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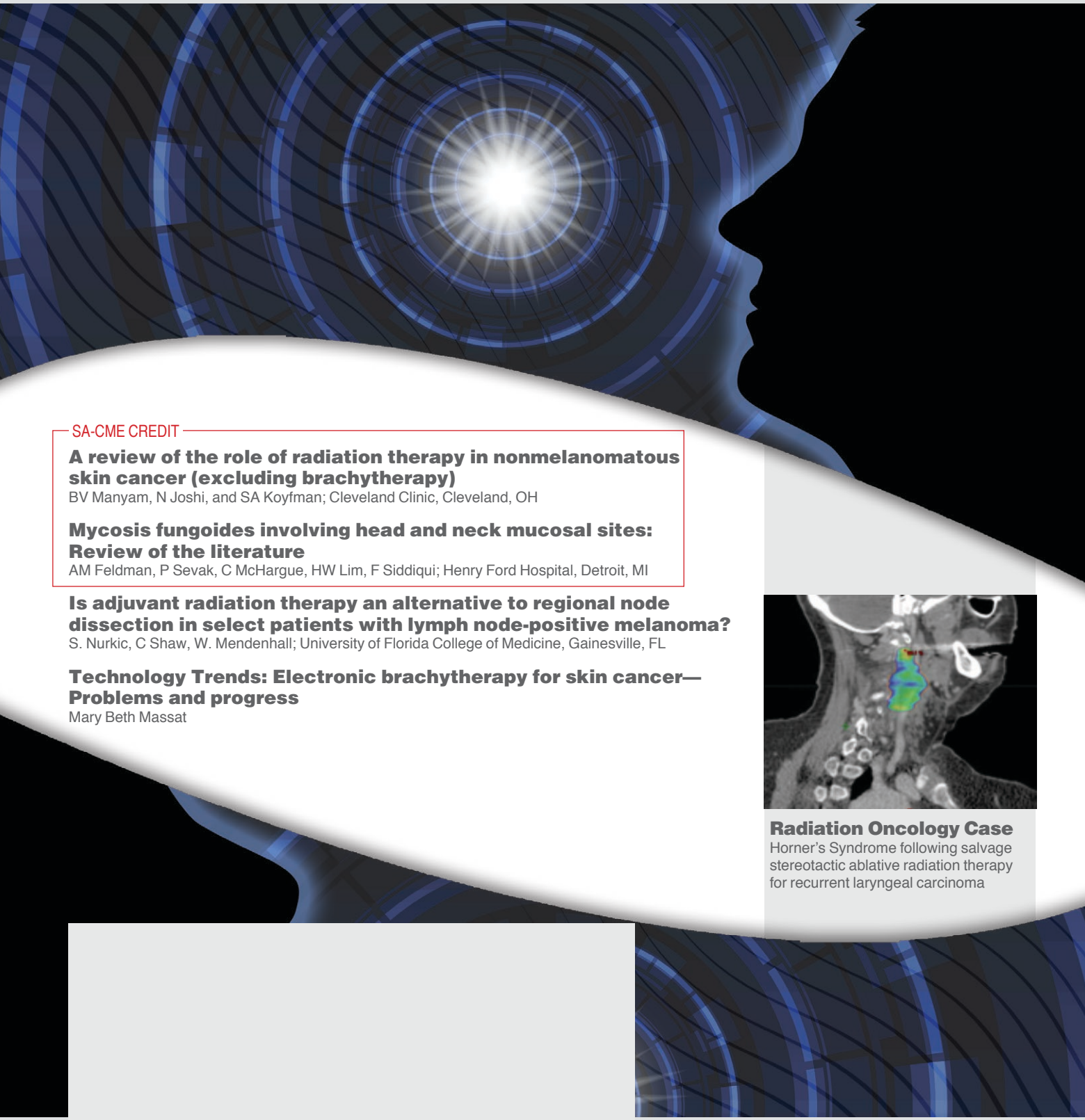

SA-CME CREDIT

A review of the role of radiation therapy in nonmelanomatous skin cancer (excluding brachytherapy)
BV Manyam, N Joshi, and SA Koyfman; Cleveland Clinic, Cleveland, OH

Mycosis fungoides involving head and neck mucosal sites: Review of the literature
AM Feldman, P Sevak, C McHargue, HW Lim, F Siddiqui; Henry Ford Hospital, Detroit, MI

Is adjuvant radiation therapy an alternative to regional node dissection in select patients with lymph node-positive melanoma?
S. Nurkic, C Shaw, W. Mendenhall; University of Florida College of Medicine, Gainesville, FL

Technology Trends: Electronic brachytherapy for skin cancer—Problems and progress
Mary Beth Massat

Radiation Oncology Case
Horner's Syndrome following salvage stereotactic ablative radiation therapy for recurrent laryngeal carcinoma

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SKIN CANCER FOCUS

SA-CME CREDITS

RADIATION ONCOLOGY RESEARCH

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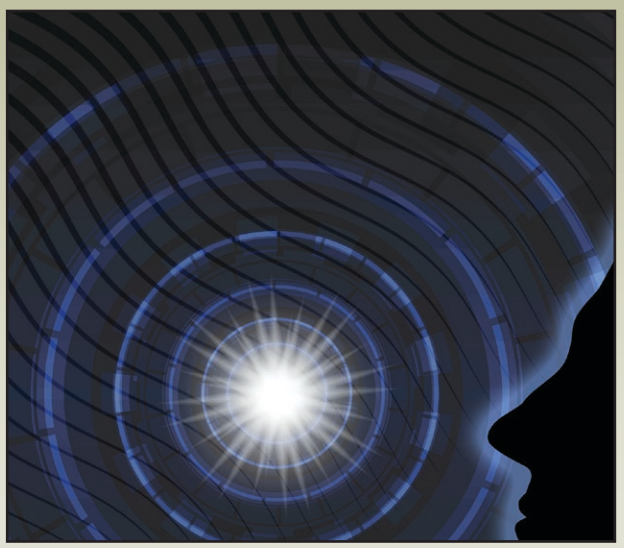

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EDITORIAL

Skin care and beyond: Radiation therapy's role in skin cancer treatment

John Suh, MD, FASTRO
Editor-in-Chief

Welcome to the June issue of *Applied Radiation Oncology!* With summer's much anticipated return, June marks an apropos time to focus on skin cancer, which remains the most common cancer. We are pleased to provide treatment updates for very common and less common cutaneous malignancies.

Our first update is *A review of the role of external-beam radiation therapy (EBRT) in nonmelanomatous skin cancer (NMSC)*, in which authors from the Cleveland Clinic discuss radiation therapy's important role in both the definitive and postoperative management of NMSC, especially in patients with high-risk disease. This informative article, which offers SA-CME credit, reviews common indications, targeting and dosing, techniques, and outcomes.

In *Mycosis fungoides involving head and neck mucosal sites: Review of the literature*, clinicians from Henry Ford Hospital review all reported cases of this rare manifestation, along with two cases from their facility (59 total). By describing risks, disease patterns, and appropriate treatment options, this comprehensive and enlightening review, which also offers SA-CME credit, will aid in treatment decision-making and more accurately predicting outcomes in affected patients.

Complementing this review is the case report, *Extensive cutaneous T-cell lymphoma and challenges with radiation treatment* from authors at McMaster University in Ontario. The report presents a compelling summary of how volumetric modulated arc therapy's novel rotational approach with photons can be used for treating extensive cutaneous disease involving uneven and curving surfaces to achieve local tumor control and provide excellent palliation with minimal dose to adjacent normal structures.

A second case report is *Horner's Syndrome following salvage stereotactic ablative radiotherapy (SABR) for recurrent laryngeal carcinoma with prior radiation and laryngectomy* from authors at the University of Pittsburgh. They report on the development of Horner's syndrome after use of salvage SABR for a patient who had undergone prior radiation therapy, which emphasizes the importance of following patients who undergo salvage treatments.

We are also pleased to present the research paper, *Is adjuvant radiotherapy an alternative to regional node dissection in select patients with lymph node-positive melanoma?* According to the authors from University of Florida, Gainesville, the answer appears to be yes. Based on their limited but promising experience, adjuvant RT for subclinical regional disease in lymph node-positive melanoma may result in durable regional control without the potential added morbidity of a completion lymph node dissection (CLND). Additionally, the risk of complications is likely lower than after a CLND and postoperative RT.

Rounding out the skin cancer focus is the Technology Trends article, *Electronic brachytherapy for skin cancer: Problems and progress,* which recaps self-referral issues and related concerns, and reviews early data regarding positive outcomes for cosmesis, toxicity and short-term response.

We hope you enjoy our skin cancer focus, and wish you an enjoyable and memorable summer season!

Dr. Suh *is the editor-in-chief of* Applied Radiation Oncology, *and professor and chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.*

SA–CME Information

NON-MELANOMATOUS SKIN CANCER (page 6)

Description: Much of the data supporting safety and efficacy of definitive radiation therapy (RT) in patients with non-melanomatous skin cancer (NMSC) is older, when its use was more common. Improvements are needed to better represent and categorize high-risk disease. Treatment should be intensified with multimodality therapy for advanced disease. Clinicians must keep abreast of evolving treatment paradigms and novel systemic therapies NMSC. This article reviews indications, dosing, techniques, and outcomes for external-beam RT for NMSC.

Learning Objectives:
After completing this activity, the participant will be able to:
1. Identify high-risk features in NMSC.
2. Understand the role of postoperative RT and systemic therapy in managing basal cell carcinoma.

Authors: Bindu V. Manyam, MD, is a resident, Nikhil Joshi, MD, is assistant professor, and Shlomo A. Koyfman, MD, is assistant professor, Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH

HEAD AND NECK MYCOSIS FUNGOIDES (page 11)

Description: Head and neck mycosis fungoides is uncommon, and few publications have been dedicated to this topic. Treatment options vary widely and include several radiation therapy regimens as well as medical management possibilities. Survival and treatment outcomes differ greatly depending on patient co-morbidities, treatment tolerance, and disease progression. This article will aid treatment selection and improve outcome predictions.

Learning Objectives:
After completing this activity, the participant will be able to:
1. Explain the disease process of mycosis fungoides, including when head and neck disease may present.
2. Identify treatment options used for head and neck mycosis fungoides.
3. Understand the prognosis, including survival expectations and significant treatment side effects.

Authors: Aharon M. Feldman, MD, and Parag Sevak, MD, are residents, Department of Radiation Oncology; Chauncey McHargue, MD, is a senior staff physician, Department of Dermatology; Henry W. Lim, MD, is chairman, Department of Dermatology; and Farzan Siddiqui, MD, PhD, is vice chair of operations and director of Head and Neck Radiation Oncology, Department of Radiation Oncology, Henry Ford Hospital, Detroit, MI.

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A review of the role of external-beam radiation therapy in nonmelanomatous skin cancer

Bindu V. Manyam, MD; Nikhil Joshi, MD; Shlomo A. Koyfman, MD

Nonmelanomatous skin cancers (NMSC), specifically basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common malignancies in the United States. Primarily managed surgically, these malignancies are associated with excellent prognosis, with a 1% to 5% rate of disease recurrence after complete excision, and exceedingly rare instances of distant metastases (1% to 3%).[1] Historically, radiation therapy (RT) has played a prominent role in definitive management as an alternative to surgery, particularly in cosmetically sensitive areas. Improvements in surgical techniques over recent decades and the widespread use of Mohs micrographic surgery (MMS) has led to a decline in the use of curative RT for skin cancers. However, it continues to be commonly used for patients who are poor surgical candidates, have larger lesions in cosmetically sensitive regions of the face, or in the postoperative setting for tumors with high-risk pathologic features. Finally, RT offers excellent symptom palliation in patients with incurable disease. Advanced treatment techniques (electronic brachytherapy with miniature X-ray tube [Xoft; San Jose, California] and high-dose rate brachytherapy) are evolving with encouraging results, but are beyond the scope of this article. This article reviews common indications, dosing, techniques, and outcomes for external-beam RT for NMSC.

