Basal Cell Carcinoma

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KEYWORDS

• Basal cell carcinoma • Diagnosis • Treatment • Management • Prevention

KEY POINTS

- Basal cell carcinoma incidence is increasing globally.
- Diagnosis is made using clinical recognition, emerging imaging techniques, and gold standard histopathologic evaluation.
- Surgical management including Mohs micrographic surgery in high-risk tumors is the most effective treatment, although alternatives including radiation, systemic, and topical therapies exist for specific situations.
- Systemic treatments for locally advanced and metastatic basal cell carcinoma include Hedgehog pathway inhibitors, targeted checkpoint therapy, among others.

INTRODUCTION

Epidemiology

Basal cell carcinoma (BCC) is the most common type of cancer in the world. In the United States, the 2012 annual estimated incidence ranged from 2.7 to 4.3 million cases.[1,2] Lifetime risk of developing BCC in the United States is 20% or greater overall, and 30% or greater for whites.[3,4] Age-adjusted BCC incidence rates in the United States have more than doubled during 2 decades.[5] Increasing annual incidence of BCC has additionally been reported globally.[6–9]

PATIENT EVALUATION OVERVIEW

Determining Patient Risk Factors

The probability of developing a BCC varies considerably based on a patient's phenotype, environmental exposures, and genetic predisposition. Many of these risk factors are intertwined by a common pathogenic link, which is exposure and susceptibility to ultraviolet radiation (UVR).

Phenotypic risk factors include male sex, red or blond hair, fair skin, pale eyes, skin that burns and never tans, and higher number of moles.[5,10–12] Multiple studies have shown that those with Fitzpatrick type I or type II skin types have relative risks of developing BCC between 2 and 4.[13–15] Type III skin alone is only a risk factor if the patient additionally has a history of severe sunburns.

Significant exposures that should be part of assessing an individual's risk include higher number of severe or blistering sunburns and higher levels of cumulative UVR, especially if it occurs during childhood or adolescence.[5,10,16] The risk for BCC may be more strongly linked to intermittent sun exposure as compared with squamous cell carcinoma (SCC), which is more heavily influenced by chronic regular sun exposure.[11,15,16] Indoor tanning bed use is a dose-related risk factor, especially for early-onset BCC.[17–19]

Occupational and iatrogenic ionizing radiations are risk factors for the development of BCC.[20] Younger age of radiation therapy (RT) and higher doses both correlate with increasing risk of BCC as well as total number of BCC.[20–22] RT for childhood malignancy such as lymphoma is a significant risk factor for developing BCC. When compared with pediatric patients with cancer who did not undergo RT, patients who received 35 Gy or greater had 40-fold increased risk of BCC.[23] Solid organ transplant and psoralen and ultraviolet A (UVA) are additional iatrogenic risks factors for BCC, although to a lesser extent than SCC.[24,25]

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Clinical Evaluation

Despite the description of more than 26 different BCC subtypes, most tumors can be classified into 4 distinct clinicopathologic subtypes: nodular, superficial, morpheaform, and fibroepithelial (fibroepithelioma of Pinkus).[26] Nodular BCC is the most common subtype, and it presents as a pearly papule with rolled borders and arborizing vessels. Superficial BCC is more common in younger patients and on the trunk.[27,28] Morpheaform BCC have a sclerotic or indurated appearance and are often poorly demarcated. Fibroepithelioma of Pinkus is a rare but unique variant, which can seem as a smooth flat plaque or pedunculated papule on the lower trunk; some debate whether it is a trichoblastoma subtype given its relatively indolent course.

High-Risk Basal Cell Carcinomas

Most BCC have a low risk of recurrence or metastasis and are treated conservatively with destructive procedures or surgery.[29] Both patient and tumor characteristics are used to risk stratify patients to guide management.

The National Comprehensive Cancer Network guidelines have indicated that a BCC should be considered high-risk if any of the factors listed in **Table 1** are present.

