
Basal cell carcinoma



Contemporary approaches to diagnosis, treatment, and prevention

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Learning objectives

After completing this learning activity, participants should be able to compare and contrast in an evidence-based fashion standard and new therapeutic approaches to BCC; explain contemporary interdisciplinary approaches to management of complex locally advanced and metastatic BCC lesions; and discuss the quality of life impact that treatment of BCC has on patients, including the elderly.

Disclosures

Editors

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As the most common human cancer worldwide and continuing to increase in incidence, basal cell carcinoma is associated with significant morbidity and cost. Continued advances in research have refined both our insight and approach to this seemingly ubiquitous disease. This 2-part continuing medical education series provides a comprehensive and contemporary review of basal cell carcinoma. The second article in this series will present both the current standard of care and newly developed approaches to diagnosis, treatment, and prevention of this disease. (*J Am Acad Dermatol* 2019;80:321-39.)

Key words: 5-fluorouracil; basal cell carcinoma; BCC; biopsy; confocal microscopy; hedgehog inhibitors; imiquimod; keratinocyte carcinoma; laser; Mohs micrographic surgery; multiphoton tomography; non-melanoma skin cancer; optical coherence tomography; photodynamic therapy; prevention; radiation.

STANDARD OF CARE IN DIAGNOSIS

Key points

- **Obtaining a skin biopsy specimen is the standard of care for diagnosing basal cell carcinoma**
- **Dermoscopy is a novel noninvasive technique that improves prebiopsy accuracy**

Obtaining a skin biopsy specimen is the standard of care for diagnosing basal cell carcinoma (BCC)

and guiding management based on histopathologic subtype. The advantages of obtaining a shave biopsy specimen include shorter procedure time, decreased cost, and minimal bleeding.¹ However, a shave biopsy may create secondary surrounding erythema and leave indistinct clinical margins.¹⁻³ A punch biopsy procedure can confirm the diagnosis while avoiding these pitfalls and may be superior in defining histopathologic patterns sometimes present only in deeper sections.^{1,4,5} A shave biopsy

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Abbreviations used:

5-FU:	5-fluorouracil
AE:	adverse event
BCC:	basal cell carcinoma
EDC:	electrodessication and curettage
Hh:	Hedgehog pathway
MMS:	Mohs micrographic surgery
NCCN:	National Comprehensive Cancer Network
OCT:	optical coherence tomography
OEBM:	Oxford Centre for Evidence Based Medicine
PDT:	photodynamic therapy
PNI:	perineural invasion
RCM:	reflectance confocal microscopy
RCT:	randomized controlled trial
RT:	radiation therapy
sBCC:	superficial basal cell carcinoma
SSEPME:	standard surgical excision with postoperative margin evaluation

procedure may allow a larger specimen size and decreased sampling error.⁶ Several studies have shown statistically equivalent accuracies of around 80% for identifying present subtype(s).⁵⁻⁸ However, other studies have called into question the accuracy of initial skin biopsy specimens in subtyping BCCs. In a study of 174 primary periocular BCCs diagnosed by either shave or punch biopsy, the overall concordance between the BCC subtype identified in the biopsy specimen and the subsequent excision specimen was 54%.⁹ The accuracy of the initial biopsy for BCC histologic subtype was highest for nodular BCC. For aggressive BCCs, biopsy was able to detect the aggressive component in only 48% of cases. Another retrospective analysis of 243 primary BCCs found that agreement regarding BCC subtype on punch biopsy and the subsequent surgical excision was 60.9%.¹⁰ Punch biopsies predict the most aggressive growth pattern in 84.4% of lesions.

Dermoscopy improves diagnostic accuracy for BCCs, helps differentiate BCCs from other neoplastic and inflammatory disorders, and allows for improved prebiopsy differentiation between subtypes.¹¹⁻¹⁴ BCC dermoscopic patterns, histopathologic correlates, and associated subtypes have been described (Table I). Diagnostic accuracy ranges from 95% to 99%.^{12-14,24,25} Dermoscopic assessment of vascular structures and fibrosis is particularly helpful (Fig 1, A-D).¹⁶⁻¹⁸ Dermoscopy helps in differentiating pigmented BCCs from other pigmented neoplasms (Fig 2).^{11,20} The presence of maple leaf–like areas (Fig 3, A) and short fine superficial telangiectasias (Fig 1, C) and absence of arborizing vessels (Fig 1, A), blue-gray ovoid nests (Fig 3, B), and ulceration is predictive of superficial BCC (sBCC)

with a sensitivity of 81.9% and specificity of 81.8%.¹⁹ Heavily pigmented BCCs are difficult to distinguish from melanocytic lesions and may contain brown to black globules/dots, blue/white veil-like structures, and nonarborizing vessels.¹²

NOVEL NONINVASIVE MODALITIES IN DIAGNOSIS

Key points

- **Reflectance confocal microscopy and optical coherence tomography are noninvasive diagnostic techniques for BCC diagnosis**

A variety of novel noninvasive approaches are being applied to BCC diagnosis. Reflectance confocal microscopy (RCM) allows for video rate imaging of thin sections of human skin in vivo, using near-infrared laser.^{26,27} It uses near-infrared laser light that is back-reflected from a desired focal point within the skin and allowed to pass back through a gating pinhole and enter the detector. Several review articles provide in-depth information regarding common BCC features on RCM (Fig 4, A-C).^{22,26-31} An algorithm for diagnosing BCCs based on RCM features was 100% sensitive and 88.5% specific when tested on nearly 800 lesions.^{32,33} A meta-analysis of 3602 lesions found a pooled sensitivity and specificity of RCM for BCC of 91.7% and 91.3%, respectively.³⁴ RCM in conjunction with dermoscopy can assist in identifying BCC subtypes without skin biopsy.³⁵ Limitations include imaging depth and learning curve with interpreting images.

Optical coherence tomography (OCT) allows for noninvasive, real-time diagnostic assessment of skin using infrared light projected onto the skin to produce an image based on the sum of light refractions of various skin structures with different optical properties.³⁶ In a cohort study, OCT had a sensitivity and specificity for sBCC diagnosis of 87% and 80%, respectively.³⁷ OCT had the highest accuracy (87.4%) when used in conjunction with dermoscopy.^{36,38}

Both based on the projection of infrared light, RCM and OCT continue to improve in terms of optical resolution and user friendliness. For both technologies, initially steep learning curves and cost continue to be barriers to commercial implementation. Current costs of the commercially available VivaScope 1500 and 3000 systems (Caliber I.D., Rochester, NY), both of which are approved for use by the US Food and Drug Administration, range in price from £62,300 to £90,224 depending on devices and manufacturers. Machine prices (\$70,000-150,000) are similarly relatively expensive.³⁶ Strengths of RCM technology include high

