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Integrating the Management of Nodal Metastasis Into the Treatment of Nonmelanoma Skin Cancer

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The two types of nonmelanoma skin cancer most apt to metastasize to lymph nodes are cutaneous squamous cell carcinoma and Merkel cell carcinoma. The clinical impact of nodal metastases of these cancers is substantial, resulting in intensification of treatment and morbidity and worsened cancer outcomes. Exact best practices are challenging to define as many specific clinical scenarios remain incompletely catalogued, characterized, or studied. In general, the role of radiation therapy is indisputably established as part of the treatment of both of these diseases although its success depends on the best available assessment of extent of disease and appropriate integration into the multimodality care plan.
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Introduction

For nonmelanoma skin cancers (NMSC), the phenomenon of nodal metastasis (N+) is one of the most poorly characterized and clinically challenging aspects of management. Because of uncertainty around the true annual incidence of primary NMSC in the United States due to a lack of tracking of basal and squamous cell carcinoma in the national cancer registries, likewise the incidence of subsidiary occurrence of nodal metastasis is not easily quantified.[1] In addition, due to the diverse anatomical sites and frequent multimodal or staged approaches to managing cutaneous malignancy, asynchronous patterns of recurrence and regional spread can be masked in relation to the primary site. The outcomes of "high risk" NMSC in the literature have mostly been irregularly reported using different end points collected in single-institution clinical programs.

For these reasons, unconditional recommendations for management of N+ NMSC are few and sometimes provisional related to complex clinical circumstances. While NMSC can be relatively easily classified as having "high risk" features or not, and for clinically N+ cases, initial therapeutic surgery to remove involved nodes is a typically straightforward decision, the indications for additional elective surgical dissection or postoperative or elective radiation therapy, and the scenarios justifying intensification using systemic therapy, are derived from limited prospective trial data and best clinical judgment essentially based on case series.[2] Moreover, while the survival impact of N+ disease is solidly established in Merkel cell carcinoma (MCC), current prognostic systems for N+ cases are not as clearly predictive of survival in cutaneous squamous cell carcinoma (cSCC), making benchmarks for risk evaluation additionally complex.[3,4] This review will address the extant state of knowledge on incidence, risk factors and treatment strategies for nodal metastasis originating from cSCC and MCC, the two types of NMSC associated with the highest risks of regional metastasis.

Cutaneous Squamous Cell Carcinoma

Incidence and Risk Factors for Recurrence

One survey of cSCC incidence data adjusted by geographically organized "sun zones" estimated that in 2012, there were 186,157 to 419,843 new diagnoses, 5604 to 12,572 cases of nodal metastasis, and 3932 to 8791 deaths, depending on the estimating assumptions used.[5] As seen in these data, nodal metastasis (N+) originating from cSCC is a rare

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event, usually thought to occur in approximately 2%-4% of cases.[6] Despite this low rate of regionally advanced presentation, due to the high annual incidence of cSCC in the general population, absolute death rates in high-incidence areas are comparable to those caused by renal cell carcinoma, oropharyngeal carcinoma in men, or melanoma,[5] and among high-risk populations, rates of nodal metastasis can exceed 20%.[7,8] Among persons with immune-related conditions causing or requiring immunosuppression, the incidence and aggressiveness of cSCC is higher.[9-11] In post-transplant patients, the usual squamous-to-basal cell carcinoma incidence ratio of 1:4 seen in the general population is reversed. A 65-fold higher incidence of cSCC occurs in transplant recipients and the highest risk seen is after heart transplantation.[12] Among patients receiving surgically-based multimodality therapy, those who are affected by human immunodeficiency virus, chronic lymphocytic leukemia, or immunosuppression related to organ transplant have decreased local control and progression-free survival.[13,14]