Table 1
National Comprehensive Cancer Network guidelines high-risk basal cell carcinomas [29]

Tumor factors	• ≥2 cm on trunk or extremities • Any size lesion located on head, neck, feet, pretibial leg, or anogenital region • Recurrent tumor • Poorly defined tumor • Perineural involvement • Aggressive histopathologic subtype (infiltrative, micronodular, morpheaform, basosquamous, sclerosing, or carcinosarcomatous differentiation)
Patient factors	• Prior RT to area • Solid organ or hematopoietic transplant • Immune deficiencies (congenital, HIV/AIDS, or autoimmune) • Treatment with immunosuppressive therapies • Patients with cancer on immunotherapies or checkpoint inhibitors

Abbreviations: HIV/AIDS, human immunodeficiency virus (HIV) / acquired immunodeficiency syndrome (AIDS)
Original table using previously published information.

Staging of Basal Cell Carcinoma

The American Joint Committee on Cancer (AJCC) eighth edition tumor staging for BCC located on the head and neck include the following[30]:

- T1—Less than 2 cm in greatest diameter
- T2—2 cm or greater but less than 4 cm in greatest diameter
- T3—4 cm or greater in greatest diameter or minor bone invasion or perineural invasion or deep invasion
- T4a—Tumor with gross cortical bone and/or marrow invasion
- T4b—Tumor with skull bone invasion and/or skull base foramen involvement

The Brigham and Women's Hospital (BWH) tumor classification system for BCC was developed as a more specific staging system.[31] BWH prioritized significant risk of metastasis and/or death and determined the following tumor stages:

- T1—Tumor diameter of less than 2 cm or tumor diameter of 2 cm or greater with 0 or 1 risk factor*
- T2—Tumor diameter of 2 cm or greater with 2 or 3 risk factors*

*Risk factors: Tumor diameter of 4 cm or greater, head and neck location, and depth beyond fat.

Within the BWH cohort of high-grade tumors the AJCC eighth edition and BWH tumor staging had equal sensitivity but BWH had higher specificity (92% vs 80%) and higher positive predictive value (24% vs 11%) for recognizing tumors at risk for metastasis and/or death.[31] The risk of metastasis or death in the BWH T1 cohort was 0%, which was significant compared with the 37% risk in the T2 cohort.[31]

Metastatic Basal Cell Carcinoma

Metastatic BCC (mBCC) is exceedingly rare, and unfortunately, not well documented in registries. The most common sites of metastasis in descending order are lymph nodes (LN; 53%), lung (33%), bone (20%), skin/subcutaneous (11%), and liver (4%).[32–35] Average time to death after diagnosis of LN metastasis is 3.6 to 7.3 years, whereas extranodal metastases survival is 8 to 24 months, although advances in therapy likely increase survival.[32,34–36]

There is an estimated 1.9% to 6.5% risk of metastasis and/or death in patients with primary tumors 2 cm or greater in diameter.[34,37] Primary tumors 4 cm or greater are 11.9 times more likely to lead to metastasis and/or death compared with tumors 2 to 3.9 cm in diameter.[34,37] The strongest predictor of metastasis and/or death in primary tumors 2 cm or greater is extension beyond fat, which independently increased the risk by a factor of 28.6.[37] Head and neck locations were nearly 12 times more likely to have metastasis or lead to death.[32,35,37] In patients with BCC 2 cm or greater, the risk of metastasis and death in those with underlying nevoid basal cell carcinoma syndrome (NBCCS) is 50%, and in nonsyndromic patients with prior RT, the risk is 22%.[37]

Noninvasive Diagnostics

Dermoscopy

Dermoscopy is a common clinical tool to aid in the identification of BCC. Some highly predictive BCC features seen with dermoscopy include arborizing vessels, blue and pink stromal hue, translucency, blue/gray ovoid nests, and if pigmented, leaf-like and spoke-wheel structures. Systematic review and meta-analysis of the reported accuracy of dermoscopy for BCC show a pooled sensitivity of 89% to 91% and specificity of 95%.[38] The combination of clinical examination in conjunction with dermoscopy outperforms clinical examination alone, with a sensitivity of 85% compared with 67%.[38] As with any diagnostic test, there are limitations to dermoscopy, most notably the skill level of the user.[38]