Table I. Dermoscopic findings with histopathologic correlation

Dermoscopic finding	Dermoscopic description	Histopathologic correlation	Associated BCC subtype(s)
Arborizing vessels (Fig 1, A)	Sharp, bright red, large-stem vessel branching into fine terminal capillaries	Dilated neovasculature tumor vessels in superficial dermis ¹⁵	Nodular, morpheic, and infiltrating ¹⁶
Short white streaks (chrysalis pattern, Fig 1, B)	Orthogonal short/thick crossing lines	Collagenous stromal fibrosis in dermis	Fibroepithelial ^{17,18}
Superficial fine telangiectasias (Fig 1, C)	Short, fine linear vessels, few branches	Telangiectatic vessels in papillary dermis	Superficial ^{16,19}
Multiple small erosions	Small brown-red to brown-yellow crusts	Thin crust overlying superficial epidermal loss	Superficial ^{16,19}
Shiny white-red structureless areas (Fig 1, D)	Translucent opaque to white to red areas	Diffuse dermal fibrosis or fibrotic tumor stroma	Superficial ^{16,19}
Maple leaf–like areas (Fig 3, A)	Translucent brown to gray/blue peripheral bulbous extensions not arising from pigmented network or adjacent confluent pigment	Multifocal tumor nests with pigment aggregates, connected to each other by lobular extensions, localized in epidermis/papillary dermis	Pigmented superficial ^{11,19-21}
Blue-gray ovoid nests (Fig 3, B)	Well circumscribed pigmented ovoid or elongated configurations not intimately connected to tumor	Large well-defined tumor nests with pigment aggregates invading dermis	Pigmented nonsuperficial ^{11,19,20}
Spoke wheel areas (Fig 3, D)	Well-circumscribed radial projections; usually tan (sometimes blue/gray); meeting at darker (brown, black, blue) central axis	Tumor nests arising and connected to epidermis with finger-like projections and centrally located pigment	Pigmented superficial ^{11,19-21}
Concentric structures	Irregularly shaped globules with different colors (blue, gray, brown, or black) and darker central area	Small tumor nests arising and connected to epidermis with centrally located pigmentation	Pigmented superficial ¹⁹
In-focus dots	Loosely arranged well-defined sharp gray dots	Free pigment deposition along dermo-epidermal junction, and/or melanophages, and/or dermal pigmented BCC cells aggregates	No clear association ²²
Multiple gray-blue globules (Fig 3, C)	Loosely arranged round to oval well-circumscribed structures; smaller than nests	Small round tumor nests with central pigmentation, localized to papillary and/or reticular dermis	No clear association ^{11,19,20}
Ulceration	Large structureless, red to black-red areas	Loss of epidermis, usually covered by hematogenous crust	No clear association ^{16,19,23}

BCC, Basal cell carcinoma.
 Adapted from Lallas et al.^{14,19}

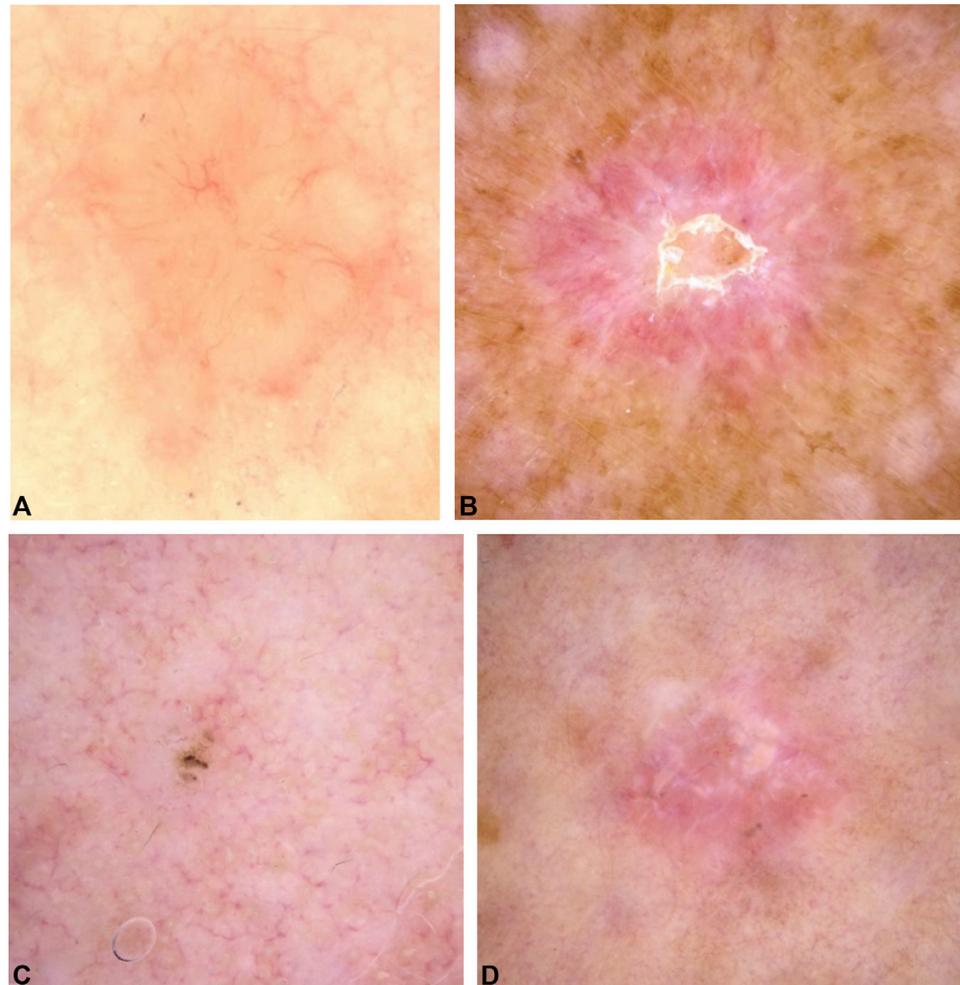


Fig 1. Vascular structures and fibrosis of basal cell carcinoma on dermoscopy. **A**, Arborizing vessels. **B**, Short white streaks (chrysalis pattern). **C**, Superficial fine telangiectasias. **D**, Shiny white-red structureless areas.

1) Must not have a pigment network, 2) Must have one or more of the following features: maple leaf-like areas (Fig 3A), large gray-blue ovoid nests (Fig 3B), multiple gray-blue globules (Fig 3C), spoke wheel areas (Fig 3D), ulceration, and arborizing "treelike" telangiectasias.

Fig 2. Algorithm for diagnosing pigmented basal cell carcinoma, found to have a sensitivity of 97% and a specificity of 92% and 93% for differentiating pigmented basal cell carcinoma from melanoma and nevi, respectively. Adapted from Menzies et al.¹¹

resolution (equivalent to 30× magnification on histopathology) and has recently received Current Procedural Terminology codes for image acquisition and interpretation (96931-9, carrier-priced).^{39,40} RCM limitations include limited depth (250 μm) and limited ability to evaluate tumor invasion and deep margins.

