Handbook of Evidence-Based Radiation Oncology

2nd Edition

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Dedication

To Keith Hansen – Compassionate and dedicated physician; loving husband, father, and grandfather. You were larger than life!

Preface to the 2nd Edition

The first edition of *Handbook of Evidence-Based Radiation Oncology* was extremely successful and well received by the worldwide oncology community. In the second edition, we have kept the same concise format in order to remain a practical quick reference guide. Yet we have also added new content and features based on the valuable feedback from readers. All chapters have been revised and include the latest key studies and radiotherapy techniques. Color figures are included for the first time. Three new chapters have been written, including management of the neck and unknown primary of the head and neck, urethral cancer, and clinical radiobiology and physics. An appendix on use of IV contrast has been added as well.

We are particularly pleased that our second edition includes the newly published 2010 AJCC and 2008 FIGO staging systems. We recognize that there will be a transition period in which the previous staging systems will continue to be widely used. For this reason and at the AJCC's specific demand, the previous staging systems are included as well.

We have again strived to maintain a balance of including the most important information for practitioners while also limiting the size of the handbook so that it did not become a full-sized textbook. As before, we strongly encourage readers to refer to the primary literature for further details and references not included here. Although this handbook provides treatment algorithms and suggestions, it remains the professional responsibility of the practitioner, relying on experience and knowledge of the patient, to determine the best treatment for each individual.

We are grateful to all the contributing authors, including multiple new ones, for 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.

Last, we owe special thanks to our families for their patience during our work on this new edition.

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

Preface to the Ist Edition

Management of patients in radiation oncology is constantly evolving as the medical literature continues to grow exponentially. Our practices have become increasingly evidence-based. In this setting, it is critical to have a practical and rapid reference. The *Handbook of Radiation Oncology* is designed with this purpose in mind.

Each clinical chapter is organized in a concise manner. First, important "pearls" of epidemiology, anatomy, pathology, and presentation are highlighted. The key facets of the work-up are then listed followed by staging and/or risk classification systems. Treatment recommendations are provided based on stage, histology, and/or risk classification. Brief summaries of key trials and studies provide the rationale for the treatment recommendations. Practical guidelines for radiation techniques are described. Finally, complications of treatment and follow-up guidelines are listed.

This handbook grew out of a practical need for a rapid reference for students, resident physicians, fellows, and other practitioners of radiation oncology. To be concise and portable, we limited the potential pages and pages of references that could have been included in the handbook (so that it did not become a textbook). Numerous sources were used to compile the information in each chapter, including the primary literature, each of the outstanding radiation oncology reference books (*Textbook of Radiation Oncology, Principles and Practice of Radiation Oncology, Radiation Oncology Rationale Technique Results, Clinical Radiation Oncology*, and *Pediatric Radiation Oncology*), the National Comprehensive Cancer Network Guidelines (at www.nccn.org), the National Cancer Institute's Physician Data Query Cancer Information Summaries (at www.cancer.gov), the American Society for Therapeutic Radiology and Oncology Annual Meeting Educational Sessions, and the notes of the radiation oncology residents at UCSF. Because a lengthy book could easily be written for many of the individual chapters, readers are encouraged to refer to the primary literature and the sources listed above for further details and references not listed in this handbook.

The handbook provides guidelines and suggestions, but it cannot replace the experience of clinicians skilled in the art of radiation oncology. It is the professional responsibility of the practitioner, relying on experience and knowledge of the patient, to determine the best treatment for each individual. Moreover, changes in care may become necessary and appropriate as new research is published, clinical experience is expanded, and/or changes occur in government regulations.

We thank all the contributors for their hours of hard work. We owe them a debt of gratitude for their excellent chapters and their promptness that made the task of editing this handbook much easier.

