GUIDELINES OF CARE FOR THE MANAGEMENT
OF BASAL CELL CARCINOMA

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ABSTRACT

Basal cell carcinoma (BCC) is the most common form of human cancer with a continually increasing annual incidence in the US. When diagnosed early, the majority of BCC 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 histopathological interpretation of BCC. In the absence of a formal staging system, the best available stratification based on risk of 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 diagnosed with BCC.
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 biological 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.

ABBREVIATIONS

AAD = American Academy of Dermatology
AJCC = American Joint Committee on Cancer
ALA = aminolevulinic acid
BCC = Basal Cell Carcinoma
C&E = curettage and electrodessication
DFMO = α-difluoromethylornithine
MAL = methylaminolevulinate
MM = Malignant Melanoma
MMS = Mohs micrographic surgery
NCCN = National Comprehensive Cancer Network
NMSC = non-melanoma skin cancer
PDT = photodynamic therapy
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 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 chemo- 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 basal cell carcinoma.

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 which was updated and reviewed for potential relevant conflicts of interest.
throughout guideline development. If a potential conflict was noted, the work group member recused him 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 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 non-melanoma skin cancer (NMSC), searches were collectively undertaken for literature on BCC and cutaneous squamous cell carcinoma (cSCC) simultaneously, using a set of search terms applicable to both BCC and/or cSCC. A parallel AAD guideline on cSCC has also been developed. MeSH terms used in various combinations in the literature search included: carcinoma, basal cell carcinoma, squamous cell 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 based on 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.\textsuperscript{2-4}

The available evidence was evaluated using a unified system called the Strength

of Recommendation Taxonomy (SORT), developed by editors of the U.S. family

medicine and primary care journals (i.e. \textit{American Family Physician}, \textit{Family Medicine},

\textit{Journal of Family Practice}, and \textit{BMJ USA}).\textsuperscript{5} Evidence was graded using a 3-point scale

based on the quality of study methodology (\textit{e.g.} randomized control trial (RCT), case-

control, prospective/retrospective cohort, case series, etc.), and the overall focus of the

study (\textit{i.e.} diagnosis, treatment/prevention/screening, or prognosis) as follows:

I. Good-quality patient-oriented evidence (\textit{i.e.} 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, or disease-

oriented evidence (\textit{i.e.} evidence measuring intermediate, physiologic, or surrogate

descriptive end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed based on 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 where documented evidence-based data was not available, expert opinion was utilized to generate clinical recommendations.

This guideline has been developed in accordance with the American Academy of Dermatology (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. 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 five years from the date of publication, unless reaffirmed, updated, or retired at or before that time.

INTRODUCTION

Basal cell carcinoma is the most common human malignancy. Non-melanoma skin cancer (NMSC; or keratinocyte carcinoma), of which BCC comprises more than half of all diagnoses, affects more than 3.3 million persons annually in the US. The treatment of BCC has long comprised a substantial component of the clinical practice of dermatologists, who are well aware of the numerous available therapeutic options. These clinical practice guidelines for the treatment of BCC provide evidence-based recommendations that offer clinicians a framework to manage patients with BCC. Both established and more recent data in support of widely accepted therapies, including curettage and electrodesiccation (C&E) as well as Mohs micrographic surgery
(MMS), are reviewed. The presence or absence of reliable evidence in support of emerging treatment modalities is discussed in detail, ranging from topical medications and energy devices for low risk tumors to systemic therapy for metastatic disease. Moreover, recommendations regarding staging, biopsy techniques, prevention and follow-up are made based on 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 healthcare 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 upon which each treatment recommendation is based is critical to selecting and providing care optimally tailored to individual patients.

While many recommendations in these guidelines reaffirm common knowledge and current practice, other recommendations may remind clinicians of alternative therapeutic or preventative options, when insufficient evidence is available to support new therapies or previously dogmatic practice patterns. As the incidence of BCC in the US continues to increase, a thorough understanding of the management of BCC and
the evidence upon 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.\(^{10}\) Due to the exceedingly low incidence of regional and distant metastasis, TNM (tumor, node, metastasis) classification and AJCC stage grouping is 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. Based on the best available literature, the most useful stratification of BCC is provided by the National Comprehensive Cancer Network (NCCN) Guidelines (recommendation Table 2; level of evidence/strength of recommendation Table 3).\(^{3}\) The NCCN stratification, listed in Table 4, takes both clinical and pathological parameters into account and is based on a combination of available evidence and expert multidisciplinary opinion, including representatives from dermatology, dermatopathology, head and neck surgery, plastic surgery, and surgical, radiation and medical oncology. Treatment recommendations throughout the current guidelines are based on this stratification.