Brantsch et al conducted a prospective clinicopathologic study at Eberhard Karls University in Germany including 615 newly diagnosed cSCC patients who underwent surgery and 3-dimensional histologic examination with thickness measured by ocular micrometer.[15] No patient received postoperative radiation. Importantly, in this study desmoplasia was defined as a stromal reaction at the periphery occupying a third of the representative specimen, and perineural and perivascular invasion were always associated with desmoplasia. At 43 months of follow-up, 3% of patients developed local recurrence and 4% of patients had a nodal metastasis. On multivariate analysis, independent prognostic factors for local recurrence were desmoplasia (hazard ratio [HR] 16.11) and thickness (HR 6.03). Factors significant for nodal metastasis were thickness (HR 4.79%), host immunosuppression (HR 4.32), ear location (HR 3.61), and horizontal size (HR 2.22). Nodal metastasis occurred in 0 tumors <2.0 mm thick, 12 (4%) tumors 2.1-6.0 mm thick, and 14 (16%) tumors >6.0 mm thick. These authors proposed enhanced surveillance for higher-risk patients including ultrasound of the neck for patients at increased risk for nodal metastasis.

Another prospective study confirmed the prognostic importance of size, depth, and perineural invasion in disease-specific survival.[16] This study enrolled and followed 210 patients from the University of Texas - M.D. Anderson Cancer Center, of whom 80 (38%) had locally or regionally recurrent cSCC. One hundred thirteen (53.8%) had wide local excision [17] or Mohs micrographic surgery, 29 (13.8%) received comprehensive nodal dissection, 16 (7.6%) received both wide excision and nodal dissection, 39 (18.6%) had one of these surgeries plus adjuvant radiation, and 6 (2.9%) received radiation alone. Seven (3.3%) had dermatologic management without depth assessment. Multivariable modeling found that size ≥4 cm and perineural invasion best predicted the outcome of disease-specific survival. On recursive partitioning analysis, size ≥4 cm was the first differentiating factor, followed by perineural invasion and invasion beyond subcutaneous tissues. The 3-year disease-specific survival was 100% without any of these factors, but it was 70% among patients in whom one of these factors was present. This study reflects the reality of cSCC management which can be widely divergent in locoregionally advanced cancers presenting as already recurrent.

In an older study, Rowe et al estimated the incidence of local recurrence and nodal metastasis from weighted averages based on reports collected from the medical literature.[18] Nodal metastases were seen in 47.3% of tumors with perineural invasion, 45.7% of tumors with depth ≥4 mm or Clark level IV-V, 37.9% of tumors arising from scar carcinoma, 32.8% of poorly differentiated tumors, 30.3% of tumors of size ≥2 cm, 30.3% of tumors previously treated, 12.9% of tumors arising in a patient with immunosuppression, and 11%-13.7% of tumors arising on ear or lip sites. These rates are higher than seen in prospective studies, likely due to reporting bias as these averages were compiled from case series including many high-risk and recurrent patients. A recent large-scale meta-analysis of this similar literature confirmed the significance of many of these factors; invasion beyond the subcutaneous fat (relative risk [RR] 11.21), Breslow thickness >6 mm (RR 6.93), diameter >20 mm (RR 6.15), poor differentiation (RR 4.98), perineural invasion (RR 2.95), location on the temple (RR 2.82), ear (RR 2.33), or lip (RR 2.28), or host immunosuppression (RR 1.59) each produced an increased risk of nodal metastasis.

These studies also demonstrate how the category of "high risk" can expand depending on the number of features considered. One well-known comparison found that a "high risk" designation was assigned to 13.9% of head and neck cSCC using American Joint Committee on Cancer (AJCC) seventh edition staging criteria, vs 87% according to the 12 criteria listed by the National Comprehensive Cancer Center Network.[19] There are further differences to the revised eighth edition AJCC and European dermatology and cancer societies' criteria.[20] For example, host factors such as immunosuppression or clinical factors such as rapid growth and recurrent status are not considered in the AJCC staging manual.

