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Basal Cell Skin Cancer, Version 1.2016

Clinical Practice Guidelines in Oncology

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Abstract

Basal cell carcinoma (BCC) of the skin is the most common cancer, with a higher incidence than all other malignancies combined. Although it is rare to metastasize, patients with multiple or frequently recurring BCC can suffer substantial comorbidity and be difficult to manage. Assessment of risk is a key element of management needed to inform treatment selection. The overall management of BCC primarily consists of surgical approaches, with radiation therapy as an alternate or adjuvant option. Many superficial therapies for BCC have been explored and continue to be developed, including topicals, cryosurgery, and photodynamic therapy. Two hedgehog pathway inhibitors were recently approved by the FDA for systemic treatment of advanced and metastatic BCC, and others are in development. The NCCN Guidelines for Basal Cell Skin Cancer, published in full herein, include recommendations for selecting among the various surgical approaches based on patient-, lesion-, and disease-specific factors, as well as guidance on when to use radiation therapy, superficial therapies, and hedgehog pathway inhibitors.

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Overview

Basal cell carcinoma (BCC) is the most common cancer in the United States.[1] Experts estimate that BCCs occur in 2 million Americans annually; this exceeds the incidence of all other cancers combined.[2–4] Due to its prevalence, treatment of nonmelanoma skin cancer (NMSC) in the United States costs Medicare more than $400 million per year.[5,6] Furthermore, the incidence of this common malignancy is rising rapidly.[1,7–13] BCCs are at least 2 times

Please Note

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Disclosures for the NCCN Basal Cell Skin Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Basal Cell Skin Cancer Panel members can be found on page 597. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

more common than squamous cell carcinomas (SCCs), the second most common type of skin cancer.[2–4,4–18] Although rarely metastatic, BCC can produce substantial local destruction along with disfigurement and may involve extensive areas of soft tissue, cartilage, and bone. Fortunately BCCs generally have a good prognosis due to low rates of metastasis.

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

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

- Skin cancer prevention and early detection. American Cancer Society. Available at: http://www.cancer.org/acs/groups/cid/documents/webcontent/003184-pdf.pdf
- SPOT skin cancer. American Academy of Dermatology. Available at: http://aad.org/spot-skin-cancer
- Prevention Guidelines. Skin Cancer Foundation. Available at: http://www.skincancer.org/prevention

Text cont. on page 583.