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PART I
Skin

Chapter 1
Skin Cancer

Tania Kaprealian, James Rembert, Lawrence W. Margolis, and Sue S. Yom

COMMON SKIN CARCINOMAS

PEARLS

- Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of skin are the most common malignancies in the US.
- Greater than one million unreported cases of BCC and SCC occur annually.
- Main histologic types: BCC (65%), SCC (35%), adnexal (5%), melanoma (1.5%).
- More common in men (4:1).
- Median age: 68 (SCC and BCC).
- Most common predisposing factor: UV exposure.
- Other predisposing factors: chronic irritation, trauma, occupational exposure, genetic disorders (phenylketonuria, basal cell nevus syndrome [Gorlin's], xeroderma pigmentosum, giant congenital nevi), immunosuppression (drug-induced, leukemia/lymphoma, HIV).
- Common routes of spread: lateral and deep along path of least resistance, perineural invasion (60–70% are asymptomatic), and regional LN.
- *Basal cell carcinoma.*
  - Pathologic subtypes: nodulo-ulcerative (50%), superficial (33%), morpheaform (sclerosing), infiltrative, pigmented, fibroepithelial tumor of Pinkus, and basosquamous (rare, almost always on face, metastatic rate same as SCC).
  - Only 0.1% perineural spread (mostly with recurrent, locally advanced, after irradiation failure), and "skip areas" common.
  - Most common CN affected: V and VII.
  - Grow very slowly and <0.01% metastasize (regional LN (66%) > lung, liver, bones (20%)).

- *Squamous cell carcinoma.*
  - Pathologic subtypes: *Bowen's disease (CIS)* grows slowly as a sharply demarcated plaque, and is treated with surgery, cryotherapy, topical 5-FU, or RT (40 Gy/10 fx). *Erythroplasia of Queyrat* is Bowen's of the penis. *Marjolin's Ulcer* is SCC within a burn scar. *Verrucous* carcinoma is low grade, exophytic, and often anogenital, oral, or on the plantar surface of the foot. *Spindle cell* presents most commonly on sun-exposed areas of whites >40-year old.
  - Approximately 7% PNI (associated with nodal involvement and base of skull invasion).
  - Nodal involvement.
    - Well differentiated: 1%.
    - Poorly differentiated, recurrent, >3 cm greatest dimension, >4 mm depth, or located on lips: 10%.
    - Located on burn scars/osteomyelitic site: 10–30%.
  - Distant Mets: 2% to lung, liver, bones.
    - Factors that determine distant mets: anatomic site, duration and size of lesion, depth or dermal invasion, and degree of differentiation.
  - SCC originating from normal appearing skin vs. sun-damaged skin appears to invade more rapidly and has greater incidence of metastases.
- *Adnexal and eccrine carcinomas* of the skin are more aggressive than SCC with propensity for nodal and hematogenous spread.
- *Melanoma and Merkel cell carcinomas* will be briefly discussed after the following discussion of SCC/BCC.

WORKUP

- H&P. Palpate for nonsuperficial extent of tumor. For head/face lesions, do a detailed CN exam. Evaluate regional LN.
- Biopsy.
- CT or MRI for suspected nodal involvement. 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.

STAGING: NONMELANOMA SKIN CARCINOMA

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 2002 AJCC staging nomenclature unless otherwise noted as the new system below was published after this chapter was written.

(AJCC 6TH ED., 2002)

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
- T2: Tumor more than 2 cm, but not more than 5 cm, in greatest dimension
- T3: Tumor more than 5 cm in greatest dimension
- T4: Tumor invades deep extradermal structures (i.e., cartilage, skeletal muscle, or bone)

Regional lymph nodes (N)

- NX: No regional lymph node metastasis can be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

Distant metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

Note: In case of multiple simultaneous tumors, the tumor with the highest T category will be classified and the number of separate tumors will be indicated in parentheses, e.g., T2 (5).

