

Face and Scalp Basal Cell Carcinoma Treatment: A Review of the Literature

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ABSTRACT Basal cell carcinoma (BCC) is the most frequent skin cancer and is characterized by slow growth, even if it can be locally invasive and rarely metastasizes. Many different phenotypic presentations and histopathologic subtypes have been described, and the current guidelines subdivide BCCs into low-risk (nodular and superficial) and high-risk subtypes (micronodular, infiltrating, and morphoeic BCC and those with squamous differentiation). Dermoscopy allows the identification of the features associated with these different subtypes. Compared with the low-risk forms of BCC, more aggressive ones tend to undergo more frequently incomplete surgical excision and perineural invasion, so the identification of these lesions before surgery is extremely important. The gold standard of treatment is surgery, particularly for the H region of the face and infiltrative lesions, but other options are available and selected according to many variables, including body area, age, comorbidities, and clinical, dermoscopic, and histopathological features of the lesion. Moreover, the possible complications of surgical approaches, namely healing defects, failure of skin grafts, and wound infection, should be considered. In this review we discuss the management of BCC localized on the face and scalp, according to the currently available treatment options.

KEY WORDS: basal cell carcinoma, face, scalp, treatment

INTRODUCTION

BCC is the most common skin cancer worldwide with increasing incidence, even if it is difficult to assess the real epidemiological data because of the current practice of under-registration (1,2). While it is still more prevalent in older people, it is also becoming frequent in younger individuals (3,4). The prognosis is usually good, but despite the low mortality rate BCC is a significant cause of morbidity, so early diagnosis and treatment is fundamental (5). Exposure to sunlight is the main risk factor, but

genetic alterations in signaling pathways have a role in carcinogenesis as well. New treatment options that selectively target these pathways have been recently introduced for advanced forms of the disease. The choice of the most appropriate treatment is based on many factors, including the body area affected, the recurrence risk, patient adherence to treatment, the extent of the disease, and histopathologic subtype (6-8). In this paper, only face and scalp localizations will be discussed.

CLINICAL SUBTYPES, DERMATOSCOPY AND HISTOPATHOLOGY

The clinical subtypes of BCC include different forms: nodular, ulcerative, superficial, sclerodermiform/morpheaform, pigmented, and fibroepithelioma of Pinkus. Many histopathological subtypes have also been described: nodular, superficial, infiltrating, sclerodermiform/morpheaform, micronodular, fibroepithelial, and basosquamous carcinoma (Figure 1). The classification system of the National Comprehensive Cancer Network (NCCN) based on growth pattern identifies two groups: indolent-growth and aggressive-growth subtypes (8). The former includes nodular and superficial BCC, corresponding to the clinical nodular and superficial subtypes, respectively; the latter, which have a higher recurrence rate and tend to cause extensive local destruction, includes the sclerodermiform/morpheaform, infiltrative, micronodular, and basosquamous subtypes. A precise correlation between clinical and histopathological variants is not always possible; in such cases dermoscopy, a non-invasive *in vivo* technique, may be helpful (9,10). Dermoscopy allows early detection of BCC and its differentiation from other pigmented and non-pigmented lesions (10-18). The spectrum of BCC-related criteria has been updated several times since the first description, and the most common dermoscopic structures currently described include globules, dots, white structureless areas, structureless gray-brown areas, leaf-like areas, spoke-wheel structures, and ulcerations (10) (Figure 2, Figure 3). The most frequently found vascular structures in BCC are short fine telangiectasia, arborizing vessels, and vascular blush (10-18). White shiny structures, which