**BIOPSY**
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 (e.g., by tangential technique) biopsy\(^1\); 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, while 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 one is 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 5, and the level of evidence/strength of the recommendation in Table 3.

The 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, as well as 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

\(^{1}\) 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.
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.

CLINICAL AND PATHOLOGICAL 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 prior to treatment. When the clinician is submitting biopsy tissue for histopathologic diagnosis, the work group recommends that when possible and appropriate, key elements of patient demographics, clinical presentation, and clinical history should be provided to the pathologist (Table 6; level of evidence/strength of recommendations in Table 3). These include patient age and biological gender\textsuperscript{17-25}, anatomic location\textsuperscript{17-21,23-26}, and if it is known whether a tumor was previously treated at the same anatomic site.\textsuperscript{17,18,23,24} Additional desirable relevant information includes the clinical size of the lesion\textsuperscript{17,18,20,22-26}, and whether the patient currently, or previously encountered additional risk factors, such as immunosuppression, radiation treatment, or solid organ transplantation.\textsuperscript{22,27}

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 (i.e., 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 (Table 6; level of evidence/strength of recommendations in Table 3).

Pathologic evaluation of skin biopsies 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 (i.e., 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 histological characteristics. With each treatment option, when appropriately selected, a practitioner is able to achieve outstanding results. For example, curettage and electrodessication (C&E) of a small, superficial BCC on the back may have an equally high cure rate as MMS for a recurrent, infiltrative BCC on the nose. When choosing the most appropriate therapy, recurrence rate, preservation of function, patient expectations and potential adverse effects must be taken into thorough consideration.\(^{31}\)

When reviewing studies evaluating the efficacy of various treatment modalities for BCC, critical attention must be paid to the length of follow-up. Due to the slow growth
rate of BCC, recurrences are frequently diagnosed beyond 5 years following definitive treatment. As an illustrative example, in a multi-center randomized trial comparing MMS to 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. \cite{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, including standard excision, MMS, and C&E. Non-surgical therapies, including radiotherapy and cryosurgery are addressed separately.

*Standard excision*

Basal cell carcinoma, regardless of the histological 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” histopathological 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. \cite{17} In this study, the local recurrence rate after excision of BCC with positive margins was 26.8% (72/269), compared to 5.9% (176/3002) following excision with histologically negative margins. However, no RCT comparing different excision margins for BCC have been performed. Based on 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, pre-and postauricular, temple and ear), aggressive/infiltrative histological growth pattern, recurrent tumor, and extension beyond the reticular dermis.\textsuperscript{17-21} According to current NCCN guidelines, location of BCC in the H-zone constitutes high risk, independent of size.\textsuperscript{3} Multiple RCT have been published comparing standard surgical excision of BCC to topical medical therapy, C&E, photodynamic therapy (PDT), cryotherapy, radiation therapy, and MMS.\textsuperscript{32,34-39} All studies consistently reported low recurrence rates after standard excision of BCC with predominantly non-aggressive histological growth patterns. Excision of nodular or superficial BCC with 3-4 mm margins in low-risk anatomic locations was associated with 2-4\% recurrence rates after 3-5 years.\textsuperscript{35,38-40} In a study comparing standard excision to C&E followed by cryosurgery for non-aggressive BCC on the head and neck, 5-year recurrence rates were 8.2\% and 17.6\%, respectively.\textsuperscript{36} Recurrence rates following surgical excision were uniformly significantly lower than 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-year follow-up.\textsuperscript{32} When evaluating cosmetic outcome following various treatment modalities, the appearance after standard excision was consistently judged more favorable than after C&E or cryotherapy.\textsuperscript{31,41} While two studies reported better cosmetic outcomes following PDT compared to 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).\textsuperscript{35,37}
Based on the available data, the workgroup recommends standard excision with 4 mm margin of uninvolved skin around the tumor and/or biopsy site to a depth of the mid subcutaneous adipose tissue with histological margin assessment for low-risk primary BCC (based on NCCN risk stratification, Table 7; level of evidence/strength of the recommendation in Table 8). 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 precludes 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 graft, or healing by second intention are 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 7. The strength of these recommendations is shown in Table 8.

