

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Basal Cell Skin Cancer

Version 1.2019 — August 31, 2018

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Basal Cell Skin Cancer

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Basal Cell Skin Cancer

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To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical_trials/clinicians.aspx](#).

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

See [NCCN Categories of Evidence and Consensus](#).

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Updates in Version 1.2019 of the NCCN Guidelines for Basal Cell Skin Cancer from Version 1.2018 include:

BCC-1

- Clinical Presentation

- ▶ Workup

- ◊ Footnote a was added: “See Principles of Pathology (BCC-A)” to bullet 3 (Biopsy). (Also added throughout the algorithm as appropriate.)

BCC-2

- Adjuvant Treatment for positive margins after standard excision

- ▶ 2nd recommendation was amended: “~~Standard~~ Re-excision for area L regions if clinically feasible.”

- Footnote “Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles). (See BCC-A)” was removed.

BCC-3

- Adjuvant Treatment for high-risk localized disease

- ▶ For patients with positive margins after standard excision with wider margins, “Re-excision, if clinically feasible” was added as an option.

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

BCC-A

- Principles of Pathology was added to the guidelines.

BCC-B

- Risk Factors for Recurrence

- ▶ Footnote 4 was amended: “Having (mixed) infiltrative, micronodular, morpheaform, basosquamous, sclerosing, or *carcinosarcomatous differentiation features...*”

- ▶ Footnote 5 was added: “See Principles of Pathology (BCC-A)”.

BCC-C

- Principles of Treatment for Basal Cell Skin Cancer

- ▶ 2nd bullet was amended: “...but considerations of function, cosmesis, and patient preference and performance status may lead to choosing radiation therapy as primary treatment in order to achieve optimal overall results.”

- ▶ 3rd bullet was amended by adding: “Consider referring patients with suspected Gorlin syndrome or xeroderma pigmentosum for genetic evaluation.”

- ▶ 5th bullet was amended by adding: “...submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.”

BCC-D

- Principles of Radiation Therapy for Basal Cell Skin Cancer

- ▶ Headings were added to the page for:

- ◊ General Principles

- ◊ General Treatment Information

- ◊ Dosing Prescription Regimen



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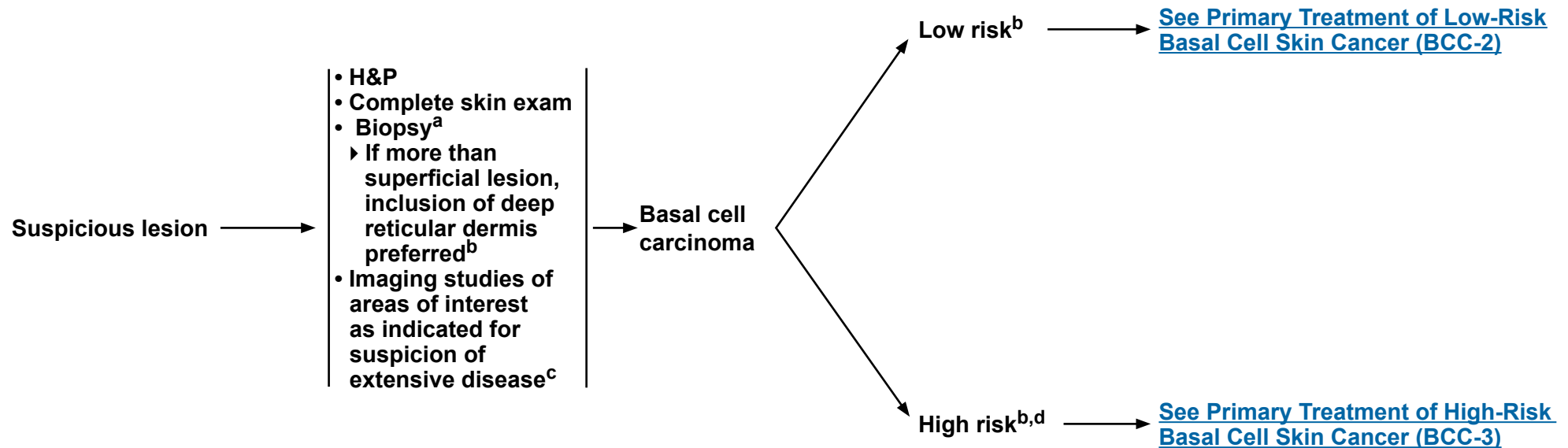
Basal Cell Skin Cancer

CLINICAL PRESENTATION

WORKUP

DIAGNOSIS

RISK STATUS



^aSee [Principles of Pathology \(BCC-A\)](#).

^bSee [Risk Factors for Recurrence \(BCC-B\)](#).

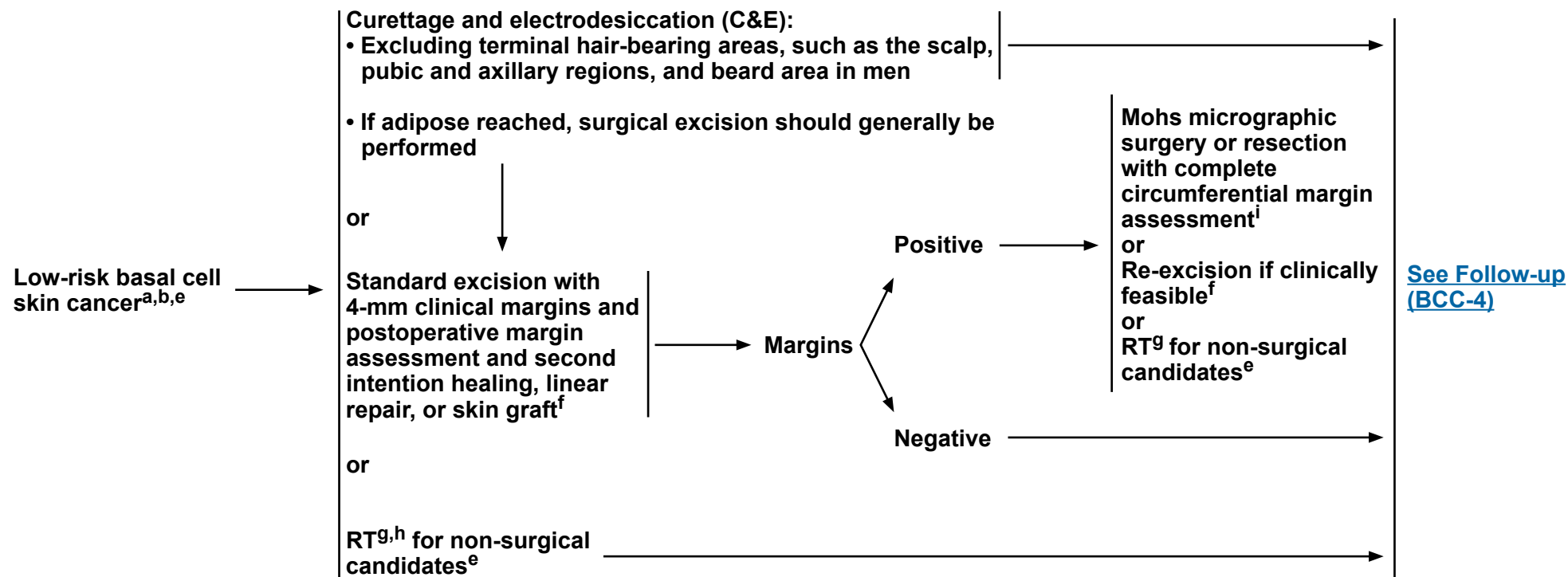
^cExtensive disease includes deep structural involvement such as bone, perineural disease, and deep soft tissue. If perineural disease is suspected, MRI with contrast is preferred. If bone disease is suspected, CT with contrast is preferred unless contraindicated.

^dAny high-risk factor places the patient in the high-risk category.

Note: All recommendations are category 2A unless otherwise indicated.
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PRIMARY TREATMENT^e

ADJUVANT TREATMENT



^aSee Principles of Pathology (BCC-A).

^bSee Risk Factors for Recurrence (BCC-B).

^eSee Principles of Treatment for Basal Cell Skin Cancer (BCC-C).

^fClosures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.

^gSee Principles of Radiation Therapy for Basal Cell Skin Cancer (BCC-D).

^hRT is often reserved for patients older than 60 years because of concerns about long-term sequelae.

ⁱExcision with complete circumferential peripheral and deep margin assessment (CCPDMA) with permanent section analysis or intraoperative frozen section analysis is an alternative to Mohs micrographic surgery.

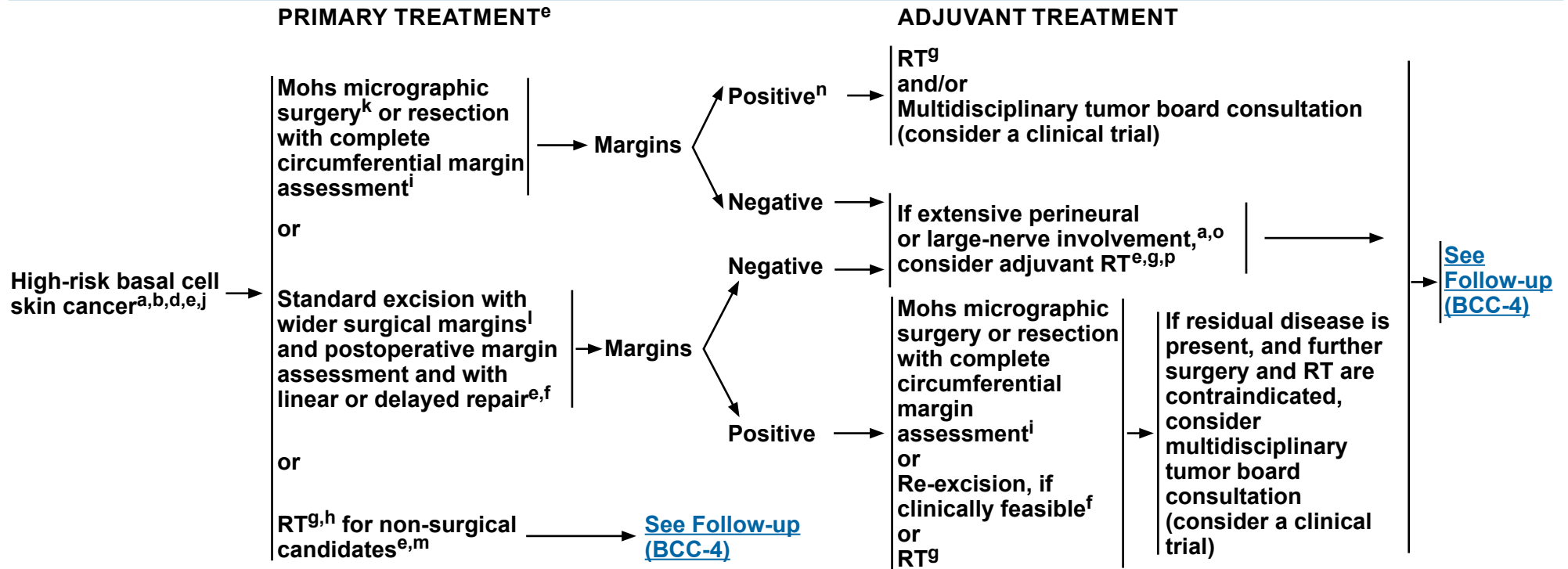
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^aSee Principles of Pathology (BCC-A).

