Basal Cell Carcinoma Review

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KEYWORDS

• Basal cell carcinoma • BCC • NMSC • Nonmelanoma skin cancer • Mohs • MMS

KEY POINTS

- Basal cell carcinoma (BCC) is the most common malignancy and the incidence and associated costs are rising.
- For superficial tumors or patients who cannot tolerate surgery, topical and nonsurgical methods are available.
- Large or aggressive histologic tumors or those arising in high-risk areas should be treated with Mohs micrographic surgery or excision with complete peripheral and deep margin assessment.
- For locally advanced or metastatic tumors, or patients with a genetic predisposition for BCC, systemic treatment with hedgehog inhibitors may be warranted.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common malignancy and the incidence is rising.[1] BCCs have low mortality but can cause significant morbidity primarily through local destruction.[2] The pathogenesis is linked to the interplay between environmental and patient-derived characteristics. There are multiple therapeutic modalities, and appropriate selection requires knowledge of complications, cosmetic outcomes, and recurrence rates. This article reviews the epidemiology, staging, treatment, and prevention of BCC.

INCIDENCE

BCC is the most common malignancy in the United States and the incidence is increasing by 4% to 8% annually, which is heavily influenced by cumulative sun exposure and an aging population.[1,3] An estimated 5.4 million nonmelanoma skin cancers

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(NMSCs) were diagnosed in 3.3 million patients in 2012.[4] Despite the high incidence rate, the metastasis and age-adjusted mortality rates are estimated at only 0.0028% to 0.5% and 0.12 per 100,000, respectively.[5] Unpublished data from Brigham and Women's Hospital suggest, however, that the risk of metastasis and death is 6.5% in tumors greater than or equal to 2 cm.[6]

Burden of Disease

From 2007 to 2011, an estimated $4.8 billion was spent on keratinocytic carcinomas annually.[7] In 2013, approximately $715 million was spent on direct BCC care in Medicare beneficiaries.[8] A study estimating both direct (health care, out-of-pocket, and informal caregiver costs), indirect (decreased productivity/output), and intangible (loss of health-related quality of life) costs in 2011 in Canada estimated the total cost per BCC to be $4312.[9]

Pathogenesis

The patched/hedgehog intracellular signaling pathway is responsible for regulating cell growth, and constitutive activation of this pathway leads to BCC development.[10] The most common mutations are inactivating mutations of *PTCH1* or activating mutations of *SMOm*, which cause aberrant hedgehog pathway activation and tumor formation. A loss-of-function mutation in *SUFU*, a negative regulator of the hedgehog pathway, has also been identified in a small portion of BCCs.[11] Other common mutations include UV-specific defects in the *p53* tumor suppressor gene, which are present in half of BCCs.[11]

RISK FACTORS

BCCs are more common in Fitzpatrick skin types I and II, with a lifetime risk estimated at 30%. BCC risk is also associated with light eye color, freckles, and blonde or red hair.[1] UV radiation exposure is the most important environmental risk factor. Other risk factors include childhood sunburns, family history of skin cancer, tanning bed use, chronic immunosuppression, photosensitizing drugs, ionizing radiation, and exposure to carcinogenic chemicals, especially arsenic.[1,12–15] Childhood and intense and intermittent sun exposure has a strong correlation to BCC development.[12,16]

Immunosuppression

The estimated incidence of BCC is double in HIV-positive patients and 5-times to 10-times greater in organ transplant patients.[17] Approximately half of organ transplant recipients develop a BCC during the 10 years after transplant and tumors are more likely to be the thinner, superficial histologic subtype and occur in younger patients.[18] Methotrexate use in patients with rheumatoid or psoriatic arthritis has been shown to have a dose-response relationship with BCC incidence.[19]