Dr. Manyam *is a resident,* ***Dr. Joshi*** *is an assistant professor, and* ***Dr. Koyfman*** *is an assistant professor, Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH.*

Indications for Definitive RT for NMSC

Both surgery and RT provide excellent cure rates for early stage NMSC; however, surgery is the preferred method of management, as it can be performed in a single session and may be associated with superior oncologic and cosmetic outcomes. A randomized study of 347 patients with < 4 cm BCC of the face compared outcomes between MMS and definitive RT, and determined a local failure rate of 0.7% with MMS, and 7.5% with RT. Additionally, the cosmetic outcome was rated "good" more often with MMS (87% vs. 69%).[2] The quality of the comparison may have been compromised by uncontrolled technique of RT (55% received interstitial brachytherapy and 45% received orthovoltage therapy). As the only randomized study, this trial remains crucial in guiding medical decision-making. Definitive RT is typically contraindicated for large tumors with bone invasion, nodal metastases, and previously irradiated recurrent tumors. RT should also be avoided in patients with genetic syndromes associated with increased radiosensitivity (xeroderma pigmentosum and basal cell nevus syndrome) and active connective tissue diseases (scleroderma and systemic lupus erythematous).[3]

Optimal candidates for definitive RT include elderly patients with comorbidities; unresectable disease; and lesions involving the eyelid, external ear (**Figure 1**), nose (**Figure 2**), canthi of the eye (**Figure 2**), brow, or lip, which may result in significant cosmetic or functional deficits from surgery.[4] Much of the data supporting the safety and efficacy of definitive RT in these patients is older, when its use was more common. A review of 986 BCC and SCC of the skin overlying the eyelid treated with definitive RT yielded a 5-year cure rate of 96.4%.[5] Similarly, an excellent local control rate was observed in a review of 334 BCC and SCC of the external ear at the Princess Margaret Hospital treated with definitive RT, with a 2-year local control rate of 87% and severe late toxicity of 7% of patients.[6] The recently approved hedgehog pathway inhibitor, vismodegib, demonstrated encouraging response rates in unresectable BCC, and

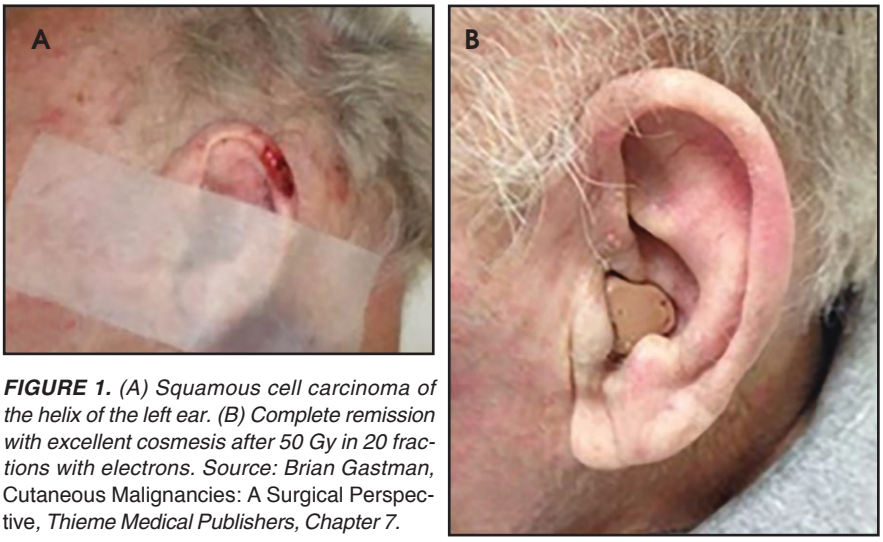

FIGURE 1. *(A) Squamous cell carcinoma of the helix of the left ear. (B) Complete remission with excellent cosmesis after 50 Gy in 20 fractions with electrons. Source: Brian Gastman,* Cutaneous Malignancies: A Surgical Perspective*, Thieme Medical Publishers, Chapter 7.*

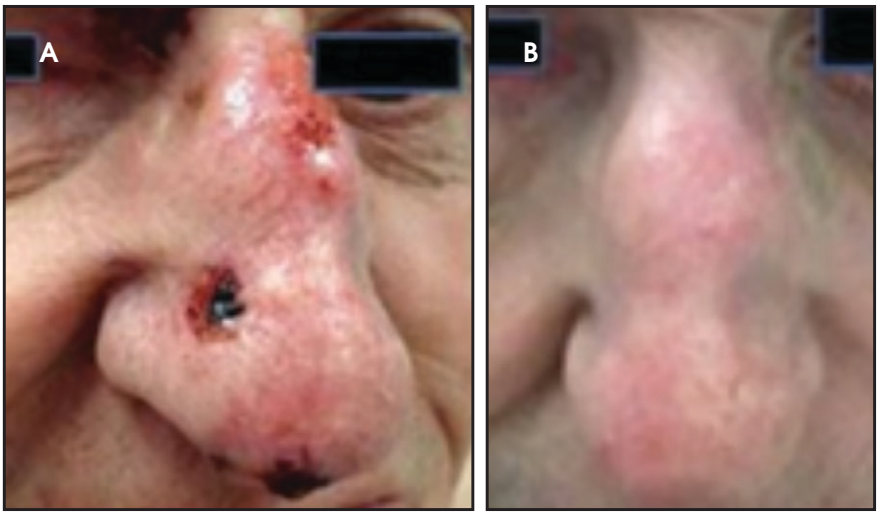

FIGURE 2. *(A) Multifocal basal cell carcinoma of the right medial canthus and nose. (B) Complete remission with excellent cosmesis 3 months after 40 Gy in 10 fractions with electrons. Source: Brian Gastman,* Cutaneous Malignancies: A Surgical Perspective, *Thieme Medical Publishers, Chapter 7.*

may become first-line therapy with additional clinical experience.[7] Our practice has shifted toward upfront vismodegib for large BCC, with RT reserved for poor responders.

While definitive RT can provide acceptable tumor control for T1-3N0 NMSC, inferior outcomes are observed for T4 tumors and nodal metastases. A local control rate of just 53% at 5 years was reported in patients with T4 BCC and SCC treated with definitive RT.[8,9] Recurrent disease ($p < 0.01$), bone involvement ($p < 0.01$), and perineural invasion (PNI) ($p < 0.01$) are associated with significantly worse local control and cause-specific survival with definitive RT. Patients with nodal metastases have locoregional recurrence rates (LRR) of 30% to 50% and cancer-related mortality as high as 30% with definitive RT.[10] These suboptimal outcomes highlight the need for intensifying treatment with multimodality therapy, including surgery and postoperative RT for patients with advanced disease.

Radiation Targeting and Doses for Definitive RT for NMSC

The dose and fractionation for definitive RT is primarily driven by proximity to normal tissues, cosmetic impact, and patient tolerance and convenience. Overall, definitive doses ranging from 45-80 Gy have demonstrated satisfactory cosmetic outcomes, with hypopigmentation (91.8%) and telangiectasia (82.2%) as the most common cosmetic change 4 years after RT. [11]

A radial margin of 1-2 cm is typically used, while smaller margins are appropriate for well-circumscribed lesions and larger margins for infiltrative lesions. Careful assessment of depth using 3-dimensional planning to ensure adequate coverage is crucial. Per the American College of Radiology Appropriateness criteria, conventionally fractionated regimens for definitive RT include 70 Gy/35 fractions and 60 Gy/30 fractions. Moderately hypofractionated courses include 55 Gy/20 fractions or 50 Gy/15 fractions. Extreme hypofractionation of 40 Gy/5 fractions (2-3 fractions weekly) or 20 Gy/2 fractions weekly can be considered in elderly or poorly performing patients.[4]

Indications for Postoperative RT for NMSC

BCC is rarely treated with postoperative RT, as it is typically associated with an exceedingly low risk of recurrence after surgery alone. Patients with positive margin, focal cartilage invasion, or PNI are often still candidates for closer observation with re-resection for salvage, if necessary.[1,12] Postoperative RT for BCC should be considered for persistently positive margins after multiple resections, T4 disease with extensive bone and soft tissue invasion, lymph node (LN) metastasis, or clinical PNI. [13]

SCC with high-risk features is associated with high rates of local recurrence from 20% to 50% with surgery alone, and postoperative RT is recommended to optimize locoregional control. Patients with T4 disease, positive

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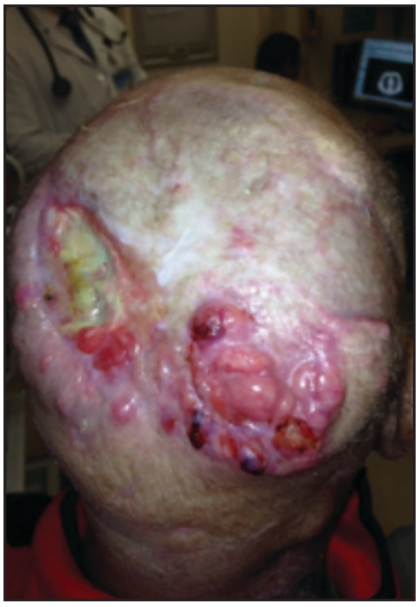

FIGURE 3. *A 58-year-old immunosuppressed man with recurrent squamous cell carcinoma of the scalp after surgery and 2 courses of postoperative radiation therapy. Source: Brian Gastman,* Cutaneous Malignancies: A Surgical Perspective, *Thieme Medical Publishers, Chapter 7.*

margin, clinical PNI, or patients with 2 or more intermediate risk factors, including tumor > 2 cm, poorly differentiation, depth > 4 mm or beyond subcutaneous fat, desmoplastic growth pattern, recurrent tumor, ear and hair-bearing lip, microscopic PNI, lymphovascular space invasion (LSVI) and immunosuppressed status (IS) should be considered for postoperative RT. [14]

PNI, while not common (5% to 10% of SCC), is an important risk factor for local recurrence, as well as regional and distant metastases. Clinical PNI is defined by neurologic manifestations, most commonly involving the trigeminal or facial nerves, or radiographic nerve enhancement.[15,16] Microscopic PNI is appreciated histologically in an asymptomatic patient. The presence of clinical PNI is associated with significantly lower rates of 5-year local control (57% vs. 90%; $p \leq 0.001$) and overall survival (57% vs. 69%; $p = 0.03$) compared to microscopic PNI in patients treated aggressively with surgery and postoperative RT.[13] Given inferior outcomes, RT is always recommended in cases of clinical PNI; however, the role of postoperative RT in the setting of microscopic PNI is less clear. Lin et al demonstrated improved relapse-free survival with focal vs. extensive microscopic PNI (86% vs. 74%; $p = 0.1$), but unfortunately the distinction between focal and extensive was not quantified.[16] Postoperative RT is recommended for microscopic PNI if multifocal, diameter of nerve > 0.1 mm, named nerves, or IS, as these factors are associated with higher local recurrence rates.[17,18] Postoperative RT may be deferred in immunocompetent patients with nonrecurrent disease, with 1 or 2 isolated areas of microscopic PNI in unnamed nerves, with a diameter of < 0.1 mm.

PNI may also be associated with increased nodal failure and its presence in combination with primary sites with a high propensity for LN metastases (cheek, ear, nasal skin) should prompt consideration for elective nodal coverage. Lin et al demonstrated that patients who developed recurrent disease with pathologic PNI had a significantly increased risk of regional recurrence (26% vs. 5%; $p = 0.02$).[16] Patients with advanced T stage, recurrent primary tumors LVSI, and IS are also at significantly higher risk for LN metastases, ranging from 29% to 50%.[10,19-21]

In patients with clinically involved LNs, a therapeutic lymph node dissection (LND) followed by postoperative RT is the current standard of care. LRR after LND alone is 11% to 38%, and even after multimodality therapy, 5-year disease-free survival is 60% to 70%. Independent predictors for worse survival include increased nodal size ≥ 3 cm, multiple LNs, extracapsular extension (ECE), incomplete dissection, and surgery monotherapy.[20-22] A review of 167 patients with SCC metastatic to the parotid or cervical LNs demonstrated significantly lower rates of LRR (20% vs. 43%) and higher 5-year disease-free (73% vs. 54%; $p = 0.004$) and overall survival (66% vs. 27%; $p = .003$) with surgery and postoperative RT compared to surgery alone.[20] Similar to mucosal SCC of the head and neck, RT can be avoided after LND in immunocompetent patients with a single LN, < 3 cm, without ECE, as regional recurrence is < 5%.[23]

Chronic immunosuppression in solid organ transplant recipients (OTR) or in patients with chronic lymphocytic leukemia (CLL) is associated with up to 100-fold higher incidence of NMSC and tend to have more high-risk features of PNI, LVSI, infiltrative, head and neck location, and nodal metastasis (**Figure 3**).[1] These patients have significantly worse disease outcomes, and skin cancer may even contribute to 5% to 10% of mortality.[24-26] Manyam et al demonstrated that immunosuppressed patients treated with surgery and postoperative RT had significantly worse 2-year locoregional recurrence-free survival (47% vs. 86%; $p < 0.001$) and progression-free survival (39% vs. 72%; $p = 0.002$) compared to immunocompetent patients, and IS status was significantly associated with increased LRR (HR 3.79; $p < 0.0001$) on multivariate analysis.[24] Postoperative RT should be strongly considered for this population, even in early stage disease. The benefit of intensifying therapy with earlier initiation of RT, dose escalation, or concurrent systemic therapy requires future prospective study. Immunosuppressive regimens in OTR are an important consideration, and transitioning of agents should be discussed with the patient and transplant physician after a new diagnosis of SCC. Phase III data has demonstrated a significantly decreased incidence in development of new SCC (22% vs. 39%; $p = 0.02$) with sirolimus, compared to tacrolimus.[27]

Appropriate prognostication using the current AJCC skin cancer staging is challenging given that T2 tumors represent an extremely heterogeneous

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population of patients with varying outcomes. Improving granularity within staging categories is important to better understand outcomes and treatment recommendations. The Brigham and Women's Hospital revised skin cancer staging system defined high-risk features of poor differentiation, tumor diameter ≥ 2 cm, PNI ≥ 0.1 mm, or tumor invasion beyond fat (excluding bone invasion, which upgrades to T3), and created a T2a (1 high-risk feature) and T2b category (2-3 high-risk features) category, which was shown to be a more effective prognostic tool.[28] However, the absence of IS status within this staging system may represent a potential area of deficiency, and should be accounted for in prognostic systems.

Radiation Targeting and Doses for Adjuvant RT for NMSC

Common postoperative regimens for the head and neck include 60 Gy in 30 fractions and 50 Gy in 20 fractions with negative margins or no ECE, and 66 Gy in 33 fractions and 55 Gy in 20 fractions with positive margins or ECE. For axilla or inguinal LNs with no ECE, 45-50 Gy in 25 fractions is used and 60-66 Gy in 30-33 fractions is used with ECE.

