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## FROM THE ACADEMY

# Guidelines of care for the management of basal cell carcinoma

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Basal cell carcinoma (BCC) is the most common form of human cancer, with a continually increasing annual incidence in the United States. When diagnosed early, the majority of BCCs are readily treated with office-based therapy, which is highly curative. In these evidence-based guidelines of care, we provide recommendations for the management of patients with BCC, as well as an in-depth review of the best available literature in support of these recommendations. We discuss biopsy techniques for a clinically suspicious lesion and offer recommendations for the histopathologic interpretation of BCC. In the absence of a formal staging system, the best available stratification based on risk for recurrence is reviewed. With regard to treatment, we provide recommendations on treatment modalities along a broad therapeutic spectrum, ranging from topical agents and superficially destructive modalities to surgical techniques and systemic therapy. Finally, we review the available literature and provide recommendations on prevention and the most appropriate follow-up for patients in whom BCC has been diagnosed. (J Am Acad Dermatol <https://doi.org/10.1016/j.jaad.2017.10.006>.)

**Key words:** basal cell carcinoma; biopsy; curettage; metastasis; phototherapy; radiotherapy; staging; surgery; surveillance; topical therapy.

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**DISCLAIMER**

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care, or be deemed inclusive of all proper methods of care, nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biologic behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

**SCOPE**

This guideline addresses the management of patients with basal cell carcinoma (BCC) from the perspective of a US dermatologist. The main focus of the guideline is on the most commonly considered and utilized approaches for the surgical and medical treatment of primary BCC, but it also includes recommendations on the treatment of recurrent tumors when applicable, appropriate biopsy techniques, staging, follow-up, and prevention of BCC. A detailed discussion of specific chemotherapeutic or radiotherapeutic approaches for distant metastatic BCC falls outside the scope of this guideline. However, general recommendations on the management of patients with advanced or metastatic BCC are included to provide guidance and facilitate consultation with a physician or multidisciplinary group with specific expertise in BCC, such as a surgical, medical, or radiation oncologist, head and neck surgeon, plastic surgeon, or dermatologist specializing in BCC.

**METHOD**

An expert work group was convened to determine the audience and scope of the guideline and to identify important clinical questions in the biopsy, staging, treatment, and follow-up of BCC (Table I). Work group members completed a disclosure of interests that was updated and reviewed for potential relevant conflicts of interest throughout the guideline development. If a potential conflict was noted, the work group member recused himself or herself from discussion and drafting of recommendations pertinent to the topic area of the disclosed interest.

An evidence-based approach was used, and available evidence was obtained by using a systematic search and review of published studies from PubMed and the Cochrane Library databases from January

**Table I.** Clinical questions used to structure the evidence review

- 
- What is the standard grading system for BCC and cSCC?
  - What are the standard biopsy techniques for BCC and cSCC?
  - What pathologic and clinical information is useful in the pathology report for BCC and cSCC?
  - What are the benefits, harm, and effectiveness/efficacy of available treatments for BCC and cSCC?
    - Surgical treatment
      - Standard excision
      - Mohs micrographic surgery
      - Curettage and electrodesiccation
      - Cryosurgery
    - Topical therapy
      - Fluorouracil
      - Imiquimod
      - Other
    - Energy devices
      - Laser
      - Photodynamic therapy\*
      - Radiation therapy
  - What are effective treatment options for the management of advanced BCC and cSCC?
    - Hedgehog inhibitors\*
  - What are the effective methods for follow-up and prevention of recurrence and new primary keratinocyte cancer formation?
    - Oral and topical retinoids
    - Celecoxib
    - $\alpha$ -Difluoromethylornithine
    - Selenium
    - $\beta$ -Carotene
- 

BCC, Basal cell carcinoma; cSCC, cutaneous squamous cell carcinoma.

\*BCC only.

1960 through April 2015 for all identified clinical questions. A secondary search was subsequently undertaken to identify and review published studies from April 2015 to August 2016 to provide the most current information. Searches were prospectively limited to publications in the English language. As BCC is traditionally known as a form of nonmelanoma skin cancer (NMSC), which also includes cutaneous squamous cell carcinoma (cSCC), searches were collectively undertaken for literature on BCC and cSCC simultaneously, using a set of search terms applicable to both BCC and cSCC. A parallel American Academy of Dermatology (AAD) guideline on cSCC has also been developed.<sup>1</sup> MeSH (Medical Subject Headings) terms used in various combinations in the literature search included *carcinoma*, *basal cell carcinoma*, *squamous cell*

*Abbreviations used:*

AAD:	American Academy of Dermatology
AJCC:	American Joint Committee on Cancer
ALA:	aminolevulinic acid
BCC:	basal cell carcinoma
C&E:	curettage and electrodesiccation
5-FU:	5-fluorouracil
MAL:	methylaminolevulinate
MM:	malignant melanoma
MMS:	Mohs micrographic surgery
NCCN:	National Comprehensive Cancer Network
NMSC:	nonmelanoma skin cancer
PDT:	photodynamic therapy
PI:	principal investigator
RCT:	randomized controlled trial
cSCC:	cutaneous squamous cell carcinoma
SMO:	smoothened (inhibitors)
STEVIE:	Safety Events in Vismodegib

*carcinoma, skin neoplasms, stage(ing), grade(ing), score(ing), biopsy, pathology, prognosis, signs and symptoms, risk factors, curettage, electrodesiccation, excision, incomplete, cryosurgery, Mohs (micrographic) surgery, topical, fluorouracil, imiquimod, laser, radiotherapy, radiation, photochemotherapy, phototherapy, metastasis, vismodegib, sonidegib, prevention, prevention and control, and recurrence.*

A total of 1120 articles were systematically reviewed for possible inclusion; 188 were retained on the basis of relevancy and the highest level of available evidence for the outlined clinical questions. Evidence tables were generated for these 188 studies and utilized by the work group in developing recommendations. Other current available guidelines on BCC were also evaluated.<sup>2-4</sup>

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy (SORT), which was developed by editors of the US family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ USA*).<sup>5</sup> Evidence was graded using a 3-point scale based on the quality of study methodology (eg, randomized controlled trial [RCT], case-control, prospective/retrospective cohort, case series, etc) and the overall focus of the study (ie, diagnosis, treatment/prevention/screening, or prognosis) as follows:

- I. Good-quality *patient-oriented evidence* (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life).
- II. Limited-quality patient-oriented evidence.
- III. Other evidence, including consensus guidelines, opinion, case studies, and *disease-oriented evidence* (ie, evidence measuring

intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed on the basis of the best available evidence tabled in the guideline. These are ranked as follows:

- A. Recommendation based on consistent and good-quality patient-oriented evidence.
- B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
- C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

In situations in which documented evidence-based data were not available, expert opinion of the authors was utilized to generate clinical recommendations.

