



REVIEW

Basal Cell Carcinoma: A Narrative Review on Contemporary Diagnosis and Management

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ABSTRACT

Basal cell carcinoma (BCC) is the most common, accounting for 80–90% of skin cancers. It arises from the basal layer of the epidermis and its appendages. A complex interplay of environmental, phenotypic and genetic variables leads to the development of BCC. Literature has documented several clinical subtypes of BCC, the most common of which are nodular, superficial and morpheaform. Expedient diagnosis and analysis are essential for improving the outcome of BCC. Preventive measures, particularly when implemented in childhood and adolescence, may play a critical role. Due to its low metastatic potential, treatment for BCC mostly focuses on local management. The standard treatment of basal cell carcinoma involved complete removal

of the lesion by excision or Mohs surgery. In special circumstances, basal cell carcinoma can be treated with cryosurgery, electrodesiccation and curettage, topical medications and photodynamic therapy. This review aimed to evaluate the contemporary diagnosis and management of basal cell carcinoma.

Keywords: Basal cell carcinoma; Diagnosis; Management; Surgical excision

Key Summary Points

Inspection by a physician and dermoscopy are used to make a preliminary diagnosis of basal cell carcinoma. Biopsy with histopathologic examination confirms the diagnosis.

The pathologic diagnosis with classification as low- or high-risk basal cell carcinoma will guide treatment. Low-risk basal cell carcinomas are removed by surgical excision or Mohs surgery, the latter with facial lesions or in areas where conserving normal adjacent tissue is required.

Metastatic or unresectable BCC can respond to treatment with Hedgehog pathway inhibitors, and because of its tumor mutation burden, it can respond to immune checkpoint inhibitors.

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common type of skin cancer [1]. Due to its low mortality rate, cancer registries in many countries do not include data on BCC; however, according to data from insurance registries and official statistics, the annual incidence of BCC in the USA is estimated to be 4.3 million [2]. The Caucasian population has a much higher prevalence of BCC. The incidence of BCC is inversely proportional to a country's geographic latitude and its inhabitants' pigment status [3]. Similar rates of incidence have been discovered in Canada, Europe and Asia, with Australia having the highest rate globally. Even though the incidence trend in Australia appears to have reached a plateau, the rate is consistently growing in all other continents, including South America and Asia. A systematic review by Perera et al. [4] reported that Australia has the highest incidence of non-melanoma skin cancer worldwide. The incidence was higher for men than women and higher for BCC than SCC. Incidence was diverse covering the states of Australia, with the highest in Queensland. However, the aggressive slip, slop, slap campaign has made a significant difference revealing substantial benefits for skin cancer prevention interventions [5]. In Europe, the incidence has risen at a rate of 5% per year over the last decade compared to approximately 2% in the USA. Due to improved diagnosis and an aging population with anamnestic ultraviolet (UV) exposure, this epidemiologic trend is projected to continue in the near future [1–3]. The incidence of BCC increases dramatically after 40 years of age, although lately, there has been an increase in its incidence among the younger population, particularly women, as a result of increased UV exposure from the sun or artificial sources [6]. The current review aims to evaluate the contemporary methods of detection and integrated treatment of basal cell carcinoma. This article is primarily based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Pathogenesis and Risk Factors

The Patched/Hedgehog intracellular signaling pathway controls cell proliferation, and its constant activation contributes to the development of BCC [7]. Inactivating mutations in PTCH1 and activating mutations in SMOM are the most prevalent mutations, resulting in abnormal Hedgehog pathway activation and tumor development. In a small percentage of BCCs, a loss-of-function mutation in SUFU gene, a negative regulator of the Hedgehog pathway, has been discovered [8]. UV-specific abnormalities in the p53 tumor suppressor gene, which are seen in half of BCCs, are another prevalent mutation [8].

Fitzpatrick skin types I and II are more likely to develop BCCs, with a lifetime risk of 30%. Light eye color, freckles and red hair are all associated with a higher risk of BCC [8]. The most significant environmental risk factor is exposure to UV radiation. Childhood sunburns, family history, photosensitizing medicines, ionizing radiation, the use of tanning beds, chronic immunosuppression and exposure to carcinogenic substances, particularly arsenic, are all risk factors [9–13]. The development of BCC is strongly linked to childhood and severe and intermittent sun exposure [10, 14].

DIAGNOSIS OF BASAL CELL CARCINOMA

Inspection is first process for diagnosis of BCC followed by dermoscopy with confirmation by biopsy and histopathologic examination. Photography of the lesion is also important so that the surgeon performing the definitive procedure can locate the site. Wrong site definitive procedures are the biggest error in this process [15, 16]. Skin biopsy is still necessary to verify the clinical interpretation. BCCs are distinguished histologically by the multiplication of propagating homogeneous basaloid cells with a hyperchromatic nucleus and a small quantity of poorly defined cytoplasm, peripheral palisading and retraction artifact [17]. While the basaloid cells are morphologically similar to epidermal basal cells, they behave similarly to follicular

germinative cells [18, 19]. BCC has a variety of clinicopathologic forms, including nodular, infiltrative, fibroepithelial, morpheaform and superficial, all of which have specific clinicopathologic characteristics. Micronodular and basosquamous BCCs are the two most histopathologically important subtypes, and the treatment options may vary according to the type of BCC.

Patients with BCC benefit from standardized follow-up because it allows for early diagnosis of local recurrence and secondary malignancies. It should be carried out in a risk-stratified manner: Isolated, surgically treated BCC and low recurrence risk: follow-up after 6 months to rule out local recurrence, then once a year. Multiple BCCs, high recurrence risk, laBCC, mBCC, syndromes: follow-up every 3 months. Follow-up once a year if no new BCC or recurrence has occurred in the previous 2 years. Closer follow-up may be performed in individual cases [20].