For OCT, strengths include both cross-sectional and en face images and greater depth penetration. Limitations of this technology include current lack of Current Procedural Terminology codes and minimal use for pigmented lesions. Other noninvasive modalities for BCC diagnosis that have been preliminarily investigated include Raman spectroscopy, high-resolution ultrasonography, and terahertz pulse imaging.⁴¹⁻⁴⁵

STANDARD OF CARE IN TREATING PRIMARY TUMORS

Key points

- Depending on the individual clinical presentation, standard surgical excision with postoperative margin evaluation and electrodesiccation and curettage are often 2 appropriate treatment options for "low-risk" BCCs

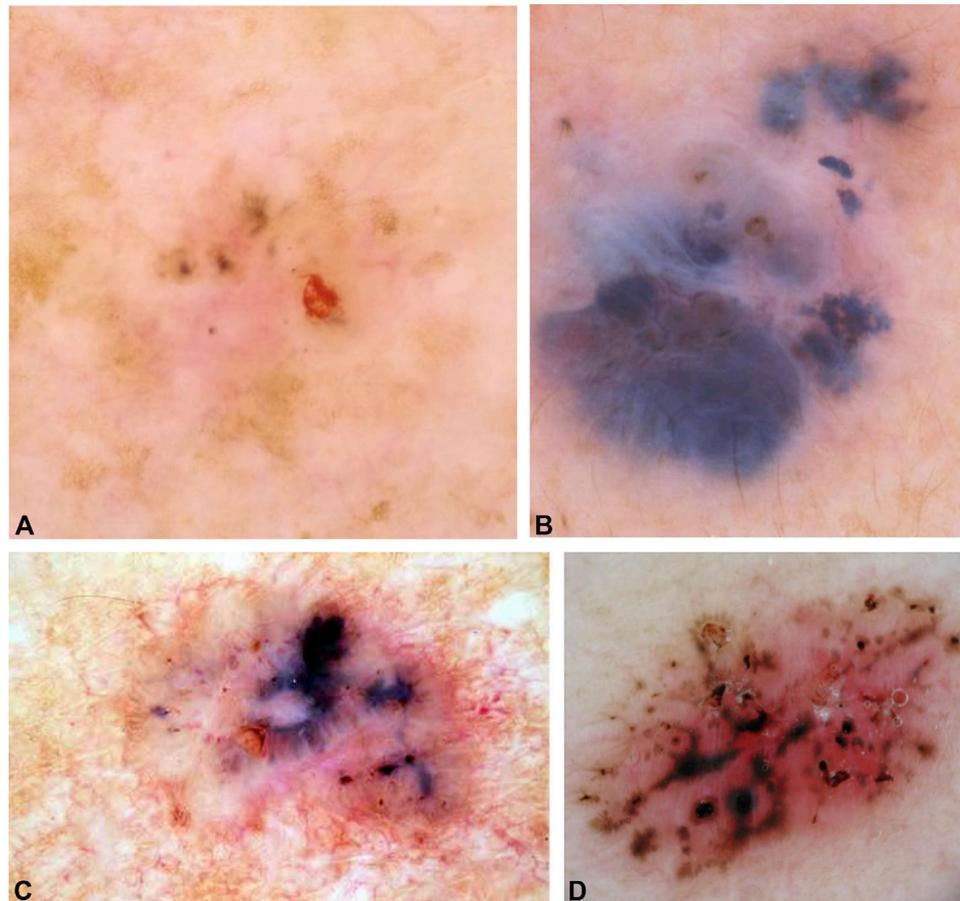


Fig 3. Dermoscopic findings associated with pigmented basal cell carcinoma. **A**, Maple leaf–like areas. **B**, Blue-gray ovoid nests. **C**, Multiple gray-blue globules. **D**, Spoke wheel areas.

- For “high-risk” BCCs, Mohs micrographic surgery is associated with lowest recurrence rates

Depending on the patient’s clinical presentation, standard surgical excision with postoperative margin evaluation (SSEPME) and electrodesiccation and curettage (EDC) are 2 appropriate treatment options for low-risk BCCs per the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines).⁴⁶ For “high-risk” BCCs, Mohs micrographic surgery (MMS) is associated with lowest recurrence rates.⁴⁷⁻⁴⁹ There are additional BCC treatment options, including topical therapies, intralesional chemotherapies, cryotherapy, photodynamic therapy, laser therapy, and radiation therapy.⁵⁰⁻⁶²

Tumor risk stratification. Various treatments exist for BCC, and recommended options for removal of the primary lesion largely depend upon tumor classification as low or high risk according to the NCCN Guidelines (Table II).⁴⁶ Risk stratification depends on factors that can affect the risk of tumor recurrence, including location, size, borders,

primary versus recurrent disease, and histologic and host factors.⁴⁶

Clinical factors. Anatomic location is a well-known risk factor for BCC recurrence.⁶³⁻⁶⁸ NCCN Guidelines and appropriate use criteria for MMS designate 3 body areas for risk stratification based on primary tumor location.^{46,69} Area H (the “mask area” of the face) constitutes the highest location-based risk (Fig 5). Lesion size and poorly defined borders are independent risk factors for recurrence.^{63-68,70-77} Size cutoffs vary based on location (Table II). All recurrent tumors, regardless of previous treatment modality, are considered high-risk.⁴⁶

Patient characteristics. Immunosuppression in the setting of organ transplant, chemotherapy, long-term use of psoralen with ultraviolet A light phototherapy, or site of previous radiation therapy are risk factors. While organ transplant and psoralen with ultraviolet A light phototherapy have a documented increased risk of BCC development, recurrence rates for these patients have surprisingly remained comparable to control subjects.⁷⁸⁻⁸² Regardless, NCCN Guidelines still classify BCCs in

