Radiation Therapy for Cutaneous Malignancies of the Head and Neck

Rohan Katipally, MD[a,*], Nishant Agrawal, MD[b], Aditya Juloori, MD[a]

KEYWORDS

• Radiotherapy • Radiation therapy • Skin cancer • Keratinocyte carcinoma • Basal cell carcinoma • Squamous cell carcinoma • Melanoma • Merkel cell carcinoma

KEY POINTS

- Radiation therapy (RT) plays an integral role in the definitive and adjuvant management of cutaneous cancers of the head and neck, including basal cell carcinoma, cutaneous squamous cell carcinoma, melanoma, and Merkel cell carcinoma.
- RT may serve as an appropriate alternative to surgery for basal cell carcinoma and squamous cell carcinoma in cosmetically and functionally sensitive areas.
- Various RT modalities are available in the treatment of cutaneous malignancies (ranging from low-energy x-rays, to megavoltage electrons or photons, to brachytherapy).

INTRODUCTION

Radiation therapy (RT) plays a significant role in the management of cutaneous cancers of the head and neck, which include basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (SCC), melanoma, and Merkel cell carcinoma (MCC). Commonly used RT modalities include kilovoltage photons, megavoltage electrons, megavoltage photons, and low-dose-rate and high-dose-rate (HDR) brachytherapy. Kilovoltage (ie, low-energy) photons include orthovoltage, superficial, contact, and soft x-rays and deposit most dose superficially with little dose penetrating into deeper tissues, which is advantageous for superficial skin tumors. Megavoltage electrons penetrate more deeply but still show rapid dose decrease with increasing tissue depth. Megavoltage photons are suitable for larger, deeply invasive tumors. Brachytherapy involves the

[a] Department of Radiation and Cellular Oncology, Duchossois Center for Advanced Medicine, University of Chicago Medicine, 5758 South Maryland Avenue, MC 9006, Chicago, IL 60637, USA; [b] Department of Surgery, Section of Otolaryngology-Head and Neck Surgery, University of Chicago Medicine, 5841 South Maryland Avenue, Chicago, IL 60637, USA
* Corresponding author.
E-mail address: rohan.katipally@uchospitals.edu

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use of applicators to bring the source of radiation close to the tumor, which may provide a more desirable dose distribution for highly nonuniform skin surfaces. It includes both radionuclide brachytherapy (frequently using iridium-192) and electronic brachytherapy (using electronically generated x-rays).[1]

BASAL CELL CARCINOMA

Indications for definitive RT include[1,2]:

- Primary BCC in patients who are not candidates for surgery
- Primary BCC located in specific anatomic locations that would result in unacceptable cosmetic/functional outcomes with surgery (medial canthus, eyelid)

Discussion

Surgery and definitive RT were compared in an older randomized controlled trial at the Gustave Roussy Institute.[3] From 1982 to 1988, patients with BCC of the face were randomized to surgery or RT (with interstitial brachytherapy, superficial contact therapy, or conventional RT). Although techniques studied in this trial do not reflect modern RT, the 4-year local recurrence (LR) was 0.7% for surgery and 7.5% for RT. Cosmetic outcomes, as evaluated by the patients, dermatologist, and photographic assessment, generally favored surgery, with 87% of patients receiving surgery grading their cosmesis as good compared with 69% with RT.

However, multiple meta-analyses have shown strong local control with definitive RT. An older meta-analysis (published in 1989) of primary treatment of BCC published a 5-year LR of 8.7% with RT, compared with 1.0% with Mohs micrographic surgery and 10.1% with surgical excision.[4] In 2017, Zaorsky and colleagues[5] published a meta-analysis of 21 studies using hypofractionated RT (predominantly T1–T2 SCCs and BCCs) with a median 1-year LR rate of 2% and 5-year LR of 14%.

Individual retrospective series (**Table 1**) report excellent local control (LC) and elucidate multiple risk factors for recurrence (such as tumor location, size, histology, and previously untreated vs recurrent setting). In general, higher LC is reported for BCC than SCC. A Washington University retrospective series showed a 94% LC for previously untreated BCC and 86% for recurrent (median follow-up 5.8 years).[6] In a retrospective series of BCC and SCC treated with soft x-rays, the crude LR was 4.5% for BCC (with mean follow-up of 77 months) and the 15-year LR rate was 6.1%.[7] A retrospective study of 604 BCCs in Spain showed a 5-year cure rate of 94.4% and 15-year cure rate of 84.8%.[8] Tumor location on the nasolabial fold and tumor size greater than or equal to 1 cm predicted for recurrence. Regarding histology, Zagrodnik and colleagues[9] reported a lower 5-year LR for nodular subtypes (8.2%) and a higher 5-year LR for sclerosing subtypes (27.7%).

