National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Basal Cell Skin Cancer

Version 2.2025 — February 7, 2025

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NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Basal Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
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Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Basal Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Basal Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 2.2025 of the NCCN Guidelines for Basal Cell Skin Cancer from Version 1.2025 include:

MS-1
- The discussion section has been updated to reflect changes in the algorithm.

Updates in Version 1.2025 of the NCCN Guidelines for Basal Cell Skin Cancer from Version 2.2024 include:

BCC-2
- Header added to top left of page: Low-Risk BCC.
- Primary Treatment:
  - Top options revised: Curettage and electrodesiccation (C&E) or Shave removal ~~(if tumor appears to extend beyond the dermis, surgical excision should generally be performed rather than C&E or shave removal)~~.
  - Bottom option, fourth bullet revised: Cryotherapy *(Useful in Certain Circumstances)*.
- New footnote i added: If tumor appears to extend beyond the dermis, surgical excision should generally be performed rather than C&E or shave removal.
- Footnotes revised:
  - Footnote l: Determination of the appropriateness of RT should be performed ~~by~~ *together with* a radiation oncologist. (Also pages BCC-3 and BCC-4)
  - Footnote n: ~~Afsar FS, et al. Postepy Dermatol Alergol 2015;32:88-93~~ *Current guidelines for low-risk BCC including superficial BCC (sBCC) recommend several treatment options including destructive treatment methods, such as cryosurgery with or without prior curettage or curettage and electrodesiccation. Backman EJ, et al. J Eur Acad Dermatol Venereol 2022;36:1758-1765*.

BCC-3
- Header added to top left of page: High-Risk BCC.
- Primary Treatment, top option revised: Mohs or other forms of PDEMA (preferred for BCCs that are ~~either recurrent, ≥1 cm in H zone, or ≥1 cm with an aggressive histologic subtype~~ *high risk*)
- Footnote s revised: Aggressive histologic subtype is defined as: BCC with squamous differentiation, infiltrative, micronodular, morpheaform, sclerodermiform, or sclerosing. van Loo E, et al. Eur J Cancer 2014;50:3011-3020. ~~Fraga SD, et al. Dermatol Surg 2022;48:704-710~~ *Curtis KK, et al. J Natl Compr Canc Netw 2024;22:e247036.*

BCC-4
- Header added to top left of page: Advanced BCC.
- First column revised: Advanced BCC *(multidisciplinary discussion and multimodality treatment merits considerations).*
- Second column, top option revised: Locally advanced BCC (laBCC) ~~(primary or recurrent extensive disease where surgery and/or RT may not result in a cure or would possibly produce a significant functional limitation).~~
- Primary Treatment:
  - Following Locally advanced BCC (laBCC), bullet removed: Multidisciplinary consultation to consider one or more of the following options:
  - Following Nodal Disease:
    - ◊ First bullet revised: Surgery ± *adjuvant RT*.
    - ◊ Bullet removed: Multidisciplinary consultation to consider one or more of the following options:
  - Following Metastatic disease, bullet removed: Multidisciplinary consultation to consider:

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Basal Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2025 of the NCCN Guidelines for Basal Cell Skin Cancer from Version 2.2024 include:

BCC-4 (continued)
- New footnote w added: Primary or recurrent extensive disease where surgery and/or RT may not result in a cure or would possibly produce a significant functional limitation.
- Footnote x revised: ~~Fraga SD, et al. Dermatol Surg 2022;48:704-710.~~ *Curtis KK, et al. J Natl Compr Canc Netw 2024;22:e247036*
- Footnote removed: For clinically diagnosed non-facial BCCs <6 mm in depth on the head, neck, hands, feet, pretibial, and anogenital area that are clinically confined to the dermis, C&E or shave removal 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). See Risk Factors for Recurrence (BCC-B).

BCC-B
- H&P:
  - First row revised: Location/~~size~~ *diameter (cm)*
  - Second row revised: *Clinical* borders
- Pathology, first row revised: *Histologic* subtype.
- Footnote b 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 ~~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.

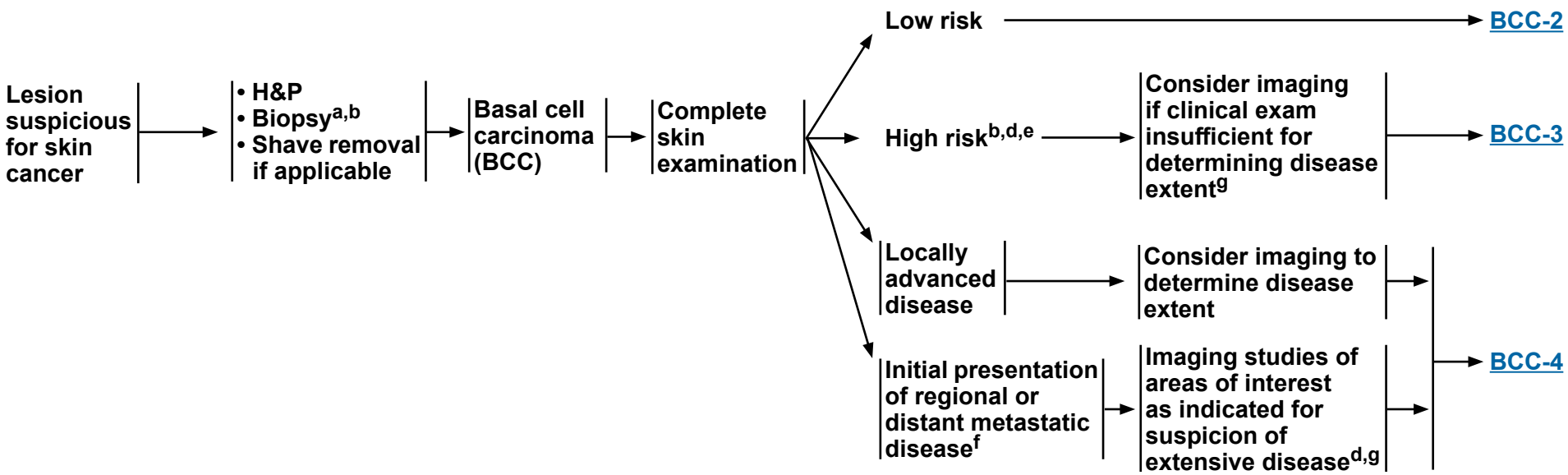
BCC-C
- Footnote removed: Cure rates are approximately 10% lower than for surgical treatment modalities. Jansen MHE, Mosterd K, Arits AHMM, et al. Five-year results of a randomized controlled trial comparing effectiveness of photodynamic therapy, topical imiquimod, and topical 5-fluorouracil in patients with superficial basal cell carcinoma. J Invest Dermatol 2018;138:527-533. Drew BA, Karia PS, Mora AN, et al. Treatment patterns, outcomes, and patient satisfaction of primary epidermally limited nonmelanoma skin cancer. Dermatol Surg 2017;43:1423-1430.
- New references added:
  - Allen NC, Martin AJ, Snaidr VA, et al. Nicotinamide for Skin-Cancer Chemoprevention in Transplant Recipients. N Engl J Med 2023;388:804-812.
  - Mainville L, Smilga AS, Fortin PR. Effect of Nicotinamide in Skin Cancer and Actinic Keratoses Chemoprophylaxis, and Adverse Effects Related to Nicotinamide: A Systematic Review and Meta-Analysis. J Cutan Med Surg 2022;26:297-308.

