FROM THE ACADEMY

Guidelines of care for the management of basal cell carcinoma

Work Group: Christopher Bichakjian, MD, (Co-Chair),[a] April Armstrong, MD, MPH[b] Christian Baum, MD,[c] Jeremy S. Bordeaux, MD, MPH,[d] Marc Brown, MD,[e] Klaus J. Busam, MD,[f] Daniel B. Eisen, MD,[g] Vivek Iyengar, MD,[h] Clifford Lober, MD, JD,[i] David J. Margolis, MD, PhD,[j] Jane Messina, MD,[k,l] Alexander Miller, MD,[m] Stanley Miller, MD,[n] Eliot Mostow, MD, MPH,[o] Christen Mowad, MD,[p] Kishwer Nehal, MD,[q] Kristi Schmitt-Burr,[r] Aleksandar Sekulic, MD, PhD,[s] Paul Storrs, MD,[h] Joyce Teng, MD, PhD,[t] Siegrid Yu, MD,[u] Conway Huang, MD,[v] Kevin Boyer, MPH,[w] Wendy Smith Begolka, MBS,[w] and Murad Alam, MD, (Co-Chair)[x]

Invited Reviewers: John Y. S. Kim, MD,[y] Jeffrey H. Kozlow, MD, MS,[z] Bharat Mittal, MD,[aa] Jeffrey Moyer, MD,[bb] Thomas Olencki, DO,[cc] and Phillip Rodgers, MD[dd]

Ann Arbor, Michigan; Denver, Colorado; Rochester, Minnesota; Cleveland, Rootstown, Burton, and Columbus, Ohio; Rochester and New York, New York; Sacramento, San Francisco, Yorba Linda, and Stanford, California; Chicago and Schaumburg, Illinois; Kissimmee and Tampa, Florida; Philadelphia, Pennsylvania; Towson and Danville, Maryland; Phoenix, Arizona; and Birmingham, Alabama

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.

From the Department of Dermatology,[a] Section of Plastic and Reconstructive Surgery,[z] Plastic/Head/Neck Surgery, Department of Otolaryngology,[bb] and Department of Family Medicine, University of Michigan School of Medicine, University of Michigan, Ann Arbor[dd]; Department of Dermatology, University of Colorado, Denver[b]; Department of Dermatology, Mayo Clinic, Rochester[c]; Case Western Reserve University School of Medicine, Cleveland[d]; Department of Dermatology, University of Rochester[e]; Dermatopathology,[f] Memorial Sloan Kettering Cancer Center, New York[q]; Department of Dermatology, University of California Davis, Sacramento[g]; Private practice, Chicago[h]; Private practice, Kissimmee[i]; University of Pennsylvania Perelman School of Medicine, Philadelphia[j]; Departments of Pathology, University of South Florida[k] and Moffitt Cancer Center, Tampa[l]; Private practice, Yorba Linda[m]; Private practice, Towson[n]; Dermatology Section, NEOMED, Rootstown[o]; Geisinger Medical Center, Danville[p]; Basal Cell Carcinoma Nevus Syndrome Life Support Network, Burton[r]; Mayo Clinic, Phoenix[s]; Stanford School of Medicine[t]; Dermatologic Surgery and Laser Center, University of California San Francisco[u]; Department of Dermatology, University of Alabama, Birmingham[v]; American Academy of Dermatology, Schaumburg[w]; and Department of Dermatology,[x] Department of Plastic and Reconstructive Surgery,[y] and Department of Radiation Oncology, Northwestern University, Chicago[aa]; and Department of Internal Medicine, Ohio State University, Columbus.[cc]

Funding sources: None.

The management of conflict of interests for this guideline series complies with the Council of Medical Special Societies' *Code of Interactions with Companies*. The authors' conflict of interest/disclosure statements appear at the end of this article.

Accepted for publication October 2, 2017.

Reprint requests: guidelines@aad.org.

Correspondence to: Wendy Smith Begolka, MBS, American Academy of Dermatology, 930 East Woodfield Rd, Schaumburg, IL 60173. E-mail: wsmithbegolka@aad.org.

Published online January 4, 2018.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2017.10.006

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 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.[1] MeSH (Medical Subject Headings) terms used in various combinations in the literature search included *carcinoma*, *basal cell carcinoma*, *squamous cell*

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 electrodessication
    - 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
  - α-Difluoromethylornithine
  - Selenium
  - β-Carotene

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

Abbreviations used:

AAD:	American Academy of Dermatology
AJCC:	American Joint Committee on Cancer
ALA:	aminolevulinic acid
BCC:	basal cell carcinoma
C&E:	curettage and electrodessication
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*, *electrodessication*, *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.[2-4]

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*).[5] 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.[6] 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.[7]

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 electrodessication (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.[8,9] 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.[10] 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 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).[2,3,11-30] 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.

Table II. Recommendation for grading and staging of BCC

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

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

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,[a] 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 in 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

[a]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†	Area L <20 mm Area M‡ <10 mm	Area L ≥20 mm Area M ≥10 mm Area H§
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‖	Aggressive¶
Perineural involvement	No	Yes

Reprinted with permission.[3]

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.

†Greatest tumor diameter.

‡Location independent of size may constitute high risk.

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

‖Other low-risk growth patterns include keratotic, infundibulocystic, and fibroepithelioma of Pinkus.

¶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.[11-16] 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

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.

BCC, Basal cell carcinoma.

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

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.