Mohs Micrographic Surgery

Dr. Frederic Mohs first described the use of chemosurgery for the removal of difficult or recurrent cutaneous tumors in the 1940s.\textsuperscript{42,43} Three decades later, the concept of \textit{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.\textsuperscript{44} This modification eliminated the pain from \textit{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 Mohs
micrographic surgery (MMS), was recommended by the authors for all recurrent or
poorly defined tumors, sclerosing BCC, and for all primary cutaneous carcinomas in
areas with a predilection for recurrence.\textsuperscript{45}

Since that time, the use of MMS for the 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.\textsuperscript{28} Until recently,
available data in support of the widespread use of MMS for BCC was limited to case
series and meta-analyses. In systematic reviews of the literature dating back to the
1940s, Rowe \textit{et al}, reported 5-year recurrence rates for MMS of 1\% and 5.6\% for
primary and recurrent BCC, respectively.\textsuperscript{46,47} In comparison, recurrence rates for other
treatment modalities, including standard excision, C&E, radiation therapy, and
cryosurgery ranged from 7.5-10.1\% and 9.8-40\% for primary and recurrent BCC,
respectively. The first RCT for MMS was conducted in the Netherlands, comparing
MMS to standard excision of primary and recurrent facial BCC. Findings were initially
reported by Smeets \textit{et al}, in 2004 and later updated with 5- and 10-year recurrence
rates in 2008 and 2014, respectively.\textsuperscript{32,33,48} In the final analysis, a 10-year recurrence
rate of 4.4\% was reported for primary facial BCC treated with MMS, compared to 12.2\%
(p=0.100) following standard excision. For recurrent BCC, 10-year recurrence rates
were 3.9\% and 13.5\% (p=0.023) after MMS and standard excision, respectively.\textsuperscript{32} Cox-
regression analysis identified an aggressive histological growth pattern as a significant
risk factor for recurrence.\textsuperscript{48} 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 based on factors such as anatomical location and histological 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<0.001) than after standard excision (116.6 vs 187.7 mm²). Smeets et al, reported that for tumors requiring more than one standard excision, or at least two stages of MMS, defects after excision were significantly larger than after MMS for primary and recurrent BCC. While smaller defects did not lead to significant differences in aesthetic outcome between MMS and standard excision in RCT, both surgical modalities were found to be superior with regard to quality of life outcomes compared to C&E.

A noteworthy limitation of MMS is that tissue blocks are not available for molecular testing or further evaluation of high-risk or unusual features using paraffin sections. To overcome this challenge, the tumor debulk specimen may be submitted for paraffin sections to document high-risk features and obtain ancillary molecular studies if indicated, without compromising the integrity of the MMS procedure. Careful selection, based on initial biopsy results, of tumors appropriate for treatment with MMS will minimize these limitations.

Based on the available data, it is the workgroup recommendation that MMS is indicated for the treatment of high-risk BCC (based on NCCN risk stratification, Table 7; level of evidence/strength of recommendation Table 8).

* Curettage and electrodessication*
No randomized trials have been published comparing C&E alone or to other surgical treatments for BCC. However, this simple procedure, quickly and easily performed in an office setting, has been successfully used by dermatologists for decades to treat BCC.\textsuperscript{46,52} When carefully selected for low-risk primary lesions (Table 4, NCCN risk stratification), C&E is one of the recommended treatment options for BCC. Lesions on terminal hair-bearing skin (scalp, pubic, axillary regions, and beard area in men) should be excluded from treatment with C&E due to potential follicular extension of tumor.\textsuperscript{3} While excellent cure rates can be achieved by experienced clinicians for selected low-risk tumors particularly off the head and neck, results are considered highly operator and location dependent.\textsuperscript{53,54} Moreover, C&E may be associated with a longer healing time and inferior cosmetic outcome compared to standard excision, and is best avoided in cosmetically sensitive areas.\textsuperscript{55}

**NON-SURGICAL 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 (e.g. 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 non-surgical therapies for BCC. Regimens combining different non-surgical treatment modalities have been used but are not well-studied. Head-to-head comparative effectiveness trials of various non-
surgical approaches are limited in number and scope. The recommendations for non-
surgical treatments are shown in Table 9, level of evidence/strength of the
recommendations in Table 10.

