous squamous cell carcinoma of the head and neck treated with surgery and radiation therapy. *J Am Acad Dermatol*. 2015;73: 221-227.