This guideline has been developed in accordance with the AAD/AAD Association *Administrative Regulations for Evidence-Based Clinical Practice Guidelines*, which includes the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.<sup>6</sup> An additional multidisciplinary panel of invited reviewers was utilized to provide cross-specialty comments on the draft guideline. This guideline will be considered current for a period of 5 years from the date of publication, unless reaffirmed, updated, or retired at or before that time.

## INTRODUCTION

BCC is the most common human malignancy. NMSC, also referred to as keratinocyte carcinoma, of which BCC comprises more than half of all diagnoses, affects more than 3.3 million persons annually in the United States.<sup>7</sup>

The treatment of BCC has long been a substantial component of the clinical practice of dermatologists, who are well versed in the numerous available therapeutic options. These clinical practice guidelines for the treatment of BCC provide evidence-based recommendations that offer clinicians a framework to manage patients with BCC. Both established and more recent data in support of widely accepted therapies, including curettage and electrodesiccation (C&E) and Mohs micrographic surgery (MMS), are reviewed. The presence or absence of reliable evidence in support of emerging treatment modalities, ranging from topical medications and energy devices for low-risk tumors to systemic therapy for metastatic disease, is discussed in detail. Moreover, recommendations regarding staging, biopsy techniques,

prevention, and follow-up are made on the basis of the best available literature.

Recently, the diagnosis and treatment of BCC among older adults with limited life expectancy has become an important and valid topic of discussion.<sup>8,9</sup> A clear distinction between advanced age and limited life expectancy is critical to this debate, as they are by no means synonymous. Every dermatologist is familiar with healthy, energetic nonagenarians, who justifiably desire and deserve treatment of their BCC with a modality that provides optimal cure rate and quality of life. Conversely, significant medical comorbidities at any age may justify a therapeutic option that may have a lower long-term cure rate but is most appropriate with regard to quality of life. In select circumstances and after careful consideration with their health care provider, patients may understandably prefer observation over any form of treatment. A thorough understanding of the entire spectrum of therapies available for BCC and the evidence on which each treatment recommendation is based is critical to selecting and providing care that is optimally tailored to individual patients.

Although many recommendations in these guidelines reaffirm common knowledge and current practice, other recommendations may remind clinicians of alternative therapeutic or preventive options when insufficient evidence is available to support new therapies or previously dogmatic practice patterns. As the incidence of BCC in the United States continues to increase, a thorough understanding of the management of BCC and the evidence on which recommendations are based is critically important for optimal patient care.

## GRADING AND STAGING

A formal staging system for risk stratification specific to patients with BCC is not available. In the American Joint Committee on Cancer (AJCC) staging manual, BCC has historically been grouped with a multitude of other cutaneous malignancies, including cSCC.<sup>10</sup> Because of the exceedingly low incidence of regional and distant metastasis, the TNM (tumor, node, metastasis) classification and AJCC stage grouping are rarely, if ever, applied to patients with localized BCC. Cross-sectional imaging to stage for metastatic disease is therefore rarely indicated for BCC; however, imaging may be considered to assess for deep structural involvement with extensive BCC.

The most clinically relevant stratification to guide the management of patients with BCC is the differentiation between localized tumors at low versus high risk for recurrence. On the basis of the best available literature, the most useful stratification of

## Table II. Recommendation for grading and staging of BCC

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Stratification of localized BCC using the NCCN guideline framework is recommended for clinical practice.

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BCC, Basal cell carcinoma; NCCN, National Comprehensive Cancer Network.

BCC is provided by the National Comprehensive Cancer Network (NCCN) Guidelines (for recommendation, see [Table II](#); for level of evidence/strength of recommendation, see [Table III](#)).<sup>2,3,11-30</sup> The NCCN stratification, listed in [Table IV](#), takes both clinical and pathologic parameters into account and is based on a combination of available evidence and expert multidisciplinary opinion, including representatives from dermatology, dermatopathology, head and neck surgery, plastic surgery, and surgical, radiation, and medical oncology. Treatment recommendations throughout the current guidelines are based on this stratification.

## BIOPSY

The available literature does not identify a single optimal biopsy technique for sampling lesions suspected of being BCC. Recommended biopsy techniques for BCC include punch biopsy, shave (eg, by tangential technique) biopsy,<sup>a</sup> and excisional biopsy. Excisional biopsy is distinguished from excision with margins in that the intent of the former is to determine and/or confirm diagnosis, whereas the intent of the latter is to remove the tumor. For all techniques, the biopsy specimen size and depth should be adequate to provide the recommended clinical information and pathology report elements to permit accurate diagnosis and guide therapy, including by identifying an aggressive growth pattern if present. Repeat biopsy may be considered if the initial biopsy specimen is inadequate for accurate diagnosis. The recommendations for biopsy of suspected BCC are shown in [Table V](#), and the level of evidence/strength of the recommendation is presented in [Table III](#).

Selection of the specific biopsy technique is contingent on the clinical characteristics of the suspected tumor, including morphology, expected histologic subtype and depth, natural history, and anatomic location; patient-specific factors, such as bleeding and wound healing diatheses; and

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<sup>a</sup>Shave biopsies are not necessarily superficial, tangential shaves of tissue. We use the term *shave* for biopsies that are saucerize or scoop techniques that may penetrate deep into the dermis.

**Table III.** Level of evidence and strength of recommendations for grading and staging, biopsy, clinical information, and pathology report for the treatment of BCC

Recommendation	Strength of recommendation	Level of evidence	References
Grading and staging	C	III	2,3
Biopsy	B	II	11-16
Clinical information provided to pathologist			
• Age	A	I, II	17-24
• Sex	B	I, II	18,20,22-25
• Anatomic location	B	I, II	17-20,22-26
• Recurrent lesion	A	I, II	17,18,22,23
• Size of lesion	A	I, II	17,18,21-26
• Immunosuppression	B	I, II	21,27
• History, especially radiation, burn, organ transplant	B	II	27
Pathology report elements	B	II	17,19,26,28
• Histologic subtype	B	II	17,19
• Invasion beyond reticular dermis	C	III	3,29,30
• Perineural involvement			

BCC, Basal cell carcinoma.

**Table IV.** National Comprehensive Cancer Network stratification of low- versus high-risk BCC

Parameters	Low risk	High risk
Clinical		
Location*/size <sup>†</sup>	Area L <20 mm Area M <sup>‡</sup> <10 mm	Area L ≥20 mm Area M ≥10 mm Area H <sup>§</sup>
Borders	Well defined	Poorly defined
Primary vs recurrent	Primary	Recurrent
Immunosuppression	No	Yes
Site of prior radiation therapy	No	Yes
Pathologic		
Growth pattern	Nodular, superficial <sup>  </sup>	Aggressive <sup>¶</sup>
Perineural involvement	No	Yes

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BCC, Basal cell carcinoma.