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,[17-25] anatomic location,[17-20,22-26] and any history of treatment at the same anatomic site.[17,18,22,23] Additional desirable relevant information includes the clinical size of the lesion[17,18,20-26] and whether the patient currently, or previously encountered additional risk factors, such as immunosuppression, radiation treatment, or solid organ transplantation.[21,27]

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,[17,19,26,28] invasion of the tumor beyond the reticular dermis,[17,19] and perineural invasion,[3,29,30] as these parameters provide prognostic information regarding the potential for recurrence (see Table 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.[31]

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

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.

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

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.[32,33]

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.[17] 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.[17-20,25] According to current NCCN guidelines, location of BCC in the H-zone constitutes high risk, independent of size.[3]

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.[32,34-39] 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.[35,38-40] 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.[36] 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.[32]

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.[31,41] 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).[35,37]

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 electrodessication; *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.[17,31-33,35-50]

MOHS MICROGRAPHIC SURGERY

Dr Frederic Mohs first described the use of chemosurgery for removal of difficult or recurrent cutaneous tumors in the 1940s.[51,52] 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.[53] 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.[54]

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.[28] 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.[42,43] 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.[32,33,49] 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.[32] Cox regression analysis identified an aggressive histologic growth pattern as a significant risk factor for recurrence.[49] 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^2).[50] 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.[33] 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.[31,33]

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.[55] 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.[56] 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.[42,57] 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.[3] 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.[58,59] 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.[44]

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.[23,34-39,41-43,46,47,60-94]

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.[41,60-62] Cryosurgery may be considered for low-risk BCC when more effective therapies are contraindicated or impractical.[2]

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.[45,64-73] 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			
• Imiquimod	A	I	39,64-77
• 5-FU	B	I, II	46,64,74-76,78,79
• Dose adjustments	A	I	39,68,70
PDT			
• ALA	A	I, II	38,47,61,74,76,77,80-85
• MAL	A	I, II	35,37,60,64,74,76,77,83,86,87
Radiation therapy			
• Traditional radiotherapies and modern superficial radiation therapy	B	I, II	23,34,42,43,46,62,88,89
• Electronic surface brachytherapy	C	II, III	90-92
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.[64] 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.[95] 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.[96-98]

Monotherapy with topical 5-FU, an antimetabolite, for superficial BCC is less well studied in well-designed RCTs.[74,75] 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.[75]

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.[35,38,64,74,76,77,80-82,86,87,99] Application of the photosensitizer is often preceded by light curettage of BCCs.[99] 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.[87] 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.[38] 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.[82] Studies directly comparing ALA-PDT and MAL-PDT have reported similar effectiveness for treatment of BCC with these therapies.[77,83] 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.[81,82] 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[64] demonstrated that imiquimod is superior and topical 5-FU is comparable to MAL-PDT for superficial BCC.[76] 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.[74]

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.[84] 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.[35,38,99] 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.[99]

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.[24,34,46,62,88,100,101] 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.[23,34,46,62,88,100,101] 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.[34] 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.[88,102] 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.[103] More recently, electronic brachytherapy, a form of superficial radiation therapy, has been used as a purely topical delivery modality.[90,91] 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.[74,93,104]

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.[105] 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.[106] In 2012, Sekulic et al, reported an objective response rate of 30% among 33 patients with metastatic BCC treated with vismodegib, a smoothened (SMO) inhibitor targeted at the hedgehog pathway, according to the Response Evaluation Criteria in Solid Tumors.[107] After 12 months of additional follow-up, the objective response rate increased to 33%.[108] 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.[109] 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

Multidisciplinary consultation and smoothened inhibitors are recommended for patients with metastatic BCC.
If treatment of metastatic BCC with smoothened 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 smoothened 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.

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.[107] 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.[108] 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%.[109] 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*, smoothened.

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.[110] 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.[111] There is initial evidence that patients resistant to one SMO inhibitor may be resistant to another.[112] 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.[106-111,113-115]

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.[116] 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.[117] 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.[118] 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.[119]

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.[120]

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 β-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*, α-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
• β-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*, α-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.[121,122] 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[123] or the incidence of BCC in those with Gorlin-Goltz syndrome.[124] 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.[125] 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.[126-129]

Limited evidence is available to support the utility of other agents, including oral nicotinamide, α-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.[130] There is also some evidence that α-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.[131,132] 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.[133,134]

The dietary supplements β-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 β-carotene or selenium.[122,135-137] Treatment-associated adverse events, notably, skin yellowing with β-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.[116-119,123,125-141]

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.

We thank Charniel McDaniels, MS, for technical assistance in development of this manuscript. We also thank the AAD Board of Directors, the Council on Science and Research, the Clinical Guidelines Committee, and all commenting Academy members for their thoughtful and excellent feedback.

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.

Disclosure: The below information represents the authors' disclosed relationships with industry during guideline development. Relevant relationships requiring recusal for drafting of guideline recommendations and content by work group members were not noted for this guideline.