Based on multiple institutional series, the cosmesis after primary RT is generally very good. In one series, cosmesis was rated as poor/fair in only 5.9% of previously untreated BCCs, and recurrent BCCs did not show a higher rate of poor/fair cosmesis.[6] Another series of 127 BCCs using orthovoltage x-rays showed good to excellent cosmetic outcome in 98%, using total doses ranging from 25 to 60 Gy.[10]

Tumors of the medial canthus and eyelids are at risk of poor cosmesis after surgery. Multiple retrospective series show strong LC with good cosmetic outcomes with RT, making them an acceptable alternative to excision. For eyelid, interstitial brachytherapy showed 96.7% LC, with a low rate of unsatisfactory functional and cosmetic outcomes (8.3%).[11] Late toxicities included nasolacrimal duct stenosis (6.7%), chronic epiphora (5%), ectropion (5%), and cataract (3.3%). Another series using kilovoltage

Table 1
Selected studies of primary radiation therapy for basal cell carcinoma

Series	Study Design	N	Intervention	Outcomes	Toxicity
Avril et al,[3] 1997	Randomized, controlled trial	347	Arm 1: surgery Arm 2: RT (radionuclide interstitial brachytherapy, ELS, conventional)	4-y LR: 0.7% (surgery) vs 7.5% (RT)	Good cosmesis: 87% (surgery) vs 69% (RT)
Locke et al,[6] 2001	Retrospective	389	Electrons, ELS, MV photons (<2%)	LC: 94% (previously untreated) and 86% (recurrent)	Fair/poor cosmesis: 5.9% Soft tissue necrosis: 2%
Schulte et al,[7] 2005	Retrospective	1019	ELS	Crude LR: 4.5% 5-y LR: 4.2% 10-y LR: 6.1% 15-y LR: 6.1%	Pooled BCC and SCC Hypopigmentation: 72.7% Telangiectasias: 51.5% Erythema: 44.5% Hyperpigmentation: 23.4%
Zagrodnik et al,[9] 2003	Retrospective	175	ELS	5-y LR: 15.8% (all histologies), 8.2% (nodular subtype), 26.1% (superficial subtype), 27.7% (sclerosing subtype)	Not reported
Seegenschmiedt et al,[10] 2001	Retrospective	127	ELS	LR: 1.6%	Acute grade 1: 100% Acute grade 2: 54% Acute grade 3: 30% Late toxicity: 2.4%
Guix et al,[19] 2000	Retrospective	102	Radionuclide interstitial brachytherapy	5-y LR: 2.0%	Pooled BCC and SCC 6-wk ulceration present: 10.3% 4-mo ulceration present: 0% 6-mo good/excellent cosmesis: 98%

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Table 1
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Series	Study Design	N	Intervention	Outcomes	Toxicity
Krengli et al,[11] 2014	Retrospective	52	Radionuclide interstitial brachytherapy	LC: 3.8%	Pooled histologies Nasolacrimal duct stenosis: 6.7% Chronic epiphora: 5% Ectropion: 5% Unilateral cataract: 3.3% Optimal cosmetic and functional outcome: 68.3% Unsatisfactory cosmetic and functional outcome: 8.3%

Abbreviations: ELS, electronically generated low-energy radiation sources (typically low-energy kilovoltage photons); LC, local control; MV, megavoltage.
Data from Refs.[3,6,7,9–11,19]

photons for medial canthus BCC showed chronic epiphora in 21%, chronic dry eye in 3%, and severe complications (including vision loss) in 0%.[12]

Indications for adjuvant RT include[1,2]:

- Postoperative bed ± cranial nerve pathways for gross perineural tumor spread
- Postoperative bed for close or positive margins not amenable to further resection
- Postoperative bed for recurrence after prior margin negative resection
- Postoperative bed for locally advanced tumors involving bone or muscle
- Nodal basins for N2 disease after lymphadenectomy

Discussion

Perineural involvement or neurotropism is a frequently used term that refers to both microscopic perineural invasion (PNI), which reflects the histologic finding of tumor infiltration of nerves and is often incidental, and perineural tumor spread (PNTS), which reflects gross tumor involvement along a nerve and is often clinically or radiographically apparent.[13] Although perineural involvement is more common in SCC, it is still considered a risk factor for LR in BCC (see **Table 3**), and the extent of perineural involvement is associated with worse locoregional control (LRC). A retrospective review of 135 patients with perineural involvement from the University of Florida included both BCC (22%) and SCC (78%).[14] Patients with clinically apparent PNTS showed a 5-year LRC of 56%, compared with 80% for patients with only microscopic PNI. However, outcomes for BCC specifically were not explicitly reported. The radiographic extent of PNTS was associated with both worse 5-year LC (25% for macroscopic disease radiographically vs 76% for negative imaging) and 5-year overall survival (OS) (58% vs 90%) in both BCC and SCC.[15]

Adjuvant RT can be considered for positive/close margins not amenable to re-excision, because positive margins have been associated with increased 5-year LR (26% compared with 14% with negative margins).[16] Based on a series where normal skin was marked and the tumor was excised with Mohs surgery, a 4-mm resection margin using conventional excision would be required to eliminate the subclinical tumor extent in tumors less than 2 cm.[17] However, this may not always be feasible in cosmetically/functionally sensitive locations.

