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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Basal Cell Skin Cancer

Version 1.2022 — November 17, 2021

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Basal Cell Skin Cancer

Chrysalyne D. Schmults, MD, MS/Chair ϖ ¶
Dana-Farber/Brigham and Women's
Cancer Center

Rachel Blitzblau, MD, PhD/Vice Chair §
Duke Cancer Institute

Sumaira Z. Aasi, MD ϖ
Stanford Cancer Institute

Murad Alam, MD, MBA, MSCI ϖ ¶ ζ
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

James S. Andersen, MD ¶ Ÿ
City of Hope National Medical Center

Brian C. Baumann, MD §
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Jeremy Bordeaux, MD, MPH ϖ
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer
Center and Cleveland Clinic Taussig
Cancer Institute

Pei-Ling Chen, MD, PhD ≠
Moffitt Cancer Center

Robert Chin, MD, PhD §
UCLA Jonsson Comprehensive Cancer Center

Carlo M. Contreras, MD ¶
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Dominick DiMaio, MD ≠
Fred & Pamela Buffett Cancer Center

Jessica M. Donigan, MD ϖ
Huntsman Cancer Institute
at the University of Utah

Jeffrey M. Farma, MD ¶
Fox Chase Cancer Center

Maxwell A. Fung, MD ϖ ≠
UC Davis Comprehensive Cancer Center

Karthik Ghosh, MD Þ
Mayo Clinic Cancer Center

Roy C. Grekin, MD ϖ ¶
UCSF Helen Diller Family
Comprehensive Cancer Center

Kelly Harms, MD, PhD ϖ
University of Michigan Rogel Cancer Center

Alan L. Ho, MD, PhD †
Memorial Sloan Kettering Cancer Center

Ashley Holder, MD ¶
O'Neal Comprehensive Cancer Center at UAB

John Nicholas Lukens, MD §
Abramson Cancer Center at the
University of Pennsylvania

Theresa Medina, MD †
University of Colorado Cancer Center

Kishwer S. Nehal, MD ϖ ¶
Memorial Sloan Kettering Cancer Center

Paul Nghiem, MD, PhD ϖ
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

Soo Park, MD †
UC San Diego Moores Cancer Center

Tejesh Patel, MD ϖ ≠
St. Jude Children's Research Hospital/
University of Tennessee Health Science
Center

Igor Puzanov, MD, MSCI †
Roswell Park Comprehensive Cancer Center

Jeffrey Scott, MD, MHS ϖ
The Sidney Kimmel Comprehensive
Cancer Center at John Hopkins

Aleksandar Sekulic, MD, PhD ϖ
Mayo Clinic Cancer Center

Ashok R. Shaha, MD ¶ ζ
Memorial Sloan Kettering Cancer Center

Divya Srivastava, MD ϖ
UT Southwestern Simmons
Comprehensive Cancer Center

William Stebbins, MD ϖ ¶
Vanderbilt-Ingram Cancer Center

Valencia Thomas, MD ϖ
The University of Texas
MD Anderson Cancer Center

Yaohui G. Xu, MD, PhD ϖ
University of Wisconsin
Carbone Cancer Center

NCCN
Mai Nguyen, PhD
Beth Lynn, RN, BS

ϖ Dermatology
Þ Internal medicine
† Medical oncology
ζ Otolaryngology
≠ Pathology/Dermatopathology
Ÿ Reconstructive surgery
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
* Discussion Section Writing Committee

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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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Updates in Version 1.2022 of the NCCN Guidelines for Basal Cell Skin Cancer from Version 2.2021 include:

BCC-1
- **Clinical Presentation**
  - ▸ Footnote e revised: For rare cases that present with regional or distant metastatic disease at diagnosis, treat as nodal or distant metastases pathway on BCC-4. ~~Imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic).~~
  - ▸ Footnote g added: Imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic). Histologic confirmation is often sufficient to diagnose local recurrence, but MRI can be considered to assess extent of local disease. For nodal or distant metastasis, histologic analysis and/or CT imaging can be employed for confirmation and to gauge extent of disease.

BCC-2
- **Category header revised:** *Local* low-risk basal cell skin cancer.
- **Primary Treatment of Local low-risk basal cell skin cancer**
  - ▸ First option, Curettage and electrodesiccation (C&E):
    - ◇ First bullet revised: Excluding terminal hair-bearing areas, such as the scalp, pubic and axillary regions, and beard area in ~~men~~ *males.*
    - ◇ Second bullet revised: If ~~adipose reached,~~ *tumor appears to extend beyond the dermis,* surgical excision should generally be performed *rather than C&E.*
  - ▸ Second option revised: Standard excision with 4-mm clinical margins and postoperative margin assessment. *Tissue rearrangement (eg, flap reconstruction, extensive undermining) should not be undertaken until clear margins are identified* ~~and~~ *(*second intention healing, linear repair, or skin graft *are acceptable).*
- **Additional Treatment of Local low-risk basal cell skin cancer**
  - ▸ Following positive margins, option revised: Mohs ~~micrographic surgery~~ or ~~resection with CCPDMA~~ *other forms of peripheral and deep en face margin assessment (PDEMA).* (Also page BCC-3)

BCC-2 (continued)
- **Footnote k revised:** ~~Excision with complete circumferential peripheral and deep margin assessment (CCPDMA)~~ *PDEMA* with permanent section analysis or intraoperative frozen section analysis is an alternative to Mohs ~~micrographic surgery~~. See Principles of PDEMA Technique (SCC-G). (Also page BCC-3A)
- **Footnotes removed:**
  - ▸ Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, should not be performed until clear margins are verified. (Also page BCC-3A)
  - ▸ RT is often reserved for patients older than 60 years because of concerns about long term sequelae. (Also pages BCC-3A and BCC-4)
- **Footnotes added:**
  - ▸ Footnote i: In patients with superficial basal cell skin cancer, therapies such as topical imiquimod, topical 5-fluorouracil, photodynamic therapy, or cryotherapy may be considered, though cure rates are approximately 10% lower than surgical treatment modalities. Jansen MHE, et al. J Invest Dermatol 2018;138:527-533. Drew BA, et al. Dermatol Surg 2017;43:1423-1430.
  - ▸ Footnote l: For tumors on cheeks, forehead, scalp, neck, and pretibia that are <6 mm in depth and confined to the dermis, C&E may be considered as an alternative primary treatment option if Mohs, resection with PDEMA, and standard excision are not feasible due to patient comorbidities. See Risk Factors for Recurrence (BCC-B).

UPDATES

Updates in Version 1.2022 of the NCCN Guidelines for Basal Cell Skin Cancer from Version 2.2021 include:

BCC-3
- Category header revised: *Local* high-risk basal cell skin cancer.
- Primary Treatment:
  - First option revised: Mohs ~~micrographic surgery~~ or ~~resection with CCPDMA~~ *other forms of PDEMA*.
  - Second option revised: Standard excision with wider surgical margins and postoperative margin assessment and ~~with~~ *second intention healing,* linear *repair,* or ~~delayed repair~~ *skin graft*.
- Additional Treatment, following Positive margins, first option revised: Mohs ~~micrographic surgery~~ or ~~resection with CCPDMA~~ *other forms of PDEMA*, if feasible or Standard re-excision if ~~CCPDMA~~ *PDEMA* not feasible.

BCC-3A
- Footnotes revised:
  - Footnote l: For tumors on cheeks, forehead, scalp, neck, and pretibia that are <6 mm *in depth* and confined to the dermis, C&E may be considered as an alternative primary treatment option if Mohs ~~micrographic surgery~~, resection with ~~CCPDMA~~ *PDEMA*, and standard excision are not feasible due to patient comorbidities. See Risk Factors for Recurrence (BCC-B).
  - Footnote m: For complicated cases (eg, locally advanced*, where high chance of surgical cure is in question*), consider multidisciplinary consultation...
  - Footnote q: There are conflicting data about the value of adjuvant RT following margin-negative surgical excision, particularly after Mohs ~~surgery~~.
- Footnotes removed:
  - When Mohs micrographic surgery with margin assessment is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.
  - Negative margins unachievable by Mohs micrographic surgery or more extensive surgical procedures.

BCC-4
- Recurrence or Advanced Disease
  - Nodal or distant metastases pathway revised: *Primary or recurrent* ~~N~~*n*odal ~~or distant~~ metastases
    - ◊ Option following Primary or recurrent nodal metastases revised: Multidisciplinary consultation to consider one or more of the following options: Surgery *or If surgery is not feasible then* RT *or systemic therapy.*
      - – Bullet added: Cemiplimab-rwlc
  - Pathway added: Distant metastases
    - ◊ Following Distant metastases pathway, options added: Multidisciplinary consultation to consider: Systemic therapy, HHI, Vismodegib, Cemiplimab-rwlc or RT or surgery for limited metastatic disease or Palliation and best supportive care.
- Footnote s added: Cemiplimab-rwlc is recommended for patients with locally advanced or mBCC previously treated with an HHI or for whom an HHI is not appropriate.
- Footnote t added: Under highly selective circumstances, in the context of multidisciplinary consultation, resection of limited metastases can be considered.

BCC-A
- Principles of Biopsy Reporting, second bullet revised: Clinical information to be submitted on biopsy requisition includes patient demographics, *clinical diameter of lesion,* anatomic location, and prior treatment of lesion. *Additional helpful features to include are* ~~clinical diameter of lesion, and risk factors such as~~ immunosuppression~~,~~ and *history of* RT~~, or solid organ transplantation~~.
- Principles of Excision Reporting
  - Third bullet revised: Minimal reporting elements to be reported for all surgical specimens include histologic subtype of basal cell carcinoma (BCC), invasion of tumor beyond deep reticular dermis, presence ~~or absence~~ of perineural invasion (if involving nerve below dermis or if largest nerve involved is >0.1 mm in caliber) and angiolymphatic invasion, and peripheral and deep margin status.

