National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Basal Cell Skin Cancer

Version 1.2023 — March 10, 2023

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Basal Cell Skin Cancer

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***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

Arya Amini, MD §
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

Karthik Ghosh, MD Þ
Mayo Clinic Comprehensive 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

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

Lawrence Mark, MD, PhD ϖ
Indiana University Melvin and Bren Simon Comprehensive Cancer Center

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 Center

Kelly Olino, MD ¶
Yale Cancer Center/Smilow Cancer Hospital

Soo Park, MD †
UC San Diego Moores Cancer Center

Tejesh Patel, MD ϖ ≠
St. Jude Children's Research Hospital/The 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 Comprehensive Cancer Center

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

Divya Srivastava, MD ϖ
UT Southwestern Simmons Comprehensive Cancer Center

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

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

Mehran Yusuf, MD §
O'Neal Comprehensive Cancer Center at UAB

NCCN
Sara Espinosa, PhD
Rashmi Kumar, PhD
Beth McCullough, RN, BS

[NCCN Guidelines Panel Disclosures]

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

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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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 1.2023 of the NCCN Guidelines for Basal Cell Skin Cancer from Version 2.2022 include:

BCC-1
- *Preliminary* Workup:
  - Bullet removed: Complete skin exam.
  - Bullet added: Shave excision if applicable.
- New option header added: Additional Workup
  - New option added: Complete skin examination.
- Risk Status, middle pathway following High risk, new option added: Consider imaging if clinical exam insufficient for following disease.
- Footnote d revised: Extensive disease includes deep ~~structural~~ involvement such as bone, *named nerves* ~~perineural disease~~, and deep soft tissue. If ~~perineural~~ disease *of named nerve(s)* is suspected, MRI with contrast is preferred. If bone disease is suspected, CT with contrast is preferred unless contraindicated.

BCC-2
- Primary Treatment:
  - Top option revised: Curettage and electrodisiccation (C&E) *or shave excision*~~: Excluding terminal hair-bearing areas, such as the scalp, pubic and axillary regions, and beard area in males.~~ *or.*
  - Second option revised: If tumor appears to extend beyond the dermis, surgical *or shave* excision should generally be performed rather than C&E.
  - New option added: Topical therapy.
- Footnote removed: 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).
- New footnotes added:
  - Footnote l: Mohs surgery should be performed by dermatologic surgeons who have specialized training and experience in this procedure. (Also page BCC-3A)
  - Footnote m: As per other appropriate use criteria. Task Force/Committee Members, Vidal CL, Armbrect EA, Andrea AA, et al. J Am Acad Dermatol 2019;80:189-207.e11. (Also page BCC-3A)

BCC-3
- Primary Treatment, new option added: For patients in whom surgery may cause significant functional damage, neoadjuvant administration of vismodegib followed by PDEMA may be considered (category 2B).

Continued

Updates in Version 1.2023 of the NCCN Guidelines for Basal Cell Skin Cancer from Version 2.2022 include:

BCC-3A
- Footnotes revised:
  - Footnote n: For ~~complicated cases (eg,~~ locally advanced *disease~~, where high chance of surgical cure is in question~~ (extensive disease where surgery and/or RT are unlikely to result in a cure or are not feasible),* consider multidisciplinary consultation~~. For locally advanced disease in which curative RT and curative surgery are not feasible, consider~~ *and* treatment with hedgehog pathway inhibitors (HHIs) (vismodegib and sonidegib) *or programmed cell death protein 1 (PD-1) inhibitor (cemiplimab-rwlc) for patients previously treated with an HHI or for whom an HHI is not appropriate.* Feasibility of surgery or radiation should be assessed by a surgeon and radiation oncologist. Principles of Systemic Therapy (BCC-E).
  - Footnote o: For ~~tumors on cheeks, forehead, scalp, neck, and pretibia that are~~ *clinically diagnosed non-facial BCCs* <6 mm in depth *on the head, neck, hands, feet, pretibia, and anogenital that are clinically* ~~and~~ confined to the dermis, C&E *or shave excision* may be considered as an alternative primary treatment option if Mohs, resection with PDEMA, and standard excision are ~~not feasible~~ *difficult to perform* due to patient comorbidities *(eg thrombocytopenia, immunosuppression, bleeding diathesis, multiple primary BCCs)*. Risk Factors for Recurrence (BCC-B).
  - Footnote r: If ~~large~~ *named* 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.
- New footnote t added: In one study of 55 patients with locally advanced basal cell carcinoma, neoadjuvant administration of vismodegib before planned surgery allowed for a smaller surgical procedure in 71% of patients, although carried a high (36.4%) recurrence risk. Bertrand N, et al. EClinicalMedicine 2021;35:100844.

BCC-4
- Recurrence or Advanced Disease:
  - Following Primary or recurrent nodal metastases, second bullet revised: *Programed cell death protein 1 (PD-1) inhibitor ~~C~~(c*emiplimab-rwlc*)*.
  - Following Distant metastases, second bullet revised: *PD-1 inhibitor ~~C~~(c*emiplimab-rwlc*)*.
- New footnote u added: Follow-up with a dermatologist is strongly recommended if any of the following criteria are met: past or imminent solid organ, marrow, or stem cell transplant, one or more cutaneous melanomas in the past 5 years, or four or more non-melanoma skin cancers in the past 5 years.

BCC-A
- Principles of Biopsy Reporting:
  - New bullet added: The intent of a biopsy is for diagnosis, not to assess the margin status.
  - Bullets revised:
    - ◊ Second bullet: Pathologic evaluation of skin biopsies is ideally performed by a dermatologist, pathologist, ~~or~~ dermatopathologist, *or Mohs surgeon* who is experienced in interpreting cutaneous neoplasms.
    - ◊ Third bullet: Clinical information to be submitted on biopsy requisition includes patient ~~demographics~~ *age and gender*, clinical diameter of lesion, anatomic location, and prior treatment of lesion. Additional helpful features to include are immunosuppression and history of RT.
    - ◊ Fourth bullet: Pathologic report should include histologic subtype and presence of any features that would increase the risk for local recurrence, including invasion of tumor beyond reticular dermis and presence *and extent* of perineural invasion ~~(if involving nerve below the dermis or >0.1 mm in caliber)~~.

Continued

Updates in Version 1.2023 of the NCCN Guidelines for Basal Cell Skin Cancer from Version 2.2022 include:

BCC-A (continued)
- Principles of Excision Reporting:
  - New bullet added: The intent of excision is to clear the tumor and thus margin status needs to be reported.
  - Bullets revised:
    - Third bullet: Clinical information to be submitted on excision requisition includes patient ~~demographics~~ *age and gender*, anatomic location, clinical diameter of lesion, and additional clinical information listed above under Principles of Biopsy Reporting.
    - Fourth bullet: 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 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.
- Reference 1 revised: ~~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~~ *Work Group; Invited Reviewers, Kim JYS, et al. Guidelines of care for the management of basal cell carcinoma. J Am Acad Dermatol 2018;78:540-559.*

BCC-B
- Stratification to Determine Treatment Options for Local BCC Based on Risk Factors for Recurrence, Location/size, High Risk, description removed: Cheeks, forehead, scalp, neck, and pretibia (any size).
- Footnote d revised: Having *basosquamous,* ~~(mixed)~~ infiltrative, *sclerosing/morpheaform,* micronodular, ~~morpheaform, basosquamous, sclerosing, or~~ *and BCC with* carcinosarcomatous differentiation features in any portion of the tumor. In some cases basosquamous tumors may be prognostically similar to *squamous cell carcinoma (*SCC*)*; clinicopathologic correlation *is recommended in these cases to further consider prognostic implication* ~~is recommended in these cases~~.

