Eric K. Hansen
Mack Roach III *Editors*

Handbook of Evidence-Based Radiation Oncology

3rd Edition

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Eric K. Hansen, MD
The Oregon Clinic
Radiation Oncology
Providence St. Vincent Medical Center
Portland, OR
USA

Mack Roach III, MD, FACR, FASTRO
Professor
Radiation Oncology and Urology
Director
Particle Therapy Research Program & Outreach
Department of Radiation Oncology
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, CA
USA

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Editors
Eric K. Hansen
The Oregon Clinic
Providence St. Vincent Medical Center
Portland, OR,
USA

Mack Roach III
University of California
San Francisco, CA,
USA

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To our patients – thank you for your trust, sharing, and the daily lessons you teach us. You keep us inspired.

Preface to the 3rd Edition

In his 1901 textbook, The Roentgen Rays in Medicine and Surgery, Dr. Francis Williams wrote in his preface, "The following pages are rather a report of progress than a final presentation on a growing subject." Never has that been more true. From 2010 to 2016, over 50,000 articles were published with "radiotherapy" in the title or abstract. Medical knowledge is expanding more rapidly than our ability to keep up and apply it to patient care, research, and education. To cope, we must identify the essential core of best practices for our specialty. Clinical expertise also requires easy access to well-organized knowledge.

In the third edition of Handbook of Evidence-Based Radiation Oncology, we strive to meet these demands. We have kept the same concise format to meet our aim of a practical quick reference guide. All chapters have been carefully revised and include the latest key trials, studies, and techniques. We encourage readers to continue to refer to primary literature for updates on the myriad subtopics not discussed herein.

We are pleased that our third edition is the first radiation oncology text to include the newly published eighth edition of AJCC Cancer Staging Manual. Because most of the literature published in the last 6 years refers primarily to the seventh edition of AJCC Cancer Staging Manual, we include it as well.

Importantly, we appreciate that experienced physicians are very capable of weighing evidence and individualizing care based on it. All patients are unique, so our treatment algorithms and recommendations are not to be considered edicts. Rather, consider our book a framework upon which you build a personalized treatment plan for each patient.

We are extremely grateful to the contributing authors for all their hard work and dedication. We believe Handbook of

Evidence-Based Radiation Oncology will continue to be an invaluable resource for students, resident physicians, fellows, and other practitioners of radiation oncology.

Finally, we owe special thanks to our families for their patience, understanding, and good humor during our many hours of work on this new edition. A round of applause for them!

Eric K. Hansen — Portland, OR, USA
Mack Roach III — San Francisco, CA, USA

Contents

Contributors

Mekhail Anwar, MD, PhD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Eleanor A. Blakely, BA, MS, PhD
Biological System Engineering, Lawrence Berkeley National Laboratory, Berkeley, CA, USA

Lauren Boreta, MD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Steve E. Braunstein, MD, PhD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Jason Chan, MD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Albert J. Chang, MD, PhD
Department of Radiation Oncology, University of California, San Francisco, San Francisco, CA, USA

Jennifer S. Chang, MD, PhD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA
Marin General Hospital, Greenbrae, CA, USA

Christopher H. Chapman, MD, MS
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Serah Choi, MD, PhD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Hans T. Chung, MD, FRCPC
Department of Radiation Oncology, Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada

Michael A. Garcia, MD, MS
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Adam Garsa, MD
Radiation Oncology, University of Southern California, Los Angeles, CA, USA

Alexander R. Gottschalk, MD, PhD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Matthew A. Gubens, MD, MS
Department of Medicine, University of California San Francisco, San Francisco, CA, USA

Daphne A. Haas-Kogan, MD
Department of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute; Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Eric K. Hansen, MD
The Oregon Clinic, Radiation Oncology, Providence St. Vincent Medical Center, Portland, OR, USA

I-Chow J. Hsu, MD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Kavita K. Mishra, MD, MPH
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

John Murnane, PhD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Jean L. Nakamura, MD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Catherine C. Park, MD
Department of Radiation Oncology, UCSF Helen Diller Family Comprehensive Cancer, San Francisco, CA, USA

Anna K. Paulsson, MD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

David R. Raleigh, MD, PhD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Mack Roach III, MD, FACR, FASTRO
Radiation Oncology and Urology, Particle Therapy Research Program & Outreach, Department of Radiation Oncology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