April Armstrong, MD, MPH, served as an advisory board member for Abbvie, Amgen, Janssen-Ortho, Merck, Novartis, Pfizer and UCB, receiving honoraria; as a consultant for Celgene, Eli Lily, Jannsen-Ortho, and Modernizing Medicine, receiving honoraria; as a speaker for Abbvie, receiving honoraria; and as a principal investigator (PI) for Eli Lily, Janssen-Ortho, Novartis, and Regeneron, receiving grants/research funding. Jeremy S. Bordeaux, MD, MPH, served as an advisory board member for Lubax, receiving honoraria; as an employee of Massachusetts General Hospital, receiving a salary; and in another role with Journal Watch Dermatology, receiving honoraria. Marc Brown, MD, served as an advisory board member for DUSA Pharmaceuticals, receiving no compensation. David J. Margolis, MD, PhD, served as an advisory board member for Astellas, Celleration, and Kerecis, receiving fees; as a PI for Valeant, receiving grants/research funding; and as a Data Safety Monitoring Board member for DermaSciences, Macrocure, and Sanofi/Regeneron, receiving fees. Stanley Miller, MD, served as an employee of UpToDate, Inc, receiving patent royalties and other compensation. Eliot Mostow, MD, MPH, served as a consultant for Elsevier, receiving a salary; as a speaker and PI for Healthpoint, receiving honoraria and grants/research funding; and as an advisory board member for Vivacare, receiving honoraria. Christen Mowad, MD, served on the board of directors for Elsevier, receiving honoraria; in other roles with UpToDate, Inc, receiving patient royalties and other compensation; and as a PI for Amgen, receiving fees. Dr Mowad also had a relative

serving as an employee of Takeda Pharmaceuticals, receiving a salary. Aleksander Sekulic, MD, PhD, served as an advisory board member for Roche and as a PI for Genentech, receiving fees. Conway Huang, MD, served as a consultant for Castle Biosciences, Inc, receiving honoraria. Murad Alam, MD, served as a consultant for Amway, receiving honoraria, and as a PI for OptMed and 3M, receiving no personal compensation. Thomas Olenecki, DO, served as a PI for BMS, Exelixis, Genentech, Pfizer, and Tracon, receiving grants and research funding. Christopher Bichakjian, MD, Christian Baum, MD, Klaus J. Busam, MD, Daniel B. Eisen, MD, Vivek Iyengar, MD, Clifford Lober, MD, JD, Jane Messina, MD, Alexander Miller, MD, Kishwer Nehal, MD, Kristi Schmitt-Burr, Paul Storrs, MD, Joyce Teng, MD, PhD, Siegrid Yu, MD, John Y.S. Kim, MD, Jeffrey H. Kozlow, MD, MS, Bharat Mittal, MD, Jeffrey Moyer, MD, Phillip Rodgers, MD, Kevin Boyer, MPH, and Wendy Smith Begolka, MBS, have no relevant relationships to disclose.

REFERENCES

1. Alam M, Armstrong A, Baum C, et al. Guidelines of care for the management of squamous cell carcinoma. *J Am Acad Dermatol*. 2017. Online ahead of print. https://doi.org/10.1016/j.jaad.2017.10.007.
2. National Comprehensive Cancer Center. NCCN Clinical practice guidelines in oncology; basal cell skin cancer. Available at: www.nccn.org. Accessed April 1, 2015.
3. National Comprehensive Cancer Center. NCCN clinical practice guidelines in oncology; basal cell carcinoma (V1.2017). Available at: www.nccn.org. Accessed October 3, 2016.
4. Telfer NR, Colver GB, Morton CA. British Association of Dermatology. Guidelines for the management of basal cell carcinoma. *Br J Dermatol*. 2008;159(1):35-48.
5. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Pract*. 2004;17(1):59-67.
6. American Academy of Dermatology. Administrative regulations; evidence based clinical practice guidelines. Available at: www.aad.org/Forms/Policies/Uploads/AR/AR%20-%20Evidence-Based%20Clinical%20Guideline.pdf. Accessed December 1, 2014.
7. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population, 2012. *JAMA Dermatol*. 2015;151(10):1081-1086.
8. Linos E, Schroeder SA, Chren MM. Potential overdiagnosis of basal cell carcinoma in older patients with limited life expectancy. *JAMA*. 2014;312(10):997-998.
