Journal of
Molecular Pathology

MDPI

Review

Basal Cell Carcinoma: Diagnosis, Management and Prevention

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Abstract: Basal cell carcinoma (BCC) is a slow-growing, locally aggressive, rarely metastasizing, low-grade cutaneous neoplasm that arises from the epidermal basal layer and invades the adjoining tissues. It is the most common skin cancer. It is fairly common in fair Caucasians and quite uncommon in dark-skinned populations. It contributes to 65–75% of cutaneous malignancies in whites and 20–30% in Asian Indians. The most important causal factors appear to be radiation exposure and genetic predisposition. It may present as a nonhealing lesion that occasionally bleeds or as a pruritic lesion with no symptoms. Tumours rarely spread to regional lymph nodes. The clinical appearances and morphology of BCC are diverse. Clinical types include nodular, cystic, superficial, pigmented, morphoeaform, (sclerosing), keratotic and fibroepithelioma of Pinkus. Most of the lesions appear on the head and neck, usually above the line joining the tragus and the angle of the mouth. A biopsy should be performed on all lesions suspected of BCC. The primary aim of treatment is the complete excision of the tumour tissue. Other treatment modalities include cryotherapy, immunomodulatory drugs, laser treatment or locally applicable chemotherapeutic agents. Prevention consists of lifestyle changes such as avoiding sunburn, tanning beds and prolonged direct sun exposure, shade seeking, sunscreen application on the skin, and physical barrier methods such as protective clothing, hats and sunglasses. Regular sunscreen use in childhood and adolescence seems more beneficial than in adulthood.

Keywords: basal cell carcinoma; head and neck malignancies; Moh's surgery; low-grade tumour; locally invading; tumour prevention

Citation: Baba, P.U.F.; Hassan, A.u.; Khurshid, J.; Wani, A.H. Basal Cell Carcinoma: Diagnosis, Management and Prevention. *J. Mol. Pathol.* **2024**, *5*, 153–170. https://doi.org/10.3390/jmp5020010

Academic Editor: Giancarlo Troncone

Received: 8 August 2023
Revised: 26 November 2023
Accepted: 1 April 2024
Published: 10 April 2024

1. Introduction

Basal cell carcinoma (BCC) is a low-grade cutaneous tumour that starts in the epidermal basal layer and invades the surrounding tissues. It is slow-growing, locally aggressive and rarely metastasizes [1–7]. Being the most frequent cutaneous malignancy [6], it is grouped along with squamous cell carcinoma (SCC) as a non-melanoma skin cancer (NMSC) to differentiate it from melanomas [5,8,9]. The NMSCs as such, in turn, are the commonest human cancers, with continually increasing numbers; about three-quarters being BCCs [4,8,10,11]. An estimate reveals an annual rise in BCC cases by 10%. It is often seen in Caucasians and is rather infrequent among dark-skinned races. As a result, it accounts for about 65–75% of cutaneous malignancies in fair populations and 25–30% in Asian Indians [3]. Ultraviolet (UV) radiation has been looked upon as of the greatest significance with about four-fifths of cases observed on the face, neck and scalp [4,7,9,12]. It is consistently seen in advanced age, particularly in those who have experienced persistent and intense sun exposure during their lives.

We aim to study the literature to highlight the multiple aspects of basal cell carcinoma ranging from epidemiology to etiopathogenesis to management and prevention.

2. Epidemiology

Basal cell and squamous cell carcinomas together (BCC + SCC) or keratinocyte carcinomas (KCs) are by far the most frequent cancers in the world, outnumbering all other cancers combined. Previously, BCCs contributed to nearly 80% of KCs. However, of late there has been an upsurge in SCCs relative to BCCs, thereby switching the conventional 4:1 ratio to 2.5:1 or even less [10,13]. The reciprocal rise in SCC lesions in the elderly due to chronic UV radiation exposure, BCC staying at the same time more common in relatively older adults, might be partially held responsible for the same. Despite this, most evidence still keeps the BCC incidence higher at a ratio of two to one [13].