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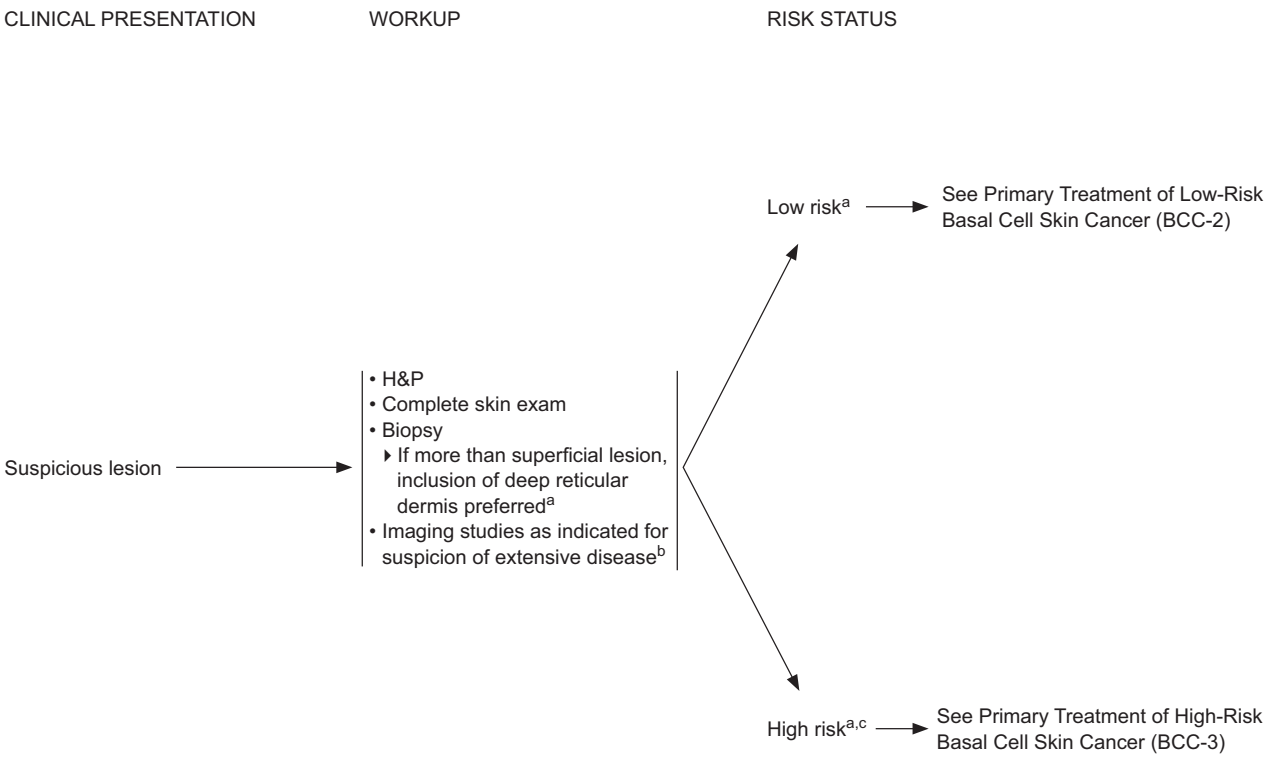
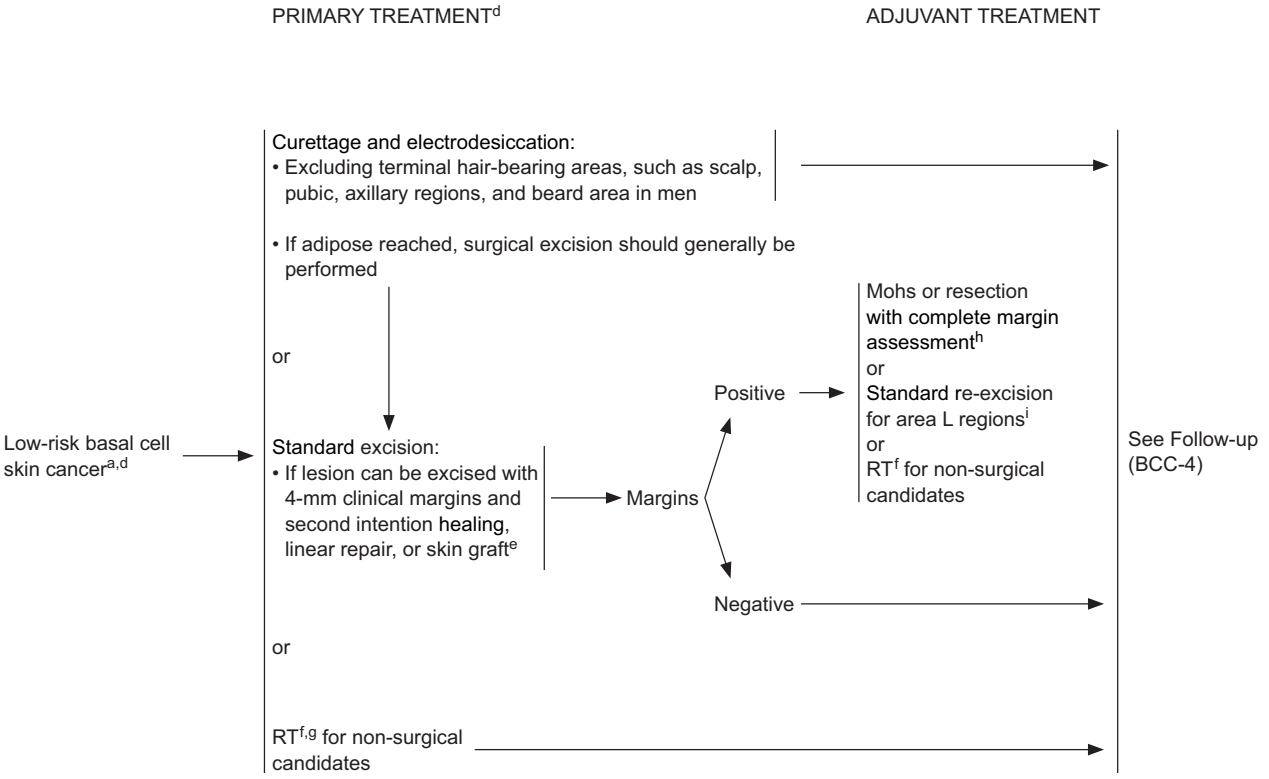


[a]See Risk Factors for Recurrence (BCC-A).