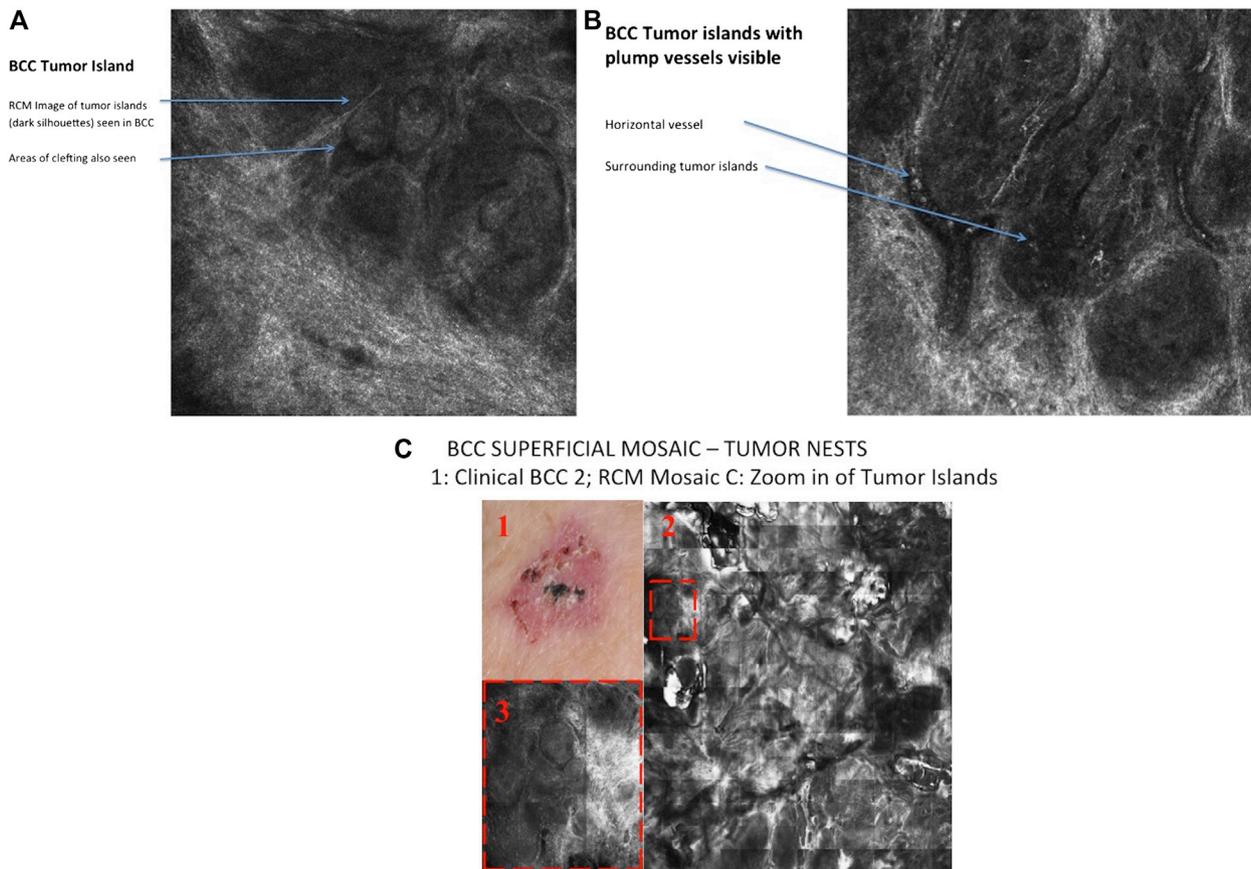


Fig 4. Reflectance confocal microscopy (RCM) findings in basal cell carcinoma (BCC). **A**, Tumor islands and areas of clefting. **B**, Tumor islands with plump vessels visible. **C**, Superficial mosaic of basal cell carcinoma tumor nests. Part C adapted from: Hibler BP, Sierra H, Cordova M, et al. Carbon dioxide laser ablation of basal cell carcinoma with visual guidance by reflectance confocal microscopy: a proof-of-principle pilot study. *Br J Dermatol.* 2016;174(6):1359-64.

immunosuppressed patients as high-risk because of anecdotal experience of consensus panel members.⁶³ BCCs arising in areas of previous radiation for unrelated conditions are also considered to be high-risk by the NCCN Guidelines because of increased risk of BCC development in this setting.^{46,63}

Histologic risk factors. The presence of perineural invasion (PNI) or aggressive histopathologic subtypes, such as micronodular, infiltrative, or morpheaform, also increases recurrence risk.^{63,83-91} One potential pitfall of classification based on histologic subtype is the potential for incomplete clinical sampling or partial histologic evaluation of a specimen. In 1 study, 18% of BCCs were misidentified, with many missing a more aggressive pattern.⁸ Another found that 22.4% of tumors initially identified as sBCC after review of the biopsy specimen had a more aggressive subtype upon further histopathologic analysis.⁹² A mixed BCC subtype was identified in about 50% of recurrent specimens,

confirming initial tumor misclassification and treatment failure implications.

PNI is rare for BCCs, ranging from 0.18% to 10% of cases.⁹³⁻⁹⁵ PNI histologic mimickers include peritumoral fibrosis, reexcision PNI, perineural inflammation, and normal cutaneous structures that appear warped on frozen sectioning.^{93,96} Lesions with PNI on average require more MMS stages to clear with larger defects and are also more likely to subsequently recur.⁹⁷ PNI may extend from the midface to the skull base.^{98,99} Cancer invasion into the perineural space allows for a path of low resistance and relative immunoprotection directly into the central nervous system.⁹³ If PNI or large nerve involvement is suspected, magnetic resonance imaging with contrast should be considered to evaluate the extent of spread.⁴⁶ Symptoms such as pain, numbness, or facial weakness should prompt the proper work-up for PNI.⁹³ Clinically symptomatic patients with identified skin carcinoma with perineural tumor extension on magnetic resonance

Table II. Risk factors for basal cell carcinoma recurrence (National Comprehensive Cancer Network Guidelines)

Clinical presentation	Low risk	High risk
Location/size	Area L <20 mm	Area L ≥20 mm
	Area M <10 mm*	Area M ≥10 mm
		Area H [‡]
Borders	Well defined	Poorly defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	Negative	Positive
Site of previous radiation	Negative	Positive
Histopathology		
Histopathologic subtype	Low-risk subtypes [†]	High-risk subtypes [§]
Perineural involvement	Negative	Positive

Area H, "Mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermillion], chin, mandible, preauricular and postauricular skin/sulci, temple, and ear), genitalia, hands, and feet (Fig 5); Area L, trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles); Area M, cheeks, forehead, scalp, neck, and pretibia.

Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology.⁶³ To view the most recent and complete version of the NCCN Guidelines, visit NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.

*Location independent of size may constitute high risk.

[†]Low-risk histologic subtypes include nodular, superficial, and other nonaggressive growth patterns, such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus.

[‡]Area H constitutes high risk based on location, independent of size. Narrow excision margins caused by 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 ≥4 mm clinically tumor-free margins can be obtained without significant anatomic or functional distortions.

[§]Having morpheiform, basosquamous, sclerosing, mixed infiltrative, or micronodular features in any portion of the tumor. In some cases, basosquamous tumors may be prognostically similar to squamous cell carcinoma; clinicopathologic correlation is recommended in these cases.

imaging have a 5-year survival rate of 50% to 60% compared with 86% to 100% for patients with negative imaging.^{100,101} PNI is more likely in BCCs >2 cm, in aggressive histologic patterns, and at certain locations including the lip, ear, forehead, scalp, temple, and the back of the hand.¹⁰²

Treatment options. *Standard excision.* SSEPME is the treatment of choice for low-risk BCCs with Oxford Centre for Evidence Based Medicine (OEBM) level I evidence (Table III).^{104,105}

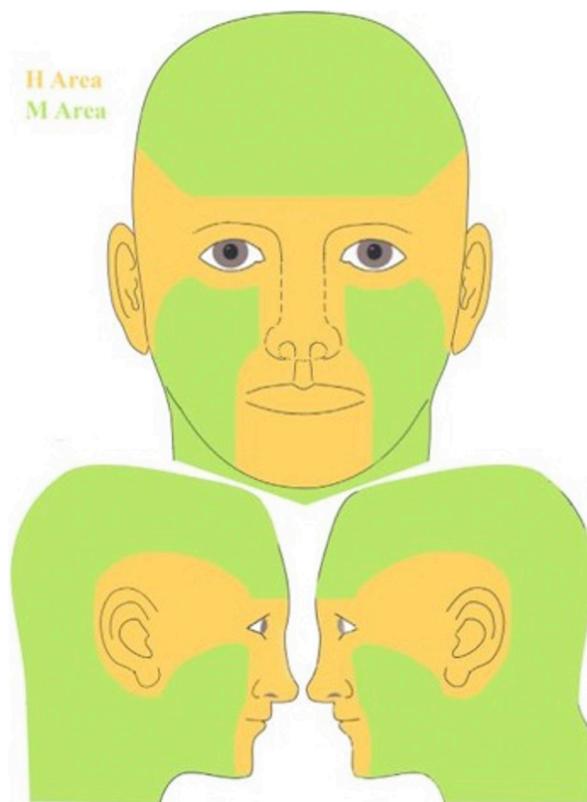


Fig 5. High-risk mask area of the face. Area H indicates the mask area of the face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermillion], chin, mandible, preauricular and postauricular skin/sulci, temple, and ear), genitalia, hands, and feet. Area M includes the cheeks, forehead, scalp, neck, and pretibial. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology.⁶³ © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed April 1, 2018. To view the most recent and complete version of the guideline, visit NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.