^bSee Risk Factors for Recurrence (BCC-B).

^dAny high-risk factor places the patient in the high-risk category.

^eSee Principles of Treatment for Basal Cell Skin Cancer (BCC-C).

^fClosures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.

^gSee Principles of Radiation Therapy for Basal Cell Skin Cancer (BCC-D).

^hRT is often reserved for patients older than 60 years because of concerns about long-term sequelae.

ⁱExcision with CCPDMA with permanent section analysis or intraoperative frozen section analysis is an alternative to Mohs micrographic surgery.

^jFor complicated cases, consider multidisciplinary tumor board consultation.

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

^lDue 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.

^mIf surgery and RT are contraindicated, consider multidisciplinary tumor board consultation and therapy.

ⁿNegative margins unachievable by Mohs micrographic surgery or more extensive surgical procedures.

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

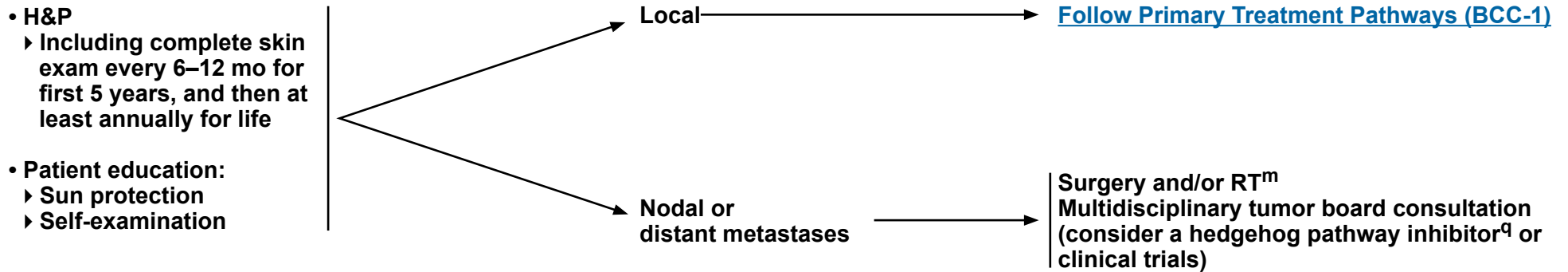
^pThere are conflicting data about the value of adjuvant RT following margin-negative surgical excision, particularly after Mohs micrographic surgery.

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FOLLOW-UP

RECURRENCE



^mIf surgery and RT are contraindicated, consider multidisciplinary tumor board consultation and therapy.

^qCurrent FDA-approved hedgehog pathway inhibitors include vismodegib and sonidegib.

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PRINCIPLES OF PATHOLOGY

Principles of Biopsy Reporting:

- Pathologic evaluation of skin biopsies is ideally performed by a dermatologist or pathologist who is experienced in interpreting cutaneous neoplasms.
- Clinical information to be submitted on biopsy requisition includes patient demographics, anatomic location, prior treatment of lesion, clinical diameter of lesion, and risk factors such as immunosuppression, radiation treatment, or solid organ transplantation.
- Pathologic report should include histologic subtype¹, and presence of any features that would increase the risk for local recurrence including invasion of tumor beyond reticular dermis and presence of perineural invasion (if involving nerve below the dermis or >0.1 mm in caliber).²

Principles of Excision Reporting:

- Saucerization specimens intended for definitive surgical therapy should be labeled as such, as they can be histopathologically difficult to distinguish from shave biopsies but must be evaluated for margin status.
- Clinical information to be submitted on excision requisition includes patient demographics, anatomic location, and clinical diameter of lesion and additional clinical information listed above under biopsy if not previously reported.
- Minimal reporting elements to be reported for all surgical specimens include histologic subtype of basal cell carcinoma,¹ invasion of tumor beyond deep reticular dermis, presence or absence of perineural invasion (if involving nerve below dermis or if largest nerve involved is >0.1 mm in caliber) and angiolymphatic invasion, and peripheral and deep margin status.
- For Mohs excisions, reporting of these elements is also encouraged. As depth of invasion (in mm) may not be reliably ascertained on Mohs specimens, anatomic level of invasion can be reported. Submission of a central section of tissue at the area of deepest invasion for permanent section evaluation may be considered to evaluate and document high-risk features that were questionable or ambiguous on Mohs sections.

¹Low-risk histologic subtypes include superficial, nodular, keratotic, infundibulocystic, and fibroepithelial BCC; high-risk subtypes include basosquamous, infiltrative, sclerosing/morpheaform, micronodular, and BCC with carcinosarcomatous differentiation.

²Alam M, Armstrong A, Baum C, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am Acad Dermatol 2018;78:560-578.

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Basal Cell Skin Cancer**RISK FACTORS FOR RECURRENCE**

H&P	Low Risk	High Risk
Location/size	Area L <20 mm	Area L ≥20 mm
	Area M <10 mm¹	Area M ≥10 mm
		Area H³
Borders	Well defined	Poorly defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT	(-)	(+)
Pathology⁵		
Subtype	Nodular, superficial²	Aggressive growth pattern⁴
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 hands, nail units, pretibia, ankles, feet).

¹Location independent of size may constitute high risk.

²Low-risk histologic subtypes include nodular, superficial, and other non-aggressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus.

³Area H constitutes high risk based on location, independent of size. Narrow excision margins due to anatomic and functional constraints are associated with increased recurrence rates with standard histologic processing. Complete margin assessment such as with Mohs micrographic surgery 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.

⁴Having (mixed) infiltrative, micronodular, morpheaform, basosquamous, sclerosing, or carcinosarcomatous differentiation features in any portion of the tumor. In some cases basosquamous tumors may be prognostically similar to SCC; clinicopathologic correlation is recommended in these cases.

⁵[See Principles of Pathology \(BCC-A\).](#)

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PRINCIPLES OF TREATMENT FOR BASAL CELL SKIN CANCER

- **The primary goal of treatment of basal cell skin cancer is the complete removal of the tumor and the maximal preservation of function and cosmesis. All treatment decisions should be customized to account for the particular factors present in the individual case and for the patient's preference.**
- **Surgical approaches often offer the most effective and efficient means for accomplishing cure, but considerations of function, cosmesis, patient preference, and performance status 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 (eg, Gorlin syndrome, xeroderma pigmentosum, history of radiation treatment), increased surveillance and consideration of prophylactic measures may be indicated. Consider referring patients with suspected Gorlin syndrome or xeroderma pigmentosum for genetic evaluation.**
- **In patients with low-risk, superficial basal cell skin cancer, where surgery and radiation are contraindicated or impractical, therapies such as topical 5-fluorouracil, topical imiquimod, photodynamic therapy (eg, aminolevulinic acid [ALA], porfimer sodium), or vigorous cryotherapy may be considered, even though the cure rates may be lower than with surgical treatment modalities.**
- **When Mohs micrographic surgery with margin assessment is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.**
- **Use of nicotinamide may be effective in reducing the development of basal cell skin cancers.**

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PRINCIPLES OF RADIATION THERAPY FOR BASAL CELL SKIN CANCER

General Principles

- **Protracted fractionation is associated with improved cosmetic results and should be utilized for poorly vascularized or cartilaginous areas.**
- **Radiation therapy is contraindicated in genetic conditions predisposing to skin cancer (eg, basal cell nevus syndrome) and relatively contraindicated for patients with connective tissue diseases (eg, scleroderma).**
- **Given higher complication rates, re-irradiation should not be routinely utilized for recurrent disease within a prior radiation field.**
- **There are insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy.**
- **Radioisotope brachytherapy could be considered in highly selected cases.**

General Treatment Information

Dosing Prescription Regimen

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

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

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 05/18/16

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.

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Overview

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

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

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

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

Genetics

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

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

Clinical Presentation and Workup

On clinical presentation of the patient with a suspicious lesion, workup for BCC begins with a history and physical examination, with an emphasis on a complete skin examination. A full skin examination is

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

Risk Stratification

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

Risk Factors for BCC

Location and Size

Anatomic location has been known to be a risk factor for BCC recurrence and metastasis for many years.⁸¹⁻⁸⁶ In general, BCCs that develop in the head and neck area are more likely to recur than those that develop on the trunk and extremities. Compared with SCC, BCCs are much less likely to metastasize, with a metastatic rate of <0.1%.⁸⁷⁻⁸⁹ The concept of a so-called high-risk “H zone” or “mask area” of the face

dates back at least to 1983.^{90,91} Size also has been shown to be a risk factor for BCC recurrence.^{84-86,92-94} Various different divisions have been used; the most commonly used has been greater than or less than 2 cm in diameter.