BCC-D
- General Principles, new bullets added:
  - Refer to the ASTRO Guideline on Definitive and Postoperative Radiation Therapy for Basal and Squamous Cell Cancers of the Skin for general indications and dose recommendations.
  - Image-guided radiation therapy (IGRT) is considered best practice when treating with intensity-modulated radiation therapy (IMRT), proton beam radiotherapy, or 3-D conformal radiation. The use of IGRT for other types of radiotherapy to treat skin cancer is considered unnecessary.
- Header removed: General Treatment Information.
- New footnote added: See Discussion.
- Footnote removed: ASTRO Guideline on Definitive and Postoperative Radiation Therapy for Basal and Squamous Cell Cancers of the Skin
- Reference added: Likhacheva A, Awan M, Barker CA, et al. Definitive and Postoperative Radiation Therapy for Basal and Squamous Cell Cancers of the Skin: Executive Summary of an American Society for Radiation Oncology Clinical Practice Guideline. Pract Radiat Oncol 2020;10:8-20.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Basal Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

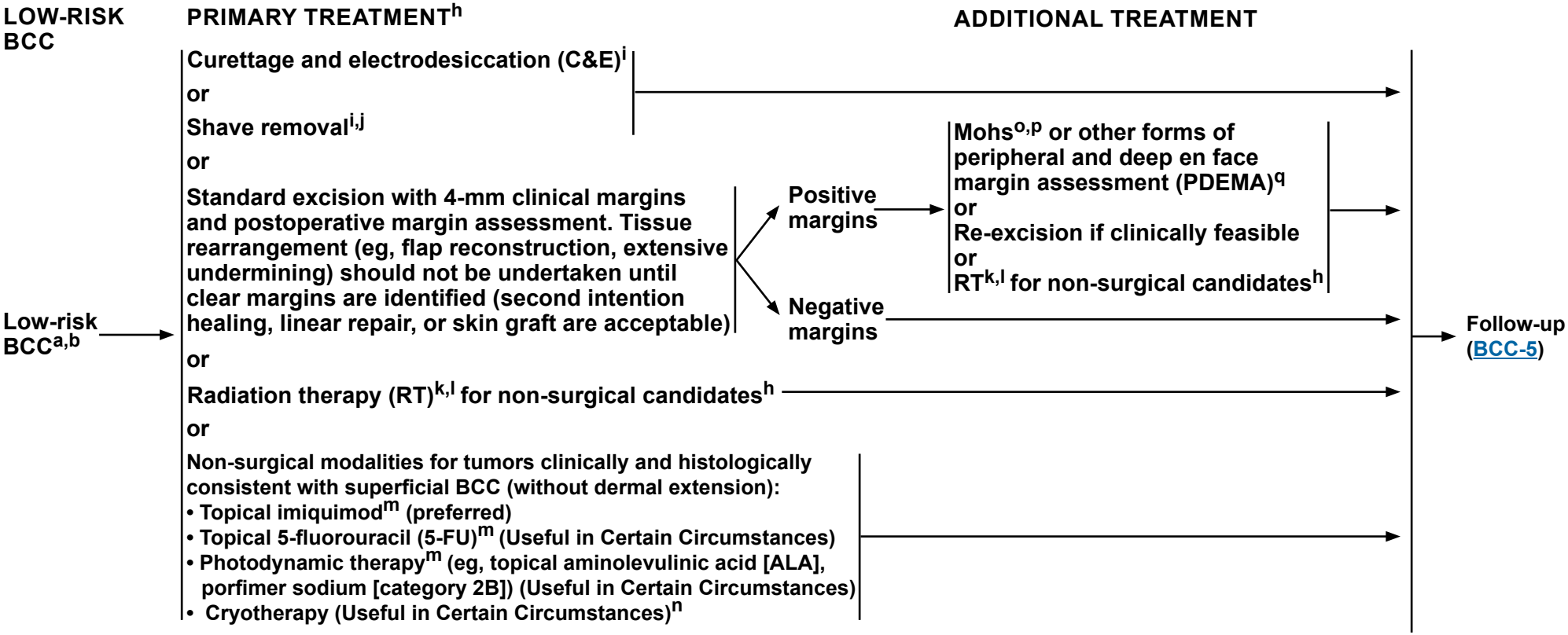


[a] Principles of Pathology (BCC-A).
[b] Risk Factors for Recurrence (BCC-B).
[c] Morgan FC, et al. J Am Acad Dermatol 2021;85:582-587.
[d] Extensive disease includes deep involvement such as bone, named nerves, and deep soft tissue. If disease of named nerve(s) is suspected, MRI with and without contrast is preferred. If bone disease is suspected, CT with contrast is preferred unless contraindicated.
[e] Any high-risk factor places the patient in the high-risk category.
[f] For rare cases that present with regional or distant metastatic disease at diagnosis, treat per nodal or metastatic pathways on BCC-4.
[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 sufficient to diagnose local recurrence, but MRI with and without contrast 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.