BCC-C
- Second bullet revised: 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/*topical therapy/systemic therapy* as primary treatment in order to achieve ~~optimal~~ *satisfactory* overall results.
- Third bullet revised: In certain patients at high risk for multiple primary tumors (eg, *basal cell nevus syndrome [*Gorlin syndrome*]*, xeroderma pigmentosum, history of RT), increased surveillance and consideration of prophylactic measures may be indicated. Consider referring patients with suspected *basal cell nevus syndrome (*Gorlin syndrome*)* or xeroderma pigmentosum for genetic evaluation.
- New footnote a added: Mohs surgery should be performed by dermatologic surgeons who have specialized training and experience in this procedure.

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Updates in Version 1.2023 of the NCCN Guidelines for Basal Cell Skin Cancer from Version 2.2022 include:

BCC-D
- General Principles, second bullet revised: RT is contraindicated for genetic conditions predisposing to skin cancer (eg, basal cell nevus *syndrome [Gorlin syndrome]***)** and relatively contraindicated for patients with connective tissue diseases (eg, scleroderma).
- General Treatment Information, new bullet added: Radiation treatments should be given by a practicing radiation oncologist with radiation physics support to meet established quality assurance and dosimetric constraints.
- Significant changes made to the *Recommended RT* Dosing Prescription Regimen Table.
  - New bullets added below table:
    - ◊ BED = Biologic Effective Dose
    - ◊ Conventionally fractionated radiotherapy consists of five daily treatments per week.
    - ◊ Hypofractionated radiotherapy consists of daily treatments or 2 to 4 treatments per week. Fraction sizes larger than 6 Gy are not routinely recommended outside of the palliative setting.
- New footnote a added: ASTRO Guidelines on Definitive and Postoperative Radiation Therapy for Basal and Squamous Cell Cancers of the Skin.

BCC-E
- First bullet, sub-bullet revised: Locally advanced disease is defined by those that have primary or recurrent ~~local~~ *extensive* disease ~~that are not amenable to~~ *where* surgery *and/*or RT *are unlikely to result in a cure***.**
- Third bullet revised: Multidisciplinary consultation may be required to determine the best treatment approach and deem the tumor not amenable to surgery or ~~radiation~~ RT.
- Fourth bullet, first sub-bullet revised: *Hedgehog pathway inhibitors (*HHIs*)* (ie, vismodegib, sonidegib).
  - First sub-bullet revised: 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)~~.
  - Second sub-bullet revised: HHIs may be considered for diffuse BCC formation (eg, *basal cell nevus syndrome [*Gorlin syndrome*]* or other genetic forms of multiple BCC). HHIs are not *FDA* approved for *basal cell nevus syndrome (*Gorlin syndrome*)*; however, they *may be used off-label and* are effective based on a randomized controlled trial.
- New bullet added: The role of adjuvant systemic therapy for resected BCC is unclear and thus, adjuvant systemic therapy is best performed in a clinical trial setting.

BCC-F
- New page added: Principles of Cancer Risk Assessment and Counseling

ABBR-1
- New page added: Abbreviations.

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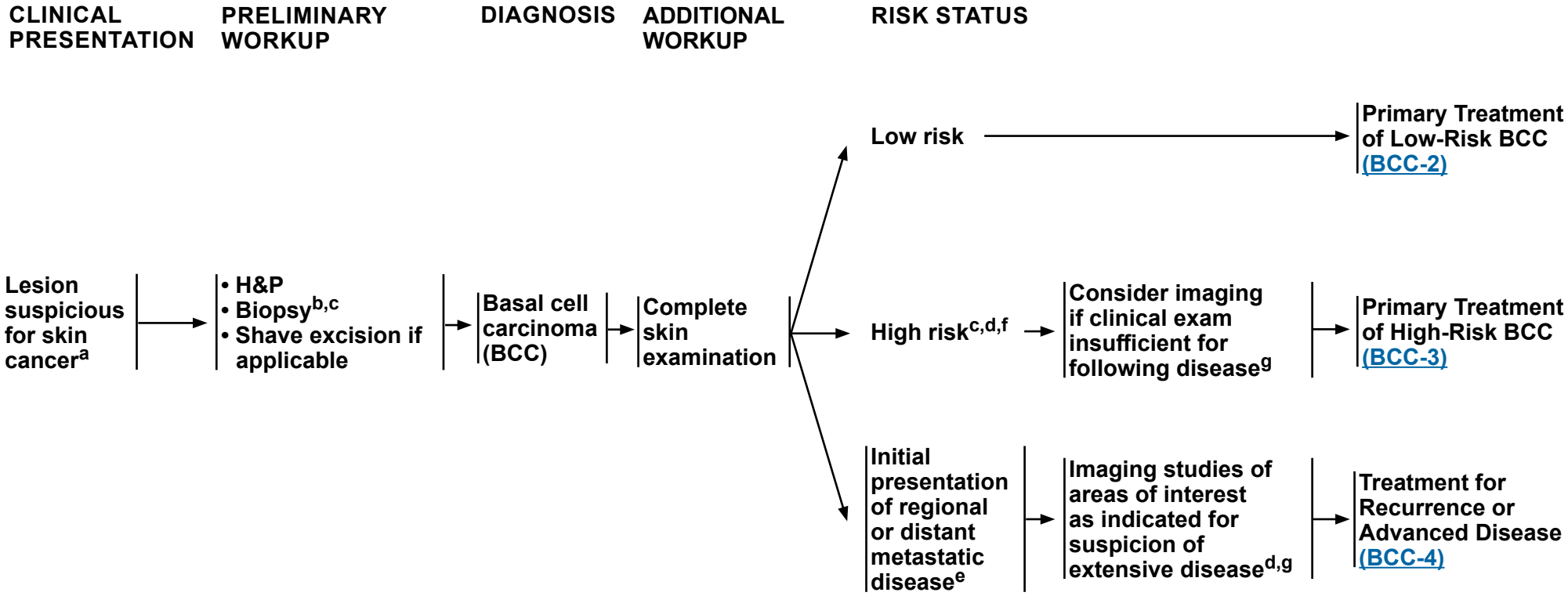
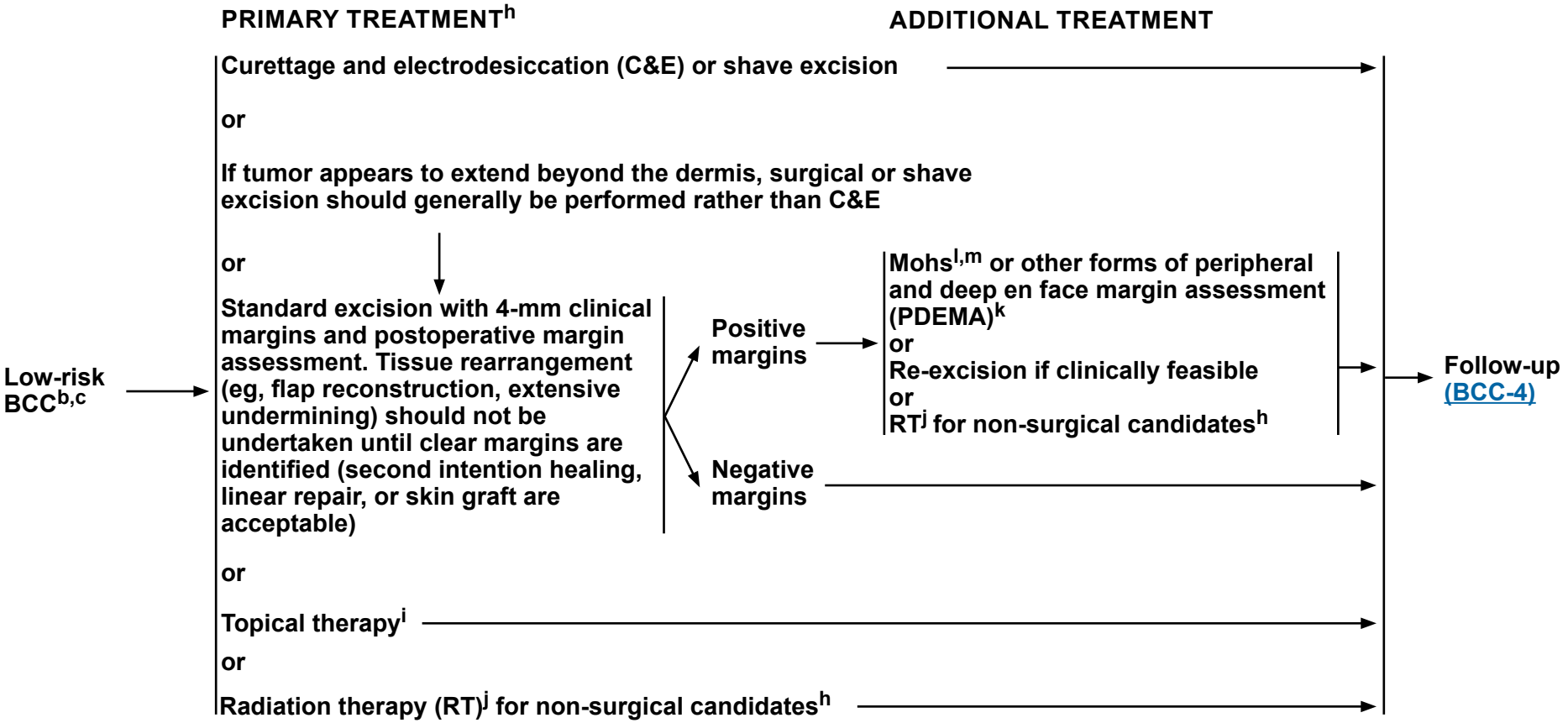