SUPERFICIAL TYPE

The superficial variety of BCC (sBCC) is usually found on the torso and limbs and accounts for approximately 20% of all BCCs [21]. The lesions are well-circumscribed, light reddish spots or thin plaques, ranging from micrometers to centimeters in width. A thin rolling border or central atrophy are other characteristics, but other lesions show just erythema and slight scale resembling a nummular eczema patch [21, 22]. Structureless hypopigmentation, short fine telangiectasia, multiple erosions, varying chromatism and a pearly crimson backdrop are all typical findings on dermoscopic inspection [16, 23]. Histologically, several minuscule enclaves of neoplastic cells adhere to the substratum of the epidermis and are generally restricted to the papillary dermis. The nests may be surrounded by a thin zone of fibrous stroma [17, 24] (Fig. 1).

NODULAR TYPE

Nodular BCC (nBCC) accounts for 60–80% of all BCCs, often appearing on the head and neck

[21, 25]. Usually, this neoplasm manifests as burl growth with thin vascular channels or transparent papules or pearly, and these lesions are often ulcerated and eroded with crusting whether large tumors or small. The nodule is commonly reported to have convoluted perimeters, suggesting that the boundaries are higher than their centers. Ulceration may be observed in larger lesions. Ramified vascular avenues and a pearly crimson backdrop are common findings on dermoscopic inspection [16, 23]. Nodular lesions are distinguished by an abnormal growth of basaloid cells that create enormous tumor nests with peripheral palisading and random central organization. The presence of retraction gaps between tumor nests and the surrounding stroma is frequently observed [17, 24] (Fig. 2).

INFILTRATIVE TYPE

BCCs of the infiltrative type are frequently found in conjunction with other categories, particularly the nodular form. Clinically, they appear as weakly defined, white or blanched dull rosy plaques that are thick, hardened, depressed or flat. There may also be ulcerations, erosions, crusts and papules on the surface [21]. On histopathology, proliferation of basaloid cells results in tumor nests with a palisading pattern around the edges, which may be seen superficially. On the periphery or base, permeating areas with extended strings of malignant cells without a fencing sequence can be detected [17, 24] (Fig. 3).

MORPHEAFORM (SCLEROSING, DESMOPLASTIC) TYPE

Morpheaform type BCC is seen on the face and neck, accounting for 5–10% of all BCCs [25]. The poorly defined edges of flesh-colored infiltrating plaques resemble cicatrization [21]. Short, thin telangiectasia, structureless and pigment-less pale dull pink plaques are all common findings on dermoscopic examination [23]. Thin protracted filaments and tiny archipelagos of neoplasms are histopathologically

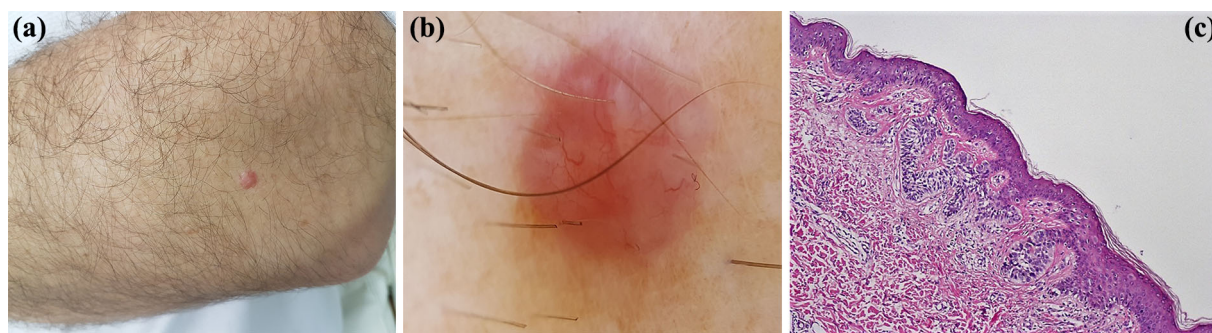


Fig. 1 **a** Clinical photograph of a 42-year-old male patient with a pink-colored, slowly growing nodule on the left forearm for 1 year. **b** Dermoscopy revealed arborizing telangiectasia. No gray-blue ovoid nests or globules were seen. The provisional clinical diagnosis was basal cell carcinoma. Elliptical excision biopsy with a 3-mm free margin was done under local anesthesia after obtaining written informed consent from the patient. The histopathology report suggested complete excision of the basal cell carcinoma. **c** Histopathology examination

revealed basaloid epithelial cells in the epidermis, typically formed palisades with cleft formation in the basaloid epithelium and crowded nuclei with scattered mitotic figures. The nests remain confined to the papillary dermis, and the lesion seemed to be completely excised from all margins. No lymphatic or perineural invasion was seen. The diagnosis was superficial basal cell carcinoma with free margins, and the lesion was excised completely (H&E staining with $\times 10$ magnification)

surrounded by a sclerotic collagenous stroma [17, 24] (Fig. 4).

PIGMENTED BCCS

BCCs with pigmented characteristics due to basal cells which produce melanin, leading to a brown clinical coloration, which can be present in all subtypes, are referred to as pigmented BCCs [26]. Asians and Africans are more likely to have pigmented lesions, while Caucasians are less likely to have them. Despite this, dermoscopic inspection reveals that about 30% of BCCs categorized as “non-pigmented BCC” include pigmented structures [27]. The lesions are histologically strongly associated with the dermoscopic findings, resulting in the identification of two brackets. The principal structure appears brown in color, signifying pigmentation at the dermo-epidermal junction. Surface and penetrating BCC are characterized by rosette-shaped areas and coaxial formations. Subsequent structures that appear blue or gray in color indicate pigmentation in the deeper layers of the dermis. Several pigmented variegated areas are diagnostic of this variety [28, 29] (Fig. 5).