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

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

Clinical Borders and Primary Versus Recurrent Disease

The risk factors of well-defined versus ill-defined clinical tumor borders and primary versus recurrent disease have been extensively documented in the literature.^{85,92,97-101}

Immunosuppression

Settings of immunosuppression, such as organ transplantation, and long-term use of psoralen and UVA light (PUVA), increase the incidence of BCC.^{17,102-108} Incidence of BCC among patients who have had organ transplants is approximately 5- to 10-fold higher than in the general

population,¹⁰⁹⁻¹¹¹ occurring in up to half of patients during the 10 years following transplant.¹¹²⁻¹¹⁵

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

Site of Prior Radiotherapy

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

Perineural Involvement

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

and/or rule out skull involvement in those with head and neck tumors.^{80,128-130}

Young Age Is Not a Risk Factor

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

The effect of age on likelihood of recurrence has been evaluated in studies with sample sizes ranging from 50 to 2000 patients, and most of these have shown no significant association between age and recurrence rate.^{85,98,136,138} One multivariate analysis, however, showed a positive relationship between increasing age and likelihood of recurrence.¹⁴¹ The prognostic value of age has also been evaluated in analyses of potential risk factors for developing a second or multiple BCCs.^{92,138,140-148} Many of these studies used fairly large databases (200–2500 patients with BCC), and found that risk of developing more than one BCC is associated with increased age.^{92,138,140-143,145,147,148}

However, one multivariate analysis of an extremely large database (71,924 patients with BCC) found a significantly higher risk of subsequent NMSC in patients who were younger than 40 years of age at the time of their first BCC diagnosis.¹⁴⁹ In addition, an analysis of 100 metastatic BCC cases reported in the literature found that patients with distant metastases tended to be younger than those with only regional metastases.¹⁵⁰ These findings suggest that while younger age is not generally associated with more aggressive BCC, there is a small subset of patients with particularly aggressive disease who tend to be younger than most patients with BCC. Consistent with this idea, multivariate analyses of patients with BCC in the Rotterdam Study showed that while risk of developing a second BCC lesion increased with age (up to ~68 years),¹⁴⁸ risk of developing multiple BCC lesions was highest in patients who were younger than 65 years at the time of their first BCC diagnosis.¹⁴⁶ Taken together, these studies do not support that young age, in and of itself, is a high-risk factor for BCC behavior, but that patients who develop BCC at a young age may benefit from regular follow-up.

Pathologic Risk Factors for BCC

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

Basosquamous Carcinoma

Basosquamous carcinomas are tumors of which one part has the histologic appearance of a BCC and another of that of an SCC. Some basosquamous tumors are the result of a BCC colliding with an

adjacent SCC. Others represent truly biphenotypic tumors, many of which may have started as BCC, but have subsequently undergone prominent partial squamous metaplasia.¹⁵⁷ It seems that the risk for metastasis of these tumors is determined by the squamous component. Data suggest that basosquamous carcinomas have a metastatic capacity that is more similar to that of SCC than BCC.¹⁵⁸⁻¹⁶⁰

Local Treatment for BCC

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

Curettage and Electrodesiccation

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

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

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

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

Excision with Postoperative Margin Assessment

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

The clinical margins chosen by the panel for low-risk tumors are based on the work of Zitelli and colleagues.¹⁷¹ Their analysis indicated that for well-circumscribed BCC lesions less than 2 cm in diameter, excision with 4-mm clinical margins should result in complete removal in more than 95% of cases. The indications for this approach were also expanded to include re-excision of low-risk primary BCC located on the

trunk and extremities excluding pretibia, hands, feet, nail units, and ankles (area L regions) if positive margins are obtained after an initial excision with postoperative margin assessment.

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

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

Mohs Micrographic Surgery or Excision with Intraoperative Frozen Section Assessment

Mohs micrographic surgery (MMS) is the preferred surgical technique for high-risk BCC because it allows intraoperative analysis of 100% of the excision margin. Two meta-analyses published in 1989 associated MMS with a 5-year recurrence rate of 1.0% for primary BCC, and 5.6% for recurrent BCC.^{162,172} In both of these meta-analyses the recurrence rate for MMS was lower than that for standard surgical excision (10.1% and 17.4% 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 to standard excision was performed in the

Netherlands.¹⁷³ After 10 years minimum follow-up, treatment of high-risk facial BCC with MMS resulted in fewer recurrences compared with standard excision, although the difference was only statistically significant for recurrent tumors.¹⁷⁴ Importantly, a large proportion of recurrences occurred more than five years after treatment: 56% for primary and 14% for recurrent BCC. This finding emphasizes the importance of long-term follow-up in therapeutic trials evaluating treatment modalities for BCC, as well as the need for long-term follow-up of patients with high-risk tumors.

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

Radiation Therapy

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

resulted in higher recurrence rates than surgery (7.5% vs. 0.7%; $P = .003$),¹⁸³ poorer cosmetic outcomes, and more postoperative complications.¹⁸⁴

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

Intensity-modulated RT (IMRT) has been gaining wide use in recent years for the concurrent treatment of the primary skin tumor and the draining lymphatic beds. The NCCN panel emphasized the importance of proper support and training by medical physicists in using this technology as primary treatment. Special attention is warranted to ensure adequate surface dose to the target area.

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

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

Superficial Therapies

Since cure rates may be lower, superficial therapies should be reserved for those patients where surgery or radiation is contraindicated or

impractical.¹⁸⁸ Superficial therapies include topical treatment with 5-fluorouracil (5-FU) or imiquimod, photodynamic therapy (PDT), and cryotherapy.

Topical Therapies

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

Cryosurgery

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

outcomes compared with other treatment options, as demonstrated by prospective randomized trials.^{196,197,199}

Photodynamic Therapy

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

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

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

Comparisons of Superficial Therapies

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

analyses found that treatment success rates were significantly higher with imiquimod versus PDT for tumors that are large or truncal, while PDT provided significantly better outcomes than imiquimod in elderly patients with lesions on the lower extremities.²¹⁴ Safety results from this randomized trial showed that PDT and topical treatments are all associated with moderate to severe local skin redness.¹⁹³ Whereas PDT causes moderate to severe pain during treatment administration, imiquimod and fluorouracil are more likely to cause moderate to severe local swelling, erosion, crust formation, itching, and wound infections.¹⁹³ Both cryosurgery and PDT are associated with pain during and after treatment, and data from a randomized trial indicate a trend toward a higher likelihood of pain with PDT.¹⁹⁶

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

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

MAL, methyl aminolevulinic acid; NR, not reported; NS, no statistically significant difference; PDT, photodynamic therapy.

^aMeta-analysis of 23 randomized and non-randomized studies.

^bTreatment success was defined as the product of the percent of patients with clearance at 3 months by the percentage with sustained clearance during the next 9 months.

Intralesional Interferon

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

NCCN Recommendations

Low-Risk BCC

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

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

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

High-Risk BCC

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

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

Adjuvant RT is also recommended for patients with negative margins after surgery but with large nerve or extensive perineural involvement. Due to the potential for skull involvement and intracranial extension, an MRI should be considered if large-nerve invasion is suspected for tumors on the head and neck.

If negative margins are not achieved after standard excision, patients should undergo MMS or resection with CCPDMA, or receive adjuvant

RT. If residual disease is still present after adjuvant treatment, and further surgery and RT are contraindicated, clinicians should consider multidisciplinary consultation to determine whether the patient should be offered systemic treatment with a hedgehog pathway inhibitor or treatment in the context of a clinical trial.

Recurrence and Metastasis

Systemic Therapy

Recent FDA approval of the new agent vismodegib, a first-in-class Hedgehog pathway inhibitor, provided another option for patients who have exhausted surgical and radiation options for treating advanced BCC.²¹⁸ Approval was based on a multicenter, single-arm, two-cohort, open-label, phase II trial enrolling 104 patients (ERIVANCE).²²⁰ About 95% of patients were previously treated with surgery, RT, and/or systemic therapies. In the most recent report, based on 21-month minimum follow-up, objective response was recorded in 48% and 33% of patients with locally advanced and metastatic disease (laBCC and mBCC), respectively, with median response duration of 9.5 months and 7.6 months, respectively.²²¹ As shown in Table 2, several other studies testing vismodegib in patients with advanced BCC reported response rates and median progression-free survival times that were similar or better to those from ERIVANCE, and found that median time to response was 2.6 to 2.8 months. A separate independent analysis of photographic evidence from the ERIVANCE trial, using a different system for scoring baseline disease severity and clinical efficacy, determined that 65% of patients with laBCC showed significant improvement, and 11% significantly worsened.²²²

Vismodegib has also been tested as BCC treatment and prophylaxis in patients with nevoid BCC syndrome. A double-blind randomized phase II study in patients with nevoid BCC syndrome and at least 10 operable

BCC lesions found that vismodegib significantly reduced incidence of new BCC lesions compared with placebo, and also significantly reduced the size of existing lesions and the number of surgeries needed to remove BCC lesions.²²³

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

Sonidegib, another hedgehog pathway inhibitor, has also been approved by the FDA for treatment of patients with locally advanced BCC that has recurred following surgery or RT, or who are not candidates for surgery or radiotherapy.²¹⁹ FDA approval was based on data from the phase II BOLT trial comparing two different doses of sonidegib in patients with either 1) laBCC not amenable to curative surgery or RT; or 2) mBCC for which all available treatment options have been exhausted.²²⁶ Whereas response rates were similar for the two doses tested (Table 2), the higher dose (800 mg/d) was associated with higher rates of SAEs (14% vs. 30%) and AEs leading to dose interruptions, reductions, or discontinuation. As with vismodegib, nearly all patients experienced at least one AE, and the most common AEs were muscle spasms, dysgeusia, alopecia, nausea, weight decrease, and fatigue. Elevated creatinine kinase was also frequently observed,

and was one of the most common grade 3–4 AEs, along with elevated lipase.

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

Ongoing clinical research is exploring various dosing regimens of vismodegib and sonidegib in a variety of BCC treatment settings, including less advanced disease or as part of primary treatment for previously untreated disease.²²⁸⁻²³⁴ An open-label single-arm trial in large (mean tumor area, 12.6 cm² [range 1.0–78.0 cm²]) high-risk BCC eligible for surgical removal (n=11) found that 3 to 6 months of vismodegib prior to resection reduced the surgical defect area by 27% compared with baseline ($P = .006$).²²⁸ A phase II, open-label, multicenter trial in lower-risk operable BCC lesions (ie, diameter <3 cm, previously untreated, nodular) tested the efficacy and safety of neoadjuvant vismodegib in patients willing to delay surgery (n = 74).²³² Although 50%

of patients achieved investigator-assessed complete clinical clearance while on vismodegib, this trial did not meet its primary endpoints based on complete histologic clearance. Safety data from patients in cohort 2 of this trial (n= 24), who received 12 weeks of vismodegib followed by 24 weeks of observation before surgery, demonstrated high rates of AE reversibility (75%–100%) for some of the most common toxicities associated with vismodegib treatment (eg, muscle spasm, alopecia, dysgeusia, ageusia).

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

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

Table 2. Hedgehog Pathway Inhibitors in Advanced BCC^a

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

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

^aTrials included patients with advanced BCC that was inappropriate for surgery or RT.

