advances
in radiation oncology

Teaching Case

Hyperthermia and Hyper-fractionated Radiation for a Cutaneous Squamous Cell Carcinoma Progressing on Standard Therapy: A Case Report

Cristina DeCesaris MD [a],*, Neha P. Amin MD [b], Jagdeep Hundal MD [c], Zeljko Vujaskovic MD, PhD [b], Manuj Agarwal MD [b]

[a]Department of Radiation Oncology, University of Maryland Medical Center, Baltimore, Maryland;
[b]Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, Maryland; and [c]First State ENT., Newark, Delaware

Introduction

Nonmelanoma skin cancer (NMSC) is the most commonly occurring malignancy worldwide. Cutaneous squamous cell carcinoma (cSCC) represents approximately 20% of cases of NMSC, with 75% to 90% of cases occurring within the head and neck (HN).[1,2] cSCC generally has a low potential for regional and distant metastasis (approximately 2%-5%)[3,4]; however, aggressive variants carry an increased potential for recurrence or progression.

In addition to having poor survival outcomes, local recurrence (LR) in the HN can lead to severe and debilitating morbidity. It is imperative to identify risk factors for recurrence and, when present, to consider more aggressive management. However, treatment paradigms for these high-risk subtypes remain poorly defined.

Concurrent chemotherapy and radiation, or radiation alone, can be used in these patients depending on the extent of disease. Radiation is often delivered in daily treatments of 1.8 to 2.0 Gy per fraction to a total dose of 50 to 70 Gy, depending on whether it is used as a primary or adjuvant intervention. Gross tumor often shrinks during the course of radiation, and tumor recurrence during radiation is unusual. If a patient progresses during treatment, options for local control (LC) are limited.

We present a case of an unusual, highly aggressive, primary cSCC of the HN that was progressing through conventional daily radiation therapy. Therapeutic hyperthermia (external thermal therapy [ETT]) was added to the radiation treatments, and the daily radiation was switched to a twice-a-day treatment (hyperfractionated), resulting in a dramatic response. This case highlights an effective solution to gaining control of a tumor that does not respond to conventional radiation.

Case description

An 81-year-old woman initially presented to the dermatology department with a right temple lesion. A local excision demonstrated moderately differentiated keratinizing squamous cell carcinoma (SqCC) measuring 3.5 cm with 9 mm thickness, with 3 mm lateral and 1 mm deep margins without lymphovascular space invasion/perineural involvement. The patient was not offered adjuvant therapy.

In 2 months, disease recurred at the excision site and the right parotid gland. Computed tomography (CT) of the neck with contrast confirmed a 1.7 × 1.5 cm mass in the gland without other pathologic adenopathy. Surgical

excision of the temple lesion and superficial parotidectomy demonstrated on the right temple moderately differentiated keratinizing SqCC measuring $1 \times 0.9 \times 0.2$ cm with a depth of invasion (DOI) of 5 mm and focal ulceration, as well as 1 mm peripheral and 5 mm deep margins. Parotidectomy showed moderately differentiated keratinizing SqCC measuring $2 \times 2 \times 1.5$ cm with focal necrosis within a rim of lymphoid tissue favoring lymph node metastases. Tumor was focally present at the inked cauterized margin.

The patient was referred to radiation oncology. Given her constellation of high-risk features, rapid recurrence, and development of regional metastases, she was advised to undergo adjuvant external beam radiation therapy (EBRT). CT simulation was delayed for a necessary dental evaluation for clearance. At that time, level II adenopathy was noted on physical examination and confirmed on CT simulation images. Given the finding of new adenopathy, positron emission tomography-CT was recommended, but the patient declined. She was referred to medical oncology, where treatment with concurrent cetuximab was recommended.

EBRT was prescribed to both tumor beds, ipsilateral facial, periparatoid, and levels IB-V neck lymphatics (Figs 1-2). Her prescription entailed 60 Gy comprehensively, followed by a small field boost to 66 Gy to both tumor beds and an additional small field boost to 70 Gy to her gross node in 2 Gy per fraction using 6X photons to generate a volumetric modulated arc therapy plan. A Supraflab skin bolus of 0.5 cm thickness was used on both tumor beds daily.