**Cryosurgery**

Given the lack of histological margin control and known subclinical extension of
BCC, cryosurgery (interchangeably referred to as cryotherapy) should only be
considered under select clinical circumstances, 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. Randomized controlled trials comparing cryosurgery to a variety
of other treatment modalities (MAL and ALA PDT, standard excision, and radiation
therapy) reported recurrence rates for cryosurgery ranging between 6.3% at one year to
39% after two year follow-up.\(^{41,56-58}\) Cryosurgery may be considered for low-risk BCC
when more effective therapies are contraindicated or impractical.\(^2\)

**Topical therapies**

Topical imiquimod, an immunomodulator, is FDA-approved for treatment of
superficial BCC on the trunk, neck, and extremities. Various regimens of imiquimod
have been used in practice, including twice daily, once daily, and every other day
applications; applications have been performed with and without occlusion, for
treatment courses ranging from 6 to 16 weeks.\(^{59-69}\) Overall, rates of 3-12 month clinical
and histologic cure have been reported to range from 60 to 80% in well-designed RCT,
with the highest rates reported for shorter follow-up and clinical cure. Moderate to
severe local treatment-associated adverse events include skin redness, swelling,
erosions, crusts, vesicles, itching, and occasionally, tingling sensations. 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. Multiple dosing approaches have been used, suggesting that adjustment
of dosing is reasonable based on tolerance. Once-every-other-day treatment, possibly
including a treatment holiday during the weekend or during 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 five times a week for 6 weeks or
longer is a routine regimen that balances patient acceptance and effectiveness. Case
report data suggest imiquimod may be used in selected cases for pretreatment prior to
surgical removal of high risk BCC or as adjuvant treatment for incompletely resected
tumor.

Monotherapy with topical 5-FU, an antimetabolite, for superficial BCC is less
well-studied in well-designed RCT. Typical regimens include twice daily application
for 3-6 weeks. Adverse events are similar to those with imiquimod, including 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, influencing decreased compliance resulting in decreased
effectiveness. Promising pilot studies have suggested short-term clearance for low-risk
tumors. Sixteen-week clinical clearance rates of 50-90% have been seen, depending
on the topical formulation used. 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 basal cell carcinoma is weak, and recommended that these approaches be reserved for patients with small tumors in low-risk locations 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 one adverse event.75

Photodynamic therapy

Photodynamic therapy for BCC is a two-part treatment consisting of topical application of a photosensitizer, either 5-ALA or MAL, followed by one to several hours of incubation by light irradiation, typically with a blue, red, or broadband light source.35,38,60,74,76-83 Application of the photosensitizer is often preceded by light curettage of BCC.79 Usually a single treatment cycle is performed at a time, but treatments may be repeated.

There is evidence that aggressive, repeated PDT may have effectiveness for small, well-demarcated nodular BCC. In two small RCT, nodular BCC (no larger than 5 mm in diameter) were treated with MAL-PDT after curettage and 3 hours incubation. Non-responding lesions were retreated at 1 week with a second cycle of PDT. Histological response was 73% in the treatment group.78 In a similar study, 2 PDT illuminations were performed with ALA-PDT after debulking of nodular BCC, with cumulative recurrence 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 60-70%, and improved response, when light irradiation is fractionated into 2
periods of illumination. Studies directly comparing ALA-PDT and MAL-PDT have reported similar effectiveness for BCC with these therapies. Post-treatment adverse events including photosensitivity, and the consequent need for light avoidance and photoprotection for 48 hours, erythema, edema, tenderness, and occasionally crust or erosions. 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.

Three-year follow-up results of an ongoing large RCT demonstrated imiquimod is superior and topical 5-FU is comparable to MAL-PDT for superficial BCC. Likelihood of tumor-free status at 3 years was 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 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 due to a dearth of studies.