Tracy Sherertz, MD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Lisa Singer, MD, PhD
Radiation Oncology, University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Michael Wahl, MD, MS
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Sue S. Yom, MD, PhD, MAS
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Yao Yu, MD
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

PART I
Skin

Chapter 1
Skin Cancer

Lisa Singer and Sue S. Yom

PEARLS

- Skin is composed of 3 layers: epidermis (melanocytes), dermis (hair follicles, sweat glands), and subcutis.
- Skin cancers can be divided into melanoma and non-melanoma skin cancers; sun/UV exposure is a major cause for both subtypes.
- Skin cancers can also be associated with immunosuppression, chronic irritation, and certain genetic disorders (Jaju, J Am Acad Dermatol 2016):
  - Gorlin syndrome (basal cell nevus syndrome, *PTCH* mutations): autosomal dominant, associated with multiple BCCs, rhabdomyosarcomas, fibrosarcomas, palmar/plantar pits
  - Xeroderma pigmentosum: X-linked, increased sensitivity to UV radiation, 1000× increased risk of skin cancer
- Non-melanoma skin cancers are the most common malignancies in the USA, with millions diagnosed each year, but true incidence is unknown as cases are not required to be reported to cancer registries (Siegel, CA Cancer J Clin 2015).
- Major subtypes of non-melanoma skin cancers include basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and Merkel cell carcinoma (MCC):

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BCC

- 80% of non-melanoma skin cancers; common in sun-exposed areas.
- >90% of cases associated with abnormal hedgehog pathway signaling (Lacouture, Oncologist 2016).
- Pathologic subtypes: nodular (most common, papule); superficial (scaly macule); morpheaform (sclerosing, can have PNI); infiltrative (Veness and Howle 2016).
- Only 0.1% have perineural spread; most common affected CN are V and VII.
- <1% metastasize (Ganti, Cancer Manag Res 2013).

SCC

- Common in sun-exposed areas.
- Actinic keratosis (AK) is a premalignant lesion that can develop into SCC, with multiple AKs, 6–10% chance of invasive SCC in 10 years.
- Pathologic subtypes: SCC in situ (*Bowen's disease*), superficial, spindle cell (may require IHC for diagnosis) (Veness and Howle 2016)
- More frequently metastasizes than BCC: about 5%.

MCC

- Rare, aggressive neuroendocrine cancer of the skin with more frequent local, regional, and distant recurrence rates than other cutaneous carcinomas.
- Cell of origin is Merkel cell (aka Tastzellen or touch cell), a tactile neuroendocrine epithelial cell, first described by Friedrich Sigmund Merkel in 1875 (Erovic and Erovic 2013).
- Merkel cell virus (MCV): polyomavirus, found to be pathogenic factor in 60–80% MCC (Feng, Science 2008).

Cutaneous Melanoma

- Rising incidence.
- Melanoma once viewed as radioresistant, but this is not supported by data.
- "ABCDE" mnemonic raises awareness of suspicious lesions (A = asymmetry, B = borders not smooth, C = color change/variegation, D = diameter > pencil eraser, E = evolving) (Chair, J Am Acad Dermatol 2015).

- Pathologic subtypes: superficial spreading, nodular, lentigo maligna (best prognosis; Hutchinson's freckle involves epidermis only), acral lentiginous (usually presents on soles, palms), desmoplastic (recurs locally).
- 85% of patients (pts) present with localized disease with 5-yr survival >90% for pts with tumor ≤1 mm thick vs 50–90% for pts with primary >1 mm thick depending on thickness, ulceration, and mitotic rate.
- LN status: most prognostic factor for recurrence and survival. In the absence of risk factors, there is <5–7% risk of +SLN if primary <1 mm thick.
- About 10% of pts present with regional disease, with 5-yr. survival 20–70% depending primarily on nodal burden.
- Historically, long-term survival was <10% for stage IV disease, but some pts have a distinct indolent course, and emerging effective systemic therapies have made long-term remission possible in more pts.
- Other prognostic factors: ulceration, thickness, anatomic site (trunk worse), gender (male worse), age (older worse), #LN involved, and mitotic rate.