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Updates in Version 1.2022 of the NCCN Guidelines for Basal Cell Skin Cancer from Version 2.2021 include:

BCC-A (continued)

‣ Fourth bullet revised: For Mohs excisions, reporting of these elements is also encouraged. ~~As depth of invasion (in mm) may not be reliably ascertained on Mohs specimens, anatomic level of invasion can be reported. Submission of a central section of tissue at the area of deepest invasion for permanent section evaluation may be considered to evaluate and document high-risk features that were questionable or ambiguous on Mohs sections.~~ *Since depth of invasion (in mm) may not be ascertained on tangentially cut Mohs specimens, anatomic level of invasion should be reported. Frozen or permanent section analysis of the clinical tumor specimen may be undertaken if needed for complete reporting of features associated with poor prognosis.*

• Footnote 3 added: Morgan FC, Ruiz ES, Karia PS, et al. Brigham and Women's Hospital tumor classification system for basal cell carcinoma identifies patients with risk of metastasis and death. J Am Acad Dermatol 2021;85:582-587.

BCC-B

• High Risk, Location/size, third row revised: ~~"Mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/ sulci, temple, and ear), genitalia, hands, and feet~~ *Head, neck, hands, feet, pretibia, and anogenital (any size).*

• Footnote 3 revised: This area constitutes high risk based on location, independent of size. Narrow excision margins due to anatomic and functional constraints are associated with increased recurrence rates with standard histologic processing. Complete margin assessment such as with Mohs ~~micrographic surgery/CCPDMA~~ *or PDEMA* is recommended for optimal tumor clearance and maximal tissue conservation...

BCC-C

• Second bullet revised: Surgical approaches often offer the most effective and efficient means for accomplishing cure, but considerations of function~~, cosmesis,~~ *and* patient preference~~, and performance status~~ may lead to choosing RT as primary treatment in order to achieve optimal overall results.

• Fifth bullet revised: When Mohs ~~micrographic surgery~~ with margin assessment is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.

BCC-D

• General Principles

‣ New bullet added: Isotope-based brachytherapy can be an effective treatment for certain sites of disease, particularly on the head and neck.

‣ Fifth bullet revised: There are insufficient long-term efficacy and safety data to support the routine use of ~~radioisotope or~~ electronic surface brachytherapy.

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Updates in Version 1.2022 of the NCCN Guidelines for Basal Cell Skin Cancer from Version 2.2021 include:

BCC-E
- **Approach**
  - ▸ **First bullet revised: Systemic therapy may be considered for** ~~locally advanced~~ *la*BCC and mBCC...
  - ▸ **Fourth bullet, Systemic therapy options include:**
    - ◊ **First bullet revised:** ~~Hedgehog pathway inhibitors~~ *HHIs* (ie, vismodegib, sonidegib).
      - – **First sub-bullet revised: Due to frequency of intolerable side effects associated with** ~~hedgehog pathway inhibitors~~ *HHIs*...
      - – **Second sub-bullet revised:** ~~Hedgehog pathway inhibitors~~ *HHIs may be considered for diffuse BCC formation (eg, Gorlin syndrome* ~~The approach for patients with diffuse BCC formation (eg, Gorlin syndrome,~~ *or* **other genetic forms of multiple BCC)**~~, hedgehog pathway inhibitors may be considered.~~ ~~Hedgehog pathway inhibitors~~ *HHIs* **are not approved for Gorlin syndrome; however, they are effective based on a randomized controlled trial.**
      - – **Third sub-bullet revised: Current FDA-approved** ~~hedgehog pathway inhibitors~~ *HHIs* **include vismodegib and sonidegib. Vismodegib is FDA approved for the treatment of adults with mBCC or** ~~with locally advanced~~ *la*BCC **that has recurred following surgery, or** *those* **who are not candidates for surgery or** ~~and who are not candidates for~~ RT. **Sonidegib is FDA approved for the treatment of adult**s ~~patients~~ **with** ~~locally advanced~~ *la*BCC **that has recurred following surgery or RT, or those who are not candidates for surgery or RT. Sonidegib is not FDA approved** *for the treatment of adults with* **mBCC.**
    - ◊ **Second bullet revised: Cemiplimab-rwlc** *is recommended* **for patients with** ~~locally advanced~~ *la*BCC **or mBCC previously treated with** *a*n ~~hedgehog pathway inhibitor [HHI]~~ **or for whom an HHI is not appropriate.**
- **Footnote 1 added: Dummer R, Guminksi A, Gutzmer R, et al. Long-term efficacy and safety of sonidegib in patients with advanced basal cell carcinoma: 42-month analysis of the phase II randomized, double-blind BOLT study. Br J Dermatol 2020;182:1369-1378.**
- **Footnote 2 added: Tang JY, et al. Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicenter, randomized, double-blind, placebo controlled, phase 2 trial. Lancet Oncol 2016;17:1720-1731.**
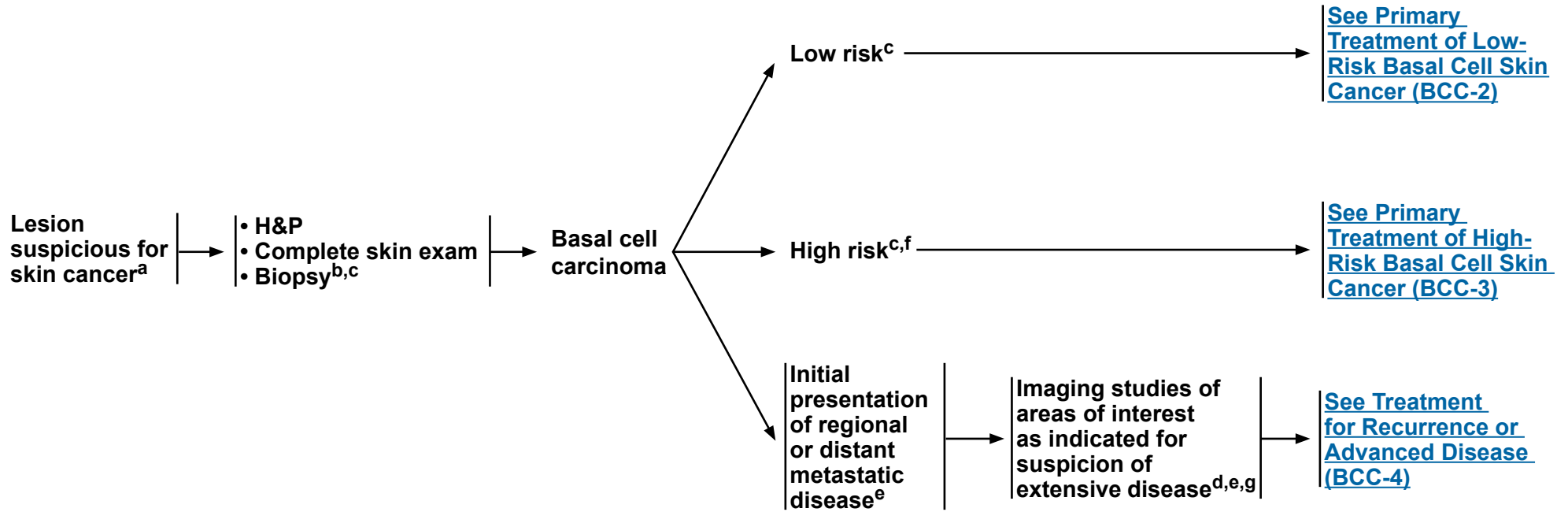
CLINICAL PRESENTATION	WORKUP	DIAGNOSIS	RISK STATUS	
Lesion suspicious for skin cancer[a]	• **H&P** • **Complete skin exam** • **Biopsy**[b,c]	**Basal cell carcinoma**	Low risk[c]	**See Primary Treatment of Low-Risk Basal Cell Skin Cancer (BCC-2)**
			High risk[c,f]	**See Primary Treatment of High-Risk Basal Cell Skin Cancer (BCC-3)**
			Initial presentation of regional or distant metastatic disease[e] → Imaging studies of areas of interest as indicated for suspicion of extensive disease[d,e,g]	**See Treatment for Recurrence or Advanced Disease (BCC-4)**

[a] For more information, see American Academy of Dermatology Association.

[b] See Principles of Pathology (BCC-A).

[c] See Risk Factors for Recurrence (BCC-B).

[d] Extensive disease includes deep structural involvement such as bone, perineural disease, and deep soft tissue. If perineural disease is suspected, MRI with contrast is preferred. If bone disease is suspected, CT with contrast is preferred unless contraindicated.

[e] For rare cases that present with regional or distant metastatic disease at diagnosis, treat as nodal or distant metastases pathway on BCC-4.

[f] Any high-risk factor places the patient in the high-risk category.

[g] Imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic). Histologic confirmation is often sufficient to diagnose local recurrence, but MRI can be considered to assess extent of local disease. For nodal or distant metastasis, histologic analysis and/or CT imaging can be employed for confirmation and to gauge extent of disease.