FIBROEPITHELIAL TYPE

This unusual variation most commonly affects the lower back. It appears as a soft papule or pedunculated papulonodular lesion with a skin-colored or erythematous appearance, similar to a fibroma or papilloma [21]. Fibroepithelial-type BCC has a prominent loose stroma and is made up of thin anastomosing strands of basaloid cells. The proliferation index of tumor cells is high [17, 24] (Fig. 6).

MANAGEMENT

Surgical Excision

Archetype surgical excision is the treatment of choice for low-risk BCCs [30, 31]. Three- to 4-mm free surgical boundaries are generally acceptable for tumor elimination in small (< 2 cm) BCCs [32, 33]. Clinical practice recommendations have proposed 4-mm clear brims [34]. The reappearance rate of BCCs following standard excision is usually modest, with the 5-year recurrence rates for low-risk lesions ranging from 0.7 to 5% [30, 32, 35–38]. Since local anatomy is altered as a result of

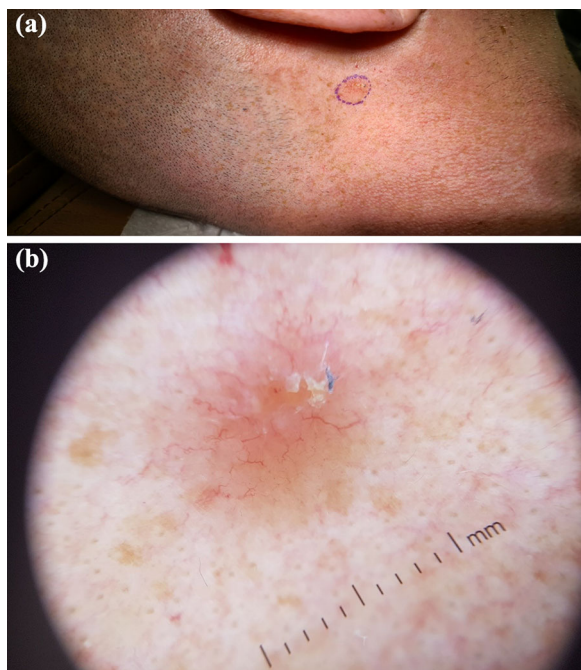


Fig. 2 **a** Clinical photograph of a 47-year-old female patient with a pinkish brown, slowly growing erythematous plaque over the right post-auricular upper neck region. The patient reported a gradual change in its size and color over the last 1 year; it had apparently become darker. **b** Dermoscopy revealed an asymmetrical pattern with irregular margins and arborizing tree-like telangiectasis in the central and peripheral areas. The provisional diagnosis was basal cell carcinoma. Elliptical excisional biopsy under local anesthesia with a 4-mm free margin was done after obtaining all consents. The histopathology report was suggestive of completely excised nodular basal cell carcinoma

tissue reorganization, linear closure or secondary intention healing should ideally be used to complete the reconstruction. Intra-surgery tumor margin evaluation should be performed to ensure tumor elimination [34]. Nonsurgical therapy may be explored in patients with non-aggressive, low-risk BCCs [34]. Individuals who are not surgical candidates may benefit from radiotherapy (RT); however, it is often reserved for those older than 60 years. Other low-risk approaches are exclusively advised for patients with the superficial variety who are unable to sustain surgery or radiation.

Mohs Surgery

Mohs micrographic surgery (MMS) is a specialized surgical technique for removing locally invasive, high-risk skin cancers [39]. MMS is an accurate, tissue-sparing method of skin cancer removal named after Frederick Mohs, the surgeon who invented it. It is a surgical methodical process for treating a wide spectrum of cutaneous neoplasms, including BCC and SCC, and has a proven high cure rate. The cornerstone benefit of MMS is that it allows for exact microscopic control of the entire tumor margin while preserving as much healthy tissue as possible [39].

Dr. Mohs developed this procedure in the 1930s. Because the approach involves the application of a chemical fixative (zinc chloride) to the in situ tumor, the treatment was originally named “chemosurgery.” The tumor was removed and microscopically inspected after 24 h of in situ fixing. The procedure was repeated until the tumor had been removed completely [40]. Mohs surgery shifted away from zinc chloride fixation in favor of processing fresh tissue that was frozen and sectioned in a cryostat microtome throughout the next few decades. When compared to traditional chemosurgery, this approach provided various benefits, including shorter processing times (15–30 min), reduced patient discomfort and improved tissue preservation [41].

Mohs surgery is used to treat skin malignancies that have a high risk of recurrence and require tissue preservation [42]. A thin margin of tissue is removed circumferentially around and deep to the clinical margins of a skin tumor during this procedure. To facilitate tissue processing, the specimen is usually removed with a 45-degree bevel. The tissue is then rapidly frozen and sectioned in a cryostat microtome, allowing for rapid tissue processing (about 15–30 min). When tissue is sectioned horizontally, practically all of the tissue margin (peripheral and deep margins) can be studied under the microscope. The procedure is repeated until the tumor’s histopathologic margins are negative [39].