Typically, the parotid and levels IB-V nodes are at risk for NMSC of the head and neck, although coverage of lymphatics heavily depends on the location of the primary. Inclusion of facial lymphatics should be considered for T3 and T4 disease, typically of the forehead, scalp, cheek, medial canthus, and nose, or in the presence of multiple high-risk features. For NMSC of the extremities and trunk, coverage of lymphatics depends on the location of the primary and surgical evaluation. The clinical target volume for irradiation of clinical PNI should include the involved nerve, portion of the nerve proximally at the skull base, the distal skin innervated by the nerve, major communicating branches, and the compartment in which the nerve is located.[29]

Role of Concurrent Systemic Therapy with RT for NMSC

Vismodegib is the first approved systemic therapy for advanced BCC and is indicated in the recurrent, inoperable setting or in the metastatic setting. A phase II study of patients with inoperable or metastatic BCC treated with vismodegib demonstrated response rates of 43% (95% CI, 31-56; $p < 0.0001$) and 30% (95%, CI 16-48; $p = 0.0001$), respectively, with a serious adverse event rate of 25%.[7] Mylagias and fatigue can be dose-limiting toxicities, which impair continuation of therapy in some patients. Recent evidence suggests that alternative dosing strategies improve the tolerability profile without compromising efficacy.[30] Future practice may be guided by studies investigating the addition of vismodegib to RT in very high-risk BCC.[31]

Currently, no prospective randomized evidence evaluates the benefit of concurrent systemic therapy with definitive or postoperative RT for high-risk SCC. The decision to include concurrent systemic therapy in the postoperative setting is extrapolated from literature in head and neck mucosal SCC. These trials demonstrated significantly improved locoregional control and progression-free survival with concurrent chemotherapy, and further analysis demonstrated that the benefit is limited to positive margins and ECE.[23,32,33] The addition of concurrent cisplatin to postoperative RT should be considered for ECE, positive margins, or with definitive RT for patients with unresectable disease.

Epidermal growth factor receptor (EGFR) inhibitors have gained interest as monotherapy and in combination with surgery and/or RT for SCC. A phase II study of neoadjuvant gefitinib followed by surgery, RT, or both in 22 patients with locally advanced SCC demonstrated a complete response rate of 18%, partial response rate of 27%, and 2-year progression-free survival of 60%.[34] Similarly, a phase II study of cetuximab monotherapy for unresectable or metastatic SCC demonstrated a 30% response rate and 70% disease stabilization rate.[35] No available data investigates the use of EGFR inhibitors concurrently with RT for cutaneous SCC in the definitive or postoperative setting, but it can be considered in elderly patients or patients with renal disease who are not candidates for cisplatin. More recently, checkpoint inhibitors have shown preliminary promise in metastatic mucosal and cutaneous SCC, and ongoing studies will further clarify the role of immunotherapy.[36,37]

Conclusion

Radiation therapy plays an important role in both the definitive and postoperative management of NMSC, especially in patients with high-risk disease. Chronic immune suppression represents a high-risk population with significantly inferior outcomes and its presence should be incorporated into clinical decision-making and multidisciplinary management. Improvements should be made in the current prognostication systems to better represent and categorize high-risk disease. Treatment paradigms will evolve with the continued development of novel systemic therapies in both BCC and SCC.

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Mycosis fungoides involving head and neck mucosal sites: Review of the literature

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Mycosis fungoides is the most common form of cutaneous T-cell lymphoma and comprises 4% of all non-Hodgkin lymphomas. It is characterized by the proliferation of mature, effector-memory T-cells in the skin. Lesions initially present as patches and may progress to plaques, tumors and erythroderma. The disease may spread to the viscera and bloodstream.

Mycosis fungoides presenting in head and neck mucosal sites is exceedingly rare. These lesions most often appear after cutaneous involvement, and progression to these areas often indicates a grave prognosis.[1] To date, 57 such cases have been reported in the literature. Here we present 2 additional cases treated in our institution, together with a comprehensive review of the literature.

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Case Report One

A 59-year-old Caucasian woman presented to the Cutaneous Lymphoma Clinic of the Department of Dermatology at our institution with a generalized pruritic erythematous rash and lesions consistent with tumors on her right upper extremity and chest. She had a 4-year history of a rash first localized to her palms that had spread to several cutaneous sites, notably the gluteal folds and inframammary areas. Although originally diagnosed as having pustular psoriasis, biopsies of the right upper extremity and right chest lesions were consistent with mycosis fungoides. Hematopathology did not reveal any disease in her blood and she was diagnosed with stage IIB (T3N0M0Bx) disease. Immunohistochemistry of the biopsy specimen revealed an infiltrate that was CD2+, CD3+, CD5+, CD4-/CD8-, CD7-, and CD56-, with TCR-beta F1+ phenotype. T-cell receptor gamma gene rearrangement was positive for a clonal T-cell population.

The patient initially underwent total skin electron-beam therapy to a total dose of 36 Gy delivered in 24 fractions of 1.5 Gy each using the 6-dual-field irradiation technique.[2] During this period, she reported symptoms of a dry and sore throat as well as odynophagia. Esophagogastroduodenoscopy by an outside gastroenterologist revealed signs of reflux, and she began taking Lansoprazole (Prevacid, Takeda Pharmaceuticals USA, Deerfield, Illinois) 30 mg twice daily, which offered short-lived mild relief. A barium swallow revealed an unremarkable esophagus. Upon further evaluation in the Department of Otolaryngology, areas of inflammation consistent with laryngeal and oropharyngeal candidiasis were identified, and she received treatment with oral fluconazole for 4 weeks. Although the candidiasis resolved at that time, the patient continued to complain

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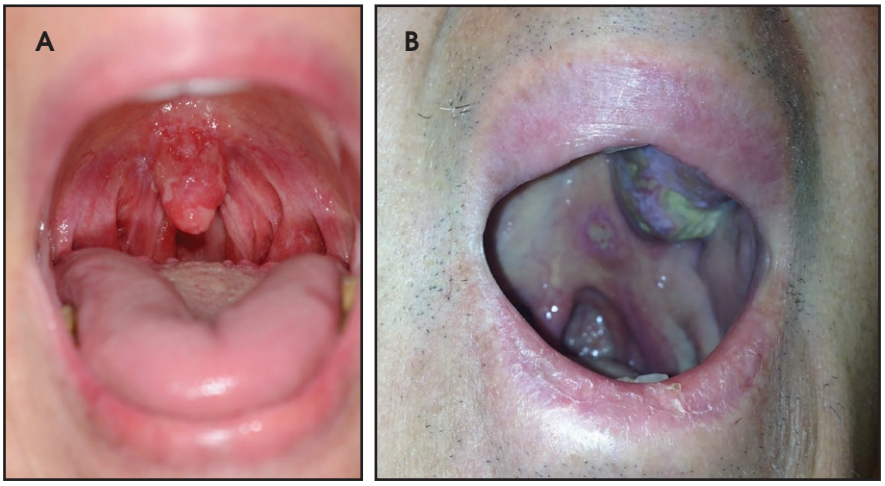

FIGURE 1. *Intraoral photographs of cases 1 (A) and 2 (B) showing mucosal lesions.*

of persistent symptoms that were worse after meals and at night. Re-examination of her throat showed an irritated appearance of the posterior soft palate, uvula, and anterior tonsillar pillars (**Figure 1A**). Flexible nasopharyngolaryngoscopy revealed irritated mucosa diffusely on the epiglottis and arytenoids bilaterally with a similar appearance along the left lateral pharyngeal wall. Biopsy specimens from the uvula and epiglottis revealed lesions consistent with her previously diagnosed mycosis fungoides including an identical TCR-gamma clone. Immunohistochemistry demonstrated an infiltrate positive for CD2, CD3, CD5, CD43 and weakly positive for beta-F1. Infiltrates were negative for CD56, CD30, and CD20. Positron emission tomography and computed tomography (PET/CT) scans showed no involvement of her viscera and mild fluorodeoxyglucose (FDG) uptake of an SUV of 2.3 in her axillary and inguinal lymph nodes. The oropharyngeal and laryngeal lesions were treated with 6-MV photons using an intensity-modulated radiation therapy (IMRT) technique. The initial planned dose was 30.6 Gy to be delivered in 17 fractions. However, she developed confluent fibrinous mucositis (grade III) and severe odynophagia, which required multiple breaks in treatment, significantly prolonging treatment duration. Ultimately, we terminated her treatment at a dose of 20.8 Gy. Two years after treatment completion, the patient has had no local recurrence of her mucosal lesions. She has subsequently undergone external-beam radiation therapy on multiple occasions for localized skin lesions. She continues to follow up with dermatology and radiation oncology.

Case Report Two

A 69-year-old Caucasian man was diagnosed with cutaneous mycosis fungoides 10 years prior to his presentation to our institution. At the time he was seen in the Department of Dermatology, he noted a 2-month history of new leather-like lesions on his bilateral extensor elbow surfaces. He also had multiple exophytic nodules on his bilateral lower and upper extremities, in addition to plaques on his torso and all 4 extremities. The mycosis fungoides lesions on his scalp had been treated with radiation therapy 5 years earlier, with no recurrence at those sites. He had also received intermittent psoralen and ultraviolet A (PUVA) light therapy and methotrexate until 3 years prior to presentation. At consultation, he was taking bexarotene (Targretin, Valeant Pharmaceuticals International Inc., Laval, Quebec, Canada) 75 mg 3 times daily in addition to using triamcinolone 0.1% cream daily. A biopsy of one of the new lesions revealed marked pseudoepitheliomatous hyperplasia with dermal granulomatous inflammation. Culture of the lesions revealed staphylococcus aureus, and he began receiving daily intravenous vancomycin 1 gm for 30 days with minimal improvement. Another biopsy taken from the left forearm lesion demonstrated cutaneous T-cell lymphoma with pseudoepitheliomatous hyperplasia, a positive monoclonal T-cell rearrangement and a CD3+, CD4+, CD8+, and CD30- phenotype. PET/CT showed no metabolic disease at any site.

The patient was treated with total skin electron-beam therapy to a total dose of 36 Gy using the technique described above. Shielded areas, including the palms, soles and buttocks, received a boost of 8 Gy in 1 fraction. This was followed by 4 cycles of weekly pralatrexate 15 mg/m^2. Although this treatment initially appeared beneficial, several weeks later the patient presented with new lesions on his torso, extremities, and on the left tonsil and alveoli (**Figure 1B**). Biopsy of the left soft palate and left superior alveolar ridge again was consistent with mycosis fungoides. The oral lesions were treated with external-beam radiation therapy to a prescribed dose of 30.6 Gy in 17 fractions. However, the patient received only 10 fractions for a total dose of 18 Gy due to severe mucositis, which was not relieved by sucralfate, and eventually required hospitalization due to significant decreased oral intake and failure to thrive. His treatment was discontinued at this dose. Although the oral lesions responded well to the therapy, he eventually began a regimen of cyclophosphamide, hydroxydaunorubicin, etoposide, vincristine, and prednisone (CHEOP) chemotherapy and intrathecal methotrexate due to overall disease progression, including involvement of his bone marrow. Unfortunately, our patient succumbed to

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disseminated disease after receiving a single cycle of CHEOP.

Materials and Methods

We performed a PubMed search for articles in English containing the following key words: mycosis fungoides, cutaneous T-cell lymphoma, oral cutaneous T-cell lymphoma, oral mycosis fungoides, oropharyngeal mycosis fungoides, and treatment of oral mycosis fungoides. Articles describing patients with only cutaneous manifestations of mycosis fungoides were excluded. Only reports of cases of head and neck mucosal mycosis fungoides were included for analysis. Additional cases were identified by reviewing and evaluating the references in articles retrieved from our PubMed search.

Results

Our literature search uncovered 57 previously reported patients with biopsy-proven mycosis fungoides manifestations in the head and neck mucosal areas,[1,3-44] with the first case reported in 1891. We report 2 additional cases treated in our institution. The age of these 59 patients ranged from 12 to 86 years (median 65 years, mean 60.4 years). Of these, 38 were men (64%) and 19 were women (32%) (**Table 1**). We were unable to verify the gender of 2 patients (3%).[7,13]

Since many case reports provide only the age of the original diagnosis, we estimated the exact age of a given patient at the time of head and neck mucosal manifestations using the time frame given in the reports.

Duration Before Oral Cavity or Oropharyngeal Involvement

All but 6 patients were previously diagnosed with cutaneous mycosis fungoides prior to head and neck mucosal presentation. Based on the limited information from prior publications, we were able to estimate the duration from initial cutaneous presentation of mycosis fungoides to mucosal involvement in 30 of the 53 patients (this excludes the 6 patients who presented initially with oral/oropharyngeal disease). These periods ranged from 1 month to 21 years (**Table 1**). The mean time was 5.7 years, with a median time of 4 years.

Histology and Sites of Disease

Atypical lymphocytes exhibiting cerebriform and indented nuclei were described in most biopsy specimens. Pautrier microabscesses were also noted in some reports. When examining cellular markers, 12 patients were CD4+, a common finding in mycosis fungoides.[1,33,34,36,38-42] Of these, 7 were CD4+/CD8-[1,33,38,39,41,42] and 3 were CD4+/CD8+.[34,43,44] Three were CD4-/CD8+[1,33] and only 1 patient was CD4-/CD8- (case 1 of this report), a rarity.