CUTANEOUS SQUAMOUS CELL CARCINOMA

Indications for definitive RT include[1,2]:

- Primary SCC in patients who are not candidates for surgery
- Primary SCC located in specific anatomic locations that would result in unacceptable cosmetic/functional outcomes with surgery (eg, eyelids, medial canthus)

Discussion

Multiple retrospective studies show excellent LC with primary RT for SCC (**Table 2**). In the aforementioned Washington University series, the LCs were 89% and 68% in the previously untreated and recurrent settings, respectively (median follow-up 5.8 years).[6] In the series by Schulte and colleagues,[7] the crude LR was 6.9% for SCC (mean follow-up of 77 months) and the 15-year LR was 12.8%.

Primary RT has not been compared with surgery for SCC in a randomized trial. In an older meta-analysis by Rowe and colleagues[18] published in 1992, RT was associated with a 6.7% LR in studies with follow-up less than 5 years and a 10.0% LR in studies

Table 2
Selected studies of primary radiation therapy for squamous cell carcinoma

Series	Study Design	N	Intervention	Outcomes	Toxicity
Locke et al, [6] 2001	Retrospective	142	Electrons, superficial therapy, MV photons (<2%)	LC: 89% (previously untreated) and 68% (recurrent)	Fair/poor cosmesis: 13% Soft tissue necrosis: 9%
Schulte et al,[7] 2005	Retrospective	245	ELS	Crude LR: 6.9% 5-y LR: 6.0% 10-y LR: 10.5% 15-y LR: 12.8%	Pooled BCC and SCC Hypopigmentation: 72.7% Telangiectasias: 51.5% Erythema: 44.5% Hyperpigmentation: 23.4%
Guix et al,[19] 2000	Retrospective	34	Radionuclide interstitial brachytherapy	5-y LR: 2.9%	Pooled BCC and SCC 6-wk ulceration present: 10.3% 4-mo ulceration present: 0% 6-mo good/excellent cosmesis: 98%

Data from Refs.[6,7,19]

with follow-up greater than or equal to 5 years, compared with 5.7% and 8.1%, respectively, for surgical excision. Mohs had an LR of 3.1% with follow-up greater than or equal to 5 years, the lowest across all treatment modalities. Factors associated with LR across all treatment modalities included size greater than 2 cm, higher grade, location on the ear or lip, perineural spread, recurrent disease, and immunosuppression.

Cosmesis is a relevant outcome after RT that historically favored surgery rather than primary RT. However, subsequent modern retrospective series demonstrated good cosmetic outcomes. In the retrospective series by Locke and colleagues,[6] cosmetic outcome was rated as good or excellent in 92% of patients, based on retrospective evaluation of telangiectasia, pigment change, and fibrosis of the skin. Cosmesis was worse (ie, poor or fair) when receiving greater than 50 Gy at less than 3 Gy per fraction. Furthermore, higher rates of poor or fair cosmesis were seen in SCC (13%) than in BCC (5.9%), attributable to higher doses administered. Brachytherapy also shows excellent cosmetic outcomes. In a series of SCC and BCC of the face using HDR brachytherapy and custom-made surface molds, only 10% had ulcerations at the 6-week follow-up and all ulcerations were healed by the 4-month follow-up (with 5-year LC 98%).[19] After 6 months, cosmesis was rated as good or excellent in 98% of patients.

The benefit of RT for particular anatomic locations (eg, eyelids and medial canthus) was previously described in relation to BCC and applies to SCC as well.

Indications for adjuvant RT include[1,2]:

- Postoperative bed ± cranial nerve pathways for gross perineural tumor spread or microscopic PNI (extensive or involving large-caliber nerve)
- Postoperative bed for close or positive margins not amenable to further resection
- Postoperative bed for recurrence after prior margin negative resection plus or minus additional resection
- Postoperative bed for T3/T4 tumors
- Postoperative bed for desmoplastic/infiltrative tumors in the setting of chronic immunosuppression
- Nodal basins for N2 disease after lymphadenectomy
- Nodal basins for clinically node-negative patients at high risk of nodal metastasis

Discussion

Clinically or radiographically apparent perineural tumor spread (PNTS) warrants adjuvant RT to improve LRC (**Table 3**). A retrospective series of BCC and SCC with clinical PNTS showed high rates of local failure with 5-year recurrence-free survival (RFS) of 39%.[20] Tumors involving cranial nerves V1/V2 or invading multiple nerves had worse RFS. Of all failures, 87% were local, underscoring the role of adjuvant local therapy. Another study of postoperative RT with clinical PNTS showed a 5-year RFS of 62%, disease-free survival (DFS) of 75%, and OS of 64%.[21] Notably, when classifying extent of PNTS into zones, less extensive spread (zone 1) had a 5-year RFS of 88%, whereas more extensive spread (zones 2 and 3) had a 5-year RFS of 51%.