Genetic Syndromes

Multiple BCCs is the hallmark of basal cell nevus syndrome (BCNS).[20] BCNS is caused by loss of *PTCH1* protein function. This defect causes constitutive activation of hedgehog signaling and tumor cell proliferation.[21] Although most cases of BCNS are inherited in an autosomal dominant manner, approximately 26% to 50% of cases are de novo.[21] Xeroderma pigmentosums a rare autosomal recessive disorder due to defects in nucleotide excision repair pathway proteins. BCC is the most common malignancy and typically diagnosed in the first decade of life.[22] Bazex-Dupre-Christol syndrome is a rare X-linked dominant disorder that presents

with follicular atrophoderma, hypohidrosis, hypotrichosis, milia, and multiple facial BCCs that first appear in the third and fourth decades.[23]

HISTOLOGIC SUBTYPES

Lower-risk histologic subtypes[24–26]:

- Superficial BCC is an indolent variant that often has a multifocal pattern. Lesions are pink, scaly, thin plaques that can mimic eczema or psoriasis.
- Nodular BCCs are the most common variant. Tumors present as well-defined, pearly, translucent papules or nodules with rolled borders and telangiectasias. Dermoscopy shows arborizing vessels, large blue-gray ovoid nests, and multiple blue-gray dots.
- Pigmented BCC is a subtype of nodular BCC that is more common in individuals with Fitzpatrick skin types III to VI. Dermoscopy can highlight the pigment globules, which help differentiate pigmented BCCs from melanocytic lesions.

Higher-risk histologic subtypes[26–28]:

- Morpheaform (sclerosing) BCCs have higher rates of recurrence and perineural invasion. Tumors present as a depressed, waxy, scarlike plaques, often accompanied by ulceration.
- Infiltrative BCC is associated with higher rates of perineural invasion and recurrence.
- Micronodular BCCs are composed of dispersed micronodules whereas nodular BCCs are composed of aggregated nodules.
- Basosquamous carcinoma behaves more similarly to squamous cell carcinoma (SCC). Basosquamous carcinoma histologically consists of BCC and SCC in different areas with a transition zone of mixed differentiation, distinguishing this tumor from collision tumors.

GRADING AND STAGING

There is no formal BCC staging system. Prior to the seventh edition of the American Joint Committee on Cancer (AJCC), BCC staging was grouped with all NMSC. The AJCC seventh edition created a distinct staging system for SCC that excluded BCCs. The most useful stratification framework is provided by the National Comprehensive Cancer Network (NCCN), which differentiates localized tumors at low-risk versus high-risk for recurrence.

Clinical Factors

Anatomic location is a known risk factor for BCC recurrence. The appropriate use criteria for Mohs micrographic surgery (MMS) and NCCN guidelines designate 3 body areas for risk stratification based on primary tumor location. Area H is considered the high-risk location, independent of tumor size. Tumors arising in the M and L areas can be classified as high risk, depending on the size, histologic subtype, and poorly defined borders. BCCs developing in the setting of immunosuppression and recurrent tumors, irrespective of prior therapy, are also considered high-risk.[24,26]

Pathologic Factors

Micronodular, infiltrative, sclerosing, and morpheaform histologic subtypes are more likely to recur than nodular or superficial BCCs.[29] Perineural involvement (PNI) is rare with an incidence of less than 1% but is an independent risk factor for recurrence and

is more common with aggressive subtypes.[30] One prospective multicenter case series found the 5-year recurrence rate of BCCs with PNI after MMS to be 7.7%.[30] MRI should be considered to evaluate nerve involvement if patients exhibit neurologic symptoms.

New Classification System

Data from the unpublished Brigham and Women's Hospital cohort found that head and neck location (odds ratio [OR] 5.3; 95% CI, 1.2–23.2), depth beyond fat (OR 28.6; 95% CI, 6.7–121), and tumor diameter greater than or equal to 4 cm (OR 11.9; 95% CI, 2.4–59.4) were significant predictors of metastasis and death.[6] A T classification system (T1, T2, and T3) has been developed based on these characteristics. T3 tumors are greater than or equal to 2 cm and contained at least 2 of the 3 high-risk factors. The 10-year cumulative incidence rates of local recurrence and metastasis or death were 47% (95% CI, 28%–70%) and 37% (95% CI, 21%–60%), respectively, in this cohort.