Although head and neck mucosal mycosis fungoides was noted in a wide array of anatomical sites, the most common sites for disease presentation were the tongue (n = 25, 42%) and hard or soft palate (n = 18, 31%). Other sites of disease were (in descending order of frequency) gingiva, epiglottis, buccal mucosa, tonsils, and lips.

Treatment Modalities

The treatment modalities of 36 patients were described. Of these, 26 patients received some form of radiation, including total skin electron-beam therapy and/or local field radiation therapy. Based on the information in the published reports, at least 18 patients received external-beam radiation therapy to their mucosal lesions. An additional 2 patients were prescribed radiation, but either declined or died before receiving radiation therapy. Prescribed doses to mucosal lesions included 65 Gy in 32 fractions, 36 Gy in 15 fractions, 30.6 Gy in 17 fractions, 27 Gy in 9 fractions, 24 Gy in 12 fractions, and 4 Gy in 1 fraction. We initially prescribed 30.6 Gy in 17 fractions to both of our patients; however, neither one could complete the entire treatment due to severe toxicities. Only 2 patients were reported to have undergone surgical tumor debulking.

Survival

Information regarding follow-up was available for 35 (59%) patients. Of these, 24 died; however, it should be noted that not all deaths were related to mycosis fungoides. The time from head and neck mucosal presentation to death in these patients ranged from 1 month to 8 years, with a mean of 1.7 years and a median of 1 year. Fourteen patients were alive at last known follow-up, which ranged from 1 month to 5 years. Of these, 7 had no evidence of oral or cutaneous disease at follow-up.

Discussion

Mycosis fungoides is the most common form of cutaneous T-cell lymphoma. Although it typically presents with cutaneous manifestations, the viscera and bloodstream may become involved. Rarely, mycosis fungoides is found in head and neck mucosal sites, generally in the context of previously diagnosed disease.[1]

The most common area for disease manifestation in the oral cavity is the tongue, with 50% of reported patients having such lesions. The palate and gingiva are the next most common areas, followed by the buccal mucosa, lips and oropharynx.[43]

Histological changes that may be seen on biopsy include Pautrier microabscesses and large, convoluted or indented nuclei. Immunostaining typically will show CD4+ and CD8- phenotypes. CD8+ cells are unusual; we report a patient with lesions found to be both CD4- and CD8- and another with CD4+ and CD8+ phenotype. In a single-center departmental review of 140 patients presenting with mycosis fungoides, 18 were found to have CD4- and CD8- staining.[45]

Treatment of oral manifestations is typically external-beam radiation therapy prescribed at doses ranging from 30-40 Gy in 15-17 fractions (ie, 1.6 to

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2.5 Gy per fractions).[43] Postorino et al, however, reported successfully treating a patient with a combination of weekly alemtuzumab 15 mg, a monoclonal CD52 antibody, once per week and 6 monthly cycles of CHOEP. Although that patient relapsed after 6 months, further treatment of alemtuzumab and gemcitabine stabilized the disease with maintenance photopheresis.[44]

Our patients both experienced severe mucositis during their treatment regimens. Reynolds et al similarly reported a patient with mucosal irritation after receiving 3000 rads to the entire oral cavity; this resolved with conservative therapy.[25] Other publications in our review did not report these or other similar treatment side effects. It is, however, important to consider these toxicities during treatment planning and to recognize them as possible impediments to treatment completion.

Conclusion

Predominantly a cancer of the skin, mycosis fungoides presenting in the oral cavity and oropharyngeal mucosa is uncommon. A review of the previously reported 57 cases and 2 new cases at our institution shows that head and neck mycosis fungoides is a rare and late manifestation of the disease and carries a poor prognosis. External-beam radiation therapy is the most common treatment modality. Toxicities can include severe mucositis and can delay or prevent full treatment regimens.

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Table 1. A Review of All Previously Reported Head and Neck Mucosal Mycosis Fungoides Cases in Chronological Order of Publication

Authors	Age at H&N presentation/ sex	Stage	Diagnostics	Pathological findings	Non H&N lesions (site and maturity)	Site in H&N	Duration before H&N presentation	Treatment	Outcome
Brocq,[3] 1891	55/F	NA	NA	NA	Cutaneous lesions	Tongue	NA	Cocaine suspension	NA
Hallopeau and Jeanselme,[4] 1892	72/M	NA	NA	NA	Cutaneous lesions	Tonsils and soft palate	NA	NA	NA
Breakley,[5] 1902	33/M	NA	Biopsy	NA	Cutaneous lesions	Tonsils and tongue	NA	NA	NA
Corbett,[6] 1914	F	NA	Biopsy	NA	NA	Soft palate	NA	Surgery	NA
Sequeria,[7] 1914	NA	NA	NA	NA	NA	Tongue and buccal mucosa	NA	NA	NA
Kren,[8] 1938	86/F	NA	Biopsy	NA	Cutaneous lesions	Tongue	NA	NA	NA
Berggreen,[9] 1939	54/M	NA	Biopsy	—	Cutaneous lesions	Tongue	NA	NA	NA
Gottron,[10] 1942	57/M	NA	Biopsy	NA	none	Tongue	Initial presentation	Potassium iodine	NA
Cheridjian,[11] 1947	45/M	NA	Biopsy	NA	NA	Pharynx, larynx	NA	NA	NA
Wertheim and Smith,[12] 1948	36/M	NA	Biopsy	NA	Diffuse cutaneous tumors	Tongue, hard/soft palate	3 years	Roentgen rays to cutaneous tumors, sodium cacodylate	DFD 2 months after H&N presentation
Strauss et al,[13] 1949	56/F	NA	NA	NA	NA	Tongue	NA	NA	NA
Strauss et al,[13] 1949	NA	NA	NA	NA	NA	Tongue	NA	NA	NA
Branscheid,[14] 1950	38/F	NA	NA	NA	NA	Pharynx, larynx	NA	NA	NA
Cawley et al,[15] 1951	72/M	NA	Biopsy	Closely packed lymphoblasts and large number of plasma cells	Cutaneous lesions	Tonsils, junction of hard/soft palate	Initial presentation	NA	DFD 2 years after diagnosis
Pautrier and Ullmor,[16] 1954	64/M	NA	Biopsy	NA	Cutaneous lesions	Tongue	NA	RT	NA
Tillman,[17] 1965	60/M	NA	NA	NA	Face, extremities	Lips	NA	NA	NA
Calhoun and Johnson,[18] 1966	43/M	NA	Biopsy	NA	Cutaneous lesions	Tongue, lips, mucosa	NA	NA	NA
Kressin and Schoeder,[19] 1968	68/M	NA	NA	NA	NA	Pharynx, larynx	NA	NA	NA
Cohn et al,[20] 1971	50/M	NA	Biopsy	NA	Cutaneous lesions	Lips, tongue, mucosa, hard palate	NA	NA	NA
Strahan and Calcaterra,[21] 1971	44/F	NA	Biopsy	"Appeared to represent mycosis fungoides"	Eyelid, bridge of nose, upper lip	Upper lip, posterior tongue, oropharynx, hypopharynx	6 months	RT to face, pharynx	Diffuse disease
Laskaris et al,[22] 1978	65/F	NA	NA	NA	Cutaneous lesions	Lips, mucosa	NA	NA	NA
Crane/Heydt,[23] 1979	73/F	NA	Biopsy	NA	Cutaneous lesions	Gingiva	NA	Radiation	NA
Hood et al,[24] 1979	80/F	NA	Biopsy	Atypical lymphocytes with hyper-chromatic cerebriform nuclei	NA	True and false vocal cords bilaterally, arytenoid cartilage, epiglottis, aryepiglottic fold	Initial presentation	6500 rads in 32 Fx to oral lesions, chemotherapy for cutaneous lesions	DFD 4 years after diagnosis

SA-CME (Release date: June 1, 2017; Expiration date: May 31, 2018)

Authors	Age at H&N presentation/ sex	Stage	Diagnostics	Pathological findings	Non H&N lesions (site and maturity)	Site in H&N	Duration before H&N presentation	Treatment	Outcome
Reynolds et al,[25] 1981	75/F	NA	Biopsy	Large and small cells, irregular nuclei	Diffuse erythroderma	Tongue; hard palate	15 years	Local RT to symptomatic lesions (hands, inframammary): 2000 rads in 3 Fx, plus 6 meV electron beam; 6 meV electron beam in single dose of 400 rads to tongue lesion	Lesions healed within 1 week; hard palate lesion presented 4 months after treatment of tongue lesion with similar treatment and results; recurrence of tongue lesion at 3 months, received 3000 rads to entire oral cavity in 10 Fx; NED at 14 months F/U
Agarwal et al,[26] 1982	55/M	NA	NA	NA	NA	Aryepiglottic fold, arytenoids, epiglottis, false vocal cords	Initial presentation	NA	DFD within 2 years of diagnosis
Damm et al,[27] 1984	68/M	NA	Biopsy, BMB, CT scan	Diffuse dense lympho-reticular cell infiltrate, scant cytoplasm, Pautrier micro-abscesses, cerebriform lymphoid cells; insufficient amount of cells for B and T-cell typing	Upper arm and back	Hard and soft palate, left nasopharynx and sinus	Initial presentation	Chemotherapy and scheduled RT	Died from complications of chemo-therapy; no evidence of disease on autopsy
Ferlito and Recher,[28] 1986	78/M	NA	BMB, biopsy	NA	Diffuse lesions	Aryepiglottic fold, arytenoids, epiglottis	4 years	TSET 40-46 Gy	DFD
Gordon et al,[29] 1992	85/M	NA	Biopsy	CD3+, CD45-, negative for UCHL-1 (T-cell lineage marker)	Diffuse involvement	Epiglottis	4 years	27 Gy in 9 Fx to larynx, PUVA, nitrogen mustard to cutaneous lesions	Died from disease complications within 1 month of H&N presentation
Kuhn et al,[30] 1992	78/M	IV-B	Biopsy, BMB, CT	Atypical lymphoid cells, Pautrier microabscesses, cerebriform nuclei; UCHL+ (T-cell lineage marker) and L-26 negative (B-cell lineage marker)	Skin, liver, bone marrow	Left tonsil, base of tongue, left epiglottis, left aryepiglottic fold, left true and false vocal cords	6 years	PUVA, TSET, chemotherapy with VP-16, vincristine, doxorubicin cyclo-phosphamide, alpha-interferon, 2-deoxycoformycin	DFD within 1 month of H&N presentation
Kuhn et al,[30] 1992	82/M	IVb	Biopsy, CT	From autopsy: atypical lympho-cytes with cerebriform nuclei, no Pautrier microabscesses, UCHL+ (T-cell lineage marker) and L-26 negative (B-cell lineage marker), mycosis fungoides found in Para-aortic and mediastinal lymph nodes, bone marrow, liver, spleen, kidneys, GI tract, lung, heart	Diffuse cutaneous involvement	Aryepiglottic fold, true vocal cords, false vocal cords	3 years	PUVA, TSET, chemotherapy with VP-16, vincristine, doxorubicin, cyclophos-phamide, alpha-interferon, 2-deoxyco-formycin, methotrexate	DFD within 1 month of H&N presentation

Authors	Age at H&N presentation/ sex	Stage	Diagnostics	Pathological findings	Non H&N lesions (site and maturity)	Site in H&N	Duration before H&N presentation	Treatment	Outcome
Redleaf et al,[31] 1993	55/M	NA	Biopsy	Leu-4, T4, and LCA+; irregular nuclei consistent with mycosis fungoides	Plaques and nodules, esophageal involvement	Arytenoids, pharynx, larynx	9 months	26 Gy to neck	Developed Sézary syndrome
Redleaf et al,[31] 1993	37/M	NA	Biopsy	NA	NA	Posterior and lateral pharyngeal wall	NA	NA	NA
Redleaf et al,[31] 1993	74/M	NA	Biopsy	NA	Also had esophageal involvement	Base of tongue, epiglottis, arytenoids	NA	NA	NA
Redleaf et al,[31] 1993	38/M	NA	Biopsy	NA	NA	Palate, oropharynx, hypopharynx	NA	NA	NA
Sirois et al,[1] 1993	75/M	IVa	Biopsy	NA	Cutaneous tumors	Gingiva, palate, tongue, lip, buccal mucosa, tonsil	4 years	RT-responded, then had recurrence	Died from other causes 2 years after H&N presentation
Sirios et al,[1] 1993	57/M	III	Biopsy (Sézary syndrome)	CD2-, CD3+, CD4+, CD8-, CD7-, CD30-	Skin lesions	Tongue	13 years	RT-responded fully	Died from other causes, 1 year after H&N presentation
Sirios et al,[1] 1993	49/M	IVa	Biopsy	CD2-, CD3+, CD4-, CD8+, CD7+, CD30-	Skin lesions	Gingiva, tongue	3 years	alpha- interferon had no effect	Died from other causes 1 year after H&N presentation
Sirios et al,[1] 1993	74/M	NA	Biopsy	NA	Skin lesions	Gingiva, palate	3 years	RT-partially responded	Partial remission at 1 year F/U
Sirios et al,[1] 1993	66/F	IIb	Biopsy	NA	Skin lesions	Gingiva, palate	2 years	RT-complete response	Died from other causes 3 years after H&N presentation
Sirios et al,[1] 1993	53/F	IVa	Biopsy	CD2-, CD3+, CD4-, CD8+, CD7+, CD30-	Skin lesions	Gingiva	2 years	RT-complete response	DFD 3 years after H&N presentation
Sirios et al,[1] 1993	73/F	Ib	Biopsy	NA	Skin lesions	Tongue	6 years	RT-complete response	Died from other causes 8 years after H&N presentation
Sirios et al,[1] 1993	51/M	III	Biopsy	NA	Skin lesions	Tongue	8 years	RT-complete response	DFD 2 years after H&N presentation
Harman,[32] 1998	57/M	NA	Biopsy, normal chest x-ray and abdominal ultrasound	NA	Scaling, plaques, and tumors	Gingiva, palate	4 years	NA	Died from other causes 7 months after H&N presentation
de la Fuente et al,[33] 2000	45/F	NA	Polymerase chain reaction of blood and lesions showed clonality; eosinophilia =1 x 109; ESR = 40 mm/h; normal CT and x-ray thorax; normal BMB	atypical lymphocytes, focal exocytosis, numerous mitosis and eosinophils; CD3+, CD4+, CD8-, CD30-	Many cutaneous plaques and tumors	Tongue, uvula, oropharynx	10 years	PUVA, interferon, methotrexate, carmustine, electron beam therapy, photo-phoresis; poly-chemotherapy and BMT after developing Hodgkin's; corticosteroids, methotrexate, etoposide after recurrence	DFD 6 months after develop-ment of H&N lesions