It is a widely recognized fact that, with the advancing years of life, there is a rise in the cases of these tumours. Age is taken as an independent risk factor. An estimated 90% of patients are aged $\geq$ 60 years. The number of cases increases by 100% when reaching the age of 70 years (from 40 years). Though nearly 15% of lesions are encountered in younger populations, between 20 and 40 years, the incidence for this age group is likewise on the rise [4,9,13]. It is typically recognized in white people (skin type 1 or type 2), who have a positive tumour history in the family. Those living at higher altitudes and in the equatorial regions (subject to more radiation) demonstrate greater incidence rates, while Asians, Blacks and Hispanics tend to have a comparatively lower incidence. Males outnumber women with a ratio of 1.5–2:1. The potential reason is the greater sun exposure of males during outdoor work and sports activities. However, this male preponderance tends to die out among the younger patients under the age of 40 [4,10,13].

A proportion of 70–80% of lesions are encountered above the torso on the face, neck and scalp, following that, the trunk (~one-quarter) and the perineum, including the genitalia (about 5%) [9,14]. Certain histological variants occur preferentially at specific anatomical sites, the torso being a favourable location for the superficial subtype, particularly at $\leq$40 years of age. This supports the premise that intermittent sun exposure causes superficial BCC. Nodular BCC, in contrast, is predominantly noticed on the face, holding up the concept that links chronic cumulative sun exposure to the nodular type of BCC [10].

3. Aetiology

Primarily, radiation and genetic makeup are thought to be responsible for the tumours. They are encountered in the perpetually sun-exposed sites; so, a huge proportion (75–80%), as already stated above, are found in the head/neck region [1,2,11,15]. Given that lesions do arise in the covered (non-exposed) locations, including the genitalia, the presence of additional contributory factors is quite relevant. Some other contributing factors include fair complexion (Fitzpatrick skin type I-II-III), immunosuppression, trauma to the anatomical location, ionizing radiation, genodermatoses and arsenic exposure. Progressive age, male gender and high dietary fat intake are other proposed risk variables [2,3].

The radiation effect results from a blend of cumulative doses of UV light radiation received over years with occasional, intermittent, exposure to intense UV light and subjection to various other radionucleotide agents. The protective effect offered by melanin pigment against UV radiation acts as a saviour. Tanning beds are blamed for a one-and-a-half-fold rise in the risk of BCC [11]. The higher cumulative UV radiation dose with prolonged exposure, ozone depletion, sun-seeking behaviours with changing clothing styles and increased longevity all contribute to the rising incidence [16]. Though the majority of photo-damaged DNA is restored, some of the cross-links not reinstituted steadily proceed to cumulative DNA damage. The immune surveillance of tumour cells too is attenuated by the sunlight. In addition, advancing age leads to the waning of biological functions leading to the depreciation of DNA repair capabilities, gene mutagenicity, dwindling immune system function and chronic inflammation [9].

George RM et al. [8], in a study from Kerela (India), observed female patients exposed to heat and carcinogenic fumes (containing polycyclic aromatic hydrocarbons) generated from repeated heating of vegetable oil during cooking, usually on earthen ovens utilizing

wood as the primary source of fuel, again producing polycyclic aromatic hydrocarbons, with no major sun exposure [8].

The occurrence of BCC in scar tissue is documented in the literature [9]. Sclerodermiform BCC has been reported in a vitiligo patch on the cheek [17].

The Protein patched homolog (PTCH) gene mutation is identified in BCC. A PTCH mutant gene (inhibiting hedgehog signalling pathway) on chromosome 9q22.3 leads to basal cell nevus syndrome. A mutant gene referred to as SMO (smoothened, frizzled class receptor) is the causal determinant [7,9].