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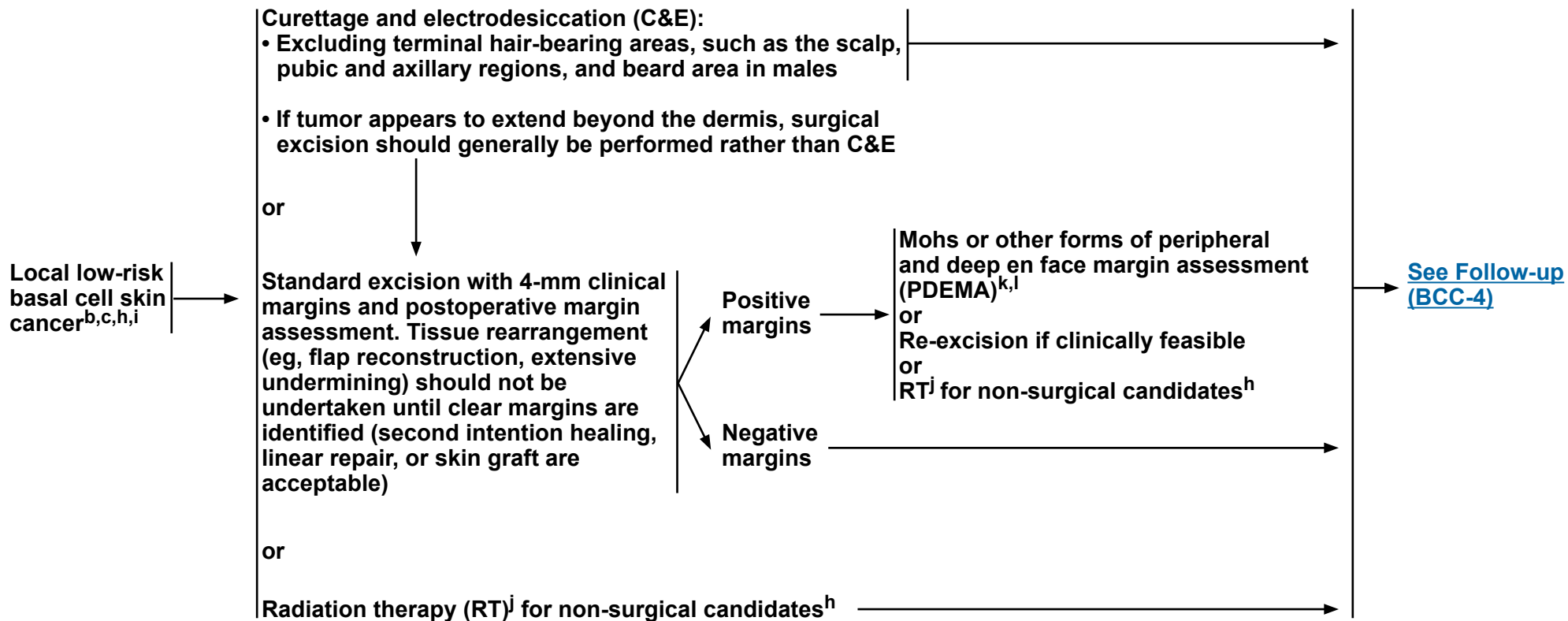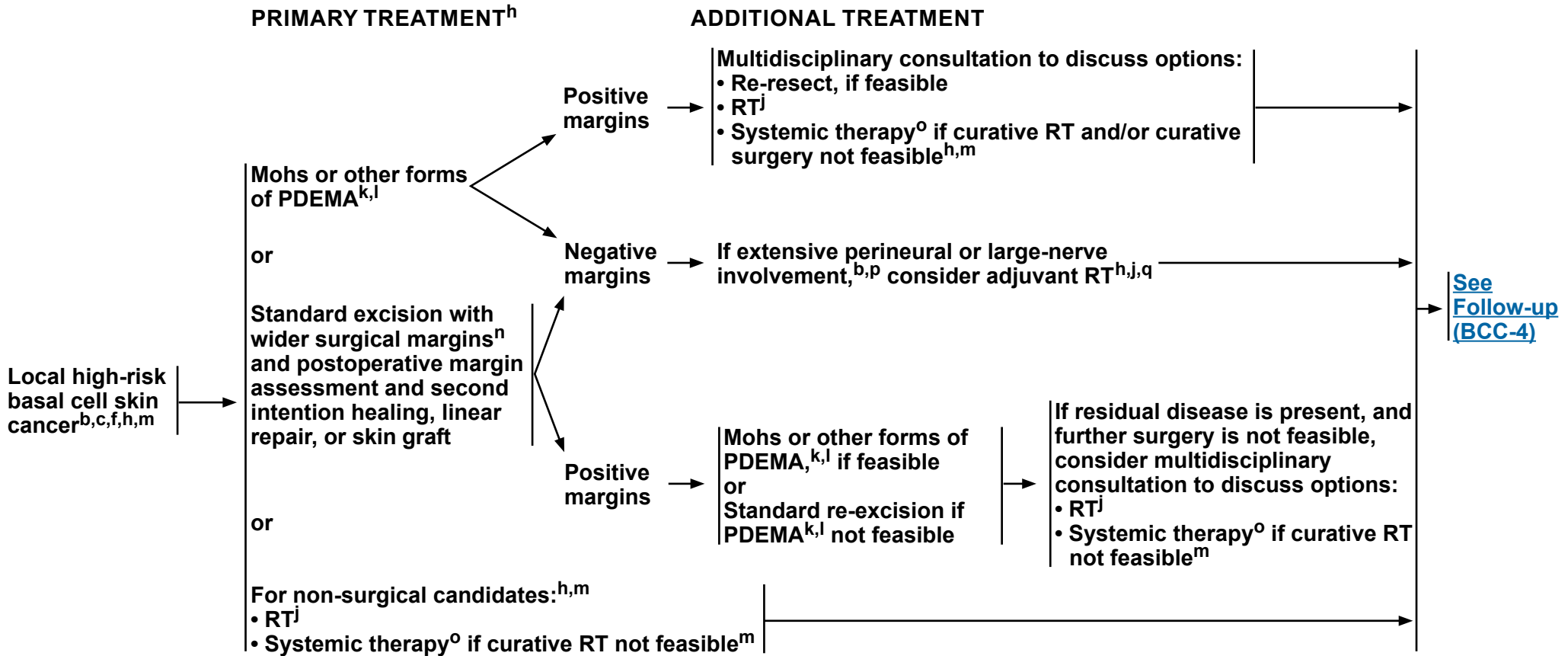
PRIMARY TREATMENT[h]

ADDITIONAL TREATMENT

Local low-risk basal cell skin cancer[b,c,h,i] →

Curettage and electrodesiccation (C&E):
• **Excluding terminal hair-bearing areas, such as the scalp, pubic and axillary regions, and beard area in males**

• **If tumor appears to extend beyond the dermis, surgical excision should generally be performed rather than C&E**

or

Standard excision with 4-mm clinical margins and postoperative margin assessment. Tissue rearrangement (eg, flap reconstruction, extensive undermining) should not be undertaken until clear margins are identified (second intention healing, linear repair, or skin graft are acceptable)

or

Radiation therapy (RT)[j] **for non-surgical candidates**[h]

→ **Positive margins** → **Mohs or other forms of peripheral and deep en face margin assessment (PDEMA)**[k,l] **or Re-excision if clinically feasible or RT**[j] **for non-surgical candidates**[h]

→ **Negative margins** →

→ **See Follow-up (BCC-4)**

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[b] See Principles of Pathology (BCC-A).
[c] See Risk Factors for Recurrence (BCC-B).
[h] See Principles of Treatment (BCC-C).
[i] In patients with superficial basal cell skin cancer, therapies such as topical imiquimod, topical 5-fluorouracil, photodynamic therapy, or cryotherapy may be considered, though cure rates are approximately 10% lower than for surgical treatment modalities. Jansen MHE, et al. J Invest Dermatol 2018;138:527-533. Drew BA, et al. Dermatol Surg 2017;43:1423-1430.
[j] See Principles of Radiation Therapy (BCC-D).
[k] PDEMA with permanent section analysis or intraoperative frozen section analysis is an alternative to Mohs. See Principles of PDEMA Technique (SCC-G).
[l] For tumors on cheeks, forehead, scalp, neck, and pretibia that are <6 mm in depth and confined to the dermis, C&E may be considered as an alternative primary treatment option if Mohs, resection with PDEMA, and standard excision are not feasible due to patient comorbidities. See Risk Factors for Recurrence (BCC-B).

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PRIMARY TREATMENT[h]　　　　　　　**ADDITIONAL TREATMENT**

Local high-risk basal cell skin cancer[b,c,f,h,m]

Mohs or other forms of PDEMA[k,l]

or

Standard excision with wider surgical margins[n] and postoperative margin assessment and second intention healing, linear repair, or skin graft

or

For non-surgical candidates:[h,m]
• **RT[j]**
• **Systemic therapy[o] if curative RT not feasible[m]**

Positive margins →
Multidisciplinary consultation to discuss options:
• **Re-resect, if feasible**
• **RT[j]**
• **Systemic therapy[o] if curative RT and/or curative surgery not feasible[h,m]**

Negative margins →
If extensive perineural or large-nerve involvement,[b,p] consider adjuvant RT[h,j,q]

Positive margins →
Mohs or other forms of PDEMA,[k,l] if feasible
or
Standard re-excision if PDEMA[k,l] not feasible
→
If residual disease is present, and further surgery is not feasible, consider multidisciplinary consultation to discuss options:
• **RT[j]**
• **Systemic therapy[o] if curative RT not feasible[m]**

See Follow-up (BCC-4)

See footnotes on **BCC-3A**

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BCC-3

FOOTNOTES

b See Principles of Pathology (BCC-A).

c See Risk Factors for Recurrence (BCC-B).

f Any high-risk factor places the patient in the high-risk category.

h See Principles of Treatment (BCC-C).

j See Principles of Radiation Therapy (BCC-D).