\*Area L consists of trunk and extremities (excluding hands, feet, nail units, pretibia, and ankles); area M consists of cheeks, forehead, scalp, neck, and pretibia; and area H consists of central face, eyelids, eyebrows, periorbital skin, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, temple, ear, genitalia, hands, and feet.

<sup>†</sup>Greatest tumor diameter.

<sup>‡</sup>Location independent of size may constitute high risk.

<sup>§</sup>Area H constitutes a high-risk area on the basis of location, independent of size.

<sup>||</sup>Other low-risk growth patterns include keratotic, infundibulocystic, and fibroepithelioma of Pinkus.

<sup>¶</sup>Having morpheaform, basosquamous (metatypical), sclerosing, mixed infiltrative, or micronodular features in any portion of the tumor.

patient preference and physician judgment. Studies that have utilized subsequent definitive excision as the reference standard for tumor detection have found that initial punch or shave biopsies were able to detect the most aggressive histologic subtypes of BCC in the vast majority of cases.<sup>11-16</sup> When recurrent tumor, deep invasion, or other aggressive features are suspected, more extensive tissue resection or multiple scouting

biopsies may in certain cases be needed to detect these if more superficial methods are insufficient. The need to obtain information through biopsy is counterbalanced by the patient and physician preferences to minimize biopsy-associated discomfort, trauma, risk for wound infection or dehiscence, scar, and loss of function, particularly on the head, neck, and other vital, functional, sensory, or cosmetically sensitive sites.

**Table V.** Recommendations for the biopsy of suspected BCC

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The recommended biopsy techniques for BCC are punch biopsy, shave biopsy, and excisional biopsy. The biopsy technique used will depend on the characteristics of the suspected malignancy (morphology, location, etc) and the judgment of the physician.

The biopsy size and depth should be adequate to provide the recommended clinical information and pathology report elements to permit accurate diagnosis and guide therapy.

Repeat biopsy may be considered if initial biopsy specimen is inadequate for accurate diagnosis.

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BCC, Basal cell carcinoma.

## CLINICAL AND PATHOLOGIC INFORMATION

Presumptive diagnosis of BCC is based on the physician's interpretation of clinical information, including clinical appearance and morphology, anatomic location, genetic risk factors, and patient-reported history. Clinical diagnosis is routinely confirmed by biopsy findings before treatment. When the clinician is submitting biopsy tissue for histopathologic diagnosis, the work group recommends that whenever possible and appropriate, key elements of patient demographics, clinical presentation, and clinical history should be provided to the pathologist (see [Table VI](#); for level of evidence/strength of recommendations, see [Table III](#)). These include patient age and biologic sex,<sup>17-25</sup> anatomic location,<sup>17-20,22-26</sup> and any history of treatment at the same anatomic site.<sup>17,18,22,23</sup> Additional desirable relevant information includes the clinical size of the lesion<sup>17,18,20-26</sup> and whether the patient currently, or previously encountered additional risk factors, such as immunosuppression, radiation treatment, or solid organ transplantation.<sup>21,27</sup>

The pathology report provided to the clinician confirms the diagnosis of BCC and provides additional information to guide therapeutic decision making. Reporting of biopsy specimens may include relevant pathologic features that can help distinguish between low- and high-risk categories, especially histologic subtype. If deeper invasion cannot be ruled out, as in the case of tumor transection (ie, tumor extension to the base of the biopsy), this may be noted. The work group recommends including, when possible, details regarding the specific histologic subtype(s) detected,<sup>17,19,26,28</sup> invasion of the tumor beyond the reticular dermis,<sup>17,19</sup> and perineural invasion,<sup>3,29,30</sup> as these parameters provide prognostic information regarding the potential for recurrence (see [Table](#)

**Table VI.** Recommendations for clinical information and pathology report for suspected BCC

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Clinical information provided to pathologist

Strongly recommended

- Age
- Sex
- Anatomic location
- Recurrent lesion

Recommended

- Size of lesion
- Immunosuppression
- History (especially radiation burn, organ transplant)

Elements to be included in final pathology report (excision specimens)

Recommended

- Histologic subtype
  - Invasion beyond reticular dermis
  - Perineural involvement
- 

BCC, Basal cell carcinoma.

[VI](#); for level of evidence/strength of recommendations, see [Table III](#)).

Pathologic evaluation of skin biopsy specimens is ideally performed by a dermatologist or pathologist who is experienced in interpreting cutaneous neoplasms. Such a physician is most able to collectively interpret the clinical tumor findings and the histologic features (ie, clinicopathologic correlation) to provide the most precise and accurate biopsy diagnosis.

## SURGICAL TREATMENT

A broad range of therapeutic modalities is available for the treatment of BCC, which may present with a wide variety of clinical and histologic characteristics. With each treatment option, when appropriately selected, a practitioner is able to achieve outstanding results. For example, C&E of a small, superficial BCC on the back may have an equally high cure rate as MMS for an infiltrative BCC on the nose. When the most appropriate therapy is being chosen, recurrence rate, preservation of function, patient expectations, and potential adverse effects must be taken into thorough consideration.<sup>31</sup>

When studies evaluating the efficacy of various treatment modalities for BCC are reviewed, critical attention must be paid to the length of follow-up. Because of the slow growth rate of BCC, recurrences are frequently diagnosed beyond 5 years following definitive treatment. As an illustrative example, in a

**Table VII.** Recommendations for the surgical treatment of BCC

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A treatment plan that considers recurrence rate, preservation of function, patient expectations, and potential adverse effects is recommended.

C&E may be considered for low-risk tumors in non-terminal hair-bearing locations.

For low-risk primary BCC, surgical excision with 4-mm clinical margins and histologic margin assessment is recommended.

Standard excision may be considered for select high-risk tumors. However, strong caution is advised when selecting a treatment modality without complete margin assessment for high-risk tumors.

Mohs micrographic surgery is recommended for high-risk BCC.

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BCC, Basal cell carcinoma; C&E, curettage and electrodesiccation.

multicenter randomized trial comparing MMS with standard excision for facial BCC, a 3% recurrence rate was found after 2.5 years of follow-up following standard excision with histologically negative margins. In the same cohort, the local recurrence rate increased to 12.2% at 10 years, with 56% of recurrences identified beyond 5 years of follow-up.<sup>32,33</sup>

Despite advances in topical and systemic therapies, as well as a variety of energy devices, surgery remains the cornerstone of BCC treatment. Three surgical treatment modalities are reviewed in this section: standard excision, MMS, and C&E. Nonsurgical therapies, including radiotherapy and cryosurgery, are addressed separately.