Furthermore, other cutaneous cancers are more likely to develop in those with a history of BCC—an approximate 10-fold increased risk [2,18]. About one-third to half of them will have a second basal cell tumour within the span of the next 5 years. Immunosuppressive medications are another risk factor for this tumour. Transplant recipients on immunosuppression have an increased likelihood of NMSCs and the rise is dependent on the duration of the immunosuppressive medication. BCCs are more common in transplant recipients by a factor of ten. Seropositivity to HIV increases the risk of BCCs twofold [18].

BCCs have also been linked to several hereditary disorders. The commonest among them is basal cell nevus syndrome (BCNS), characterized by many such tumours developing in children, particularly on the face; however, the trunk and scalp might also be involved. Some other characteristic features comprise characteristic facies, jaw cysts, other bony abnormalities, palmar pits, ectopic falx cerebri calcifications, medulloblastomas, meningiomas and ovarian fibromas. It is also linked to other diseases and syndromes like nevus sebaceous, xeroderma pigmentosum, epidermodysplasia verruciformis, Gardner's disease, multiple hereditary infundibolocystic BCC, Rombo syndrome, Bazex–Dupré–Christol syndrome, epidermolysis bullosa simplex, Dowling–Meara and albinism [18–20].

4. Clinical Features

BCCs can have a wide range of clinical manifestations, so a tissue biopsy is frequently used to confirm the diagnosis [21]. They often manifest as slow-growing, translucent/pearly white, dome-shaped papules with elevated, telangiectatic edges; they may also be pigmented [9,11,16]. They may present as a nonhealing lesion that may occasionally bleed, as a pruritic lesion or with no symptoms at all [13]. Draining lymph node basins are rarely (0.01–0.50%) involved, but locally progressive tumours can involve the adjoining tissues resulting in symptoms like weakness, pain and anaesthesia [16]. Sometimes, differential from non-malignant skin disorders like eczema or psoriasis may be challenging [9]. At times, even differentiation of herpes labialis from BCC may be tough because of the sharing of site and morphology [14].

5. Clinical Variants of BCC

BCCs present diversely clinically as well as morphologically [2]. Clinical types encompass nodular, cystic, superficial, pigmented, morphoeaform, (sclerosing), keratotic and fibroepithelioma of Pinkus. Mostly, the tumours are encountered in the head/neck region, classically placed above the line joining the oral commissure with the tragus on the same side [2,8,16]. Clinically, nodular, superficial spreading and infiltrating variants are the commonest types identified [19]. Metastasis is extremely rare and morbidity results from local tissue invasion and destruction, particularly on the face, head and neck [2].

5.1. Nodular Basal Cell Carcinoma (nBCC)

The nodular variant is found in three-quarters to four-fifths of patients. It is often detected on actinic-damaged skin [9,20]. Characteristically seen on the face, scalp and neck, it exhibits insidious growth [4,21]. Clinically, it may appear as an elevated, exophytic pearl-shaped nodule with peripheral and surface telangiectasia. At times, it may proceed to an ulcer or a cyst. The haemorrhagic lesions can mimic a haemangioma or a pigmented melanoma. The big lesions with central necrosis are classified as ulcus rodens [21].

5.2. Cystic BCC (cBCC)

Clinically, this is recognized by one or more cystic nodules of varying dimensions situated towards the perimeter of central tumour nests [21].

5.3. Sclerodermiform (Morphoeaform) BCC (mBCC)

Clinically, shining infiltrative plaques having ill-defined borders are seen, or it may look like a cicatrix or a small patch [4,21]. It represents around 6% of all BCCs with 95% of lesions restricted to the head/neck area. Being more aggressive, it sometimes tends to infiltrate deeper into muscles or fat tissue. These lesions rarely ulcerate and/or bleed [4].