Table III. Levels of evidence based on Oxford Centre for Evidence Based Medicine¹⁰³

Level of evidence	Description
I	Systematic review of randomized trials
II	Randomized trial or observational study with dramatic effect
III	Nonrandomized controlled cohort/follow-up study
IV	Case series, case-control studies, or historically controlled studies
V	Mechanism-based reasoning

Table IV. Topical therapies in basal cell carcinoma and their efficacy and levels of evidence

Topical therapy	Superficial BCC		Nodular BCC	
	Evidence*	Efficacy	Evidence*	Efficacy
5-fluorouracil	II	68.2% 3-year CC ¹³¹	IV	— ^{132,133}
Imiquimod	I	78-80% 5-year CC ^{53,123,124}	II	76% PT CC ¹²⁵
Ingenuol mebutate	II	63% HC ¹³⁴	—	—
Retinoids ¹³⁵⁻¹³⁷	IV	58.5% PT CC ¹³⁷	IV	—
Dobesilate [†]	IV	—	IV	— ^{138,139}
BEC-5 [‡]	II	66% PT CC ¹⁴⁰	II	66% PT CC ¹⁴⁰

BCC, Basal cell carcinoma; CC, clinical clearance; HC, histologic clearance; PT, post-treatment.

*Levels of evidence based on Oxford Centre for Evidence Based Medicine (Table III).¹⁰³

[†]Commercially unavailable.

[‡]Solasodine glycoside cream.

Table V. Intralesional chemotherapies in basal cell carcinoma, efficacy, and levels of evidence

Intralesional chemotherapy	Superficial BCC		Nodular BCC	
	Evidence*	Efficacy	Evidence*	Efficacy
5-fluorouracil [†]	III	91% HC ¹⁴¹	IV	91% HC ¹⁴¹
Interferons [‡]	II	67-86% HC ¹⁴²⁻¹⁴⁵	II	67-86% HC ¹⁴²⁻¹⁴⁵
Interleukin-2 [§]	IV	66% HC ¹⁴⁶	IV	66% HC ¹⁴⁶
Bleomycin with electrochemotherapy [§]	IV	94% 18-month PT CC ¹⁴⁷	IV	94% 18-month CC ¹⁴⁷

BCC, Basal cell carcinoma; CC, clinical clearance; HC, histologic clearance; PT, post-treatment.

Adapted from Micali et al.¹²¹

*Levels of evidence based on Oxford Centre for Evidence Based Medicine (Table III).¹⁰³

[†]Commercially unavailable proprietary gel (5-fluorouracil, epinephrine, and bovine collagen).

[‡]Interferon α or recombinant interferon- β -1 α .

[§]BCC subtype not specified.

For small (<2 cm) BCCs 3- to 4-mm surgical margins are usually sufficient to achieve tumor clearance.^{106,107} NCCN Guidelines recommend 4-mm clinical margins for SSEPME of low-risk tumors.⁴⁶ Recurrence rates after standard excision are generally low, with reported 5-year recurrence rates of 0.7% to 5% for low-risk lesions.^{47,64,104,106,108,109} Post-SSEPME reconstruction should ideally be accomplished with linear closure or healing by secondary intention; tissue rearrangement alters local anatomy, presenting future issues if recurrence occurs. If tissue rearrangement is needed, intraoperative margin assessment should be conducted to ensure tumor eradication.⁴⁶ In select individuals with nonaggressive low-risk BCCs, nonsurgical therapies may at times be considered.⁴⁶ Radiotherapy (RT) is recommended for patients who are not candidates for surgery, although it is often reserved for patients >60 years of age because of concerns about long-term sequelae. Other nonsurgical modalities are only considered appropriate for patients with low-risk superficial BCCs where surgery and radiation are contraindicated or impractical.

Mobs micrographic surgery. High-risk BCCs (Table II) are most adequately treated with excision with intraoperative complete surgical margin evaluation (OEBM I).¹¹⁰⁻¹¹² Five-year recurrence rates for MMS are 1.0% and 5.6% for primary and recurrent BCC, respectively, compared with 10.1% and 17.4%, respectively, for SSEPME.^{47,48} A randomized controlled trial (RCT) comparing MMS to SSEPME in 408 facial BCCs found a 4.1% 5-year recurrence rate for SSEPME compared with 2.5% for MMS.¹¹³ Mosterd et al.¹¹³ originally suggested that there was no statistical difference in recurrence rates for primary BCCs. However, 10-year follow up data in this same group demonstrated a statistically significant recurrence rate of 12.2% for SSEPME and 4.4% for MMS, emphasizing the need for complete margin assessment for high-risk tumors.⁴⁹ In 2012, appropriate use criteria were defined in order to identify tumor and patient characteristics amenable to MMS.¹¹⁴ The NCCN Guidelines cite SSEPME with complete margin assessment with intraoperative frozen section analysis or permanent margin analysis with delayed tissue repair as appropriate treatment for high-risk BCCs.⁴⁶ SSEPME with wider margins (than for low-risk tumors)

Table VI. Physical qualities of radiotherapy sources used in basal cell carcinoma

Radiation quality	Energy, kV	D50,* mm
Superficial x-ray (low voltage x-ray therapy)	60-150	7-10
Orthovoltage x-rays (deep x-ray therapy, conventional x-ray therapy)	150-400	50-80
Megavoltage x-rays, electrons and protons (betatron, linear accelerator, cyclotron, and particle therapy)	>1000	10-200

kV, Kilovolt.