9. Fosko SW. Counterpoint: limited life expectancy, basal cell carcinoma, health care today, and unintended consequences. *J Am Acad Dermatol*. 2015;73(1):162-164.
10. Edge SB, American Joint Committee on Cancer, American Cancer Society. *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.
11. Roozeboom MH, Mosterd K, Winnepenninckx VJ, Nelemans PJ, Kelleners-Smeets NW. Agreement between histological subtype on punch biopsy and surgical excision in primary basal cell carcinoma. *J Eur Acad Dermatol Venereol*. 2013;27(7):894-898.
12. Haws AL, Rojano R, Tahan SR, Phung TL. Accuracy of biopsy sampling for subtyping basal cell carcinoma. *J Am Acad Dermatol*. 2012;66(1):106-111.
13. Mosterd K, Thissen MR, van Marion AM, et al. Correlation between histologic findings on punch biopsy specimens and subsequent excision specimens in recurrent basal cell carcinoma. *J Am Acad Dermatol*. 2011;64(2):323-327.
14. Smith LC, Cox NH, Dawn G. Shave biopsy without local anaesthetic to diagnose basal cell carcinoma and other skin tumours prior to definitive treatment: analysis of 109 lesions. *Br J Dermatol*. 2009;160(1):180-182.
15. Russell EB, Carrington PR, Smoller BR. Basal cell carcinoma: a comparison of shave biopsy versus punch biopsy techniques in subtype diagnosis. *J Am Acad Dermatol*. 1999;41(1):69-71.
16. Kadouch DJ, van Haersma de With A, Limpens J, et al. Is a punch biopsy reliable in subtyping basal cell carcinoma? A systematic review. *Br J Dermatol*. 2016;175(2):401-403.
17. Codazzi D, Van Der Velden J, Carminati M, et al. Positive compared with negative margins in a single-centre retrospective study on 3957 consecutive excisions of basal cell carcinomas. Associated risk factors and preferred surgical management. *J Plast Surg Hand Surg*. 2014;48(1):38-43.
18. Kumar P, Watson S, Brain AN, et al. Incomplete excision of basal cell carcinoma: a prospective multicentre audit. *Br J Plast Surg*. 2002;55(8):616-622.
19. Farhi D, Dupin N, Palangie A, Carlotti A, Avril MF. Incomplete excision of basal cell carcinoma: rate and associated factors among 362 consecutive cases. *Dermatol Surg*. 2007;33(10):1207-1214.
20. Hansen C, Wilkinson D, Hansen M, Soyer HP. Factors contributing to incomplete excision of nonmelanoma skin cancer by Australian general practitioners. *Arch Dermatol*. 2009;145(11):1253-1260.
21. Khan L, Breen D, Zhang L, et al. Predictors of recurrence after radiotherapy for non-melanoma skin cancer. *Curr Oncol*. 2014;21(2):e326-329.
22. Silverman MK, Kopf AW, Bart RS, Grin CM, Levenstein MS. Recurrence rates of treated basal cell carcinomas. Part 3: surgical excision. *J Dermatol Surg Oncol*. 1992;18(6):471-476.
23. Silverman MK, Kopf AW, Gladstein AH, Bart RS, Grin CM, Levenstein MJ. Recurrence rates of treated basal cell carcinomas. Part 4: x-ray therapy. *J Dermatol Surg Oncol*. 1992;18(7):549-554.
24. Silverman MK, Kopf AW, Grin CM, Bart RS, Levenstein MJ. Recurrence rates of treated basal cell carcinomas. Part 2: curettage-electrodesiccation. *J Dermatol Surg Oncol*. 1991;17(9):720-726.
25. Talbot S, Hitchcock B. Incomplete primary excision of cutaneous basal and squamous cell carcinomas in the Bay of Plenty. *N Z Med J*. 2004;117(1192):U848.
26. Rieger KE, Linos E, Egbert BM, Swetter SM. Recurrence rates associated with incompletely excised low-risk nonmelanoma skin cancer. *J Cutan Pathol*. 2010;37(1):59-67.
27. Lott DG, Manz R, Koch C, Lorenz RR. Aggressive behavior of nonmelanotic skin cancers in solid organ transplant recipients. *Transplantation*. 2010;90(6):683-687.
28. Connolly SM, Baker DR, Coldiron BM, et al, Ad Hoc Task Force. AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery. *J Am Acad Dermatol*. 2012;67(4):531-550.
29. Cho M, Lee J, James CL, Marshman G, Huilgol SC. Scalp basal cell carcinoma: review of 2,202 cases. *Dermatol Surg*. 2016;42(7):834-841.
30. Niazi ZB, Lamberty BG. Perineural infiltration in basal cell carcinomas. *Br J Plast Surg*. 1993;46(2):156-157.

