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Review Article

Treatment of basal cell carcinoma: An overview

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ABSTRACT

Basal cell carcinoma (BCC) is the most common cutaneous cancer worldwide, but accounts for only 2–4% of skin cancers in Asian population. Tumor characteristics such as size, location, pathology, and risk of recurrence, as well as treatment tolerability, cost, and patient preference influence the selection of treatment. The goal of treatment is complete tumor removal in superficial/locally invasive BCCs and prolongation of survival in the rare setting of metastatic BCC. Various treatment options available include conventional surgical excision, Mohs micrographic surgery, cryosurgery, electrodesiccation and curettage, topical application of imiquimod or 5-fluorouracil, and photodynamic, and radiotherapy. Surgical excision and Mohs surgery are preferred because of low recurrence rate and the possibility to evaluate the clearance through histology. In the treatment of metastatic or locally advanced lesions, hedgehog pathway inhibitors and the recently approved drug cemiplimab can be beneficial. Sun protection and regular skin self-checks are recommended for all patients with BCC. This literature review gives an overview of the treatment of BCC.

Keywords: Basal cell carcinoma, Mohs, Imiquimod, Hedgehog pathway inhibitors, Cemiplimab

INTRODUCTION

Basal cell carcinoma (BCC) is by far the most common skin cancer worldwide, accounting for 65–70% of cutaneous cancers. While BCC amounts to nearly 35–40% skin cancers in Caucasians, it comprises only about 2–4% in Asian and 1–2% in black population.[1]

A number of treatment options are available today and the choice offered to the patient is based not only on the characteristics of the BCC, which include the anatomical location, size, clinical appearance, and histological diagnosis, but also on patient-specific factors such as general fitness and coexisting serious medical conditions.[2] The final decision is also influenced by the patient's choice, ease of access to treatment, and the expertise/preference of the treating clinician.[2]

LOW-RISK VERSUS HIGH-RISK 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 [Table 1].[3,4] Lesions <1 cm in size on the cheeks, scalp, forehead, neck, and pretibial region were considered low risk previously, but in the current classification, all lesions in these areas are deemed to be high-risk, irrespective of the size.[4]

TREATMENT GOAL

The aim of treatment of a superficial/locally invasive BCC is complete removal of the tumor with the least cosmetic and functional impact.[4] In the rare setting of metastatic BCC, the treatment goal would be to attain remission with prolongation of survival.[5] Treatment modalities may be classified into surgical and non-surgical therapies [Table 2].

SURGICAL TECHNIQUES

Although there are various treatment options available for BCC today, surgery remains the keystone of treatment.[3]

STANDARD EXCISION

Excision with pre-determined margins to include clinically normal skin is the usual surgical treatment for BCC. On comparison with other treatments, recurrence rates following surgical excision were consistently and notably lower.[3] The cosmetic result has also been found to be more agreeable following standard excision when compared to results after cryosurgery or curettage and electrodessication (C&E).[6,7]

Excision with a 4 mm peripheral margin and to a depth of the mid-subcutaneous fat is recommended for a low-risk primary BCC.[3] Excision with a 4 mm peripheral margin attained a complete clearance of the tumor, in 98% of well-demarcated BCC of <20 mm size.[8]

Standard excision is recommended for tumors in low-risk group. It may also be performed for certain high-risk BCCs with wider margins and with linear or delayed repair.[4]

MOHS MICROGRAPHIC SURGERY (MMS)

This is a margin-controlled surgical technique, first devised in 1938 by Frederic Edward Mohs, an American physician.[9] The initial technique employed a chemical paste containing zinc chloride to fix the excised tissue, followed by microscopic examination.[10] This procedure was repeated till tumor-free margins were achieved.[10] Mohs technique was later modified by Perry Robins in the 1970s, using fresh tissue frozen histology.[9] The use of cryostat microtome has now condensed the processing time to 15–30 minutes.[10]

A Swedish study has reported a cure rate of 93.5% and 90% for primary and recurrent BCC respectively at 5 years.[11] Another study found the 10-year recurrence rate of 4.4% for primary facial BCC treated with MMS in contrast to 12.2% following standard excision.[12] An advantage of MMS is tissue conservation resulting in smaller surgical defects as compared with results following standard excision.[3] High-risk BCC as adjudged by the National Comprehensive Cancer Network risk stratification is the indication for MMS.[3]

CURETTAGE AND ELECTRODESSICATION (C&E)

This is a type of electrosurgery in which a skin lesion is scraped off and cauterized under local anesthesia.[13] This stops bleeding and helps destroy any remaining tumor cells.[13] The drawback of this procedure is that multiple fragments

Table 1: National Comprehensive Cancer Network stratification of low-risk versus high-risk BCC parameters.[4]