*Depth from the skin's surface at which 50% of the total radiation is absorbed.

and with linear or delayed repair is an additional option.⁴⁶

Electrodesiccation and curettage. EDC is a fast, cost-effective, and convenient BCC treatment (OEBM II).^{63,115} Disadvantages include the lack of histopathologic margin assessment and inability to use this technique in terminal-hair bearing areas because the tumor may extend down follicular units.⁶³ If the subcutaneous layer is reached, conversion to SSEPME should commence to ensure tumor eradication. Five-year EDC cure rates range from 91% to 97% in studies with proper low-risk selection.^{47,115} Others have reported higher recurrence rates (19-27%), likely from high-risk tumors.^{104,116-118}

Topical therapies. Topical 5-fluorouracil (5-FU) 5% cream and imiquimod 5% cream are treatments for sBCC that have been approved by the US Food and Drug Administration.¹¹⁹⁻¹²² An RCT of twice daily imiquimod for 12 weeks demonstrated 100% histologic clearance at 6 weeks posttherapy.⁵³ Other studies showed clearance rates of 77.9% and 80.4% for sBCC at 5-year follow-up, emphasizing the need for long-term studies to accurately assess tumor recurrence.^{123,124} Nodular BCCs demonstrate similar treatment success, obtaining 76% clinical clearance with once daily imiquimod application for 12 weeks.¹²⁵ An RCT comparing topical imiquimod to SSEPME for sBCCs and nBCCs found a 5-year 82.5% clinical success rate, compared with 97.7% for SSEPME.¹²⁶ Cosmetic outcomes were significantly better for imiquimod.¹²⁷ Imiquimod is also used in the setting of nevoid basal cell carcinoma syndrome.^{128,129}

Topical 5-FU is an additional topical treatment option typically reserved for sBCCs.⁵⁰⁻⁵² A RCT demonstrated statistically equivalent efficacy for 5-FU and imiquimod in treating sBCC at a

12-month follow-up.¹³⁰ Additional long-term studies suggest superiority of imiquimod with a 79.7% clearance rate at 3 years compared with 68.2% for 5-FU.¹³¹ 5-FU efficacy in treating nBCC is limited to case reports and is not generally recommended.^{132,133} Various other BCC topical treatments have been preliminarily described but long-term evidence is largely lacking (Table IV).¹³⁴⁻¹⁴⁰

Intralesional therapies. Penetration of topical therapies is often limited because of the protective stratum corneum layer. An alternate modality involves direct medication delivery into the tumor with intralesional injection. Several intralesional chemotherapies have been evaluated for BCC treatment with varying efficacies (Table V). Adverse events (AEs) are uncommon and typically dose dependent.⁵⁴ Common AEs include local effects at the treatment site and flu-like symptoms.

Cryosurgery. Tumor destruction using aggressive cryosurgery is an alternative treatment option. Prospective trials have found large variability in recurrence rates (1-39%), likely because of a lack of uniformity regarding patient and tumor selection, follow-up time, and interoperator performance techniques (OEBM II).⁵⁵⁻⁵⁹ One dermatologist reported a 99% cure rate in 5 years of follow-up for 415 BCCs treated with cryosurgery.⁵⁵ Longer-term data demonstrated a 98.6% overall cure rate for nonmelanoma skin cancers (including BCC) over a 30-year period. Other studies have shown similarly high 5-year cure rates for nonmelanoma skin cancers.¹⁴⁸⁻¹⁵¹ Cryotherapy results in inferior cosmetic outcomes compared with surgery.¹⁵² Cryosurgery is contraindicated in hair-bearing areas for fear of scarring alopecia and the lower legs because of the risk of ulceration.¹⁰⁸ Cryosurgery is not recommended for large tumors, aggressive histologic subtypes, recurrences, fixation to underlying bone, and deep invasion.

Photodynamic therapy. Photodynamic therapy (PDT) is another treatment option for low-risk BCCs (OEBM I). Methyl aminolevulinate and aminolevulinic acid have similar efficacy as photosensitizers.¹⁵³ Both compounds are approved by the US Food and Drug Administration for the treatment of nonhypertrophic actinic keratosis of the face and scalp. Methyl aminolevulinate works best with a red light source, while aminolevulinic acid obtains best results with a blue light source. A metaanalysis (n = 1583) found that 86.4% of BCCs treated with PDT had complete clearance compared with 98.2% of surgically treated lesions.⁶⁰ While less efficacious than surgery, PDT had significantly better cosmesis. PDT has been described in the off-label neoadjuvant setting to decrease tumor burden, as

Table VII. Prospective randomized controlled trials comparing radiotherapy to other treatment modalities for basal cell carcinoma

Study (year)	Treatment groups	No. of patients	Recurrence rate (time assessed)	Clinician-assessed transformed cosmesis score* (time assessed)	Patient-assessed transformed cosmesis score* (time assessed)
Hall et al (1986) ⁵⁹	RT (various regimens)	49	4% (2 years)	56% (1 year)	NR
	Cryotherapy	44	39% (2 years)	53% (1 year)	NR
Garcia-Martin et al (2011) ¹⁶²	RT (various regimens)	15	0% (2 years)	NR	50% (1 year)
	Imiquimod	12	0% (2 years)	NR	100% (1 year)
Avril et al (1997) ⁶²	RT (various regimens)	173	8% (4 years)	64% (4 years)	73% (4 years)
	Surgery	174	1% (4 years)	89% (4 years)	93% (4 years)
Landthaler and Braun-Falco (1989) ¹⁶³	RT (48 Gy/12 fractions/4 weeks/50 kV)	144	10% (≥ 3 years)	NR	NR
	RT (60 Gy/20 fractions/4 weeks/50 kV)	148	8% (≥ 3 years)	NR	NR

kV, Kilovolt; NR, not reported; RT, radiotherapy.

*Lower score = worse cosmesis.

well as in the adjuvant setting to decrease the chance of tumor recurrence.¹⁵⁴⁻¹⁵⁶

Laser therapy. Laser therapy has been investigated preliminarily as both monotherapy and adjunct therapy for BCC (OEBM II).⁶¹ A retrospective study examining superpulsed carbon dioxide laser therapy for sBCC and nBCC reported 100% histologic clearance and no recurrences in 3-year follow-up.¹⁵⁷ A retrospective study of 2719 facial BCCs treated with pulsed neodymium-based laser therapy found a recurrence rate of 1.8% for follow-up ranging between 3 months and 5 years.¹⁵⁸ sBCC treatment with pulsed-dye laser obtained histologic clearance at 6 months posttreatment in 78.6% of cases.¹⁵⁹ AEs include reactive hyperemia, edema, scarring, and soreness.⁶¹ Laser-assisted delivery of the PDT photosensitizers has also been investigated as a new emerging treatment option. Two RCTs found significantly lower recurrence rates of aminolevulinic acid PDT with erbium:yttrium aluminium garnet laser pretreatment compared with PDT and erbium:yttriumaluminium garnet monotherapies.^{160,161}

Radiotherapy. The goal of RT is complete eradication of the malignancy while maximally preserving healthy tissue. Two types of RT have been used for the treatment of BCC: teletherapy (external beam RT) and brachytherapy. The size, depth of invasion, and anatomic location will determine the most appropriate form and quality of RT for each particular case (Table VI).