[a] For more information, see American Academy of Dermatology Association.
[b] Principles of Pathology (BCC-A).
[c] Risk Factors for Recurrence (BCC-B).
[d] Extensive disease includes deep involvement such as bone, named nerves, and deep soft tissue. If disease of named nerve(s) is suspected, MRI with 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 used for confirmation and to gauge extent of disease.

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.



[b] Principles of Pathology (BCC-A).
[c] Risk Factors for Recurrence (BCC-B).
[h] 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, although 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] 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] Mohs surgery should be performed by dermatologic surgeons who have specialized training and experience in this procedure.
[m] As per other appropriate use criteria. Task Force/Committee Members, Vidal CI, Armbrect EA, Andrea AA, et al. J Am Acad Dermatol 2019;80:189-207.e11.

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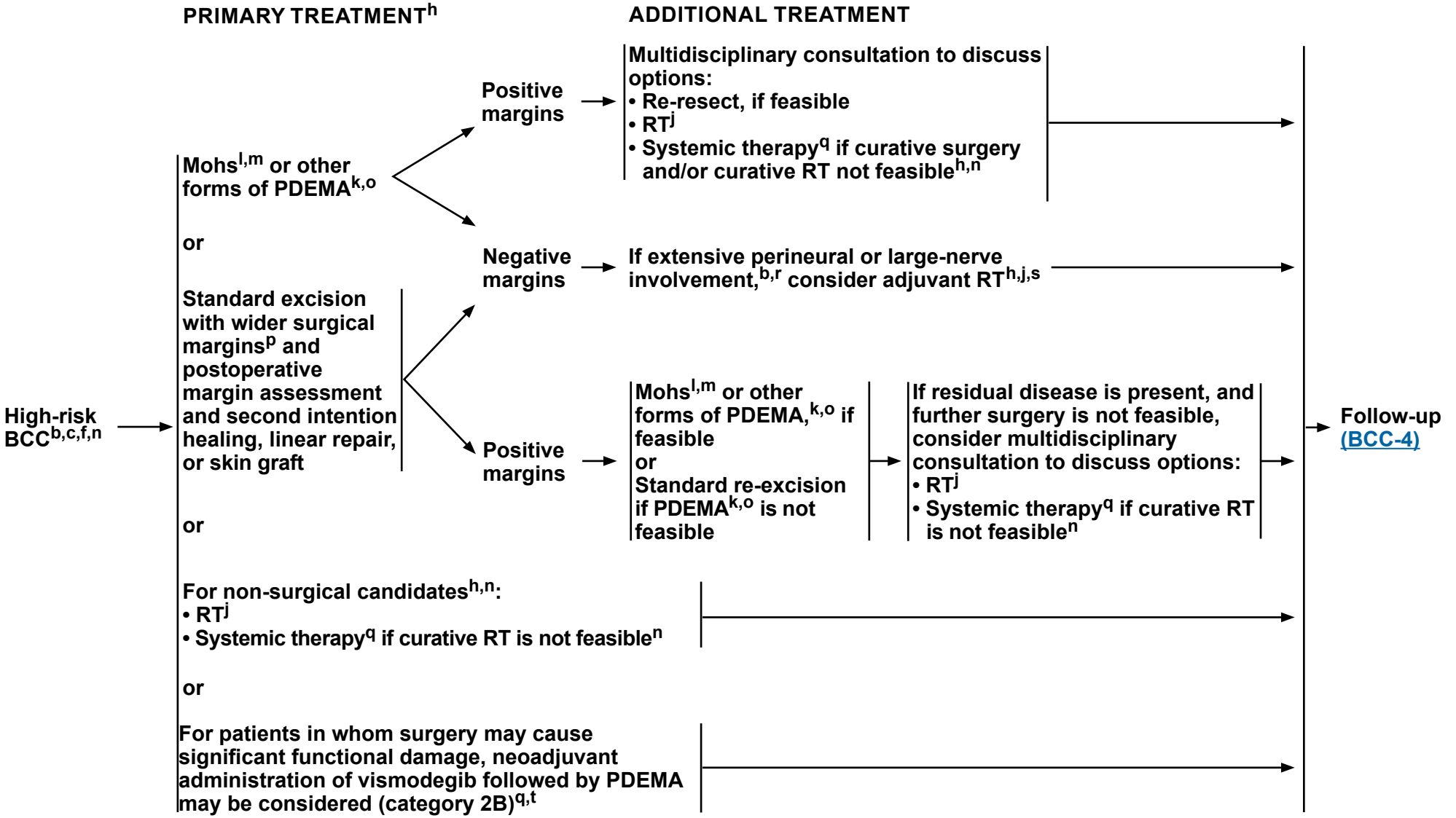