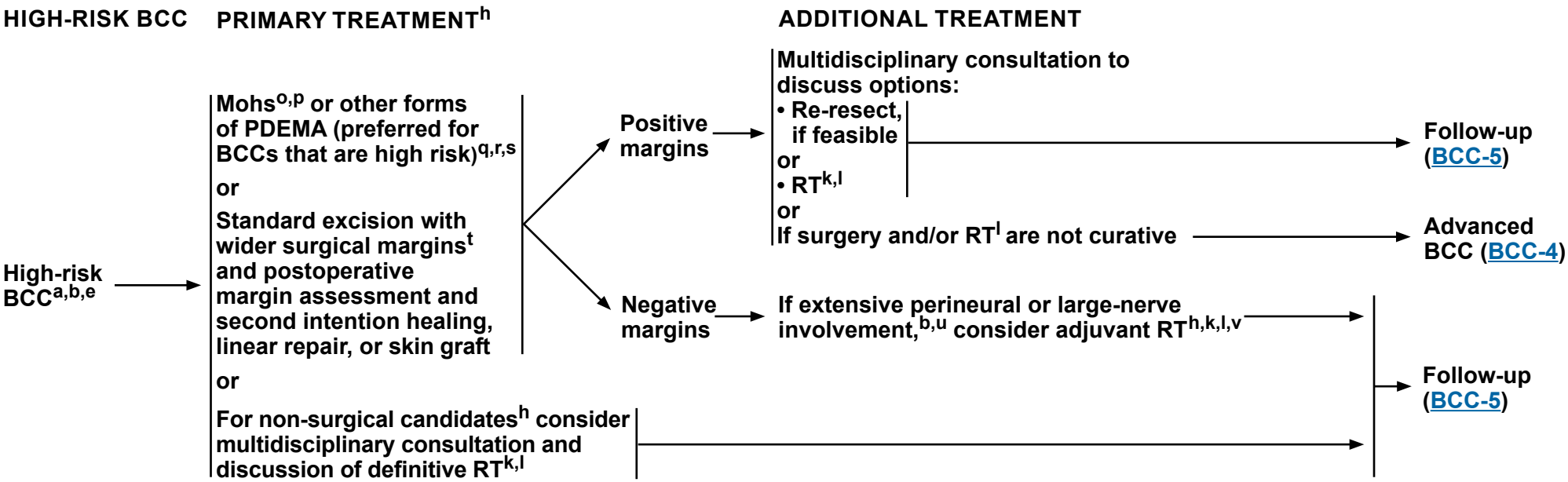
NCCN Guidelines Version 2.2025
Basal Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion



[a] Principles of Pathology (BCC-A).
[b] Risk Factors for Recurrence (BCC-B).
[h] Principles of Treatment (BCC-C).
[i] If tumor appears to extend beyond the dermis, surgical excision should generally be performed rather than C&E or shave removal.
[j] Shave removal (shaving of epidermal or dermal lesion) is a sharp removal by transverse bowl-shaped slicing to remove epidermal and dermal lesions (without including fat) and does not require suture closure. Emmett AJ, et al. Plast Reconstr Surg 1987;80:47-54; Abramson AK, et al. Dermatol Surg 2013;39:387-392; Wu X, et al. J Am Acad Dermatol 2015;73:791-798; Dando EE, et al. Dermatol Surg 2023;49:130-134.
[k] Principles of Radiation Therapy (BCC-D).
[l] Determination of the appropriateness of RT should be performed together with a radiation oncologist.
[m] 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.
[n] Current guidelines for low-risk BCC including superficial BCC (sBCC) recommend several treatment options including destructive treatment methods, such as cryosurgery with or without prior curettage or curettage and electrodesiccation. Backman EJ, et al. J Eur Acad Dermatol Venereol 2022;36:1758-1765.
[o] Mohs surgery should be performed by dermatologic surgeons who have specialized training and experience in this procedure.
[p] As per other appropriate use criteria. Task Force/Committee Members; Vidal CI, et al. J Am Acad Dermatol 2019;80:189-207.
[q] PDEMA with permanent section analysis or intraoperative frozen section analysis is an alternative to Mohs. See Principles of PDEMA Technique (SCC-G) within the NCCN Guidelines for Squamous Cell Skin Cancer.

Note: All recommendations are category 2A unless otherwise indicated.



[a] Principles of Pathology (BCC-A).
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[q] PDEMA with permanent section analysis or intraoperative frozen section analysis is an alternative to Mohs. See Principles of PDEMA Technique (SCC-G) within the NCCN Guidelines for Squamous Cell Skin Cancer.
[r] For clinically diagnosed non-facial BCCs <6 mm in depth on the head, neck, hands, feet, pretibial, and anogenital area that are clinically confined to the dermis, C&E or shave removal 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). See Risk Factors for Recurrence (BCC-B).
[s] Aggressive histologic subtype is defined as: BCC with squamous differentiation, infiltrative, micronodular, morpheaform, sclerodermiform, or sclerosing. van Loo E, et al. Eur J Cancer 2014;50:3011-3020; Curtis KK, et al. J Natl Compr Canc Netw 2024;22:e247036.
[t] 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.
[u] If named nerve involvement is suspected, consider MRI with and without contrast of region of interest to evaluate extent and rule out base of skull involvement or intracranial extension in head and neck tumors.
[v] There are conflicting data about the value of adjuvant RT following margin-negative surgical excision, particularly after Mohs.