31. Chren MM, Sahay AP, Bertenthal DS, Sen S, Landefeld CS. Quality-of-life outcomes of treatments for cutaneous basal cell carcinoma and squamous cell carcinoma. *J Invest Dermatol*. 2007;127(6):1351-1357.
32. van Loo E, Mosterd K, Krekels GA, et al. Surgical excision versus Mohs' micrographic surgery for basal cell carcinoma of the face: a randomised clinical trial with 10 year follow-up. *Eur J Cancer*. 2014;50(17):3011-3020.
33. Smeets NW, Krekels GA, Ostertag JU, et al. Surgical excision vs Mohs' micrographic surgery for basal-cell carcinoma of the face: randomised controlled trial. *Lancet*. 2004;364(9447):1766-1772.
34. Avril MF, Auperin A, Margulis A, et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. *Br J Cancer*. 1997;76(1):100-106.
35. Rhodes LE, de Rie MA, Leifsdottir R, et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. *Arch Dermatol*. 2007;143(9):1131-1136.
36. Kuijpers DI, Thissen MR, Berretty PJ, Ideler FH, Nelemans PJ, Neumann MH. Surgical excision versus curettage plus cryosurgery in the treatment of basal cell carcinoma. *Dermatol Surg*. 2007;33(5):579-587.
37. Szeimies RM, Ibbotson S, Murrell DF, et al. A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8-20 mm), with a 12-month follow-up. *J Eur Acad Dermatol Venereol*. 2008;22(11):1302-1311.
38. Roozeboom MH, Aardoom MA, Nelemans PJ, et al. Fractionated 5-aminolevulinic acid photodynamic therapy after partial debulking versus surgical excision for nodular basal cell carcinoma: a randomized controlled trial with at least 5-year follow-up. *J Am Acad Dermatol*. 2013;69(2):280-287.
39. Bath-Hextall F, Ozolins M, Armstrong SJ, et al. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial. *Lancet Oncol*. 2014;15(1):96-105.
40. Gulleth Y, Goldberg N, Silverman RP, Gastman BR. What is the best surgical margin for a basal cell carcinoma: a meta-analysis of the literature. *Plast Reconstr Surg*. 2010;126(4):1222-1231.
41. Thissen MR, Nieman FH, Ideler AH, Berretty PJ, Neumann HA. Cosmetic results of cryosurgery versus surgical excision for primary uncomplicated basal cell carcinomas of the head and neck. *Dermatol Surg*. 2000;26(8):759-764.
42. Rowe DE, Carroll RJ, Day CL Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol*. 1989;15(3):315-328.
43. Rowe DE, Carroll RJ, Day CL Jr. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. *J Dermatol Surg Oncol*. 1989;15(4):424-431.
44. Rodriguez-Vigil T, Vazquez-Lopez F, Perez-Oliva N. Recurrence rates of primary basal cell carcinoma in facial risk areas treated with curettage and electrodesiccation. *J Am Acad Dermatol*. 2007;56(1):91-95.
45. Spencer JM. Pilot study of imiquimod 5% cream as adjunctive therapy to curettage and electrodesiccation for nodular basal cell carcinoma. *Dermatol Surg*. 2006;32(1):63-69.
46. Bath-Hextall FJ, Perkins W, Bong J, Williams HC. Interventions for basal cell carcinoma of the skin. *Cochrane Database Syst Rev*. 2007;(1):CD003412.
47. Mosterd K, Thissen MR, Nelemans P, et al. Fractionated 5-aminolaevulinic acid-photodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma: results of a randomized controlled trial. *Br J Dermatol*. 2008;159(4):864-870.
48. Unlu RE, Altun S, Kerem M, Koc MN. Is it really necessary to make wide excisions for basal cell carcinoma treatment? *J Craniofac Surg*. 2009;20(6):1989-1991.
49. Mosterd K, Krekels GA, Nieman FH, et al. Surgical excision versus Mohs' micrographic surgery for primary and recurrent basal-cell carcinoma of the face: a prospective randomised controlled trial with 5-years' follow-up. *Lancet Oncol*. 2008;9(12):1149-1156.
50. Muller FM, Dawe RS, Moseley H, Fleming CJ. Randomized comparison of Mohs micrographic surgery and surgical excision for small nodular basal cell carcinoma: tissue-sparing outcome. *Dermatol Surg*. 2009;35(9):1349-1354.
51. Mohs FE. Chemosurgery: a microscopically controlled method of cancer excision. *Arch Surg*. 1941;42(2):279-295.
52. Mohs FE. Chemosurgical treatment of cancer of the nose; a microscopically controlled method. *Arch Surg*. 1946;53:327-344.
53. Tromovitch TA, Stegeman SJ. Microscopically controlled excision of skin tumors. *Arch Dermatol*. 1974;110(2):231-232.
54. Tromovitch TA, Stegman SJ. Microscopie-controlled excision of cutaneous tumors: chemosurgery, fresh tissue technique. *Cancer*. 1978;41(2):653-658.
55. Ebede TL, Lee EH, Dusza SW, Busam KJ, Nehal KS. Clinical value of paraffin sections in association with Mohs micrographic surgery for nonmelanoma skin cancers. *Dermatol Surg*. 2012;38(10):1631-1638.
56. American Academy of Dermatology. Appropriate uses of paraffin sections in association with Mohs micrographic surgery; 2014. Available at: https://www.aad.org/Forms/Policies/Uploads/PS/PS%20Appropriate%20Uses%20of%20Paraffin%20Sections%20in%20Association%20with%20Mohs%20Micrographic%20Surgery.pdf. Accessed February 1, 2017.
57. Knox JM, Lyles TW, Shapiro EM, Martin RD. Curettage and electrodesiccation in the treatment of skin cancer. *Arch Dermatol*. 1960;82:197-204.
58. Salasche SJ. Curettage and electrodesiccation in the treatment of midfacial basal cell epithelioma. *J Am Acad Dermatol*. 1983;8(4):496-503.
59. Goldman G. The current status of curettage and electrodesiccation. *Dermatol Clin*. 2002;20(3):569-578. ix.
60. Basset-Seguin N, Ibbotson SH, Emtestam L, et al. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. *Eur J Dermatol*. 2008;18(5):547-553.
61. Wang I, Bendsoe N, Klinteberg CA, et al. Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. *Br J Dermatol*. 2001;144(4):832-840.
62. Hall VL, Leppard BJ, McGill J, Kesseler ME, White JE, Goodwin P. Treatment of basal-cell carcinoma: comparison of radiotherapy and cryotherapy. *Clin Radiol*. 1986;37(1):33-34.
63. Mallon E, Dawber R. Cryosurgery in the treatment of basal cell carcinoma. Assessment of one and two freeze-thaw cycle schedules. *Dermatol Surg*. 1996;22(10):854-858.
64. Arits AH, Mosterd K, Essers BA, et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. *Lancet Oncol*. 2013;14(7):647-654.