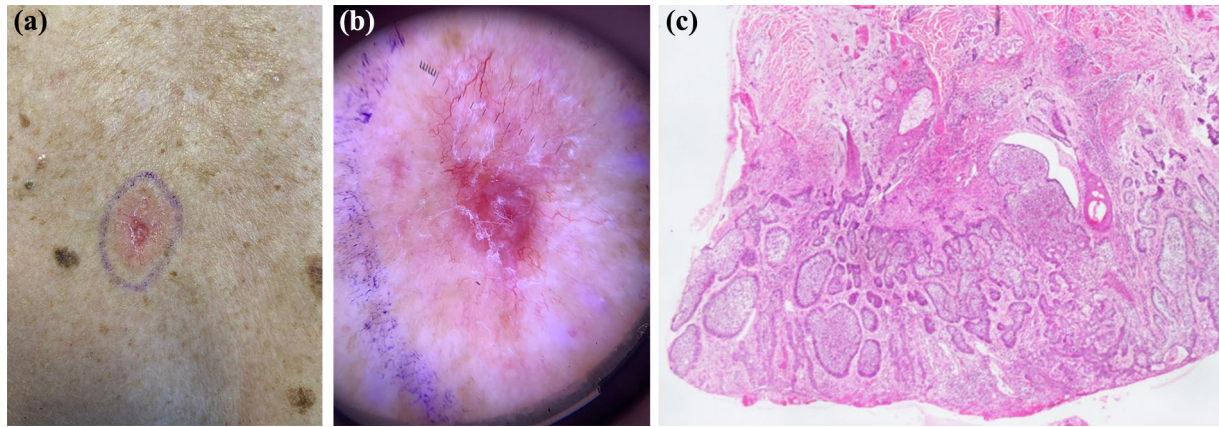


Fig. 3 **a** Clinical photograph of a 70-year-old female patient with a variable pinkish-colored, slowly growing erythematous plaque over the back. An unchanged previously known benign nevus is also seen. **b** Dermoscopy revealed an asymmetric, flat, pink macule with no pigment network. Multiple arborizing vascular patterns were noted in a patchy and radial distribution. The provisional

diagnosis was basal cell carcinoma. **c** Histopathology revealed basaloid epithelial cells in the epidermis and dermis, typically formed palisades with cleft formation in the basaloid epithelium and crowded nuclei with scattered mitotic figures. The diagnosis was invasive basal cell carcinoma with an infiltrative pattern (H&E staining with $\times 10$ magnification)

Electrodessication and Curettage (EDC)

EDC is usually used for lesions on the trunk, which can be monitored for recurrence by the patient since the cure rate is not as high as other approaches. It is relatively quick and inexpensive and often done following a shave biopsy procedure [43]. EDCs are fast, inexpensive and easy to use [44, 45]. However, the absence of histopathologic margin evaluation and the difficulty in utilizing this procedure in terminal hair bearing regions because of the tumor's potential to extend down follicular units are its disadvantages [44]. To ensure tumor eradication, conversion to standard surgical excision with postoperative margin evaluation (SSEPME) should begin once the subcutaneous layer is reached. In studies with suitable low-risk selection, 5-year EDC cure rates vary from 91 to 97% [35, 45]. Other studies have reported greater recurrence rates (19–27%), most likely due to malignancies with a high risk of recurrence [30, 46–48].

Topical Therapies

Topical 5-fluorouracil (5-FU) 5% cream and imiquimod 5% cream have been approved by the US Food and Drug Administration (FDA) for the treatment of sBCC [49–52]. Six weeks after treatment, a randomized controlled trial of imiquimod administered twice daily for 12 weeks showed 100% histologic remission [53]. At the 5-year follow-up, further studies found clearance rates of 77.9% and 80.4% for sBCC, highlighting the necessity for long-term research to reliably detect tumor recurrence [54, 55]. Topical imiquimod has a 5-year clinical success rate of 82.5% for sBCCs and nBCCs compared to 97.7% for standard surgical excision with postoperative margin evaluation (SSEPME), according to an RCT comparing topical imiquimod and SSEPME for sBCCs and nBCCs. Imiquimod provided substantially better cosmetic outcomes [56]. For a period of 12 weeks, imiquimod was used once a day, and nBCCs showed similar therapeutic effectiveness, with 76% clinical clearance [57]. Imiquimod is also prescribed to patients with necessitated BCC syndrome [58, 59]. Topical 5-FU is a topical therapeutic option for sBCCs