### Standard excision

BCC, regardless of the histologic growth pattern, is characterized by asymmetrical subclinical extension beyond the clinically visible tumor. To ensure complete removal with histologically negative margins, standard excision with conventional “bread loaf” histopathologic sectioning must include a margin of clinically normal-appearing skin. A large retrospective cohort study by Codazzi et al in 2014 contradicted the pervasive notion that the recurrence rate of BCC following excision with histologically positive margins is trivial.<sup>17</sup> In this study, the local recurrence rate after excision of BCC with positive margins was 26.8% (72 of 269), compared with 5.9% (176 of 3002) following excision with histologically negative margins. However, to our knowledge, no RCT comparing different excision margins for BCC has been performed. On the basis of several retrospective and prospective cohort studies, a positive surgical excision margin for BCC is most associated with tumor location

in the “H-zone” of the face (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, temple, and ear), aggressive/infiltrative histologic growth pattern, recurrent tumor, and extension beyond the reticular dermis.<sup>17-20,25</sup> According to current NCCN guidelines, location of BCC in the H-zone constitutes high risk, independent of size.<sup>3</sup>

Multiple RCTs comparing standard surgical excision of BCC with topical medical therapy, C&E, photodynamic therapy (PDT), cryotherapy, radiation therapy, and MMS have been published.<sup>32,34-39</sup> All the studies consistently reported low recurrence rates after standard excision of BCC with predominantly nonaggressive histologic growth patterns. Excision of nodular or superficial BCC with 3- to 4-mm margins in low-risk anatomic locations was associated with 2% to 4% recurrence rates after 3 to 5 years.<sup>35,38-40</sup> In a study comparing standard excision with C&E followed by cryosurgery for nonaggressive BCC on the head and neck, the 5-year recurrence rates were 8.2% and 17.6%, respectively.<sup>36</sup> Recurrence rates following surgical excision were uniformly significantly lower than those following treatment with topical therapy, radiation therapy, or destructive modalities. Only MMS was superior to standard excision for the treatment of primary and recurrent facial BCC after 5- and 10-years of follow-up.<sup>32</sup>

When cosmetic outcome following various treatment modalities were evaluated, the appearance after standard excision was consistently judged more favorable than that after C&E or cryotherapy.<sup>31,41</sup> Although 2 studies reported better cosmetic outcomes following PDT compared with standard excision, recurrence rates were significantly higher with PDT (9.3% and 14% after 1 and 5 years, respectively) than with standard excision (0% and 4% after 1 and 5 years, respectively).<sup>35,37</sup>

On the basis of the available data, the work group recommends standard excision with a 4-mm margin of uninvolved skin around the tumor and/or biopsy site to a depth of the mid-subcutaneous adipose tissue with histologic margin assessment for low-risk primary BCC (on the basis of NCCN risk stratification [Table VII]; for level of evidence/strength of the recommendation, see Table VIII). Standard excision may be considered for select high-risk tumors. However, strong caution is advised when selecting a treatment modality without complete margin assessment for high-risk BCC. Insufficient data preclude recommendation of defined peripheral and deep margins for excision of high-risk tumors with standard excision. When standard excision is performed for high-risk tumors, a linear repair, skin



**Table VIII.** Level of evidence and strength of recommendations for the surgical treatment of BCC

Recommendation	Strength of recommendation	Level of evidence	References
Treatment plan	A	II	31,41
C&E for low-risk tumors	B	I, II	24,31,36,42-45
Standard excision with 4-mm margins			35-41,46-58
• Low-risk BCC	A	I	Expert opinion
• High-risk BCC	C	III	
MMS for high-risk BCC	A	I, II	17,32,33,42,43,49,50

BCC, Basal cell carcinoma; C&E, curettage and electrodesiccation; MMS, Mohs micrographic surgery.

graft, or healing by second intention is recommended. If a repair requiring significant tissue rearrangement is indicated, closure should be delayed until negative histologic margins are confirmed. Recommendations for standard excision of BCC are summarized in Table VII. The strength of these recommendations is shown in Table VIII.<sup>17,31-33,35-50</sup>

#### MOHS MICROGRAPHIC SURGERY

Dr Frederic Mohs first described the use of chemosurgery for removal of difficult or recurrent cutaneous tumors in the 1940s.<sup>51,52</sup> Three decades later, the concept of *en face* horizontal sectioning for complete peripheral and deep margin control pioneered by Mohs to achieve optimal cure rate and maximum tissue conservation was adapted to the “fresh tissue” technique by Tromovitch and Stegman.<sup>53</sup> This modification eliminated the pain from *in vivo* fixation with zinc chloride paste, shortened the time required to perform surgery, and allowed immediate repair of a fresh surgical wound. Microscopic controlled excision, later referred to as MMS, was recommended by the authors for all recurrent or poorly defined tumors, for sclerosing BCC, and for all primary cutaneous carcinomas in areas with a predilection for recurrence.<sup>54</sup>

Since that time, the use of MMS for treatment of BCC has significantly increased and indications have expanded to include many other cutaneous malignancies. In 2012, a combined task force of the AAD, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and American Society for Mohs Surgery, developed appropriate use criteria for MMS.<sup>28</sup> Until recently, available data in support of the widespread use of MMS for BCC were limited to case series and meta-analyses. In systematic reviews of the literature dating back to the 1940s, Rowe et al, reported 5-year recurrence rates for MMS of 1% and 5.6% for primary and recurrent BCC, respectively.<sup>42,43</sup> In comparison, recurrence rates for other treatment modalities, including standard excision, C&E,

radiation therapy, and cryosurgery ranged from 7.5% to 10.1% and from 9.8% to 40% for primary and recurrent BCC, respectively. The first RCT for MMS comparing MMS with standard excision of primary and recurrent facial BCC was conducted in the Netherlands. Findings were initially reported by Smeets et al, in 2004 and later updated with 5- and 10-year recurrence rates in 2008 and 2014, respectively.<sup>32,33,49</sup> In the final analysis, a 10-year recurrence rate of 4.4% was reported for primary facial BCC treated with MMS, compared with 12.2% ( $P = .100$ ) following standard excision. For recurrent BCC, the 10-year recurrence rates were 3.9% and 13.5% ( $P = .023$ ) after MMS and standard excision, respectively.<sup>32</sup> Cox regression analysis identified an aggressive histologic growth pattern as a significant risk factor for recurrence.<sup>49</sup> These findings cannot necessarily be extrapolated beyond the scope of the study population with facial BCC. However, the results strongly support the use of MMS for both primary and recurrent BCC at increased risk for recurrence on the basis of factors such as anatomic location and histologic growth pattern.

Tissue conservation resulting in smaller surgical defects provides an additional benefit of MMS. In a small randomized trial, Muller et al reported that defect size after MMS for nodular BCC was significantly smaller ( $P < .001$ ) than after standard excision (116.6 vs 187.7 mm<sup>2</sup>).<sup>50</sup> Smeets et al reported that for tumors requiring more than 1 standard excision, or at least 2 stages of MMS, defects after excision were significantly larger than after MMS for primary and recurrent BCC.<sup>33</sup> Although smaller defects did not lead to significant differences in aesthetic outcome between MMS and standard excision in RCTs, both surgical modalities were found to be superior to C&E with regard to quality of life outcomes.<sup>31,33</sup>

A noteworthy limitation of MMS is that tissue blocks are not available for molecular testing or further evaluation of high-risk or unusual features by using paraffin sections.<sup>55</sup> To overcome this challenge, the tumor debulk specimen may be submitted

**Table IX.** Recommendations for the nonsurgical therapy of BCC

Cryosurgery may be considered for low-risk BCC when more effective therapies are contraindicated or impractical.