Footnotes on BCC-3A

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FOOTNOTES

[b] Principles of Pathology (BCC-A).
[c] Risk Factors for Recurrence (BCC-B).
[f] Any high-risk factor places the patient in the high-risk category.
[h] Principles of Treatment (BCC-C).
[j] 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] Mohs surgery should be performed by dermatologic surgeons who have specialized training and experience in this procedure.
[m] As per other appropriate use criteria. Task Force/Committee Members, Vidal CI, Armbrect EA, Andrea AA, et al. J Am Acad Dermatol 2019;80:189-207.e11.
[n] For locally advanced disease (extensive disease where surgery and/or RT are unlikely to result in a cure or are not feasible), consider multidisciplinary consultation and treatment with hedgehog pathway inhibitors (HHIs) (vismodegib and sonidegib) or programmed cell death protein 1 (PD-1) inhibitor (cemiplimab-rwlc) for patients previously treated with an HHI or for whom an HHI is not appropriate. Feasibility of surgery or radiation should be assessed by a surgeon and radiation oncologist. Principles of Systemic Therapy (BCC-E).
[o] For clinically diagnosed non-facial BCCs <6 mm in depth on the head, neck, hands, feet, pretibia, and anogenital that are clinically confined to the dermis, C&E or shave excision may be considered as an alternative primary treatment option if Mohs, resection with PDEMA, and standard excision are difficult to perform due to patient comorbidities (eg, thrombocytopenia, immunosuppression, bleeding diathesis, multiple primary BCCs). Risk Factors for Recurrence (BCC-B).
[p] 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.
[q] Principles of Systemic Therapy (BCC-E).
[r] If named 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.
[s] There are conflicting data about the value of adjuvant RT following margin-negative surgical excision, particularly after Mohs.
[t] In one study of 55 patients with locally advanced basal cell carcinoma, neoadjuvant administration of vismodegib before planned surgery allowed for a smaller surgical procedure in 71% of patients, although it carried a high (36.4%) recurrence risk. Bertrand N, et al. EClinicalMedicine 2021;35:100844.

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FOLLOW-UP

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

RECURRENCE OR ADVANCED DISEASE

Local recurrence → **Follow Primary Treatment pathway for 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[q]
- Hedgehog pathway inhibitor (HHI)
  - Vismodegib
  - Sonidegib (category 2B)
- Programmed cell death protein 1 (PD-1) inhibitor (cemiplimab-rwlc)[w]
- Clinical trial

Distant metastases →

Multidisciplinary consultation to consider:
Systemic therapy[q]
- HHI
  - Vismodegib
- PD-1 inhibitor (cemiplimab-rwlc)[w]

or
RT[j] or surgery for limited metastatic disease[x]
or
Palliation and best supportive care

[j] Principles of Radiation Therapy (BCC-D).
[q] Principles of Systemic Therapy (BCC-E).
[u] Follow-up with a dermatologist is strongly recommended if any of the following criteria are met: past or imminent solid organ, marrow, or stem cell transplant, one or more cutaneous melanomas in the past 5 years, or four or more non-melanoma skin cancers in the past 5 years.
[v] 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 used for confirmation and to gauge extent of disease.
[w] Cemiplimab-rwlc is recommended for patients with locally advanced or metastatic basal cell carcinoma (mBCC) previously treated with an HHI or for whom an HHI is not appropriate.
[x] 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:

- **The intent of a biopsy is for diagnosis, not to assess the margin status.**
- **Pathologic evaluation of skin biopsies is ideally performed by a dermatologist, pathologist, dermatopathologist, or Mohs surgeon who is experienced in interpreting cutaneous neoplasms.**
- **Clinical information to be submitted on biopsy requisition includes patient age and gender, 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[a] and presence and extent of any features that would increase the risk for local recurrence, including invasion of tumor beyond reticular dermis and presence of perineural invasion.[1]**

Principles of Excision Reporting:

- **The intent of excision is to clear the tumor and thus margin status needs to be reported.**
- **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 age and gender, 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 BCC,[a] 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.[2]**

[a] 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.

[1] Work Group; Invited Reviewers, Kim JYS, et al. Guidelines of care for the management of basal cell carcinoma. J Am Acad Dermatol 2018;78:540-559.
[2] 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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STRATIFICATION TO DETERMINE TREATMENT OPTIONS FOR LOCAL BCC BASED ON RISK FACTORS FOR RECURRENCE[a]

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

[a] Any high-risk factor places the patient in the high-risk category.
[b] Low-risk histologic subtypes include nodular, superficial, and other non-aggressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus.
[c] 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.
[d] Having basosquamous, infiltrative, sclerosing/morpheaform, micronodular, and BCC with carcinosarcomatous differentiation features in any portion of the tumor. In some cases, basosquamous tumors may be prognostically similar to squamous cell carcinoma (SCC); clinicopathologic correlation is recommended in these cases to further consider prognostic implication.

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PRINCIPLES OF TREATMENT

- **The primary treatment goal 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/topical therapy/systemic therapy as primary treatment in order to achieve satisfactory overall results.**
- **In certain patients at high risk for multiple primary tumors (eg, basal cell nevus syndrome [Gorlin syndrome], xeroderma pigmentosum, history of RT), increased surveillance and consideration of prophylactic measures may be indicated. Consider referring patients with suspected basal cell nevus syndrome (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[a] 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.[1,2]**

[a] Mohs surgery should be performed by dermatologic surgeons who have specialized training and experience in this procedure.

[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.
[2] 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[a]

- 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 [Gorlin 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

- Radiation treatments should be given by a practicing radiation oncologist with radiation physics support to meet established quality assurance and dosimetric constraints.

Primary Tumor	RT Dosing
Definitive RT	BED10 of 70–93 Gy for conventional fractionation BED10 of 56–88 Gy for hypofractionation
Postoperative adjuvant RT	BED10 of 60–79 Gy for conventional fractionation BED10 of 56–70 Gy for hypofractionation
Regional Disease	
• Lymph node regions, after lymph node dissection	
▸ Negative margins, no Extracapsular Extension (ECE)	50–60 Gy over 5 to 6 weeks
▸ Positive margins or ECE	60–66 Gy over 6 to 7 weeks
• Lymph node regions, without lymph node dissection	
▸ Clinically negative, at risk	50 Gy over 5 to 7 weeks
▸ Clinically positive	60–70 Gy over 6 to 7 weeks
• Clinically at-risk nerves	50–60 Gy over 5 to 6 weeks

- BED = Biologic Effective Dose
- Conventionally fractionated radiotherapy consists of five daily treatments per week.
- Hypofractionated radiotherapy consists of daily treatments or 2 to 4 treatments per week. Fraction sizes larger than 6 Gy are not routinely recommended outside of the palliative setting.