TREATMENT

BCC treatment is primarily directed at local control given its low metastatic potential. When comparing the cure rates for treatments based on different studies, several factors should be considered, including the duration of follow-up and the percentage of high-risk and recurrent tumors. For example, due to the slow growth rate of BCCs, recurrences are often diagnosed after 5 years.[31] The recurrence rate in a randomized controlled trial (RCT) of surgical excision was 3% and 12% at 2.5 years and 10 years, respectively, and 56% of recurrences occurred more than 5 years post-treatment.[32]

Surgical Excision

The NCCN recommends 4-mm clinical margins for low-risk tumors treated with standard excision with postoperative margin assessment (SEPMA).[33] Primary tumors of any size on the neck, trunk, and extremities have in excess of 95% 5-year cure rate.[34] Rates of incomplete excisions are estimated at 3% to 16.6% and are associated with a recurrence rate of approximately 38%.[35] Surgical excision is less effective for BCCs arising in the H-area possibly due to narrower margins used, more aggressive histology, or increased subclinical spread.[36]

Mohs Micrographic Surgery

MMS has superior long-term cure rates compared with other treatment modalities and is the treatment of choice for high-risk and recurrent BCCs. The 5-year recurrence rates for primary and recurrent BCCs treated with MMS are 1% and 5.6%, respectively, compared with 10.1% and 17.4%, respectively, for SEPMA.[37] The 10-year recurrence rates in the only RCT comparing MMS with SEPMA for primary facial BCCs were 4.4% for MMS and 12.2% for SEPMA (P = .10) for primary BCCs.[32] For recurrent BCCs, the 10-year recurrence rates were 3.9% and 13.5% (P = .023) for MMS and SEPMA, respectively.[32] The high cure rate is due to the complete peripheral and deep margin assessment (CCPDMA), where approximately 100% of the margin is assessed, whereas standard vertical sectioning evaluates approximately 1% of the margins.[38] In 2012, the appropriate use criteria for MMS were released and guidelines for BCC are summarized in **Table 1**.[26]

Table 1
Appropriate use criteria for treatment of basal cell carcinoma with Mohs micrographic surgery

Basal Cell Carcinoma Subtype	Area H	Area M	Area L
Primary superficial BCC	Appropriate	Appropriate • If ≥0.6 cm for non-IC • Any size if IC	Not indicated[a]
Primary nodular BCC	Appropriate	Appropriate	Appropriate • If >1 cm for non-IC • If >2 cm IC
Primary high-risk BCC	Appropriate	Appropriate	Appropriate[a] • If >0.5 cm
Recurrent BCC	Appropriate	Appropriate	Appropriate (except for superficial subtype)[a]

Abbreviation: IC, immunocompromised.

[a] Mohs surgery is indicated, regardless of lesion size or superficial histology, under special clinical circumstances, including previously irradiated field, genetic syndromes, chronic ulcer or inflammation, and traumatic scar.

Adapted from Connolly SM, Baker DR, Coldiron BM, et al. AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery. J Am Acad Dermatol 2012;67(4):542; with permission.

Curettage and Electrodessication

Curettage and electrodessication (CE) is recommended by the NCCN for properly selected, low-risk tumors. CE is fast and cost-effective; however, it does not allow for histologic margin assessment and is operator-dependent.[39] Areas with terminal hair growth should be avoided due to the risk of follicular tumor extension. Larger lesion diameter and high-risk anatomic sites have been shown to be independent factors for recurrence. A study of more than 2300 BCCs found a 5-year recurrence rate of 3.3% (standard error [SE] = 1.5%) for lesions of any diameter treated in the L area. For tumors in the M area, the 5-year recurrence rates were 5.3% (SE = 2.7%) and 22.7% (SE = 7.2%) for BCCs with diameters of less than 10 mm or greater than 10 mm, respectively. For BCCs in the H area, the 5-year recurrence rates were 4.5% (SE $\leq$ 2.6%) and 17.6% (SE $\leq$ 5.4%) for tumors less than 6 mm or greater than 6 mm, respectively.[40] Patients treated with CE have reported worse cosmetic outcomes compared with MMS.[41]