65. Ezughah FI, Dawe RS, Ibbotson SH, Fleming CJ. A randomized parallel study to assess the safety and efficacy of two different dosing regimens of 5% imiquimod in the treatment of superficial basal cell carcinoma. *J Dermatolog Treat*. 2008; 19(2):111-117.
66. Eigentler TK, Kamin A, Weide BM, et al. A phase III, randomized, open label study to evaluate the safety and efficacy of imiquimod 5% cream applied thrice weekly for 8 and 12 weeks in the treatment of low-risk nodular basal cell carcinoma. *J Am Acad Dermatol*. 2007;57(4): 616-621.
67. Schulze HJ, Cribier B, Requena L, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. *Br J Dermatol*. 2005;152(5):939-947.
68. Geisse J, Caro I, Lindholm J, Golitz L, Stampone P, Owens M. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. *J Am Acad Dermatol*. 2004;50(5): 722-733.
69. Geisse JK, Rich P, Pandya A, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: a double-blind, randomized, vehicle-controlled study. *J Am Acad Dermatol*. 2002;47(3):390-398.
70. Sterry W, Ruzicka T, Herrera E, et al. Imiquimod 5% cream for the treatment of superficial and nodular basal cell carcinoma: randomized studies comparing low-frequency dosing with and without occlusion. *Br J Dermatol*. 2002;147(6):1227-1236.
71. Marks R, Gebauer K, Shumack S, et al. Imiquimod 5% cream in the treatment of superficial basal cell carcinoma: results of a multicenter 6-week dose-response trial. *J Am Acad Dermatol*. 2001;44(5):807-813.
72. Shumack S, Robinson J, Kossard S, et al. Efficacy of topical 5% imiquimod cream for the treatment of nodular basal cell carcinoma: comparison of dosing regimens. *Arch Dermatol*. 2002;138(9):1165-1171.
73. Beutner KR, Geisse JK, Helman D, Fox TL, Ginkel A, Owens ML. Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream. *J Am Acad Dermatol*. 1999;41(6):1002-1007.
74. Roozeboom MH, Arits AH, Nelemans PJ, Kelleners-Smeets NW. Overall treatment success after treatment of primary superficial basal cell carcinoma: a systematic review and meta-analysis of randomized and nonrandomized trials. *Br J Dermatol*. 2012;167(4):733-756.
75. Love WE, Bernhard JD, Bordeaux JS. Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: a systematic review. *Arch Dermatol*. 2009;145(12):1431-1438.
76. Roozeboom MH, Arits AH, Mosterd K, et al. Three-year follow-up results of photodynamic therapy vs. imiquimod vs. fluorouracil for treatment of superficial basal cell carcinoma: a single-blind, noninferiority, randomized controlled trial. *J Invest Dermatol*. 2016;136(8):1568-1574.
77. Kuijpers DI, Thissen MR, Thissen CA, Neumann MH. Similar effectiveness of methyl aminolevulinate and 5-aminolevulinate in topical photodynamic therapy for nodular basal cell carcinoma. *J Drugs Dermatol*. 2006;5(7):642-645.
78. Romagosa R, Saap L, Givens M, et al. A pilot study to evaluate the treatment of basal cell carcinoma with 5-fluorouracil using phosphatidyl choline as a transepidermal carrier. *Dermatol Surg*. 2000;26(4):338-340.
79. Miller BH, Shavin JS, Cognetta A, et al. Nonsurgical treatment of basal cell carcinomas with intralesional 5-fluorouracil/epinephrine injectable gel. *J Am Acad Dermatol*. 1997;36(1):72-77.
80. Soler AM, Angell-Petersen E, Warloe T, et al. Photodynamic therapy of superficial basal cell carcinoma with 5-aminolevulinic acid with dimethylsulfoxide and ethylendiaminetetraacetic acid: a comparison of two light sources. *Photochem Photobiol*. 2000;71(6):724-729.
81. Osiecka B, Jurczyszyn K, Ziolkowski P. The application of Levulan-based photodynamic therapy with imiquimod in the treatment of recurrent basal cell carcinoma. *Med Sci Monit*. 2012;18(2):PI5-PI9.
82. de Vijlder HC, Sterenborg HJ, Neumann HA, Robinson DJ, de Haas ER. Light fractionation significantly improves the response of superficial basal cell carcinoma to aminolaevulinic acid photodynamic therapy: five-year follow-up of a randomized, prospective trial. *Acta Derm Venereol*. 2012; 92(6):641-647.
83. Schleier P, Berndt A, Kolossa S, Zenk W, Hyckel P, Schultze-Mosgau S. Comparison of aminolevulinic acid (ALA)-thermogel-PDT with methyl-ALA-thermogel-PDT in basal cell carcinoma. *Photodiagnosis Photodyn Ther*. 2007; 4(3):197-201.
84. Apalla Z, Sotiriou E, Chovarda E, Lefaki I, Devliotou-Panagiotidou D, Ioannides D. Skin cancer: preventive photodynamic therapy in patients with face and scalp cancerization. A randomized placebo-controlled study. *Br J Dermatol*. 2010;162(1):171-175.
85. Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, et al. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. *JAMA Dermatol*. 2013;149(4):402-410.
86. Wang H, Xu Y, Shi J, Gao X, Geng L. Photodynamic therapy in the treatment of basal cell carcinoma: a systematic review and meta-analysis. *Photodermatol Photoimmunol Photomed*. 2015;31(1):44-53.
87. Foley P, Freeman M, Menter A, et al. Photodynamic therapy with methyl aminolevulinate for primary nodular basal cell carcinoma: results of two randomized studies. *Int J Dermatol*. 2009;48(11):1236-1245.
88. Ashby MA, Smith J, Ainslie J, McEwan L. Treatment of nonmelanoma skin cancer at a large Australian center. *Cancer*. 1989;63(9):1863-1871.
89. Cognetta AB, Howard BM, Heaton HP, Stoddard ER, Hong HG, Green WH. Superficial x-ray in the treatment of basal and squamous cell carcinomas: a viable option in select patients. *J Am Acad Dermatol*. 2012;67(6): 1235-1241.
90. Bhatnagar A. Nonmelanoma skin cancer treated with electronic brachytherapy: results at 1 year. *Brachytherapy*. 2013; 12(2):134-140.
91. Paravati AJ, Hawkins PG, Martin AN, et al. Clinical and cosmetic outcomes in patients treated with high-dose-rate electronic brachytherapy for nonmelanoma skin cancer. *Pract Radiat Oncol*. 2015;5(6):e659-664.
92. Ballester-Sanchez R, Pons-Llanas O, Candela-Juan C, et al. Electronic brachytherapy for superficial and nodular basal cell carcinoma: a report of two prospective pilot trials using different doses. *J Contemp Brachytherapy*. 2016;8(1): 48-55.
93. Smucler R, Vlk M. Combination of Er:YAG laser and photodynamic therapy in the treatment of nodular basal cell carcinoma. *Lasers Surg Med*. 2008;40(2):153-158.
94. Tran HT, Lee RA, Oganesyan G, Jiang SB. Single treatment of non-melanoma skin cancers using a pulsed-dye laser with stacked pulses. *Lasers Surg Med*. 2012;44(6):459-467.
95. Kulp J, Levy S, Fein MC, Adams M, Furst J, Meng TC. Pharmacokinetics of imiquimod 3.75% cream applied daily