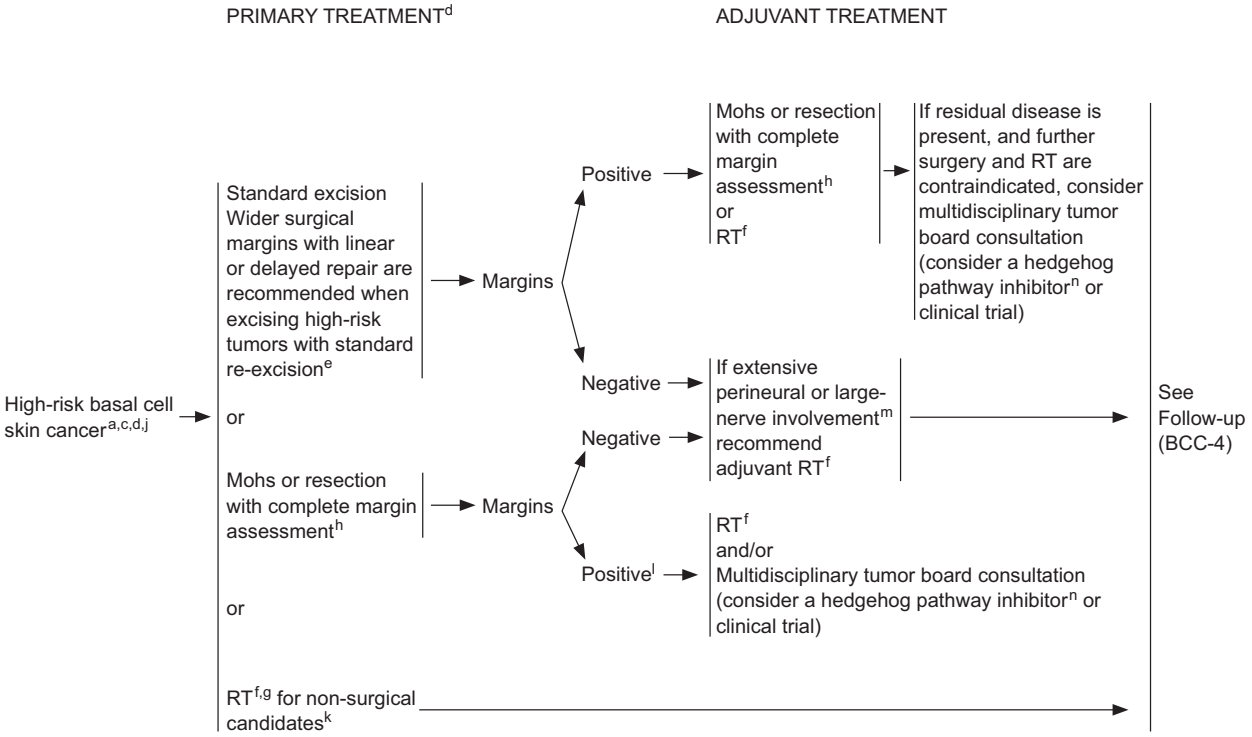
[b]Extensive disease includes deep structural involvement such as bone, perineural disease, and deep soft tissue. If perineural disease is suspected, MRI is preferred.

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



[a]See Risk Factors for Recurrence (BCC-A).
[d]See Principles of Treatment for Basal Cell Skin Cancer (BCC-B).
[e]Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[f]See Principles of Radiation Therapy for Basal Cell Skin Cancer (BCC-C).
[g]RT often reserved for patients over 60 years because of concerns about long-term sequellae.
[h]Excision with complete circumferential peripheral and deep margin assessment (CCPDMA) with frozen or permanent section is an alternative to Mohs surgery.
[i]Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles). (See BCC-A)

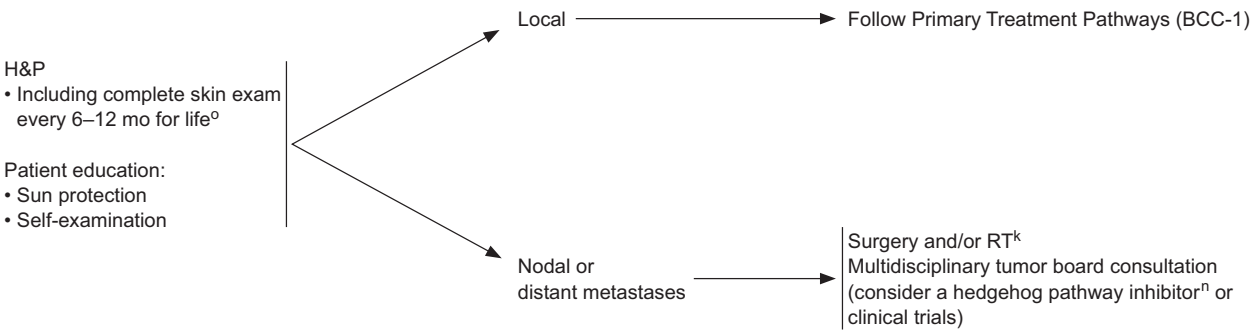
BCC-2



[a]See Risk Factors for Recurrence (BCC-A).
[c]Any high-risk factor places the patient in the high-risk category.
[d]See Principles of Treatment for Basal Cell Skin Cancer (BCC-B).
[e]Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[f]See Principles of Radiation Therapy for Basal Cell Skin Cancer (BCC-C).
[g]RT often reserved for patients over 60 years because of concerns about long-term sequellae.
[h]Excision with complete circumferential peripheral and deep margin assessment (CCPDMA) with frozen or permanent section is an alternative to Mohs surgery.
[j]For complicated cases, consider multidisciplinary tumor board consultation.
[k]If surgery and RT are contraindicated, consider multidisciplinary tumor board consultation and therapy.
[l]Negative margins unachievable by Mohs surgery or more extensive surgical procedures.
[m]If large nerve involvement is suspected, consider MRI to evaluate extent and rule out base of skull involvement.
[n]Current FDA-approved hedgehog pathway inhibitors include vismodegib and sonidegib.