Reflectance confocal microscopy

Reflectance confocal microscopy (RCM) focuses a beam of near infrared light at specific target within the skin, which is then reflected through a pinhole, to a highly sensitive detector. Multiple captured points within the tissue are combined to produce high-resolution images of in vivo skin.[39]

RCM requires highly specialized training for accurate diagnosis. Experienced providers using RCM can diagnosis BCC with a sensitivity of 91.7% and specificity of 91.3%.[40] A randomized controlled trial designed in real-world application compared RCM versus punch biopsy in the diagnosis and subtyping of BCC. This trial showed equivalent sensitivity in BCC diagnosis (99%) but RCM had inferior specificity (59% vs 100%) and was less sensitive in detecting aggressive BCC subtypes compared with standard of care punch biopsy (33.3% vs 77.3%).[41] RCM is limited by required training, high cost, and limitations of only viewing the upper dermis.

Optical coherence tomography

Optical coherence tomography (OCT) takes advantage of the differences in optical properties exhibited by structures in the skin. An image is produced by using the summation of refracted infrared light. OCT images have relatively less resolution than RCM but can reach a much greater depth (1.5 mm vs 200 μm). Prospective cohort studies evaluating OCT accuracy of BCC diagnosis with in vivo tissue demonstrated a sensitivity ranging from 79% to 94% and specificity ranging from 85% to 96%.[42–44] OCT has exhibited utility in delineating surgical margins but real-world clinical use is limited by poor resolution, expense, and required training.[45]

BASAL CELL CARCINOMA TREATMENT

Low-Risk Basal Cell Carcinoma Treatment

Although treatments should be individualized, in general low-risk BCC are denoted by the absence of any high-risk features (see **Table 1**).

Curette and electrodesiccation

Curette and electrodesiccation (C&E) involves using a curette to delineate tumor margins and removing tumor down to level of dermis. Electrodessication is then used to destroy residual neoplastic cells. This is traditionally performed with 3 cycles of alternating C&E. Problems include the lack of histopathologic margin assessment; hence, it is recommended only for superficial lesions lacking terminal hair follicles. Treatment efficacy is largely based on observational and retrospective data, which is additionally limited by inadequate follow-up. Reported C&E recurrence rates vary from 4% to 27%.[46–50] If during C&E the clinician reaches subcutaneous tissue, the contrast in tumor and surrounding stroma is lost, and the procedure should be discontinued and substituted for treatment that will provide a surgical margin evaluation.

Standard excision

Low-risk tumors are often treated with excision with 4-mm clinical margins. This standard excision technique has shown recurrence rates less than 5% in low-risk BCC.[47,51,52] In facial BCC, which by location alone are considered high-risk, the recurrence rate at 10 years is 12.2%.[53] Postoperative margin assessment is required. Intraoperative surgical margin assessment should be obtained if surgical closure will require tissue rearrangement or skin graft, due to concern for residual tumor seeding and risk of higher risk recurrence.[29,54]

Table 2
Alternative basal cell carcinoma treatments

Treatment	Dosing	Efficacy	Side Effects
Imiquimod 5% cream	Apply daily 3–5 d per week, for 6 wk[a]	70%–85% clearance in sBCC[55–58]	Local sclerosis, ulceration, vesiculation, flu-like symptoms
5-FU cream	Apply twice daily for 6 wk	64% 5-y clearance rate in sBCC[57,58]	Local crusting, pruritus, edema, pain
Cryosurgery[b]	Two freeze cycles of 25–30 s each, separated by 2–4-min thaw period	Recurrence rates vary from 19% to 39% in prospective trials[59–61]	Poor cosmetic outcomes, ulceration, pain, scarring, pigment changes
PDT	Topical application of photosensitizer (5-ALA or MAL) followed hours after by exposure with blue, red, or broadband light irradiation. Treatment repeated for incomplete response	86.4% complete clearance rate and 10.3% 1-y recurrence rate[62]	Local pain, burning, pruritus, crusting, bleeding

Abbreviations: 5-ALA, 5-aminolevulinic acid; 5-FU, 5-Fluorouracil; MAL, methylaminolevulinic acid; PDT, Photodynamic therapy; sBCC, superficial basal cell carcinoma.
[a] Frequency dependent on patient tolerability.
[b] High variability reliant on provider experience and tumor characteristics.