So-called ‘field treatment’ is designed to treat small incipient BCC within an anatomic area or region. Topical treatments have been reported to be effective for combatting field cancerization. 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 with debulking or curettage, as well as when they are delivered repeatedly.\textsuperscript{35,38,79} Cure rates after surgical excision are 10-20\% 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.\textsuperscript{79}

\textit{Radiation Therapy}

While surgery remains the first line, and most effective treatment for BCC, primary radiation therapy can be used in special situations when surgery is not feasible, contraindicated, or not preferred by the patient after a discussion of risks and benefits.\textsuperscript{24,34,58,86-88} Several different types of radiotherapy can be used to treat BCC, including superficial radiation therapy, brachytherapy (interstitial, or topical contact), or 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.\textsuperscript{24,34,58,86-88} 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.\textsuperscript{89} Brachytherapy traditionally used custom molds and catheters, which either conformed to the external contours of the skin or penetrated the skin to treat deeper tumors (e.g., interstitial
approach). High-dose rate (HDR) brachytherapy is generally more practical for patients because of the shorter treatment time. More recently, so-called electronic brachytherapy has been used as a purely topical delivery modality. In the US, 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 clinical apparent recurrence used to estimate short- and medium-term tumor control rates. Post-radiation 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.

While adjuvant radiation has been recommended in patients with high risk BCC, no randomized trial 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 is lacking regarding the safety and effectiveness of pulsed dye or of Er:YAG laser for treatment of BCC.

**MANAGING PATIENTS WITH METASTATIC BCC**
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. 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. 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 RECIST (Response Evaluation Criteria in Solid Tumors). After 12 months of additional follow-up, the objective response rate increased to 33%. While all 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. 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 or referred to best supportive and palliative care, to optimize symptom
management and maximize quality of life.

Locally destructive tumors, typically associated with long delays in presentation,
are encountered more often than metastatic BCC and may present a significant
therapeutic dilemma. While surgery and radiation therapy remain the gold 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.95 Patients had at least one tumor ≥10 mm in diameter, which was
considered inoperable or inappropriate for surgery in the opinion of a specialist in MMS,
head and neck, or plastic surgery. Inoperable or inappropriate for surgery was defined
as either (1) the recurrence of BCC after two 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.96 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%.97 Notably, 180 (36%) of 499 patients in the STEVIE trial
discontinued treatment due to adverse events, 108 (22%) were recorded to have
serious adverse events and among 31 deaths during the trial, 21 were the result of
adverse events. 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 due to adverse events and seven patients (one with metastatic and six 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. At the 12-month analysis of the BCC Outcomes with LDE225 Treatment (BOLT) trial, 44-58% overall response rates were found in patients with locally advanced BCC and 8-17% in patients with metastatic BCC. There is initial evidence that patients resistant to one SMO inhibitor may be resistant to another. While the same limitations regarding adverse events and drug resistance apply, SMO inhibitors may be considered for patients with nevoid basal cell carcinoma (Gorlin) syndrome with excessively numerous or aggressive BCC.

For localized BCC, the overwhelming majority of tumors are readily treated with local treatment modalities, including surgery, radiation therapy, or topical therapy. If surgery and radiation therapy are contraindicated or inappropriate for the treatment of locally advanced tumors, or 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 workgroup 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 11 and the level of evidence/strength of the
recommendations are in Table 12.

**FOLLOW-UP AND REDUCING RISK OF FUTURE SKIN CANCERS**

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

A 2010 meta-analysis by Wheless and colleagues determined that the summary
random-effects relative risk (SRR) of developing a second NMSC after diagnosis of a
first was 1.12 (based on 12 cohort studies from cancer registries) and 1.49 based upon
3 studies with patient level data. 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 one. At 10 years the chances increased to
59.6% of another NMSC after the first and 91.2% after diagnosis of a non-first NMSC.

Initial diagnosis of BCC increases the risk of subsequent malignant melanoma
(MM). Song and colleagues found a relative risk of 1.99 for men and 2.58 for women of
developing MM after diagnosis of a NMSC. This data was based upon two 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
a BCC.