Stage grouping		~5-Year local control
0:	TisN0M0	All comers: Mohs 99%, other tx ~90%
I:	T1N0M0	RT for SCC: T1 98%, T2 80%, T3 50%
II:	T2–3N0M0	RT for BCC: up to 5–10% better than SCC
III:	T4N0M0, AnyTN1M0	
IV:	M1	

(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 nonhair-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

continued

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

TREATMENT RECOMMENDATIONS

- Six major therapies: cryotherapy, curettage/electrodesiccation, chemotherapy, surgical excision, Mohs micrographic surgery, and RT
- Treatment indications
  - *Cryotherapy*: small, superficial BCC, and well-differentiated SCC with distinct margins
  - *Curettage and electrodesiccation*: same indications as cryotherapy, but typically not used for recurrences or cancers overlying scar tissue, cartilage, or bone
  - *Chemotherapy*
    - *Imiquimod or topical 5-FU*: premalignant or superficial lesions confined to epidermis, or large superficial areas of actinic keratosis
    - *Systemic:* not typically used but PR 60–70%, CR 30%
  - *Surgical excision*: reconstructive advances have made more patients surgical candidates
  - *Mohs micrographic surgery*: maximal skin sparing through staged micrographic examination of each horizontal and deep margin; if persistent positive margins or perineural invasion should be followed by post-op RT
  - *RT:* typically recommended for primary and recurrent lesions of the central face >5 mm (especially for the eyelids, tip/ala of the nose, and lips) and large lesions (>2 cm) on the ears, forehead, and scalp that would potentially have poor functional and cosmetic outcomes after Mohs
- Positive margins after excision
  - One-third BCC recur if lateral margin + and >50% if deep margin+
  - Most SCC recur at + margin and can recur loco-regionally with <50% salvage rate if LN+
  - Both types should be retreated with reexcision or radiotherapy if + margin. For SCC, retreatment should be done immediately
- *Post-op RT indications*: + margins, PNI of named nerve, >3 cm primary, extensive skeletal muscle invasion, bone/cartilage invasion, and SCC of the parotid
- *Relative RT contraindications*: age <50 (cosmetic results worsen over time), postradiation recurrences (suboptimal salvage rates with reirradiation – use Mohs), area prone to repeated trauma (dorsum of hand, bony prominence, belt line), poor blood supply (below knees/elbows), high occupational sun exposure, impaired lymphatics, exposed cartilage/bone, Gorlin's syndrome, CD4 count <200

continued

- Approximately 5-year local control
  - All comers: Mohs 99%, other treatment(tx)~90%
  - RT for SCC: T1 98%, T2 80%, T3 50%
  - RT for BCC: up to 5–10% better than SCC

RADIATION TECHNIQUES
SIMULATION AND FIELD DESIGN

- Superficial/orthovoltage X-rays and megavoltage electrons are most commonly used to cure skin cancers.
- Orthovoltage advantages: less margin on skin surface, less expensive than electrons, D_{max} at skin surface, skin collimation with lead cutout (0.95 mm Pb for <150 kV beam; 1.9 mm Pb for >150 kV beam).
- Most common orthovoltage energies: 50, 100, 150, 200, 250, 300 kV; must specify filter/HVL.
- Select an energy so that the 90% depth dose encompasses tumor (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).
- Orthovoltage is not appropriate for >1 cm deep lesions.
- *f* factor (roentgen-rad conversion): increases dramatically below 300 kV which can lead to much higher dose to tissue with high atomic number (e.g., bone). Thus, if carcinomas invade bone, megavoltage beams give a more homogeneous distribution. There is little variation in dose delivered to cartilage, regardless of orthovoltage energy.
- Must specify filtration (HVL's) in orthovoltage beams; generally choose thickest filter providing a dose rate >50 cGy/min (Al typically for 50/100 kV and Cu for higher energy; now most machines provide only one filter per energy).
- RBE of orthovoltage X-rays is 10–15% higher than RBE of megavoltage electrons/photons, so must raise daily and total doses by 10–15% with megavoltage electrons/photons compared to suggested orthovoltage doses.
- Lead shields should be used to block the lens, cornea, nasal septum, teeth, etc. as appropriate.
- Backscattered electrons/photons can lead to conjunctival/mucosal irritation. For eyelids, thin coating of dental acrylic/wax should be used; for other areas, a thicker coating should be applied.
- General orthovoltage margins.