[a] ASTRO Guideline on Definitive and Postoperative Radiation Therapy for Basal and Squamous Cell Cancers of the Skin.

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.

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 extensive disease where surgery and/or RT are unlikely to result in a cure.**
- **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 RT.**
- **Systemic therapy options include:**
  - **Hedgehog pathway inhibitors (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.**
    - **HHIs may be considered for diffuse BCC formation (eg, basal cell nevus syndrome [Gorlin syndrome] or other genetic forms of multiple BCC). HHIs are not FDA approved for basal cell nevus syndrome (Gorlin syndrome); however, they may be used off-label and 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.**
- **The role of adjuvant systemic therapy for resected BCC is unclear and thus, adjuvant systemic therapy is best performed in a clinical trial setting.**

[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, Ally MS, Chanana AM, et al. Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2016;17:1720-1731.

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.

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- **The decision to offer genetic testing involves three related stages:**
  1) **Pre-test counseling prior to ordering testing;**
  2) **Consideration of the most appropriate testing strategy; and**
  3) **Testing result disclosure and post-test counseling.**
- **In certain patients at high risk for multiple primary tumors (eg, basal cell nevus syndrome [Gorlin syndrome], xeroderma pigmentosum, history of RT), increased surveillance and consideration of prophylactic measures may be indicated. Patients with these conditions should be referred to a cancer center with particular expertise in BCC prevention and prophylaxis.**
- **It is recommended that a genetic counselor, medical geneticist, endocrinologist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics be involved at each stage whenever possible. Clinicians without direct referral access to the appropriate expertise should be aware of the telehealth genetic counseling options available. These resources can be found through the National Society of Genetic Counselors (NSGC) "Find a Genetic Counselor" tool (www.nsgc.org).**

See the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic for the following:
- **Principles of Cancer Risk Assessment and Counseling (EVAL-A)**
- **Pedigree: First-, Second-, and Third-Degree Relatives of Proband (EVAL-B)**
- **General Testing Criteria (CRIT-1)**

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.

ABBREVIATIONS

BCC	**basal cell carcinoma**
BED	**biologically effective dose**
C&E	**curettage and electrodessication**
ECE	**extracapsular extension**
H&P	**history and physical**
HHI	**hedgehog pathway inhibitors**
mBCC	**metastatic basal cell carcinoma**
NSGC	**National Society of Genetic Counselors**
PDEMA	**peripheral and deep en face margin assessment**
RT	**radiation therapy**

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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Basal Cell Skin Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Basal Cell Skin Cancer. Last updated: January 31st, 2022.

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Overview

Basal cell carcinoma (BCC) is the most common cancer in the United States. It is estimated that BCCs occur in 2 million Americans annually, exceeding the incidence of all other cancers combined.[1-3] BCCs are at least 2 times more common than squamous cell carcinomas (SCCs), the second most common type of skin cancer.[1-6] Furthermore, the incidence of this common malignancy is rising rapidly.[1,3,6,7] Compared with SCC, BCCs are much less likely to metastasize, with a metastatic rate of <0.1%, and thus generally have a good prognosis.[8-10] Although rarely metastatic, BCC can produce substantial local destruction along with disfigurement and may involve extensive areas of soft tissue, cartilage, and bone.

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.[11-15] 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.[13,15-22] BCC risk is increased by both UV-A and -B radiation as well as by ionizing radiation. Radiation treatment (RT) for other conditions, especially at a young age, is also associated with an increased risk for developing BCC.[23-27] Most BCC tumors develop on skin sites exposed to radiation—either from the sun or from therapy.[23-25]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Basal Cell Skin Cancer, an electronic search of the PubMed database was performed to obtain key literature using the following search term: basal cell carcinoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[28]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

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.[29-31] 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.[32-40] Specific UV-induced mutations in the tumor suppressor gene *p53* appear to be a common event in BCC development.[34,37,40,41] Certain genetic syndromes greatly predispose affected individuals to skin cancer formation, including BCC, such as albinism[42,43] and xeroderma pigmentosum (in which defects exist in UV light-induced unscheduled DNA repair).[44-50]

Clinical Presentation and Workup

On clinical presentation of the patient with lesion suspicious of skin cancer, 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 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.[51] A skin biopsy is then performed on any suspicious lesion. The biopsy should include deep reticular dermis. 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.[52,53]

Risk Stratification of Local BCC Based on Risk Factors for Recurrence

After workup, a risk assessment should be performed to determine the treatment plan. The NCCN Panel examined risk factors for BCC associated with recurrence (Refer to Guidelines section *BCC-B Risk Factors for Recurrence*). Any high-risk factor places the patient in the high-risk category. 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. For rare cases that present with regional or distant metastatic disease at diagnosis, the disease should be treated as nodal or distant metastases. Imaging studies may be clinically evident when extensive disease, such as bone involvement, perineural invasion (PNI), or deep soft tissue involvement, is suspected. If perineural disease is suspected, MRI with contrast is preferred.[54,55] If bone disease is suspected, CT with contrast is preferred unless contraindicated. 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 metastases, histologic analysis and/or CT imaging can be used for confirmation and to gauge extent of disease.

History & Physical Examination

Location and Size

Anatomic location[56-62] and size[58-64] have been known to be a risk factor for BCC recurrence and metastasis for many years. In general, BCCs that develop in the head and neck area, which includes the “H zone” or “mask area” of the face, are more likely to recur than those that develop on the trunk and extremities. Based on a 27-year retrospective review of 5755 BCCs, recurrences were significantly more common when tumors in high-risk locations (central face, eyebrows, nose, lips, chin, ear, temple, genitalia, nipples/areola, hands, feet, ankles nail units) were greater than or equal to 6 mm in diameter and when tumors in moderate-risk locations (cheeks, forehead, scalp, neck, jawline, pretibial surface) were greater than or equal to 10 mm in diameter.[65] More recently, the American Academy of Dermatology 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 document in the treatment of cutaneous neoplasms based on 270 clinical scenarios including 69 BCCs,[66] which has been incorporated into Guidelines section *BCC-B Risk Factors for Recurrence*.

Clinical Borders and Primary Versus Recurrent Disease

The low- and high-risk factors of well-defined versus ill-defined clinical tumor borders[67-69] and primary versus recurrent disease,[60,68,70] respectively, have been extensively documented in the literature.

Immunosuppression

Settings of immunosuppression, such as organ transplantation,[71-76] and long-term use of psoralen and UVA light (PUVA),[77,78] increase the incidence of BCC. In particular, among patients who have had organ transplants, BCC incidence is approximately 5- to 10-fold higher than in the general population,[79-81] occurring in up to half of patients during the 10 years following transplant.[82-85] Several large retrospective studies found that BCCs in patients who had received organ transplants were more likely to have the superficial histologic subtype and to occur in extracephalic locations and in younger patients (mean age of onset 15 years lower). [86-88] Two of these studies showed similar low recurrence rates for transplant recipients and controls.[87,88] 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 RT 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 RT for unrelated, frequently benign conditions is a risk factor for BCC development.[23-27,89,90]

Pathology

Pathologic Subtypes

Histologic subtyping of BCC as a predictor of risk of recurrence is a well-established concept.[91,92] 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.[63,67,68,70,93-97] Non-aggressive subtypes include the keratotic variant, infundibulocystic variant, and fibroepithelioma of Pinkus.