Patients who have had BCC should be counseled regarding the risk of 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 (e.g., the back) that are not easily assessed by the patient.\textsuperscript{105}

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.\textsuperscript{106,107} 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 of 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 of subsequent BCC in patients with prior 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,\textsuperscript{108} or BCC in those with Gorlin-Goltz syndrome.\textsuperscript{109} In addition, topical retinoids used for prolonged periods were associated in a single study with increased mortality, although some investigators have discounted this result as spurious.\textsuperscript{110} 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.\textsuperscript{111-114}
Limited evidence is available to support the utility of other agents, including oral nicotinomide, α-difluoromethylornithine, and celecoxib, in reducing the risk of keratinocyte cancer in patients with history of BCC. There is early evidence from a small trial that oral nicotinomide may reduce the risk of subsequent keratinocyte carcinoma in transplant patients with prior such cancer. There is also some evidence that α-difluoromethylornithine (DFMO), an irreversible inhibitor of the pathway that produces polyamines in humans, may reduce the risk of BCC in those with prior history of keratinocyte cancer, although treatment-associated audiometric abnormalities have been reported. While 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 cardiovascular event risk associated with this medication.

The dietary supplements beta-carotene and selenium have also been studied, and are not recommended for reducing risk of BCC or cSCC in patients with prior history of BCC. Several RCT have shown no protective benefit against NMSC associated with either beta-carotene or selenium. Treatment-associated adverse events, notably skin yellowing with beta-carotene use, and gastrointestinal upset with selenium have been noted.

Recommendations for the follow-up of BCC patients and recommendations to reduce the risk of future tumors are found in Table 13; level of evidence/strength of recommendation in Table 14.

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. While the treatment of localized tumors is usually successful, significant gaps in research were identified with regard to the identification of non-invasive treatment modalities with comparable recurrence rates to 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 high-level evidence. Management of BCC should therefore always be tailored to meet individual patients’ needs.

REFERENCES


**Publishable Conflict of Interest Statement**

The American Academy of Dermatology (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...
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.

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 PI for Eli Lily, Janssen-Ortho, Novartis, and Regeneron receiving grants/research funding.

Jeremy S. Bordeaux, MD, MPH served as an advisor board member for Lubax receiving honoraria; as an emplyee of Massachusetts General Hospital receiving salary; and in other 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, Celleraion, and Kerecis receiving fees; as a PI for Valeant receiving grants/research funding; and as a Data Safety Monitoring Board member for DermaSciences, Macrocur, and Sanofi/Regeneron receiving fees.
Stanley Miller, MD served as an employee of UpToDate, Inc. receiving patent royalties/other compensation.

Eliot Mostow, MD, MPH served as a consultant for Elsevier receiving salary; as a speaker and PI for Healthpoint receiving honoraria and grants/research funding; 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/other compensation, and as a PI for Amgen receiving fees. Dr. Mowad also had a relative serving as an employee of Takeda Pharmaceuticals receiving salary.

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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 YS 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 relationships to disclose.
Table 1. 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, harms, and effectiveness/efficacy of available treatments for BCC and cSCC?
  - Surgical treatment
    - Standard Excision
    - Mohs Micrographic Surgery
    - Curettage and Electrodesiccation
    - Cryosurgery
  - Topical therapy
    - Fluorouracil
    - Imiquimod
    - Other
  - Energy devices
    - Laser
    - Photodynamic therapy*
    - Radiation therapy
- What are effective treatment options for the management of advanced BCC and cSCC?
  - Hedgehog inhibitors*
- What are the effective methods for follow-up and preventing recurrence and new primary keratinocyte cancer formation?
  - Oral and topical retinoids
  - Celecoxib
  - α-difluoromethylornithine
  - Selenium
  - Beta-carotene

* BCC only
Table 2: Recommendation for grading and staging of BCC

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

Table 3: Level of evidence and strength of recommendations for grading and staging, biopsy, clinical information and pathology report for the treatment of BCC