After her first round of cetuximab and 7 fractions (14 Gy) of EBRT, the patient developed pneumonia that required hospitalization, and cetuximab was discontinued. Given her frailty and poor tolerance of cetuximab, no additional systemic therapy was recommended. After discharge, she resumed radiation alone but shortly developed recurrent lesions at the temple bed that progressed through EBRT. After 19 fractions (38 Gy), her therapy was halted and re-evaluated.

Given the rapid progression of her disease during only a brief treatment break and its refractory nature, EBRT was escalated to 150 cGy fractions delivered twice daily, with dose calculated to achieve a similar equivalent biologic dose as if delivered in 2 Gy per fraction. Hyperfractionated EBRT was paired with concurrent twice-weekly ETT (Fig 3).

This treatment regimen required extensive coordination between 2 separate facilities within 1 large university health care system. EBRT was delivered primarily at a community site on non-ETT days and at both the community site and main campus on ETT days. ETT was delivered at the main campus.

Before the initiation of hyperfractionation and ETT, a composite plan was generated using biologically equivalent dose and equivalent dose (EQD2) calculations to ensure oncologically equivalent dose and safety to normal tissues. To further ensure safety while treating between 2 facilities, a unique electronic medical record document was created to be accessed by both sites; each fraction of EBRT and ETT was recorded daily to track individual and cumulative doses as well as change registrations. This planning document underwent daily review by radiation therapists and weekly review by both clinical physicians and physics for enhanced quality assurance given the unique nature of multisite treatment delivery. ETT was delivered twice weekly for 45 to 60 minutes to the superficial temple lesions. Temperature ranged from 39°C to 44°C and was graded over 8 thermal probes with respect to distance from the orbit.

She developed grade 3 dermatitis and fatigue, grade 2 dysgeusia and esophagitis, and grade 1 xerostomia and mucositis. One month after the conclusion of treatment, taste and xerostomia improved, and the skin had healed considerably. There was no residual dysphagia or odynophagia.

At subsequent follow-up, the patient had no further superficial or nodal recurrence or associated subacute/late toxicity (Fig 4). Unfortunately, approximately 6 months after the conclusion of treatment, she was noted to have thoracic adenopathy and lung parenchymal lesions and a single 1.3-cm brain metastasis. She was referred for intracranial stereotactic radiation surgery but experienced rapid decompensation and died shortly thereafter. At the time of death, she had not recurred within her radiated volume.

Discussion

Although the prognosis for cSCC of the HN is typically excellent, the presence of nodal metastases significantly decreases overall survival (OS), with estimates of 5-year OS ranging from 20% to 50%.[5-7] In cSCC of the HN, parotid and cervical lymph node involvement carries an exceptionally poor prognosis,[8] particularly when disease is present in both locations simultaneously.