If surgical therapy is not feasible or preferred, topical therapy (eg, imiquimod or 5-FU), MAL- or ALA-PDT, and radiation therapy (eg, superficial radiation therapy, brachytherapy, external electron beam, and other traditional radiotherapy forms for BCC) can be considered when tumors are low risk, with the understanding that the cure rate may be lower.

Adjustment of topical therapy dosing regimen on the basis of side effect tolerance is recommended.

There is insufficient evidence to recommend the routine use of laser or electronic surface brachytherapy in the treatment of BCC.

ALA, Aminolevulinic acid; BCC, basal cell carcinoma; 5-FU, 5-fluorouracil; MAL, methylaminolevulinate; PDT, photodynamic therapy.

for paraffin sections to document high-risk features and obtain ancillary molecular studies, if indicated, without compromising the integrity of the MMS procedure.<sup>56</sup> Careful selection, on the basis of initial biopsy results, of tumors appropriate for treatment with MMS will minimize these limitations.

On the basis of the available data, it is the work group recommendation that MMS be indicated for the treatment of high-risk BCC (on the basis of NCCN risk stratification [Table VII]; for level of evidence/strength of recommendation, see Table VIII).

**CURRETAGE AND ELECTRODESSICATION**

To our knowledge, no randomized trials comparing C&E with other surgical treatments for BCC have been published. However, this simple procedure, which is quickly and easily performed in an office setting, has been successfully used by dermatologists for decades to treat BCC.<sup>42,57</sup> When carefully selected for low-risk primary lesions (Table IV, NCCN risk stratification), C&E is one of the recommended treatment options for BCC. For lesions on terminal hair-bearing skin (scalp, pubic, and axillary regions and the beard area in men), C&E is considered less effective because of potential follicular extension of tumor.<sup>3</sup> Although excellent cure rates can be achieved by experienced clinicians for selected low-risk tumors, particularly on the trunk and extremities, the results are considered highly operator and location dependent.<sup>58,59</sup> Moreover, C&E may be associated with a longer healing time and inferior cosmetic outcome compared with standard excision, and it is best avoided in cosmetically sensitive areas.<sup>44</sup>

**NONSURGICAL TREATMENT**

In general, treatment of BCC is most effectively accomplished by surgical therapy. There are relatively few exceptions to this guiding principle. If surgical therapy is not feasible or preferred, cryosurgery, topical therapy (eg, imiquimod or 5-fluorouracil [5-FU]), PDT (with aminolevulinic acid [ALA] or methyl aminolevulinate [MAL]), or radiation therapy for BCC can be considered when tumors are low risk, with the understanding that the cure rate may be lower. Further research is needed to better establish the comparative safety and effectiveness of nonsurgical therapies for BCC. Regimens combining different nonsurgical treatment modalities have been used but are not well studied. Head-to-head comparative effectiveness trials of various nonsurgical approaches are limited in number and scope. The recommendations for nonsurgical treatments are shown in Table IX and the level of evidence/strength of the recommendations is presented in Table X.<sup>23,34-39,41-43,46,47,60-94</sup>

**Cryosurgery**

Given the lack of histologic margin control and known subclinical extension of BCC, cryosurgery (interchangeably referred to as cryotherapy) should be considered only under select clinical circumstances, and when more effective therapies are contraindicated or impractical. The objective of cryosurgery in the treatment of BCC is to cause selective destruction of the same volume of tissue that would have been removed with standard excision. RCTs comparing cryosurgery with a variety of other treatment modalities (MAL and ALA PDT, standard excision, and radiation therapy) have reported recurrence rates for cryosurgery ranging between 6.3% at 1 year to 39% after 2 years of follow-up.<sup>41,60-62</sup> Cryosurgery may be considered for low-risk BCC when more effective therapies are contraindicated or impractical.<sup>2</sup>

**Topical therapies**

Topical imiquimod, an immunomodulator, is US Food and Drug Administration–approved for treatment of superficial BCC on the trunk, neck, and extremities. Various regimens of imiquimod have been used in practice, including application twice daily, once daily, and every other day; applications have been performed with and without occlusion for treatment courses ranging from 6 to 16 weeks.<sup>45,64-73</sup> Overall, rates of 3- to 12-month clinical and histologic cure have been reported to range from 60% to 80% in well-designed RCTs, with the highest rates reported for shorter follow-up and clinical

**Table X.** Level of evidence and strength of recommendations for the nonsurgical treatment of BCC as alternatives to surgical therapy

Recommendation	Strength of recommendation	Level of evidence	References
Cryosurgery	A	I	36,41,46,60-63
Topical therapy	A	I	39,64-77
• Imiquimod	B	I, II	46,64,74-76,78,79
• 5-FU	A	I	39,68,70
• Dose adjustments			
PDT	A	I, II	38,47,61,74,76,77,80-85
• ALA	A	I, II	35,37,60,64,74,76,77,83,86,87
• MAL			
Radiation therapy	B	I, II	23,34,42,43,46,62,88,89
• Traditional radiotherapies and modern superficial radiation therapy	C	II, III	90-92
• Electronic surface brachytherapy			
Laser therapy	C	II	74,93,94

ALA, Aminolevulinic acid; BCC, basal cell carcinoma; 5-FU, 5-fluorouracil; MAL, methylaminolevulinate.

cure. Moderate-to-severe local treatment-associated adverse events include skin redness, swelling, erosions, crusts, vesicles, itching, and, occasionally, tingling sensations.<sup>64</sup> These tissue effects may vary greatly in severity from one individual to the next and may limit patient compliance. In addition, imiquimod use for larger surface areas may be associated with systemic symptoms, including fatigue, influenza-like symptoms, myalgia, and headache.<sup>95</sup> Multiple dosing approaches have been used, suggesting that adjustment of dosing on the basis of tolerance is reasonable. Once-every-other-day treatment, possibly including a treatment holiday during the weekend or in the midst of the treatment course, appears to be as effective and better tolerated than more frequent applications without breaks from treatment. Once-a-day treatment 5 times a week for 6 weeks or longer is a routine regimen that balances patient acceptance and effectiveness. Case report data suggest that imiquimod may be used in selected cases for pretreatment before surgical removal of high-risk BCC or as adjuvant treatment for incompletely resected tumor.<sup>96-98</sup>

Monotherapy with topical 5-FU, an antimetabolite, for superficial BCC is less well studied in well-designed RCTs.<sup>74,75</sup> Typical regimens include twice-daily application for 3 to 6 weeks. Adverse events are similar to those with imiquimod and include erythema, swelling, crust, erosions, ulcers, and eschar. These associated adverse events can limit patient compliance, as they can interfere with patients' presentability and ability to work or attend social activities, resulting in decreased effectiveness.