k PDEMA with permanent section analysis or intraoperative frozen section analysis is an alternative to Mohs. See Principles of PDEMA Technique (SCC-G).

l For tumors on cheeks, forehead, scalp, neck, and pretibia that are <6 mm in depth and confined to the dermis, C&E may be considered as an alternative primary treatment option if Mohs, resection with PDEMA, and standard excision are not feasible due to patient comorbidities. See Risk Factors for Recurrence (BCC-B).

m For complicated cases (eg, locally advanced, where high chance of surgical cure is in question), consider multidisciplinary consultation. For locally advanced disease in which curative RT and curative surgery are not feasible, consider treatment with hedgehog pathway inhibitors (HHIs) (vismodegib and sonidegib). Feasibility of surgery or radiation should be assessed by a surgeon and radiation oncologist. See Principles of Systemic Therapy (BCC-E).

n Due to the wide variability of clinical characteristics that may define a high-risk tumor, it is not feasible to recommend a defined margin for standard excision of high-risk BCC. Keen awareness of the subclinical extension of BCC is advised when selecting a treatment modality without complete margin assessment for a high-risk tumor. These margins may need to be modified based on tumor- or patient-specific factors.

o See Principles of Systemic Therapy (BCC-E).

p If large nerve involvement is suspected, consider MRI with contrast of region of interest to evaluate extent and rule out base of skull involvement or intracranial extension in head and neck tumors.

q There are conflicting data about the value of adjuvant RT following margin-negative surgical excision, particularly after Mohs.

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BCC-3A

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FOLLOW-UP

RECURRENCE OR ADVANCED DISEASE

- **H&P**
  - ‣ **Including complete skin exam every 6–12 mo for first 5 years, and then at least annually for life**
- **Consider imaging if clinical exam insufficient for following disease[r]**
- **Patient education:**
  - ‣ **Sun protection**
  - ‣ **Self-examination**

Local recurrence → **Follow Primary Treatment pathway for Local, high-risk disease (BCC-3)**

Primary or recurrent nodal metastases →

Multidisciplinary consultation to consider one or more of the following options:
Surgery
or
If surgery is not feasible then RT[j] or systemic therapy[o]
- **Hedgehog pathway inhibitor (HHI)**
  - ‣ **Vismodegib**
  - ‣ **Sonidegib (category 2B)**
- **Cemiplimab-rwlc[s]**
- **Clinical trial**

Distant metastases →

Multidisciplinary consultation to consider:
Systemic therapy[o]
- **HHI**
  - ‣ **Vismodegib**
- **Cemiplimab-rwlc[s]**
or
RT[j] or surgery for limited metastatic disease[t]
or
Palliation and best supportive care

---

[j] See Principles of Radiation Therapy (BCC-D).
[o] See Principles of Systemic Therapy (BCC-E).
[r] Imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic). Histologic confirmation is often sufficient to diagnose local recurrence, but MRI can be considered to assess extent of local disease. For nodal or distant metastasis, histologic analysis and/or CT imaging can be employed for confirmation and to gauge extent of disease.
[s] Cemiplimab-rwlc is recommended for patients with locally advanced or mBCC previously treated with an HHI or for whom an HHI is not appropriate.
[t] Under highly selective circumstances, in the context of multidisciplinary consultation, resection of limited metastases can be considered.

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PRINCIPLES OF PATHOLOGY

Principles of Biopsy Reporting:
- Pathologic evaluation of skin biopsies is ideally performed by a dermatologist, pathologist, or dermatopathologist who is experienced in interpreting cutaneous neoplasms.
- Clinical information to be submitted on biopsy requisition includes patient demographics, clinical diameter of lesion, anatomic location, and prior treatment of lesion. Additional helpful features to include are immunosuppression and history of RT.
- Pathologic report should include histologic subtype[1] and presence of any features that would increase the risk for local recurrence, including invasion of tumor beyond reticular dermis and presence of perineural invasion (if involving nerve below the dermis or >0.1 mm in caliber).[2]

Principles of Excision Reporting:
- Saucerization specimens intended for definitive surgical therapy should be labeled as such, as they can be histopathologically difficult to distinguish from shave biopsies but must be evaluated for margin status.
- Clinical information to be submitted on excision requisition includes patient demographics, anatomic location, clinical diameter of lesion, and additional clinical information listed above under Principles of Biopsy Reporting.
- Minimal reporting elements to be reported for all surgical specimens include histologic subtype of basal cell carcinoma (BCC),[1] invasion of tumor beyond deep reticular dermis, presence of perineural invasion (if involving nerve below dermis or if largest nerve involved is >0.1 mm in caliber) and angiolymphatic invasion, and peripheral and deep margin status.
- For Mohs excisions, reporting of these elements is also encouraged. Since depth of invasion (in mm) may not be ascertained on tangentially cut Mohs specimens, anatomic level of invasion should be reported. Frozen or permanent section analysis of the clinical tumor specimen may be undertaken if needed for complete reporting of features associated with poor prognosis.[3]

[1] Low-risk histologic subtypes include nodular, superficial, and other non-aggressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus; high-risk subtypes include basosquamous, infiltrative, sclerosing/morpheaform, micronodular, and BCC with carcinosarcomatous differentiation.
[2] Alam M, Armstrong A, Baum C, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am Acad Dermatol 2018;78:560-578.
[3] Morgan FC, Ruiz ES, Karia PS, et al. Brigham and Women's Hospital tumor classification system for basal cell carcinoma identifies patients with risk of metastasis and death. J Am Acad Dermatol 2021;85:582-587.

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BCC-A

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STRATIFICATION TO DETERMINE TREATMENT OPTIONS FOR LOCAL BCC BASED ON RISK FACTORS FOR RECURRENCE[1]

Risk Group	Low Risk	High Risk
Treatment Options	**See BCC-2**	**See BCC-3**
H&P		
Location/size	**Trunk, extremities <2 cm**	**Trunk, extremities ≥2 cm**
		Cheeks, forehead, scalp, neck, and pretibia (any size)
		Head, neck, hands, feet, pretibia, and anogenital (any size)[3]
Borders	**Well-defined**	**Poorly defined**
Primary vs. recurrent	**Primary**	**Recurrent**
Immunosuppression	**(-)**	**(+)**
Site of prior RT	**(-)**	**(+)**
Pathology (See BCC-A)		
Subtype	**Nodular, superficial[2]**	**Aggressive growth pattern[4]**
Perineural involvement	**(-)**	**(+)**

[1] Any high-risk factor places the patient in the high-risk category.
[2] Low-risk histologic subtypes include nodular, superficial, and other non-agressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus.
[3] This area constitutes high risk based on location, independent of size. Narrow excision margins due to anatomic and functional constraints are associated with increased recurrence rates with standard histologic processing. Complete margin assessment such as with Mohs or PDEMA is recommended for optimal tumor clearance and maximal tissue conservation. For tumors <6 mm in size, without other high-risk features, other treatment modalities may be considered if at least 4-mm clinically tumor-free margins can be obtained without significant anatomic or functional distortions.
[4] Having (mixed) infiltrative, micronodular, morpheaform, basosquamous, sclerosing, or carcinosarcomatous differentiation features in any portion of the tumor. In some cases basosquamous tumors may be prognostically similar to SCC; clinicopathologic correlation is recommended in these cases.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BCC-B

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PRINCIPLES OF TREATMENT

- The primary goal of treatment of basal cell skin cancer is the complete removal of the tumor and the maximal preservation of function and cosmesis. All treatment decisions should be customized to account for the particular factors present in the individual case and for the patient's preference.

- Surgical approaches often offer the most effective and efficient means for accomplishing cure, but considerations of function and patient preference may lead to choosing RT as primary treatment in order to achieve optimal overall results.

- In certain patients at high risk for multiple primary tumors (eg, Gorlin syndrome, xeroderma pigmentosum, history of RT), increased surveillance and consideration of prophylactic measures may be indicated. Consider referring patients with suspected Gorlin syndrome or xeroderma pigmentosum for genetic evaluation.

- In patients with superficial basal cell skin cancer, therapies such as topical imiquimod, topical 5-fluorouracil, photodynamic therapy (eg, aminolevulinic acid [ALA], porfimer sodium), or cryotherapy may be considered, even though the cure rates may be lower than with surgical treatment modalities.

- When Mohs with margin assessment is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.

- Use of nicotinamide may be effective in reducing the development of basal cell skin cancers.[1]

[1] Chen AC, Martin AJ, Dalziell RA, et al. A phase II randomized controlled trial of nicotinamide for skin cancer chemoprevention in renal transplant recipients. Br J Dermatol 2016;175:1073-1075. Chen AC, Martin AJ, Choy B, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. N Engl J Med 2015;373:1618-1626.

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PRINCIPLES OF RADIATION THERAPY

General Principles
- Protracted fractionation is associated with improved cosmetic results and should be utilized for poorly vascularized or cartilaginous areas.
- RT is contraindicated for genetic conditions predisposing to skin cancer (eg, basal cell nevus syndrome) and relatively contraindicated for patients with connective tissue diseases (eg, scleroderma).
- Given higher complication rates, re-irradiation should not be routinely utilized for recurrent disease within a prior radiation field.
- Isotope-based brachytherapy can be an effective treatment for certain sites of disease, particularly on the head and neck.
- There are insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy.