WORK-UP

- H&P. Describe the primary lesion (see Table 1.1); identify lesion number, location/distribution, borders, color, shape (linear, round, etc.), and any secondary features (scale, induration, erosion, ulceration, etc.). Palpate for the deep edge of the tumor. For head/neck lesions, do a cranial nerve exam. Palpate for lymph node involvement.
- Biopsy the lesion and suspicious lymph nodes.
- Breslow thickness = measured depth of lesion.

Table 1.1 Primary lesion characteristics

Primary lesion characteristics	Size <0.5 cm	Size >0.5 cm
Flat, non-palpable	Macule	Patch
Elevated	Papule	Nodule (plaque is >1 cm, flat topped)
Fluid filled	Vesicle	Bullae
Pus filled	Pustule	Abscess

- Clark level = related to histologic level of dermis (I = epidermis only, II = invasion of papillary dermis, III = filling papillary dermis compressing reticular dermis, IV = invading reticular dermis, V = invades subcutaneous tissues).
- SLN biopsy is typically performed in clinically node-negative patients with MCC or with >0.75 mm thick melanoma.
- Additional imaging: MRI if PNI suspected and for lesions of medial/lateral canthi, to rule out orbit involvement. CT is useful to rule out suspected bone invasion.
- Melanoma: imaging to work-up suspected sites of additional disease.
- PET/CT often ordered for melanoma and MCC due to high rates of metastasis.

BASAL CELL CARCINOMA AND SQUAMOUS CELL CARCINOMA

STAGING

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 2010 AJCC staging nomenclature unless otherwise noted as the new system below was published after this chapter was written (Tables 1.2, 1.3, 1.4, and 1.5).

Table 1.2 (AJCC 7TH ED., 2010)

Primary tumor (T)*	
TX:	Primary tumor cannot be assessed
T0:	No evidence of primary tumor
Tis:	Carcinoma in situ
T1:	Tumor 2 cm or less in greatest dimension with less than two high-risk features**
T2:	Tumor greater than 2 cm in greatest dimension or tumor any size with two or more high-risk features*
T3:	Tumor with invasion of maxilla, mandible, orbit, or temporal bone
T4:	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base

**Note*: Excludes cSCC of the eyelid
**High-risk features for the primary tumor (T) staging
Depth/invasion: >2 mm thickness, Clark level ≥ IV, perineural invasion
Anatomic location: primary site ear, primary site non-hair-bearing lip
Differentiation: poorly differentiated or undifferentiated

Regional lymph nodes (N)	
NX:	Regional lymph nodes cannot be assessed
N0:	No regional lymph node metastases
N1:	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2:	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, not more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, not more than 6 cm in greatest dimension
N2a:	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b:	Metastasis in multiple ipsilateral lymph nodes, not more than 6 cm in greatest dimension
N2c:	Metastasis in bilateral or contralateral lymph nodes, not more than 6 cm in greatest dimension
N3:	Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant metastasis (M)	
M0:	No distant metastases
M1:	Distant metastases

Anatomic stage/prognostic groups	
0:	Tis N0 M0
I:	T1 N0 M0
II:	T2 N0 M0
III:	T3 N0 M0, T1–T3 N1 M0
IV:	T1–T3 N2 M0, T any N3 M0, T4 N any M0, T any N any M1

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Table 1.3 (AJCC 8TH ED., 2017)

Definitions of AJCC TNM	
Definition of primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be identified
Tis	Carcinoma in situ
Tl	Tumor smaller than 2 cm in the greatest dimension
T2	Tumor 2 cm or larger but smaller than 4 cm in the greatest dimension
T3	Tumor 4 cm or larger in maximum dimension or minor bone erosion or perineural invasion or deep invasion*
T4	Tumor with gross cortical bone/marrow, skull base invasion, and/or skull base foramen invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement

*Deep invasion is defined as invasion beyond the subcutaneous fat or> 6 mm (as measured from the granular layer of the adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression

DEFINITION OF REGIONAL LYMPH NODE (N) CLINICAL N (CN)

Table 1.4 (AJCC 8TH ED., 2017)