Basosquamous carcinomas are tumors of which have the histologic appearance of both a BCC and 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.[98] Data suggest that basosquamous carcinomas have a metastatic capacity that is more similar to that of SCC than BCC.[99-101]

Perineural Involvement

PNI is uncommon in any nonmelanoma skin cancer (NMSC) (2%–6%), and develops less frequently and is less aggressive in BCC versus SCC.[102-107] BCC with PNI 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, morpheaform, and basosquamous subtypes.[106,108,109] 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.[55,110-112]

Age and Its Effect on BCC Behavior

Whether young age (typically ≤40 years) is an independent risk factor for aggressive BCC behavior is debatable. An analysis of a large database of patients with BCC (N = 3381) documented an increased percentage of BCC with aggressive histologic growth patterns in young persons.[113] In contrast, results from other analyses of large databases (N = 1000 to >10,000) indicate that patients presenting with BCC at a young age are more likely to have the superficial subtype.[114-117] Other analyses report no significant differences in BCC histologic subtype between young versus older patients.[118-120] The relationship between tumor location and patient age is also unclear, as several studies showed that younger patients were more likely to present with BCCs on

the trunk or extremities,[114,119,121,122] but other studies found no significant association.[118]

Most large studies (N = 50-2000) have shown no significant association between age and recurrence rate.[60,68,118,120] One multivariate analysis, however, showed a positive relationship between increasing age and likelihood of recurrence.[123] Age has also been evaluated as a risk factor for developing a second or multiple BCCs.[63,120,122-130] Many of these studies used fairly large databases (N = 200–2500), and found that risk of developing more than one BCC is associated with increased age.[63,120,122-125,127,129,130] On the contrary, an analysis of a very large database (N = 71,924) found a significantly higher risk of subsequent NMSC in patients younger than 40 years at the time of their first BCC diagnosis.[131] In addition, an analysis of 100 metastatic BCC cases found that patients with distant metastases tended to be younger than those with only regional metastases.[132] Consistent with this idea, the Rotterdam Study showed that while the risk of developing a second BCC increased with age,[130] the risk of developing multiple BCC lesions was highest in patients who were younger than 65 years at the time of their first BCC diagnosis.[128] Taken together, these studies suggest that young age, in and of itself, is not considered a risk factor for aggressive BCC. Nevertheless, there is a small subset of patients who develop BCC at a young age and may have particularly aggressive disease. These patients may benefit from regular follow-up.

Treatment Modalities for BCC

Curettage and Electrodesiccation

Although a fast and cost-effective technique for superficial lesions, curettage and electrodesiccation (C&E) does not allow histologic margin assessment. Studies have reported overall 5-year recurrence rates ranging from 1.2% to 40% in patients with BCC selected for C&E, with high-risk locations and histologically aggressive subtypes reporting higher recurrence rates.[58,133-141]

This technique is deemed effective for properly selected, local, low-risk BCC with three caveats.[58,139] First, C&E 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. Since subcutaneous adipose is even softer than tumor tissue, the ability of the curette to distinguish and, therefore, selectively and completely remove tumor cells diminishes. Third, if C&E has been performed based only on the appearance of a low-risk tumor, biopsy results of the tissue taken at the time of C&E should be reviewed to make sure that there are no high-risk pathologic features that would require additional therapy. For tumors on the cheeks, forehead, scalp, neck, and pretibial that are less than 6 mm in depth and confined to the dermis, C&E may be considered as an alternative primary treatment option if Mohs micrographic surgery (Mohs) or resection with peripheral and deep en face margin assessment (PDEMA), and standard excision are not feasible due to patient comorbidities.

Standard 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 recurrence rates of 0.8% to 17.4% for BCC, with lower recurrence rates associated with low-risk tumors and higher recurrence rates associated with high-risk tumors.[133,135,141-144] Studies have reported variable margins required to completely excise 95% of all tumor.[145-149] These margins have been suggested to be 2 to 4 mm for low-risk, well-demarcated tumors smaller than 2 cm,[145-149] whereas margins of 4 to 6 mm,[146] and in one study, 8 mm[145] were suggested for high-risk BCC. Given this wide variability, studies have reported incomplete excision rates after standard excision ranging from 3.2% to 61.5% depending on tumor location, histologic subtype, and medical provider's specialty.[150-159] Therefore, postoperative margin assessment and identification of clear margins are critical to ensure favorable outcomes with standard excision.

The clinical margins chosen by the panel for the primary treatment of local, low-risk BCC are based on the work of Zitelli et al.[160] Their analysis indicated that for well-circumscribed BCC lesions smaller 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 if positive margins are obtained after an initial excision with postoperative margin assessment. For local, high-risk BCC, standard excision with wider surgical margins is recommended as the primary treatment. 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. Kean 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. When standard excision with wider surgical margins yields positive margins, Mohs) or other forms of PDEMA or standard re-excision is recommended (if PDEMA is not feasible).

For either local, low-risk or local, high-risk BCC, when standard excision is used, 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 options.

Mohs Micrographic Surgery and Peripheral and Deep En Face Margin Assessment

Mohs is the preferred surgical technique over standard excision for re-excision of local, low-risk BCC after positive margins with standard excision, as well as the primary surgical technique of choice for local, high-risk BCC because it allows intraoperative analysis of 100% of the excision margin. Mohs is also recommended when standard excision with wider surgical margins is unable to achieve negative margins in local, high-risk BCC. Two meta-analyses published in 1989 associated Mohs with 5-year recurrence rates of 1.0% for primary BCC, and 5.6% for recurrent BCC.[133,141] In these studies, the recurrence rates for Mohs were lower than those for standard excision (10.1% and 17.4% for primary and recurrent BCC, respectively), and lower than those for any other treatment modality included in the analysis (C&E, cryotherapy, and RT).[133,141] More recent studies on the long-term outcomes (~ 4 years) of Mohs have reported overall recurrence rates of 2.9% to 3.8%,[161,162] specifically 0% to 6.5% for primary and 4% to 20% for recurrent BCCs.[92,163-168] The only prospective randomized trial comparing Mohs to standard excision reported fewer 10-year recurrences with Mohs for both primary (2.5% vs. 4.1%; $P = .397$) and recurrent BCC (2.4% vs. 12.1%; $P = .015$), although the difference was only statistically significant for recurrent tumors. Importantly, a large proportion of recurrences occurred more than 5 years after

treatment.[169-171] Besides lower recurrence rates, Mohs has also been associated with significant tissue sparing compared with standard excision.[172,173] It has been demonstrated that H-zone location, recurrent tumor, aggressive subtype, PNI, and tumor size greater than or equal to 11 mm are significantly associated with two or more Mohs stages.[108,174] However, superficial BCC, despite being generally considered less aggressive, was shown in a Brazilian study to be 9.03 times more likely to require more than one Mohs stage, likely due to "skip areas" and clinically indistinct borders.[175]

Excision with PDEMA with permanent section analysis or intraoperative frozen section analysis is an acceptable alternative to Mohs provided it includes a complete assessment of all deep and peripheral margins. A 5-year recurrence rate of 0.58% has been reported with slow Mohs using formalin-fixed paraffin-embedded sections and delayed closure in a UK-based prospective study.[176] The descriptive term PDEMA underscores the panel's belief that complete histologic assessment of the entire marginal surface is the key to optimal tumor removal. For more information, refer to the NCCN Guidelines® for Squamous Cell Skin Cancer *SCC-G Principles of PDEMA Technique*.