General Treatment Information

Dosing Prescription Regimen

Definitive RT	Examples of Electron Beam Dose and Fractionation
Tumor diameter <2 cm	60–64 Gy over 6–7 weeks
	50–55 Gy over 3–4 weeks
	40 Gy over 2 weeks
	30 Gy in 5 fractions over 2–3 weeks
Tumor diameter ≥2 cm, T3/T4, or those with invasion of bone or deep tissue	60–70 Gy over 6–7 weeks
	45–55 Gy over 3–4 weeks
Postoperative Adjuvant RT	60–64 Gy over 6–7 weeks
	50 Gy over 4 weeks

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BCC-D

PRINCIPLES OF SYSTEMIC THERAPY

Locally Advanced (laBCC) or Metastatic Basal Cell Carcinoma (mBCC)

Approach
- **Systemic therapy may be considered for laBCC and mBCC. It is not used where topical therapy, surgery, or RT is likely to be curative.**
  - **Locally advanced disease is defined by those that have primary or recurrent local disease that are not amenable to surgery or RT.**
- **Systemic therapy may be considered for cases of nodal or distant metastatic disease, especially if surgery and RT are not feasible.**
- **Multidisciplinary consultation may be required to determine the best treatment approach and deem the tumor not amenable to surgery or radiation.**
- **Systemic therapy options include:**
  - **HHIs (ie, vismodegib, sonidegib[1]).**
    - **Due to frequency of intolerable side effects associated with HHIs, drug holidays or other alternatives to daily dosing can be used to reduce side effects to improve adherence to therapy and quality of life (see Discussion for details).**
    - **HHIs may be considered for diffuse BCC formation (eg, Gorlin syndrome or other genetic forms of multiple BCC). HHIs are not approved for Gorlin syndrome; however, they are effective based on a randomized controlled trial.[2]**
    - **Current FDA-approved HHIs include vismodegib and sonidegib.[1] Vismodegib is FDA approved for the treatment of adults with mBCC or laBCC that has recurred following surgery, or those who are not candidates for surgery or RT. Sonidegib[1] is FDA approved for the treatment of adults with laBCC that has recurred following surgery or RT, or those who are not candidates for surgery or RT. Sonidegib is not FDA approved for the treatment of adults with mBCC.**
  - **Cemiplimab-rwlc is recommended for patients with laBCC or mBCC previously treated with an HHI or for whom an HHI is not appropriate.**

[1] Dummer R, Guminksi A, Gutzmer R, et al. Long-term efficacy and safety of sonidegib in patients with advanced basal cell carcinoma: 42-month analysis of the phase II randomized, double-blind BOLT study. Br J Dermatol 2020;182:1369-1378.
[2] Tang JY, et al. Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicenter, randomized, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2016;17:1720-1731.

Note: All recommendations are category 2A unless otherwise indicated.
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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

Discussion

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This discussion corresponds to the NCCN Guidelines for Basal Cell Skin Cancer. Last updated: May 18, 2016.

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Overview

Basal cell carcinoma (BCC) is the most common cancer in the United States.[1] It is estimated that BCCs occur in 2 million Americans annually; this exceeds the incidence of all other cancers combined.[2-4] Due to its prevalence, treatment of non-melanoma skin cancer (NMSC) in the United States costs Medicare more than $400 million per year.[5,6] Furthermore, the incidence of this common malignancy is rising rapidly.[1,7-13] BCCs are at least 2 times more common than squamous cell carcinomas (SCCs), the second most common type of skin cancer.[2-4,14-18] Although rarely metastatic, BCC can produce substantial local destruction along with disfigurement and may involve extensive areas of soft tissue, cartilage, and bone. Fortunately BCCs generally have a good prognosis due to low rates of metastasis.

A number of risk factors are associated with development of BCC. The most recognized environmental carcinogen is sunlight. Evidence reveals that the relationship between sun exposure and BCC is complex, depending on the timing, pattern and amount of ultraviolet (UV) radiation.[19-23] Fair skin, red or blond hair, and light eye color are associated with BCC as independent risk factors due to greater susceptibility to UV damage.[21,23-29] BCC risk is increased by both UV-A and -B radiation as well as by ionizing radiation. Radiation treatment for other conditions, especially at a young age, is also associated with an increased risk for developing BCC.[30-35] Most BCC tumors develop on skin sites exposed to radiation—either from the sun or from therapy.[30-32,34] BCC tends to occur in the head and neck area, and within the treatment field of prior radiation therapy (RT).[8,9,11,15,19-21,36-38]

All patients should be made aware of the various resources that discuss skin cancer prevention. Some of the useful resources are listed below:

- Skin Cancer Prevention and Early Detection. American Cancer Society. Available at: http://www.cancer.org/acs/groups/cid/documents/webcontent/003184-pdf.pdf

- SPOT Skin Cancer. American Academy of Dermatology. Available at: http://aad.org/spot-skin-cancer

- Prevention Guidelines. Skin Cancer Foundation. Available at: http://www.skincancer.org/prevention

Genetics

Extensive research has led to advances in the understanding of the genetics of BCC. The sonic hedgehog signaling pathway has emerged as playing a pivotal role in the pathogenesis of BCC, and mutations in a number of molecules in this pathway have been implicated in the development of the disease.[39-41] Mutations in the *PTCH1* (patched 1) gene on chromosome 9q, which codes for the sonic hedgehog receptor, are the underlying cause of nevoid BCC syndrome, and are present in approximately 30% to 90% of sporadic BCCs.[40-57] Specific UV-induced mutations in the tumor suppressor gene *p53* appear to be a common event in BCC development.[46,52,55,58-60]

Finally, certain genetic syndromes greatly predispose affected individuals to skin cancer formation, including BCC, such as albinism (in which skin pigment is absent)[61,62] and xeroderma pigmentosum (in which defects exist in UV light-induced unscheduled DNA repair).[56,63-75]

Clinical Presentation and Workup

On clinical presentation of the patient with a suspicious lesion, workup for BCC begins with a history and physical examination, with an emphasis on a complete skin examination. A full skin examination is recommended, because individuals with a skin cancer often have additional, concurrent precancers or cancers located at other, usually sun-exposed skin sites. These individuals are also at increased risk of

developing cutaneous melanoma.[76] A skin biopsy is then performed on any suspicious lesion. The biopsy should include deep reticular dermis if the lesion is suspected to be more than a superficial process. This procedure is preferred because an infiltrative histology may sometimes be present only at the deeper, advancing margins of a tumor, and superficial biopsies will frequently miss this component.[77,78] Skin lesions in high-risk populations may be difficult to assess clinically; therefore, a low threshold for performing skin biopsies in these patients is necessary. Imaging studies should be performed when extensive disease, such as bone involvement, perineural invasion, or deep soft tissue involvement, is suspected. MRI is preferred over CT scan if perineural disease is suspected because of its higher sensitivity.[79,80]

Risk Stratification

After workup, a risk assessment should be performed to determine the treatment plan. The NCCN Panel examined risk factors for BCC associated with recurrence. These are listed in table format in the algorithm. If any high-risk feature is present, the patient should be managed according to the high-risk treatment pathway.

Risk Factors for BCC

Location and Size
Anatomic location has been known to be a risk factor for BCC recurrence and metastasis for many years.[81-86] In general, BCCs that develop in the head and neck area are more likely to recur than those that develop on the trunk and extremities. Compared with SCC, BCCs are much less likely to metastasize, with a metastatic rate of <0.1%.[87-89] The concept of a so-called high-risk "H zone" or "mask area" of the face dates back at least to 1983.[90,91] Size also has been shown to be a risk factor for BCC recurrence.[84-86,92-94] Various different divisions have been used; the most commonly used has been greater than or less than 2 cm in diameter.

The location and size criteria are mainly based on a 27-year retrospective review of 5755 BCCs by the Skin and Cancer Unit of the New York University (NYU) School of Medicine.[83,95] The high-risk sites correspond roughly to the mask areas of the face. Recurrences in the NYU study were significantly more common when tumors in high-risk locations were 6 mm or more in diameter and when tumors in moderate-risk locations were 10 mm or more in diameter.

More recently, the American Academy of Dermatology (AAD) in collaboration with American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and American Society for Mohs Surgery developed an appropriate use criteria (AUC) document in the treatment of cutaneous neoplasms.[96] This was based on 270 clinical scenarios including 69 BCCs. Areas of the body are described in detail in the algorithm under *Risk Factors for Recurrence*.

Clinical Borders and Primary Versus Recurrent Disease
The risk factors of well-defined versus ill-defined clinical tumor borders and primary versus recurrent disease have been extensively documented in the literature.[85,92,97-101]

Immunosuppression
Settings of immunosuppression, such as organ transplantation, and long-term use of psoralen and UVA light (PUVA), increase the incidence of BCC.[17,102-108] Incidence of BCC among patients who have had organ transplants is approximately 5- to 10-fold higher than in the general population,[109-111] occurring in up to half of patients during the 10 years following transplant.[112-115]

Several large retrospective studies compared BCC in patients with or without a history of organ transplant.[116-118] These found that BCCs in patients who had received organ transplants were more likely to have the superficial histologic subtype (and be thinner), were more likely to

occur in extracephalic locations, and were more likely to occur in younger patients (mean age of onset 15 years lower).[116,117] Two of these studies showed similar low recurrence rates for transplant recipients and controls.[117,118] Nevertheless, because of NCCN Guidelines Panel Members' own anecdotal experiences, the panel decided to classify BCCs developing in settings of immunosuppression as potentially high-risk tumors.