Microscopic PNI that warrants adjuvant RT must involve a large-caliber nerve (nerve sheath measuring at least 0.1 mm in caliber or located deeper than the dermis). A retrospective cohort study of SCC showed that tumors with large nerve ($\geq$0.1 mm) invasion were associated with increased risk of nodal metastasis (hazard ratio [HR], 5.6) and death from disease (HR, 4.5), but invasion of small nerves (<0.1 mm) was not associated with worse outcomes.[22] Extensive PNI is another microscopic finding that may increase risk of recurrence. A University of Michigan series defined extensive

Table 3
Selected studies of adjuvant radiation therapy for basal cell carcinoma and squamous cell carcinoma

Series	Study Population	Study Design	N	Intervention	Outcomes	Toxicity
Garcia-Serra et al,[14] 2003	Microscopic PNI and clinical PNTS (BCC and SCC)	Retrospective	135	Adjuvant or primary RT (ELS, electrons, MV photons)	5-y LC: 87% (microscopic PNI) vs 55% (clinical PNTS) 5-y LRC: 72% vs 50%	Overall RT complications: 10% (microscopic PNI) vs 33% (clinical PNTS) Soft tissue necrosis: 5.1% vs 9.2% Transient CNS disorder: 0% vs 3% Osteoradionecrosis: 1.7% vs 1.3%
Lin et al,[20] 2013	Clinical PNTS (BCC and SCC)	Retrospective	56	Adjuvant or primary RT (electrons, MV photons)	5-y RFS: 48% (all), 39% (SCC) vs 80% (BCC)	Severe blindness: 4 of 30 (receiving RT to orbit)
Warren et al,[21] 2014	Clinical PNTS (SCC)	Retrospective	50	Adjuvant RT	5-y RFS: 62% 5-y DSS: 75% 5-y OS: 64%	Orbital exenteration: 2 of 50 (eye complications, precluded IMRT)
Carter et al,[22] 2013	Microscopic PNI (SCC)	Retrospective	114	Surgery ± adjuvant RT (18%)	Large-caliber PNI ($\geq$0.1 mm): disease-specific death HR 4.5 and nodal metastasis HR 5.6	Not reported
Sapir et al,[23] 2016	Extensive microscopic PNI (SCC)	Retrospective	102	Adjuvant RT (MV photons with IMRT or 3DCRT, electrons) or observation	RFS: 94% (RT) vs 25% (no RT)	Not reported
Strassen et al,[26] 2017	Recurrent SCC	Retrospective	67	Adjuvant RT or observation	5-y RFS: 78% (RT) vs 30% (no RT) 5-y OS: 79% vs 46%	Not reported
Kim et al,[27] 2018	T3/T4 (BCC and SCC)	Retrospective	71	Adjuvant or primary RT	3-y DSS: 86% (BCC with adjuvant RT), 93% (SCC with adjuvant RT)	Not reported
Manyam et al,[28] 2017	Immuno-suppression (SCC)	Retrospective	205	Adjuvant RT (electrons, MV photons with 3DCRT or IMRT)	2-y PFS: 38.7% (immunosuppressed) vs 71.6% (immunocompetent) 2-y OS: 60.9% vs 78.1%	Not reported

Wang et al,[30] 2012	SCC with nodal metastases	Retrospective	122	Surgery ± adjuvant RT (MV photons, electrons)	5-y DFS: 74% (RT) vs 34% (no RT) 5-y OS: 66% vs 27%	Not reported
Ebrahimi et al,[31] 2012	SCC with nodal metastases (N1)	Retrospective	168	Surgery ± adjuvant RT	(N1 disease) 5-y LRC: 87% (RT) vs 91% (no RT) 5-y DFS: 90% vs 97%	Not reported

Abbreviations: 3DCRT, three-dimensional conformal RT; CNS, central nervous system; DSS, disease-specific survival; HR, hazard ratio; IMRT, intensity-modulated RT; RFS, recurrence-free survival.

Data from Refs.[14,20–23,26–28,30,31]

PNI as involvement of more than 2 nerves.[23] RFS in the nerves (94% vs 25%) and overall DFS (73% vs 40%) were improved with adjuvant RT. In contrast, adjuvant RT did not improve outcomes for focal PNI (1–2 nerves involved).

For positive/close margins not amenable to reexcision, adjuvant RT has been shown to improve RFS (9% relapse with adjuvant RT compared with 57% without, using $\leq$2 mm to define close margins).[24] With conventional excision, surgical margins greater than 4 mm have been recommended (>6 mm if high-risk features are present, based on size, grade, invasion, and location), based on assessment of subclinical tumor extension.[25]

For recurrent disease, adjuvant RT may improve locoregional control, with 1 series noting improved 5-year RFS (78% vs 30%) and OS (79% vs 46%) compared with no adjuvant treatment.[26] Multiple series show that tumor size greater than 2 cm and T3/T4 tumors are associated with high recurrence rates.[18,27] However, with surgery followed by adjuvant RT for SCC, Memorial Sloan Kettering reported 3-year disease-specific survival (DSS) of 92.9%.[27]