FOLLOW-UP

RECURRENCE



[k]If surgery and RT are contraindicated, consider multidisciplinary tumor board consultation and therapy.

[n]Current FDA-approved hedgehog pathway inhibitors include vismodegib and sonidegib.

[o]If no further skin cancers are identified in the first 2 years, then less frequent follow-up may be appropriate.

RISK FACTORS FOR RECURRENCE

H&P	Low Risk	High Risk
Location/size	Area L <20 mm	Area L ≥20 mm
	Area M <10 mm[1]	Area M ≥10 mm
	Area H <6 mm[1]	Area H ≥6 mm
Borders	Well defined	Poorly defined
Primary vs. Recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT	(-)	(+)
Pathology		
Subtype	Nodular, superficial[2]	Aggressive growth pattern[3]
Perineural involvement	(-)	(+)

Area H = "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.
Area M = cheeks, forehead, scalp, neck, and pretibia.
Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles).

[1]Location independent of size may constitute high risk.
[2]Low-risk histologic subtypes include nodular, superficial, and other non-agressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus.
[3]Having morpheaform, basosquamous (metatypical), sclerosing, mixed infiltrative, or micronodular features in any portion of the tumor. In some cases basosquamous (metatypical) tumors may be prognostically similar to SCC. Clinicopathologic consultation is recommended.

BCC-A

PRINCIPLES OF TREATMENT FOR BASAL CELL SKIN CANCER

- The goal of primary treatment of basal cell skin cancer is the cure 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. Customary age and size parameters may have to be modified.
- 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 radiation therapy as primary treatment in order to achieve optimal overall results.
- In certain patients at high risk for multiple primary tumors, increased surveillance and consideration of prophylactic measures may be indicated.
- In patients with low-risk, superficial basal cell skin cancer, where surgery or radiation is contraindicated or impractical, topical therapies such as 5-fluorouracil, imiquimod, photodynamic therapy (eg, aminolevulinic acid [ALA], porfimer sodium), or vigorous cryotherapy may be considered, even though the cure rate may be lower.

BCC-B

PRINCIPLES OF RADIATION THERAPY FOR BASAL CELL SKIN CANCER

Dose and Field Size

Tumor Diameter	Margins	Examples of Electron Beam Dose and Fractionation
<2 cm	1–1.5 cm[1]	64 Gy in 32 fractions over 6–6.4 weeks[2] 55 Gy in 20 fractions over 4 weeks 50 Gy in 15 fractions over 3 weeks 35 Gy in 5 fractions over 5 days
≥2 cm	1.5–2 cm[1]	66 Gy in 33 fractions over 6–6.6 weeks 55 Gy in 20 fractions over 4 weeks
Postoperative adjuvant		50 Gy in 20 fractions over 4 weeks 60 Gy in 30 fractions over 6 weeks

- Protracted fractionation is associated with improved cosmetic results.
- Radiation therapy is contraindicated in genetic conditions predisposing to skin cancer (eg, basal cell nevus syndrome, xeroderma pigmentosum) and connective tissue diseases (eg, scleroderma)

[1]When using electron beam, wider field margins are necessary than with orthovoltage x-rays due to the wider beam penumbra. Tighter field margins can be used with electron beam adjacent to critical structures (eg, the orbit) if lead skin collimation is used. Bolus is necessary when using electron beam to achieve adequate surface dose. An electron beam energy should be chosen that achieves adequate surface dose and encompasses the deep margin of the tumor by at least the distal 90% line. Appropriate medical physics support is essential.

[2]Electron beam doses are specified at 90% of the maximal depth dose (Dmax). Orthovoltage x-ray doses are specified at Dmax (skin surface) to account for the relative biologic difference between the two modalities of radiation.

BCC-C

Text cont. from page 575.