Promising pilot studies have suggested short-term clearance for low-risk tumors. Depending on the topical formulation used, 16-week clinical clearance rates of 50% to 90% have been seen. Longer-term follow-up and response rates for higher-risk or more aggressive tumors are not available.

A systematic review assessing treatment of NMSC with topical 5-FU and imiquimod concluded that the strength of evidence for the routine use of either of these agents as monotherapy for treatment of primary BCC is weak and recommended that these approaches be reserved for patients with small tumors in low-risk locations who are unable to tolerate more definitive therapies. This review also noted that 97% and 100% of patients treated with these topical medications for skin cancer, respectively, experienced at least 1 adverse event.<sup>75</sup>

## PHOTODYNAMIC THERAPY

PDT for BCC is a 2-part treatment consisting of topical application of a photosensitizer, either 5-ALA or MAL, followed by 1 to several hours of incubation by light irradiation, typically with a blue, red, or broadband light source.<sup>35,38,64,74,76,77,80-82,86,87,99</sup> Application of the photosensitizer is often preceded by light curettage of BCCs.<sup>99</sup> Usually a single treatment cycle is performed, but treatments may be repeated.

There is evidence that aggressive, repeated PDT may have effectiveness for small, well-demarcated nodular BCC. In 2 small RCTs, nodular BCC (no larger than 5 mm in diameter) were treated with MAL-PDT after curettage and 3 hours incubation.

Nonresponding lesions were retreated at 1 week with a second cycle of PDT. The histologic response rate was 73% in the treatment group.<sup>87</sup> In a similar study, 2 PDT illuminations were performed with ALA-PDT after debulking of nodular BCC, with a cumulative recurrence rate of 31% after 5 years and best response in small BCC less than 0.7 mm thick.<sup>38</sup> Other data with ALA-PDT are similar, with complete response rates of at least 60% to 70% and improved response when light irradiation was fractionated into 2 periods of illumination.<sup>82</sup> Studies directly comparing ALA-PDT and MAL-PDT have reported similar effectiveness for treatment of BCC with these therapies.<sup>77,83</sup> Post-treatment adverse events include photosensitivity and the consequent need for light avoidance and photoprotection for 48 hours, erythema, edema, tenderness, and, occasionally, crust or erosions.<sup>81,82</sup> As with other topical treatments for BCC, there are individual differences in patient discomfort after treatment.

### Comparative effectiveness of topical therapies

Treatment of BCC with topical therapies is most appropriate for small, low-risk BCC when surgery is impractical or declined by the patient. Discussion with the patient of the benefits and limitations of therapy, as well as the relative effectiveness and tolerability of available therapies, is appropriate.

The 3-year follow-up results of an ongoing large RCT<sup>64</sup> demonstrated that imiquimod is superior and topical 5-FU is comparable to MAL-PDT for superficial BCC.<sup>76</sup> The likelihoods of tumor-free status at 3 years were 80%, 68%, and 58% for imiquimod, 5-FU, and MAL-PDT, respectively. The only subgroup in which MAL-PDT was superior to imiquimod was elderly patients with BCC of the lower extremities. Earlier pooled data from 28 studies of variable quality indicated the 12-week post-treatment complete response rates of superficial BCC to be 86% for imiquimod and 79% for PDT, with inadequate data for 5-FU because of a dearth of studies.<sup>74</sup>

So-called “field treatment” is designed to treat small incipient BCCs within an anatomic area or region. Topical treatments have been reported to be effective for combatting field cancerization.<sup>84</sup> In patients unable to tolerate the downtime associated with weeks to months of local skin irritation, PDT may be a preferred topical modality for BCC.

The evidence indicates that topical treatments used for thin, small, low-risk BCC are inferior in effectiveness to surgery, even when topical treatments are preceded by debulking or curettage, as well as when they are delivered repeatedly.<sup>35,38,99</sup>

Cure rates after surgical excision are 10% to 20% higher than those for topical therapies, including PDT, with excision associated with recurrence rates of less than 5%. Surgical excision may also be less painful and better tolerated.<sup>99</sup>

### Radiation therapy

Although surgery remains the first-line and most effective treatment for BCC, primary radiation therapy can be used in special situations in which surgery is not feasible, contraindicated, or not preferred by the patient after a discussion of risks and benefits.<sup>24,34,46,62,88,100,101</sup> Several different types of radiotherapy can be used to treat BCC, including superficial radiation therapy, isotope-based brachytherapy (interstitial or topical contact), and external electron beam radiation. Primary or adjuvant radiation is an effective treatment option for selected patients with BCC, resulting in good tumor control and cosmesis, with the understanding that cure rates may be lower.<sup>23,34,46,62,88,100,101</sup> One RCT demonstrated that in terms of long-term cosmesis, surgery is superior to radiotherapy for primary BCCs of the face smaller than 4 cm.<sup>34</sup> The radiation technique is modified depending on the site, size, shape, and depth of the tumor. Superficial radiation therapy uses rays that are more energetic than Grenz rays but less so than orthovoltage external beam radiation. This form of radiation has been used for many decades by dermatologists and others to treat selected skin cancers.<sup>88,102</sup> Brachytherapy traditionally used custom molds and catheters that either conformed to the external contours of the skin or penetrated the skin to treat deeper tumors (eg, interstitial approach). High-dose rate brachytherapy is generally more practical for patients because of the shorter treatment time.<sup>103</sup> More recently, electronic brachytherapy, a form of superficial radiation therapy, has been used as a purely topical delivery modality.<sup>90,91</sup> In the United States, external beam radiation remains in widespread use in large radiation oncology departments.

In general, radiation treatment to a particular BCC is delivered in several to many fractions over several weeks. Cure rates have not typically been assessed histologically, with lack of clinically apparent recurrence used to estimate short- and medium-term tumor control rates. Postradiation adverse events include acute radiation-related skin toxicity, potential radiation-related changes to underlying structures, and the increased difficulty of managing recurrences within the radiation field. Late adverse events can result in alopecia, cartilage necrosis, and skin pigmentary changes in addition to the risk for secondary malignancy.

Although adjuvant radiation has been recommended in patients with high-risk BCC, it appears that no RCT has been conducted to prove its benefit.