- 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.
- Additional margin is needed in these circumstances.
  - *Electrons*: lateral constriction of isodose curves in deep portion of tumor volume increases with decreasing field sizes, so add 0.5 cm additional margin at skin surface.
  - *Recurrent and morpheaform BCC*: infiltrate more widely, so add extra 0.5–1.0 cm margin at skin surface.
  - *High-risk SCC*: 2 cm margin around tumor should be used if possible, and consider including regional LN.
  - *PNI*: if present, include named nerve retrograde to the skull base. Consider IMRT.
- Nodal treatment should be considered for recurrences after surgery and is indicated for poorly differentiated, >3 cm tumors, and/or large infiltrative-ulcerative SCC; consider IMRT depending on anatomy.
- Irradiation of a *graft* should not begin until after it is well-healed and healthy (usually 6–8 weeks), and the entire graft should be included in the target volume.

DOSE PRESCRIPTIONS (ORTHOVOLTAGE)

- Less than 2 cm: 3 Gy/fx to 45–51 Gy
- >2 cm (no cartilage involvement): 2.5 Gy/fx to 50–55 Gy
- >2 cm (cartilage involved): 2 Gy/fx to 60–66 Gy
- For electrons, add 10–15% to the daily and total dose to account for lower RBE. While treating cartilage, always keep daily dose <3 Gy/fx
- Prescription points: orthovoltage = D_{max}, electrons = D_{max} or 95%

SPECIAL RECOMMENDATIONS BY ANATOMIC SITE

- Dorsum of hand and feet
  - Generally, avoid RT at these locations due to high risk of necrosis due to repeated trauma to the region. If ≤4 mm in thickness, radioactive surface molds can be used.
  - As a rule, lesions beyond elbow and knees are at risk of poor healing and ulceration after RT due to poor vascular supply, especially for elderly.
- Eyelid
  - Surgery preferred for lesions 5 mm or less.
  - Radiation is very effective for lesions 0.5–2 cm. With lead shielding, the lens dose is negligible as is the risk of

RT-induced cataracts. Ophthalmic anesthetic drops are applied prior to insertion of shield.
  - Ectropion/epiphora can occur regardless of treatment modality. Fifty percent are improved with corrective surgery.
  - Mild conjunctivitis can occur due to the use of eye-shields and from RT.
  - Lacri-Lube ophthalmic ointment can improve burning/pruritis.
  - For tumors of 0.5–2 cm, recommended dose is 48 Gy/16 fx over 3.5 weeks with 100 kV/0.19 mmCu or equivalent.
- Lip
  - RT/Mohs/surgery are all good options.
  - Place lead shield behind lip to shield teeth/mandible.
  - For tumors <2.0 cm, recommended dose is 48 Gy/16 fx using 150 kV X-rays with 0.52 mm Cu HVL or 6–9 MeV electrons with appropriate bolus. Energy selection may vary depending on the depth of the lesion being treated, see above.
  - Include neck nodes if SCC recurrent, grade 3, >3 cm greatest dimension, or >4 mm thickness.
- Nose and ear
  - Place wax covered lead strip in nose to prevent irritation.
  - Include nasolabial fold for nasal ala lesions.
  - Use wax bolus on irregular surfaces for homogeneity.
  - For tumors 0.5–2.0 cm, recommended dose is 52.8 Gy/16 fx over 3.5 weeks with electrons or 45–51 Gy/15–17 fx using orthovoltage.
  - Selection of electron and orthovoltage energy will depend on the depth of the lesion, see above.

DOSE LIMITATIONS

- Cartilage: chondritis rare if <3 Gy/day given.
- Skin: larger volumes of tissue do not tolerate radiation as well, and thus, require smaller daily fractions; moist desquamation is expected.
- Bone: see *f* factor discussion above.