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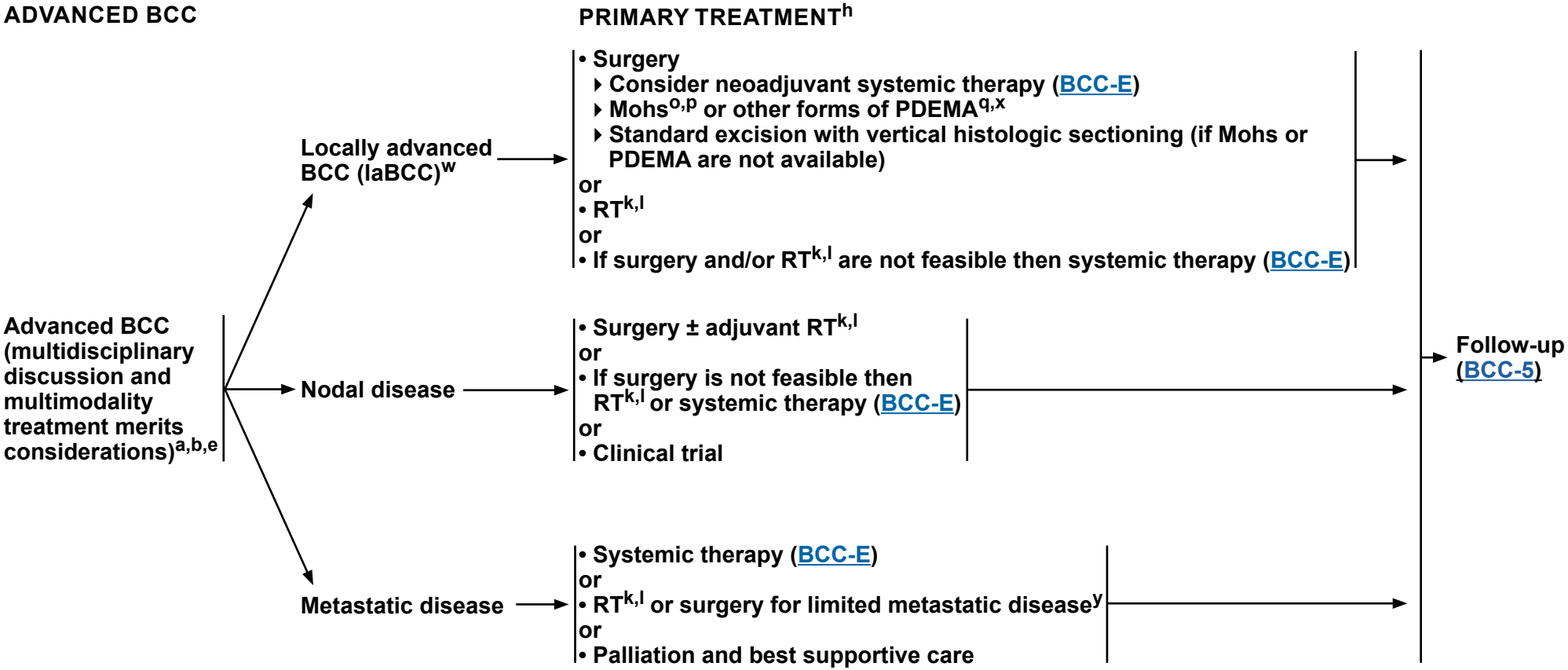

[a] Principles of Pathology (BCC-A).
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[q] PDEMA with permanent section analysis or intraoperative frozen section analysis is an alternative to Mohs. See Principles of PDEMA Technique (SCC-G) within the NCCN Guidelines for Squamous Cell Skin Cancer.
[w] Primary or recurrent extensive disease where surgery and/or RT may not result in a cure or would possibly produce a significant functional limitation.
[x] Curtis KK, et al. J Natl Compr Canc Netw 2024;22:e247036.
[y] Under highly selective circumstances, in the context of multidisciplinary consultation, resection of limited metastases can be considered.

Note: All recommendations are category 2A unless otherwise indicated.

FOLLOW-UP

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

RECURRENCE

Local → **Follow Primary Treatment pathway for High-risk disease (BCC-3)**

Advanced disease:
- **Locally advanced**
- **Nodal metastases**
- **Distant metastases**

→ **Follow Primary Treatment pathways for Advanced BCC (BCC-4)**

[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 sufficient to diagnose local recurrence, but MRI with and without contrast 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.

[z] Follow-up with a dermatologist is strongly recommended if any of the following criteria are met: past or imminent solid organ, marrow, or hematopoietic 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.

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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]**

Footnotes

[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.

References

[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.

Note: All recommendations are category 2A unless otherwise indicated.

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/diameter (cm)	Trunk, extremities <2 cm	Trunk, extremities ≥2 cm
		Head, neck, hands, feet, pretibial, and anogenital area (any size)[b]
Clinical borders	Well-defined	Poorly-defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT	(-)	(+)
Pathology (BCC-A)		
Histologic subtype	Nodular, superficial[c]	Aggressive growth pattern[d]
Perineural involvement	(-)	(+)

[a] Any high-risk factor places the patient in the high-risk category.
[b] Narrow excision margins due to anatomic and functional constraints are associated with increased recurrence rates with standard histologic processing. Complete margin assessment with Mohs/PDEMA is recommended. 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.
[c] Low-risk histologic subtypes include nodular, superficial, and other non-aggressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus.
[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.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF TREATMENT

- **The primary treatment goals of BCC 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, cosmesis, and patient preference may lead to choosing RT/topical therapy/systemic therapy as primary treatment in order to achieve optimal 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. Refer patients with suspected basal cell nevus syndrome or xeroderma pigmentosum for genetic evaluation.**
- **In patients with superficial basal cell skin cancer, non-surgical modalities may be considered. (See BCC-2)**
- **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.[1-4]**

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

References
[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.
[3] Allen NC, Martin AJ, Snaidr VA, et al. Nicotinamide for Skin-Cancer Chemoprevention in Transplant Recipients. N Engl J Med 2023;388:804-812.
[4] Mainville L, Smilga AS, Fortin PR. Effect of Nicotinamide in Skin Cancer and Actinic Keratoses Chemoprophylaxis, and Adverse Effects Related to Nicotinamide: A Systematic Review and Meta-Analysis. J Cutan Med Surg 2022;26:297-308.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

General Principles

- **Refer to the ASTRO Guideline on Definitive and Postoperative Radiation Therapy for Basal and Squamous Cell Cancers of the Skin[1] for general indications and dose recommendations.**
- **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, reirradiation 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.[a]**
- **There are insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy.[a]**
- **Image-guided radiation therapy (IGRT) is considered best practice when treating with intensity-modulated radiation therapy (IMRT), proton beam radiotherapy, or 3-D conformal radiation. The use of IGRT for other types of radiotherapy to treat skin cancer is considered unnecessary.[a]**
- **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 extranodal extension (ENE)	50–60 Gy over 5 to 6 weeks
▸ Positive margins or ENE	60–66 Gy over 6 to 7 weeks
• Lymph node regions, without lymph node dissection	
▸ Clinically positive	60–70 Gy over 6 to 7 weeks
• Clinically at-risk nerves	50–60 Gy over 5 to 6 weeks

- **BED = Biologically effective dose**
- **Conventionally fractionated radiotherapy consists of five daily treatments per week.**
- **Hypofractionated radiotherapy consists of daily treatments or two to four treatments per week. Fraction sizes larger than 6 Gy are not routinely recommended outside of the palliative setting.**

Footnote

[a] See Discussion

Reference

[1] Likhacheva A, Awan M, Barker CA, et al. Definitive and Postoperative Radiation Therapy for Basal and Squamous Cell Cancers of the Skin: Executive Summary of an American Society for Radiation Oncology Clinical Practice Guideline. Pract Radiat Oncol 2020;10:8-20.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY

Locally Advanced (laBCC), Nodal or Distant Metastatic Basal Cell Carcinoma (mBCC)

- **Systemic therapy may be considered for laBCC. Locally advanced disease is defined by those that have primary or recurrent extensive disease where surgery and/or RT may not result in a cure or would possibly produce a significant functional limitation.**
- **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 amendable to surgery or RT.**
- **Hedgehog pathway inhibitors (HHIs)**
  - **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 or other genetic forms of multiple BCC). HHIs are not FDA approved for basal cell nevus syndrome; however, they may be used off-label and are effective based on a randomized controlled trial.[1]**
- **The role of adjuvant systemic therapy for resected BCC is unclear and thus, adjuvant systemic therapy is best performed in a clinical trial setting.**

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Locally Advanced Disease - Neoadjuvant	• None	• Vismodegib[a,2] (category 2B)	• Cemiplimab-rwlc[b] (category 2B)
Locally Advanced Disease	• None	• Sonidegib[3] • Vismodegib[4,5]	• Cemiplimab-rwlc[b,c,6]
Nodal Disease	• None	• Vismodegib • Sonidegib[3] (category 2B)	• Cemiplimab-rwlc[b]
Metastatic Disease	• None	• Vismodegib[4,5]	• Cemiplimab-rwlc[b,6]

[a] In one study of 55 patients with laBCC, 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.[2]
[b] Cemiplimab-rwlc is FDA approved for patients with laBCC or mBCC previously treated with an HHI or for whom an HHI is not appropriate.
[c] A multinational single-arm phase 2 trial, consisting of 84 patients with locally advanced BCC (local invasion precluding complete resection or in locations for which surgery may result in severe disfigurement or dysfunction) whose disease had progressed on or was intolerant to prior HHI therapy, was conducted. Thirty-one percent had an objective response, including 6% with a complete response. See Discussion.[6]

References on BCC-E (2 of 2)

Note: All recommendations are category 2A unless otherwise indicated.

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[6] Stratigos AJ, Sekulic A, Peris K, et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial. Lancet Oncol 2021;22:848-857.

Note: All recommendations are category 2A unless otherwise indicated.

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, 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.

ABBREVIATIONS

ALA	**aminolevulinic acid**
BCC	**basal cell carcinoma**
BED	**biologically effective dose**
C&E	**curettage and electrodesiccation**
ENE	**extranodal extension**
H&P	**history and physical**
HHI	**hedgehog pathway inhibitors**
IGRT	**image-guided radiation therapy**
IMRT	**intensity-modulated radiation therapy**
laBCC	**locally advanced basal cell carcinoma**
mBCC	**metastatic basal cell carcinoma**
NSGC	**National Society of Genetic Counselors**
PDEMA	**peripheral and deep en face margin assessment**
sBCC	**superficial basal cell carcinoma**
SCC	**squamous cell carcinoma**

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

NCCN Guidelines Version 2.2025
Basal Cell Skin Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Basal Cell Skin Cancer. Last updated: February 7, 2025.

Table of Contents

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 two 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 the development of BCC. The most recognized environmental carcinogen is sunlight. Evidence reveals that the relationship between sun exposure and BCC is complex, and depends 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 therapy (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]

Guidelines Update Methodology

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

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Basal Cell Skin Cancer, an electronic search of the PubMed database was performed to obtain key literature published since the previous Guidelines update, using the search terms: basal cell skin carcinoma. The PubMed database was chosen because 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, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Meta-Analysis; Practice Guideline; 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 as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[29] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do

not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

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.[30-32] 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.[33-41] Specific UV-induced mutations in the tumor suppressor gene *p53* appear to be a common event in BCC development.[35,38,41,42] Certain genetic syndromes greatly predispose affected individuals to skin cancer formation, including BCC, such as albinism[43,44] and xeroderma pigmentosum (in which defects exist in UV light-induced unscheduled DNA repair).[45-51]

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, biopsy, and if applicable a shave removal. 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] After BCC diagnosis, 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.[54]

Risk Stratification of Local BCC Based on Risk Factors for Recurrence

After the complete skin examination, a risk assessment should be performed to determine the treatment plan.[55] The NCCN Panel examined risk factors for BCC associated with recurrence (see *Risk Factors for Recurrence* in the algorithm). Any high-risk factor places the skin lesion in the high-risk category and imaging should be considered if a clinical exam is insufficient to determine disease extent. Skin lesions in populations placed at increased risk may be difficult to assess clinically; therefore, a low threshold for performing skin biopsies in these patients is necessary. Patients with locally advanced disease, which is defined as primary or recurrent extensive disease where surgery and/or RT may not result in a cure or would potentially yield a significant functional limitation, should consider imaging to determine disease extent. For rare cases when patients present with regional or distant metastatic disease at diagnosis, imaging of areas of interest can be performed when there is suspicion of extensive disease prior to treatment 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 or without contrast is preferred.[56,57] 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 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 the extent of disease.

History & Physical Examination

Location and Diameter

Anatomic location[58-64] and diameter[60-66] have been known to be a risk factor for BCC recurrence and metastasis for many years. Historically, anatomical areas have been filtered based on the risk of recurrence for high (H-zone), medium (M-zone), and low risk (L-zone).[67-70] Based on a 27-year retrospective review of 5755 BCCs, recurrences were significantly more common when tumors in high-risk locations (H-zone: central face, eyebrows, nose, lips, chin, ear, temple, genitalia, nipples/areola, hands, feet, ankles, and nail units) were ≥6 mm in diameter and when tumors in moderate-risk locations (M-zone: cheeks, forehead, scalp, neck, jawline, pretibial surface) were ≥10 mm in diameter.[71] In general, BCCs that develop in the head and neck area, which includes the H-zone of the face, are more likely to recur than those that develop on the trunk and extremities (L-zone). 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,[72] which has been incorporated into *Risk Factors for Recurrence* within the algorithm.

Clinical Borders and Primary Versus Recurrent Disease

The low- and high-risk factors of well-defined versus ill-defined clinical tumor borders[73-75] and primary versus recurrent disease,[62,74,76] respectively, have been extensively documented in the literature.

Immunosuppression

Settings of immunosuppression, such as organ transplantation,[77-82] and long-term use of psoralen and UVA (PUVA) light,[83,84] 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,[85-87] occurring in up to half of patients during the 10 years following transplant.[88-91] 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).[92-94] Two of these studies showed similar low recurrence rates for transplant recipients and controls.[93,94] 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.[23-27,95,96]

Pathology

Pathologic Subtypes

Histologic subtyping of BCC as a predictor of risk of recurrence is a well-established concept.[97,98] 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.[65,73,74,76,99-103] Non-aggressive subtypes include the keratotic variant, infundibulocystic variant, and fibroepithelioma of Pinkus.