### Laser therapy

Pulsed dye laser as a single treatment, whether double-pass or double-stacked, is not recommended for the treatment of superficial or nodular BCC. Long-term data regarding the safety and effectiveness of pulsed dye or Er:YAG lasers for treatment of BCC are lacking.<sup>74,93,104</sup>

## MANAGING PATIENTS WITH METASTATIC AND ADVANCED BASAL CELL CARCINOMA

Metastatic BCC is exceedingly rare, with an estimated incidence of 0.0028% to 0.55%, but has historically been associated with a very poor prognosis.<sup>105</sup> Lymphatic metastasis to the regional lymph node basin followed by hematogenous spread to lung and bone is the most common pathway of progression. Until recently, no approved therapy was available for metastatic BCC, and studies were limited to case reports and series using primarily platinum-based chemotherapeutic agents.<sup>106</sup> In 2012, Sekulic et al, reported an objective response rate of 30% among 33 patients with metastatic BCC treated with vismodegib, a smoothed (SMO) inhibitor targeted at the hedgehog pathway, according to the Response Evaluation Criteria in Solid Tumors.<sup>107</sup> After 12 months of additional follow-up, the objective response rate increased to 33%.<sup>108</sup> Although all the responses were partial, the majority of patients (73%) experienced tumor shrinkage, with a median duration of objective response of 7.6 months. Similar findings were reported in the Safety Events in Vismodegib (STEVIE) trial, in which an overall response rate of 37.9% was found among 29 patients with metastatic BCC.<sup>109</sup> Oral vismodegib has been approved by the US Food and Drug Administration as the first systemic therapy for metastatic BCC.

Few other treatment options are available for patients with metastatic BCC. When metastatic disease is limited to the regional lymph node basin, surgery and/or radiation therapy remain the most appropriate treatment, when possible. For patients with distant metastases, multidisciplinary consultation is recommended to consider systemic therapy with hedgehog pathway inhibitors. If this is not feasible, platinum-based chemotherapy may be considered. Patients with advanced disease should also be provided with or referred to best supportive and palliative care to optimize symptom management and maximize quality of life.

### Table XI. Recommendations for managing locally advanced or metastatic BCC

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Multidisciplinary consultation and smoothed inhibitors are recommended for patients with metastatic BCC. If treatment of metastatic BCC with smoothed inhibitors is not feasible, platinum-based chemotherapy or best supportive care is recommended. If surgery and radiation therapy are contraindicated or inappropriate for the treatment of locally advanced BCC, or if residual tumor persists following surgery and/or radiation therapy and further surgery and radiation therapy are contraindicated or inappropriate, systemic therapy with a smoothed inhibitor should be considered. Patients with advanced disease should be provided with or referred for best supportive and palliative care, to optimize symptom management and maximize quality of life.

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BCC, Basal cell carcinoma.

Locally destructive tumors, which are typically associated with long delays in presentation, are encountered more often than metastatic BCC and may pose a significant therapeutic dilemma. Although surgery and radiation therapy remain the criterion standard of therapy, curative treatment may be associated with substantial morbidity. In the study by Sekulic et al, the efficacy of vismodegib was also evaluated in patients with locally advanced BCC.<sup>107</sup> Patients had at least 1 tumor 10 mm or larger in diameter that was considered inoperable or inappropriate for surgery in the opinion of a specialist in MMS, head and neck surgery, or plastic surgery. Inoperable or inappropriate for surgery was defined as either (1) the recurrence of BCC after 2 or more surgical procedures and an expectation that curative resection would be unlikely, or (2) substantial morbidity or deformity anticipated from surgery. In the cohort of 63 patients with locally advanced BCC, the objective response rate was 43%, with complete responses in 13 patients (21%) and a median duration of response of 7.6 months. After 12 months of additional follow-up, the objective response rate increased to nearly 48%, with a median duration of response of 9.5 months.<sup>108</sup> However, drug toxicity was substantial, with serious adverse events reported in 26 patients (25%). Higher response rates among 453 patients with locally advanced BCC were reported in the STEVIE trial, with an overall response rate of 66.7%.<sup>109</sup> Notably, 180 of 499 patients in the STEVIE trial (36%) discontinued treatment because of adverse events, 108 (22%) were recorded as having serious adverse events, and among 31 deaths during the trial, 21 were the result of adverse events.

**Table XII.** Level of evidence and strength of recommendations for the management of metastatic BCC

Recommendation	Strength of recommendation	Level of evidence	References
Treatment with SMO inhibitors			
• Metastatic and Locally advanced BCC	A	I, II	107-111,113,114
• Gorlin syndrome	B	I	115
Platinum-based chemotherapy for metastatic BCC	C	III	106
Palliative care	C	III	Expert opinion

BCC, Basal cell carcinoma; SMO, smoothed.

Routine adverse events that patients find troublesome include muscle spasms and arthralgias, alopecia, and dysgeusia often culminating in weight loss. Thirteen patients (12%) discontinued the study because of adverse events and 7 patients (1 with metastatic and 6 with locally advanced disease) died, though the relationship between vismodegib and the deaths was unknown.

Comparable findings were more recently reported with use of another SMO inhibitor, sonidegib, in patients with locally advanced BCC.<sup>110</sup> At the 12-month analysis of the BCC Outcomes with LDE225 Treatment (BOLT) trial, response rates of 44% to 58% overall were found in patients with locally advanced BCC and 8% to 17% in patients with metastatic BCC.<sup>111</sup> There is initial evidence that patients resistant to one SMO inhibitor may be resistant to another.<sup>112</sup> Although the same limitations regarding adverse events and drug resistance apply, SMO inhibitors may be considered for patients with nevoid BCC (Gorlin) syndrome with excessively numerous or aggressive BCCs.

For localized BCC, the overwhelming majority of tumors are readily treated with local treatment modalities, including surgery, radiation therapy, and topical therapy. If surgery and radiation therapy are contraindicated or inappropriate for the treatment of locally advanced tumors, or if residual tumor persists following surgery and/or radiation therapy and further surgery and radiation therapy are contraindicated or inappropriate, multidisciplinary consultation is advised to consider systemic therapy with a hedgehog pathway inhibitor. It is acknowledged by the work group that *locally advanced, inoperable, inappropriate, and substantial morbidity or deformity from surgery* are subjective and highly operator-dependent terms. Therefore, multidisciplinary consultation is strongly encouraged. The recommendations for the treatment of metastatic BCC are shown in Table XI, and the level of evidence/strength of the recommendations are in Table XII.<sup>106-111,113-115</sup>

### FOLLOW-UP AND REDUCING RISK FOR FUTURE SKIN CANCERS

Once BCC has been diagnosed in a patient, in-office screening for new primary skin cancers, including BCC, cSCC, and melanoma, should be performed at least once per year. This recommendation derives from the considerable evidence from cohort studies and registries that a patient with at least 1 BCC is at risk for additional BCC as well other skin cancers, including cSCC and melanoma.