N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph node metastasis
Nl	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in the greatest dimension and ENE(-)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in the greatest dimension and ENE(-)
	Metastases in multiple ipsilateral lymph nodes, not larger than 6 cm in the greatest dimension and ENE(-),*or* in bilateral or contralateral lymph nodes, not larger than 6 cm in the greatest dimension and ENE(-)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in the greatest dimension and ENE(-)
N2b	Metastasis in multiple ipsilateral nodes, not larger than 6 cm in the greatest dimension and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph nodes, not larger than 6 cm in the greatest dimension and ENE(-)
N3	Metastasis in a lymph node larger than 6 cm in the greatest dimension and ENE(-) *or* metastasis in any node(s) and clinically overt ENE [ENE(+)]
N3a	Metastasis in a lymph node larger than 6 cm in the greatest dimension and ENE(-)
N3b	Metastasis in any node(s) and ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L) Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+)

PATHOLOGICAL N (PN)

Table 1.5 (AJCC 8TH ED., 2017)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
Nl	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in the greatest dimension and ENE(-)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in the greatest dimension and ENE(+), *or* larger than 3 cm but not larger than 6 cm in the greatest dimension and ENE(-), *or* metastases in multiple ipsilateral lymph nodes, not larger than 6 cm in the greatest dimension and ENE(-), *or* in bilateral or contralateral lymph nodes, not larger than 6 cm in the greatest dimension, ENE(-)
N2a	Metastasis in single ipsilateral or contralateral node 3 cm or smaller in the greatest dimension and ENE(+) *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in the greatest dimension and ENE(-)
N2b	Metastasis in multiple ipsilateral nodes, not larger than 6 cm in the greatest dimension and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph nodes, not larger than 6 cm in the greatest dimension and ENE(-)
N3	Metastasis in a lymph node larger than 6 cm in the greatest dimension and ENE(-) *or* in a single ipsilateral node larger than 3 cm in the greatest dimension and ENE(+) *or* multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in the greatest dimension and ENE(-)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in the greatest dimension and ENE(+) *or* multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L) Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+)

DEFINITION OF DISTANT METASTASIS (M)

Table 1.6 (AJCC 8TH ED., 2017)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC PROGNOSTIC STAGE GROUPS

Table 1.7 (AJCC 8TH ED., 2017)

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1	Nl	M0	III
T2	Nl	M0	III
T3	Nl	M0	III
T1	N2	M0	IV
T2	N2	M0	IV
T3	N2	M0	IV
Any T	N3	M0	IV
T4	Any N	M0	IV
Any T	Any N	M1	IV

Used with permission from the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the *AJCC Cancer Staging Manual,* Eighth Edition (2017) published by Springer International Publishing

Table 1.8 NCCN BCC and SCC risk factors for recurrence

High risk	Location (regardless of size): mask areas (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular, postauricular, temple), genitalia, hands, feet. If >1 cm: cheek, forehead, scalp, neck, pretibia. If >2 cm: trunk, extremities
	Border: poorly defined
	Recurrent
	Immunosuppression
	Site of prior RT or chronic inflammation
	BCC subtype: morpheaphorm, basosquamous, sclerosing, micronodular features
	SCC subtype: adenoid, adenosquamous, desmoplastic, metaplastic
	SCC: rapidly growing. Neurologic symptoms. >2 mm depth or Clark level IV–V. PNI or LVSI.
Low risk	None of above

Table 1.9 TREATMENT RECOMMENDATIONS

Localized, low risk	If surgical candidate: curettage and electrodessication (not used for hair-bearing areas), surgical excision, or Mohs micrographic surgery (staged resection with micrographic examination of each horizontal and deep margin), with re-resection for positive margin. Recommended margin: BCC 2–4 mm, SCC 4–6 mm
	RT: if not surgical candidate due to poor functional/cosmetic outcome with resection or re-resection for close/+ margin(s)
	Relative RT contraindications include postradiation recurrence, area prone to repeated trauma such as bony prominences, poor blood supply, high occupational sun exposure, exposed cartilage/bone, Gorlin's, CD4 count <200
	RT contraindicated for xeroderma pigmentosum, basal cell nevus syndrome, scleroderma

Table 1.9 (continued)