Basosquamous carcinomas are tumors that 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.[104] Data

suggest that basosquamous carcinomas have a metastatic capacity that is more similar to that of SCC than BCC.[105-107]

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.[108-113] 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 certain subtypes (infiltrating, morpheaform, and basosquamous).[112,114,115] 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.[57,116-118] Additionally, in the presence of PNI, a thorough cranial nerve exam is indicated.

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.[119] 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.[120-123] Other analyses report no significant differences in BCC histologic subtype between younger versus older patients.[124-126] 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,[120,125,127,128] while another found no significant association.[124]

Most large studies (N = 50–2000) have shown no significant association between age and recurrence rate.[62,74,124,126] One multivariate analysis, however, showed a positive relationship between increasing age and likelihood of recurrence.[129] Age has also been evaluated as a risk factor for developing a second or multiple BCCs and many of these studies using fairly large databases (N = 200–2500) found that the risk of developing more than one BCC is associated with increased age.[65,126,128-134] On the contrary, an analysis of a very large database (N = 71,924) found a significantly higher risk of subsequent NMSC in patients <40 years of age at the time of their first BCC diagnosis.[135] In addition, an analysis of 100 metastatic BCCs found that patients with distant metastases tended to be younger than those with only regional metastases.[136] Consistent with this idea, the Rotterdam Study showed that while the risk of developing a second BCC increased with age,[134] the risk of developing multiple BCC lesions was highest in patients who were <65 years of age at the time of their first BCC diagnosis.[137] 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.[60,69,138-146]

This technique is deemed effective for properly selected, low-risk BCC with three caveats.[60,144] 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 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 removal 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 <6 mm in depth and confined to the dermis, C&E may be considered as an alternative primary treatment option if Mohs micrographic surgery or resection with peripheral and deep en face margin assessment (PDEMA) and standard excision are not feasible due to patient comorbidities.

Shave Removal

Shave removal, the shaving of epidermal or dermal lesions, is a sharp removal by bowl-shaped slicing of the epidermal and dermal lesions, without including fat, and does not require suture closure.[147] Like C&E, there is concern for inaccurate margin status assessment with shave removal.[148] However, it is a recommended technique for low-risk BCCs located in the trunk or extremities. Shave removal studies have reported 0.5% to 30% rate of recurrence over a 3- to 5-year follow-up, multiple tumors treated in single visits, and a risk for misdiagnosis of only 1%.[147-150]

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.[138,140,146,151-153] Studies have reported variable margins required to completely excise 95% of all tumor.[154-159] These margins have been suggested to be 2 to 4 mm for low-risk, well-demarcated tumors <2 cm,[154-158] whereas margins of 4 to 6 mm,[155] and in one study, 8 mm[154] 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.[160-169] 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 low-risk BCC are based on the work of Zitelli et al.[170] Their analysis indicated that for well-circumscribed BCC lesions <2 cm in diameter, excision with 4-mm clinical margins should result in complete removal in >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 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 are recommended (if PDEMA is not feasible).

For either low-risk or 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

PDEMA, or complete margin assessment, is a term used for a subset of surgical techniques for high-quality histologic visualization and interpretation of the margin surface or surgically excised tissue. Mohs micrographic surgery is the most common utilized PDEMA technique. Mohs procedures are particularly successful in non-metastatic basal and squamous cell skin cancers where tissue-sparing and precision microscopic control of margins is a priority and has been associated with lower recurrence rates.[171,172] While PDEMA is a team procedure that requires the participation of physicians from multiple disciplines, Mohs physicians serve as both the surgeon and pathologist requiring highly specialized training. Efforts have been extended to generate consensus recommendations to offer Mohs surgeons guidance and promote standardization to make data aggregate from multicenter clinical trials possible.[173]

Mohs is the preferred surgical technique over standard excision for re-excision of low-risk BCC after positive margins with standard excision, as well as the primary surgical technique of choice for 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 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.[138,146] 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).[138,146] Studies on the long-term outcomes (~4 years) of Mohs have reported overall recurrence rates of 2.9% to 3.8%,[174,175] specifically 0% to 6.5% for primary and 4% to 20% for recurrent BCCs.[98,176-181]

A 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.[69,182,183] It has been demonstrated that H-zone location, recurrent tumor, aggressive subtype, PNI, and tumor size ≥11 mm are significantly associated with two or more Mohs stages.[114,184] 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.[185]

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.[186] 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 non-surgical candidates for both low-risk and high-risk as well as patient with advanced BCC (locally advanced, nodal, and metastatic BCC).[187] The appropriateness of RT should be determined by a radiation oncologist with radiation physics support to meet established quality assurance and dosimetric constraints. If resection is no

longer feasible to obtain negative margins, RT can be considered as an additional treatment option after multidisciplinary consultation for low-risk and high-risk BCC with positive margins. Adjuvant RT is also a recommended treatment option when resection is not feasible for high-risk BCC after negative margins in case of extensive perineural or large-nerve involvement.[188] In these patients, local control has been reported to be 50% to 90% with postoperative RT.[187,189] There are conflicting data about the value of adjuvant RT following margin-negative surgical excision, particularly after Mohs. For patients with locally advanced BCC (laBCC) or metastatic disease, RT is recommended as an option for primary treatment. RT is also a primary treatment option in instances where surgery is not feasible or as an adjuvant RT combination with surgery.

Two meta-analyses reported 5-year recurrence rates of 8.7% and 9.8% after RT on primary and recurrent BCC, respectively.[138,146] Retrospective analyses of BCC treated with RT have reported 5-year local control, cure, or complete response rates ranging from 93% to 96%,[190-193] and 5-year recurrence rates from 4% to 16%.[194-196] Efficacy of RT was better for BCCs that were less advanced, primary (vs. recurrent), or had smaller diameter or nodular histologic subtype.[190,191,193-195] 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%; $P = .003$),[197] poorer cosmetic outcomes, and more postoperative complications.[198]

A small number of prospective studies have reported high rates of tumor control with specific radiation dose fractionation regimens for small BCCs.[197,199,200] A systematic review and meta-analysis also reported hypofractionated RT regimens associated with positive cosmetic outcomes.[201] The NCCN Panel recommends ranges of electron beam dose for regional disease and fractionation that can be used for definite RT and postoperative adjuvant RT. For general dosing recommendations, refer to the ASTRO Guideline on Definitive and Postoperative Radiation Therapy for Basal and Squamous Cell Cancers of the Skin.[202]

Isotope-based brachytherapy can be an effective treatment for certain sites of disease, particularly on the head and neck.[203-206] Image-guided radiation therapy (IGRT) is considered best practice when treating with intensity-modulated radiation therapy (IMRT), proton beam radiotherapy, or 3-D conformal radiation.[207-209] The use of IGRT for other types of radiotherapy to treat skin cancer is considered unnecessary.