^bInhibitors were taken orally once daily. Vismodegib dose was 150 mg.

^cTimes are reported in months.

^dResponse criteria varied between studies.

^eERIVANCE data per independent review facility assessment.

^fTrial was terminated early due to FDA approval of vismodegib.

NCCN Recommendations

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

Follow-Up

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

NCCN Recommendations

The frequency of follow-up should be based on risk. In addition to patient education about sun protection and self-examination, patients should be monitored with regular physical exams including complete

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

Discussion
update in
progress

References

1. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. *J Am Acad Dermatol* 1994;30:774-778. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8176018>.
2. Asgari MM, Moffet HH, Ray GT, Quesenberry CP. Trends in basal cell carcinoma incidence and identification of high-risk subgroups, 1998-2012. *JAMA Dermatol* 2015;151:976-981. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26039887>.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66:7-30. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26742998>.
4. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population, 2012. *JAMA Dermatol* 2015;151:1081-1086. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25928283>.
5. Chen JG, Fleischer AB, Jr., Smith ED, et al. Cost of nonmelanoma skin cancer treatment in the United States. *Dermatol Surg* 2001;27:1035-1038. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11849266>.
6. Mudigonda T, Pearce DJ, Yentzer BA, et al. The economic impact of non-melanoma skin cancer: a review. *J Natl Compr Canc Netw* 2010;8:888-896. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20870635>.
7. Christenson LJ, Borrowman TA, Vachon CM, et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. *JAMA* 2005;294:681-690. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16091570>.
8. Athas WF, Hunt WC, Key CR. Changes in nonmelanoma skin cancer incidence between 1977-1978 and 1998-1999 in Northcentral New Mexico. *Cancer Epidemiol Biomarkers Prev* 2003;12:1105-1108. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14578151>.
9. Brewster DH, Bhatti LA, Inglis JH, et al. Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland, 1992-2003. *Br J Dermatol* 2007;156:1295-1300. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17535229>.
10. Hayes RC, Leonfellner S, Pilgrim W, et al. Incidence of nonmelanoma skin cancer in New Brunswick, Canada, 1992 to 2001. *J Cutan Med Surg* 2007;11:45-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17374314>.
11. Karagas MR, Greenberg ER, Spencer SK, et al. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. *Int J Cancer* 1999;81:555-559. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10225444>.
12. Staples MP, Elwood M, Burton RC, et al. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. *Med J Aust* 2006;184:6-10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16398622>.
13. Demers AA, Nugent Z, Mihalciou C, et al. Trends of nonmelanoma skin cancer from 1960 through 2000 in a Canadian population. *J Am Acad Dermatol* 2005;53:320-328. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16021129>.
14. Kricker A, English DR, Randell PL, et al. Skin cancer in Geraldton, Western Australia: a survey of incidence and prevalence. *Med J Aust* 1990;152:399-407. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2329947>.
15. Abbas M, Kalia S. Trends in non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) in Canada: a descriptive analysis of available data. *J Cutan Med Surg* 2016;20:166-175. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26458408>.

16. Rudolph C, Schnoor M, Eisemann N, Katalinic A. Incidence trends of nonmelanoma skin cancer in Germany from 1998 to 2010. *J Dtsch Dermatol Ges* 2015;13:788-797. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26213814>.
17. Bernat Garcia J, Morales Suarez-Varela M, Vilata JJ, et al. Risk factors for non-melanoma skin cancer in kidney transplant patients in a Spanish population in the Mediterranean region. *Acta Derm Venereol* 2013;93:422-427. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23303600>.
18. Sella T, Goren I, Shalev V, et al. Incidence trends of keratinocytic skin cancers and melanoma in Israel 2006-11. *Br J Dermatol* 2015;172:202-207. Available at:
19. Kricger A, Armstrong BK, English DR, Heenan PJ. Does intermittent sun exposure cause basal cell carcinoma? a case-control study in Western Australia. *Int J Cancer* 1995;60:489-494. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7829262>.
20. Kricger A, Armstrong BK, English DR, Heenan PJ. A dose-response curve for sun exposure and basal cell carcinoma. *Int J Cancer* 1995;60:482-488. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7829261>.
21. Zanetti R, Rosso S, Martinez C, et al. Comparison of risk patterns in carcinoma and melanoma of the skin in men: a multi-centre case-control study. *Br J Cancer* 2006;94:743-751. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16495934>.
22. Gallagher RP, Hill GB, Bajdik CD, et al. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. I. Basal cell carcinoma. *Arch Dermatol* 1995;131:157-163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7857111>.
23. Ramsay HM, Fryer AA, Hawley CM, et al. Factors associated with nonmelanoma skin cancer following renal transplantation in Queensland, Australia. *J Am Acad Dermatol* 2003;49:397-406. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12963901>.
24. Kaskel P, Lange U, Sander S, et al. Ultraviolet exposure and risk of melanoma and basal cell carcinoma in Ulm and Dresden, Germany. *J Eur Acad Dermatol Venereol* 2015;29:134-142. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24684198>.
25. Khalesi M, Whiteman DC, Tran B, et al. A meta-analysis of pigmentary characteristics, sun sensitivity, freckling and melanocytic nevi and risk of basal cell carcinoma of the skin. *Cancer Epidemiol* 2013;37:534-543. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23849507>.
26. Walther U, Kron M, Sander S, et al. Risk and protective factors for sporadic basal cell carcinoma: results of a two-centre case-control study in southern Germany. *Clinical actinic elastosis may be a protective factor*. *Br J Dermatol* 2004;151:170-178. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15270887>.
27. Box NF, Duffy DL, Irving RE, et al. Melanocortin-1 receptor genotype is a risk factor for basal and squamous cell carcinoma. *J Invest Dermatol* 2001;116:224-229. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11179997>.
28. Lock-Andersen J, Drzewiecki KT, Wulf HC. Eye and hair colour, skin type and constitutive skin pigmentation as risk factors for basal cell carcinoma and cutaneous malignant melanoma. A Danish case-control study. *Acta Derm Venereol* 1999;79:74-80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10086866>.
29. Chinem VP, Miot HA. Prevalence of actinic skin lesions in patients with basal cell carcinoma of the head: a case-control study. *Rev Assoc Med Bras* 2012;58:188-196. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22569613>.

30. Perkins JL, Liu Y, Mitby PA, et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2005;23:3733-3741. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15923570>.
31. Karagas MR, Nelson HH, Zens MS, et al. Squamous cell and basal cell carcinoma of the skin in relation to radiation therapy and potential modification of risk by sun exposure. *Epidemiology* 2007;18:776-784. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17917604>.
32. Watt TC, Inskip PD, Stratton K, et al. Radiation-related risk of basal cell carcinoma: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2012;104:1240-1250. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22835387>.
33. Schwartz JL, Kopecky KJ, Mathes RW, et al. Basal cell skin cancer after total-body irradiation and hematopoietic cell transplantation. *Radiat Res* 2009;171:155-163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19267540>.
34. Lichter MD, Karagas MR, Mott LA, et al. Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. The New Hampshire Skin Cancer Study Group. *Arch Dermatol* 2000;136:1007-1011. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10926736>.
35. Karagas MR, McDonald JA, Greenberg ER, et al. Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. For The Skin Cancer Prevention Study Group. *J Natl Cancer Inst* 1996;88:1848-1853. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8961975>.
36. Kumar S, Mahajan BB, Kaur S, et al. A study of Basal cell carcinoma in South asians for risk factor and clinicopathological characterization: a hospital based study. *J Skin Cancer* 2014;2014:173582. Available at:
37. English DR, Krickler A, Heenan PJ, et al. Incidence of non-melanocytic skin cancer in Geraldton, Western Australia. *Int J Cancer* 1997;73:629-633. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9398037>.
38. Zargaran M, Moghimbeigi A, Monsef A, et al. A clinicopathological survey of Basal cell carcinoma in an Iranian population. *J Dent (Shiraz)* 2013;14:170-177. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24724141>.
39. Lesiak A, Sobolewska-Sztychny D, Majak P, et al. Relation between sonic hedgehog pathway gene polymorphisms and basal cell carcinoma development in the Polish population. *Arch Dermatol Res* 2016;308:39-47. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26590974>.
40. Reifemberger J, Wolter M, Weber RG, et al. Missense mutations in SMOH in sporadic basal cell carcinomas of the skin and primitive neuroectodermal tumors of the central nervous system. *Cancer Res* 1998;58:1798-1803. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9581815>.
41. Xie J, Murone M, Luoh SM, et al. Activating Smoothed mutations in sporadic basal-cell carcinoma. *Nature* 1998;391:90-92. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9422511>.
42. Gailani MR, Bale SJ, Leffell DJ, et al. Developmental defects in Gorlin syndrome related to a putative tumor suppressor gene on chromosome 9. *Cell* 1992;69:111-117. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1348213>.
43. Soufir N, Gerard B, Portela M, et al. PTCH mutations and deletions in patients with typical nevoid basal cell carcinoma syndrome and in patients with a suspected genetic predisposition to basal cell carcinoma: a French study. *Br J Cancer* 2006;95:548-553. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16909134>.