RT has been compared with several other treatment modalities for BCC in prospective RCTs (Table VII). One study compared cryotherapy with superficial RT; among 93 patients evaluated 2 years after treatment, 4% recurred after RT, while 39%

recurred after cryotherapy.⁵⁹ Tumor necrosis and serious patient inconvenience were rare (2%). RT telangiectasias occurred in 14% of patients. Overall cosmetic effect in both groups were "mild." Another RCT investigated EDC followed by 6 weeks of topical imiquimod 5% versus superficial RT for BCC of the eyelids.¹⁶² Among the 27 patients enrolled, all had evidence of pathologic complete response 6 weeks after treatment, and no patient had clinical evidence of recurrence 24 months after treatment. Finally, a landmark RCT compared surgery to RT for newly diagnosed facial BCCs.⁶² The majority of patients (55%) treated with RT (n = 173) received inpatient low dose rate interstitial brachytherapy, while relatively few (12%) received conventional outpatient teletherapy. Recurrence ≤ 4 years after treatment occurred in 0.7% of the surgery group, and 7.5% of the RT group (8.8% after brachytherapy, 5% after teletherapy). Among the various RT approaches, there have been few high-quality comparative analyses performed. No study has prospectively compared brachytherapy and teletherapy.

TREATMENT APPROACHES IN DIFFICULT AND ADVANCED DISEASE

Key points

- **Adjuvant RT may be considered for deeply invasive BCCs that are resected to positive margins or have clinically significant PNI**
- **Unresectable BCCs can be cured with definitive RT**
- **Unresectable or metastatic BCC that is not amenable to RT can be treated with systemic therapy**

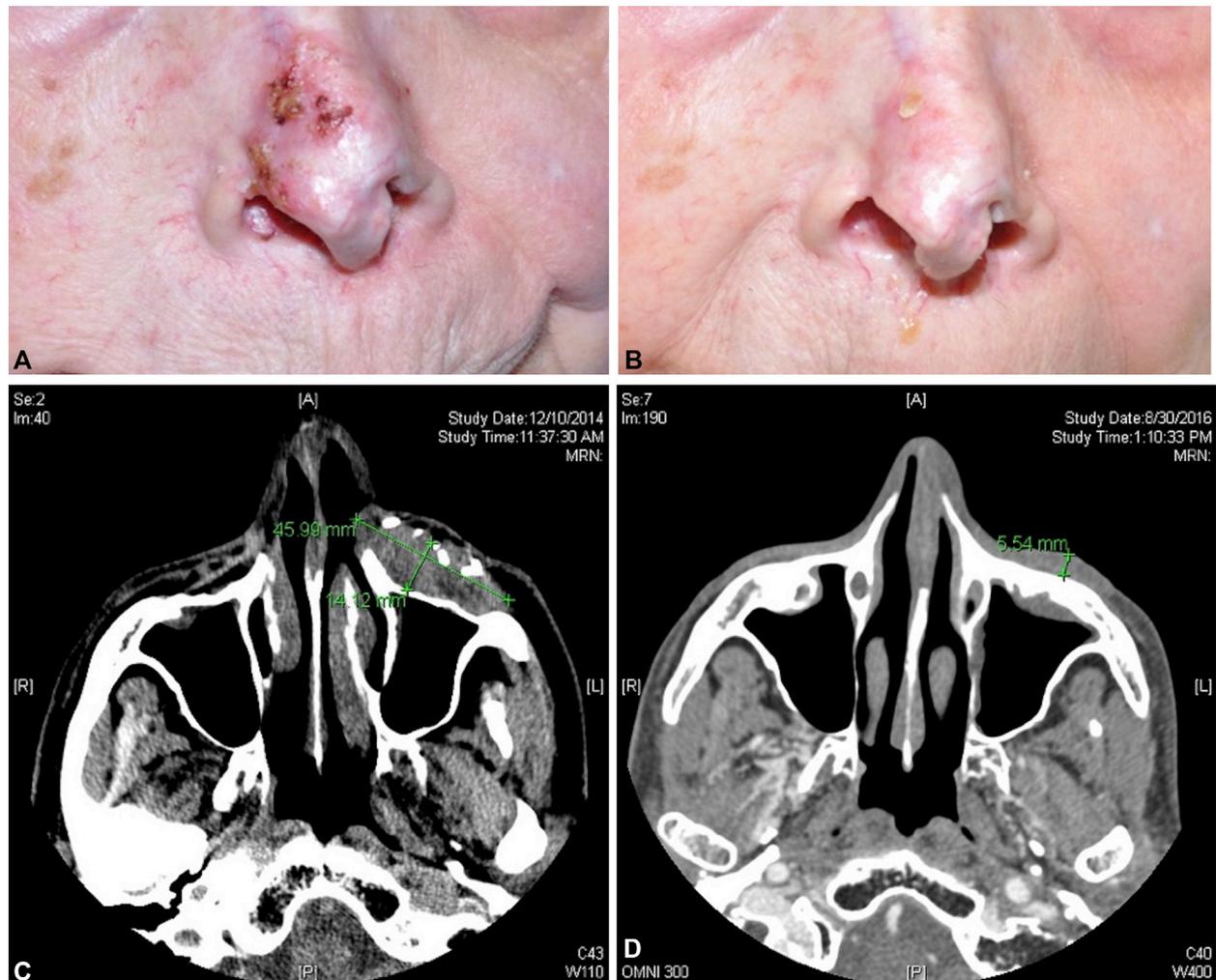


Fig 6. Response of advanced basal cell carcinoma treated with vismodegib. **A**, A 71-year-old woman with a history of multiple nonmelanoma skin cancers presented with locally recurrent basal cell carcinoma of the nose that was previously treated with resections and radiation. The patient refused potentially morbid surgery and reconstruction and was started on vismodegib. **B**, After 5 months of vismodegib, the patient had a complete response. **C**, An 83-year-old man with a history of basal cell carcinoma of the left cheek with high-risk features underwent vismodegib induction therapy followed by concomitant vismodegib treatment with radiation therapy. A computed tomography scan of the sinuses before vismodegib induction shows heterogeneously enhancing mass lesion in the premaxillary space at 4.6×1.4 cm, with medial extension to the nasal ala and lateral extension superficial to the zygomaticomaxillary suture. **D**, Significantly decreased soft tissue thickening in the premaxillary space after 19 months of treatment (vismodegib induction followed by concurrent vismodegib and radiation therapy). There is no evidence of new disease or disease progression.