Cryosurgery

Cryosurgery is a fast, destructive technique but lacks histologic assessment of tumor margin. The goal is to achieve -50°C to the tumor with a surrounding margin of 3 mm to 5 mm. Although multiple large case series report cures rates of 94% to 99%, careful patient and tumor selection is essential and should be reserved to superficial and low-risk tumors.[42]

Photodynamic Therapy

Photodynamic therapy (PDT) with aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) have similar outcomes and pain scores when used to treat nodular BCC.[43] Cure rates range from 70% to 90%, although approximately all studies have short follow-up periods.[44,45] The 5-year recurrence rates in an RCT were 30.7%

(95% CI, 21.5%–42.6%) for ALA-PDT and 2.3% (95% CI, 0.6%%–8.8%) for surgical excision ($P < .0001$). When stratified by tumor thickness, however, the ALA-PDT cure rate approached 95% for primary thin nodular BCCs ($\leq$0.7-mm thick).[46] PDT should be considered for patients with superficial BCCs, in particular those with extensive/multifocal disease or diffuse actinic damage.

Radiation

Radiation therapy (RT) can be considered a primary therapy in patients for whom surgery is contraindicated or for tumors that are unresectable. The NCCN recommends adjuvant RT for any BCC with large caliber or extensive PNI.[24] RT is generally reserved for patients over 60 years of age and is contraindicated in patients with predisposing genetic syndromes, such as BCNS, due to their risk of other ionizing radiation-induced malignancies.[47] Retrospective studies report 5-year recurrence rates up to 27.7% for BCCs.[48] RT tends to be more effective for treating tumors that are primary (vs recurrent), less than 1 cm, and have less aggressive histologic subtypes.[49,50] RT is also associated with poorer cosmetic outcomes and more postoperative complications.[51]

Topical Therapies

Imiquimod and fluorouracil creams are approved by the US Food and Drug Administration (FDA) to treat superficial BCCs. The recommended treatment regimen for imiquimod is a once-daily application 5 days per week for 6 weeks to 12 weeks and has been associated with up to 81% cure rates.[52] An RCT comparing the efficacy of imiquimod, fluorouracil, and MAL-PDT for the treatment of superficial BCC found that at 3 years, imiquimod (tumor-free survival: 79.7%; 95% CI, 71.6%–85.7%) was superior to MAL-PDT (tumor free survival: 58.0%; 95% CI, 47.8%–66.9%) and fluorouracil (tumor-free survival: 68.2%, 95% CI, 58.1%–76.3%).[53] Topical therapies are associated with adverse side effects, including erythema, swelling, and erosions, which can limit compliance and decrease effectiveness. Use should be limited to superficial BCCs and small tumors in low-risk locations that cannot undergo treatment with more definitive therapies.[52]

Systemic Therapies

Although a majority of BCCs are easily cured with local treatment, a subset of patients, including those with BCNS and locally advanced or metastatic disease, require systemic treatment. In 2012, the FDA approved vismodegib, a first-in-class hedgehog pathway inhibitor, for the treatment of locally advanced or metastatic BCCs.[54] Approval was granted based on the clinical efficacy demonstrated in the ERIVANCE phase 2 study (**Tables 2** and **3**).[55] Objective responses of 48% and 33% for patients with locally advanced and metastatic disease, respectively, were reported at 21-month follow-up.[56] Nearly all patients treated with vismodegib experienced at least 1 adverse effect, including muscle spasms, alopecia, dysgeusia, weight loss, fatigue, or diarrhea. Grade 3 or 4 adverse effects occurred in 25% of patients.[57] A double-blind randomized phase 2 study of patients with BCNS found that vismodegib significantly reduced the incidence of new BCCs and the size of existing tumors. Unfortunately, only 17% of patients tolerated vismodegib continuously for the full 36-month study duration. Vismodegib can be taken with or without food and does not require laboratory work prior to or after initiation.[54] There are reports, however, of hepatotoxicity, so caution should be taken in patients with severe liver disease.[58]

Sonidegib, the second hedgehog pathway inhibitor, is approved by the FDA for treatment of locally advanced BCCs that recur after surgery or RT or who are not candidates for surgery or radiotherapy. The phase 2 Basal Cell Carcinoma Outcomes with