Localized, high risk	If surgical candidate: WLE or Mohs. Recommended margin: BCC 4–10 mm, SCC ≥10 mm
	Post-op RT indications: positive margin(s), extensive PNI, or involvement of large-caliber nerves (≥0.1 mm)
	Definitive RT: if not surgical candidate
	Relative RT contraindications as above
Node-positive BCC or SCC	Resection with lymph node dissection
	Post-op RT indicated as above for primary lesions or for nodal ECE or multiple nodes involved. Consider post-op RT vs surveillance for 1 LN involved if <3 cm without ECE
	Inoperable: RT with or without systemic therapy (typically regimens used for head and neck SCC primaries are used) – Results much better for BCC than SCC
Systemic therapy	BCC: Vismodegib and sonidegib are small molecule inhibitors of hedgehog pathway; FDA approved for metastatic BCC and in BCC patients who are not candidates for surgery or RT (Lacouture, Oncologist 2016). About 30–65% response rate with median response duration 7–10 months
	SCC: TROG 05.01 post-op RT +/– concurrent carboplatin, results pending. Cetuximab may sometimes produce tumor regression with unresectable or metastatic SCC. Biochemotherapy or chemotherapy as used in head/neck cancer (e.g., cisplatin or cisplatin/5FU) may be considered

Other topical therapies:

- Imiquimod: topical immunomodulator FDA approved for <2 cm trunk/extremity superficial BCC (5× weekly for 6 weeks) or actinic keratosis (2× weekly for 16 weeks) (Hanna, Int J Dermatol 2016).
- Topical 5-fluorouracil: can be used for superficial BCC or AKs (Moore, J Dermatolog Treat 2009).

STUDIES IDENTIFYING POINTS THAT MAY BENEFIT FROM POST-OP RT

- Review of 1818 cutaneous SCC cases identified 4 risk factors for recurrence: size ≥2 cm, poorly differentiated, PNI (≥0.1 mm nerves), and tumor invasion beyond fat. 10-yr. local recurrence: 0 factors = 0.6%, 1 factor = 5%, 2–3 factors = 21%, 4 factors or bone invasion = 67%. 10-yr nodal mets: 0 factors = 0.1%, 1 factor = 3%, 2–3 factors = 21%, 4 factors or bone invasion = 67% (Karia, JCO 2014).
- 122 pts with cutaneous SCC of head and neck with cervical LN involvement. Post-op RT reduced LRR (23% vs 55%) and improved DFS (74% vs 34%) and OS (66% vs 27%) (Wang, Head Neck 2011).

- Multi-institutional retrospective review of SCC found that immunocompromised status was associated with higher locoregional recurrence (Manyam, IJROBP 2016).

MULTIPLE RETROSPECTIVE STUDIES REPORT EXCELLENT LC WITH RT

- 389 patients with BCC were included in a retrospective study at Washington University in St. Louis; excellent outcomes were achieved for RT alone (LC >90% for tumors <=3 cm treated with SRT and >80% for tumors <=3 cm treated with electrons; for tumors >5 cm treated w/electrons, LC was 100% w/margins >2 cm, 67% for margins 1.1–2 cm, and 80% for margins <=1 cm) (Locke, IJROBP 2001).
- 604 BCCs and 106 SCCs treated with RT. 97% of lesions involved face and head. 18% of lesions were recurrent. 5/15-yr. LC: BCC 94%/85%, SCC 93%/79%. Tumor size >1 cm and nasolabial fold location were independent predictors for BCC recurrence. Recurrent SCC had higher recurrence risk (Hernández-Machin, Int J Dermatol 2007).
- 129 eyelid and 857 lesions overlying nasal cartilage treated with RT, 98% BCC, 2% SCC. 5-yr. LC eyelid 96%, nose 92% (Caccialanza, G Ital Dermatol Venereol 2013).
- 712 BCCs and 994 SCCs treated with RT. 5-yr. LC: BCC 96%, SCC 94%. Tumors >2 cm had increased recurrence risk (Cognetta, J Am Acad Dermatol 2012).

OTHER STUDIES

- *Vismodegib*: ERIVANCE was a single-arm phase II study of vismodegib; of the 33 patients in the study with metastatic BCC, 30% responded; of the 63 with locally advanced BCC, 43% responded (response was defined as a decrease of at least 30% in the externally visible or radiographic dimension of the lesion or complete resolution of ulceration) (Sekulic, NEJM 2012).
- *p16 status*: positive in 31% of SCC but not prognostic in an Australian study of 143 patients with cutaneous SCC of the head and neck (McDowell, Cancer 2016).