Alternative treatments

Due to lower efficacy, alternative treatments are reserved for extenuating situations when standard of care treatment is not feasible. Treatments are summarized in **Table 2**.

High-Risk Basal Cell Carcinoma Treatment

Mohs micrographic surgery

High-risk BCCs have propensity to extend beyond the clinical margins, penetrate deeper tissues, or are in areas critical to function or cosmesis, where standard excision margins are not possible. For these reasons, Mohs micrographic surgery (MMS) is the most effective treatment because intraoperative complete margin evaluation before reconstruction is required. In the treatment of primary BCC, MMS provides lower 5-year recurrence rates compared with standard excision (1.0% vs 10.1%).[63] Similar benefit is seen when comparing recurrence rates in the treatment of recurrent BCC (5.6% vs 17.4%).[64] **Fig. 1**A demonstrates the initial clinically identified BCC. **Fig. 1**B demonstrates the subclinical extent of the tumor identified on MMS. **Fig. 1**C, D demonstrates the same day surgical repair followed by 6-month follow-up.

Radiation therapy

RT is most often used as an alternative when patient or tumor factors preclude surgical treatment. Treatments take place over a series of weeks. Randomized controlled studies comparing radiotherapy versus excision show greater than 10-fold higher failure rates and significantly worse cosmetic outcomes in those who received radiation as judged by both clinicians and patients.[65,66]

Postoperative RT is recommended for tumors with either clinical or radiologic perineural extension or following surgical lymphadenectomy for nodal metastasis.[29,67] RT can be considered in the setting of positive surgical margins not amendable to surgery, BCC recurrence, and locally advanced BCC (LaBCC) with bone or muscle infiltration.[67]

Considerations for RT include age due to the risk of long-term sequelae of radiation. Additionally, genetic syndromes that predispose patients to developing skin cancer should avoid RT. A history of connective tissue disease is an additional relative contraindication.

Locally Advanced and Metastatic Basal Cell Carcinoma Treatment

In rare circumstances in which BCC spreads beyond the cure of surgery or RT, systemic treatments are needed. The Hedgehog (HH) pathway is normally quiescent in adulthood but in embryonic development plays a role in cell proliferation and differentiation.[68,69] HH ligands are extracellular signaling molecules that interact with protein