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Authors	Age at H&N presentation/ sex	Stage	Diagnostics	Pathological findings	Non H&N lesions (site and maturity)	Site in H&N	Duration before H&N presentation	Treatment	Outcome
de la Fuente et al,[33] 2000	66/F	NA	Biopsy of lesions; CT revealed enlarged soft palate and tonsils with no extra cutaneous involvement	Atypical lymphocytes, irregular nuclei, many mitotic figures, exocytosis, microabscesses; CD3+, CD4-, CD8+, CD30-	Head, neck, trunk, leg-plaques, papules and nodules	Uvula	4 years	Interferon then carmustine for original disease; CHOP for recurrent disease	Alive with NED at 5 years
Chua and Veness,[34] 2002	81/M	NA	NA	CD3+, CD8+, CD4+, CD5-, CD15-, CD30-, no Pautrier microabscesses	Erythematous plaques	Hard palate, upper gingivae	1-2 years	PUVA + psoralen, external beam radiation	NED at 12 month F/U
Lippert et al,[35] 2002	75/F	NA	Biopsy	CD3+; Pautrier microabscesses	Multiple lesions on arms/legs	Left larynx, paranasal sinuses	1 year	Initial treatment of cutaneous lesions with TSET 6 x 5 Gy, cylophosphamide, vincristine, steroids; 6 Gy boost to larynx with total dose to larynx and maxillary sinuses of 40/46 Gy planned doses	DFD 4 months after H&N presentation
Wain,[36] 2003	12/M	Ib	Biopsy; PCR	Enlarged lymphocytes, Pautrier micro-abscesses; CD2+, CD3+, CD4+, CD8-, CD30-	Papules on upper/lower extremities, trunk	Right soft palate, tongue	8 years	UVB (6 weeks), emollients, topical steroids, patient declined oral PUVA and RT	H&N disease but no systemic or cutaneous disease at 3 years
Viswanathan et al,[37] 2004	69/M	NA	Biopsy; BMB	CD3+, CD20-, cytokeratin negative	Multiple skin lesions	Base of tongue, left lateral pharyngeal wall, soft palate	NA	Steroids, Levamisole	NA
Le et al,[38] 2006	36/M	IIb	Biopsy	CD4+, CD8-; residual lesions after therapy found to be CD4- and CD8+	Diffuse patches and plaques including on eyelids	Tonsils	4 years	Bexarotene interferon, PUVA, 6 cycles of doxyrubicin	NA
Wahie et al,[39] 2006	69/M	NA	Biopsy, CT scan identified inguinal and left iliac nodes; CBC, LFT, LDH all WNL	CD2+, CD3+, CD4+, CD5+, CD8-, CD20-	Diffuse involvement	Epiglottis	7 years	PUVA, gamma interferon, RT to oropharynx 24 Gy in 12 Fx	NED at 6 months F/U
Gruson,[40] 2007	60/M	Ib-IIb	NA	large atypical lymphocytes, Pautrier micro-abscesses; CD4+, CD30-, CD56-	Patches/plaques over 40% surface area, knee	Left nostril	4 years	Original: PUVA then UVB; acitretin and alpha interferon, narrow UVB; radiation for nasal lesion	Nasal lesion healed with radiation, continued treatment for other lesions at 12 months
May et al,[41] 2007	40/F	NA	CT, PET, BMB, BM aspiration all normal	CD2+, CD3+, CD4+, CD5+, CD43+, CD8-, CD10-, CD20-, CD23-, CD30-, CD56-, CD57-, cyclin D-	Left fingers, after H&N involvement	Tongue	Initial presentation	Cyclophos-phamide, vincristine, dexamethasone, then cytarabine and methotrexate	NED at 13 months F/U to stem cell transplant
May et al,[41] 2007	44/M	NA	CT, PET, BMB, BM aspiration all normal	CD3+, CD4+, CD8-, CD20-, CD30-, CD56-	Finger	Tongue	4 years	Chemotherapy and stem cell transplant, radiation after cutaneous relapse	NED 21 months after cutaneous relapse

Authors	Age at H&N presentation/ sex	Stage	Diagnostics	Pathological findings	Non H&N lesions (site and maturity)	Site in H&N	Duration before H&N presentation	Treatment	Outcome
Maleki and Azmi,[42] 2010	69/M	NA	Biopsy	D3+, CD4+, CD 7-, D8-, CD20-	Diffuse involvement	Left true vocal cord	21 years	Nitrogen mustard, total body irradiation, photopheresis, methotrexate and alpha-interferon surgical debulking of tonsillar mass	NA
Goldsmith et al,[43] 2014	64/F	NA	Biopsy of lesions	Sheets of atypical large mononuclear cells with nuclear indentations; CD3+, CD4+ CD8+; CD56-, CD68-, FoxP3-, IL-17-	Diffuse involvement	Posterior right palate	20 years	Full body radiotherapy; PUVA; topical corticosteroids; received 36 Gy in 15 Fx to oral lesion	NED at 2 ½ year F/U
Postorino et al,[44] 2016	60/M	NA	Biopsy	CD3+, CD2+, CD4+, CD8+, CD7	Tumor on leg	Buccal mucosa	Initial presentation	Alemtuzumab and CHEOP	Relapsed at 6 months, treated with alemtuzumab and gemcitabine
Our case report 1	59/F	IIb	Biopsy	CD2+, CD3+, CD4-, CD8-, CD5+, CD56-; TCR-beta F1+ immunophenotype	Diffuse involvement	Epiglottis, uvula	< 1 year from beginning of treatment	Initially with UVB, bexarotene and prednisone, then TSET 36 Gy in 12 Fx + 12 Gy boost to soles, 20.8 Gy/ 30.6 Gy to oral lesions	TSET relieved all areas aside from inframammary folds, infraglutial region, palms and soles
Our case report 2	69/M	NA	Biopsy	NA	Patches, plaques keratotic nodules; upper and lower extremities, trunk, scalp	Oral cavity and tonsils	11 years	TSET 36 Gy in 24 Fx, 8 Gy in 1 Fx to soles, palms, ventral penis, and buttocks, HDR 8 Gy in 1 Fx to left knee, PUVA, bexarotene, methotrexate, triamcinolone; 18Gy/ 30.6 Gy to oral lesions and later, systemic pralatrexate and CHEOP	Initially responded well to TSET; DFD within 1 year of oral presentation

Abbreviations: BMB, bone marrow biopsy; CBC, complete blood count; CHEOP, cyclophosphamide, hydroxyduanorubicin, etoposide, vincristine (Oncovin, Genus Pharmaceuticals, Newbury, UK) and prednisone; CHOP, cyclophosphamide, hydroxyduanorubicin, vincristine (Oncovin, Genus Pharmaceuticals, Newbury, UK) and prednisone; CT, computed tomography; DFD, died from disease; ESR, estimated sedimentation rate; F, female; F/U, follow-up; Fx, fractions; GI, gastrointestinal (tract); H&N, head and neck (mucosa); LDH, lactate dehydrogenase; LFT, liver function tests; M, male; NA, not available; NED, no evidence of disease; PUVA, psoralen and ultraviolet A radiation; RT, radiation therapy; TSET, total skin electron therapy; UVB, ultraviolet B radiation; WNL, within normal limits.

Is adjuvant radiation therapy an alternative to regional node dissection in select patients with lymph node-positive melanoma?

Sommer R. Nurkic, MD, MPH; Christiana Shaw, MD, MS; William M. Mendenhall, MD

Abstract

Objective: We report on regional lymph node irradiation for regional control of subclinical nodal disease in patients with node-positive melanoma.

Methods and Materials: We reviewed the medical records of 7 patients with biopsy-proven lymph node-positive melanoma treated with radiation therapy (RT) between 2007 and 2015 to assess treatment outcomes and toxicity. Patients who underwent completion lymph node dissection (CLND) or those with evidence of distant metastatic disease were excluded. Following sentinel lymph node biopsy (SLNB) or excision of a lymph node recurrence, subclinical regional disease was treated to 30 Gy in 5 fractions over 2.5 weeks. Two patients received adjuvant interferon. Median age at diagnosis was 70 years (range, 42-86 years). Median follow-up was 49 months (range, 10-114 months).

Results: No in-field or locoregional failures were observed. One patient was lost to follow-up 4 years after completing RT; at last follow-up, he was alive with no evidence of disease. One patient reported grade 1 extremity lymphedema after adjuvant RT to the inguinal lymph nodes. No other > grade 3 acute or late toxicities were recorded.

Conclusions: Based on our limited experience, adjuvant RT for subclinical regional disease in lymph node-positive melanoma may result in durable regional control without the potential added morbidity of a CLND. The risk of complications is likely lower than after a CLND and postoperative RT.

Standard-of-care treatment for lymph node-positive melanoma is a completion regional lymph node dissection (CLND). Routine CLND successfully identifies additional metastases in approximately 20% of patients who present with a positive sentinel lymph node biopsy.[1-5] As a result, roughly 80% of patients undergo CLND with questionable survival benefit and the risk of potential anesthetic complications, postoperative wound problems, and chronic morbidities including lymphedema and paresthesias.[6,7] Although hematogenous dissemination is the primary pattern of failure in patients with node-positive melanoma, the risk of locoregional failure after surgery alone is at least 20%, and increases with the number of positive lymph nodes and the presence of extracapsular extension.[8-11] Furthermore, locoregional recurrence is often associated with significant morbidity.

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Although adjuvant RT probably does not improve overall survival in patients with locally advanced melanoma, it has been associated with improved locoregional control in patients with subclinical regional disease.[12] Most studies on RT for lymph node-positive melanoma have reported on the role of adjuvant RT following CLND.[13-16] A single-institutional retrospective review of 36 patients with clinically apparent, nonsentinel parotid or cervical nodes treated with excision and postoperative RT alone reported a 5-year regional control rate of 93%.[17]

We undertook this study to examine whether adjuvant RT without CLND for subclinical regional disease in patients with sentinel node-positive melanoma or recurrent nodal melanoma after excision results in adequate regional control with

Table 1. Characteristics, Treatment and Outcomes of Patients with Lymph Node-Positive Melanoma Treated with Adjuvant Radiotherapy Alone, 1980-2015

Pt no.	Age	Sex	Location	Method of detection	AJCC stage	Breslow (mm)	Clark	ECE	Region treated	Duration of follow-up (months)	Status at last follow-up	Toxicities†
1	62	M	Thigh T3b N1a M0	SLNB	Stage IIIB	3.1	IV	No	Primary site + ipsilateral inguinal and iliac lymph nodes	45	ANED	—
2	86	M	Posterior scalp	SLNB	Stage IIIB T3b N1b M0	3.5	V	No	Occipital nodes	23	Died inter-current	—
3	84	M	Auricular helix	SLNB	Stage III T4a N1 M0	5.0	V	No	Primary site + parotid + ipsilateral neck: levels II-V lymph nodes	34	Died inter-current	Grade 1 trismus
4	73	M	Leg	SLNB	Stage III T1 N2 M0	2.8	IV	No	Primary site + ipsilateral inguinal and iliac lymph nodes	10	ANED	Grade 1 lymph-edema
5	63	M	Parotid, recurrence	Clinically	Recurrent	1.3	IV	—	Parotid + ipsilateral neck: levels II-V lymph nodes	114	ANED	—
6	81	M	Level V lymph node, recurrence	Clinically	Recurrent	0.5	III	No	Ipsilateral neck: levels II-V + occipital lymph nodes	71	ANED	—
7	42	M	Supra-clavicular, recurrence	Clinically	Recurrent	—	—	—	Ipsilateral neck: levels II-V + supraclavicular lymph nodes	47	ANED, lost to follow-up	—

Abbreviations: AJCC, American Joint Committee on Cancer; ANED, alive no evidence of disease; ECE, extracapsular extension; pt no., patient number; SLNB, sentinel lymph node biopsy.