Risk group	Low risk	High risk
History and physical (H and P)		
Location/size	Trunk, extremities <2 cm	Trunk and extremities ≥2 cm Cheeks, forehead, scalp, neck and pretibial any size "Mask areas" of face,[a,b] chin, mandible, preauricular and post-auricular skin/sulci, temple and ears[b] Genitalia, hands, and feet [b]
Borders	Well defined	Poorly defined
Primary versus recurrent	Primary	Recurrent
Immunosuppression	No	Yes
Site of prior radiotherapy	No	Yes
Pathology		
Growth pattern	Nodular, superficial[c]	Aggressive[d]
Perineural involvement	No	Yes

Reproduced with permission from the NCCN guidelines for basal cell skin cancer V.2.2021. National Comprehensive Cancer Network, Inc. 2021. All rights reserved. The NCCN guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN.[4] [a]Mask areas encompass the central face, eyelids, eyebrows, periorbital, nose, and lips (cutaneous and vermillion). [b]These areas constitute high risk based on location, independent of size. Margin-controlled procedures like Mohs surgery are recommended. [c]Low-risk histology subtypes also include other non-aggressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus. [d]High-risk aggressive subtype includes morpheaform, mixed (infiltrative), micronodular, basosquamous, sclerosing, or carcinosarcomatous differentiation in any portion of the tumor. In some cases, basosquamous tumors may be prognostically similar to SCC; clinicopathologic correlation is recommended in such cases, BCC: Basal cell carcinoma

Table 2: Classification of BCC treatment options.

Surgical treatment	Non-surgical treatment
Standard excision with 4 mm margins	Topical therapy – imiquimod and 5-fluorouracil
MMS	Photodynamic therapy
C&E	Radiotherapy
Cryosurgery	Systemic therapy – vismodegib, sonidegib, and cemiplimab
Laser therapy	Electrochemotherapy

MMS: Mohs micrographic surgery, C&E: Curettage and electrodessication, BCC: Basal cell carcinoma

of specimen are created and the presence of disease-free margins cannot be commented on.[14] It is the performing clinician who decides if the lesion is satisfactorily removed.[14] Modifications in the types of curette and number of cycles of treatment have been attempted, but there are no clear published guidelines for this technique.[2] A literature review has shown an overall 5-year cure rate of 92.3% after C&E for selected primary BCC and 60% for recurrent BCC.[15,16] C&E is less successful for BCC on areas with terminal hair such as beard region due to possible follicular continuation of the tumor.[3] As opposed to standard excision, C&E may be associated with a longer healing interval and less acceptable cosmetic result.[3] C&E is, therefore, recommended only for low-risk primary BCC in less cosmetically important areas.[3]

CRYOSURGERY

Cryosurgery or cryotherapy employs liquid nitrogen to remove BCC tissue by generating a tissue temperature of at least –50 to –60° C.[2] Repeated freeze-thaw cycles and inclusion of 3–5 mm margin are recommended.[17] A French study that evaluated 395 BCCs reported a recurrence rate of 9% in 5 years which was consistent with previous reports.[18] Cryosurgery wounds heal with nominal tissue contraction, rendering good cosmetic outcome.[2] Howbeit, one study reported better cosmetic outcome after surgical excision as against cryosurgery for BCC on head-and-neck region.[7] Cryotherapy can result in hypopigmentation and hence is not preferred for patients with darker skin types.[7] Since the technique is not suited to get histologic confirmation of tumor free margins, cryosurgery is recommended only when more efficacious treatment options are contraindicated or unfeasible.[3]

TOPICAL THERAPIES

The two commonly used topical treatments are imiquimod and 5-fluorouracil (5-FU).

Imiquimod

Imiquimod is an immunomodulator that acts through the toll-like receptor 7 and/or 8, triggering a helper T-cell cytokine cascade, and interferon production.[19] Imiquimod also blocks the activation of the hedgehog (Hh)/glioma-associated oncogene (GLI) signaling pathway which is involved in the pathogenesis of BCC.[20] In 2004, The United States Food and Drug Administration (FDA) approved imiquimod for the treatment of biopsy-proven primary superficial BCC (sBCC) with largest diameter of 2.0 cm, located on the trunk (barring anogenital region), neck, or extremities (excluding hands and feet) in immunocompetent adults.[21,22] It is recommended only in situations when surgical methods are deemed less feasible and if the patient can be appropriately followed up.[21,22] The prescriber information dictates that imiquimod cream is to be applied 5 times per week for a full 6 weeks.[22] A systematic review of imiquimod treatment for sBCC in 28 studies found complete response in a pooled estimate of 86.2% at 12 weeks, while tumor-free status at 1 year was reported to be 87.3% for imiquimod in a pooled estimate from 23 similar studies.[23] Imiquimod application produces local effects such as redness, erosions, crusting, blistering, and pruritus.[3] Systemic adverse effects include fatigue, influenza-like symptoms, myalgia, and headache.[22] These can occur and even precede local reaction, if imiquimod is applied to larger surface areas.[22] Both local and systemic effects may require interruption of treatment depending on the severity.[22]