Radiation Therapy

Although surgery is the mainstay of local treatment for BCC, consideration of function and patient preference and other factors may lead to the choice of RT as primary therapy for both local, low-risk and local, high-risk BCC.[177] The recommendations for RT extend to additional treatment for local, low-risk BCC after positive margins with standard excision. RT is also recommended for local, high-risk BCC as additional treatment after positive margins with Mohs or other forms of PDEMA and adjuvant treatment after negative margins with Mohs or other forms of PDEMA in case of extensive perineural or large-nerve involvement.[178] In these patients, local control has been reported to be 50% to 90% with postoperative RT.[177,179] There are conflicting data about the value of adjuvant RT following margin-negative surgical excision, particularly after Mohs. For local, high-risk BCC that has undergone multiple resections, and further surgery is not feasible, RT is recommended as part of multidisciplinary consultation if residual disease is present. For specifics about the application of RT, refer to Guidelines section *BCC-D Principles of Radiation Therapy*.

Two meta-analyses reported 5-year recurrence rates of 8.7% and 9.8% after RT on primary and recurrent BCC, respectively.[133,141] Retrospective analyses of BCC treated with RT have reported 5-year local control, cure, or complete response rates ranging from 93% to 96%,[180-183] and 5-year recurrence rates from 4% to 16%.[184-186] Efficacy of RT was better for BCCs that were less advanced, primary (vs. recurrent), or had smaller diameter or nodular histologic subtype.[180,181,183-185] A prospective study randomizing 347 patients to receive either surgery (standard excision with free margins ≥2 mm from visible borders) or RT as primary treatment of BCC reported higher recurrence rates with RT than surgery (7.5% vs. 0.7%; $P = .003$),[187] poorer cosmetic outcomes, and more postoperative complications.[188]

A small number of prospective studies have reported high rates of tumor control with specific radiation dose fractionation regimens for small BCCs.[187,189,190] A recent systematic review and meta-analysis also reported hypo-fractionated RT regimens associated with positive cosmetic outcomes.[191] The NCCN Panel recommends ranges of electron beam dose and fractionation that can be used for definite RT and postoperative adjuvant RT. Isotope-based brachytherapy can be an effective treatment for certain sites of disease, particularly on the head and neck.[192-195] However, there are insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy.[196,197]

Superficial Therapies

In patients with superficial BCC, therapies such as topical imiquimod, topical 5-fluorouracil (5-FU), photodynamic therapy (PDT), or cryotherapy may be considered, although cure rates are approximately 10% lower than for surgical treatment modalities.[198-200] These options are also recommended for patients where surgery or RT is contraindicated or impractical.

Topical Therapies

Imiquimod was found to be effective for treating nodular[201,202] and superficial[201,203-206] BCC in randomized studies. Two 5-year follow-up studies reported overall treatment success rates of 80.4% and 77.9%, respectively, in patients with superficial BCC treated with imiquimod.[205,207] Recurrence seems to be associated with tumor thickness.[208] A phase III randomized trial in patients with superficial or nodular BCC showed that imiquimod provided an 82.5% clinical success rate.[209,210] For all of these studies, tumors in the H-zone were excluded. Although the clinical success rate was significantly higher with surgical excision using a 4-mm margin (97.7%; $P < .001$), cosmetic outcomes by dermatologist assessment were significantly better with imiquimod (excellent/good at 3-year follow-up: 61% vs. 36%; $P < .001$). Another topical cream with efficacy against BCC is fluorouracil (5-FU),[211,212] which has been shown in a large randomized trial to have a 5-year tumor-free survival probability of 70.0%.[199,213,214] Other studies have reported cure rates of up to 90% with this treatment.[215-217]

Photodynamic Therapy

PDT with photosensitizing agents including methyl aminolevulinate (MAL), 5-aminolevulinic acid (ALA), and porfimer sodium is another option for superficial BCC.[218-220] MAL is no longer produced in the United States. Multiple randomized trials and a meta-analysis have shown that rates of excellent or good cosmetic outcomes were higher with PDT versus surgery, although surgery was superior to PDT in terms of disease control.[143,221-228] Data from clinical trials reported cure rates from 60% to 100% by PDT for patients with BCC.[224,229-234] Most of these studies have focused on the superficial and nodular histologic subtypes, and several have found higher cure rates for superficial versus nodular subtypes in both low- and high-risk locations.[224,229,234] Ulceration and thickness are associated with lower response to therapy,[234] and within the nodular subtype, cure rates are better with thinner lesions.[223] Clinical studies have demonstrated PDT activity against “difficult-to-treat” lesions, with 24-month complete response rate of 78%.[229,235] Currently, PDT is being used 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.[236,237]

Cryotherapy

Cryotherapy 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 cryotherapy ranging from 0% to 13%, and mean recurrence rates from pooled analyses ranging between 3% and 4%.[133,135,238,239] In prospective trials, cryotherapy has been shown to result in recurrence rates ranging from 5% to 39%.[189,240-242] A key limitation of cryotherapy is poorer cosmetic outcomes compared with other treatment options, as demonstrated by prospective randomized trials.[241-243]

Comparisons of Superficial Therapies

Several randomized studies and meta-analyses have compared superficial therapies for BCC (Table 1). In summary, these studies indicate that in patients with superficial BCC, PDT has similar efficacy as cryotherapy but much better cosmetic outcomes. Whereas a meta-analysis of 23 randomized and non-randomized trials found no significant difference in efficacy for PDT versus imiquimod,[244] a more recent randomized trial showed that treatment success was more likely

with imiquimod.[199,214] This study also demonstrate superior imiquimod outcomes compared to 5-FU cream. Exploratory sub-analyses found that treatment success rates were significantly higher with imiquimod for tumors that are large or truncal, while PDT provided significantly better outcomes in elderly patients with lesions on the lower extremities.[245] Safety results showed that while PDT causes moderate to severe pain during treatment administration, imiquimod and 5-FU are more likely to cause moderate to severe local swelling, erosion, crust formation, itching, and wound infections.[213] Both cryotherapy 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.[241]

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

Study	*Histologic Subtype*	*Tumor Locations*	*Treatments (n)*	*Efficacy*			*Cosmetic Outcome*		
Phase III randomized trial Wang 2001[241]	Superficial and nodular	Trunk, limb, head, neck	Cryosurgery (39) ALA-PDT (44)	1-year recurrence:	15% 25%	NS	Excellent:	8% 50%	$P < .001$
Randomized trial Basset-Seguin 2008[242]	Superficial	Trunk, limb, head, neck, face	Cryotherapy (58) MAL-PDT (60)	5-year recurrence:	20% 22%	NS	Excellent:	16% 60%	$P = .00078$
Meta-analysis Roozeboom 2012[244]	Superficial	Locations depend on individual studies	Imiquimod (1088) PDT (934)	1-year tumor-free survival:	87% 84%	NS			NR
Randomized, single-blind, non-inferiority trial Jansen 2018[199]	Superficial	Trunk, limb, head, neck	MAL-PDT (202) Imiquimod cream (198) Fluorouracil cream (201)	Treatment Success[a]:	63% 81% 70	$P < .001$ $P = .04$ NS	Good/ excellent:	62% 61% 58%	All comparisons NS

MAL, methyl aminolevulinate; NR, not reported; NS, no statistically significant difference; PDT, photodynamic therapy.
[a]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.