†Grading per Common Terminology Criteria for Adverse Events (CTCAE), version 4

minimal morbidity, obviating the need for CLND. Standard practice at our institution for patients with node-positive melanoma is CLND which, depending on the extent of disease, may be followed by postoperative RT. Seven patients were treated with excision and adjuvant RT without CLND at our institution in the last 20 years. Herein we report their outcomes.

Methods and Materials

We reviewed the medical records of 7 patients with either sentinel lymph node-positive melanoma or melanoma recurrent to a single regional lymph node treated with excision and postoperative adjuvant RT at our institution between January 1986 and July 2015. Patients were excluded if they had undergone CLND, received previous RT to the involved lymph node basin, or had radiographic evidence on computed tomography (CT) or positron emission tomography (PET)-CT of residual or systemic disease following lymph node excision. Primary disease sites, which included the head and neck in 5 patients and an extremity in 2 patients, were treated with wide local excision +/- adjuvant RT. Four patients had sentinel lymph node-positive disease treated with adjuvant RT alone and 3 patients had a nodal recurrence of their previously excised primary melanoma treated with excision and adjuvant RT (**Table 1**).

RT was delivered using either 3-dimensional conformal or intensity-modulated techniques. Beam orientation varied depending on the disease location and would encompass the entire lymph node region determined to be at high risk for subclinical disease. Regional lymph node basins were appropriate to the primary lesion (**Table 1**). Head and neck nodal regions included cervical levels II-V with the addition of a low anterior neck field to include the supraclavicular nodes when appropriate. The parotid lymph nodes were included if thought to be at high risk. In patients with lower-extremity primaries, the inguinal and ipsilateral pelvic nodes were treated with intensity-modulated radiation therapy

(IMRT). All patients were treated with a hypofractionated course of RT to a total dose of 30 Gy in 5 fractions over the course of 2.5 weeks as described by investigators at the University of Texas MD Anderson Cancer Center (Houston). Two patients were treated with adjuvant interferon, per the discretion of the treating medical oncologist.

Patients were seen in follow-up every 3 to 4 months during the first and second years and every 6 months thereafter. Toxicities were recorded and documented in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.[18] Endpoints for the study were in-field locoregional control, disease-free survival, and overall survival.

Results

The median patient age at treatment was 70 years (range, 42-86 years). All patients were male. The median follow-up was 49 months (range, 10-114 months).

No in-field locoregional failures were observed. At last follow-up, no patient had developed distant disease. Two patients died of intercurrent disease at 2 and 3 years, respectively. The locoregional control, disease-free survival, and overall survival rates were 100%, 100%, and 71%, respectively.

No patient required a treatment break. There were no ≥ grade 3 acute or late toxicities based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. One patient developed grade 1 lower extremity edema. Another patient developed grade 1 trismus.

Discussion

A recent Cochrane review[7] sought to assess the effects and safety of SLNB followed by CLND for the treatment of localized previously untreated cutaneous melanoma. Based on available clinical evidence, we concluded that there is no clear benefit in overall survival or melanoma-specific survival in patients undergoing SLNB followed by CLND. Although no randomized data address this specific issue at present, SLNB followed by CLND remains the standard of care at most clinical practices owing to the risk of additional positive lymph nodes if an SLNB is positive. Although the risk of additional pathologically positive residual nodes after CLND for positive SLNB ranges from 17% to 28%,[2-5] a substantial proportion of patients undergoing CLND risk complications, including postoperative wound-healing problems, chronic lymphedema, paresthesias, and anesthetic complications without a proven survival benefit.[6]

Although we are limited by our small patient population, we believe that CLND may not be necessary in node-positive melanoma treated with excision of clinically positive nodes and adjuvant postoperative RT for subclinical regional disease. This may be especially appropriate for patients thought likely to require postoperative RT. Adjuvant RT for subclinical regional disease appears to yield good locoregional control as evidenced by the absence of in-field or locoregional recurrences in our limited study population with a median follow-up of nearly 5 years. In the absence of a survival benefit, CLND may expose patients to an unnecessary additional morbidity without improving the likelihood of regional control.

Conclusion

Based on our limited data as well as that reported by Ballo et al,[17] postoperative adjuvant RT for subclinical regional disease in lymph node-positive melanoma may result in durable regional control without the potential added morbidity of a CLND. Additionally, the risk of complications is less likely with postoperative RT than after a CLND. Further research is needed before adjuvant RT may be considered an alternative to CLND.

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Electronic brachytherapy for skin cancer: Problems & progress

Mary Beth Massat

Over the last several years, the growing use of electronic brachytherapy (EBT) for nonmelanoma skin cancer (NMSC) has met with concerns, including physician self-referral and its use in the Medicare population. While evidence may show EBT as having high long-term curative rates with minimal side effects from local radiation, many—such as authors of a 2015 viewpoint article in *JAMA Dermatology*—say adequate data has yet to be accumulated.[1]

One author of the article, Jack Resneck, Jr., MD, professor and vice chair of dermatology at the University of California, San Francisco, said that the "appropriate solution is probably to have new CPT codes that will be valued appropriately for skin brachytherapy."[2] And, in January 2016, new category III codes from the American Medical Association for the treatment of skin cancer took effect. For HDR EBT, skin surface application, per fraction, including basic dosimetry, the code is 0394T.

In November 2015, an article in *Medical Devices: Evidence and Research* discussed EBT as a novel treatment option for NMSC and described 3 EBT systems: Xoft Axxent (iCAD, Inc.; Nashua, New Hampshire), Intrabeam (Carl Zeiss Meditec; Dublin California), and the Esteya (Elekta; Stockholm, Sweden).[3] In their discussion, the authors suggest that "radiotherapy for NMSC is likely underutilized" and conclude that, "EBT appears to be a quick and convenient method to replicate, and possibly improve upon, other radiotherapy techniques for small, superficial lesions."

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While the American Academy of Dermatology's 2014 position statement on EBT for NMSC supports consideration of EBT as a secondary option for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in special circumstances when surgical intervention is contraindicated or the patient refuses surgical management, it states that surgical management is the most effective treatment for BCC and SCC. The statement also calls for additional long-term outcomes research on EBT use.

Among research efforts, Christopher B. Zachary, MBBS, FRCP, Department of Dermatology, University of California, Irvine, is conducting a multicenter study comparing EBT with Mohs micrographic surgery. The 720-patient, prospective, randomized study is sponsored by iCAD.

Recent Clinical Studies

While no long-term outcomes data currently support the efficacy of EBT, a handful of single-center, short-term outcomes data show promise.

Gauden et al assessed Leipzig surface applicators (Varian Medical Systems, Palo Alto, California) for high-dose rate (HDR) brachytherapy for treating NMSC. In 200 patients with 236 lesions, 36 Gy was given in daily 3 Gy fractions in an area between 3-4 mm. Of the lesions, 121 were BCCs and 115 were SCCs. Local control was 98%, and grade 1 skin toxicity was detected in 71% of the lesions while grade 2 was detected in 34%. Overall, the authors reported good to excellent cosmesis in 85% of the patients (208 cases), with late skin hypopigmentation changes observed in 5.5% (13 cases).[4]

Another single-center study reported good to excellent cosmesis, acceptable toxicities at 1 year and no recurrences at 1 year. While the study included 122 patients with 171 nonmelanoma lesions treated with EBT, 40 Gy in 8 fractions delivered twice weekly, follow-up data at 1 year or more was available in 42 patients with 46 lesions. No grade 3 or higher adverse events were reported during the study or follow-up. Cosmesis at 1 year was excellent in 92.9% and good in 7.1% of the lesions.[5]

In a retrospective analysis of 127 patients with 154 NMSC lesions treated with HDR EBT, 40 Gy in 8 fractions, authors evaluated local control, acute toxic-

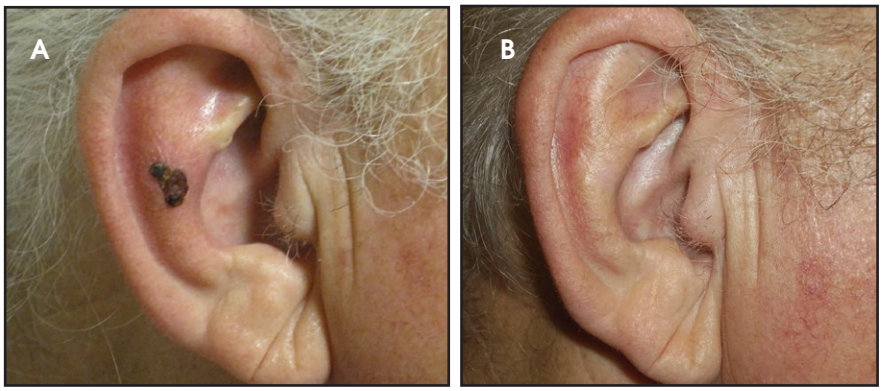

FIGURE 1. *Squamous cell carcinoma on right antihelix treated with 40 Gy to a 3-mm depth. Photo/credit: Jonathan Baron, MD, Santa Ana, CA; and Ajay Bhatnagar, MD, Casa Grande, AZ.*

ity, late toxicity and cosmetic outcomes. Grade 0-1 acute radiation dermatitis was detected in 52.6%, grade 2 in 34.4% and grade 3 in 13% of the treated lesions. Late toxicity, grade 0-1, was observed in 94.2% and grade 2 in 5.8% of all cases. Cosmesis was excellent in 94.2%, good in 3.3%, fair in 0.7% and poor in 0.7% of treated lesions. The authors conclude that HDR EBT should be considered ideal for NMSC of the head, neck and central facial locations where surgical cosmesis may be inferior.[6]

Using the Valencia skin applicator (Elekta, Stockholm, Sweden), 32 patients with 45 NMSC lesions received a dose of 42 Gy in 6 or 7 fractions with a depth of 3 mm delivered twice each week. The authors reported 98% local control at 47 months post-treatment, and only grade 1 skin toxicity that was resolved with topical treatment. According to the authors, superficial BCC lesions < 25 mm in maximum diameter treated with the Valencia applicator using a hypofractionated treatment offers excellent results for cosmesis and local control at 3-year follow-up.[7]

Another retrospective case series of 57 lesions in 39 elderly (> 70 years), eligible patients were treated with HDR brachytherapy using the Valencia surface applicator. A prescribed dose of 40 Gy in 8 fractions was used to treat 48 lesions, and 50 Gy in 10 fractions was used in 9 lesions; all treatments were delivered 2-3 times a week. At 12 months, 96.25% of the lesions demonstrated a complete response while 2 cases had a partial remission. Overall, cosmesis was excellent in 86%, good in 10.5% and fair in 2.3% of the lesions.[8]

Clinical Implementation

In a 2014 review paper, clinicians discussed implementation of the Esteya system in their facilities.[9]

The authors followed The American Joint Committee on Cancer (AJCC) criteria for inclusion of patients with clinical stage T1 or T2 status. The maximum diameter was 20 mm with a maximum depth of 3-4 mm measured by ultrasound or punch biopsy.

A prescription depth of 3 mm was determined for lesions with a depth of ≤ 3 mm while deeper lesions had a maximum depth of 5 mm. Based on recent data supporting a 2 mm dermoscopically detected excision margin that achieved histologically confirmed complete excisions in 98.5% of cases,[10] the authors utilized a dermatoscope to assess gross tumor volume (GTV).

The authors determined a biologically equivalent dose (BED) of around 70 Gy with an alpha/beta value of 10; the selected dose prescription was 42 Gy in 6 fractions (7 G/fraction) twice each week for a total BED of 71.4. A quality assurance check was performed each day before treatment.

The authors found that the Esteya system was simple for both providers and patients, allowing for safe, precise treatment of NMSC.

Conclusion

While there is unquestionably a need for continued research examining patient outcomes after treatment with EBT for NMSC, early data looks promising in terms of cosmesis, toxicity and short-term response. While Mohs surgery will remain the standard of care for many NMSC patients, EBT provides options in cases where surgery is not a viable, or patient-preferred, therapy.

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RADIATION ONCOLOGY CASE

Horner's Syndrome following salvage stereotactic ablative radiation therapy (SABR) for recurrent laryngeal carcinoma with prior radiation and laryngectomy

Clark M. Hatheway, BA; Douglas E. Holt, MD; Brian J. Gebhardt, MD; Dwight E. Heron, MD, MBA, FACR, FACRO; James P. Ohr, DO; Robert L. Ferris, MD, PhD; David A. Clump, MD, PhD

CASE SUMMARY

A 56-year-old woman with a 50-plus pack-year smoking history was diagnosed with stage II (T2N0M0) squamous cell carcinoma of the right true vocal cord and was initially treated with radiation therapy alone consisting of 70 Gy in 35 fractions to the larynx, along with elective treatment of bilateral levels II, III, and IV lymph nodes. After 15 months, the patient developed locally recurrent disease involving the right anterior vocal cord and underwent a total laryngectomy with bilateral neck dissection, right thyroid lobectomy, pectoral flap graft and tracheostomy. Nine months following surgical salvage, the patient developed an isolated local recurrence involving a left level III lymph node. She was treated with salvage stereotactic ablative radiation therapy (SABR) to a dose of 44 Gy in 5 fractions (**Figure 1**) along with concurrent and adjuvant cetuximab and docetaxel as part of an institutional protocol for patients with recurrent head and neck squamous cell carcinoma (NCT02057107).[1] The patient reported the expected acute toxicities consisting of grade 1 fatigue, acneiform rash, mucositis, and as first reported here, a new late toxicity consisting of a left-sided miosis, ptosis, and facial anhidrosis (**Figure 2**) 6 months following the completion of salvage SABR. The patient remains disease-free > 24 months following salvage re-irradiation with no additional late toxicity.