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grading and Staging</td>
<td>C</td>
<td>III</td>
<td>2,3</td>
</tr>
<tr>
<td>Biopsy</td>
<td>B</td>
<td>II</td>
<td>11-16</td>
</tr>
<tr>
<td>Clinical Information Provided to Pathologist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age</td>
<td>A</td>
<td>I, II</td>
<td>17-19,21-25</td>
</tr>
<tr>
<td>- Gender</td>
<td>B</td>
<td>I, II</td>
<td>18,20,21,23-25</td>
</tr>
<tr>
<td>- Anatomic location</td>
<td>B</td>
<td>I, II</td>
<td>17,21,23-26</td>
</tr>
<tr>
<td>- Recurrent lesion</td>
<td>A</td>
<td>I, II</td>
<td>17,18,23,24</td>
</tr>
<tr>
<td>- Size of lesion</td>
<td>A</td>
<td>I, II</td>
<td>17,18,20,22-26</td>
</tr>
<tr>
<td>- Immunosuppression</td>
<td>B</td>
<td>I, II</td>
<td>22,27</td>
</tr>
<tr>
<td>- Prior history, esp radiation, burn, organ transplant</td>
<td>B</td>
<td>II</td>
<td>27</td>
</tr>
<tr>
<td>Pathology Report Elements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Histologic subtype</td>
<td>B</td>
<td>II</td>
<td>17,19,26,28</td>
</tr>
<tr>
<td>- Invasion beyond reticular dermis</td>
<td>B</td>
<td>II</td>
<td>17,19</td>
</tr>
<tr>
<td>- Perineural involvement</td>
<td>C</td>
<td>III</td>
<td>3,29,30</td>
</tr>
</tbody>
</table>
### Table 4. National Comprehensive Cancer Network stratification of low versus high risk BCC

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location¹/Size</td>
<td>Area L &lt; 20 mm</td>
<td>Area L ≥ 20 mm</td>
</tr>
<tr>
<td></td>
<td>Area M² &lt; 10 mm</td>
<td>Area M ≥ 10 mm</td>
</tr>
<tr>
<td></td>
<td>Area H³</td>
<td></td>
</tr>
<tr>
<td>Borders</td>
<td>Well defined</td>
<td>Poorly defined</td>
</tr>
<tr>
<td>Primary vs Recurrent</td>
<td>Primary</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Site of prior radiation therapy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Pathological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth pattern</td>
<td>Nodular, superficial⁴</td>
<td>Aggressive⁵</td>
</tr>
<tr>
<td>Perineural involvement</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

¹Area L = trunk and extremities (excluding hands, feet, nail units, pretibia and ankles).
²Area M = cheeks, forehead, scalp, neck, and pretibia.
³Area H = central face, eyelids, eyebrows, periorbital skin, nose, lips, chin, mandible, pre- and postauricular skin/sulci, temple, ear, genitalia, hands, and feet.
⁴Location independent of size may constitute high risk.
⁵Area H constitutes high risk based on location, independent of size.
⁶Other low-risk growth patterns include keratotic, infundibulocystic, and fibroepithelioma of Pinkus.
⁷Having morpheaform, basosquamous (metatypical), sclerosing, mixed infiltrative, or micronodular features in any portion of the tumor.
Table 5: 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 upon 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.

Table 6: Recommendations for clinical information and pathology report for suspected BCC

**Clinical information provided to pathologist:**
- **Strongly recommended**
  - Age
  - Gender
  - Anatomic location
  - Recurrent lesion
- **Recommended**
  - Size of lesion
  - Immunosuppression
  - Prior 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
Table 7: 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.

Table 8: Level of evidence and strength of recommendations for the surgical treatment of BCC

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment plan</td>
<td>A</td>
<td>II</td>
<td>31,41</td>
</tr>
<tr>
<td>C&amp;E for low-risk tumors</td>
<td>B</td>
<td>I, II</td>
<td>25,31,36,46,47,55,59</td>
</tr>
<tr>
<td>Standard excision w/ 4mm margins:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-risk BCC</td>
<td>A</td>
<td>I</td>
<td>35-41,88,123,124</td>
</tr>
<tr>
<td>High-risk BCC</td>
<td>C</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>MMS for high-risk BCC</td>
<td>A</td>
<td>I, II</td>
<td>17,32,33,46-49</td>
</tr>
</tbody>
</table>
Table 9: Recommendations for the non-surgical 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 (e.g. imiquimod or 5-FU), MAL- or ALA-PDT, and radiation therapy (e.g. 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 based on 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.