Nicotinamide in Reducing BCC Development

Data from phase II and phase III randomized trials indicated that treatment of actinic keratoses with nicotinamide reduced the occurrence of new BCCs, specifically by 20% at 12-month follow-up.[246,247] This is supported by data from another study.[248] Other agents that might be effective for the prevention of BCC in individuals at high risk for developing NMSCs include celecoxib,[249] acitretin,[250] capecitabine,[251] and tazarotene.[252]

Systemic Therapy

For local, high-risk BCC, systemic therapy is recommended after positive margin with Mohs or other forms of PDEMA, for residual disease after multiple resections (with Mohs or other forms of PDEMA or standard excision), or as primary treatment if curative RT and/or curative surgery is not feasible. The indication for systemic therapy is also extended to recurrent BCC after surgery, locally advanced (laBCC) or metastatic BCC (mBCC) where topical therapy, surgery, or RT is unlikely to be curative. The systemic therapy options for BCC include hedgehog pathway inhibitor (HHI) and immunotherapy.

Vismodegib is an HHI approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with laBCC or mBCC that has recurred following surgery, or those who are not candidates for surgery or RT.[253] 39-month follow-up data from the ERIVANCE trial, a multicenter phase II trial enrolling 104 patients reported an objective response rate (ORR) of 48.5% in the mBCC group and 60.3% in the laBCC group, with a median duration of response of 14.8 months and 26.2 months for each group, respectively.[254-257] Results from other clinical trials testing vismodegib in BCC are summarized in Table 2. According to these data, 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).[256,258,259] Serious AEs (SAEs) occurred in 25% to 32% of patients in these studies. The most common AEs included muscle spasms, alopecia, taste loss, weight loss, decreased appetite, fatigue, nausea, and diarrhea.

Vismodegib has also been tested as BCC treatment and prophylaxis in patients with nevoid BCC syndrome. A 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.[260-262]

Sonidegib is another HHI FDA-approved for the treatment of patients with laBCC that has recurred following surgery or RT, or who are not candidates for surgery or RT.[263] Sonidegib is not FDA approved for mBCC. 42-month follow-up data from the phase II BOLT trial reported similar ORRs for the two doses tested among patients with laBCC.[264-268] 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 HHI therapies is that advanced BCC can develop resistance, which limits the duration of response. 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.[269] Results from systematic reviews and meta-analyses on HHI in BCC are summarized in Table 2.

Ongoing clinical research is exploring various dosing regimens of vismodegib and sonidegib in a variety of BCC treatment settings, including in the neoadjuvant setting, in patients with multiple BCCs, in patients with radiation-induced multiple BCCs of the scalp, as maintenance therapy after laBCC complete remission.[270-275] Notably, in the neoadjuvant setting, while one trial reported negative results (unmet predefined complete histologic clearance rate),[271] results from two studies indicated vismodegib may reduce surgical defect area and allow for downstaging of the surgical procedure for laBCCs in functionally sensitive locations.[270,273] However, all of these studies included small

numbers of patients, and thus their results need to be carefully interpreted.

Other HHIs are also 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) have shown that itraconazole and saridegib can elicit responses in patients with BCC, although not in patients who previously received vismodegib.[276,277]

Cemiplimab-rwlc is an anti-PD-1 immunotherapy FDA-approved for patients with laBCC or mBCC previously treated with an HHI or for whom an HHI is not appropriate.[278] Results from a phase II trial testing cemiplimab-rwlc (N = 84) with a median follow-up of 15 months reported an ORR of 31% and grade 3-4 TEAEs in 48% of patients. SAEs occurred in 35% of patients.[279]

Due to the rarity of advanced cases, the literature on chemotherapy for BCC is limited to case reports.[280-286]

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

Study		*Tx[b]*	*Patients, n*		*Objective Response Rate[d]*		*Duration of Response, Median[c]*		*Progression-free Survival, Median[c]*		*Overall Survival, Median[c]*	
Name and References	*Design*		*laBCC*	*mBCC*	*laBCC*	*mBCC*	*laBCC*	*mBCC*	*laBCC*	*mBCC*	*laBCC*	*mBCC*
ERIVANCE – 39-month follow-up NCT00833417[254-257]	Phase II OL	Vismo	63	33	60%	49%	26.2	14.8	12.9	9.3	NE	33.4
STEVIE – 12-month follow-up NCT01367665[259,287,288]	Phase II OL	Vismo	1077	84	69%	37%	23.0	13.9	23.2	13.1	NR	NR
NCT01160250[258, e]	Phase II OL	Vismo	56	39	46%	31%	NR	NR	NR	NR	NR	NR
RegiSONIC NCT01604252[289, f]	Obs	Vismo	66	–	68%	–	5.95	–	NE	–	NR	–
BOLT – 42-month follow-up NCT01327053[264-268]	Phase II RDB	Soni 200 mg	66	13	56%	8%	26.1	24.0	22.1	13.1	NR	NR
		Soni 800 mg	128	23	46%	17%	23.3	NE	24.9	11.1	NR	NR
Jacobsen et al[290]	Systematic review	Vismo	704		65%	34%						
Xie et al[291]	Systematic review	Vismo	1102		69%	39%						
		Soni			57%	15%						

laBCC, locally advanced BCC; mBCC, metastatic BCC; NE, not reached; NR, not reported; 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]Trial was terminated early due to FDA approval of vismodegib.

[f]Trial was terminated early by the sponsor due to the high rate of discontinuation of subjects unrelated to patient safety.

Follow-up

Follow-up for BCC should include history and physical examination, including complete skin examination every 6 to 12 months for the first 5 years, and then at least annually for life. Imaging may be considered if clinical examination is insufficient for following the disease. 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 imaging can be considered to assess extent of disease. As part of follow-up, the patients should be educated on sun protection and self-examination. For local recurrence, the primary treatment pathway for local, high-risk BCC should be followed. For primary and recurrent nodal metastases, multidisciplinary consultation should take place to consider one or more of the following options: surgery, HHI or cemiplimab-rwlc (as indicated in the previous section), or clinical trial enrollment. For distant metastases, multidisciplinary consultation should take place to consider one or more of the following options: vismodegib or cemiplimab-rwlc (as indicated in the previous section), RT or surgery for limited metastatic disease, or palliation and best supportive care.

An estimated 30% to 50% of patients with BCC will develop another BCC within 5 years.[124,129,292-295] This represents a 10-fold increase in risk compared to the general population.[293] Patients with a prior BCC are also at increased risk of developing SCC and cutaneous melanoma.[124,295] 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.[128] Therefore, close follow-up of patients with BCC in both the short- and long-term is critical.

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