COMPLICATIONS

- Telangectasias, skin atrophy, hypopigmentation, skin necrosis (~3%), osteoradionecrosis (~1%), chondritis/cartilage necrosis (rare if fx <300 cGy/day), hair loss/ loss of sweat glands.

FOLLOW-UP (ADAPTED FROM NCCN 2009 RECOMMENDATIONS)

- BCC: H&P, complete skin exam q6–12 months for life
- SCC localized: H&P q3–6 months for 2 years, then q6–12 months for 3 years, then q1 year for life
- SCC regional: H&P q1–3 months for year 1, then q2–4 months for year 2, then q4–6 months for years 3–5, then q6–12 months for life

MERKEL CELL CARCINOMA (MCC)

- Rare, deadly (mortality rate > melanoma), neuroendocrine malignancy of the skin
- No consensus on management due to lack of randomized data to compare treatment modalities
- Prior to publication of the new AJCC 7th Ed staging (below), many institutions (including UCSF) use a simpler system: Stage I = localized (IA ≤2 cm; IB >2 cm); II = LN+; III = DM

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

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.

continued

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
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

- Local recurrences common (postsurgery alone ~75%, with adjuvant RT ~15%).
- Approximately 20% have + LN at diagnosis, and sentinel LN biopsy is rapidly becoming the standard means of assessing nodal status and should be performed before resection of the primary site.
- Distant metastases develop in 50–60% of cases, usually within 10 months of diagnosis.
- Role of chemotherapy is unclear, but with the high rate of DM, it is occasionally given either concurrently or after RT. Platinum-based regimens similar to those for SCLC are commonly used (cisplatin or carboplatin with etoposide or irinotecan).
- The UCSF approach to radiotherapy for MCC is as follows:
  - Clinically N0 nodes: 45–50 Gy/1.8–2.0 Gy fx
  - Microscopic disease/–margins: 45–50 Gy/1.8–2.0 Gy fx
  - Microscopic disease/+ margins: 55–60 Gy/1.8–2.0 Gy fx
  - Macroscopic disease: 55–60 Gy/1.8–2.0 Gy fx
  - Cover primary site, in-transit lymphatics, regional LN with wide margins

  - May consider eliminating RT to regional LN if small primary cancer with negative SLN, or if regional LND performed for positive SLN, but patient cN0
  - Margins on primary site = 2 cm in head and neck, 3–5 cm elsewhere depending on site
- Three-year DSS for local/regional disease ~75%.
- Three-year OS: localized ~70–80%, nodal metastasis ~50–60%, distant metastasis ~30%.
- Data suggest almost no MCC-related deaths occur after 3 years from diagnosis.

FOLLOW-UP (ADAPTED FROM NCCN 2009 RECOMMENDATIONS)

- q1–3 months for year 1, q3–6 months for year 2, then annually for life.

MELANOMA

PEARLS

- Incidence increased by 1,800% from the 1930s and increasing 3.1% per year 1992–2004. Rising incidence not due to increased surveillance or changes in diagnostic criteria. 1/87 Americans will be diagnosed with melanoma.
- Mainly Caucasians. Caucasian:African American: 10:1.
- 62,480 new cases and 8,420 deaths from melanoma in 2008.
- Fifteen percent derive from preexisiting melanocytic nevi.
- Less than 10% develop in noncutaneous sites.
- Gender difference in predominant locations: M = trunk, F = extremities.
- Approximately 15% have + LN at diagnosis (~5% for T1, ~25% for >T1).
- Approximately 5% have DM at diagnosis (1/3 with no evidence of primary).
- Subtypes: superficial spreading (~65%), nodular (~25%), lentigo maligna (least common – 7%), acral lentiginous (5% in whites, but most common form in dark-skinned populations).
- Lentigo maligna has the best prognosis with LN mets in only 10% cases, and 10-year OS 85% after WLE alone. Hutchinison's freckle = lentigo maligna involving epidermis only.
- Acral lentiginous generally presents on palms, soles, or subungual.