Risk factors for LR and distant spread include large tumor size, DOI, poor differentiation, high-risk anatomic location, perineural involvement, lymphovascular invasion, LR, the presence of multiple synchronous tumors, and immunosuppression.[3,9,10] If high-risk, localized disease is identified postoperatively, recommendations for treatment include adjuvant EBRT with or without chemotherapy to the surgical site and at-risk nodal regions.[11,12] Data demonstrate improvements in LC and recurrence rates with radiation therapy without statistically significant impact on OS. In node-positive or confirmed parotid disease, excision followed by EBRT[7,13,14] and more recently chemoradiation therapy[5] has improved LC. Elective irradiation of the clinically negative ipsilateral neck decreases neck recurrence
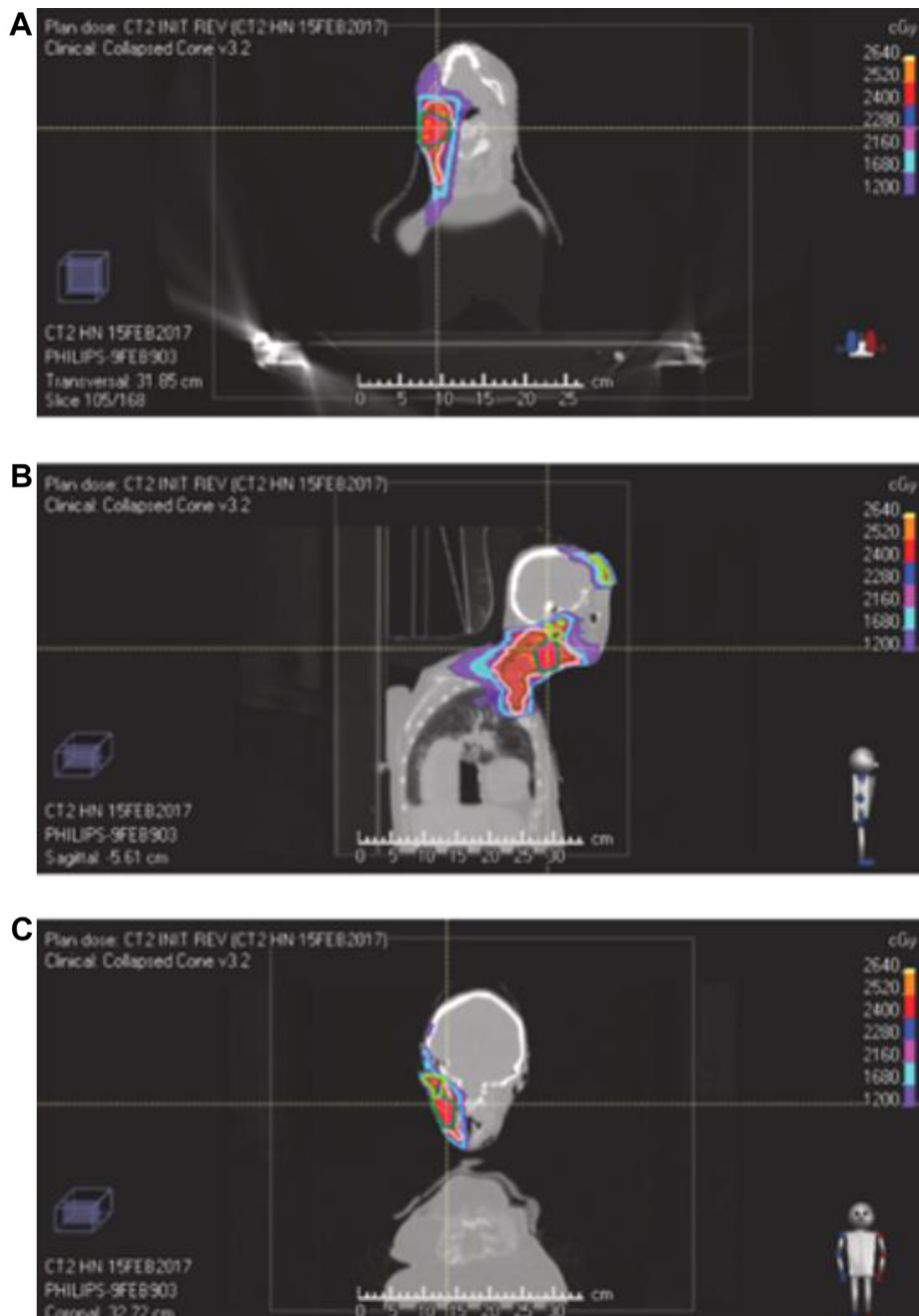
Figure 1 Radiation dose distribution to the initial comprehensive volume after hyperfractionation was prescribed. (A) Representative axial slice and (B) representative sagittal slice.

without statistically significant improvements in OS.[13] However, these recommendations are poorly defined, particularly in the recurrent setting. Additionally, there have been no studies to date examining the role of hyperthermia or altered-fractionation EBRT in NMSC.

ETT is a modality that acts as a sensitizer when combined with radiation therapy. Hyperthermia works through several mechanisms, including inactivation of DNA repair proteins that are involved in the repair of sublethal damage caused by ionizing radiation, which is a

driving force behind its synergistic relationship with radiation therapy. Additionally, hyperthermia is thought to induce an increased immune response through the generation of heat-shock proteins.[15] Hyperthermia significantly improves complete response rates and helps achieve more durable LC while adding minimal toxicity in several different solid tumors.[16]