Indications for Elective Radiation for cSCC

For a cSCC patient determined to be in a "high risk" categorization, there exists considerable controversy over the indications for further explorations to stage or electively treat draining nodal basins. Imaging of the potentially involved nodal regions, with an absence of lymph nodes meeting morphologic or size criteria for abnormality, can serve to rule out the need for a therapeutic dissection but does not fully resolve the question of whether to apply elective treatment.[21,22] Sentinel lymph node biopsy (SLNB) is one approach that has been proposed to enhance staging of clinically N0 (cN0) patients, although its use has not become widespread due to lack of technical expertise, added cost and risk, uncertainty about the proper indications for it, and concern about inaccuracy in the postbiopsy setting.[23] While higher T stage is associated with confirming an involved SLN and a positive SLN is prognostic for poor survival,[24,25] the ultimate impact of the SLNB procedure on outcomes of

cN0 patients when compared to standard treatments has not been established.[26]

Alternatively, elective treatment of the neck may be performed. For head and neck cN0 cSCC, despite wide variations in practice, the recommendation of parotidectomy with elective neck dissection (END) has been most generally accepted for T3-4 tumors.[27,28] The strategy of END may be concordant with a need for therapeutic dissection or a dissection to identify vessels for reconstructive flap placement, or a medical situation prohibitive of elective radiation therapy. One prospective study in China allowed 111 cN0 head and neck cSCC patients to choose observation, parotidectomy, or parotidectomy with level I-III END. Patients with pathologic N+ status received postoperative radiation. Among 100 patients remaining in follow-up, regional recurrence occurred in 16, of whom 15 had T3-4 stage. Recurrence rates were 17.8% with observation, 3.3% after parotidectomy, and 0.8% after parotidectomy-END. Regional and disease-specific survival was significantly better in patients receiving END.[29] However, it should be noted that an influential decision tree analysis of this clinical situation recommended observation if the probability of occult cervical metastasis was less than 20%, and no study has yet demonstrated a survival benefit from END in cN0 patients compared to initial observation and subsequent salvage.[30,31]

Likewise the indications for elective nodal irradiation (ENI) are variable among centers and clinical situations.[32] One study including cN0 patients with an estimated risk of 10% of nodal relapse documented a reduction to 2.8% nodal relapse within the ENI volume, with no occurrence of high-grade toxicity. The indications for ENI in this study were broad, including patients with recurrent tumors, poor differentiation, perineural invasion, size >2 cm, positive margin, or immunosuppression.[33] If based on stricter criteria similar to those governing END, multiple clinical and pathologic high-risk factors could be considered in the determination to offer ENI, such as a scenario of advanced T stage and periparotid location, in cN0 patients without a clinical reason for END, and with a primary tumor location that can be localized to a draining nodal basin with a reasonable level of certainty. The anticipated morbidity of ENI varies with location, body habitus, and extent of elective coverage, and these negative sequelae should be balanced against the possibility of nodal metastasis.

Therapeutic Management of N± cSCC

Among patients with radiologically or clinically apparent N+ cSCC, surgical dissection is considered the optimal initial treatment. It is standard to follow a therapeutically directed neck surgery with postoperative radiation therapy.[34] A number of studies have documented rapid regional recurrence in an unacceptably high proportion of patients after surgery alone, especially in patients with involvement of multiple nodes or extranodal extension (ENE).[35] One such study of 74 patients with involved nonparotid cervical nodes, reported a 5-year disease-specific survival rate of 75% for surgery and radiation therapy, vs 52% for radiation alone and 18% for surgery alone (P = 0.001).[36] It has been proposed by some experts that for a select minority of patients having N+ head and neck cSCC with only one pathologically involved lymph node of size ≤3 cm and no other adverse pathologic features, postoperative radiation might be omitted.[37] This is presumptive on the patient having received an adequate parotidectomy as well as a high-quality END, because in patients with parotid adenopathy, there is up to 35% risk of occult involvement of the neck, and only 18% of N+ patients have isolated cervical adenopathy without parotid involvement.[38,39]