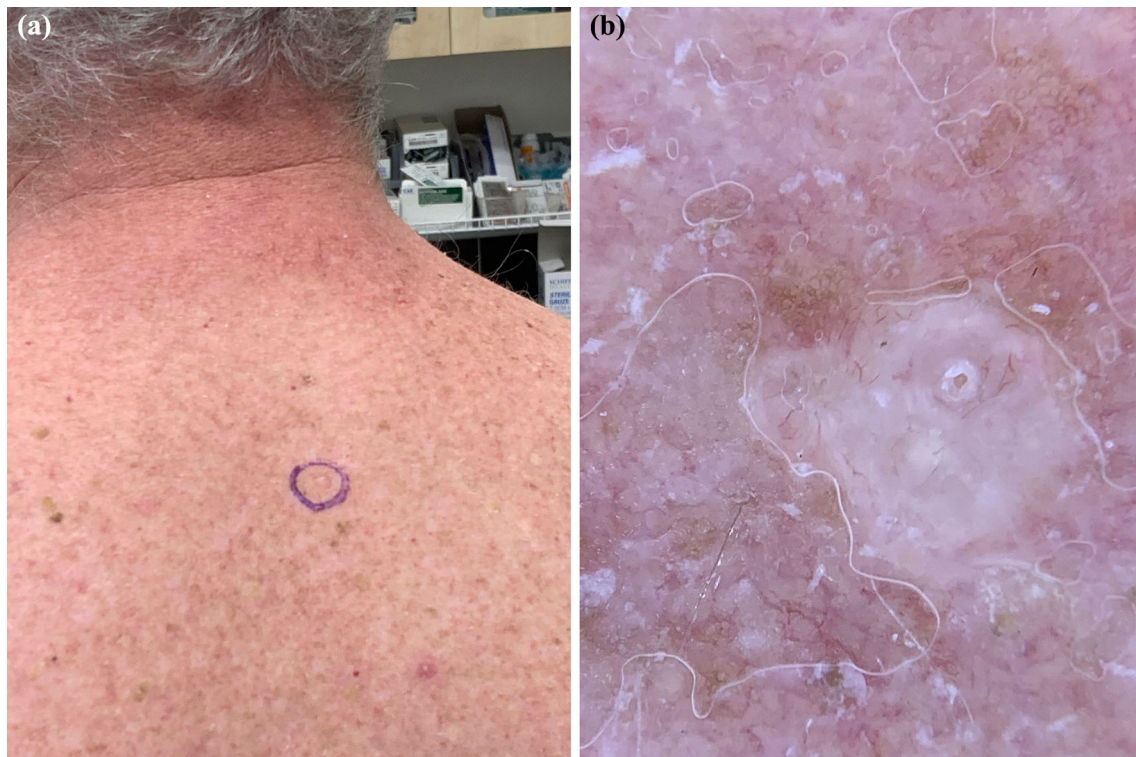


Fig. 4 **a** Clinical photograph of a 75-year-old male patient with a pale white-colored slowly growing plaque with brownish incomplete margins over the right upper back region. **b** Dermoscopy revealed an asymmetrical pattern with irregular margins superomedially and ill-defined margins inferomedially and arborizing tree-like

telangiectasis in the central and peripheral areas. The provisional diagnosis was basal cell carcinoma. Elliptical excisional biopsy was done under local anesthesia with a 4-mm free margin, after obtaining all consents. The histopathology report was suggestive of morpheiform/sclerotic basal cell carcinoma

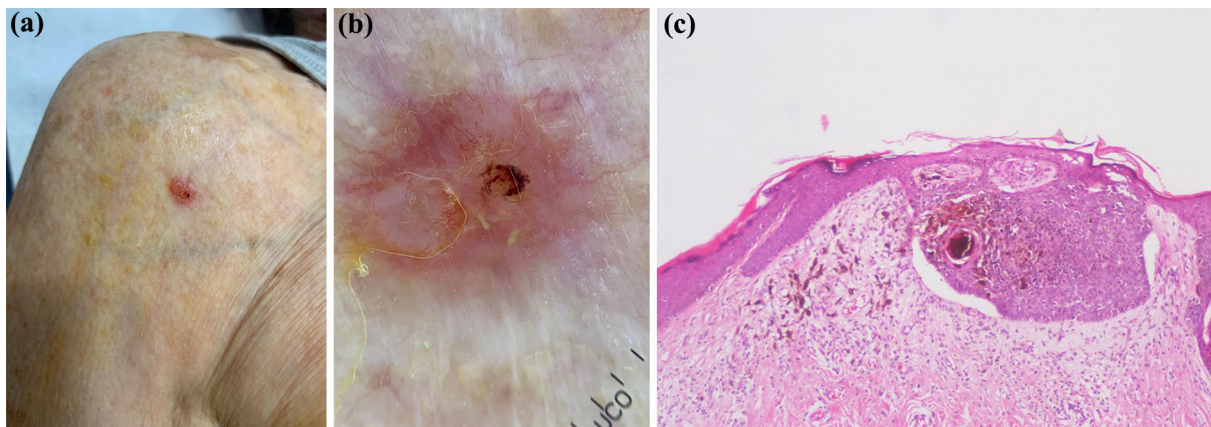


Fig. 5 **a** Clinical photograph of an 83-year-old male patient with a pinkish nodule over the right shoulder region anteriorly. **b** Dermoscopy revealed an asymmetric, pinkish red nodule. An arborizing vascular pattern in a

patchy distribution was noted. The provisional diagnosis was basal cell carcinoma. **c** The histopathologic diagnosis was pigmented basal cell carcinoma (H&E staining with $\times 20$ magnification)

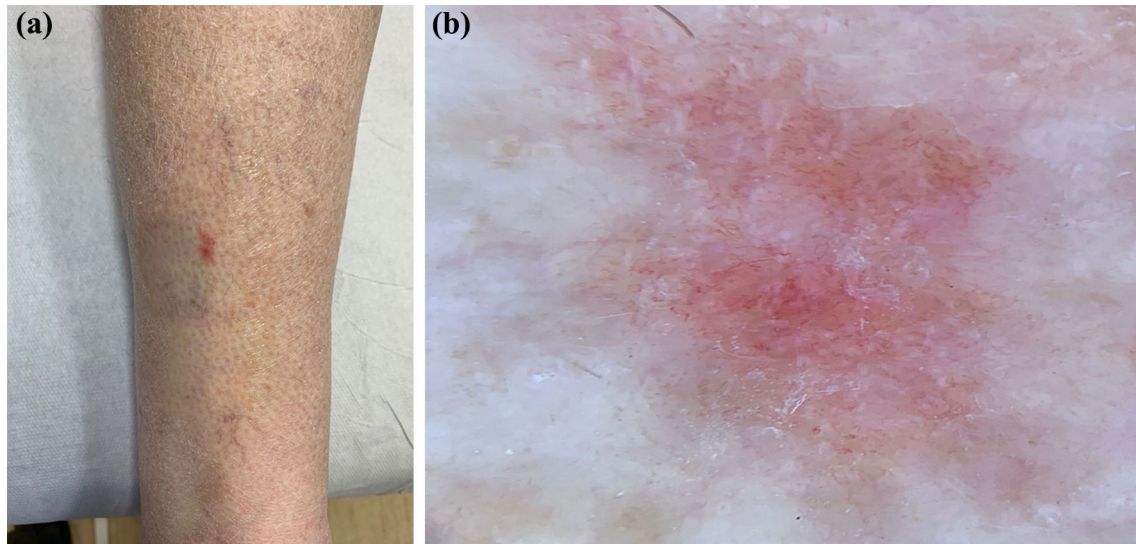


Fig. 6 **a** Clinical photograph of a 75-year-old male patient with an erythematous, slowly growing, flat macule over the back. **b** Dermoscopy revealed an asymmetric, flat, pink macule with no pigment network. Comma-shaped and