A 2010 meta-analysis by Wheless et al determined that the summary random-effects relative risk for development of a second NMSC after diagnosis of a first was 1.12 (based on 12 cohort studies from cancer registries) and 1.49 based on 3 studies with patient level data.<sup>116</sup> More recently Wehner et al. found in their prospective cohort that the 5-year probability of another NMSC after diagnosis of a first was 40.7%, and 82% after more than 1.<sup>117</sup> At 10 years, the chances increased to 59.6% of another NMSC after the first and 91.2% after diagnosis of a nonfirst NMSC.

Initial diagnosis of BCC increases the risk for subsequent malignant melanoma (MM). Song et al found a relative risk for development of MM after diagnosis of a NMSC of 1.99 for men and 2.58 for women.<sup>118</sup> These data were based on 2 large prospective cohort studies with 46,237 men and 107,339 women under study. A smaller study including 3548 people found the relative risk for MM to be 3.28 after diagnosis of BCC.<sup>119</sup>

Patients who have had BCC should be counseled regarding the risk for new primary skin cancers, the need for in-office screening, and the potential benefits of self-screening. Concurrent patient self-surveillance for BCC and other skin cancers may be of additional utility in detecting new primary tumors while they are still small and easily treated. Family members can also help patients detect skin cancers, as they may be able to detect suspicious lesions at anatomic sites (eg, the back) that are not easily assessed by the patient.<sup>120</sup>

**Table XIII.** Recommendations for the follow-up of BCC and reduction of risk for future skin cancer

After diagnosis of a first BCC, skin cancer screening for new keratinocyte cancers (BCC or cSCC) and for melanoma should be performed on at least an annual basis.

Patients with a history of BCC should be counseled on skin self-examination and sun protection.

The use of topical and oral retinoids (eg, tretinoin, retinol, acitretin, and isotretinoin) is not recommended to reduce the incidence of future keratinocyte cancers in those with a history of BCC.

Dietary supplementation of selenium and  $\beta$ -carotene is not recommended to reduce the incidence of future keratinocyte cancers in those with a history of BCC.

There is insufficient evidence to make a recommendation on the use of oral nicotinamide, DFMO, or celecoxib in the chemoprevention of BCC.

BCC, Basal cell carcinoma; DFMO,  $\alpha$ -difluoromethylornithine; cSCC, cutaneous squamous cell carcinoma.

**Table XIV.** Level of evidence and strength of recommendations for the follow-up of BCC and reduction of risk for future tumors

Recommendation	Strength of recommendation	Level of evidence	References
Annual follow-up skin cancer screening	A	I	116-119,138-140
Skin self-examination and sun protection after BCC	A	III	Expert opinion
Against the use of topical and oral retinoids			
• Tretinoin	A	I, II	123,125,141
• Acitretin	B	I	129
• Isotretinoin	A	I	126,127
• Oral retinol	A	I	127,128
Against dietary supplementation with			
• Selenium	A	I	135,136
• $\beta$ -Carotene	A	I	137
Chemoprevention of BCC			
• Celecoxib	B	I	133,134
• DFMO	A	I	131,132
• Oral nicotinamide	B	I	130

BCC, Basal cell carcinoma; DFMO,  $\alpha$ -difluoromethylornithine.

Patients with a history of BCC should be counseled regarding the need for sun protection, sun avoidance, and tanning booth avoidance. Broad-spectrum chemical and physical sunscreens have been shown to reduce ultraviolet light exposure per unit time when properly applied.<sup>121,122</sup> Routine use of sunscreens is recommended in combination with other sun-protective behaviors such as seeking shade and wearing broad-brimmed head coverings.

Many topical and oral agents have been recommended to reduce the risk for a new BCC or other skin cancer after an initial diagnosis of BCC, but the evidence for these agents is mixed. Topical and oral retinoids are not recommended for reducing risk for subsequent BCC in patients with a history of BCC. Topical retinoids have not been found to reduce the incidence of keratinocyte cancers or actinic keratosis

in those with a history of a keratinocyte cancer<sup>123</sup> or the incidence of BCC in those with Gorlin-Goltz syndrome.<sup>124</sup> In addition, topical retinoids used for prolonged periods were associated with increased mortality in a single study, although some investigators have discounted this result as spurious.<sup>125</sup> Oral retinoids (acitretin, oral retinol, and isotretinoin) also do not appear to reduce the incidence of BCC in those with a history of a keratinocyte cancer.<sup>126-129</sup>

Limited evidence is available to support the utility of other agents, including oral nicotinamide,  $\alpha$ -difluoromethylornithine, and celecoxib, in reducing the risk for keratinocyte cancer in patients with history of BCC. There is early evidence from a small trial that oral nicotinamide may reduce the risk for subsequent keratinocyte carcinoma in nonimmunosuppressed individuals with a history of such

cancer.<sup>130</sup> There is also some evidence that  $\alpha$ -difluoromethylornithine, an irreversible inhibitor of the pathway that produces polyamines in humans, may reduce the risk for BCC in those with a history of keratinocyte cancer, although treatment-associated audiometric abnormalities have been reported.<sup>131,132</sup> Although there is evidence that oral celecoxib makes NMSC in general, and BCC in particular, less likely in patients with previous NMSC, the potential benefits should be weighed against the significant risk for a cardiovascular event that is associated with this medication.<sup>133,134</sup>

The dietary supplements  $\beta$ -carotene and selenium have also been studied, and are not recommended for reducing risk for BCC or cSCC in patients with a history of BCC. Several RCTs have shown no protective benefit against NMSC associated with either  $\beta$ -carotene or selenium.<sup>122,135-137</sup> Treatment-associated adverse events, notably, skin yellowing with  $\beta$ -carotene use and gastrointestinal upset with selenium have been noted.

Recommendations for the follow-up of patients with BCC and recommendations to reduce the risk for future tumors are found in Table XIII and level of evidence/strength of recommendation is presented in Table XIV.<sup>116-119,123,125-141</sup>

## GAPS IN RESEARCH

In review of the currently available highest-level evidence, the expert work group acknowledges that much has yet to be learned regarding the optimal management of patients with BCC. Significant gaps in research were identified, including but not limited to the use and value of dermoscopy and other imaging modalities in the diagnosis of BCC, as well as the clinical and prognostic value of biomarkers that may aid in the identification of tumors susceptible to targeted systemic therapy. Although the treatment of localized tumors is usually successful, significant gaps in research have been identified with regard to the identification of noninvasive treatment modalities with recurrence rates comparable to those with surgery. Moreover, much remains to be learned about the optimal use of currently available systemic inhibitors of the hedgehog pathway, as well as the identification of novel therapies that are able to achieve high response rates with a more tolerable side effect profile. Because of these and other gaps in knowledge, the recommendations provided by the expert work group are occasionally based on consensus opinion rather than on high-level evidence. Management of BCC should

therefore always be tailored to meet individual patients' needs.

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The AAD strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies' *Code of Interactions with Companies*. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors throughout the guideline development process, and recusal is used to manage identified relationships. The AAD conflict of interest policy summary may be viewed at [www.aad.org](http://www.aad.org).

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