For resected N+ cSCC, the addition of a concurrent systemic therapy to postoperative radiation is practiced at many centers despite a lack of evidence. Postoperative systemic therapy has been given to cSCC patients for indications analogous to those in the head and neck mucosal SCC literature. For mucosally-based SCC of the head and neck, a combined analysis of 2 major studies established that the addition of concurrent cisplatin to postoperative radiation improved overall survival among patients who had positive margins or ENE[40], and cetuximab, a targeted therapy directed against the epidermal growth factor receptor, has been shown to improve survival when added to definitive radiation therapy intended to treat unresected HN mucosal SCC.[41]

In direct contradistinction to these practices, the phase III randomized Trans-Tasman Radiation Oncology Group trial (TROG 05.01) of 321 patients did not show any advantage in local or regional control or survival from the addition of six cycles of weekly carboplatin to 60-66 Gy of radiation therapy in a resected cSCC population deemed to be at high risk of recurrence.[42] In this trial, eligibility was determined based on either a high-risk primary site or high-risk nodal disease. For the primary tumor, high-risk criteria included size >5 cm, invasion of cartilage, skeletal muscle, or bone, or in-transit metastasis. High-risk nodal disease was defined as intraparotid nodal disease or cervical nodal disease involving ≥2 nodes, a node ≥3 cm, or ENE. No significant differences in outcome between the two randomized groups were observed. The 2- and 5-year disease-free-survival rates for radiation therapy (RT) alone were 78% and 67%, whereas for chemoradiation (CRT), they were 83% and 73% (P = 0.44). The 2- and 5-year overall survival rates for RT were 88% and 76%, whereas for CRT, they were 88% and 79% (P = 0.86). Therefore, at this time, postoperative concurrent carboplatin cannot be recommended, and the benefit of concurrent cisplatin and cetuximab remain unproven. This study provided an important baseline metric illustrating that even in patients with high-risk disease, long-term disease-free survival rates of approximately 70% can be expected from surgery followed by postoperative radiation.

Most recently, a clinical trial of cemiplimab-rwlc, an immunotherapy based on blockade of the PD-1 axis, has shown a very promising 47% response rate among patients with recurrent and metastatic cSCC.[43] At least 2 large-scale

phase III clinical trials are being planned with the intention to test the integration of immunotherapy into postoperative management of high-risk resected cSCC.

Merkel Cell Carcinoma

Incidence and Risk Factors for Recurrence

MCC is a primary cutaneous neuroendocrine tumor arising from the dermis. It is rare although the incidence is increasing. According to data from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, the annual age-adjusted incidence rate in the United States in 1986 was 0.15/100,000 persons per year and 0.44/100,000 in 2001.[44,45] In 2013, the incidence rate was 0.70/100,000, corresponding to 2488 cases. Based on the aging demographics of the United States, the incidence is predicted to reach 2835 cases in 2020 and 3284 cases in 2025.[46]

MCC can present as a bland pink papule with sudden rapid onset of bulky growth and metastasis.

Among the few thousand cases of MCC in the United States each year, only half present as localized to the skin and half present with either nodal or distant metastasis.[44] The incidence of MCC is higher among the elderly over the age of 65 years and in patients who are immunosuppressed, particularly among the organ transplant population where the incidence is 23.8-fold higher than the general population.[47]

A number of pathologic features have been associated with a higher risk of disease progression and death, including indices of antiapoptosis (p63, Bcl-2), proliferation (Ki-67), or lymphatic vessel invasion associated with nodal metastasis.[48,49] Nearly all MCC are associated with Merkel cell polyomavirus depending on the sensitivity of the detection method,[50] and the 80% of cases clearly demonstrated to be associated with the polyomavirus are thought to have a better prognosis.[51] Because these pathologic features have only been recently associated with MCC, their incorporation into therapeutic decision-making remains undeveloped.