dotted vascular patterns in patchy distribution were also noted. The provisional diagnosis was basal cell carcinoma. The histopathology report was suggestive of fibroepithelial basal cell carcinoma

and is usually reserved for them [60–62]. An RCT found that at the 12-month follow-up, 5-FU and imiquimod were statistically similar in treating sBCC [63]. Various additional topical therapies for BCC have been proposed; however, there is little long-term evidence [64–66]. Long-term studies show that imiquimod is better than 5-FU, with a clearance rate of 79.7% after 3 years, compared to 68.2% with 5-FU. The effectiveness of 5-FU for treating nBCC is documented only through case studies and is therefore not widely advised [67, 68]. Several topical therapies and the level of evidence for nodular and superficial BCCs are listed in Table 1.

Immunotherapy

BCC has been successfully treated with immunotherapy and molecular-targeted therapy. For BCCs that are locally advanced or metastatic, there are currently no FDA approvals for first-line or upfront immunotherapy. On the other hand, BCC has one of the greatest tumor mutation burdens, making it a strong candidate for immune checkpoint inhibitor

treatment. In the first-line setting, there are currently no pivotal trial data, but several case reports with anti-CTLA-4 therapy and anti-PD-1 agents have reported activity and responses in advanced disease [69–72]. Pembrolizumab has shown anticancer efficacy against advanced BCC in a recent phase Ib research. Pembrolizumab with vismodegib was administered to seven individuals, while pembrolizumab alone was administered to nine others [73]. For the monotherapy versus combination therapy cohorts, the overall response rates (ORRs) at 18 weeks were 44% and 29%, respectively, and the progression-free survival at 1 year was 62% and 83%, respectively. Pembrolizumab has also been used in the treatment of BCC, according to five case reports with complete and partial responses, as well as a report of worsening of metastatic BCC bone lesions on medication. Cemiplimab and nivolumab have also proved to be effective in the treatment of advanced BCC [70–72, 74–78]. Cemiplimab resulted in a partial response (PR) in a patient with HHI-refractory recurrent metastatic BCC [77]. Two patients with metastatic BCC were treated with nivolumab, one of whom had a PR and a progression-free survival (PFS) of 116 weeks, while the other

Table 1 Topical therapies in BCC, their efficacy and levels of evidence

Topical therapy	Nodular BCC		Superficial BCC	
	Evidence	Efficacy	Evidence	Efficacy
5-Fluorouracil	IV	–	II	68.2% 3-year CC [63]
Retinoids	IV	–	IV	58.5% PT CC [64]
BEC-5	II	66% PT CC [60]	II	66% PT CC [60]
Dobesilatey	IV	–	IV	–
Imiquimod	II	76% PT CC [47]	I	78–80% 5-year CC [47–49]

CC clinical clearance, HC histologic clearance, PT post-treatment

Table 2 FDA-approved agents for BCCs and tissue-agnostic approvals

Indication	Therapeutic agent	Approval date	Mechanism	Subjects enrolled	Biologic License Application (BLA)/New drug application (NDA)
Superficial BCC	Imiquimod	14-07-2004	TLR agonist	364	NDA020723
Superficial BCC	Fluorouracil	30-06-1975	Anti-metabolite	54	NDA016831
Locally advanced BCC	Sonidegib phosphate	24-07-2015	Smoothened inhibitor	194	NDA205266
Locally advanced/metastatic BCC	Vismodegib	30-01-2012	Hedgehog inhibitor	96	NDA203388
Locally advanced/metastatic BCC, refractory setting	Cemiplimab-RWLC	09-02-2021	PD-1 targeted antibody	112	BLA761097

had an SD and a PFS of 22 weeks [70, 79]. Cemiplimab obtained accelerated FDA approval in February 2021 for the treatment of patients with locally advanced or metastatic BCC who suffered disease progression on HHI or who were HHI-therapy intolerant. The approval was based on the findings of a phase II open-label, multicenter, non-randomized experiment (NCT03132636). With the FDA’s recent approval of immunotherapy in the HHI refractory scenario, further research and trials (Phase Ib/NCT04323202) in advanced BCC are expected to result in an increase in FDA-approved

indications. Several FDA-approved agents for BCCs and tissue-agnostic approvals are presented in Table 2.

OTHER OPTIONS

Intralesional Therapies

The penetration of topical medicines is sometimes limited because of the protective stratum corneum layer. Direct intralesional injection is an alternative treatment option. Several

intralesional chemotherapies for BCC therapy have been studied with varying degrees of success such as methotrexate, rituximab and 5-fluorouracil. Adverse events (AEs) are uncommon and are typically dose related [80]. However, local effects at the treatment site and flu-like symptoms are common AEs.