5.4. Infiltrated Basal Cell Carcinoma

Clinically, this looks like a white compact plaque. The usual sites include the upper trunk and face. However, perineural invasion seldom presents as paraesthesia or hyperesthesia of the face [21]. Some authors equate it with morphoeaform or nodular BCC. So, the infiltrative variant is considered a continuum between NBCC and MBCC [4,9].

5.5. Micronodular Basal Cell Carcinoma

This type is recognized as raised or sometimes level but infiltrating growths. They appear as light-yellow lesions, thick on palpation, and do not ulcerate. They are commonly seen on the back [21].

5.6. Superficial Basal Cell Carcinoma (sBCC)

This is seen as a reddish plaque having defined margins or a pearl-shaped edge with superficial erosion, however, with no predisposition for invasion. It demonstrates variability in size (ranging from as small as a few millimetres to above 10 cm). It constitutes up to 30% of cases, often involving the back, chest and limbs, even though 40 per cent still occurs in the face, neck and scalp [4,19,21]. These are linked to acute sun exposure, particularly teenage painful sunburns [19]. These need to be distinguished from Bowen disease, psoriasis or eczema. Superficial BCCs, usually several, can be seen frequently in cases with arsenic exposure [21].

5.7. Pigmented Basal Cell Carcinoma

The pigment is seen in several types of BCCs, viz., the nodular, micronodular, multifocal and superficial variants, with the colour varying from a brown shade to black. Malignant melanoma can be a common differential diagnosis in these cases [21].

5.8. Fibroepithelioma of Pinkus

This is frequently seen as a solitary, raised erythematous (pink) nodule, especially affecting women. These are mostly located on the torso, especially the back and lumbar region [4,21]. Radiotherapy is believed to be a predisposing factor [21]. These tumours are to be distinguished from actinic keratosis, keratoacanthoma, seborrheic keratosis, squamous cell carcinoma, acrochordon or a fibroepithelial polypus [21].

5.9. Metatypic BCC

This is known to have the combined clinical features of both BCC and SCC—nodular BCC and cSCC [4,9]. Being more virulent than the other types, it potentially grows and extends as SCC does, with evidence of metastasis [4].

5.10. BCC Syndrome

This syndrome is very uncommon, with autosomal dominant inheritance with the predilection for multiple BCCs. Conventionally, three clinical features, viz., multiple BCCs, palmar/plantar pits and jaw cysts, are regarded as pathognomonic. A few cases may exhibit aggressive behaviour, involving the craniofacial bones. Usually, the diagnosis is suspected in a very young BCC patient with multiple lesions [20]. Its gene is plotted to

chromosome 9q22.3-q31 [22,23]. It is proven that mutations of the PATCHED1 (PTCH1) gene are correlated with this syndrome [4].

5.11. Linear Basal Cell Carcinoma

This represents the specific clinical type, demonstrating a line-like or linear form along a wrinkle line [24–27]. The commonest locations include the lower eyelid, cheek and neck. Although a limited number of cases are described in the published writings, still no case has been so far reported from Asia. Microscopically, they belong to the "nodular" subtype with a low recurrence character like the basal cell [26–31]. Nevertheless, one-third to two-fifths of the lesions belong to high-risk subtypes with a recurrence rate almost identical to infiltrative and morphoeic subtypes. Hence, such lesions are meticulously followed up [32].

6. Histopathology

Basal cell carcinomas originate in the basal cell layer of the epidermis—basal keratinocytes of the epidermis, hair follicles and eccrine sweat ducts [7,11]. The basal cell layer and outer root sheath of the hair follicles contain pluripotent epithelial cells [33,34]. The origin of BCC from the bulge region of the hair follicle is indicated by the absence of cytokeratin 15 [9]. Given the supporting stroma around the lesion, it is essentially devoid of any blood or lymphatic metastasis [11].

Classically, the cytoplasm is scarce with a big, oval nucleus—a larger nucleus-to-cytoplasm ratio suggests malignant rather than normal cells. The nuclei forming a palisading or a picket fence-like arrangement in the cell layer surrounding the tumour mass were considered to be pathognomonic of BCC.