Genetics

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

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

Clinical Presentation and Workup

On clinical presentation of the patient with a suspicious lesion, workup for BCC begins with a history and physical examination, with an emphasis on a complete skin examination. A full skin examination is recommended because individuals with a skin cancer often have additional, concurrent precancers or cancers located at other, usually sun-exposed skin sites. These individuals are also at increased risk of developing cutaneous melanoma.[76] A skin biopsy is then performed on any suspicious lesion. The biopsy should include deep reticular dermis if the lesion is suspected to be more than a superficial process. This procedure is preferred because an infiltrative histology may sometimes be present only at the deeper, advancing margins of a tumor, and superficial biopsies will frequently miss this component.[77,78] Skin lesions in high-risk populations may be difficult to assess clinically; therefore, a low threshold for performing skin biopsies in these patients is necessary. Imaging studies should be performed when extensive disease such as bone involvement, perineural invasion, or deep soft tissue involvement is suspected. MRI is preferred over CT scan if perineural disease is suspected, because of its higher sensitivity.[79,80]

Risk Stratification

After workup, a risk assessment should be performed to determine the treatment plan. The NCCN Panel examined risk factors for BCC associated with recurrence. These are listed in table format in the algorithm (see page 580). If any high-risk feature is present, the patient should be managed according to the high-risk treatment pathway.

Risk Factors for BCC

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

The location and size criteria are mainly based on a 27-year retrospective review of 5755 BCCs by the Skin and Cancer Unit of the New York University School of Medicine.[83,95] The high-risk sites correspond roughly to the mask areas of the face. Recurrences in the NYU study were significantly more common when tumors in high-risk locations were 6 mm or more in diameter and when tumors in moderate-risk locations were 10 mm or more in diameter. More recently, the American Academy of Dermatology (AAD), in collaboration with American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and American Society for Mohs Surgery, developed an appropriate use criteria (AUC) document in the treatment of cutaneous neoplasms.[96] This was based on 270 clinical scenarios including 69 BCCs. Areas of the body are described in detail in the algorithm section "Risk Factors for Recurrence" (see page 580).

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

Immunosuppression: Settings of immunosuppression, such as organ transplantation and long-term

use of psoralen and UV-A light (PUVA), increase the incidence of BCC.[17,102–108] Incidence of BCC among patients who have undergone organ transplantation is approximately 5- to 10-fold higher than in the general population,[109–111] occurring in up to half of patients during the 10 years after transplantation.[112–115]

Several large retrospective studies compared BCC in patients with or without a history of organ transplant.[116–118] These found that BCCs in patients who had received organ transplants were more likely to have the superficial histologic subtype (and be thinner), more likely to occur in extracephalic locations, and more likely to occur in younger patients (mean age of onset, 15 years lower).[116,117] Two of these studies showed similar low recurrence rates for transplant recipients and controls.[117,118] Nevertheless, because of anecdotal experiences from panel members, the panel decided to classify BCCs developing in settings of immunosuppression as potentially high-risk tumors.

Site of Prior Radiotherapy: Tumors developing in sites of prior radiotherapy refer to primary BCCs arising in areas within radiation fields given previously for unrelated conditions. All recurrent tumors, irrespective of prior therapy, are defined as high risk. Data from a number of studies with large sample sizes support that prior radiotherapy for unrelated (frequently benign) conditions is a risk factor for BCC development.[30–36,119]

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

Young Age Is Not a Risk Factor: Whether young age (typically, younger than 40 years) is an independent risk factor for aggressive BCC behavior is debatable. Studies report conflicting results regarding the relationship between age and other high-risk features. For example, analysis of a large database of patients with BCC (N=3381) by Leffell et al[131] documented an increased percentage of BCC with aggressive histologic growth patterns in young persons. In contrast, results from several other analyses of large databases (1000 to >10,000 patients with BCC) indicate that patients presenting with BCC at a young age are more likely to have the superficial subtype.[132–135] Still other analyses report no significant differences in BCC histologic subtype among young versus older patients.[136–138] The relationship between tumor location and age is also unclear, as several studies showed that younger patients were more likely to have BCCs that were on the trunk or extremities at presentation,[132,137,139,140] but other studies found no significant association.[136] Moreover, histologic subtype and tumor location are already separate risk factors in the algorithm.

The effect of age on likelihood of recurrence has been evaluated in studies with sample sizes ranging from 50 to 2000 patients, and most of these have shown no significant association between age and recurrence rate.[85,98,136,138] One multivariate analysis, however, showed a positive relationship between increasing age and likelihood of recurrence.[141] The prognostic value of age has also been evaluated in analyses of potential risk factors for developing a second or multiple BCCs.[92,138,140–148] Many of these studies used fairly large databases (200–2500 patients with BCC) and found that the risk of developing more than one BCC is associated with increased age.[92,138,140–143,145,147,148] However, one multivariate analysis of an extremely large database (71,924 patients with BCC) found a significantly higher risk of subsequent NMSC in patients who were younger than 40 years old at the time of their first BCC diagnosis.[149] In addition, an analysis of 100 metastatic BCC cases reported in the literature found that patients with distant metastases tended to be younger than those with only regional metastases.[150]

These findings suggest that while younger age is not generally associated with more aggressive BCC, a small subset of patients with particularly aggressive disease tend to be younger than most patients with BCC. Consistent with this idea, multivariate analyses of patients with BCC in the Rotterdam Study showed that although risk of developing a second BCC lesion increased with age (up to approximately 68 years),[148] risk of developing multiple BCC lesions was highest in patients who were younger than 65 at the time of their first BCC diagnosis.[146] Taken to-

gether, these studies do not support that young age, in and of itself, is a high-risk factor for aggressive BCC behavior, but that patients who develop BCC at a young age may benefit from regular follow-up.