5-FU

5-FU is an antimetabolite that works by inhibiting thymidylate synthase that affects DNA synthesis in neoplastic cells.[24] 5-FU is approved by the FDA for the treatment of sBCC.[24] A study of 31 biopsy-proven sBCC treated with 5-FU reported a histologic cure rate of 90% and a mean time to clinical cure of 10.5 weeks.[25] One randomized controlled trial reported a tumor-free survival at 5 years of 80.5% for imiquimod and 70.0% for 5-FU.[26]

The recommended protocol is twice daily application for at least 3–6 weeks, although the treatment may need to be continued till 10–12 weeks before the lesion is completely cleared.[27] Adverse effects include erythema, crusting, erosions, ulcers, and even eschar formation, which may limit compliance as seen with imiquimod therapy.[3]

PHOTODYNAMIC THERAPY (PDT)

PDT uses light to destroy tumors cells.[28] A photosensitizing pro-drug such as 5-aminolevulinic acid or methyl aminolevulinate is applied on the lesion which is then activated by light after an incubation period of 1 to a few hours.[29,30] The recommended wavelength for management of BCC is centered around 630 nm (red light).[31] In general, a single treatment cycle is enough, but non-responding lesions are given another course of PDT at 1 week.[3] PDT is an elegant, non-scarring treatment, although it can cause prolonged photosensitivity (up to 2–3 days), pain, burning, erythema, edema, ulceration,

and transient dyspigmentation locally.[3] Healing is usually achieved by 2 weeks with good cosmetic outcome.[3] A systematic review of total of 1583 patients with BCC reported no statistically significant difference in complete clearance rate or 1-year recurrence rate, when PDT was compared with cryotherapy or pharmacological treatment (topical imiquimod and 5-FU). Moreover, PDT gave cosmetically better results than surgery or cryotherapy.[29] PDT is approved in more than 18 countries and is considered for treating sBCC and thin nodular BCC (nBCC) with thickness <2 mm, when surgery is deemed less appropriate or contraindicated.[31-33]

RADIOTHERAPY (RT)

RT in the form of external beam radiation, superficial X-ray therapy, and brachytherapy, is considered for treating nBCC in select situations wherein surgery is unfeasible, contraindicated, or not preferred by the patient.[3] It is a valuable treatment postoperatively for BCC with involved histological margins, when further surgical excision is inappropriate.[2] A randomized study in 347 patients, that compared standard excision to RT for facial BCCs measuring <4 cm, reported a failure rate of 0.7% for surgery and 7.5% for RT at 4 years.[34] The cosmetic outcomes at 4 years, were reported as "good" in 87% of those who had surgery and 69% of those who received RT.[34] RT is not recommended for morpheaform or infiltrative BCC due to higher recurrence rates.[35]

The immediate adverse effects of RT include dermatitis, ulceration, and pain which subside in 3–4 weeks in most cases.[2,36] Delayed effects are alopecia, dyspigmentation, fibrosis, chronic radiation dermatitis, and skin/cartilage/bone necrosis which may take months to years to appear.[2,37] There is an increased risk for secondary skin malignancy (BCC and squamous cell carcinoma) at the irradiated site.[37] Therefore, RT is contraindicated for BCC that has recurred after previous RT and in patients with diseases like Gorlin syndrome and xeroderma pigmentosum that show a genetic predisposition to skin cancers.[2,37]

MANAGEMENT OF PATIENTS WITH METASTATIC BCC AND LOCALLY ADVANCED BCC

Metastatic BCC (MBCC) is infrequent, with an incidence rate of about 0.0028–0.55%, however, it has been associated with a dismal prognosis.[3] Locally advanced BCC (laBCC) is mostly due to delayed treatment.[3] Surgery and RT are the main treatment modalities for laBCC but are associated with significant post-treatment morbidity.[3] In such circumstances, smoothened (SMO) inhibitors and immunotherapy can be attempted.