44. Hahn H, Wicking C, Zaphiropoulous PG, et al. Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. *Cell* 1996;85:841-851. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8681379>.
45. Chidambaram A, Goldstein AM, Gailani MR, et al. Mutations in the human homologue of the Drosophila patched gene in Caucasian and African-American nevoid basal cell carcinoma syndrome patients. *Cancer Res* 1996;56:4599-4601. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8840969>.
46. Ling G, Ahmadian A, Persson A, et al. PATCHED and p53 gene alterations in sporadic and hereditary basal cell cancer. *Oncogene* 2001;20:7770-7778. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11753655>.
47. Pastorino L, Cusano R, Nasti S, et al. Molecular characterization of Italian nevoid basal cell carcinoma syndrome patients. *Hum Mutat* 2005;25:322-323. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15712338>.
48. Wang W, Wang J, Li J, et al. New mutation of the patched homologue 1 gene in a Chinese family with naevoid basal cell carcinoma syndrome. *Br J Oral Maxillofac Surg* 2009;47:366-369. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19008023>.
49. Aszterbaum M, Rothman A, Johnson RL, et al. Identification of mutations in the human PATCHED gene in sporadic basal cell carcinomas and in patients with the basal cell nevus syndrome. *J Invest Dermatol* 1998;110:885-888. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9620294>.
50. Heitzer E, Lassacher A, Quehenberger F, et al. UV fingerprints predominate in the PTCH mutation spectra of basal cell carcinomas independent of clinical phenotype. *J Invest Dermatol* 2007;127:2872-2881. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17597822>.
51. Danaee H, Karagas MR, Kelsey KT, et al. Allelic loss at Drosophila patched gene is highly prevalent in Basal and squamous cell carcinomas of the skin. *J Invest Dermatol* 2006;126:1152-1158. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16484983>.
52. Reifenger J, Wolter M, Knobbe CB, et al. Somatic mutations in the PTCH, SMOH, SUFUH and TP53 genes in sporadic basal cell carcinomas. *Br J Dermatol* 2005;152:43-51. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15656799>.
53. Kim MY, Park HJ, Baek SC, et al. Mutations of the p53 and PTCH gene in basal cell carcinomas: UV mutation signature and strand bias. *J Dermatol Sci* 2002;29:1-9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12007715>.
54. Gailani MR, Stahle-Backdahl M, Leffell DJ, et al. The role of the human homologue of Drosophila patched in sporadic basal cell carcinomas. *Nat Genet* 1996;14:78-81. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8782823>.
55. Zhang H, Ping XL, Lee PK, et al. Role of PTCH and p53 genes in early-onset basal cell carcinoma. *Am J Pathol* 2001;158:381-385. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11159175>.
56. Daya-Grosjean L, Sarasin A. UV-specific mutations of the human patched gene in basal cell carcinomas from normal individuals and xeroderma pigmentosum patients. *Mutat Res* 2000;450:193-199. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10838143>.
57. Teh MT, Blaydon D, Chaplin T, et al. Genomewide single nucleotide polymorphism microarray mapping in basal cell carcinomas unveils uniparental disomy as a key somatic event. *Cancer Res* 2005;65:8597-8603. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16204023>.
58. Ziegler A, Leffell DJ, Kunala S, et al. Mutation hotspots due to sunlight in the p53 gene of nonmelanoma skin cancers. *Proc Natl Acad Sci U S A* 1993;90:4216-4220. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8483937>.

59. Ghaderi R, Haghighi F. Immunohistochemistry assessment of p53 protein in Basal cell carcinoma. *Iran J Allergy Asthma Immunol* 2005;4:167-171. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17301441>.
60. Rosenstein BS, Phelps RG, Weinstock MA, et al. p53 mutations in basal cell carcinomas arising in routine users of sunscreens. *Photochem Photobiol* 1999;70:798-806. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10568172>.
61. Oluwasanmi JO, Williams AO, Alli AF. Superficial cancer in Nigeria. *Br J Cancer* 1969;23:714-728. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/5367332>.
62. Yakubu A, Mabogunje OA. Skin cancer in Zaria, Nigeria. *Trop Doct* 1995;25 Suppl 1:63-67. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7879275>.
63. Halkud R, Shenoy AM, Naik SM, et al. Xeroderma pigmentosum: clinicopathological review of the multiple oculocutaneous malignancies and complications. *Indian J Surg Oncol* 2014;5:120-124. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25114464>.
64. Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases. *Arch Dermatol* 1987;123:241-250. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3545087>.
65. Bradford PT, Goldstein AM, Tamura D, et al. Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterises the role of DNA repair. *J Med Genet* 2011;48:168-176. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21097776>.
66. Kraemer KH, Lee MM, Andrews AD, Lambert WC. The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer. The xeroderma pigmentosum paradigm. *Arch Dermatol* 1994;130:1018-1021. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8053698>.
67. Kraemer KH, Lee MM, Scotto J. DNA repair protects against cutaneous and internal neoplasia: evidence from xeroderma pigmentosum. *Carcinogenesis* 1984;5:511-514. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6705149>.
68. Couve-Privat S, Le Bret M, Traiffort E, et al. Functional analysis of novel sonic hedgehog gene mutations identified in basal cell carcinomas from xeroderma pigmentosum patients. *Cancer Res* 2004;64:3559-3565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15150112>.
69. Couve-Privat S, Bouadjar B, Avril MF, et al. Significantly high levels of ultraviolet-specific mutations in the smoothed gene in basal cell carcinomas from DNA repair-deficient xeroderma pigmentosum patients. *Cancer Res* 2002;62:7186-7189. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12499255>.
70. D'Errico M, Calcagnile A, Canzona F, et al. UV mutation signature in tumor suppressor genes involved in skin carcinogenesis in xeroderma pigmentosum patients. *Oncogene* 2000;19:463-467. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10656695>.
71. Cleaver JE. Defective repair replication of DNA in xeroderma pigmentosum. *Nature* 1968;218:652-656. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/5655953>.
72. Thielmann HW, Popanda O, Edler L, Jung EG. Clinical symptoms and DNA repair characteristics of xeroderma pigmentosum patients from Germany. *Cancer Res* 1991;51:3456-3470. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2054785>.
73. Grossman L. Epidemiology of ultraviolet-DNA repair capacity and human cancer. *Environ Health Perspect* 1997;105 Suppl 4:927-930. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9255582>.

74. Bodak N, Queille S, Avril MF, et al. High levels of patched gene mutations in basal-cell carcinomas from patients with xeroderma pigmentosum. *Proc Natl Acad Sci U S A* 1999;96:5117-5122. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10220428>.
75. Miller KL, Karagas MR, Kraft P, et al. XPA, haplotypes, and risk of basal and squamous cell carcinoma. *Carcinogenesis* 2006;27:1670-1675. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16513681>.
76. Chen J, Ruczinski I, Jorgensen TJ, et al. Nonmelanoma skin cancer and risk for subsequent malignancy. *J Natl Cancer Inst* 2008;100:1215-1222. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18728282>.
77. Maloney ME, Miller SJ. Aggressive vs nonaggressive subtypes (basal cell carcinoma). In: Miller SJ, Maloney ME, eds. *Cutaneous Oncology Pathophysiology, diagnosis, and management*. Malden, MA: Blackwell Science; 1998:609-613.
78. Salasche SJ. Features associated with recurrence (squamous cell carcinoma). In: Miller SJ, Maloney ME, eds. *Cutaneous Oncology Pathophysiology, diagnosis, and management*. Malden, MA: Blackwell Science; 1998:494-499.
79. Gandhi MR, Panizza B, Kennedy D. Detecting and defining the anatomic extent of large nerve perineural spread of malignancy: comparing "targeted" MRI with the histologic findings following surgery. *Head Neck* 2011;33:469-475. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20645285>.
80. Williams LS, Mancuso AA, Mendenhall WM. Perineural spread of cutaneous squamous and basal cell carcinoma: CT and MR detection and its impact on patient management and prognosis. *Int J Radiat Oncol Biol Phys* 2001;49:1061-1069. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11240248>.
81. Boeta-Angeles L, Bennett RG. Features associated with recurrence (basal cell carcinoma). In: Miller SJ, Maloney ME, eds. *Cutaneous Oncology Pathophysiology, diagnosis, and management*. Malden, MA: Blackwell Science; 1998:646-656.
82. Silverman MK, Kopf AW, Bart RS, et al. Recurrence rates of treated basal cell carcinomas. Part 3: Surgical excision. *J Dermatol Surg Oncol* 1992;18:471-476. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1592998>.
83. Silverman MK, Kopf AW, Grin CM, et al. Recurrence rates of treated basal cell carcinomas. Part 2: Curettage-electrodesiccation. *J Dermatol Surg Oncol* 1991;17:720-726. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1820764>.
84. Dubin N, Kopf AW. Multivariate risk score for recurrence of cutaneous basal cell carcinomas. *Arch Dermatol* 1983;119:373-377. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6847215>.
85. Bogelund FS, Philipsen PA, Gniadecki R. Factors affecting the recurrence rate of basal cell carcinoma. *Acta Derm Venereol* 2007;87:330-334. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17598036>.
86. Rigel DS, Robins P, Friedman RJ. Predicting recurrence of basal-cell carcinomas treated by microscopically controlled excision: a recurrence index score. *J Dermatol Surg Oncol* 1981;7:807-810. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7298981>.
87. von Domarus H, Stevens PJ. Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. *J Am Acad Dermatol* 1984;10:1043-1060. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6736323>.
88. Nguyen-Nielsen M, Wang L, Pedersen L, et al. The incidence of metastatic basal cell carcinoma (mBCC) in Denmark, 1997-2010. *Eur J Dermatol* 2015;25:463-468. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26105129>.

89. Snow SN, Sahl W, Lo JS, et al. Metastatic basal cell carcinoma. Report of five cases. *Cancer* 1994;73:328-335. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8293396>.
90. Swanson NA. Mohs surgery. Technique, indications, applications, and the future. *Arch Dermatol* 1983;119:761-773. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6351758>.
91. Swanson NA, Johnson TM. Management of basal and squamous cell carcinoma. In: Cummings C, ed. *Otolaryngology Head and Neck Surgery*. New York: Mosby Yearbook; 1998:486-501.
92. van Iersel CA, van de Velden HV, Kusters CD, et al. Prognostic factors for a subsequent basal cell carcinoma: implications for follow-up. *Br J Dermatol* 2005;153:1078-1080. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16225637>.
93. Spiller WF, Spiller RF. Treatment of basal cell epithelioma by curettage and electrodesiccation. *J Am Acad Dermatol* 1984;11:808-814. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6512037>.
94. Petrovich Z, Kuisk H, Langholz B, et al. Treatment results and patterns of failure in 646 patients with carcinoma of the eyelids, pinna, and nose. *Am J Surg* 1987;154:447-450. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3661851>.
95. Silverman MK, Kopf AW, Grin CM, et al. Recurrence rates of treated basal cell carcinomas. Part 1: Overview. *J Dermatol Surg Oncol* 1991;17:713-718. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1890243>.
96. Connolly AH, Baker DR, Coldiron BM, et al. AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery. *Dermatol Surg* 2012;38:1582-1603. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22958088>.
97. Dixon AY, Lee SH, McGregor DH. Histologic features predictive of basal cell carcinoma recurrence: results of a multivariate analysis. *J Cutan Pathol* 1993;20:137-142. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8320358>.
98. Jacobs GH, Rippey JJ, Altini M. Prediction of aggressive behavior in basal cell carcinoma. *Cancer* 1982;49:533-537. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7059912>.
99. de Rosa G, Vetrani A, Zeppa P, et al. Comparative morphometric analysis of aggressive and ordinary basal cell carcinoma of the skin. *Cancer* 1990;65:544-549. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2297645>.
100. Sloane JP. The value of typing basal cell carcinomas in predicting recurrence after surgical excision. *Br J Dermatol* 1977;96:127-132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/843446>.
101. Codazzi D, Van Der Velden J, Carminati M, et al. Positive compared with negative margins in a single-centre retrospective study on 3957 consecutive excisions of basal cell carcinomas. Associated risk factors and preferred surgical management. *J Plast Surg Hand Surg* 2014;48:38-43. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23731130>.
102. Stern RS, Liebman EJ, Vakeva L. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. *J Natl Cancer Inst* 1998;90:1278-1284. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9731734>.
103. Archier E, Devaux S, Castela E, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol* 2012;26 Suppl 3:22-31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22512677>.