Immunosuppression is associated with worse outcomes, even with bimodality therapy. Manyam and colleagues[28] published a retrospective analysis of head and neck SCC receiving surgery and postoperative RT showing that immunosuppressed patients had a worse 2-year locoregional RFS compared with immunocompetent patients (47.3% vs 86.1%) and a trend for worse 2-year OS (60.9% vs 78.1%). Furthermore, desmoplastic histology was strongly associated with LR (HR, 16.11), based on a prospective cohort of SCC undergoing surgery.[29]

In patients with regional lymph node metastases undergoing therapeutic lymphadenectomy, adjuvant RT is recommended for N2 or greater disease. A retrospective series of SCC with nodal metastases showed that adjuvant RT was associated with a higher 5-year DFS than surgery alone (74% vs 34%) and higher 5-year OS (66% vs 27%).[30] However, with a single nodal metastasis less than or equal to 3 cm (N1), 5-year DSS was 97%, making this subgroup suitable for omitting adjuvant RT.[31] For clinically node-negative patients, factors associated with increased risk of metastasis were tumor thickness (HR, 4.79), tumor horizontal size (HR, 2.22), tumor location at ear (HR, 3.61), and immunosuppression (HR, 4.32).[29] Although these risk factors are well defined, the indication for elective nodal irradiation must be balanced against possible toxicities. Thus, ASTRO (American Society for Radiation Oncology) Clinical Practice Guidelines conditionally recommend elective nodal RT when at high risk of nodal metastasis and undergoing RT to the primary site with overlap of an adjacent nodal basin.[2]

Technique for Basal Cell Carcinoma and Squamous Cell Carcinoma

Based on the ASTRO Clinical Practice Guideline, all RT modalities (eg, kilovoltage/megavoltage photons, electrons, brachytherapy) result in similar in LC and cosmesis, supported by multiple retrospective studies.[2,6,7,19] Modality choice should be individualized to specific tumor characteristics and normal tissue constraints. The American Brachytherapy Society (ABS) consensus statement recommends that electronic brachytherapy only be used on a prospective clinical trial or registry, requiring more mature follow-up to understand late toxicity, and recommends radionuclide brachytherapy as an option for T1 to T2 tumors (using radionuclide-based applicators, molds/flaps, or interstitial catheters).[1]

A wide array of appropriate doses and fractionation schemes are appropriate per ASTRO and ABS guidelines.[1,2] With definitive RT, conventional fractionation (1.8–2.0 Gy/fraction) regimens should have a biologically effective dose (BED_{10}) of 70 to 93.5 Gy and hypofractionated (2.1–5.0 Gy/fraction) regimens should have a BED_{10}

of 56 to 88 Gy. With postoperative RT, conventional fractionation (1.8–2.0 Gy/fraction) regimens should have a biologically effective dose (BED_{10}) of 70 to 93.5 Gy and hypofractionated (2.1–5.0 Gy/fraction) regimens should have a BED_{10} of 56 to 88 Gy. Adjuvant RT to nodal basins after lymphadenectomy should be 60 to 66 Gy at 1.8 to 2.0 Gy/fraction and elective nodal RT should typically be 50 to 54 Gy at 1.8 to 2.0 Gy/fraction.

For large-caliber or extensive PNI or clinical/radiographic PNTS, target volumes typically include involved cranial nerve pathways (frequently CN V and CN VII) located retrograde (toward the base of skull).[13] For clinical/radiographic PNTS, volumes should include anterograde coverage (nerve pathways away from the base of skull) and include communicating interconnections between cranial nerves.[13]

CUTANEOUS MELANOMA

Indications for definitive RT include:

- Lentigo maligna or lentigo maligna melanoma in patients who are not candidates for surgery

Discussion

RT is typically not recommended in the definitive management of malignant melanoma. However, definitive RT is considered for lentigo maligna and lentigo maligna melanoma in patients who are not candidates for surgery (**Table 4**). A meta-analysis of 9 studies using definitive RT for lentigo maligna reported a 5% LR (18 recurrences among 349 assessable patients with a median follow-up time of 3 years).[32] Only 5 patients (1.4%) experienced progression to lentigo maligna melanoma. Another retrospective series of lentigo maligna and early lentigo maligna melanoma showed 88% complete clearance after 1 treatment course (involving treatments twice weekly over 3 weeks to total doses for 100–160 Gy using Grenz rays).[33]

Technique

The optimal dose prescription and modality have not been established, although Fogarty and colleagues[32] recommend 54 to 60 Gy in 2-Gy fractions prescribed to a 5-mm depth.