Standard therapy for MCC is surgical removal followed by postoperative radiation therapy. Radiation therapy has been consistently shown to reduce the risk of primary site recurrence and given how well it is usually tolerated at the primary site, only very favorable circumstances (tumors <1 cm, excised with wide margins, without evidence of lymphovascular invasion or infiltrative growth pattern) justify a consideration of omitting primary site adjuvant radiation.[52-55] One case series of 113 patients from Moffitt Cancer Center showed major improvements in 3-year actuarial rates of both local control (68.1%-89.4%; $P = 0.005$) and regional control among both clinical node-negative (44.7%-100%; $P = 0.03$) and clinical/pathological node-positive patients (55.6%-90.9%; $P = 0.047$) due to the addition of postoperative radiation. The positive contribution of adjuvant radiation has been shown to remain significant after both Mohs micrographic surgery and after SLNB procedures.[56,57] Where greater controversies exist at present are in regard to the relative contribution of completion lymph node dissection after SLNB in the face of planned adjuvant radiation therapy to the regional lymphatics and the potential role of radiation as a primary nonsurgical management strategy for either microscopic or macroscopic disease.

Indications for Elective Radiation for MCC

An important study in France attempted to evaluate the benefit of elective nodal therapy for stage I MCC patients.[58] In this trial, patients who received wide local excision followed by postoperative radiation therapy to the resected primary tumor bed were randomized to the addition of regional radiation therapy to the draining nodal bed vs observation of the draining nodal regions. Unfortunately this study was conceived just before the development of SLNB and as a result, due to the ascent of SLNB technology, accrual slowed and the trial had to close. Among the 83 patients who were randomized, the addition of regional radiation therapy reduced the probability of regional recurrence from 16.7% in the observation arm to 0% in the treatment arm ($P = 0.007$). No significant improvement in OS ($P = 0.989$) or PFS ($P = 0.4$) could be demonstrated from this prematurely closed trial. Meaningful application of this trial's result is unclear in the era of SLNB.

Based on large institutional case series and systematic reviews, rates of occult nodal metastases identified by SLNB in cN0 patients are as high as 25%-32% but the false-negative rate of SLNB is 17%-20%.[17,59] In keeping with these data, single-institution reports clearly indicate that survival is markedly improved due to some form of additional nodal therapy if the SLNB is positive but if the SLNB is negative, survivals appear to be slightly but non-significantly worse with omission of further therapy. Consistently across these series, a cN0 patient with a positive SLNB was much more likely to receive additional nodal-directed therapy. Thus the largest single-institution series in the literature found no difference in mortality or recurrence in patients who had positive SLNB compared to those with a negative SLNB, possibly due to highly tailored application of traditional adjuvant therapies such as completion lymphadenectomy and/or regional radiation.[60]

Most institutional groups have concluded that after negative SLNB, additional therapy can usually be omitted with a finite but low risk of nodal recurrence. For instance, one case series of 122 patients from the Dana-Farber reported that patients with a positive SLNB who received adjuvant therapy (completion nodal dissection, radiation, and/or chemotherapy) had a relapse-free survival rate of 51% at 3 years compared with 0% for the few patients who did not receive additional therapy ($P < 0.01$). Among patients with a negative SLNB, the difference in 3-year relapse-free survival rates was considered nonsignificant at 90% for patients receiving additional therapy and 70% for those who did not ($P = 0.26$). Another study from the Mayo Clinic found that after negative SLNB, the 3-year cumulative incidence (CI) of any nodal recurrence was 15% and within the same nodal basin as where the SLNB had been removed, the

rate was 8.4%. Among 14 patients receiving adjuvant nodal radiation after a negative SLNB, only 1 developed a regional recurrence, for a CI of 9.1% at 3 years. Among 97 patients who did not receive adjuvant nodal radiation after a negative SLNB, 14 developed a regional recurrence, for a CI of 15.5 % at 3 years ($P = 0.45$).[61]