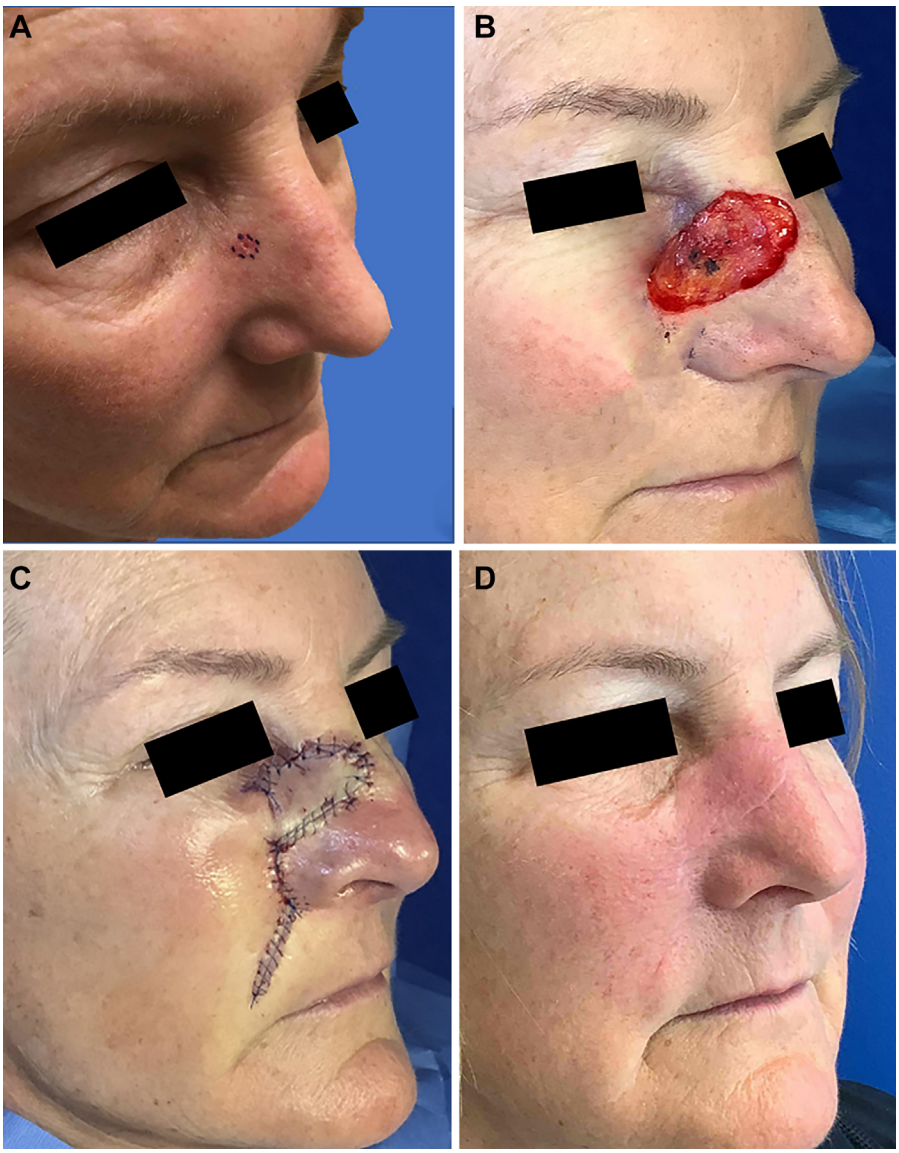

Fig. 1. (*A*) The initial clinically identified BCC. (*B*) The subclinical extent of the tumor identified on MMS. (*C*) Same day reconstruction. (*D*) Follow up 6 months after surgery.

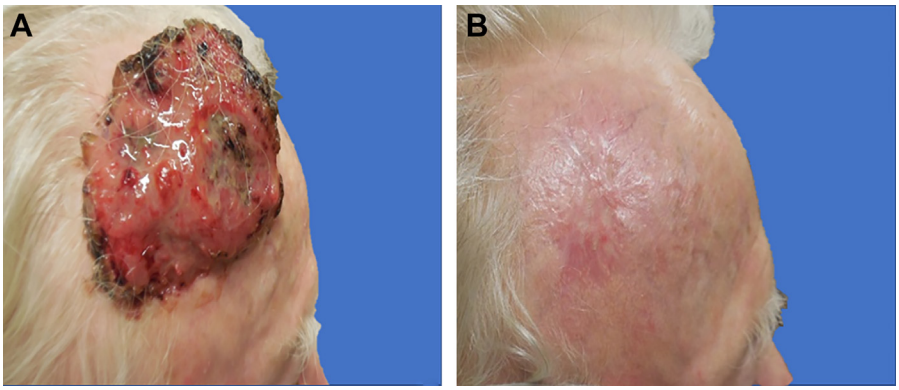

Fig. 2. Shows a LaBCC at initial presentation (*A*) and after treatment with SMO antagonist (*B*).