Table 2
Efficacy of sonidegib and vismodegib in patients with locally advanced basal cell carcinoma

	Sonidegib, 200 mg	Vismodegib, 150 mg		
	BOLT 12-mo Analysis	ERIVANCE 21-mo Analysis	Vismodegib Expanded Access	STEVIE
Minimum follow-up	12	21	Not reported	12
Patients, n	42	71	56	453
Objective response rate	43%	48%	46%	67%
Time to response, median	3.9	Not reported	2.6	2.6
Duration response, median	Not reached	9.5	Not reported	22.7
Progression free survival, median months (% progressed)	Not reached (12%)	9.5 (3%)	Not reported (0%)	24.5 (2%)

Times are reported in months.
Abbreviation: STEVIE study, Safety Events in Vismodegib.
Data from Refs.[56,59,66,67]

LDE225 Treatment (BOLT) trial found response rates of 44% to 58% for locally advanced BCC and 8% to 17% for metastatic BCC (see **Tables 2** and **3**).[59] Nearly all patients experienced at least 1 adverse effect with elevated creatinine kinase and lipase the most common grade 3 or grade 4 adverse effects. Sonidegib should be taken on an empty stomach and should not be administered concomitantly with strong and moderate CYP3A inhibitors.[60]

Two main limitations to hedgehog pathway inhibitor therapy are the high frequency of adverse effects and development of tumor resistance. Intermittent dosing regimens have been trialed as a way to minimize side effects while not compromising efficacy.[61] Patients with BCNS respond to vismodegib and have a low acquired resistance.[62] Advanced and metastatic BCC patients, however, have lower overall response rates (approximately 48%) and an estimated 20% develop resistance during their first year.[63]

Table 3
Efficacy of sonidegib and vismodegib in patients with metastatic basal cell carcinoma

	Sonidegib, 200 mg	Vismodegib, 150 mg		
	BOLT 12-mo Analysis	ERIVANCE 21-mo Analysis	Vismodegib Expanded Access	STEVIE
Minimum follow-up	12	21	Not reported	12
Patients, n	13	33	39	29
Objective response rate	15%	33%	31%	38%
Time to response, median	4.6	Not reported	2.6	2.8
Duration response, median	Not reached	7.6	Not reported	10
Progression free survival, median months (% progressed)	13.1 (31%)	9.5 (13%)	Not reported (8%)	13.1 (14%)

Times are reported in months.
Abbreviation: STEVIE, Safety Events in Vismodegib.
Data from Refs.[56,59,66]

Anti–programmed death-1 (PD-1) immunotherapy is another emerging treatment option for advanced BCC. A clinical trial investigating cemiplimab, a fully human anti–PD-1 monoclonal antibody, in patients with locally advanced or metastatic BCC who experienced progression of disease or stable disease on or who cannot tolerate hedgehog pathway inhibitor therapy is under way.

FOLLOW-UP AND PREVENTION

Patients with a history of BCC are at risk for additional skin cancers, including NMSC and melanoma.[64] A prospective cohort study of 1426 patients found the risk for subsequent NMSC to be 40.7% (95% CI, 36.5%–45.2%) after a first and 82% (95% CI, 80.2%–83.7%) after more than 1 NMSC at 5 years.[64] Thus, continued long-term surveillance of patients with a history of BCC is essential. The NCCN recommends skin examinations at least every 6 months to 12 months for the first 2 years after BCC diagnosis and then reduced to annually if appropriate.[24] Patients also should be educated about UV protection.[65]

SUMMARY

BCC is a slowly growing tumor that can generally be cured easily with office-based surgical methods. For superficial tumors or patients who cannot tolerate surgery, topical and nonsurgical methods are available. Large or aggressive histologic tumors or those arising in high-risk areas should be treated with MMS or excision with CCPDMA. For locally advanced or metastatic tumors, or in patients with a genetic predisposition for BCC, systemic treatment with hedgehog inhibitors may be warranted. Close follow-up for early diagnosis and treatment of subsequent BCCs is essential.

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