Therapeutic Management of N± MCC

There are small-scale retrospective reports that cN+ patients can be treated successfully with radiation therapy alone. There is no randomized data indicating whether this approach is equivalent in its oncologic outcomes to upfront surgery with or without adjuvant radiation therapy or what can be expected in terms of toxicity compared to a multimodality program. Retrospective series reporting definitive radiation results suffer from severe selection bias, in that this approach has mostly been applied to patients who had inoperable tumors, comorbidities making them poor surgical candidates, or tumors for which surgery was deemed to carry risk of unacceptable functional compromise. Correspondingly, in-field local control rates after radiation therapy alone are quite good, ranging from 75% to 100%, but distant recurrence rates are increased and rates of cancer-specific and overall survival are inferior to those reported in patients undergoing surgical resection. One retrospective review of 43 patients treated with definitive radiation found that 53% relapsed outside of the radiation field, mostly to visceral organs, and the 5-year overall survival at 5 years was 37%.[62] This was comparable to another study of 57 patients that reported an overall survival rate of 39%.[63] The most comprehensive systematic review to date included 264 patients who were definitively irradiated producing an in-field recurrence rate of 14.3% at a mean time of 6.3 months.[64]

A few isolated reports propose the value of radiation therapy independent of a preceding surgery. One small study compared 25 patients treated with definitive radiation to a median dose of 65 Gy to an earlier cohort of 25 patients who received surgical resection followed by postoperative radiation therapy to a median dose of 55 Gy. Two patients relapsed in the radiation-alone group and 4 relapsed in the surgery group, with no apparent differences in disease-free or overall survival.[65] Another study from the University of Washington included 50 patients, 43 of whom were enrolled and followed prospectively. Among 26 patients presenting with microscopic lymph node disease, regional control was 100% regardless of whether they received irradiation only or a completion nodal dissection with or without adjuvant radiation. Among 24 patients presenting with clinically positive lymph nodes, the 2-year regional recurrence-free survival rates were 78% for the patients receiving radiation only (of note, 18 of these patients had a limited nodal excision and only 6 had gross disease at the time of radiation) vs 73% in the completion nodal dissection group. The authors advocated for a choice between radiation vs more extensive dissection based on the anticipated side effect profile. [66]

TROG 96.07 was a phase II trial aimed at high-risk MCC patients and designed to determine the outcome of postoperative radiation combined with concurrent carboplatin at AUC 4.5 and etoposide 80 mg/m^2 days 1-3 in weeks 1, 4, 7, and 10. Patients were eligible if they had recurrent MCC, involved lymph nodes, primary MCC tumor size >1 cm, gross disease after surgery, or occult primary with nodes. Among 53 patients, the 3-year overall survival, locoregional control, and distant control were 76%, 75%, and 76%, but grade 3 or 4 neutropenia was seen in 57% of patients and grade 3 or 4 skin reaction occurred in 64%.[67] A small study of 18 patients receiving weekly carboplatin only resulted in lower toxicity.[68] However, the role of adjuvant chemotherapy for MCC remains controversial with differing opinions about the superiority over results of the standard therapies of surgery and radiation. A systematic review and an analysis of the National Cancer Database both concluded that adjuvant chemotherapy did not improve survival.[69,70]

Immunotherapy has recently been shown to produce high response rates in recurrent and metastatic MCC,[71,72] but it is unclear whether and how to integrate immunotherapy into definitive-intent treatment paradigms. Trials of adjuvant/maintenance immunotherapy for very high-risk disease, such as stage IIIB, have been proposed but the expected slow accrual of these rare presentations is a barrier. In one small study, neoadjuvant immunotherapy prior to surgery induced radiologic response and major pathologic response in 45% and 64% of patients, respectively.[73]

Radiation Techniques

While there are differences in indications, techniques, and dosing for cSCC and MCC, several general technical principles can be outlined for irradiation of N+ skin cancers. It should be noted that specific skin cancer radiation practices can be idiosyncratic depending on institutional preferences and that pronounced variabilities of fractionation schedules and techniques are recognized and acceptable for these cancers. If radiation is planned for resected nodal metastases, the suspected primary tumor bed should be treated simultaneously with the nodal bed if there is a suspect primary site and less than 2-3 years have elapsed since the primary site surgery. For primary site treatment, if electrons or 3D/intensity-modulated techniques are used, the surface of the skin circumferential to the primary scar should be covered with bolus and a generous margin should be irradiated (Figure 1). Superficial radiation may be used to treat the primary site in limited circumstances and does not require bolus. For cSCC, the irradiated margin may be 1-2 cm but for MCC, larger margins such as a minimum of 3-5 cm are preferred due to this cancer's marked predisposition for intradermal lymphatic spread.