for 3 weeks to actinic keratoses on the face and/or balding scalp. *Arch Dermatol Res*. 2010;302(7):539-544.
96. Roldan-Marin R, Toussaint-Caire S. Imiquimod 5% as adjuvant therapy for incompletely excised iInfiltrative nodular basal cell carcinoma and dermoscopy to monitor treatment response. *Dermatol Ther (Heidelb)*. 2015;5(4):265-272.
97. Bonilla R, Solebo AL, Khandwala MA, Jones CA. Imiquimod 5% cream as an adjuvant pre-operative treatment for basal cell carcinoma of the periocular area. *Orbit*. 2014;33(6):471-473.
98. Thissen MR, Kuijpers DI, Krekels GA. Local immune modulator (imiquimod 5% cream) as adjuvant treatment after incomplete Mohs micrographic surgery for large, mixed type basal cell carcinoma: a report of 3 cases. *J Drugs Dermatol*. 2006;5(5):461-464.
99. Berroeta L, Clark C, Dawe RS, Ibbotson SH, Fleming CJ. A randomized study of minimal curettage followed by topical photodynamic therapy compared with surgical excision for low-risk nodular basal cell carcinoma. *Br J Dermatol*. 2007;157(2):401-403.
100. American Academy of Dermatology. Position statement on superficial radiation therapy for basal cell carcinoma (BCC) and squamous cell carcinomas (SCC). Available at: https://www.aad.org/Forms/Policies/Uploads/PS/PS-Superficial%20Radiation%20Therapy.pdf. Accessed November 5, 2016.
101. American Academy of Dermatology. Position statement on electronic surface brachytherapy for basal cell carcinoma (BCC) and squamous cell carcinomas (SCC). Available at: https://www.aad.org/Forms/Policies/Uploads/PS/PS%20-%20Electronic%20Surface%20Brachytherapy.pdf. Accessed November 5, 2016.
102. Bart RS, Kopf AW, Gladstein AH. Treatment of morphea-type basal cell carcinomas with radiation therapy. *Arch Dermatol*. 1977;113(6):783-786.
103. Gauden R, Pracy M, Avery AM, Hodgetts I, Gauden S. HDR brachytherapy for superficial non-melanoma skin cancers. *J Med Imaging Radiat Oncol*. 2013;57(2):212-217.
104. Choi SH, Kim KH, Song KH. Er:YAG ablative fractional laser-primed photodynamic therapy with methyl aminolevulinate as an alternative treatment option for patients with thin nodular basal cell carcinoma: 12-month follow-up results of a randomized, prospective, comparative trial. *J Eur Acad Dermatol Venereol*. 2016;30(5):783-788.
105. von Domarus H, Stevens PJ. Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. *J Am Acad Dermatol*. 1984;10(6):1043-1060.
106. Moeholt K, Aagaard H, Pfeiffer P, Hansen O. Platinum-based cytotoxic therapy in basal cell carcinoma—a review of the literature. *Acta Oncol*. 1996;35(6):677-682.
107. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med*. 2012;366(23):2171-2179.
108. Sekulic A, Migden MR, Lewis K, et al. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC. *J Am Acad Dermatol*. 2015;72(6):1021-1026.e1028.
109. Basset-Seguin N, Hauschild A, Grob JJ, et al. Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial. *Lancet Oncol*. 2015;16(6):729-736.
110. Migden MR, Guminski A, Gutzmer R, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. *Lancet Oncol*. 2015;16(6):716-728.
111. Dummer R, Guminski A, Gutzmer R, et al. The 12-month analysis from Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT): a phase II, randomized, double-blind study of sonidegib in patients with advanced basal cell carcinoma. *J Am Acad Dermatol*. 2016;75(1):113-125.e115.
112. Danial C, Sarin KY, Oro AE, Chang AL. An Investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. *Clin Cancer Res*. 2016;22(6):1325-1329.
113. Chang AL, Solomon JA, Hainsworth JD, et al. Expanded access study of patients with advanced basal cell carcinoma treated with the hedgehog pathway inhibitor, vismodegib. *J Am Acad Dermatol*. 2014;70(1):60-69.
114. Jacobsen AA, Aldahan AS, Hughes OB, Shah VV, Strasswimmer J. Hedgehog pathway inhibitor therapy for locally advanced and metastatic basal cell carcinoma: a systematic review and pooled analysis of interventional studies. *JAMA Dermatol*. 2016;152(7):816-824.
115. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *N Engl J Med*. 2012;366(23):2180-2188.
116. Wheless L, Black J, Alberg AJ. Nonmelanoma skin cancer and the risk of second primary cancers: a systematic review. *Cancer Epidemiol Biomarkers Prev*. 2010;19(7):1686-1695.
117. Wehner MR, Linos E, Parvataneni R, Stuart SE, Boscardin WJ, Chren MM. Timing of subsequent new tumors in patients who present with basal cell carcinoma or cutaneous squamous cell carcinoma. *JAMA Dermatol*. 2015;151(4):382-388.
118. Song F, Qureshi AA, Giovannucci EL, et al. Risk of a second primary cancer after non-melanoma skin cancer in white men and women: a prospective cohort study. *PLoS Med*. 2013;10(4):e1001433.
119. Rees JR, Zens MS, Gui J, Celaya MO, Riddle BL, Karagas MR. Non melanoma skin cancer and subsequent cancer risk. *PLoS One*. 2014;9(6):e99674.
120. Robinson JK, Wayne JD, Martini MC, Hultgren BA, Mallett KA, Turrisi R. Early detection of new melanomas by patients with melanoma and their partners using a structured skin self-examination skills training intervention: a randomized clinical trial. *JAMA Dermatol*. 2016;152(9):979-985.
121. van der Pols JC, Williams GM, Pandeya N, Logan V, Green AC. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. *Cancer Epidemiol Biomarkers Prev*. 2006;15(12):2546-2548.
122. Green A, Williams G, Neale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet*. 1999;354(9180):723-729.
123. Weinstock MA, Bingham SF, Digiovanna JJ, et al. Tretinoin and the prevention of keratinocyte carcinoma (basal and squamous cell carcinoma of the skin): a veterans affairs randomized chemoprevention trial. *J Invest Dermatol*. 2012;132(6):1583-1590.
124. Tang JY, Chiou AS, Mackay-Wiggan JM, et al. Tazarotene: randomized, double-blind, vehicle-controlled, and open-label concurrent trials for basal cell carcinoma prevention and therapy in patients with basal cell nevus syndrome. *Cancer Prev Res (Phila)*. 2014;7(3):292-299.
125. Weinstock MA, Bingham SF, Lew RA, et al. Topical tretinoin therapy and all-cause mortality. *Arch Dermatol*. 2009;145(1):18-24.
126. Tangrea JA, Edwards BK, Taylor PR, et al. Long-term therapy with low-dose isotretinoin for prevention of basal cell