Laser Therapy

Preliminary research has investigated laser therapy as both an adjuvant therapy and monotherapy for BCC (OEBM II) [81]. A retrospective study employing superpulsed carbon dioxide laser therapy for sBCC and nBCC has shown 100% histologic eradication and no recurrence during a 3-year follow-up [82]. A retrospective study employing superpulsed carbon dioxide laser therapy for sBCC and nBCC showed 100% histologic eradication and no recurrence during a 3-year follow-up [83]. In 78.6% of patients, sBCC therapy with a pulsed-dye laser resulted in histologic clearance at 6 months [84]. Reactive hyperemia, edema, scarring and discomfort are some of the reported side effects [85]. The laser-assisted administration of PDT photosensitizers has been examined as a novel therapeutic approach. The recurrence rates of aminolevulinic acid PDT with erbium were considerably reduced in two RCTs: (1) compared to PDT and erbium: yttrium aluminum garnet laser pretreatment; (2) monotherapies using erbium: yttrium aluminum garnet [85, 86].

Cryosurgery

The use of vigorous cryosurgery to destroy tumors is another treatment option. Large variations in recurrence rates (1–39%) have been noted in prospective studies, owing to a lack of homogeneity in patient and tumor selection, follow-up period and inter-operator performance approaches (OEBM II) [87–90]. After 5 years of follow-up, one dermatologist reported a 99% cure rate for 415 BCCs treated with cryosurgery [87]. Over a 30-year period, non-melanoma skin tumors had a 98.6% overall cure rate according to longer-term statistics.

Non-melanoma skin malignancies have also shown good 5-year cure rates in other trials [91, 92]. Compared to surgery, cryotherapy has poorer aesthetic results [93]. Therefore, it is not recommended in hair-bearing regions to avoid scarring alopecia and in the lower legs to avoid ulceration [37]. Large tumors, aggressive histologic subtypes, fixation to the underlying bone, recurrences and deep penetration are not indications for cryosurgery.

Radiotherapy (RT)

The objective of RT is to completely eradicate cancer while preserving as much healthy tissue as possible. For the treatment of BCC, two forms of RT have been used: teletherapy (external beam RT) and brachytherapy. The most appropriate form and quality of RT for each patient is determined by the size, depth and anatomic placement of the invasion. In prospective RCTs, RT has been compared with a variety of alternative treatment options for BCC. In one study, cryotherapy was compared with superficial RT; recurrence occurred 2 years after RT in 4% of 93 patients, whereas after cryotherapy, the recurrence rate was 39% [94]. There were no cases of tumor necrosis or severe pain. Telangiectasias were observed in 14% of the patients after RT. Both groups had a “mild” cosmetic effect. Another RCT compared EDC with 5% topical imiquimod for 6 weeks to superficial RT for BCC of the eyelids [95]. Six weeks following therapy, all 27 patients exhibited evidence of pathologic full response, and after 24 months, there were no clinical signs of recurrence in any of the patients. For newly diagnosed BCCs on the face, a landmark RCT compared surgery with RT [96]. Most RT patients (55%) received inpatient low-dose-rate interstitial brachytherapy, whereas only a small percentage (12%) received traditional outpatient teletherapy. Recurrence occurred in 0.7% of the surgery group and 7.5% of the RT group 4 years after therapy. There have been only a few high-quality comparative assessments of the various RT techniques.

Photodynamic Therapy

Another therapeutic option for low-risk BCCs is photodynamic therapy (PDT) (OEBM I). As photosensitizers, aminolevulinic acid and methyl aminolevulinate have equal efficiency [97]. The US FDA has authorized both substances for the treatment of non-hypertrophic actinic keratosis of the face and scalp. A red-light source is optimal for methyl aminolevulinate, whereas a blue light source is better for aminolevulinic acid. In a meta-analysis ($n = 1583$) of BCCs treated with PDT, 86.4% of the patients showed full clearance compared to 98.2% of surgically treated lesions [98]. PDT provided much better cosmesis than did surgery, but it was less effective. It has been used as an off-label neoadjuvant treatment to reduce the tumor burden and as an adjuvant treatment to reduce the risk of tumor recurrence [99–101].

Fractional lasers such erbium:YAG (Er:YAG) are among popular options for facial rejuvenation. Lasers with infrared wavelength ranges such as long pulse Nd:YAG have been used in nonablative rejuvenation of skin with variable outcomes [102]. Laser may be an alternative treatment for BCC cases according to many hypotheses. Vascular laser such as pulsed dye (595, 585 nm) and long-pulse Nd YAG laser (1064 nm) could be used, relying on the selective photothermolysis theory and selectively targeting tumor's vascular supply [103].

Vismodegib and Sonidegib

Currently, the FDA has approved two treatments that target the Hedgehog pathway for the treatment of recurrent, metastatic or locally advanced BCC that is not responsive to surgery or radiation. Mutations in the PTCH1 or SMO genes frequently cause the Hedgehog signaling pathway to be dysregulated in BCCs. The FDA approved Vismodegib as the first Hedgehog inhibitor (HHI) in 2012, based on the phase II ERIVANCE (NCT00833417) experiment. At 12 months, an ORR of 47.6% for locally advanced BCC and 30% for metastatic BCC was observed [104, 105]. After 39 months of follow-up, updated study findings revealed an ORR of

60.3% for locally advanced BCC and 48.5% for metastatic BCC [104].

Sonidegib was the second oral HHI to be approved by the FDA for the treatment of BCC. It was approved in 2015 for the treatment of locally advanced BCC that recurred after surgery or radiation therapy, or in patients who were considered ineligible for surgery or radiation therapy. The phase II BOLT pivotal study (NCT01327053) indicated a 56.1% ORR, a median duration of response of 26.1 months and a 93.2% 2-year survival rate for locally advanced BCC. For metastatic BCC, an ORR of 7.7% was recorded [106].