Site of Prior Radiotherapy

Tumors developing in sites of prior radiotherapy refer to primary BCCs arising in areas previously irradiated for unrelated conditions. All recurrent tumors, irrespective of prior therapy, are defined as high risk. Data from a number of studies with large sample sizes support that prior radiotherapy for unrelated (frequently benign) conditions is a risk factor for BCC development.[30-35,119]

Perineural Involvement

Perineural involvement is uncommon in any NMSC (2%–6%), and develops less frequently and is less aggressive in BCC versus SCC.[120-125] BCC with perineural involvement poses a greatly increased risk of recurrence, and is associated with other risk factors including previous recurrent tumors, high grade, larger lesion size, and infiltrating, morpheic, and basosquamous subtypes.[125-127] If large nerve involvement is suspected, MRI should be considered to evaluate extent and/or rule out skull involvement in those with head and neck tumors.[80,128-130]

Young Age Is Not a Risk Factor

Whether young age (typically, younger than 40 years) is an independent risk factor for aggressive BCC behavior is debatable. Studies report conflicting results regarding the relationship between age and other high-risk features. For example, analysis of a large database of patients with BCC (N = 3381) by Leffell and colleagues documented an increased percentage of BCC with aggressive histologic growth patterns in young persons.[131] In contrast, results from several other analyses of large databases (1000 to >10,000 patients with BCC) indicate that patients presenting with BCC at a young age are more likely to have the superficial subtype.[132-135] Still, other analyses report no significant differences in BCC histologic subtype among young versus older patients.[136-138] The relationship between tumor location and age is also unclear, as several studies showed that younger patients were more likely to have BCCs that were on the trunk or extremities at presentation,[132,137,139,140] but other studies found no significant association.[136] Moreover, histologic subtype and tumor location are already separate risk factors in the algorithm.

The effect of age on likelihood of recurrence has been evaluated in studies with sample sizes ranging from 50 to 2000 patients, and most of these have shown no significant association between age and recurrence rate.[85,98,136,138] One multivariate analysis, however, showed a positive relationship between increasing age and likelihood of recurrence.[141] The prognostic value of age has also been evaluated in analyses of potential risk factors for developing a second or multiple BCCs.[92,138,140-148] Many of these studies used fairly large databases (200–2500 patients with BCC), and found that risk of developing more than one BCC is associated with increased age.[92,138,140-143,145,147,148] However, one multivariate analysis of an extremely large database (71,924 patients with BCC) found a significantly higher risk of subsequent NMSC in patients who were younger than 40 years of age at the time of their first BCC diagnosis.[149] In addition, an analysis of 100 metastatic BCC cases reported in the literature found that patients with distant metastases tended to be younger than those with only regional metastases.[150] These findings suggest that while younger age is not generally associated with more aggressive BCC, there is a small subset of patients with particularly aggressive disease who tend to be younger than most patients with BCC. Consistent with this idea, multivariate

analyses of patients with BCC in the Rotterdam Study showed that while risk of developing a second BCC lesion increased with age (up to ~68 years),[148] risk of developing multiple BCC lesions was highest in patients who were younger than 65 years at the time of their first BCC diagnosis.[146] Taken together, these studies do not support that young age, in and of itself, is a high-risk factor for BCC behavior, but that patients who develop BCC at a young age may benefit from regular follow-up.

Pathologic Risk Factors for BCC

Histologic subtyping of BCC as a predictor of risk of recurrence is a well-established concept.[151,152] The subtypes encompassed by the term "aggressive growth pattern," including micronodular, infiltrative, sclerosing, and morpheaform (or desmoplastic) patterns, are more likely to recur than the nodular and superficial BCC.[153-156] Non-aggressive subtypes include the keratotic variant, infundibulocystic variant, and fibroepithelioma of Pinkus.

Basosquamous Carcinoma

Basosquamous carcinomas are tumors of which one part has the histologic appearance of a BCC and another of that of an SCC. Some basosquamous tumors are the result of a BCC colliding with an adjacent SCC. Others represent truly biphenotypic tumors, many of which may have started as BCC, but have subsequently undergone prominent partial squamous metaplasia.[157] It seems that the risk for metastasis of these tumors is determined by the squamous component. Data suggest that basosquamous carcinomas have a metastatic capacity that is more similar to that of SCC than BCC.[158-160]

Local Treatment for BCC

Localized BCC is most commonly treated with surgery. Traditional techniques such as curettage and electrodessication are mostly supported by older studies, and data from prospective trials with long-term follow-up are limited. In an evidence-based review of the literature, the best results were obtained with surgery.[161] However, consideration of function, cosmetic outcome, and patient preference may lead to the choice of RT as primary treatment in order to achieve optimal overall results.

Curettage and Electrodesiccation

Curettage and electrodesiccation (C&E) is the process of alternatively scraping away tumor tissue with a curette down to a firm layer of normal dermis and denaturing the area by electrodessication. Up to 3 cycles may be performed in a session. Although a fast and cost-effective technique for superficial lesions, it does not allow histologic margin assessment. Observational and retrospective studies have reported overall 5-year cure rates ranging from 91% to 97% in patients with BCC selected for C&E.[162,163] However, some studies have reported higher recurrence rates (19%–27%),[164,165] possibly due to high-risk locations (21%) and histologic subtypes (27%).[83,166,167] It should also be noted that results are highly operator-dependent and optimal cure rates are achieved by experienced practitioners.[168]

This technique is deemed effective for properly selected, low-risk tumors with three caveats.[83,167] First, this technique should not be used to treat areas with terminal hair growth such as the scalp, pubic and axillary regions, or beard area in males due to the risk that a tumor extending down follicular structures might not be adequately removed.

Second, if the subcutaneous layer is reached during the course of C&E, then surgical excision should generally be performed instead. This change in therapy is necessary as the effectiveness of the C&E technique rests on the ability of the clinician to distinguish between firm, normal dermis, and soft tumor tissue when using a sharp curette. Because subcutaneous adipose is even softer than tumor tissue, the

ability of the curette to distinguish and, therefore, selectively and completely remove tumor cells disappears.

Third, if curettage has been performed based only on the appearance of a low-risk tumor, biopsy results of the tissue taken at the time of curettage should be reviewed to make sure that there are no high-risk pathologic features that would require additional therapy.

Excision with Postoperative Margin Assessment

Another therapeutic option for BCC is standard surgical excision followed by postoperative pathologic evaluation of margins. This technique has been reported to achieve 5-year disease-free rates of over 98% for BCC.[162,164,169,170]

The clinical margins chosen by the panel for low-risk tumors are based on the work of Zitelli and colleagues.[171] Their analysis indicated that for well-circumscribed BCC lesions less than 2 cm in diameter, excision with 4-mm clinical margins should result in complete removal in more than 95% of cases. The indications for this approach were also expanded to include re-excision of low-risk primary BCC located on the trunk and extremities excluding pretibia, hands, feet, nail units, and ankles (area L regions) if positive margins are obtained after an initial excision with postoperative margin assessment.

If lesions can be excised with the recommended margins, then linear closure, skin grafting, or second intention healing (ie, closures that do not rotate tissue around and/or alter anatomy where residual "seeds" of tumor may remain) are all appropriate reconstructive approaches. However, if tissue rearrangement or skin graft placement is necessary to close the defect, the NCCN Panel believes intraoperative surgical margin assessment is necessary before closure.

As noted below, excision with comprehensive intraoperative margin control is the preferred surgical technique for high-risk BCC. However, if standard excision with postoperative margin assessment is used for treatment of a high-risk tumor due to patient-related clinical circumstances or other variables, wider surgical margins than those recommended for low-risk lesions must be taken and increased recurrence rates should be expected.

Mohs Micrographic Surgery or Excision with Intraoperative Frozen Section Assessment

Mohs micrographic surgery (MMS) is the preferred surgical technique for high-risk BCC because it allows intraoperative analysis of 100% of the excision margin. Two meta-analyses published in 1989 associated MMS with a 5-year recurrence rate of 1.0% for primary BCC, and 5.6% for recurrent BCC.[162,172] In both of these meta-analyses the recurrence rate for MMS was lower than that for standard surgical excision (10.1% and 17.4% in primary and recurrent BCC, respectively), and lower than the recurrence rate for any other treatment modality included in the analysis (C&E, cryotherapy, and RT). The only prospective randomized trial comparing MMS to standard excision was performed in the Netherlands.[173] After 10 years minimum follow-up, treatment of high-risk facial BCC with MMS resulted in fewer recurrences compared with standard excision, although the difference was only statistically significant for recurrent tumors.[174] Importantly, a large proportion of recurrences occurred more than five years after treatment: 56% for primary and 14% for recurrent BCC. This finding emphasizes the importance of long-term follow-up in therapeutic trials evaluating treatment modalities for BCC, as well as the need for long-term follow-up of patients with high-risk tumors.

Excision with complete circumferential peripheral and deep-margin assessment (CCPDMA) using intraoperative frozen section (IOFS) assessment is acceptable as an alternative to MMS provided it includes

a complete assessment of all deep and peripheral margins. The descriptive term CCPDMA underscores the panel's belief that intraoperative assessment of all tissue margins is the key to complete tumor removal for high-risk tumors.

Radiation Therapy

Although surgery is the mainstay of local treatment for BCC, patient preference and other factors may lead to the choice of RT as primary therapy.[175] Two meta-analyses reported 5-year recurrence rates of 8.7% and 10% after RT on primary and recurrent BCC, respectively.[162,172] More recent retrospective analyses of BCC treated with RT have reported 5-year local control, cure, or complete response rates ranging from 93% to 96%,[176-179] and 5-year recurrence rates from 4% to 16%.[180-182] Efficacy of RT was better for BCCs that were less advanced, primary (vs. recurrent), or had smaller diameter or nodular histologic subtype (vs. any other subtype).[176,177,179-181] A prospective study randomized 347 patients to receive either surgery (standard excision with free margins ≥2 mm from visible borders) or RT as primary treatment of BCC. RT resulted in higher recurrence rates than surgery (7.5% vs. 0.7%; P = .003),[183] poorer cosmetic outcomes, and more postoperative complications.[184]

Specifics about the application of RT, including total doses and fractionation ranges, are described under *Principles of Radiation Therapy* in the algorithm. RT is contraindicated in genetic conditions predisposing to skin cancer (eg, basal cell nevus syndrome, xeroderma pigmentosum) and connective tissue diseases (eg, lupus, scleroderma).