104. Krynitz B, Olsson H, Lundh Rozell B, et al. Risk of basal cell carcinoma in Swedish organ transplant recipients: a population-based study. *Br J Dermatol* 2016;174:95-103. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26333521>.
105. Mackintosh LJ, Geddes CC, Herd RM. Skin tumours in the West of Scotland renal transplant population. *Br J Dermatol* 2013;168:1047-1053. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23137036>.
106. Karczewski M, Stronka M, Karczewski J, Wiktorowicz K. Skin cancer following kidney transplantation: a single-center experience. *Transplant Proc* 2011;43:3760-3761. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22172842>.
107. Bordea C, Wojnarowska F, Millard PR, et al. Skin cancers in renal-transplant recipients occur more frequently than previously recognized in a temperate climate. *Transplantation* 2004;77:574-579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15084938>.
108. DePry JL, Vyas R, Lazarus HM, et al. Cutaneous malignant neoplasms in hematopoietic cell transplant recipients: a systematic review. *JAMA Dermatol* 2015;151:775-782. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25902409>.
109. Park GH, Chang SE, Won CH, et al. Incidence of primary skin cancer after organ transplantation: An 18-year single-center experience in Korea. *J Am Acad Dermatol* 2014;70:465-472. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24342756>.
110. Jensen AO, Svaerke C, Farkas D, et al. Skin cancer risk among solid organ recipients: a nationwide cohort study in Denmark. *Acta Derm Venereol* 2010;90:474-479. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20814621>.
111. Hartevelt MM, Bavinck JN, Kootte AM, et al. Incidence of skin cancer after renal transplantation in The Netherlands. *Transplantation* 1990;49:506-509. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2316011>.
112. Harwood CA, Mesher D, McGregor JM, et al. A surveillance model for skin cancer in organ transplant recipients: a 22-year prospective study in an ethnically diverse population. *Am J Transplant* 2013;13:119-129. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23072567>.
113. Brewer JD, Colegio OR, Phillips PK, et al. Incidence of and risk factors for skin cancer after heart transplant. *Arch Dermatol* 2009;145:1391-1396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20026847>.
114. Rashtak S, Dierkhising RA, Kremers WK, et al. Incidence and risk factors for skin cancer following lung transplantation. *J Am Acad Dermatol* 2015;72:92-98. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25440431>.
115. Fortina AB, Piaserico S, Caforio AL, et al. Immunosuppressive level and other risk factors for basal cell carcinoma and squamous cell carcinoma in heart transplant recipients. *Arch Dermatol* 2004;140:1079-1085. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15381547>.
116. Kanitakis J, Alhaj-Ibrahim L, Euvrard S, Claudy A. Basal cell carcinomas developing in solid organ transplant recipients: clinicopathologic study of 176 cases. *Arch Dermatol* 2003;139:1133-1137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12975154>.
117. Harwood CA, Proby CM, McGregor JM, et al. Clinicopathologic features of skin cancer in organ transplant recipients: a retrospective case-control series. *J Am Acad Dermatol* 2006;54:290-300. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16443060>.
118. Lott DG, Manz R, Koch C, Lorenz RR. Aggressive behavior of nonmelanotic skin cancers in solid organ transplant recipients. *Transplantation* 2010;90:683-687. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20808266>.
119. Martin H, Strong E, Spiro RH. Radiation-induced skin cancer of the head and neck. *Cancer* 1970;25:61-71. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/4312028>.

120. Hassanein AM, Proper SA, Depcik-Smith ND, Flowers FP. Peritumoral fibrosis in basal cell and squamous cell carcinoma mimicking perineural invasion: potential pitfall in Mohs micrographic surgery. *Dermatol Surg* 2005;31:1101-1106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16164857>.

121. Jackson JE, Dickie GJ, Wiltshire KL, et al. Radiotherapy for perineural invasion in cutaneous head and neck carcinomas: toward a risk-adapted treatment approach. *Head Neck* 2009;31:604-610. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19132719>.

122. Lin C, Tripcony L, Keller J, et al. Perineural infiltration of cutaneous squamous cell carcinoma and basal cell carcinoma without clinical features. *Int J Radiat Oncol Biol Phys* 2012;82:334-340. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21093171>.

123. Garcia-Serra A, Hinerman RW, Mendenhall WM, et al. Carcinoma of the skin with perineural invasion. *Head Neck* 2003;25:1027-1033. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14648861>.

124. Lin C, Tripcony L, Keller J, et al. Cutaneous carcinoma of the head and neck with clinical features of perineural infiltration treated with radiotherapy. *Clin Oncol (R Coll Radiol)* 2013;25:362-367. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23489870>.

125. Leibovitch I, Huilgol SC, Selva D, et al. Basal cell carcinoma treated with Mohs surgery in Australia III. Perineural invasion. *J Am Acad Dermatol* 2005;53:458-463. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16112353>.

126. Ratner D, Lowe L, Johnson TM, Fader DJ. Perineural spread of basal cell carcinomas treated with Mohs micrographic surgery. *Cancer* 2000;88:1605-1613. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10738219>.

127. Brown CI, Perry AE. Incidence of perineural invasion in histologically aggressive types of basal cell carcinoma. *Am J Dermatopathol* 2000;22:123-125. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10770431>.

128. Galloway TJ, Morris CG, Mancuso AA, et al. Impact of radiographic findings on prognosis for skin carcinoma with clinical perineural invasion. *Cancer* 2005;103:1254-1257. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15693020>.

129. Balamucki CJ, DeJesus R, Galloway TJ, et al. Impact of radiographic findings on for prognosis skin cancer with perineural invasion. *Am J Clin Oncol* 2015;38:248-251. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23648439>.

130. Cernea CR, Ferraz AR, de Castro IV, et al. Perineural invasion in aggressive skin carcinomas of the head and neck. Potentially dangerous but frequently overlooked. *ORL J Otorhinolaryngol Relat Spec* 2009;71:21-26. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18946230>.

131. Leffell DJ, Headington JT, Wong DS, Swanson NA. Aggressive-growth basal cell carcinoma in young adults. *Arch Dermatol* 1991;127:1663-1667. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1952969>.

132. McCormack CJ, Kelly JW, Dorevitch AP. Differences in age and body site distribution of the histological subtypes of basal cell carcinoma. A possible indicator of differing causes. *Arch Dermatol* 1997;133:593-596. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9158412>.

133. Bastiaens MT, Hoefnagel JJ, Bruijn JA, et al. Differences in age, site distribution, and sex between nodular and superficial basal cell carcinoma indicate different types of tumors. *J Invest Dermatol* 1998;110:880-884. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9620293>.

134. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. *Br J Dermatol* 2002;147:41-47. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12100183>.

135. Raasch BA, Buettner PG, Garbe C. Basal cell carcinoma: histological classification and body-site distribution. *Br J Dermatol* 2006;155:401-407. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16882181>.

136. Dinehart SM, Dodge R, Stanley WE, et al. Basal cell carcinoma treated with Mohs surgery. A comparison of 54 younger patients with 1050 older patients. *J Dermatol Surg Oncol* 1992;18:560-566. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1624629>.

137. Milroy CJ, Horlock N, Wilson GD, Sanders R. Aggressive basal cell carcinoma in young patients: fact or fiction? *Br J Plast Surg* 2000;53:393-396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10876275>.

138. Roudier-Pujol C, Auperin A, Nguyen T, et al. Basal cell carcinoma in young adults: not more aggressive than in older patients. *Dermatology* 1999;199:119-123. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10559576>.

139. Lear JT, Smith AG, Bowers B, et al. Truncal tumor site is associated with high risk of multiple basal cell carcinoma and is influenced by glutathione S-transferase, GSTT1, and cytochrome P450, CYP1A1 genotypes, and their interaction. *J Invest Dermatol* 1997;108:519-522. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9077484>.

140. Ramachandran S, Fryer AA, Lovatt T, et al. The rate of increase in the numbers of primary sporadic basal cell carcinomas during follow up is associated with age at first presentation. *Carcinogenesis* 2002;23:2051-2054. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12507928>.

141. Cheretis C, Angelidou E, Dietrich F, et al. Prognostic value of computer-assisted morphological and morphometrical analysis for detecting the recurrence tendency of basal cell carcinoma. *Med Sci Monit* 2008;14:MT13-19. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18443558>.

142. Karagas MR, Stukel TA, Greenberg ER, et al. Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. Skin Cancer Prevention Study Group. *JAMA* 1992;267:3305-3310. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1597912>.

143. Lovatt TJ, Lear JT, Bastrilles J, et al. Associations between ultraviolet radiation, basal cell carcinoma site and histology, host characteristics, and rate of development of further tumors. *J Am Acad Dermatol* 2005;52:468-473. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15761425>.

144. Levi F, Randimbison L, Maspoli M, et al. High incidence of second basal cell skin cancers. *Int J Cancer* 2006;119:1505-1507. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16642479>.

145. Richmond-Sinclair NM, Pandeya N, Williams GM, et al. Clinical signs of photodamage are associated with basal cell carcinoma multiplicity and site: a 16-year longitudinal study. *Int J Cancer* 2010;127:2622-2629. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20196068>.

146. Kiiski V, de Vries E, Flohil SC, et al. Risk factors for single and multiple basal cell carcinomas. *Arch Dermatol* 2010;146:848-855. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20713815>.

147. Flohil SC, Koljenovic S, de Haas ER, et al. Cumulative risks and rates of subsequent basal cell carcinomas in the Netherlands. *Br J Dermatol* 2011;165:874-881. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21711333>.