BCCs may not be completely resectable. If surgery yields a microscopically positive margin, adjuvant RT may reduce risk of local recurrence. A retrospective analysis reported that the probability of local recurrence within 5 years of a microscopically positive margin excision is approximately 39%, and that in patients selected for adjuvant RT the probability is 9%. Not all patients with microscopically positive margins develop clinically significant recurrence. The decision to deliver adjuvant RT

should be made on a case-by-case basis.¹⁶⁴ For BCCs unresectable at presentation (ie, T3/T4 tumors), RT may be an effective treatment option. Kim and Barker¹⁶⁵ found that 3-year disease-specific survival among 25 BCC patients with T3/T4 tumors was 88% to 93% whether RT was delivered as the exclusive definitive treatment or if it was used as an adjuvant therapy after surgery. This suggests that radical operations for advanced primary tumors may not be necessary.¹⁶⁵ These observations are

corroborated by studies from other investigators as well.¹⁶⁶⁻¹⁷⁰

If BCC metastasizes beyond the regional lymph node basin or cannot be treated with surgery or RT, systemic drug therapy should be considered. The Hedgehog pathway (Hh) inhibitors vismodegib and sonidegib (suppressors of the transmembrane protein Smoothed) are oral medications that are approved by the US Food and Drug Administration for the treatment of mBCC and laBCC (OEBM II).¹⁷¹ These drugs can result in marked improvement of both local and systemic disease (Fig 6 A-D). Approval of vismodegib is based on a 2-cohort, non-randomized study evaluating oral vismodegib 150 mg daily for mBCC (n = 33) or inoperable laBCC (n = 63).¹⁷² The most recent report showed response rates of 33.3% and 47.6% and median response durations of 9.5 months and 7.6 months for mBCC and laBCC, respectively.¹⁷³ Other studies have shown similar or better response rates and progression-free survivals.^{174,175} Most patients treated with vismodegib have ≥ 1 AE including muscle spasms, alopecia, taste loss, weight loss, decreased appetite, fatigue, nausea, or diarrhea.⁶³ Serious AEs occur in one-half to one-third of patients.^{172,174,175} A study found that BCC patients treated with vismodegib had an increased risk of developing squamous cell carcinoma.¹⁷⁶ Approximately 50% of advanced BCCs are initially vismodegib refractory, while >20% of initial responders develop resistance and experience disease progression or recurrence.^{174,177-181}

Regarding sonidegib, a randomized trial (n = 381) compared 2 different doses in patients with treatment-refractory mBCC or laBCC not amenable to curative surgery or RT. The 2 doses (200 and 800 mg/day) were associated with similar objective response rates (32% and 34%, respectively), while the higher dose had significantly increased AEs.¹⁸² Elevated creatinine kinase and lipase were the most common grade 3 to 4 AEs. Hh inhibitors are also being used in the neoadjuvant setting. A trial of 15 large BCCs treated with vismodegib for a mean of 4 ± 2 months showed a 27% average decrease in surgical defect size.¹⁸³ Four of 11 patients could not complete >3 months of treatment because of drug-related AEs and had less response. A phase II trial (n = 74) evaluated various regimens of vismodegib in operable nBCC and achieved its highest complete histologic clearance rate of 44% in the 8 weeks on/4 weeks off and repeat regimen.¹⁸⁴

Saridegib, a newer Hh inhibitor, has also been preliminarily tested in a phase I trial.¹⁸⁵ Unfortunately, there were no objective responses among the patients previously treated with

Table VIII. Patient resources for skin cancer prevention/early detection

Resource	Website
Cancer Society	http://www.cancer.org/acs/groups/cid/documents/webcontent/003184-pdf.pdf
SPOT Skin Cancer, American Academy of Dermatology	http://aad.org/spot-skin-cancer
Prevention Guidelines, Skin Cancer Foundation	http://www.skincancer.org/prevention

Adapted from Bichakjian et al.⁶³

vismodegib. Itraconazole also inhibits the Hh pathway. Nineteen BCCs treated with itraconazole showed reduced cell proliferation, Hh pathway activity, and tumor area by 45%, 65%, and 24%, respectively.¹⁸⁶ AEs included fatigue and congestive heart failure. Combined use of itraconazole with intravenous arsenic trioxide in vismodegib-resistant mBCC achieved stable disease in 3 of 5 patients, but no signs of tumor shrinkage.¹⁸⁷ Novel molecules that bypass vismodegib resistance by regulating Hh downstream of Smoothed are being developed.¹⁸⁸ Successful treatment of advanced BCCs with chemotherapies (ie, carboplatin/paclitaxel, cisplatin/paclitaxel, and doxorubicin) has been described.¹⁸⁹⁻¹⁹²

QUALITY OF LIFE AND TREATMENT IN THE ELDERLY AND DISEASE FOLLOW-UP AND PREVENTION

Key points

- **Quality of life concerns for skin cancer patients include diagnosis-related anxiety, scarring, and fear of future skin cancers**
- **The incidence of BCCs is anticipated to increase in the United States with the aging population**
- **Oral nicotinamide and retinoids are preventative therapies for high-risk patients with varying levels of evidence**

Quality of life concerns in the skin cancer population include scarring and disfigurement from treatment, anxiety, and fear of future skin malignancies.¹⁹³⁻¹⁹⁵ While treatment efficacy has historically focused on minimizing recurrence rates and complications, patient-reported outcomes are increasingly important in treatment by allowing the patient's perspective to be integrated into care.¹⁹³ A number of studies have evaluated quality of life after skin cancer treatment.¹⁹⁶⁻¹⁹⁸ Skin cancer patients have cited scarring and fear of disfigurement among their top concerns, yet this is often overlooked.^{193,199}

A systematic review of patient-reported outcome instruments found limited skin cancer specific instruments.^{193,200} Among these, the Skin Cancer Index and Skin Cancer Quality of Life Assessment Tool have only 1 and 3 questions, respectively, related to appearance, suggesting this is an area for improvement in future patient-reported outcome instruments.^{193,195,197,201-206} The US population is aging, with the oldest population (≥ 85 years of age) anticipated to increase significantly by 2050.²⁰⁰ The number of skin cancers diagnosed in this age group is expected to rise. Some studies have suggested that treatment in the very elderly should be reconsidered because of their comorbidity burden and limited life expectancy.^{207,208} A patient-centered discussion of the biology of the tumor, treatment options, and the anticipated results of treatment in a shared decision approach is recommended, with considerations of comorbidities, functional status, and social support system.²⁰⁹

Patients with a history of BCC have a 3-year cumulative risk of 44% and 10-fold increase in BCC incidence compared with the general population.²¹⁰ A second BCC diagnosis is most likely during the short-term follow-up period after initial diagnosis.^{63,211} BCC patients are also at increased risk for other cutaneous malignancies, including melanoma, making long-term surveillance prudent.²¹¹⁻²¹³ A systematic review based on World Health Organization criteria determined that because size is a major determinant of treatment choice, early detection and adequate management of BCC is preferred.²¹⁴ The NCCN Guidelines recommend a whole-body skin examination every 6 to 12 months for the first 5 years after BCC diagnosis, and then at least annually for life.⁴⁶ Patients should also be educated about sun protection, the need for regular self skin-examination, and available resources on skin cancer prevention (Table VIII).

In patients at increased risk for skin cancer, oral nicotinamide has shown promise as a potential preventative measure (OEBM II). Nicotinamide prevents ultraviolet light-induced cellular effects of adenosine triphosphate depletion, glycolytic blockade, and immunosuppression while boosting cellular energy and enhancing DNA repair.²¹⁵⁻²²⁰ In a phase III RCT, oral nicotinamide (500 mg) administered twice daily for 12 months with skin examination quarterly found a decreased 12-month overall keratinocyte carcinoma development rate of 23%.²²¹ Systemic retinoids have been used in the genetically at risk and immunosuppressed as a chemopreventative measure (OEBM II).²²²⁻²²⁸ While studies have shown a significant preventative effect

for squamous cell carcinoma in these populations, the effect did not extend to BCC.

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Answers to CME examination

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1. c
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3. b
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