- Most powerful prognostic factor for recurrence and survival: sentinel LN status.
- >20% chance of involved sentinel LN if melanoma is >2 mm thick.
- ≥20% risk of regional recurrence in those with involved regional LN treated with surgery alone, especially with ECE or multiple LN involvement.
- Other prognostic factors: ulceration, thickness (Breslow = measured depth, Clark = related to histologic level of dermis), anatomic site (trunk worse), gender (male worse), age (young better), number of nodes.
- ABCD rule outlining warning signs of most common type of melanoma: A – asymmetry, B – border irregularity, C – color, D – diameter > 6 mm.
- Clark levels: I = epidermis only, II = invasion of papillary dermis (localized), III = filling papillary dermis compressing reticular dermis, IV = invading reticular dermis, V = invades subcutaneous tissues.

WORKUP

- Less than 1 mm thick lesions – same as for SCC/BCC
- >1 mm thick lesions – need CBC, LFTs, CXR, evaluation of suspicious nodes, pelvic CT if inguino-femoral adenopathy

STAGING: MELANOMA

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 2002 AJCC staging nomenclature unless otherwise noted as the new system below was published after this chapter was written.

(AJCC 6TH ED., 2002)

Primary tumor (T)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Melanoma in situ
T1: Melanoma ≤1.0 mm with or without ulceration
- T1a: Melanoma ≤1.0 mm in thickness and level II or III, no ulceration
- T1b: Melanoma ≤1.0 mm in thickness and level IV or V, or with ulceration

T2: Melanoma 1.01–2.0 mm in thickness with or without ulceration
- T2a: Melanoma 1.01–2.0 mm in thickness, no ulceration
- T2b: Melanoma 1.01–2.0 mm in thickness, with ulceration

T3: Melanoma 2.01–4.0 mm in thickness with or without ulceration
- T3a: Melanoma 2.01–4.0 mm in thickness, no ulceration
- T3b: Melanoma 2.01–4.0 mm in thickness, with ulceration

T4: Melanoma greater than 4.0 mm in thickness with or without ulceration
- T4a: Melanoma >4.0 mm in thickness, no ulceration
- T4b: Melanoma >4.0 mm in thickness, with ulceration

Regional lymph nodes (N)

NX: No regional lymph node metastasis can be assessed
N0: No regional lymph node metastasis
N1: Metastasis in one lymph node
- N1a: Clinically occult (microscopic) metastasis
- N1b: Clinically apparent (macroscopic) metastasis

N2: Metastasis in 2–3 regional nodes or intralymphatic regional metastasis
- N2a: Clinically occult (microscopic) metastasis
- N2b: Clinically apparent (macroscopic) metastasis
- N2c: Satellite or in-transit metastasis without nodal metastasis

(AJCC 7TH ED., 2010)

Primary tumor (T)

TX: Primary tumor cannot be assessed (e.g., curettaged or severely regressed melanoma)
T0: No evidence of primary tumor
Tis: Melanoma in situ
T1: Melanomas 1.0 mm or less in thickness
T2: Melanomas 1.01–2.0 mm
T3: Melanomas 2.01–4.0 mm
T4: Melanomas more than 4.0 mm

Note: a and b subcategories of T are assigned based on ulceration and number of mitoses per mm² as shown below.

T classification	*Thickness (mm)*	*Ulceration status/mitoses*
T1	≤1.0	a) Without ulceration and mitosis <1/mm² b) With ulceration or mitoses ≥1/mm²
T2	1.01–2.0	a) Without ulceration b) With ulceration
T3	2.01–4.0	a) Without ulceration b) With ulceration
T4	>4.0	a) Without ulceration b) With ulceration

Regional lymph nodes (N)

NX: Patients in whom the regional nodes cannot be assessed (e.g., previously removed for another reason)
N0: No regional metastases detected

continued