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IMAGE FINDINGS

A preoperative positron emission tomography/computed tomography (PET/CT) scan demonstrated a hypermetabolic lesion of the left level 3 lymph node, which measured 3.5 × 2.1 cm (**Figure 1**). There was no additional evidence of regional or systemic disease.

DIAGNOSIS

Pathology from laryngectomy and neck dissection demonstrated ulcerated, invasive squamous cell carcinoma. Biopsy of the suspected lymph node recurrence by ultrasound-guided fine-needle aspiration was positive for malignant squamous cells.

DISCUSSION

The treatment of head and neck squamous cell carcinoma (HNSCC) often requires a multimodal approach including definitive concurrent chemoradiation or surgical resection with adjuvant radiation with or without chemotherapy. Despite these aggressive

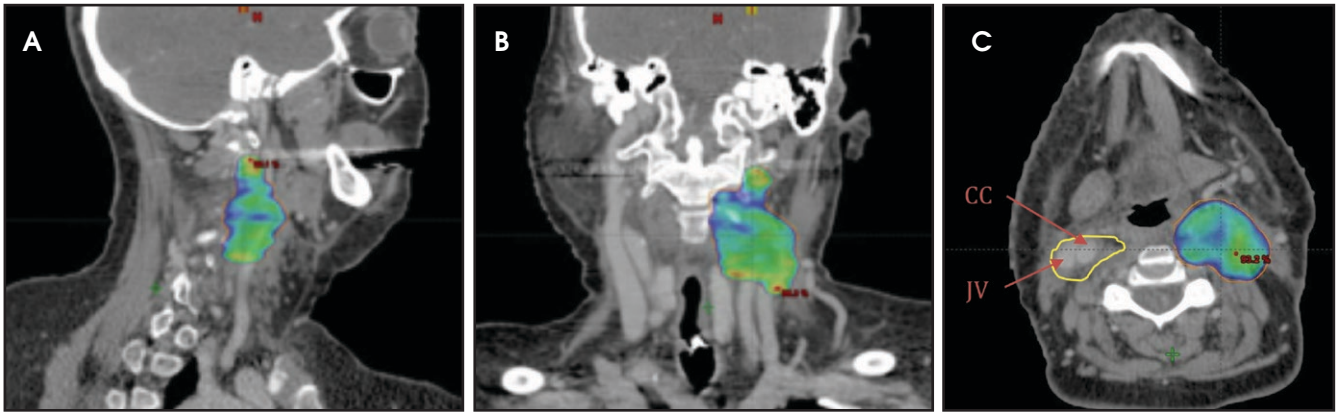

FIGURE 1. *Treatment plan for stereotactic body radiotherapy (SBRT) of the left-sided, recurrent level 3 lesion in sagittal (A), coronal (B) and axial (C) views. The orange line delineates the planning target volume (PTV) of 43.0 cm^3, which received a minimum dose of 35.4 Gy and a maximum of 55.0 Gy. On the untreated side (C), the sympathetic chain lies within the fat space of the carotid sheath (represented by the yellow contour) adjacent to the common carotid (CC), internal jugular (JV) and the longus capitis muscle.*

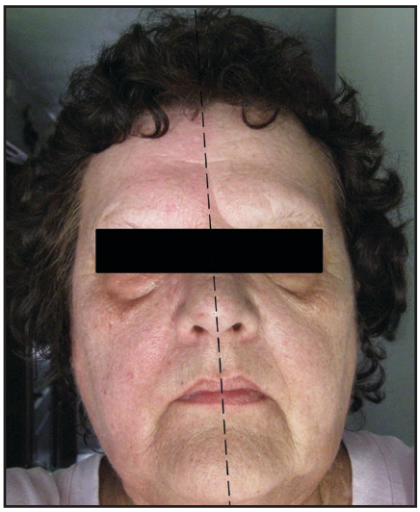

FIGURE 2. *Picture of patient after cardiovascular exercise, noting the left-sided facial anhydrosis, plus mild miosis and ptosis (not visible).*

approaches, locoregional recurrence rates can be as high as 30% to 35%.[2-4] Salvage surgical resection is the preferred treatment following recurrence;[5] however, this approach can be limited for various reasons including disease involvement of critical structures such as the carotid artery.

In patients with unresectable locoregional recurrences of HNSCC, SABR has emerged as a viable curative treatment approach. Its success is largely due to the ability to deliver highly conformal radiation at a high dose per fraction to disease sites with improved sparing of normal tissue. The use of reirradiation with SABR has been associated with favorable toxicity rates ranging from 4% to 11% acute, and 3% to 19% late grade ≥ 3 toxicity, most commonly mucositis, xerostomia, dysphagia and edema.[6-9] The treatment regimen used in this patient of 44 Gy in 5 fractions with concurrent cetuximab in particular has been demonstrated to be both safe and effective, with progression-free survival of 33%, and acute and late grade 3 toxicity rates of 6%.[9] Per the protocol under which this patient was treated (NCT02057107), dose to normal tissues and sensitive head and neck structures, such as the carotid and spinal cord, should be limited. Cumulative dose to the spinal cord is not to exceed 50 Gy.[1] Dose to the sympathetic trunk is not generally calculated or constrained during treatment planning. While not used during treatment planning, maximum and mean dose to the carotid was determined to be 53 Gy and 32 Gy, respectively.

Regarding our patient who underwent salvage SABR with prior radiation, treatment has led to sustained local control with no evidence of recurrent disease. Interestingly, she developed left-sided ipsilateral ptosis, miosis and anhidrosis of her face, which was appreciated 6 months after treatment. In our institution's extensive experience with SABR with concurrent and adjuvant docetaxel and cetuximab for previously irradiated HNSCC, this is the first case of Horner's syndrome suspected as a treatment-related toxicity. This complication possibly reflects this patient's multimodality treatment including reirradiation with SABR along with systemic therapy. Her treatment was focused at the level III nodal location, with treatment overlap of the sympathetic nerve fibers of either the 2nd order neuron or the distal portion of the 3rd order postganglionic neuron (**Figure 1C**).

In our literature review, we were unable to identify a prior report of Horner's Syndrome occurring as a result of reirradiation with SABR. Horner's Syndrome presents classically with unilateral miosis, ptosis and anhidrosis of varying severity due to disruption of sympathetic output to the ipsilateral face. Causes vary based on the location of the neuron involved, and include

compression from tumors, CNS lesions, trauma, and iatrogenic causes.[10] While Horner's Syndrome can result from radiation-induced brachial plexopathy following treatment for lung and breast tumors, it is a rare toxicity and is more often associated with mass effect from the neoplasm itself.[11] Other radiation-induced neuropathies from radiation therapy to the head and neck include cranial nerve palsies of both upper and lower cranial nerves, none of which include Horner's Syndrome as their presenting symptoms.[12] The lack of other neurological symptoms in our patient makes radiation-induced damage to the cervical chain the most likely diagnosis. In ruling out other causes of new-onset Horner's Syndrome in this patient, the most recent head-and-neck PET/CT reveals no malignancy within the sympathetic pathway. Recent medical history includes no trauma that could explain the patient's symptoms. Surgical resection of her first recurrence is unlikely to have damaged her sympathetic chain, considering that symptoms of Horner's Syndrome weren't noted following surgery, but appeared 6 months after subsequent salvage SABR treatment. However, it is possible that post-surgical scarring following the patient's laryngectomy could partially contribute to her symptoms.

CONCLUSION

To date, there are no reports of the development of Horner's Syndrome as a result of salvage SABR after prior radiation therapy for HNSCC. SABR has been reported to have a relatively favorable toxicity profile compared to reirradiation with fractionated radiation therapy; however, as SABR for recurrent HNSCC increases in utilization, and survivors are followed, it is imperative to maintain close follow-up and report toxicities accordingly.

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Extensive cutaneous T-cell lymphoma and challenges with radiation treatment

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CASE SUMMARY

An 82-year-old woman with extensive cutaneous lesions involving the face and torso from a T-cell lymphoma, stage IV, was seen for consideration of palliative radiation therapy to the skin lesions. Her chief complaint was intense pruritus. The skin lesions progressed rapidly within a few months to more confluent 3 to 4-cm tumor and plaque lesions causing facial disfigurement (**Figures 1A-B**). In addition, multiple tumor nodules were noted in bilateral axillae, groins, lateral flanks and lower extremities. She had small adenopathy in the axillae and groins. Her medical history included gout, hypertension, dyslipidemia and arthritis. Her hemoglobin was 13g/dL, white blood count was 33500/**µL** and lymphocyte count was 20500/**µL**. A blood chemistry profile showed elevated creatinine-2.02mg/dL, urate-13.2mg/dL and LDH-538 IU/L. HTLV-1 and HTLV-2 serology was negative. Peripheral blood flow cytometry showed abnormal T-cell population. Bone marrow aspirate and biopsy were positive for CD3 and CD4, negative for CD26 and TDT. The marrow cytogenetics was normal. CT scans of the chest, abdomen and pelvis showed small volume adenopathy in the axillae. The skin biopsies demonstrated T-cell lymphoproliferative disorder with the atypical infiltrate positive for CD3, CD5, CD25 and CD30. Few cells were positive for CD20. There was no expression of CD26, CD56 and CD57. There was no evidence of lymphoepidermotropism that is typical of cutaneous T-cell lymphoma. The differential was peripheral T-cell lymphoma, adult T-cell leukemia/lymphoma and sezary syndrome.

The patient was initially treated with chlorambucil, etoposide and dexamethasone, but the response was transient. Given her age and performance status, she was not a candidate for aggressive chemotherapy. She was referred to radiation oncology for palliative radiation to her skin lesions. The radiation therapy team was faced with technical challenges in treating the multiple confluent skin lesions with variable sizes interposed with crevices involving the entire facial skin and scalp in a circumferential fashion.

DISCUSSION

Mycosis fungoides (MF) and its variants represent the most common form of cutaneous T-cell lymphomas.[1] The malignant cell is derived from a post-thymic T-cell that typically bears

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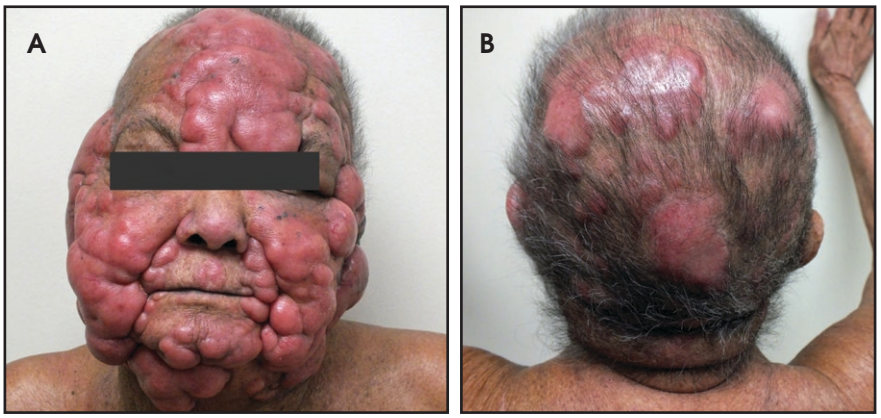


FIGURE 1. *Face lesions (A) and scalp lesions (B) before treatment.*

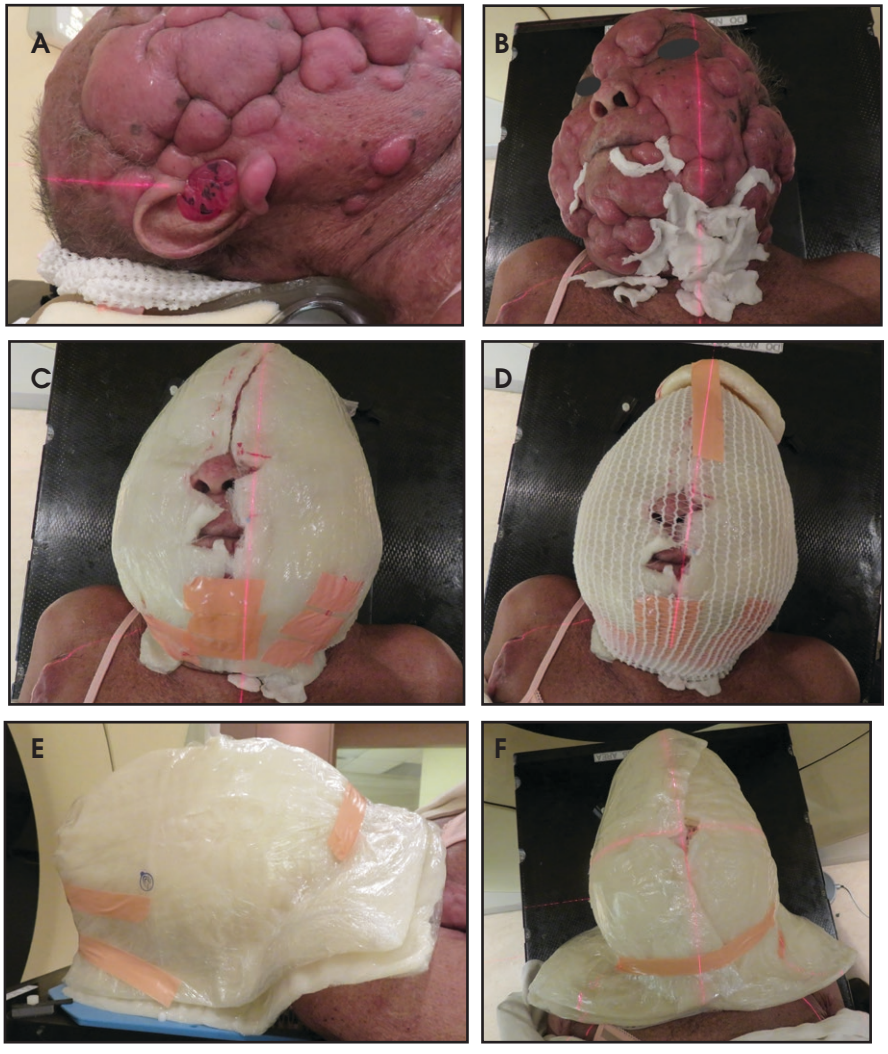


FIGURE 2. *Bolus on head pad and wax bolus in bilateral ear canal (right lateral view) (A). Wet guaze to fill the crevices between lesions (B), 2 c 0.5-cm Vaseline bolus-first layer (C). Surgilast to secure bolus and vertex bolus taped (D.). 1-cm Vaseline bolus—second layer, lateral view (E). 1-cm Vaseline bolus—second layer, anterior view (F).*

a CD4+ helper/memory antigen profile. The disease is characterized by erythematous patches in sun-protected areas that progress to plaques and tumors. Pathology from a skin lesion typically shows lymphoepidermotropism, which is absent in our patient.