148. Verkouteren JA, Smedinga H, Steyerberg EW, et al. Predicting the risk of a second basal cell carcinoma. *J Invest Dermatol* 2015;135:2649-2656. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26121210>.
149. Milan T, Pukkala E, Verkasalo PK, et al. Subsequent primary cancers after basal-cell carcinoma: A nationwide study in Finland from 1953 to 1995. *Int J Cancer* 2000;87:283-288. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10861488>.
150. McCusker M, Basset-Seguín N, Dummer R, et al. Metastatic basal cell carcinoma: prognosis dependent on anatomic site and spread of disease. *Eur J Cancer* 2014;50:774-783. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24412051>.
151. Dixon AY, Lee SH, McGregor DH. Factors predictive of recurrence of basal cell carcinoma. *Am J Dermatopathol* 1989;11:222-232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2729527>.
152. Smeets NW, Kuijpers DI, Nelemans P, et al. Mohs' micrographic surgery for treatment of basal cell carcinoma of the face--results of a retrospective study and review of the literature. *Br J Dermatol* 2004;151:141-147. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15270883>.
153. Cigna E, Tarallo M, Maruccia M, et al. Basal cell carcinoma: 10 years of experience. *J Skin Cancer* 2011;2011:476362. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21151696>.
154. Szewczyk MP, Pazdrowski J, Danczak-Pazdrowska A, et al. Analysis of selected recurrence risk factors after treatment of head and neck basal cell carcinoma. *Postepy Dermatol Alergol* 2014;31:146-151. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25097485>.
155. Bartos V, Pokorny D, Zacharova O, et al. Recurrent basal cell carcinoma: a clinicopathological study and evaluation of histomorphological findings in primary and recurrent lesions. *Acta Dermatovenerol Alp Pannonica Adriat* 2011;20:67-75. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21993704>.
156. Sartore L, Lancerotto L, Salmaso M, et al. Facial basal cell carcinoma: analysis of recurrence and follow-up strategies. *Oncol Rep* 2011;26:1423-1429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21922143>.
157. Costantino D, Lowe L, Brown DL. Basosquamous carcinoma--an under-recognized, high-risk cutaneous neoplasm: case study and review of the literature. *J Plast Reconstr Aesthet Surg* 2006;59:424-428. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16756261>.
158. Martin RC, 2nd, Edwards MJ, Cawte TG, et al. Basosquamous carcinoma: analysis of prognostic factors influencing recurrence. *Cancer* 2000;88:1365-1369. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10717618>.
159. Garcia C, Poletti E, Crowson AN. Basosquamous carcinoma. *J Am Acad Dermatol* 2009;60:137-143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19103364>.
160. Wermker K, Roknic N, Goessling K, et al. Basosquamous carcinoma of the head and neck: clinical and histologic characteristics and their impact on disease progression. *Neoplasia* 2015;17:301-305. Available at:
161. Bath-Hextall F, Bong J, Perkins W, Williams H. Interventions for basal cell carcinoma of the skin: systematic review. *BMJ* 2004;329:705. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15364703>.
162. Rowe DE, Carroll RJ, Day CL, Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol* 1989;15:315-328. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2646336>.

163. Barlow JO, Zalla MJ, Kyle A, et al. Treatment of basal cell carcinoma with curettage alone. *J Am Acad Dermatol* 2006;54:1039-1045. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16713459>.

164. Thissen MR, Neumann MH, Schouten LJ. A systematic review of treatment modalities for primary basal cell carcinomas. *Arch Dermatol* 1999;135:1177-1183. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10522664>.

165. Julian C, Bowers PW, Pritchard C. A comparative study of the effects of disposable and Volkmann spoon curettes in the treatment of basal cell carcinoma. *Br J Dermatol* 2009;161:1407-1409. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19681879>.

166. Blixt E, Nelsen D, Stratman E. Recurrence rates of aggressive histologic types of basal cell carcinoma after treatment with electrodesiccation and curettage alone. *Dermatol Surg* 2013;39:719-725. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23379543>.

167. Rodriguez-Vigil T, Vazquez-Lopez F, Perez-Oliva N. Recurrence rates of primary basal cell carcinoma in facial risk areas treated with curettage and electrodesiccation. *J Am Acad Dermatol* 2007;56:91-95. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17190625>.

168. Kopf AW, Bart RS, Schragger D, et al. Curettage-electrodesiccation treatment of basal cell carcinomas. *Arch Dermatol* 1977;113:439-443. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/848972>.

169. Kuijpers DI, Thissen MR, Berretty PJ, et al. Surgical excision versus curettage plus cryosurgery in the treatment of basal cell carcinoma. *Dermatol Surg* 2007;33:579-587. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17451581>.

170. Rhodes LE, de Rie MA, Leifsdottir R, et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. *Arch Dermatol* 2007;143:1131-1136. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17875873>.

171. Wolf DJ, Zitelli JA. Surgical margins for basal cell carcinoma. *Arch Dermatol* 1987;123:340-344. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3813602>.

172. Rowe DE, Carroll RJ, Day CL, Jr. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. *J Dermatol Surg Oncol* 1989;15:424-431. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2925988>.

173. Mosterd K, Krekels GA, Nieman FH, et al. Surgical excision versus Mohs' micrographic surgery for primary and recurrent basal-cell carcinoma of the face: a prospective randomised controlled trial with 5-years' follow-up. *Lancet Oncol* 2008;9:1149-1156. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19010733>.

174. van Loo E, Mosterd K, Krekels GA, et al. Surgical excision versus Mohs' micrographic surgery for basal cell carcinoma of the face: A randomised clinical trial with 10 year follow-up. *Eur J Cancer* 2014;50:3011-3020. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25262378>.

175. Mendenhall WM, Amdur RJ, Hinerman RW, et al. Radiotherapy for cutaneous squamous and basal cell carcinomas of the head and neck. *Laryngoscope* 2009;119:1994-1999. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19688856>.

176. Wilder RB, Kittelson JM, Shimm DS. Basal cell carcinoma treated with radiation therapy. *Cancer* 1991;68:2134-2137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1913451>.

177. Wilder RB, Shimm DS, Kittelson JM, et al. Recurrent basal cell carcinoma treated with radiation therapy. *Arch Dermatol* 1991;127:1668-1672. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1952970>.

178. Childers BJ, Goldwyn RM, Ramos D, et al. Long-term results of irradiation for basal cell carcinoma of the skin of the nose. *Plast Reconstr Surg* 1994;93:1169-1173. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8171136>.

179. Hernandez-Machin B, Borrego L, Gil-Garcia M, Hernandez BH. Office-based radiation therapy for cutaneous carcinoma: evaluation of 710 treatments. *Int J Dermatol* 2007;46:453-459. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17472670>.

180. Silverman MK, Kopf AW, Gladstein AH, et al. Recurrence rates of treated basal cell carcinomas. Part 4: X-ray therapy. *J Dermatol Surg Oncol* 1992;18:549-554. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1624628>.

181. Zagrodnik B, Kempf W, Seifert B, et al. Superficial radiotherapy for patients with basal cell carcinoma: recurrence rates, histologic subtypes, and expression of p53 and Bcl-2. *Cancer* 2003;98:2708-2714. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14669293>.

182. Cognetta AB, Howard BM, Heaton HP, et al. Superficial x-ray in the treatment of basal and squamous cell carcinomas: a viable option in select patients. *J Am Acad Dermatol* 2012;67:1235-1241. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22818756>.

183. Avril MF, Auperin A, Margulis A, et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. *Br J Cancer* 1997;76:100-106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9218740>.

184. Petit JY, Avril MF, Margulis A, et al. Evaluation of cosmetic results of a randomized trial comparing surgery and radiotherapy in the treatment of basal cell carcinoma of the face. *Plast Reconstr Surg* 2000;105:2544-2551. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10845311>.

185. Neville JA, Welch E, Leffell DJ. Management of nonmelanoma skin cancer in 2007. *Nat Clin Pract Oncol* 2007;4:462-469. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17657251>.

186. Mendenhall WM, Ferlito A, Takes RP, et al. Cutaneous head and neck basal and squamous cell carcinomas with perineural invasion. *Oral Oncol* 2012;48:918-922. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22425152>.

187. Han A, Ratner D. What is the role of adjuvant radiotherapy in the treatment of cutaneous squamous cell carcinoma with perineural invasion? *Cancer* 2007;109:1053-1059. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17279578>.

188. Braathen LR, Szeimies RM, Basset-Seguín N, et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. *International Society for Photodynamic Therapy in Dermatology, 2005. J Am Acad Dermatol* 2007;56:125-143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17190630>.

189. Geisse J, Caro I, Lindholm J, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. *J Am Acad Dermatol* 2004;50:722-733. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15097956>.

190. Schulze HJ, Cribier B, Requena L, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. *Br J Dermatol* 2005;152:939-947. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15888150>.

191. Quirk C, Gebauer K, De'Ambrosio B, et al. Sustained clearance of superficial basal cell carcinomas treated with imiquimod cream 5%: results of a prospective 5-year study. *Cutis* 2010;85:318-324. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20666194>.

192. Bath-Hextall F, Ozolins M, Armstrong SJ, et al. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial. *Lancet Oncol* 2014;15:96-105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24332516>.

193. Arits AH, Mosterd K, Essers BA, et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. *Lancet Oncol* 2013;14:647-654. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23683751>.

194. Hall VL, Leppard BJ, McGill J, et al. Treatment of basal-cell carcinoma: comparison of radiotherapy and cryotherapy. *Clin Radiol* 1986;37:33-34. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3514075>.

195. Mallon E, Dawber R. Cryosurgery in the treatment of basal cell carcinoma. Assessment of one and two freeze-thaw cycle schedules. *Dermatol Surg* 1996;22:854-858. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9246168>.

196. Wang I, Bendsoe N, Klinteberg CA, et al. Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. *Br J Dermatol* 2001;144:832-840. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11298545>.

197. Basset-Seguín N, Ibbotson SH, Emtestam L, et al. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. *Eur J Dermatol* 2008;18:547-553. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18693158>.

198. Kuflik EG. Cryosurgery for skin cancer: 30-year experience and cure rates. *Dermatol Surg* 2004;30:297-300. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14871224>.

199. Thissen MR, Nieman FH, Ideler AH, et al. Cosmetic results of cryosurgery versus surgical excision for primary uncomplicated basal cell carcinomas of the head and neck. *Dermatol Surg* 2000;26:759-764. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10940063>.

200. Kuijpers DI, Thissen MR, Thissen CA, Neumann MH. Similar effectiveness of methyl aminolevulinate and 5-aminolevulinate in topical photodynamic therapy for nodular basal cell carcinoma. *J Drugs Dermatol* 2006;5:642-645. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16865869>.