Table 3
Systemic treatments for locally advanced and metastatic basal cell carcinoma

Drug (Class)	LaBCC Response	mBCC Response	Side Effects and Considerations
Vismodegib (selective SMO antagonist)	• 31%–32% complete[a] • 29%–35% partial • 24%–37% stable • 2%–10% progression	• 0%–4% complete • 30%–48% partial • 42%–48% stable • 6%–11% progression	• Muscle spasms • Alopecia • Taste disturbances • Weight loss • Fatigue • Gastrointestinal disturbance • Embryofetal toxicity Note: Nearly one-third of patient discontinue therapy due to side effect
Sonidegib (selective SMO inhibitor)	• 3% complete • 54% partial • 42% stable • 1% progression	• 0% complete • 15% partial • 82% stable • 3% progression	
Cemiplimab (PD-1 inhibitor)	• 6% complete • 25% partial • 49% stable • 22% progression	• 0% complete • 21% partial • 36% stable • 25% progression	• Fatigue • Hypertension • Pruritus • Colitis • Pneumonitis • Endocrinopathy

[a] Patients with NBCCS have improved response (46% with complete response).

patched homolog 1 (PTCH1) receptor. The interaction of HH ligand and PTCH1 receptor results in activation of smoothened (SMO), ultimately leading to the activation of downstream proteins and gene transcription.[69] Abnormal HH signaling is present in 95% of BCC including the loss of PTCH1 function or activating mutation of SMO leading to constitutionally activated HH pathway.[68,69] In NBCCS, germline mutations of *PTCH1* gene are prototypical. HH pathway inhibitors are first-line treatments in LaBCC and mBCC. **Fig. 2** shows a LaBCC at initial presentation (2A) and after treatment with SMO antagonist (2B). Systemic treatments for advanced disease are summarized in **Table 3**.

Additional treatments: Itraconazole, which has HH signaling inhibitory properties, and combination carboplatin and paclitaxel have both been reported in the treatment of mBCC, although conclusions are limited to small reports and exploratory trials.[70,71]

Prevention

Sun protection is highly recommended for the prevention of skin cancers. Surprisingly, results from a randomized controlled trial evaluating daily sunscreen use in Australia compared with discretionary use of sunscreen found no difference in BCC diagnoses.[72,73] Although the strength of sunscreen (sun protection factor 15), the length of follow-up (4.5 years), among other factors may have diluted the results. Regardless, sun protection starting at a young age is still recommended.

Nicotinamide successfully reduces nonmelanoma skin cancers and actinic keratoses. When isolating BCC alone, nicotinamide reduced the rate of diagnosis by 20% although this was not statistically significant.[74] With nicotinamide dosing of 500 mg twice daily, there are minimal safety concerns; thus, it may be recommended due to potential benefit.

BASAL CELL CARCINOMA FOLLOW-UP

Patients diagnosed with BCC are at increased risk of developing additional BCC, as well as developing SCC and melanoma.[75–77] Estimates suggest within 3 years of BCC diagnosis there is a nearly 30-fold risk of subsequent BCC and 14-fold risk of SCC. For these reasons, after BCC diagnosis, we recommend a total body skin examination 1 to 2 times annually with subsequent changes in frequency based on additional skin cancer diagnosis. In high-risk patients or patients with high-risk tumors, increased skin surveillance may be warranted.

SUMMARY

BCC is the most common cancer globally and the rate of incidence is increasing. Patient risk factors for BCC include susceptibility to and high exposures to UVR. Identification can be made on clinical examination, which is enhanced with dermoscopy. Several novel imaging techniques have been studied, although utility and justification for widespread clinical use is unproven. Tumors can be delineated into low-risk or high-risk BCC,

which guides appropriate treatment. Surgical management including MMS for high-risk tumors is the most effective treatment. RT can be considered in patients not amendable to surgery. SMO inhibitors are first-line treatment of LaBCC and mBCC. Future directions should be aimed at prevention, earlier detection, and treatment of advanced disease.

CLINICS CARE POINTS

- Clinical examination aided by dermoscopy increases recognition and diagnosis of BCC
- Margin assessment is essential: in low-risk BCC, postoperative margin assessment should be obtained, and in high-risk BCC, intraoperative margin assessment is indicated
- Newer oral (vismodegib, sonidegib) or intravenous agents (cemiplimab) are the recommended treatment in LaBCC and mBCC

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DISCLOSURE

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