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

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

Local Treatment for BCC

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

Curettage and Electrodesiccation

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

This technique is deemed effective for properly selected, low-risk tumors with 3 caveats.[83,167] First, this technique should not be used to treat areas with terminal hair growth such as the scalp, pubic, 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 surgery, surgical excision should generally be performed instead. This change in therapy is necessary because the effectiveness of the C&E technique rests on the ability of the clinician to distinguish between firm, normal dermis and soft tumor tissue when using a sharp curette. Because subcutaneous adipose is even softer than tumor tissue, the ability of the curette to distinguish and, therefore, to selectively and completely remove tumor cells, disappears.

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

Excision With Postoperative Margin Assessment

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

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

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

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

Mohs Micrographic Surgery or Excision With Intraoperative Frozen Section Assessment

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

Excision with complete circumferential peripheral and deep-margin assessment (CCPDMA) using intraoperative frozen section (IOFS) assessment is acceptable as an alternative to MMS provided it includes a complete assessment of all deep and peripheral margins. The descriptive term *CCPDMA* underscores the panel's belief that intraoperative assessment of all tissue margins is the key to complete tumor removal for high-risk tumors.

Radiation Therapy

Although surgery is the mainstay of local treatment for BCC, patient preference and other factors may lead to the choice of RT as primary therapy.[175] Two meta-analyses reported 5-year recurrence rates of 8.7% and 10% after RT on primary and recurrent BCC, respectively.[164,174] More recent retrospective analyses of BCC treated with RT have reported 5-year local control, cure, or complete response rates ranging from 93% to 96%,[176–179] and 5-year recurrence rates from 4% to 16%.[180–182] Efficacy of RT was better for BCCs that were less advanced, primary (vs recurrent), and that had smaller diameter or nodular histologic subtype (vs any other subtype).[176,177,179–181] In a randomized study involving 347 patients receiving either surgery or RT as primary treatment, RT resulted in higher recurrence rates than surgery (7.5% vs 0.7%; P=.003),[183] poorer cosmetic outcomes, and more postoperative complications.[184]

Specifics about the application of RT, including total doses and fractionation ranges, are described under "Principles of Radiation Therapy" (see page 582). RT is contraindicated in genetic conditions predisposing to skin cancer (eg, basal cell nevus syndrome, xeroderma pigmentosum) and connective tissue diseases (eg, lupus, scleroderma).

Intensity-modulated RT (IMRT) has been gaining wide use in recent years for the concurrent treatment of the primary skin tumor and the draining lymphatic beds. The panel emphasized the importance of proper support and training by medical physicists in using this technology as primary treatment. Special attention is warranted to ensure adequate surface dose to the target area. RT is often reserved for patients older than 60 years because of concerns about long-term sequelae.[185]

The value of postoperative radiation in reducing the rate of recurrence in high-risk patients has been widely accepted.[175] The panel recommends adjuvant radiotherapy for any BCC that shows evidence of substantial perineural involvement (ie, involvement of more than just a few small sensory nerve branches or large nerve involvement).[186] In select patients,

local control approaches 100% with postoperative RT.[187] Adjuvant RT should also be considered if tissue margins are positive after MMS or CCPDMA.

Superficial Therapies

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

Topical Therapies Imiquimod was found to be effective for treating multiple superficial BCC in randomized studies.[189–191] A prospective trial reported an 85% 5-year disease-free rate in superficial BCC.[191] A phase III randomized trial in patients with superficial or nodular BCC showed that imiquimod provided an 84% rate of clinical success, defined as absence of initial treatment failure or signs of recurrence at 3 years from start of treatment.[192] Although the clinical success rate was significantly higher in patients treated with surgical excision using a 4-mm margin (98%, $P<.001$), cosmetic outcomes by dermatologist assessment were significantly better with imiquimod (excellent/good at 3 years: 61% vs 36%; $P<.0001$). Another topical cream with efficacy against BCC is 5-FU, which has been shown in a randomized trial to have similar efficacy, safety, and cosmetic outcomes as imiquimod.[193]

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

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

Reviews of clinical trials reported cure rates from 70% to 90% by PDT for patients with BCC.[201,207] Most of the studies of PDT for BCC have focused on the superficial and nodular histologic subtypes, and several have found higher cure rates for superficial versus nodular subtypes.[208,209] Ulceration and thickness are associated with lower response to therapy,[208] and within the nodular subtype, cure rates are better with thinner lesions.[204] Clinical studies have demonstrated PDT activity against "difficult to treat" lesions, with a 24-month complete response rate of 78%.[209,210] 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.[211,212]