However, there is insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy.[210,211] Electronic brachytherapy (EB) uses electrically generated X-rays, which are not regulated by the Nuclear Regulatory Commission. One of the apparent advantages of EB devices is the decreased shielding requirements and the portability of the units, however, this may lead to EB use in settings unfamiliar with the hazards of therapeutic radiation delivery.[212] The American Association of Physicists in Medicine (AAPM) task group 152 has provided guidelines for proper and safe EB use including having an authorized medical physicist (AMP) physically present from the initiation through the duration of all treatments involving an EB unit. The AMP is responsible for output calibration, quality assurance, training and treatment planning.[212] Furthermore, training and educational requirements for those administering EB vary considerably from state to state, and users should consult their local radiation safety committee to confirm appropriate compliance. The American Brachytherapy Society (ABS) has published a consensus statement for electronic brachytherapy, noting a paucity of long-term clinical outcome data and lack of comparison to surgery or standard radiotherapy techniques.[213] Particularly concerning is the absence of standardized dosimetry (in comparison to high dose rate [HDR] brachytherapy and external beam radiotherapy) to ensure adequate target coverage, skin surface dose, and plan quality assurance. The ABS, therefore, recommends that “EB treatment should be performed on clinical

registry or trial at this time". The American Academy of Dermatology (AAD) has published a Position Statement: "The AAD believes additional research is needed on electronic surface brachytherapy particularly on long-term outcomes". The AAD acknowledges concerns regarding aggressive marketing to dermatologists with a focus on revenue streams, potentially undermining quality of care and patient safety. The AAD also cautions dermatologists to be mindful of the Stark physician self-referral law. Recently, image guidance CPT codes have been used for the delivery of EB, despite a lack of evidence demonstrating a benefit in clinical outcomes with image guidance. We do not support the use of image guidance with EB currently. In conclusion, EB should only be performed by Radiation Oncologists with Medical Physics support, on registry or clinical trial, with appropriate safeguards, and in adherence with all State and Federal regulations. Further research is needed regarding dose deposition and long-term clinical outcomes.

Superficial Therapies

In patients with superficial BCC, therapies such as topical imiquimod, topical 5-fluorouracil (5-FU), or photodynamic therapy (PDT) may be considered, although cure rates are approximately 10% lower than for surgical treatment modalities.[214-216] Another option for patients with superficial BCC is cryotherapy.[217] These options are also recommended for patients where surgery or RT is contraindicated or impractical and are considered as useful in certain circumstances.

Topical Therapies

Imiquimod was found to be effective for treating nodular and superficial BCC in randomized studies.[218-223] 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.[222,224] Recurrence seems to be associated with tumor thickness.[225] A phase III randomized trial in patients with superficial or nodular BCC showed that imiquimod provided an 82.5% clinical success rate.[226,227] 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 dermatologic 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 5-FU,[228,229] which has been shown in a large randomized trial to have a 5-year tumor-free survival probability of 70.0%.[215,230,231] Other studies have reported cure rates of up to 90% with this treatment.[232-234]

Photodynamic Therapy

PDT with photosensitizing agents including 5-aminolevulinic acid (ALA) and porfimer sodium is another option for superficial BCC.[235-237] 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.[152,238-245] Data from clinical trials reported cure rates from 60% to 100% by PDT for patients with BCC.[241,246-251] 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.[241,246,251] Ulceration and thickness are associated with lower response to therapy,[251] and within the nodular subtype, cure rates are better with thinner lesions.[240] Clinical studies have demonstrated PDT activity against "difficult-to-treat" lesions, with a 24-month complete response rate of 78%.[246,252] 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.[253,254]

Cryotherapy

Cryotherapy has been used for many years as a fast and cost-effective means for removal of BCCs.[217] 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%.[138,140,255,256] In prospective trials, cryotherapy has been shown to result in recurrence rates ranging from 5% to 39%.[199,257-259] Current guidelines for low-risk BCC, which include superficial BCC, recommend several treatment options such as cryosurgery with or without prior curettage or C&E.[217] A key limitation of cryotherapy is poorer cosmetic outcomes compared with other treatment options, as demonstrated by prospective randomized trials.[258-260]

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,[261] a randomized trial showed that treatment success was more likely with imiquimod.[215,231] This study also demonstrates superior imiquimod outcomes compared to 5-FU cream. Exploratory subanalyses found that treatment success rates were significantly higher with imiquimod for tumors that are large or truncal, while PDT provided significantly better outcomes in patients who are older with lesions on the lower extremities.[262] 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.[230] 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.[258]

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.[263,264] A systemic review and meta-analysis of randomized controlled trials determined that there was a significant association between nicotinamide and a reduction in BCCs and SCCs with a noted increased risk for digestive adverse events.[265] On the other hand, a phase III trial in recipients of organ transplants found no significant difference in the prevalence of SCC, BCC, or actinic keratosis between the groups randomly assigned to nicotinamide or placebo.[266] Other agents that might be effective for the prevention of BCC in individuals at high risk for developing NMSCs include celecoxib,[267] acitretin,[268] capecitabine,[269] and tazarotene.[270]

Systemic Therapy

For advanced BCC, systemic therapy is recommended as a treatment option for laBCC, metastatic (mBCC), and nodal BCC after multidisciplinary consultation. Other options include surgery, RT, and palliation and best supportive care for certain patients. The systemic therapy options for BCC include hedgehog pathway inhibitor (HHI) and immunotherapy. Vismodegib and cemiplimab are currently recommended options for all advanced BCCs while sonidegib is only recommended for nodal and laBCC.