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Most skin cancers are treated with superficial radiation therapy (SRT) (50–100 kVp), orthovoltage (150–300 kVp), or with megavoltage electrons (McDermott and Orton 2010).
- SRT advantages (vs electrons): less margin (electrons require additional margin at skin surface), less expensive, maximum dose at surface (vs electrons which have built up and require bolus) (Cognetta and Mendenhall 2013); disadvantages: SRT not appropriate for >1 cm deep lesion.
- For SRT a photon energy is selected, so tumor is encompassed by 90% depth dose (90% IDL: 50 kV [0.7 mm Al] ~1 mm; 100 kV [4–7 mm Al] ~5 mm; 150 kV [0.52 mm Cu] ~1.0 cm).
- At energies below 300 kV, photoelectric effect is dominant, varying with Z^3; bone is high Z due to calcium, and therefore f-factor, or Roentgen to rad conversion, is important (note that cartilage is not similar to bone in terms of absorption) (Atherton, Clin Oncol 1993).
- Lead shields should be used to block the lens, cornea, nasal septum, oral cavity, etc.; backscattered electrons/photons can lead to conjunctival/mucosal irritation; therefore, for eyelids, thin coating of wax or porcelain can be used over lead.
- Margins
  - Orthovoltage: Tumor size <2 cm = 0.5–1.0 cm horizontal margin; tumor size >2 cm = 1.5–2 cm horizontal margin. Deep margin should be at least 0.5 cm deeper than the suspected depth of tumor.
  - Electron margins: Add additional 0.5 cm margin at skin surface due to lateral constriction of isodose curves in deep portion of tumor volume, respecting adjacent normal tissues such as orbit.
  - Recurrent and morpheaform BCCs are more infiltrative, requiring 0.5–1.0 cm additional margin at skin surface.
  - High-risk SCC: Add 2 cm margin around tumor if possible.

- Gross or extensive PNI: consider IMRT to cover named nerve from the primary to skull base.
  - Recommend careful review of target volumes following cranial nerves V and/or VII as appropriate (Anwar, Pract Radiat Oncol 2016; Gluck, IJROBP 2009).
- Elective nodal treatment should be considered for recurrences after surgery and is indicated for poorly differentiated, >3 cm tumors, and/or large infiltrative-ulcerative SCC.
- Irradiation of a *graft* should not begin until after it is well healed; entire graft should be included in the target volume.

DOSE PRESCRIPTIONS

- For SRT or orthovoltage prescribe to surface $D_{max.}$
- For electrons, prescribe to 90% to account for lower RBE.
- Fractionation
  - Size <2 cm: 64 Gy/32 fx, 55 Gy/20 fx, 45–51 Gy/15–17 fx, 40–44 Gy/10 fx, 35 Gy/5 fx.
  - Size >2 cm and no cartilage involvement: 55 Gy at 2.5 Gy/fx.
  - Size >2 cm and cartilage involved: 64–66 Gy at 2 Gy/fx.
  - While treating cartilage, always keep daily dose <3 Gy/fx.
  - Hypofractionation reduces long-term cosmesis but is an option for selected patients or for palliative treatment.
  - Elective LN (high-risk SCC; rarely BCC): 50 Gy/25 fx.
  - Grossly involved LN 66–70 Gy at 2 Gy/fx:
    - Post-op adjuvant
    - Primary negative margins: 60 Gy/30 fx or 50 Gy/20 fx
    - Primary, +margin: as primary definitive
  - LN: 50–56 Gy at 2 Gy/fx if no ECE; 60 Gy if ECE.
- Electronic surface brachytherapy: 5 Gy/fraction given twice a week to 40 Gy.

DOSE LIMITATIONS

- Cartilage: Chondritis rare if fraction size <3 Gy.
- Skin: Larger volumes of tissue require smaller daily fractions; moist desquamation is expected for larger surface areas.