201. Savoia P, Deboli T, Prevgliano A, Broganelli P. Usefulness of photodynamic therapy as a possible therapeutic alternative in the treatment of basal cell carcinoma. *Int J Mol Sci* 2015;16:23300-23317. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26426005>.

202. Berroeta L, Clark C, Dawe RS, et al. A randomized study of minimal curettage followed by topical photodynamic therapy compared with surgical excision for low-risk nodular basal cell carcinoma. *Br J Dermatol* 2007;157:401-403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17573890>.

203. Szeimies RM, Ibbotson S, Murrell DF, et al. A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8-20 mm), with a 12-month follow-up. *J Eur Acad Dermatol Venereol* 2008;22:1302-1311. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18624836>.

204. Roozeboom MH, Aardoom MA, Nelemans PJ, et al. Fractionated 5-aminolevulinic acid photodynamic therapy after partial debulking versus surgical excision for nodular basal cell carcinoma: a randomized controlled trial with at least 5-year follow-up. *J Am Acad Dermatol* 2013;69:280-287. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23566914>.

205. Cosgarea R, Susan M, Crisan M, Senila S. Photodynamic therapy using topical 5-aminolaevulinic acid vs. surgery for basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2013;27:980-984. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22738399>.
206. Wang H, Xu Y, Shi J, et al. Photodynamic therapy in the treatment of basal cell carcinoma: a systematic review and meta-analysis. *Photodermatol Photoimmunol Photomed* 2015;31:44-53. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25377432>.
207. Stebbins WG, Hanke CW. MAL-PDT for difficult to treat nonmelanoma skin cancer. *Dermatol Ther* 2011;24:82-93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21276161>.
208. Fantini F, Greco A, Del Giovane C, et al. Photodynamic therapy for basal cell carcinoma: clinical and pathological determinants of response. *J Eur Acad Dermatol Venereol* 2011;25:896-901. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21054566>.
209. Horn M, Wolf P, Wulf HC, et al. Topical methyl aminolaevulinate photodynamic therapy in patients with basal cell carcinoma prone to complications and poor cosmetic outcome with conventional treatment. *Br J Dermatol* 2003;149:1242-1249. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14674903>.
210. Vinciullo C, Elliott T, Francis D, et al. Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. *Br J Dermatol* 2005;152:765-772. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15840111>.
211. Sotiriou E, Apalla Z, Maliamani F, et al. Intraindividual, right-left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities. *J Eur Acad Dermatol Venereol* 2009;23:1061-1065. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19470041>.
212. Morton CA, McKenna KE, Rhodes LE. Guidelines for topical photodynamic therapy: update. *Br J Dermatol* 2008;159:1245-1266. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18945319>.
213. Roozeboom MH, Arits AH, Nelemans PJ, Kelleners-Smeets NW. Overall treatment success after treatment of primary superficial basal cell carcinoma: a systematic review and meta-analysis of randomized and nonrandomized trials. *Br J Dermatol* 2012;167:733-756. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22612571>.
214. Roozeboom MH, Nelemans PJ, Mosterd K, et al. Photodynamic therapy vs. topical imiquimod for treatment of superficial basal cell carcinoma: a subgroup analysis within a noninferiority randomized controlled trial. *Br J Dermatol* 2015;172:739-745. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25066012>.
215. Tucker SB, Polasek JW, Perri AJ, Goldsmith EA. Long-term follow-up of basal cell carcinomas treated with perilesional interferon alfa 2b as monotherapy. *J Am Acad Dermatol* 2006;54:1033-1038. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16713458>.
216. Cornell RC, Greenway HT, Tucker SB, et al. Intralesional interferon therapy for basal cell carcinoma. *J Am Acad Dermatol* 1990;23:694-700. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2229497>.
217. Chimenti S, Peris K, Di Cristofaro S, et al. Use of recombinant interferon alfa-2b in the treatment of basal cell carcinoma. *Dermatology* 1995;190:214-217. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7599384>.
218. Prescribing information: ERIVEDGE (vismodegib) capsule for oral use. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203388s005s006s007s008lbl.pdf. Accessed April 1, 2016.

219. Prescribing information: ODOMZO (sonidegib) capsules, for oral use. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205266s001bl.pdf. Accessed April 1, 2016.

220. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med* 2012;366:2171-2179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22670903>.

221. Sekulic A, Migden MR, Lewis K, et al. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC. *J Am Acad Dermatol* 2015;72:1021-1026 e1028. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25981002>.

222. Dreno B, Basset-Seguín N, Caro I, et al. Clinical benefit assessment of vismodegib therapy in patients with advanced basal cell carcinoma. *Oncologist* 2014;19:790-796. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25001266>.

223. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *N Engl J Med* 2012;366:2180-2188. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22670904>.

224. Chang AL, Solomon JA, Hainsworth JD, et al. Expanded access study of patients with advanced basal cell carcinoma treated with the Hedgehog pathway inhibitor, vismodegib. *J Am Acad Dermatol* 2014;70:60-69. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24189279>.

225. Basset-Seguín N, Hauschild A, Grob JJ, et al. Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial. *Lancet Oncol* 2015;16:729-736. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25981813>.

226. Migden MR, Guminski A, Gutzmer R, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. *Lancet Oncol* 2015;16:716-728. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25981810>.

227. Danial C, Sarin KY, Oro AE, Chang AL. An investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. *Clin Cancer Res* 2016;22:1325-1329. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26546616>.

228. Ally MS, Aasi S, Wysong A, et al. An investigator-initiated open-label clinical trial of vismodegib as a neoadjuvant to surgery for high-risk basal cell carcinoma. *J Am Acad Dermatol* 2014;71:904-911 e901. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24929884>.

229. Mortier L, Saiag P, Leccia MT, et al. A phase II study to assess vismodegib in the neoadjuvant treatment of locally advanced basal cell carcinoma (laBCC): The Vismodegib Neoadjuvant (VISMONEO) study. *ASCO Meeting Abstracts* 2014;32:TPS9104. Available at: http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/TPS9104.

230. Leiter U, Hillen U, Gutzmer R, et al. A phase II, single-armed, multicenter trial of neoadjuvant vismodegib in patients with large and/or recurrent basal cell carcinoma: NICCI. *ASCO Meeting Abstracts* 2014;32:TPS9116. Available at: http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/TPS9116.

231. Kunstfeld R, Hauschild A, Zloty D, et al. MIKIE: A randomized, double-blind, regimen-controlled, phase II, multicenter study to assess the efficacy and safety of two different vismodegib regimens in patients with multiple basal cell carcinomas. *ASCO Meeting Abstracts* 2014;32:TPS9121. Available at: http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/TPS9121.

232. Sofen H, Gross KG, Goldberg LH, et al. A phase II, multicenter, open-label, 3-cohort trial evaluating the efficacy and safety of vismodegib in operable basal cell carcinoma. *J Am Acad Dermatol* 2015;73:99-105 e101. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25913533>.

233. Lacouture ME, Tang JY, Rogers GS, et al. The RegiSONIC disease registry: Preliminary effectiveness and safety in the first 66 newly diagnosed locally advanced basal cell carcinoma (BCC) patients treated with vismodegib. *ASCO Meeting Abstracts* 2015;33:9023. Available at: http://meeting.ascopubs.org/cgi/content/abstract/33/15_suppl/9023.

234. Tauber G, Pavlovsky L, Fenig E, Hodak E. Vismodegib for radiation-induced multiple basal cell carcinomas (BCCs) of the scalp. *J Am Acad Dermatol* 2015;73:799-801. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26320385>.

235. Jimeno A, Weiss GJ, Miller WH, Jr., et al. Phase I study of the Hedgehog pathway inhibitor IPI-926 in adult patients with solid tumors. *Clin Cancer Res* 2013;19:2766-2774. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23575478>.

236. Kim DJ, Kim J, Spaunhurst K, et al. Open-label, exploratory phase II trial of oral itraconazole for the treatment of basal cell carcinoma. *J Clin Oncol* 2014;32:745-751. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24493717>.

237. Carneiro BA, Watkin WG, Mehta UK, Brockstein BE. Metastatic basal cell carcinoma: complete response to chemotherapy and associated pure red cell aplasia. *Cancer Invest* 2006;24:396-400. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16777692>.

238. Jefford M, Kiffer JD, Somers G, et al. Metastatic basal cell carcinoma: rapid symptomatic response to cisplatin and paclitaxel. *ANZ J Surg* 2004;74:704-705. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15315581>.

239. Ganti AK, Kessinger A. Systemic therapy for disseminated basal cell carcinoma: an uncommon manifestation of a common cancer. *Cancer Treat Rev* 2011;37:440-443. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21216106>.

240. Wysong A, Aasi SZ, Tang JY. Update on metastatic basal cell carcinoma: a summary of published cases from 1981 through 2011. *JAMA Dermatol* 2013;149:615-616. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23677097>.

241. Pfeiffer P, Hansen O, Rose C. Systemic cytotoxic therapy of basal cell carcinoma. A review of the literature. *Eur J Cancer* 1990;26:73-77. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2138485>.

242. Moeholt K, Aagaard H, Pfeiffer P, Hansen O. Platinum-based cytotoxic therapy in basal cell carcinoma--a review of the literature. *Acta Oncol* 1996;35:677-682. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8938213>.

243. Guthrie TH, Jr., Porubsky ES, Luxenberg MN, et al. Cisplatin-based chemotherapy in advanced basal and squamous cell carcinomas of the skin: results in 28 patients including 13 patients receiving multimodality therapy. *J Clin Oncol* 1990;8:342-346. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2405109>.

244. Robinson JK. Follow-up and prevention (basal cell carcinoma). In: Miller SJ, Maloney ME, eds. *Cutaneous Oncology Pathophysiology, diagnosis, and management*. Malden, MA: Blackwell Science; 1998:695-698.

245. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. *Arch Dermatol* 2000;136:1524-1530. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11115165>.

246. Ramachandran S, Rajaratnam R, Smith AG, et al. Patients with both basal and squamous cell carcinomas are at a lower risk of further basal cell carcinomas than patients with only a basal cell carcinoma. *J Am Acad Dermatol* 2009;61:247-251. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19481292>.

247. Flohil SC, van der Leest RJ, Arends LR, et al. Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis. *Eur J Cancer* 2013;49:2365-2375. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23608733>.

Discussion
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