include shiny white lines (chrysalis and crystalline structures), shiny white areas, and rosettes, only visible with polarized dermoscopy, represent additional criteria to diagnose BCCs (19-20). According to the results of recent studies (21-22), some differences in dermoscopic appearance between infiltrating and other BCC subtypes have been identified. Infiltrative BCC tend to manifest arborizing vessels and ulceration less frequently than nodular BCC, but with a greater frequency of shiny white-red structureless areas. A study to classify distinct BCC subtypes by reflectance confocal microscopy (RCM), a non-invasive imaging modality, was carried out as well (23). These results are extremely important because the current guidelines for the management of BCC suggest implementing a different therapeutic approach according to histopathologic subtype, as it is well known that infiltrative BCC have higher rates of incomplete surgical excision and perineural invasion compared with more indolent BCC subtypes. A recent study has allowed the identification of a new dermoscopic pattern in infiltrative BCC, described by the authors as a "stellate pattern" (8,24,25). This pattern consists of a geometric star extending outwards from the circumferential peripheral edge of the tumor and identified by white lines, vessels, or uneven skin surface morphology. This evidence highlights how dermoscopy can be useful in providing information on the tumor subtype in the preoperative assessment (26-29).

TREATMENT

The choice of BCC treatment should take into account several factors such as anatomic site, histologic features, tumor recurrence, and the patient's general



Figure 1. Clinical aspect of basal cell cancer of the ear.



Figure 2. Dermoscopic image of nodular basal cell carcinoma with short fine telangiectasia.



characteristics. The NCCN stratifies BCCs into low- and high-risk subtypes based on location, size, borders, recurrence, immunosuppression, site of prior radiation treatment, pathological subtype, and evidence of perineural involvement (8). Treatment modalities include surgical excision, electrodesiccation and curettage, cryotherapy, topical immunotherapy, photodynamic therapy, and radiation therapy. Moreover, locally advanced or metastatic BCC are currently treated with the new targeted molecular drugs (30).

Surgical or destructive modalities **Standard excision**

Standard excision represents the gold standard treatment for the histological forms of primary non-aggressive BCCs (nodular or superficial) or for those occurring on low-risk sites (trunk/extremities). Classifying primary or recurrent tumors is essential for surgical planning, because primary BCCs have lower recurrence rates than previously treated BCCs and the margins necessary for complete eradication of recurrent tumors are almost twice as big as those required to eradicate primary BCCs. A 4 mm excision margin is indicated in lesions smaller than 2 cm in diameter.

Mohs' micrographic surgery

Mohs' micrographic surgery (MMS) allows optimal margin control with the preservation of normal tissue. It is the treatment of choice for all high-risk lesions, recurrent BCCs, as well as primary BCCs located on anatomic sites requiring functional and aesthetic



Figure 3. Dermoscopic image of superficial basal cell carcinoma characterized by a structureless gray-brown area and arborizing vessels.

maintenance such as those localized on the eyes, lips, or nose (30,31).

Electrodesiccation and curettage

For appropriately selected lesions, electrodesiccation and curettage remains an efficacious and cost-effective treatment modality for BCC, but it is now less frequently used due to new treatment modalities and the lack of histopathological examination of the lesion (32).

Cryosurgery

BCC can also be treated with cryosurgery (liquid nitrogen at -196°C) according to the principle that freezing cycles with subzero temperatures destroy the tumor tissue with subsequent healing. A margin of clinically normal tissue must be included to also eradicate subclinical extension. Cryosurgery is only occasionally used for superficial or small-sized BCCs (31).

Non-surgical options

These include topical, systemic, and radiation therapy (33).

Imiquimod

Imiquimod 5% cream has been approved by the US Food and Drug Administration (FDA) for the six week treatment duration of primary superficial BCCs smaller than 2 cm, in low-risk anatomic locations. Moreover, a recent study demonstrated that it can be a valuable adjuvant therapy for the treatment of incompletely excised nodular BCC in elderly people (34-36).