ETT may be administered as superficial, deep, intracavitary, intraoperative, and total-body therapy. When superficial ETT is used, it is typically delivered twice
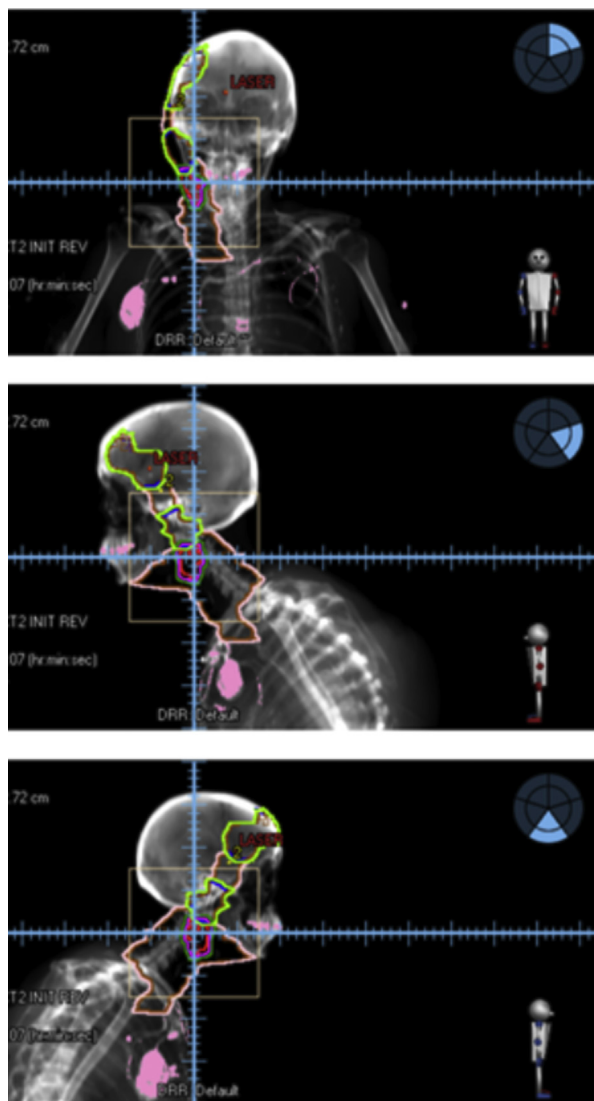
Figure 2　Radiation dose distribution to the initial comprehensive volume after hyperfractionation was prescribed. Digitally reconstructive radiograph. Pacemaker is represented in pink.

Figure 3　Patient receiving hyperthermia treatment. The patient had a robust response to altered treatment and demonstrated complete response at 6 weeks posttherapy.

weekly, immediately before/after daily EBRT for 45 to 60 minutes. Tumors are heated to a range of 40°C to 44°C based on data showing significant response with T90 (temperature above that recorded for 90% of measurements) ± 40°C while maintaining minimal toxicity.[17,18]

Literature on concurrent ETT has largely focused on breast cancer, melanoma, and epithelial malignancies of the HN. There have been no large studies or series examining the use of ETT for NMSC, likely because these lesions are so frequently managed with surgical excision and/or radiation alone. However, this warrants additional research because these superficial lesions are easily treated with ETT and can be exceptionally morbid if recurrent. Additionally, many of the studies that examine the utility of ETT focus on the reirradiation setting; however, we present a case in which the upfront

inclusion of ETT played an integral role in tumor response.

In the current case, the initial excised lesion exhibited several high-risk features, including tumor size, DOI, and margin status. Although the patient was appropriately referred for EBRT after rapid recurrence, her disease had already advanced significantly.

Adjuvant radiation is classically delivered to the surgical bed to 60 to 64 Gy, with elective 54 Gy nodal irradiation if clinically appropriate. Unfortunately, our patient progressed through this traditional regimen and during a brief treatment break despite resumption of therapy. More aggressive treatment was warranted, particularly because systemic therapy was no longer an option.

ETT was prescribed with the intention to sensitize the patient's tumor to the effects of EBRT. This was further combined with hyperfractionated EBRT to increase the biological tumor dose while sparing damage to normal tissues. The patient had a robust response to this altered regimen and tolerated the treatment well despite her advanced age and relative fragility. Although the patient eventually progressed distantly, LC was maintained. In its absence, the patient may have suffered significant morbidity and functional decline because of pain, infection, skin breakdown, and/or speech and swallow impairments.

In lesions that display this level of local aggression, the upfront addition of ETT as a means of radio sensitization can be reasonably considered, given its proven efficacy and favorable toxicity profile, particularly when systemic therapy is not an option. Further research is needed to better delineate the role of ETT for NMSC.

ETT is a relatively infrequently used treatment modality and may not be readily available outside of major

Figure 4 Superficial temple lesions mid-treatment recurrence (A), one (B) and three (C) months post-treatment.

academic centers. However, this case highlights care coordination between 2 facilities 60 miles apart, one a community network site and the other a major medical center, both within the same academic health care system. This demonstrates the feasibility of incorporating ETT and other advanced modalities across treatment facilities where the technology may not be readily available.