Table 10: Level of evidence and strength of recommendations for the non-surgical treatment of BCC as alternatives to surgical therapy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryosurgery</td>
<td>A</td>
<td>I</td>
<td>36,41,56-58,88,125</td>
</tr>
<tr>
<td>Topical therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Imiquimod</td>
<td>A</td>
<td>I</td>
<td>39,60-69,74-76,88</td>
</tr>
<tr>
<td>- 5-FU</td>
<td>B</td>
<td>I, II</td>
<td>60,74-76,88,126,127</td>
</tr>
<tr>
<td>- Dose adjustments</td>
<td>A</td>
<td>I</td>
<td>39,64,66</td>
</tr>
<tr>
<td>PDT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ALA</td>
<td>A</td>
<td>I, II</td>
<td>38,57,74,76,80-85,123,128</td>
</tr>
<tr>
<td>- MAL</td>
<td>A</td>
<td>I, II</td>
<td>35,37,56,60,74,76-78,80,84</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Traditional radiotherapies and modern superficial radiation therapy</td>
<td>B</td>
<td>I, II</td>
<td>24,34,46,47,58,88,129</td>
</tr>
<tr>
<td>- Electronic surface brachytherapy</td>
<td>C</td>
<td>II, III</td>
<td>91,130</td>
</tr>
<tr>
<td>Laser therapy</td>
<td>C</td>
<td>II</td>
<td>74,92,131</td>
</tr>
</tbody>
</table>
Table 11: Recommendations for managing locally advanced or metastatic BCC

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multidisciplinary consultation and smoothened inhibitors are recommended for</td>
<td>A</td>
<td>I, II</td>
<td>95-99,132,133</td>
</tr>
<tr>
<td>patients with metastatic BCC.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If treatment of metastatic BCC with smoothened inhibitors is not feasible,</td>
<td>B</td>
<td>I</td>
<td>134</td>
</tr>
<tr>
<td>platinum-based chemotherapy or best supportive care is recommended.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If surgery and radiation therapy are contraindicated or inappropriate for the</td>
<td>C</td>
<td>III</td>
<td>94</td>
</tr>
<tr>
<td>treatment of locally advanced BCC, or residual tumor persists following surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and/or radiation therapy and further surgery and radiation therapy are</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>contraindicated or inappropriate, systemic therapy with a smoothened inhibitor</td>
<td></td>
<td></td>
<td>Expert opinion</td>
</tr>
<tr>
<td>should be considered.</td>
<td></td>
<td></td>
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<tr>
<td>Patients with advanced disease should be provided or referred for best</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>supportive and palliative care, to optimize symptom management and maximize</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>quality of life.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 12: Level of evidence and strength of recommendations for the management of metastatic BCC
Table 13: Recommendations for the follow-up of BCC and reducing risk of 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-exam and sun protection.

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

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

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

Table 14: Level of evidence and strength of recommendations for the follow-up of BCC and reducing risk of future tumors

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual follow-up skin cancer screening</td>
<td>A</td>
<td>I</td>
<td>101-104,135-137</td>
</tr>
<tr>
<td>Against the use of topical and oral retinoids:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tretinoin</td>
<td>A</td>
<td>I, II</td>
<td>108,110,138</td>
</tr>
<tr>
<td>Acitretin</td>
<td>B</td>
<td>I</td>
<td>114</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>A</td>
<td>I</td>
<td>111,112</td>
</tr>
<tr>
<td>Oral retinol</td>
<td>A</td>
<td>I</td>
<td>112,113</td>
</tr>
<tr>
<td>Against dietary supplementation with:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenium</td>
<td>A</td>
<td>I</td>
<td>120,121</td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>A</td>
<td>I</td>
<td>122</td>
</tr>
<tr>
<td>Chemoprevention of BCC:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>B</td>
<td>I</td>
<td>118,119</td>
</tr>
<tr>
<td>DFMO</td>
<td>A</td>
<td>I</td>
<td>116,117</td>
</tr>
<tr>
<td>Oral nicotinamide</td>
<td>B</td>
<td>I</td>
<td>115</td>
</tr>
</tbody>
</table>