Indications for adjuvant RT include:

- Postoperative bed for desmoplastic histology with high-risk features, which include head and neck location, extensive neurotropism, close margins where re-resection is unfeasible, or locally recurrent disease
- Nodal basins for high-risk features after lymphadenectomy (specifically gross or microscopic extranodal extension, $\geq$1 parotid node, $\geq$2 cervical nodes, $\geq$2–3-cm cervical node size)

Discussion

Although there are no strong indications for adjuvant RT in melanoma (**Table 5**), desmoplastic variants display low predisposition for regional lymph node or distant metastasis, so increased risk of LR may drive morbidity and mortality. A retrospective series of 130 patients with nonmetastatic desmoplastic melanoma (62% located in head and neck) showed a 24% LR rate for surgery alone and 7% for surgery followed by RT (median follow-up of 6.6 years).[34] In tumors with PNI, postoperative RT was associated with improved 10-year LC (91% vs 63%), whereas there was no benefit in tumors without any neurotropism. Another series from Moffitt Cancer Center also

Table 4
Selected studies of primary radiation therapy for melanoma

Series	Study Population	Study Design	N	Intervention	Outcomes	Toxicity
Fogarty et al,[32] 2013	Lentigo maligna	Systematic review	349	ELS (superficial RT and Grenz rays)	Pooled LR: 5%	Not pooled
Hedblad et al,[33] 2012	Lentigo maligna	Retrospective	593	ELS (Grenz rays)	LR: 9.8%	Hypopigmentation: 15% Hyperpigmentation: 20% Severe acute dermatitis: 2%

Data from Fogarty GB, Hong A, Scolyer RA, et al. Radiotherapy for lentigo maligna: a literature review and recommendations for treatment. Br J Dermatol. 2014;170(1):52-58. https://doi.org/10.1111/bjd.12611; and Hedblad M-A, Mallbris L. Grenz ray treatment of lentigo maligna and early lentigo maligna melanoma. J Am Acad Dermatol. 2012;67(1):60-68. https://doi.org/10.1016/j.jaad.2011.06.029.

Table 5
Selected studies of adjuvant radiation therapy for melanoma

Series	Study Population	Study Design	N	Intervention	Outcomes	Toxicity
Guadagnolo et al,[34] 2013	Desmoplastic melanoma	Retrospective	130	Surgery ± adjuvant RT (electrons, MV photons)	Crude LR: 7% (RT) vs 24% (no RT) 10-y LR if PNI present: 91% (RT) vs 63% (no RT)	RT complications: 21% Osteoradionecrosis: 4.2% Nonhealing wound: 2.8%
ANZMTG 01.02/TROG 02.01[36]	High-risk, node-positive melanoma	Randomized controlled trial	217	Arm 1: adjuvant RT Arm 2: observation	LN relapse: 21% (RT) vs 36% (no RT) 5-y OS: 40% vs 45%	Among head and neck sites RT toxicity: All grade 2: 63% All grade 3: 11% All grade 4: 7% Grade 2–4 fibrosis: 54% (RT) vs 34% (no RT) Grades 2–4 pain: 24% vs 10%
Agrawal et al,[38] 2009	High-risk, node-positive melanoma	Retrospective	615	Surgery ± RT	Regional recurrence: 10.2% (RT) vs 40.6% (no RT) 5-y regional control (cervical nodes only): 93% vs 43% 5-y DSS: 51% vs 30%	Grade 2–3 treatment-related morbidity: 16% 5-y treatment-related morbidity: 20% (RT) vs 13% (no RT) 5-y lymphedema rate: 1% (cervical) vs 44% (inguinal)
EORTC 1325 (KEYNOTE-054)[39]	Resected stage III melanoma	Randomized controlled trial	1019	Arm 1: surgery + pembrolizumab Arm 2: surgery + placebo No RT	1-y RFS: 75.4% (pembrolizumab) vs 61.0% (placebo)	Grades 3–5: 14.7% (pembrolizumab) vs 3.4% (placebo)

Abbreviation: EORTC, European Organisation for Research and Treatment of Cancer.
Data from Refs.[34,36,38,39]

showed that adjuvant RT improved LC in the setting of positive margins (LR, 14% vs 54%) or negative margins with high-risk features (head and neck location, Breslow depth >4 mm, Clark level V).[35] Almost all patients in both studies received 30 Gy in 5 fractions (twice weekly over 2.5 weeks). The benefit of adjuvant RT for neurotropic melanoma of the head and neck is currently being investigated in the ongoing ANZMTG (Australia and New Zealand Melanoma Trials Group) 01.09/TROG (Trans-Tasman Radiation Oncology Group) 08.09 (RTN2) randomized trial.

Treatment of the regional lymph nodes can be considered in patients at high risk for nodal recurrence. The benefit was best shown in the ANZMTG 01.02/TROG 02.01 randomized trial of clinically node-positive melanoma with high-risk features after lymphadenectomy (defined as $\geq$1 parotid, $\geq$2 cervical/axillary, $\geq$3 inguinofemoral nodes, extranodal extension, or maximum node diameter $\geq$3 cm for cervical or $\geq$4 cm for an axillary or inguinal node).[36] The risk of nodal relapse was reduced with adjuvant RT (HR, 0.56), but there was no difference in RFS or OS. Longer follow-up (median follow-up 73 months) confirmed a decreased risk of lymph node relapse with adjuvant RT (21% vs 36%; HR, 0.52), again with no difference in RFS or OS.[37]

The decreased rate of nodal relapse was also reported in a large retrospective series from MD Anderson and Roswell Park.[38] In patients with high-risk nodal disease (eg, $\geq$2 cm size of largest cervical node, $\geq$2 cervical nodes, or the presence of extranodal extension), adjuvant RT was associated with a lower regional recurrence rate than lymphadenectomy alone (10.2% vs 40.6%). Furthermore, there was improved 5-year distant metastasis–free survival (43% vs 28%) and DSS (51% vs 30%) with adjuvant RT.