Hedgehog Pathway Inhibitors

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.[271] The 9-month follow-up data from the SHH4476g trial, a centrally reported, multicenter, phase I, open-label study had an initial enrollment of 104 patients (laBCC N = 71, mBCC N = 33); however, pathology results excluded eight laBCC patients from the efficacy analysis (N = 63). This trial reported an objective response rate of 30% in the mBCC group and 43% in the laBCC group, with a median duration of response (DOR) of 7.6 months and 9.5-month median progression-free survival (PFS).[272] A 39-month follow-up to these data from the ERIVANCE trial, an investigator-

reported, multicenter, phase II trial, conveyed an objective response rate of 48.5% in the mBCC group and 60.3% in the laBCC group, with a median DOR of 14.8 months and 26.2 months for each group, respectively.[272-275] Results from these trials for 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).[272-274] Serious adverse events (SAEs) occurred in 25% to 32% of patients in these studies. The most common adverse events (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.[276-278]

Sonidegib is another HHI FDA-approved agent for the treatment of patients with laBCC that has recurred following surgery or RT, or who are not candidates for surgery or RT.[271] Sonidegib is FDA approved for laBCC. The 42-month follow-up data from the centrally reported randomized, multicenter, phase II BOLT trial reported similar objective response rates for the 200-mg and 800-mg doses tested among patients with laBCC (56% and 46%, respectively), while there was a 2-fold difference for patients with mBCC (8% and 17%, respectively).[279-283] This trial also reported, for each dose and patient group, median DOR and PFS results that are summarized in **Table 2**. The 30-month investigator-reviewed data for the BOLT trial analyzing only the 200-mg dose showed a higher objective response rate of 71.2% for laBCC and 23.1% for mBCC (**Table 2**).[281,284] 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 DOR. 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 in 5 of 9 patients with disease progression.[285]

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 or with radiation-induced multiple BCCs of the scalp, and as maintenance therapy after laBCC complete remission.[286-291]

Notably, in the neoadjuvant setting, while one trial reported negative results (unmet predefined complete histologic clearance rate),[287] 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.[286,289] Vismodegib neoadjuvant efficacy and safety was evaluated in the multicenter, open-label, phase II VISMONEO study, 55 patients were enrolled and 80% (N = 44) presented with downstaging after a mean 6-month treatment duration.[289] This study reported an objective response rate of 71%, with 36% recurrence at the 3-year follow-up.[289] Additionally, a new surgical classification was presented in this publication according to morbidity where six predetermined stages (stage A–F) were used to determine the surgical procedure complexity with details for each area of the face.[289] Some 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.[292,293]

Immunotherapy

Cemiplimab-rwlc is an anti-programmed cell death protein 1 (PD-1) immunotherapy FDA-approved for patients with laBCC or mBCC previously treated with an HHI or for whom an HHI is not appropriate.[271] Cemiplimab is a recommended treatment option for certain patients with advanced BCC including in the neoadjuvant setting for laBCC. A centrally reported, multicenter, phase II, open-label trial tested cemiplimab-rwlc (N = 84) for patients with laBCC where local invasion precluding complete resection or in locations for which surgery may result in sever disfigurement or dysfunction and whose disease has progressed on or was intolerant to prior HHI therapy.[294] This study reported a median follow-up of 15 months, objective response rate of 31%, and grade 3–4 TEAEs in 48% of patients, while SAEs occurred in 35% of patients.[294]

Due to the rarity of advanced BCC cases, the literature on chemotherapy for BCC is limited to case reports.[295-301]

Follow-up

Follow-up for BCC should include a history and physical examination, along with a 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. Follow-up with a dermatologist is strongly recommended if any of the following criteria are met: past or imminent solid organ, marrow, or hematopoietic cell transplant; one or more cutaneous melanomas in the past 5 years; or four or more NMSCs within the past 5 years.

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 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 high-risk BCC should be followed. For locally advanced, nodal metastases, and distant metastases, the appropriate path should be followed as found within *Advanced BCC* in the algorithm with a consideration for multidisciplinary discussion and multimodality treatments.

An estimated 30% to 50% of patients with BCC will develop another BCC within 5 years.[130,133,302-305] This represents a 10-fold increase in risk compared to the general population.[303] Patients with a prior BCC are also at increased risk of developing SCC and cutaneous melanoma.[130,305] 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.[137] Therefore, close follow-up of patients with BCC in both the short- and long-term is critical.

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[258]	Superficial and nodular	Trunk, limb, head, neck	Cryosurgery (39) ALA-PDT (44)	1-year recurrence: 15% vs 25% } NS	Excellent: 8% vs 50% } $P < .001$
Randomized trial Basset-Seguin 2008[259]	Superficial	Trunk, limb, head, neck, face	Cryotherapy (58) MAL-PDT (60)	5-year recurrence: 20% vs 22% } NS	Excellent: 16% vs 60% } $P = .00078$
Meta-analysis Roozeboom 2012[261]	Superficial	Locations depend on individual studies	Imiquimod (1088) PDT (934)	1-year tumor-free survival: 87% vs 84% } NS	NR
Randomized, single-blind, non-inferiority trial Jansen 2018[215]	Superficial	Trunk, limb, head, neck	MAL-PDT (202) Imiquimod cream (198) Fluorouracil cream (201)	Treatment success[a]: 63% vs 81% } $P < .001$; 70 } $P = .04$ } NS	Good/excellent: 62% vs 61% vs 58% All comparisons NS

BCC, basal cell carcinoma; MAL, methyl aminolevulinate; NR, not reported; NS, no statistically significant difference; PDT, photodynamic therapy.
[a]Treatment success was defined as the product of the percentage of patients with clearance at 3 months by the percentage with sustained clearance during the next 9 months.

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*
BOLT – 42-month follow-up NCT01327053[279,280,282,283]	Phase II RDB, CR	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
BOLT – 30-month follow-up NCT01327053[281,284]	Phase II RBD, IR	Soni 200 mg	66	13	71%	23.1%	15.7	17.7–18.4	NR	NR	NR	NR
SHH4476g – 9-month follow-up NCT00833417[272]	Phase I OL, CR	Vismo	63	33	43%	30%	7.6	7.6	9.5	9.5	NR	NR
ERIVANCE – 39-month follow-up NCT00833417[273-275]	Phase II OL, IR	Vismo	63	33	60%	49%	26.2	14.8	12.9	9.3	NE	33.4

BCC, basal cell carcinoma; CR, centrally reviewed; IR, investigator reviewed; laBCC, locally advanced BCC; mBCC, metastatic BCC; NE, not reached; NR, not reported; 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.

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