Photodynamic therapy

According to the results of a recent meta-analysis, photodynamic therapy (PDT) represents a useful method for the treatment of BCC, with similar efficacy to cryosurgery and pharmacologic treatments and lower only compared with surgical excision (37). PDT involves the activation of a photosensitizing drug: 5-aminolevulinic acid (5-ALA) or methylaminolevulinic acid (MAL) by a source of light to produce reactive oxygen species (ROS) that destroy cancer cells. It is indicated for patients with multiple non-aggressive BCCs (i.e. Gorlin-Goltz patients) or for those that are not candidates for surgery. Recently, MAL-PDT has been described as an effective treatment in the management of thin nodular BCC (thickness <2 mm) (38). MAL-PDT has been reported to also be effective in reducing tumor size in sclerodermiform BCC before surgery and may also be considered for pigmented

BCCs after an adequate debulking; however, patients should be closely followed due to the higher recurrence risk (38-40). Finally, MAL-PDT has shown good results in treating giant BCC, particularly in association with topical imiquimod, allowing a considerable reduction in the tumoral dimension with subsequent more conservative excision (38,41).

Targeted molecular therapy

Until 2012, when Vismodegib, a Smoothed (SMO) inhibitor acting on the Hedgehog molecular pathway, was approved, the therapeutic approach for patients with locally advanced or metastatic BCC was exclusively represented by conventional chemotherapy. Vismodegib received approval by the FDA in January 2012 and by the European Medicines Agency (EMA) in July 2013 after a phase II study on 96 advanced BCCs, where it demonstrated a response rate of 30% in patients with metastatic BCC and 43% in locally advanced tumors (42). New SMO antagonists and itraconazole are currently under investigation in phase I-III clinical trials (43,44).

Radiation therapy

Radiotherapy represents a treatment option for those patients who cannot undergo surgery or who refuse surgical approach. It is also used as adjuvant therapy for BCC where postoperative margins are positive or in case of perineural involvement (32).

Future Perspectives in BCC Treatment

Daylight photodynamic therapy (DL-PDT) is a promising treatment. It has been used in a preliminary study of 21 patients with 32 BCCs, where it achieved 90% 3-month complete clinical response rate, even if 6 patients presented with a recurrence during the 12-month follow-up (44). Recent studies investigated the use of ingenol mebutate for patients with BCC who failed or were ineligible for conventional treatments (45,46). The complete clinical response rates were 82% and 57% after 1 and 15 months, respectively. In another phase II trial (46), the histologically confirmed clearance of the treated lesions was reported in 65% of the study population, with higher efficacy in those patients treated for 2 consecutive days.

FOLLOW-UP, RISK OF RECURRENCE AND PREDICTORS FOR A SECOND BCC

The NCCN recommendations for follow-up of patients with BCC include 6- to 12-month total body skin examination by a dermatologist, sun protection measures, and skin self-examinations (8). Up to 50% of patients with primary BCC is estimated to develop

at least one other BCC within 5 years. Verkouteren *et al.* have recently carried out a study in which they concluded that a combination of clinical characteristics (phenotypic traits, lifestyle, and tumor-specific characteristics) could identify patients at high risk for a second BCC (47). The recurrence rate is higher in incompletely excised lesions, and primary BCC recurs less often than previously treated BCC. It is not well known whether gender can influence the recurrence rate of BCC, but data from the literature report that BCC recurs more often in men (48-50). Incomplete excision has been reported to be more common in women, however, probably due to major aesthetic needs (51).

CONCLUSION

BCC is the most common skin cancer worldwide with increasing incidence, affecting mainly photo-exposed areas, even if genetic alterations play a pivotal role in its carcinogenesis. Different histopathologic subtypes have been described, presenting different behaviors. In particular, the superficial type has the most indolent prognosis. Dermoscopy aids in identifying the features associated with these different subtypes and is extremely important for management since the current guidelines suggest different therapeutic approaches according to histopathologic subtype. Although surgical excision is the gold standard of treatment, preservation of functions, cosmetic concerns, and patient age, as well as tumor prognostic factors, should guide the treatment choice. Therefore, a multidisciplinary approach is strongly recommended for the optimal management of BCC.

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