Conclusions

This case reports a unique presentation of an unusually aggressive cSCC with high-risk features that progressed through standard EBRT but responded dramatically to hyperfractionation in conjunction with ETT, with durable local control and sparing significant local morbidity. A review of the literature suggests that when managing cSCC of the HN, upfront recognition of high-risk factors is imperative because node-positive disease carries an exceptionally poor prognosis. ETT can be considered as a combined modality with EBRT for increased radio-sensitization of superficial tumors, particularly in the locally aggressive or recurrent setting.

Acknowledgments

References

1. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population, 2012. *JAMA Dermatol.* 2015;151:1081.
2. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol.* 2010;146:283-287.
3. Brougham NDLS, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. *J Surg Oncol.* 2012;106:811-815.
4. Baum CL, Wright AC, Martinez JC, et al. A new evidence-based risk stratification system for cutaneous squamous cell carcinoma into low, intermediate, and high-risk groups with implications for management. *J Am Acad Dermatol.* 2018;78:141-147.
5. Brantsch KD, Meisner C, Schönfi B, et al. Articles analysis of risk factors determining prognosis of cutaneous squamous cell carcinoma: A prospective study. *Lancet Oncol.* 2008;9:713-720.
6. Martinez JC, Cook JL. High-risk cutaneous squamous cell carcinoma without palpable lymphadenopathy: Is there a therapeutic role for elective neck dissection? *Dermatol Surg.* 2007;33:410-420.
7. O'Brien CJ, McNeil EB, McMahon JD, Pathak I, Lauer CS, Jackson MA. Significance of clinical stage, extent of surgery, and pathologic findings in metastatic cutaneous squamous carcinoma of the parotid gland. *Head Neck.* 2002;24:417-422.
8. Hildebrandt B, Wust P, Ahlers O, et al. The cellular and molecular basis of hyperthermia. *Crit Rev Oncol Hematol.* 2002;43:33-56.
9. Triantopoulou S, Efstathopoulos E, Platoni K, Uzunoglou N, Kelekis N, Kouloulias V. Radiation therapy in conjunction with superficial and intracavitary hyperthermia for the treatment of solid tumors: Survival and thermal parameters. *Clin Transl Oncol.* 2013;15:95-105.
10. Zagar TM, Oleson JR, Vujaskovic Z, et al. Hyperthermia combined with radiation therapy for superficial breast cancer and chest wall recurrence: A review of the randomized data. *Int J Hyperthermia.* 2010;26:612-617.

11. Leopold KA, Dewhirst MW, Samulski TV, et al. Cumulative minutes with T90 greater than tempindex is predictive of response of superficial malignancies to hyperthermia and radiation. *Int J Radiat Oncol.* 1993;25:841-847.

12. Amoils M, Lee CS, Sunwoo J, et al. Node-positive cutaneous squamous cell carcinoma of the head and neck: Survival, high-risk features, and adjuvant chemoradiotherapy outcomes. *Head Neck.* 2017;39:881-885.

13. Kraus DH, Carew JF, Harrison LB. Regional lymph node metastasis from cutaneous squamous cell carcinoma. *Arch Otolaryngol Neck Surg.* 1998;124:582.

14. Veness MJ, Morgan GJ, Palme CE, Gebski V. Surgery and adjuvant radiation therapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: Combined treatment should be considered best practice. *Laryngoscope.* 2005;115:870-875.

15. Tanvetyanon T, Padhya T, McCaffrey J, et al. Postoperative concurrent chemotherapy and radiation therapy for high-risk cutaneous squamous cell carcinoma of the head and neck. *Head Neck.* 2015;37:840-845.

16. Fisher K, Gastman B, Ghosh K, et al. *NCCN guidelines, version 2.2018: Squamous cell skin cancer*; 2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed October 21, 2017.

17. Chen AM, Grekin RC, Garcia J, Bucci MK, Margolis LW. Radiation therapy for cutaneous squamous cell carcinoma involving the parotid area lymph nodes: Dose and volume considerations. *Int J Radiat Oncol Biol Phys.* 2007;69:1377-1380.

18. Hinerman RW, Indelicato DJ, Amdur RJ, et al. Cutaneous squamous cell carcinoma metastatic to parotid-area lymph nodes. *Laryngoscope.* 2008;118:1989-1996.