For treatment of the nodal basin, intensity-modulated radiation therapy (IMRT) is favored to reduce toxicity although a 3D technique is very acceptable.[74] The accuracy of daily setup is important, especially if IMRT is used, and particular care should be taken to stabilize positioning of any involved extremities. Immobilization with thermoplastic shells or moldable cradles is highly recommended. If a nodal

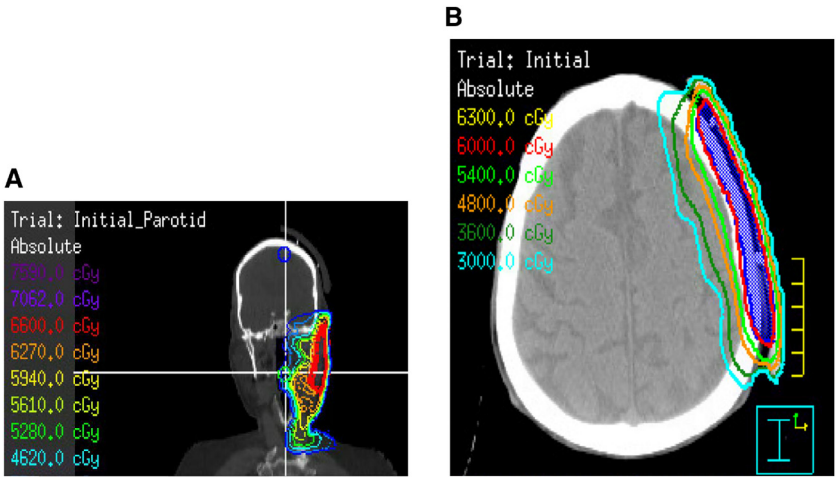

Figure 1 (A) Intensity-modulated radiation plan for the upper neck in a patient with positive margins due to extranodal extension of cutaneous squamous cell carcinoma. The radiation prescription dose was 66 Gy. (B) The scalp was treated separately with electron therapy to 60 Gy, with wires to demarcate the field and bolus placed over the primary treatment area.

dissection has been performed, the dissection scars should be wired with consideration of applying bolus and all areas of soft tissue disruption should be included in the scanned and irradiated volume.

If elective radiation is planned, the volumes to be included are based on the primary skin site. Drainage is typically to either the axilla or groin from the lower body while drainage from the scalp and face will concentrate in the parotid or proximate levels of the anterior or posterior neck.[39,75] It should be emphasized that nodal drainage from skin cancers can be unpredictable. If there is doubt about localization of drainage for reasons of prior surgical disruption or anatomical ambiguity, those issues should be discussed with the surgical team and ideally managed with a multidisciplinary approach and forethought. In-transit metastasis requires large margins and treatment of intervening dermal and lymphatic regions tracking from the primary site. This is a very challenging and frequently lethal situation.

Postoperative radiation is generally given to doses of 60-66 Gy for cSCC and 50-56 Gy for MCC depending on the