COMPLICATIONS

- Telangiectasias, skin atrophy, hypopigmentation, alopecia, loss of sweat glands, skin necrosis (~3%), osteoradionecrosis (~1%), chondritis/cartilage necrosis (rare if fx <3Gy)

FOLLOW-UP (BASED ON NCCN GUIDELINES)

- BCC: H&P every 6–12 months for life with sun protection education
- Localized SCC: H&P every 3–12 months × 2 years, then every 6–12 months × 3 years, then annually; sun protection education
- Regionally metastatic SCC: H&P every 1–3 months × 1 year, then every 2–4 months × 1 year, then every 4–6 months × 3 years, then every 6–12 months long term; sun protection education

MERKEL CELL CARCINOMA (MCC)

Table 1.10 Staging (AJCC 7TH ED., 2010): Merkel cell carcinoma

Primary tumor (T)	
TX:	Primary tumor cannot be assessed
T0:	No evidence of primary tumor (e.g., nodal/metastatic presentation without associated primary)
Tis:	In situ primary tumor
T1:	Less than or equal to 2 cm maximum tumor dimension
T2:	Greater than 2 cm, but not more than 5 cm maximum tumor dimension
T3:	Over 5 cm maximum tumor dimension
T4:	Primary tumor invades bone, muscle, fascia, or cartilage

Table 1.10 (continued)

Regional lymph nodes (N)	
NX:	Regional lymph nodes cannot be assessed
N0:	No regional lymph node metastasis
cN0:	Nodes negative by clinical exam* (no pathologic node exam performed)
pN0:	Nodes negative by pathologic exam
N1:	Metastasis in regional lymph node(s)
N1a:	Micrometastasis**
N1b:	Macrometastasis***
N2:	In-transit metastasis****

**Note*: Clinical detection of nodal disease may be via inspection, palpation, and/or imaging
**Micrometastases are diagnosed after sentinel or elective lymphadenectomy
***Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or needle biopsy
****In-transit metastasis: a tumor distinct from the primary lesion and located either (1) between the primary lesion and the draining regional lymph nodes or (2) distal to the primary lesion

Table 1.11 (AJCC 7TH ED., 2010)

Distant metastasis (M)	
M0:	No distant metastasis
M1:	Metastasis beyond regional lymph nodes
M1a:	Metastasis to skin, subcutaneous tissues, or distant lymph nodes
M1b:	Metastasis to lung
M1c:	Metastasis to all other visceral sites

ANATOMIC STAGE/PROGNOSTIC GROUPS

Patients with primary Merkel cell carcinoma with no evidence of regional or distant metastases (either clinically or pathologically) are divided into two stages: Stage I for primary tumors ≤2 cm in size and stage II for primary tumors >2 cm in size. Stages I and II are further divided into A and B substages based on the method of nodal evaluation

Patients who have pathologically proven node-negative disease (by microscopic evaluation of their draining lymph nodes) have improved survival (substaged as A) compared with those who are only evaluated clinically (substaged as B). Stage II has an additional substage (IIC) for tumors with extracutaneous invasion (T4) and negative node status, regardless of whether the negative node status was established microscopically or clinically. Stage III is also divided into A and B categories for patients with microscopically positive and clinically occult nodes (IIIA) and macroscopic nodes (IIIB). There are no subgroups of stage IV Merkel cell carcinoma

Table 1.12 (AJCC 7TH ED., 2010)

0:	Tis N0 M0
IA:	T1 pN0 M0
IB:	T1 cN0 M0
IIA:	T2/T3 pN0 M0
IIB:	T2/T3 cN0 M0
IIC:	T4 N0 M0
IIIA:	Any T N1a M0
IIIB:	Any T N1b/N2 M0
IV:	Any T Any N M1

Used with the permission from the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer Science + Business Media

Table 1.13 (AJCC 8TH ED., 2017)

Definitions of AJCC TNM	
Definition of primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed (e.g., curetted)
T0	No evidence of primary tumor
Tis	In situ primary tumor
T1	Maximum clinical tumor diameter ≤ 2 cm
T2	Maximum clinical tumor diameter > 2 but ≤ 5 cm
T3	Maximum clinical tumor diameter > 5 cm
T4	Primary tumor invades the fascia, muscle, cartilage, or bone

DEFINITION OF REGIONAL LYMPH NODE (N) CLINICAL (N)

Table 1.14 (AJCC 8TH ED., 2017)

N category	**N criteria**
NX	Regional lymph nodes cannot be clinically assessed (e.g., previously removed for another reason or because of body habitus)
N0	No regional lymph node metastasis detected on clinical and/or radiologic examination
N1	Metastasis in regional lymph node(s)
N2	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin or distal to the primary tumor) *without* lymph node metastasis
N3	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin or distal to the primary tumor) *with* lymph node metastasis