In addition, adjuvant immunotherapy plays an increasing role in the treatment of resected high-risk melanoma.[39] The role of regional nodal RT is unclear in this setting, and further prospective study is needed to determine the population of patients who remain at high risk of locoregional relapse in the setting of immunotherapy.

Technique

When treating the postoperative bed, the recommended fractionation is 30 Gy in 5 fractions delivered twice weekly using either electrons or photons per the MD Anderson series.[34] For regional lymph nodes, the recommended dose is 48 Gy delivered in 20 fractions starting within 12 weeks of lymph node dissection, per the ANZMTG 01.02/TROG 02.01 trial. The treatment volume included the dissected nodal basins and the lymphadenectomy scar. Another regimen used is 30 Gy in 5 fractions delivered twice weekly over 2.5 weeks per the MD Anderson/Roswell Park series.[38]

MERKEL CELL CARCINOMA

Indications for definitive RT include:

- Primary MCC in patients who are not candidates for surgery

Discussion

Primary management of MCC is typically surgical, and definitive RT is reserved for patients that are not surgical candidates. The efficacy of primary RT is supported by small retrospective series (**Table 6**). Gunaratne and colleagues[40] published a meta-analysis of 23 studies encompassing 264 patients showing that primary RT can provide adequate locoregional control. Mean RT dose was 48.7 $\pm$ 13.2 Gy to the primary and 49.4 Gy $\pm$ 10.1 Gy to the regional nodes. Rates of recurrence were 7.6% for primary sites and 16.3% for regional sites.

Table 6
Selected studies of primary radiation therapy for Merkel cell carcinoma

Series	Study Design	N	Intervention	Outcomes	Toxicity
Gunaratne et al,[40] 2017	Systematic review	23 (studies) 332 (sites)	Dose: 49.1 Gy ± 11.7 Gy Primary site RT (51.5%), regional nodal RT (48.2%)	In-field recurrence: 11.7% Primary site recurrence: 7.6% Regional site recurrence: 16.3%	Not reported
Wright and Holtzmann,[41] 2018	NCDB	2454	Primary surgery or primary RT	Median OS (stage I/II): 76 mo (surgery) vs 25 mo (RT) 5-y OS (stage I/II): 61% vs 32% Median OS (stage III): 30 mo vs 15 mo 5-y OS (Stage III): 34% vs 19%	Not reported

Abbreviation: NCDB, National Cancer Database.

Data from Gunaratne DA, Howle JR, Veness MJ. Definitive radiotherapy for Merkel cell carcinoma confers clinically meaningful in-field locoregional control: A review and analysis of the literature. J Am Acad Dermatol. 2017;77(1):142-148.e1. https://doi.org/10.1016/j.jaad.2017.02.015; and Wright GP, Holtzman MP. Surgical resection improves median overall survival with marginal improvement in long-term survival when compared with definitive radiotherapy in Merkel cell carcinoma: A propensity score matched analysis of the National Cancer Database. Am J Surg. 2018;215(3):384-387. https://doi.org/10.1016/j.amjsurg.2017.10.045.

The quality of evidence comparing surgery versus definitive RT is poor, because surgery has been the historical standard of care. In a National Cancer Database (NCDB) analysis comparing surgery (39% receiving postoperative RT) and definitive RT, median OS was better in the surgery group for both stage I/II patients (76 vs 25 months) and stage III disease (30 vs 15 months).[41] However, despite propensity-score matching, surgery was recommended but not performed in only 8% of patients receiving primary RT and the cohorts still differed in terms of primary site of origin and tumor size. The University of Wisconsin also showed a worse OS with nonsurgical management on univariate analysis with HR 4.4 (although limited by a multivariate analysis not being performed).[42]

Technique

The recommended dose regimen is 60 to 66 Gy at 2 Gy/fraction, typically with wide margins (5 cm) and the use of electrons with bolus to optimize skin dose. Retrospective data suggest excellent in-field control with greater than or equal to 55 Gy for gross disease and greater than or equal to 50 Gy for microscopic disease.[43]

Indications for adjuvant RT include:

- Postoperative bed for all cases (although it is reasonable to observe small $\leq$1 cm, low-risk tumors)
- Postoperative bed in the setting of chronic immune suppression, LVSI, or positive margins not amenable to further surgery
- Nodal basins for clinically node-positive disease (with or without lymphadenectomy)
- Nodal basins in the setting of positive sentinel lymph node biopsy (SLNB) but no lymphadenectomy is performed
- Nodal basins for clinically node-negative disease when no SLNB is performed but there is high risk of nodal disease

Discussion

Although limited to heterogeneous retrospective series, adjuvant RT generally decreases LR and may improve progression-free survival (PFS), but improvements in OS are less certain (**Table 7**). The British Columbia Cancer Agency showed that adjuvant RT to the primary site decreased locoregional recurrence in the setting of less than 1-cm margins (5.3% vs 25%).[44] Recurrence rates were low with margins greater than or equal to 1 cm with RT (6.7%) and without RT (7.7%). However, 5-year cancer-specific survival was not improved by adjuvant RT.