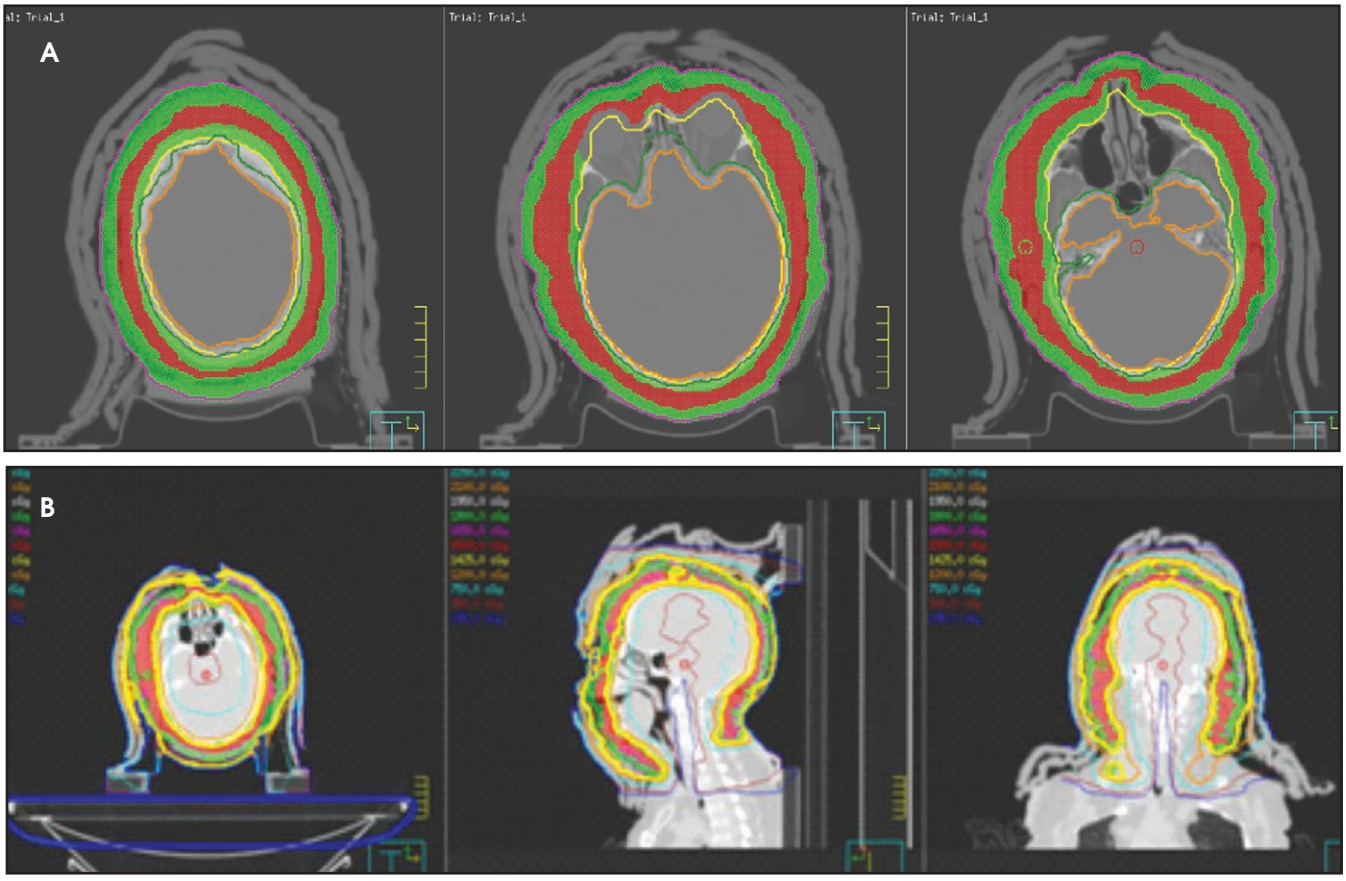
The radiation treatment for MF includes total skin electron-beam therapy with 6 MeV electrons for superficial skin lesions not exceeding a 1-cm thickness. This approach was not ideal for our patient given the variable thickness of the multiple tumors and complex contour of the tumor surfaces resulting in inhomogeneous dose distribution.[2]

Hence, the team chose the volumetric-modulated arc therapy (VMAT) technique with 6 MV photons to decrease the thickness of the most symptomatic skin lesions in the head and neck area prior to considering total skin electron-beam therapy.

TREATMENT PLANNING AND SETUP

The patient underwent a radiation treatment planning process that included an Aquaplast (Qfix, Avondale, Pennsylvania) mask with bolus covering the entire skin over the head and neck areas (**Figures 2A-F**).

Subsequently, CT simulator images were acquired for treatment planning. The entire scalp, facial skin and the skin of the neck including tumors were contoured as clinical target volume (CTV). A variable expansion of 8 mm out and 5 mm in was applied to the CTV to create a planning target volume (PTV). An optimized PTV was then delineated after carving out eyes and adding a 3-mm margin around the brain for planning organ at risk volume (PRV). A 2-arc 6 MV VMAT-optimized plan was generated.[3] A total dose of 15 Gy in 10 fractions with a low dose per fraction was chosen due to high tumor radiosensitivity and to minimize acute and late side effects. A low total dose would also allow for the use of



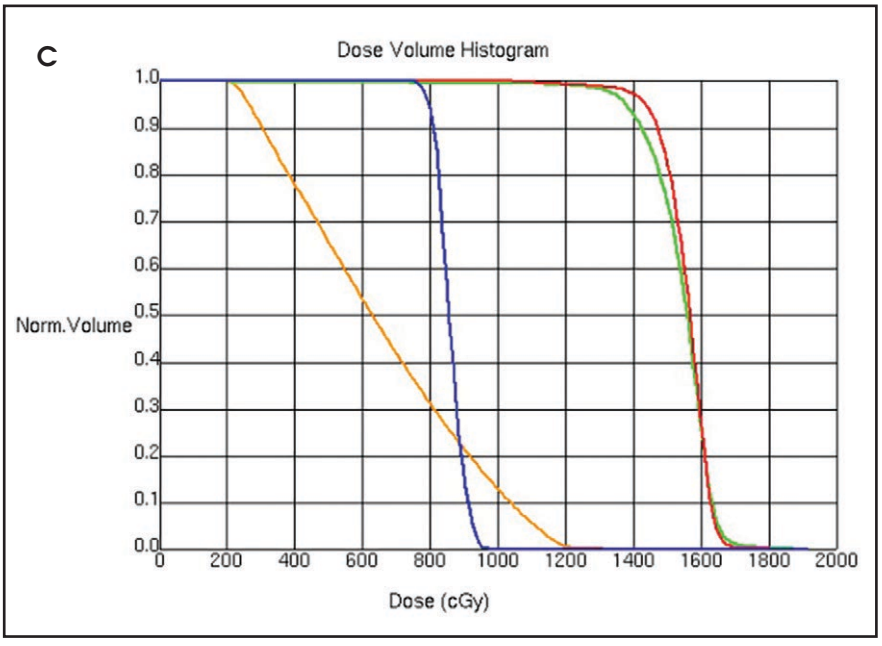


FIGURE 3. *Clinical target volume (CTV) (red), planning target volume (PTV) (green colorwash) and PRV (green line) at 3 axial levels (3A). Volumetric-modulated arc therapy (VMAT) plan: axial, sagittal and coronal views (3B). Dose volume histogram (3C).*

total skin electron-beam therapy later if needed. Organs at risk dose constraints—especially for brain, eyes and lips—were met as shown in the dose volume histograms **(Figures 3A-C).**

Daily treatment setup took approximately 30 minutes. Wet gauze was used to fill the gaps on the skin surface to achieve a uniform thickness prior to placing the custom-made layers of Vaseline-impregnated gauze built up to a thickness of 0.5-cm bolus, then secured with Surgilast (Derma Sciences, Princeton, New Jersey). After a 1-cm bolus on the vertex was taped, the patient was immobilized with an Aquaplast cast. Finally, another 1-cm bolus was placed on the cast.

Image-guided radiation therapy using daily cone-beam CT matched to bony anatomy and assessed eye position was used to ensure precise alignment of the intended target.

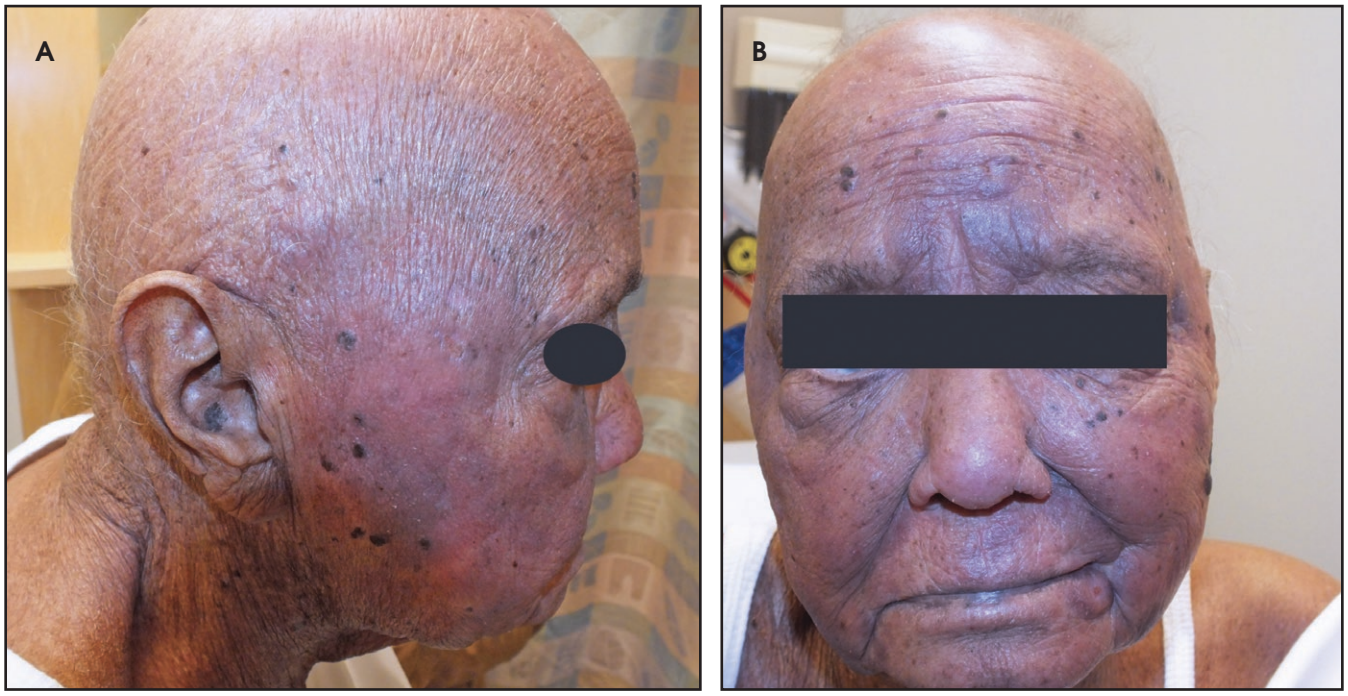


FIGURE 4. *Right lateral face (4A). Complete resolution of lesions 6 weeks after treatment (4B).*

TREATMENT RESULTS

The patient tolerated the treatment extremely well with minimal radiation dermatitis. Six weeks after completing the radiation, she achieved a complete response of the tumors treated **(Figures 4A-B)**. We also noted spontaneous regression of some untreated tumors on the torso, indicating an abscopal effect.

CONCLUSION

Novel VMAT's rotational approach with photons can be utilized for treating extensive cutaneous disease involving uneven and curving surfaces such as the scalp, head and neck, or torso with the goal of achieving local tumor control and providing excellent palliation with minimal radiation dose to adjacent normal structures.

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