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

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

Table 1. Studies Comparing Superficial Therapies in Patients with Superficial Basal Cell Carcinoma

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

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

are large or truncal, whereas PDT provided significantly better outcomes than imiquimod in elderly patients with lesions on the lower extremities.[214]

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

NCCN Recommendations

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

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

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

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

Patients treated with MMS or resection with CCPDMA should receive adjuvant therapy if clear margins cannot be achieved. Recommended adjuvant therapy options include radiation and/or multidisciplinary consultation to consider systemic therapy with a hedgehog pathway inhibitor or treatment in the context of a clinical trial. FDA-approved hedgehog pathway inhibitors include vismodegib and sonidegib.[215,216]

Adjuvant RT is also recommended for patients with negative margins after surgery but with large

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

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

Recurrence and Metastasis

Systemic Therapy

Recent FDA approval of the new agent vismodegib, a first-in-class hedgehog pathway inhibitor, provided another option for patients who have exhausted surgical and radiation options for treating advanced BCC.[215] Approval was based on a multicenter, single-arm, 2-cohort, open-label, phase II trial enrolling 104 patients (ERIVANCE).[217] About 95% of patients were previously treated with surgery, RT, and/or systemic therapies. In the most recent report, based on 21-month minimum follow-up, objective response was recorded in 48% and 33% of patients with locally advanced and metastatic disease (mBCC), respectively, with median response duration of 9.5 months and 7.6 months, respectively.[218] As shown in Table 2, several other studies testing vismodegib in patients with advanced BCC reported response rates and median progression-free survival times that were similar or better to those from ERIVANCE, and found that median time to response was 2.6 to 2.8 months. A separate independent analysis of photographic evidence from the ERIVANCE trial, using a different system for scoring baseline disease severity and clinical efficacy, determined that 65% of patients with locally advanced BCC showed significant improvement, and 11% significantly worsened.[219]

Vismodegib has also been tested as BCC treatment and prophylaxis in patients with nevoid BCC syndrome. A double-blind randomized phase II study in patients with nevoid BCC syndrome and at least 10 operable BCC lesions found that vismodegib significantly reduced incidence of new BCC lesions compared with placebo, and also significantly reduced the size of existing lesions and the number of surgeries needed to remove BCC lesions.[220]

Data from ERIVANCE and other studies have shown that nearly all patients treated with vismodegib experienced at least one treatment-emergent

Table 2. Hedgehog Pathway Inhibitors in Advanced Basal Cell Carcinoma[a]

Study			Patients, n		Follow-up Time, Minimum (median)[c]		Objective Response Rated[d]		Time to Response, median[c]		Duration Response, median[c]		Progression-Free Survival, median[c] (% progressed)	
Name and References	Phase, Design	Tx[b]	laBCC	mBCC	laBCC	mBCC	laBCC	mBCC	laBCC	mBCC	laBCC	mBCC	laBCC	mBCC
ERIVANCE NCT00833417[218,e]	II OL	Vismo	71	33	≥21; (22.4)	≥21; (21.7)	48%	33%	NR	NR	9.5	7.6	9.5 (3%)	9.5 (13%)
NCT01160250[221]	II OL	Vismo	56	39	NR[f] (6.5)		46%	31%	2.6	2.6	NR	NR	NR (0%)	NR (8%)
STEVIE NCT01367665[222]	II OL	Vismo	453	29	≥12; (12.7)	≥12; (12.9)	67%	38%	2.6	2.8	22.7	10	24.5 (2%)	13.1 (14%)
RegiSONIC NCT01604252[230]	Obs	Vismo	66	-	(13.2)	-	68%	-	NR	-	5.95	-	NE	-
BOLT NCT01327053[221]	II RDB	Soni 200 mg	42	13	≥6 (13.9)		43%	15%	3.9	4.6	NE	NE	NE (12%)	13.1 (31%)
		Soni 800 mg	93	23			38%	17%	3.7	1.0	NE	NE	NE (9%)	7.6 (43%)

Abbreviations: BCC, basal cell carcinoma; laBCC, locally advanced BCC; mBCC, metastatic BCC; NR, not reported; NE, not reached; Obs, prospective observational; OL, open-label; RDB, randomized double-blind; soni, sonidegib; Tx, treatment; vismo, vismodegib.

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

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

[c]Times are reported in months.

[d]Response criteria varied between studies.

[e]ERIVANCE data per independent review facility assessment.

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

adverse event (TEAE), but a significant proportion of these were low grade (grade ≤2).[218,221,222] Serious AEs occurred in 25% to 32% of patients in these studies. Across studies the most common TEAEs (any grade) include muscle spasms, alopecia, taste loss, weight loss, decreased appetite, fatigue, nausea, and diarrhea. These AEs were also the most likely to lead to discontinuation. Median time to onset is less than 6 months for all the most common AEs, but for some AEs the incidence continues to increase beyond 12 months from the start of treatment.