Hh PATHWAY INHIBITORS (SMO INHIBITORS)

Upregulation of Hh signaling is thought to be the central anomaly in all BCCs.[38] Hh is a family of extracellular ligand which binds to the patched 1 (PTCH1) receptor encoded by the PTCH1 gene, which is a tumor suppressor gene.[38] Binding of Hh to the PTCH1 receptor results in loss of inhibition of the downstream SMO protein.[38] This allows SMO to activate GLI family of transcription factors, ultimately resulting in tumorigenesis.[38] Nearly 90% of sporadic BCCs have mutations in PTCH1 gene, and another 10% have activating mutations in SMO protein.[38]

Vismodegib (FDA approved in 2012) and sonidegib (FDA approved in 2015) are the licensed Hh pathway inhibitors for the treatment of adults with laBCC, who are not candidates for surgery or RT.[39,40] Vismodegib is also approved for patients with mBCC.[2]

The ERIVANCE trial measured complete and partial responses with vismodegib.[41] Complete response was defined as absence of residual BCC in a tumor biopsy sample taken at week 24 or at best response, while partial response was defined as ≥30% reduction in the diameter, that was appreciated clinically or radiographically.[41] The trial demonstrated a combined complete and partial response rate of 60.3% for laBCC and 48.5% (all partial responses) for mBCC at 39 months.[41] The BOLT trial similarly demonstrated clinical effectiveness of sonidegib.[2] In addition, vismodegib treatment has shown a significant decrease in the number of new BCCs, requiring surgery in patients with Gorlin syndrome.[42]

Vismodegib and sonidegib are oral medications and are continued either till disease progression halts or till intolerable toxicity develops.[43] The adverse effects of these SMO inhibitors are mainly muscle cramps, dysgeusia, alopecia, nausea, and fatigue.[44]

IMMUNOTHERAPY

In February 2021, FDA approved cemiplimab as the first immunotherapy for patients with advanced BCC.[45] It is licensed for treating laBCC and mBCC which have not responded to or for whom Hh inhibitor treatment is not suitable.[46] Cemiplimab is a fully human, immunoglobulin G4 monoclonal antibody aimed against programmed cell death receptor-1 (PD-1) or its ligand (PD-L1).[47]

PD-1 is expressed on a variety of immune cells such as B and T cells and tumor-infiltrating lymphocytes (TILs) and functions as immune checkpoint, by downregulating immune response.[48] This is critical in prevention of autoimmunity and in immunosurveillance against malignant cells.[48] PD-1/PD-L1 is upregulated in the tumor cells of various malignancies.[48] One study of 138 BCCs reported PD-1 expression in 89.9% tumor cells and 94.9% of TILs.[49] PD-1/PD-L1 inhibitors such

as cemiplimab, thereby prevent the PD-1/PD-L1 interaction with a resultant positive immune response against tumor cells.[48] A multicenter study of 84 patients with BCCs treated with cemiplimab showed that 6% and 25% of study participants showed complete and partial response respectively.[47]

Cemiplimab is given as 350 mg intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity appears.[46] Adverse effects have been reported in 48% of patients which included urinary tract infection, immune-mediated colitis, hepatitis, pneumonitis, dermatitis, acute kidney injury, endocrinopathies, anemia, infected neoplasm, and somnolence among others.[47]

OTHER TREATMENTS

Various other therapies for BCC have been studied, but have shown insufficient evidence to be recommended as the first- or second-line treatment options. Electrochemotherapy is one such procedure, which involves combining systemic or intratumoral chemotherapy agents like bleomycin with electric pulses, which increase permeability of cancer cells to the drug.[50]

Laser ablation has also been tried using lasers such as pulsed dye, Er:YAG, and CO2 lasers. Complete remission rate with CO2 at 3 months for sBCC was found to be comparable to cryotherapy, but much less than surgery in one study.[51]

Topical agents such as ingenol mebutate and solasodine glycoalkaloids have been found to be superior against placebo/vehicle, but need further studies to determine long-term recurrence rates. Similarly, different combinations of therapies need more studies to evaluate their effectiveness. These combinations include diclofenac with calcitriol, imiquimod and MMS, interferon-α and standard surgical excision, topical PDT and MMS, and lasers and topical PDT.[52-59]

FOLLOW-UP AND PREVENTION

There is inadequate evidence to recommend follow-up for patients with solitary, successfully treated, low-risk, BCC. However, long-term follow up should be advised for patients with inadequately treated, high-risk BCC or those with a history of multiple BCCs (immunosuppressed or patients with Gorlin syndrome).[2]

Sun protection and regular skin self-checks are recommended for all patients with BCC.[2] At present, there is insufficient evidence aside from potential adverse effects, to routinely suggest drugs such as oral acitretin, nicotinamide, or non-aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) as measures to prevent BCC, but these may be recommended for patients with a history of multiple BCCs.[2]

CONCLUSION

In the Indian setting, a dermatologist may encounter BCC in their practice.[60] Surgical excision is recommended for treating most BCCs, while topical measures/PDT may be preferred for sBCC. Hh inhibitors and cemiplimab can be tried in mBCC and laBCC. We hope that this literature review of various treatment options would aid the clinician to choose the appropriate therapeutic modality.

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

There are no conflicts of interest.

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