Intensity-modulated RT (IMRT) has been gaining wide use in recent years for the concurrent treatment of the primary skin tumor and the draining lymphatic beds. The NCCN panel emphasized the importance of proper support and training by medical physicists in using this

technology as primary treatment. Special attention is warranted to ensure adequate surface dose to the target area.

RT is often reserved for patients older than 60 years because of concerns about long-term sequelae.[185]

The value of postoperative radiation in reducing the rate of recurrence in high-risk patients has been widely accepted.[175] The NCCN Panel recommends adjuvant radiotherapy for any BCC that shows evidence of substantial perineural involvement (ie, involvement of more than just a few small sensory nerve branches or large nerve involvement).[186] In select patients, local control approaches 100% with postoperative radiotherapy.[187] Adjuvant RT should also be considered if tissue margins are positive after MMS or CCPDMA.

Superficial Therapies

Since cure rates may be lower, superficial therapies should be reserved for those patients where surgery or radiation is contraindicated or impractical.[188] Superficial therapies include topical treatment with 5-fluorouracil (5-FU) or imiquimod, photodynamic therapy (PDT), and cryotherapy.

Topical Therapies

Imiquimod was found to be effective for treating multiple, superficial BCC in randomized studies.[189-191] A prospective trial reported an 85% 5-year disease-free rate in superficial BCC.[191] A phase III randomized trial in patients with superficial or nodular BCC showed that imiquimod provided an 84% rate of clinical success, defined as absence of initial treatment failure or signs of recurrence at 3 years from start of treatment.[192] Although the clinical success rate was significantly higher in patients treated with surgical excision using a 4-mm margin (98%, P < .001), cosmetic outcomes by dermatologist assessment were significantly better with imiquimod (excellent/good at 3-year follow-up:

61% vs. 36% *P* < .0001). Another topical cream with efficacy against BCC is 5-FU, which has been shown in a randomized trial to have similar efficacy, safety, and cosmetic outcomes as imiquimod.[193]

Cryosurgery
Cryosurgery, which destroys tumor cells by freeze-thaw cycles, has been used for many years as a fast and cost-effective means for removal of BCCs. Systematic reviews of historical data in primary BCCs have reported recurrence rates for cryosurgery ranging from 0% to 13%, and mean recurrence rates from pooled analyses ranging between 3% and 4%.[162,164] In prospective trials, cryosurgery has been shown to result in BCC recurrence rates ranging from 5% to 39%.[194-197] Variability in reported recurrence rates may be due in part to patient selection, variable follow-up durations, and differences in technique and operator skill. One of the lowest recurrence rates reported (5-year cure rate 99%) is from a retrospective review of 415 BCCs treated by a single clinician.[198] A key limitation of cryotherapy is poorer cosmetic outcomes compared with other treatment options, as demonstrated by prospective randomized trials.[196,197,199]

Photodynamic Therapy
PDT involves the application of a photosensitizing agent on the skin followed by irradiation with a light source. Photosensitizing agents often used include methyl aminolevulinate (MAL) and 5-aminolevulinic acid (ALA). These two agents have similar efficacy outcomes and pain scores when used to treat patients with nodular BCC.[200,201] Multiple randomized trials and a meta-analysis including 4 of these trials have shown that rates of excellent or good cosmetic outcomes were higher with PDT versus surgery, even though surgery was superior to PDT in terms of efficacy (complete clearance, 1-year and 5-year recurrence rates).[170,202-206]

Reviews of clinical trials reported cure rates from 70% to 90% by PDT for patients with BCC.[201,207] Most of the studies of PDT for BCC have focused on the superficial and nodular histologic subtypes, and several have found higher cure rates for superficial versus nodular subtypes.[208,209] Ulceration and thickness are associated with lower response to therapy,[208] and within the nodular subtype, cure rates are better with thinner lesions.[204] Clinical studies have demonstrated PDT activity against "difficult-to-treat" lesions, with 24-month complete response rate of 78%.[209,210] Currently, PDT is being utilized at some NCCN Member Institutions for premalignant or superficial low-risk lesions on any location on the body, although response rates may be higher on the face and scalp.[211,212]

Although MAL is an approved photosensitizer for PDT, it is no longer produced in the United States.

Comparisons of Superficial Therapies
Several randomized studies and meta-analyses have compared superficial therapies for BCC. Table 1 summarizes efficacy and cosmetic outcome results from the most informative studies. Results from these studies indicate that in patients with superficial BCC, 1) PDT has similar efficacy as cryotherapy but much better cosmetic outcomes; and 2) PDT, imiquimod, and fluorouracil have similar efficacy and cosmetic outcomes, although risk of recurrence may be somewhat higher with PDT versus imiquimod. Whereas a meta-analysis of 23 randomized and non-randomized trials found no significant difference in efficacy for PDT versus imiquimod in patients with superficial BCC,[213] a more recent randomized trial (ISRCTN 79701845) showed that treatment success was more likely with imiquimod.[193] Exploratory sub-analyses found that treatment success rates were significantly higher with imiquimod versus PDT for tumors that are large or truncal, while PDT provided significantly better outcomes than imiquimod in elderly patients with lesions on the lower extremities.[214] Safety results from this

randomized trial showed that PDT and topical treatments are all associated with moderate to severe local skin redness.[193] Whereas PDT causes moderate to severe pain during treatment administration, imiquimod and fluorouracil are more likely to cause moderate to severe local swelling, erosion, crust formation, itching, and wound infections.[193] Both cryosurgery and PDT are associated with pain during and after treatment, and data from a randomized trial indicate a trend toward a higher likelihood of pain with PDT.[196]

Table 1. Studies Comparing Superficial Therapies in Patients with Superficial BCC

Study	Histologic Subtype	Treatments (n)	Efficacy		Cosmetic Outcome	
Phase III randomized trial Wang 2001[196]	Superficial and nodular	Cryosurgery (39) ALA-PDT (44)	1-year recurrence:	15% } NS 25%	Excellent:	8% } P<.001 50%
Randomized trial Basset-Seguin 2008[197]	Superficial	Cryotherapy (58) MAL-PDT (60)	5-year recurrence:	20% } NS 22%	Excellent:	16% } P=.00078 60%
Meta-analysis[a] Roozeboom 2012[213]	Superficial	Imiquimod (1088) PDT (934)	1-year tumor-free survival:	87% } NS 84%	NR	
Randomized, single-blind, non-inferiority ISRCTN 79701845 Arits 2013[193]	Superficial	MAL-PDT (202) Imiquimod cream (198) Fluorouracil cream (201)	Treatment success[b]:	73% } P=.021 83% } NS 80% } NS } NS	Good/ excellent:	62% All 61% comparisons 58% NS

MAL, methyl aminolevulinate; NR, not reported; NS, no statistically significant difference; PDT, photodynamic therapy.
[a]Meta-analysis of 23 randomized and non-randomized studies.
[b]Treatment success was defined as the product of the percent of patients with clearance at 3 months by the percentage with sustained clearance during the next 9 months.

Intralesional Interferon

Data from non-comparative open-label studies and a double-blind randomized trial with placebo control showed that intralesional interferon alfa-2b can be effective for treating low-risk, superficial BCC.[215-217] However, the panel members discussed that this approach was generally not used at their institutions because of expense, impractical treatment regimen (injections 3 times a week for 3 weeks), and associated flu-like side effects. Based on their discussion the panel consensus was to not include interferon injections for patients with low-risk, superficial BCC in the algorithm.

NCCN Recommendations
Low-Risk BCC

Primary treatment options for low-risk BCC include: 1) C&E in areas without hair growth (ie, excluding terminal hair-bearing regions, such as the scalp, pubic and axillary regions, and beard area in men), provided that the treatment be changed to excision if the adipose is reached; 2) standard excision if lesion can be excised with 4-mm clinical margins and with closure techniques such as linear closure, second intention healing, or skin graft; and 3) RT for non-surgical candidates, generally limited to those older than 60 years of age because of risk of long-term toxicity.

If margins are positive after excision, patients should receive adjuvant therapy. MMS, resection with CCPDMA with frozen or permanent section, or standard re-excision for area L regions (trunk and extremities, excluding pretibia, hands, feet, nail units, and ankle) are recommended, while radiation may be administered to non-surgical candidates.

The NCCN Panel discussed the use of alternative therapies as first-line treatment in patients with low-risk, superficial BCC where surgery or radiation is contraindicated or impractical. These include 5-FU, imiquimod, PDT with porfimer sodium or ALA, or vigorous cryotherapy. Data suggest that the cure rate of these approaches may be lower compared with surgery. On the other hand, panelist experience indicated that they may be effective for anatomically challenging locations, and recurrences are often small and manageable. Panelists agreed that these therapies may be considered for superficial BCCs based on patient preference.

High-Risk BCC
Recommended options for high-risk lesions include: 1) standard excision, using wider margins with linear or delayed repair with standard re-excision; 2) MMS or resection with CCPDMA; and 3) RT for non-surgical candidates.