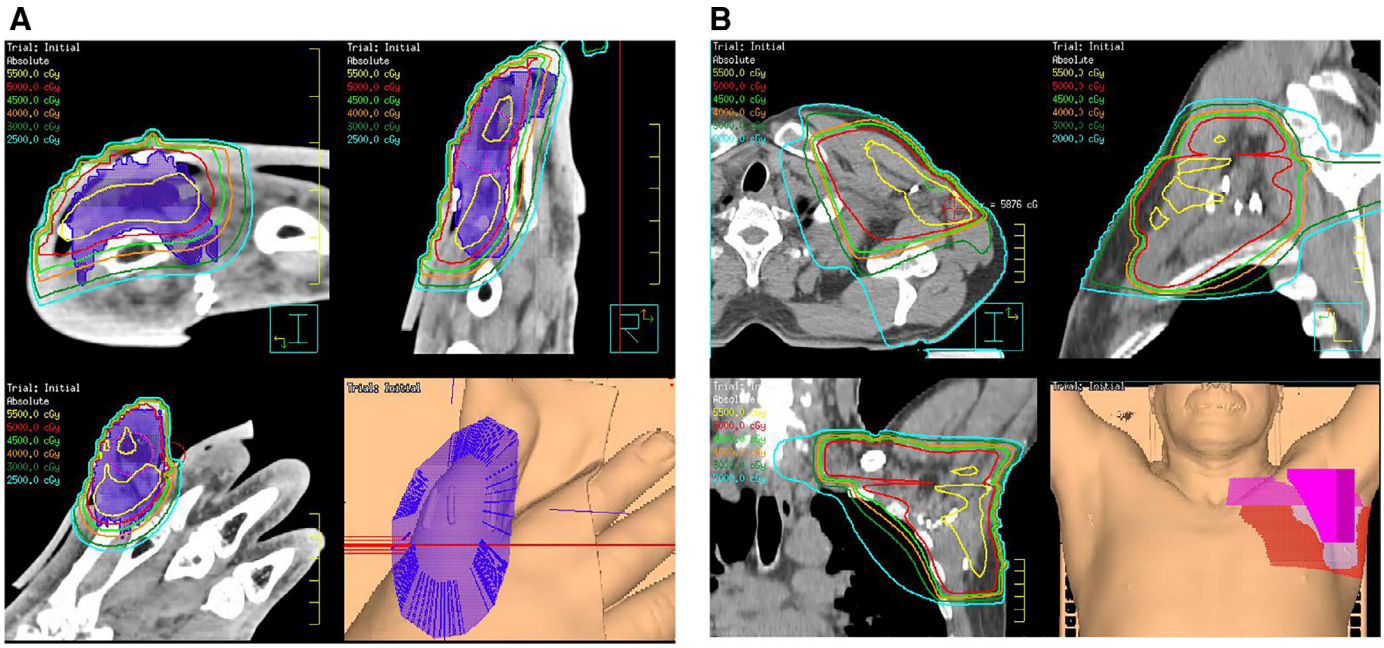

Figure 2 (A) Electron therapy plan (6:9 MeV in 40:60 ratio) using a custom 5 mm thermoplastic bolus for a Merkel cell carcinoma primary on the thumb surface which was excised with narrow margins, treated to a dose of 50 Gy. (B) The axillary region was dissected showing very bulky nodal disease and thus the axilla and supraclavicular regions were treated with postoperative 3D conformal therapy to 50 Gy.

surgical margin status.[42,76] For purely elective treatment, 50-56 Gy can be considered for cSCC and 50 Gy can be considered for MCC (Figure 2).[32,77] Gross residual or unresected MCC can be effectively treated with doses of 60-66 Gy although up to 70 Gy has been used.[62,63,65,66] Definitive radiation therapy without preceding surgery is only moderately successful for gross residual or unresected cSCC but if attempted, the dose should be at least 70 Gy and consideration of 74 Gy is not unreasonable. One prospective study of chemoradiation combining 70 Gy of radiation with concurrent weekly cisplatin at 40 mg/m^2 or carboplatin at AUC 2 reported a complete response rate of 52.6% in 19 evaluable patients, and after additional salvage surgery in 3 of these patients, at 6 months an absence of locoregional progression was achieved in 13 of 21 originally enrolled patients (61.9%).[78]

For palliation, standard radiation schedules are used for cSCC, such as 20-30 Gy in 5-10 fractions, although in cases where more durable control is desired, 45-50-55 Gy in 15-20 fractions may be considered. For MCC, similar schedules may also be used although a popular treatment in patients with metastatic disease is 8 Gy x 1-3 fractions. A single fraction of 8 Gy has been shown to be effective in producing local and possibly systemic immune-mediated response,[79,80] but three fractions of 8 Gy may produce more durable local control.[81]

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