Sonidegib, another hedgehog pathway inhibitor, has also been approved by the FDA for treatment of patients with locally advanced BCC that has recurred following surgery or RT, or who are not candidates for surgery or RT.[216] FDA approval was based on data from the phase II BOLT trial comparing 2 different doses of sonidegib in patients with either 1) locally advanced BCC not amenable to curative surgery or RT or 2) mBCC for which all available treatment options have been exhausted.[223] Whereas response rates were similar for the 2 doses tested (Table 2), the higher dose (800 mg/d) was associated with higher rates of serious AEs (14% vs 30%) and AEs leading to dose interruptions, reductions, or discontinuation. As with vismodegib, nearly all patients experienced at least one AE, and the most common AEs were muscle spasms, dysgeusia, alopecia, nausea, weight decrease, and fatigue. Elevated creatinine kinase was also frequently observed, and was one of the most common grade 3 to 4 AEs, along with elevated lipase.

A key limitation to hedgehog pathway inhibitor therapies is that advanced BCC can develop resistance, which limits the duration of response (Table 2). A small investigator-initiated trial in patients with vismodegib-resistant advanced BCC saw no responses during treatment with sonidegib for a median of 6 weeks (range, 3–58 weeks), and 5 of 9 patients experienced progression.[224]

Ongoing clinical research is exploring various dosing regimens of vismodegib and sonidegib in a variety of BCC treatment settings, including less advanced disease or as part of primary treatment for previously untreated disease.[225–231] An open-label single-arm trial in large (mean tumor area, 12.6 cm^2 [range 1.0–78.0 cm^2]) high-risk BCC eligible for surgical removal (n=11) found that 3 to 6 months of vismodegib before resection reduced the surgical defect area by 27% compared with baseline (P=.006).[225] A phase II open-label, multicenter trial in lower-risk operable BCC lesions (diameter <3 cm, previously untreated, nodular) tested the efficacy and safety of neoadjuvant vismodegib in patients willing to delay surgery (n=74).[229] Although 50% of patients experienced investigator-assessed complete clinical clearance while on vismodegib, this trial did not meet its primary endpoints based on complete histologic clearance. Safety data from cohort 2 in this trial (n=24), who received 12 weeks of vismodegib followed by 24 weeks of observation before surgery, showed high rates of AE reversibility (75%–100%) for some of the most common toxicities associated with vismodegib treatment (muscle spasm, alopecia, dysgeusia, ageusia).

Other hedgehog pathway inhibitors are being tested in patients with BCC to see if they can provide higher rates of response, more durable responses, responses in less advanced BCC or responses in BCC resistant to vismodegib. Results from phase I-II trials with small BCC sample sizes (N<40 patients) have shown that itraconazole and saridegib can elicit responses in patients with BCC, although not in patients who previously received vismodegib (n=12 patients tested).[232,233] Due to the rarity of advanced cases, the literature on chemotherapy for BCC is limited to case reports.[234–240]

NCCN Recommendations

For the management of local tumor recurrence, the algorithm directs clinicians to follow the appropriate pathways for primary treatment. Although the behavior of cutaneous BCC is characteristically indolent, the disease does rarely metastasize to distant sites. Whenever possible, nodal or distant metastases should be treated with surgery with or without RT, and managed by a multidisciplinary tumor board. The board should consider systemic therapy with a hedgehog pathway inhibitor or treatment in the context of a clinical trial. FDA-approved hedgehog pathway inhibitors include vismodegib and sonidegib.[215,216] The panel agreed that many patients with metastatic basosquamous carcinoma will also likely respond to vismodegib.

Follow-Up

Two well-established points about patients with BCC underlie the follow-up schedules. One point

is that 30% to 50% of these patients will develop another BCC within 5 years.[142,147,241–244] This represents a 10-fold increase in risk compared with the general population.[242] Patients with a prior BCC are also at increased risk of developing SCC and cutaneous melanoma.[142,244] Therefore, continued long-term surveillance of these patients is essential, as is patient education about the values of sun protection and regular self-examination of the skin. A prospective population-based cohort study found that development of a second BCC is most likely during the short-term follow-up period after diagnosis of the first lesion.[146] Therefore, close follow-up of these patients during this time period is critical.

NCCN Recommendations

The frequency of follow-up should be based on risk. In addition to patient education about sun protection and self-examination, patients should be monitored with regular physical examinations, including complete skin examination. Monitoring during the first 2 years is the most critical, and examinations should occur at least every 6 to 12 months during this timeframe. If no further skin cancer develops in the first 2 years, then it may be appropriate to reduce exam frequency.

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Individuals Disclosures of the NCCN Basal Cell Skin Cancer

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