Patients treated with MMS or resection with CCPDMA should receive adjuvant therapy if clear margins cannot be achieved. Recommended adjuvant therapy options include radiation and/or multidisciplinary consultation to consider systemic therapy with a hedgehog pathway inhibitor or treatment in the context of a clinical trial. FDA-approved hedgehog pathway inhibitors include vismodegib and sonidegib.[218,219]

Adjuvant RT is also recommended for patients with negative margins after surgery but with large nerve or extensive perineural involvement.

Due to the potential for skull involvement and intracranial extension, an MRI should be considered if large-nerve invasion is suspected for tumors on the head and neck.

If negative margins are not achieved after standard excision, patients should undergo MMS or resection with CCPDMA, or receive adjuvant RT. If residual disease is still present after adjuvant treatment, and further surgery and RT are contraindicated, clinicians should consider multidisciplinary consultation to determine whether the patient should be offered systemic treatment with a hedgehog pathway inhibitor or treatment in the context of a clinical trial.

Recurrence and Metastasis
Systemic Therapy
Recent FDA approval of the new agent vismodegib, a first-in-class Hedgehog pathway inhibitor, provided another option for patients who have exhausted surgical and radiation options for treating advanced BCC.[218] Approval was based on a multicenter, single-arm, two-cohort, open-label, phase II trial enrolling 104 patients (ERIVANCE).[220] About 95% of patients were previously treated with surgery, RT, and/or systemic therapies. In the most recent report, based on 21-month minimum follow-up, objective response was recorded in 48% and 33% of patients with locally advanced and metastatic disease (laBCC and mBCC), respectively, with median response duration of 9.5 months and 7.6 months, respectively.[221] As shown in Table 2, several other studies testing vismodegib in patients with advanced BCC reported response rates and median progression-free survival times that were similar or better to those from ERIVANCE, and found that median time to response was 2.6 to 2.8 months. A separate independent analysis of photographic evidence from the ERIVANCE trial, using a different system for scoring baseline disease severity and clinical efficacy,

determined that 65% of patients with laBCC showed significant improvement, and 11% significantly worsened.[222]

Vismodegib has also been tested as BCC treatment and prophylaxis in patients with nevoid BCC syndrome. A double-blind randomized phase II study in patients with nevoid BCC syndrome and at least 10 operable BCC lesions found that vismodegib significantly reduced incidence of new BCC lesions compared with placebo, and also significantly reduced the size of existing lesions and the number of surgeries needed to remove BCC lesions.[223]

Data from ERIVANCE and other studies have shown that nearly all patients treated with vismodegib experienced at least one treatment-emergent adverse event (TEAE), but a significant proportion of these were low grade (grade ≤2).[221,224,225] Serious AEs occurred in 25% to 32% of patients in these studies. Across studies the most common TEAEs (any grade) included muscle spasms, alopecia, taste loss, weight loss, decreased appetite, fatigue, nausea, and diarrhea. These adverse events (AEs) were also the most likely to lead to discontinuation. Median time to onset is less than 6 months for all the most common AEs, but for some AEs the incidence continues to increase beyond 12 months from the start of treatment.

Sonidegib, another hedgehog pathway inhibitor, has also been approved by the FDA for treatment of patients with locally advanced BCC that has recurred following surgery or RT, or who are not candidates for surgery or radiotherapy.[219] FDA approval was based on data from the phase II BOLT trial comparing two different doses of sonidegib in patients with either 1) laBCC not amenable to curative surgery or RT; or 2) mBCC for which all available treatment options have been exhausted.[226] Whereas response rates were similar for the two doses tested (Table 2), the higher dose (800 mg/d) was associated with higher rates of SAEs (14% vs. 30%) and AEs leading to dose

interruptions, reductions, or discontinuation. As with vismodegib, nearly all patients experienced at least one AE, and the most common AEs were muscle spasms, dysgeusia, alopecia, nausea, weight decrease, and fatigue. Elevated creatinine kinase was also frequently observed, and was one of the most common grade 3–4 AEs, along with elevated lipase.

A key limitation to Hedgehog pathway inhibitor therapies is that advanced BCC can develop resistance, which limits the duration of response (Table 2). A small investigator-initiated trial in patients with vismodegib-resistant advanced BCC observed no responses during treatment with sonidegib for a median of 6 weeks (range 3–58 weeks), and 5 of 9 patients progressed.[227]

Ongoing clinical research is exploring various dosing regimens of vismodegib and sonidegib in a variety of BCC treatment settings, including less advanced disease or as part of primary treatment for previously untreated disease.[228-234] An open-label single-arm trial in large (mean tumor area, 12.6 cm^2 [range 1.0–78.0 cm^2]) high-risk BCC eligible for surgical removal (n=11) found that 3 to 6 months of vismodegib prior to resection reduced the surgical defect area by 27% compared with baseline (P = .006).[228] A phase II, open-label, multicenter trial in lower-risk operable BCC lesions (ie, diameter <3 cm, previously untreated, nodular) tested the efficacy and safety of neoadjuvant vismodegib in patients willing to delay surgery (n = 74).[232] Although 50% of patients achieved investigator-assessed complete clinical clearance while on vismodegib, this trial did not meet its primary endpoints based on complete histologic clearance. Safety data from patients in cohort 2 of this trial (n= 24), who received 12 weeks of vismodegib followed by 24 weeks of observation before surgery, demonstrated high rates of AE reversibility (75%–100%) for some of the most common toxicities associated with vismodegib treatment (eg, muscle spasm, alopecia, dysgeusia, ageusia).

Other Hedgehog pathway inhibitors are being tested in patients with BCC to see if they can provide higher rates of response, more durable responses, responses in less advanced BCC, or responses in BCC resistant to vismodegib. Results from phase I–II trials with small BCC sample sizes (N < 40 patients) have shown that itraconazole and saridegib can elicit responses in patients with BCC, although not in patients who previously received vismodegib (n = 12 patients tested).[235,236]

Due to the rarity of advanced cases, the literature on chemotherapy for BCC is limited to case reports.[237-243]

Table 2. Hedgehog Pathway Inhibitors in Advanced BCC[a]

Study	Tx[b]		Patients, n		Follow-up Time, Minimum (median)[c]		Objective Response Rate[d]		Time to Response, Median[c]		Duration Response, Median[c]		Progression-free Survival, Median[c] (% progressed)	
Name and References	*Phase, Design*		*laBCC*	*mBCC*	*laBCC*	*mBCC*	*laBCC*	*mBCC*	*laBCC*	*mBCC*	*laBCC*	*mBCC*	*laBCC*	*mBCC*
ERIVANCE NCT00833417[e,221]	II OL	Vismo	71	33	≥21; (22.4)	≥21; (21.7)	48%	33%	NR	NR	9.5	7.6	9.5 (3%)	9.5 (13%)
NCT01160250[224]	II OL	Vismo	56	39	NR[f] (6.5)		46%	31%	2.6	2.6	NR	NR	NR (0%)	NR (8%)
STEVIE NCT01367665[225]	II OL	Vismo	453	29	≥12; (12.7)	≥12; (12.9)	67%	38%	2.6	2.8	22.7	10	24.5 (2%)	13.1 (14%)
RegiSONIC NCT01604252[233]	Obs	Vismo	66	-	(13.2)	-	68%	-	NR	-	5.95	-	NE	-
BOLT NCT01327053[226]	II RDB	Soni 200 mg	42	13	≥6 (13.9)		43%	15%	3.9	4.6	NE	NE	NE (12%)	13.1 (31%)
		Soni 800 mg	93	23			38%	17%	3.7	1.0	NE	NE	NE (9%)	7.6 (43%)

laBCC, locally advanced BCC; mBCC, metastatic BCC; NR, not reported; NE, not reached; Obs, prospective observational; OL, open-label; RDB, randomized double-blind; Soni, sonidegib; Tx, treatment; Vismo, vismodegib.

[a]Trials included patients with advanced BCC that was inappropriate for surgery or RT.

[b]Inhibitors were taken orally once daily. Vismodegib dose was 150 mg.

[c]Times are reported in months.

[d]Response criteria varied between studies.

[e]ERIVANCE data per independent review facility assessment.

[f]Trial was terminated early due to FDA approval of vismodegib.

NCCN Recommendations

For the management of local tumor recurrence, the algorithm directs clinicians to follow the appropriate pathways for primary treatment. Although the behavior of cutaneous BCC is characteristically indolent, the disease does occasionally metastasize to distant sites. Whenever possible, nodal or distant metastases should be treated with surgery with or without RT, and managed by a multidisciplinary tumor board. The board should consider systemic therapy with a hedgehog pathway inhibitor or treatment in the context of a clinical trial. FDA-approved hedgehog pathway inhibitors include vismodegib and sonidegib.[218,219] The panel agreed that in many patients metastatic basosquamous carcinoma will also likely respond to vismodegib.

Follow-Up

Two well-established points about patients with BCC underlie the follow-up schedules. One point is that 30% to 50% of these patients will develop another BCC within 5 years.[142,147,244-247] This represents a 10-fold increase in risk compared to the general population.[245] Patients with a prior BCC are also at increased risk of developing SCC and cutaneous melanoma.[142,247] Therefore, continued long-term surveillance of these patients is essential, as is patient education about the values of sun protection and regular self-examination of the skin. A prospective population-based cohort study found that development of a second BCC is most likely during the short-term follow-up period after diagnosis of the first lesion.[146] Therefore, close follow-up of these patients during this time period is critical.

NCCN Recommendations

The frequency of follow-up should be based on risk. In addition to patient education about sun protection and self-examination, patients should be monitored with regular physical exams including complete skin examination. Monitoring during the first 2 years is the most critical,

and exams should occur at least every 6 to 12 months during this timeframe. If no further skin cancer develops in the first 2 years, then it may be appropriate to reduce exam frequency.

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