Selection of Appropriate Management Plan

It is imperative to decide from the pathology biopsy report whether the BCC is low or high risk. Table 3 shows the differentiating criteria between high- and low-risk BCC [107].

Advanced BCC is either metastatic or locally advanced BCC with one or more high-risk factors where currently available standard treatments are contraindicated. Locally advanced cases also include BCC > 5 cm in size, which would require extensive surgery, multiple coexisting neoplasms, infiltrative tumors with poorly defined margins and multi-time recurrences. Once these categories and staging are firmly established, the treating consultant can follow this flow chart for management [107] (Fig. 7).

CONCLUSION

Advances in BCC biology have allowed us to better understand the pathways of lesional evolution, prompting clinicians to demand both precision and accuracy in morphologic classification. Since the precise categorization and staging of BCC have such a significant influence on therapy, all practicing surgical pathologists should be familiar with the histologic criteria for diagnosis and the sub-classification of this human malignancy, which is one of the most prevalent. Smoothed inhibitors, which block the activity of the Hedgehog

Table 3 How to differentiate between high- and low-risk basal cell carcinoma (BCC) [107]

	High risk	Low risk
Clinical factors		
Location and size	BCC on trunk and extremities (but not on hands, nail units, genitals, pretibia, ankles and feet) > 20 mm (maximum clinical diameter)	BCC on trunk and extremities (but not on hands, nail units, genitals, pretibia, ankles and feet) ≤ 20 mm (maximum clinical diameter)
	BCC on cheeks, forehead, scalp, neck and pretibia > 10 mm (maximum clinical diameter)	BCC on cheeks, forehead, scalp, neck and pretibia ≤ 10 mm (maximum clinical diameter)
	BCC on mask areas of face, genital areas; hands, nail units, ankles and feet, but excluding the eyelid	
Borders	Poorly defined	Well defined
Primary vs. recurrent	Recurrent	Primary
Site of prior radiotherapy	Yes	No
Immunosuppression	Yes	No
Pathologic factors BCC and stage		
Growth pattern	Infiltrative (infiltrating, morpoeic, micronodular)	Nodular or superficial
Basosquamous differentiation	Present with or without lympho-vascular invasion	Absent
Level of invasion	Beyond subcutaneous fat	Dermis, subcutaneous fat
Depth/thickness	> 6 mm	≤ 6 mm
Perineural invasion	Present	Absent
Histologic margins	Involved (0 mm) or histologically close (< 1 mm)	Not involved (≥ 1 mm)
Pathologic TNM staging	pT2 > 20 mm but ≤ 40 mm (maximum diameter) pT3 > 40 mm (maximum diameter), or Upstaged pT1 or pT2, or Minor bone invasion pT4 major bone invasion	pT1 ≤ 20 mm (maximum diameter)

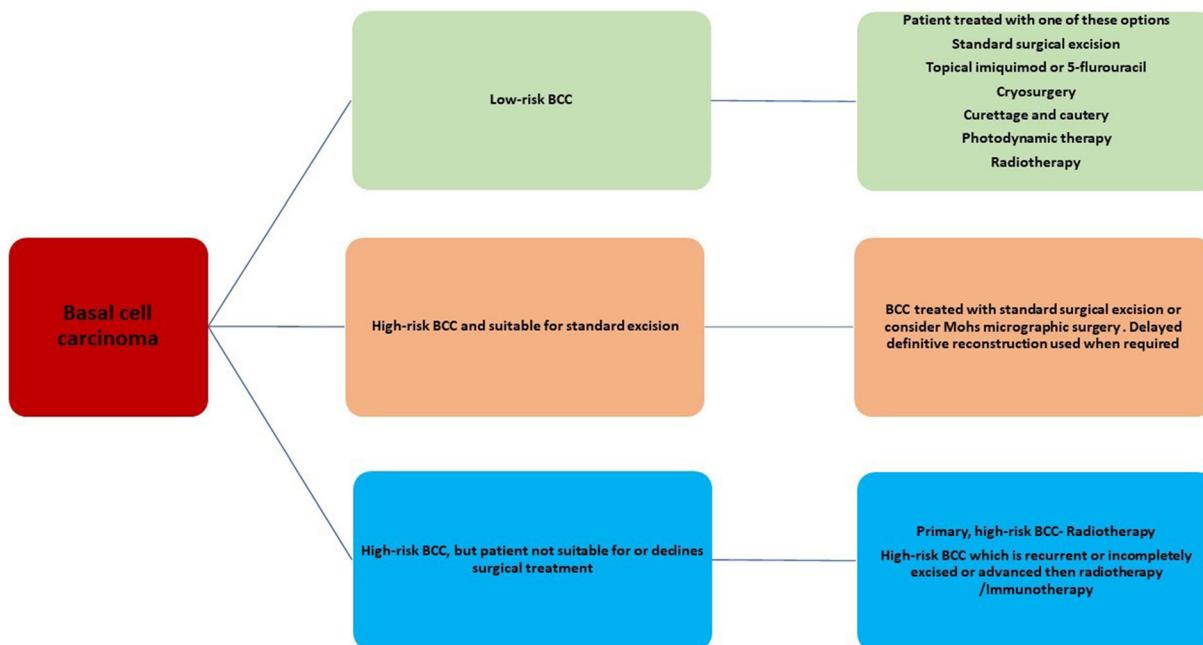


Fig. 7 Flow chart for management of BCC

signaling pathway, have recently been approved for the treatment of metastatic or locally advanced tumors, and remarkable tumor shrinkage results have been reported. Although the exact prognosis of metastatic BCC is yet to be determined, it is likely to be poor, given the rarity of the condition. However, emerging molecular targeting agents hold therapeutic promise.

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