carcinoma: a multicenter clinical trial. Isotretinoin-Basal Cell Carcinoma Study Group. *J Natl Cancer Inst*. 1992;84(5):328-332.

127. Levine N, Moon TE, Cartmel B, et al. Trial of retinol and isotretinoin in skin cancer prevention: a randomized, double-blind, controlled trial. Southwest Skin Cancer Prevention Study Group. *Cancer Epidemiol Biomarkers Prev*. 1997;6(11):957-961.
128. Moon TE, Levine N, Cartmel B, et al. Effect of retinol in preventing squamous cell skin cancer in moderate-risk subjects: a randomized, double-blind, controlled trial. Southwest Skin Cancer Prevention Study Group. *Cancer Epidemiol Biomarkers Prev*. 1997;6(11):949-956.
129. Kadakia KC, Barton DL, Loprinzi CL, et al. Randomized controlled trial of acitretin versus placebo in patients at high-risk for basal cell or squamous cell carcinoma of the skin (North Central Cancer Treatment Group Study 969251). *Cancer*. 2012;118(8):2128-2137.
130. Chen AC, Martin AJ, Choy B, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. *N Engl J Med*. 2015;373(17):1618-1626.
131. Kreul SM, Havighurst T, Kim K, et al. A phase III skin cancer chemoprevention study of DFMO: long-term follow-up of skin cancer events and toxicity. *Cancer Prev Res (Phila)*. 2012;5(12):1368-1374.
132. Bailey HH, Kim K, Verma AK, et al. A randomized, double-blind, placebo-controlled phase 3 skin cancer prevention study of {alpha}-difluoromethylornithine in subjects with previous history of skin cancer. *Cancer Prev Res (Phila)*. 2010;3(1):35-47.
133. Elmets CA, Viner JL, Pentland AP, et al. Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial. *J Natl Cancer Inst*. 2010;102(24):1835-1844.
134. Tang JY, Aszterbaum M, Athar M, et al. Basal cell carcinoma chemoprevention with nonsteroidal anti-inflammatory drugs in genetically predisposed *PTCH1*+/- humans and mice. *Cancer Prev Res (Phila)*. 2010;3(1):25-34.
135. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA*. 1996;276(24):1957-1963.
136. Duffield-Lillico AJ, Slate EH, Reid ME, et al. Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. *J Natl Cancer Inst*. 2003;95(19):1477-1481.
137. Greenberg ER, Baron JA, Stukel TA, et al. A clinical trial of beta carotene to prevent basal-cell and squamous-cell cancers of the skin. The Skin Cancer Prevention Study Group. *N Engl J Med*. 1990;323(12):789-795.
138. Chen J, Ruczinski I, Jorgensen TJ, et al. Nonmelanoma skin cancer and risk for subsequent malignancy. *J Natl Cancer Inst*. 2008;100(17):1215-1222.
139. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. *Arch Dermatol*. 2000;136(12):1524-1530.
140. Flohil SC, van der Leest RJ, Arends LR, de Vries E, Nijsten T. Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis. *Eur J Cancer*. 2013;49(10):2365-2375.
141. Geng A, Weinstock MA, Hall R, et al. Tolerability of high-dose topical tretinoin: the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Br J Dermatol*. 2009;161(4):918-924.