Although observation is considered for small low-risk tumors, adjuvant RT may still decrease LR in this group. The University of Washington published a series of low-risk head and neck MCCs (tumor size $\leq$2 cm, negative margins, negative SLNB, and no immunosuppression) where RT significantly decreased LR (0% vs 26%). Still, DSS and OS were not affected.[45] All 6 patients experiencing a recurrence were successfully salvaged (all receiving RT).

Historically, the benefit of elective RT to regional nodal basins in stage I MCC was supported by a French randomized trial, but the ability to generalize to modern practice is limited because this preceded the use of SLNB and PET for staging.[46] Patients were randomized to regional nodal RT or observation. The regional recurrence rate was reduced with adjuvant nodal irradiation (0% vs 16.7%) but there was no difference in PFS or OS. This trial was ultimately closed prematurely because of the widespread adoption of SLNB.

Table 7
Selected studies of adjuvant radiation therapy for Merkel cell carcinoma

Series	Study Population	Study Design	N	Intervention	Outcomes	Toxicity
Harrington and Kwan,[44] 2015	Margins <1 cm	Retrospective	179	Surgery ± adjuvant RT	LR (margin <1 cm): 4.9% (RT) vs 25% (no RT) LR (margin >1 cm): 7.1% (RT did not improve) 5-y DSS: 77% (RT did not improve)	Not reported
Takagishi et al,[45] 2016	Low-risk MCC	Retrospective	46	Surgery ± RT (electrons, MV photons)	LR: 0% (RT) vs 26% (no RT) DSS and OS not improved with RT	Significant late toxicity: 0% (RT)
Jouary et al,[46] 2011	Elective nodal RT for stage I MCC (preceding SLNB era)	Randomized controlled trial	83	Arm 1: surgery + adjuvant RT (primary and nodal) Arm 2: surgery + adjuvant RT (primary only)	Regional recurrence: 0% (nodal RT) vs 16.7% (no nodal RT) 3-y PFS: 89.7% vs 81.2% 3-y OS: 92.3% (nodal RT did not improve)	Grade 1 skin: 19.3% Grade 2 skin: 7.2% Nodal RT did not affect toxicity
Strom et al,[47] 2016	MCC, including node positive	Retrospective	171	Surgery ± adjuvant RT	Node positive: 3-y LC: 91.2% (RT) vs 76.9% (no RT) 3-y LRC: 79.5% vs 59.1% 3-y DSS: 57.0% vs 30.2% 3-y OS: 73% vs 66%	Not reported

Data from Refs.[44–47]

A Moffitt Cancer Center series showed improved 3-year LC (91.2% vs 76.9%), LRC (79.5% vs 59.1%), and OS (73% vs 66%) with adjuvant RT among pathologically node-positive patients.[47] Another small retrospective series showed that nodal RT decreases regional recurrence in node-positive patients (18% vs 33%), which included patients receiving SLNB, SLNB followed by lymphadenectomy, and upfront lymphadenectomy.[48]

Technique

Adjuvant RT should begin as soon as possible (within 4 weeks) because rapid recurrences occur with treatment delays.[49] Dose regimens to the tumor bed are typically 50 to 56 Gy after negative margins, 56 to 60 Gy with microscopic positive margins, and 60 to 66 Gy with grossly positive margins at 2 Gy/fraction. Dose regimens to the regional nodal basins are 60 to 66 Gy for gross lymphadenopathy, 50 to 60 Gy after lymphadenectomy or positive SLNB (with higher doses for extracapsular extension), and 46 to 50 Gy for elective nodal irradiation at 2 Gy/fraction.

SUMMARY

RT plays an integral role in the management of head and neck cutaneous cancers. In BCC and SCC, it shows excellent outcomes in the definitive setting, serving as an appropriate alternative in cosmetically and functionally sensitive areas, or when patient comorbidities preclude safe surgery. Although definitive RT plays a smaller role in melanoma and MCC, adjuvant RT improves locoregional control in specific clinical contexts across BCC, SCC, melanoma, and MCC. These improvements in locoregional control do not always translate to improvements in DSS or OS, which underscores the importance of individualized clinical judgment weighing risks and benefits for each patient. In addition, the wide array of modalities available (ranging from low-energy x-rays to megavoltage electrons or photons to brachytherapy) exemplify the versatile application of RT to cutaneous cancer treatment and inspire many future directions of study.

DISCLOSURES

None.

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