Histopathological variants include nodular type (21 per cent), superficial type (17 per cent), micronodular type (15 per cent), pigmented type, infiltrative type (7 per cent), morphoeaform type (1 per cent), metatypical and fibroepithelioma of Pinkus; a mixed pattern with $\geq$2 major histologic patterns is observed in about 40% of patients [2,4,8,9,11]. Other less frequently encountered variants are keratotic, adenoid, clear cell, granular and BCC with sebaceous/eccrine differentiation [8]. The basosquamous variant, being very uncommon, has zones of basaloid as well as squamoid differentiation; some consider it to be a separate subtype, while others believe it to be synonymous with the metatypical subtype [8].

Morphoeaform (sclerosing, desmoplastic), infiltrative, micronodular and basosquamous subtypes are regarded as aggressive variants [2,13]. The tumour infiltration happens in a 3D fashion by way of digit-like outgrowths or projections into the surrounding tissues. The attributes of perivascular or perineural invasion suggest the most aggressive nature of the lesions [2], with enhanced rates of metastasis and locoregional recurrence [13].

nBCC typically consists of basaloid cell nests with a peculiar peripheral cell palisading along with characteristic clefting. The aggregation of mucin may lead to cyst formation [33]. Long undulating cases may demonstrate calcifications in the lesions [9,20,34].

mBCC demonstrates islands of neoplastic cells with a lack of peripheral palisading [9]. The tumour cell masses or clumps are enclosed by thick fibrotic stroma with an expression of smooth muscle alpha-actin (on immunochemistry) [21].

Infiltrated basal cell carcinoma presents as basaloid cell nests between the dermal collagenous fibres and infiltrates into the depth [21]. Contemplated as a continuum, it is typified by mucinous stroma studded with multiple variable-sized nodules and atypical basaloid cells. Adnexa and subcutaneous tissue are also involved [9,20,34,35].

In micronodular basal cell carcinoma, basaloid cells arrange to form little rounded nodules, with occasional palisading and myxoid surrounding stroma [21,31].

The superficial type has basaloid cell nests with prominent palisading. Basaloid cell nests are limited to the papillary dermis with no infiltration beyond this to the reticular one [20,21].

Pigmented basal cell carcinoma manifests with basaloid cell nests having copious amounts of melanin and melanophages, along with a modest quantity of inflammatory

infiltrate. While the melanocytes are visible among the tumour nests, the stroma exhibits melanophages [21].

Adenoidal BCC is regarded as a subtype of the nodular type, identified as nests of cells going deep into the dermis [36]. Another subtype of the same is basal cell epithelioma with very large-sized cells termed Monster Cells having single or multiple nuclei [37].

In addition, many other variants are reported in the literature like the granular cell type and BCC with peripheral micronodularity, the latter having more recurrent potential [31].

"Basosquamous carcinoma" refers to a lesion with areas of squamous cell carcinoma differentiation. The zones of the basal cell and squamous cell with a transition area between the two can be delineated [38,39]. The basosquamous carcinoma term is reserved for lesions having contiguous zones of basal cell and squamous cell carcinomas [39].

Metatypic BCC is recognized by eosinophilic basaloid cells having a high mitotic index and several apoptotic cells. At times, peripheral palisading might be lacking [40,41]. Perineural and lymphatic involvement can be demonstrated in such lesions [18].

7. Classification

Basal cell carcinoma comprises multiple clinical variants and is often classified into the below-mentioned types [1,9,18,42]:

i. Nodular basal cell carcinoma (classic BCC): the most frequent type (50% to 80%) often seen on the sun-exposed areas of the head/neck area (85% to 90%).
ii. Cystic basal cell carcinoma: recognized by dome-shaped, blue-grey cystic nodules.
iii. Morphoeic/morphoeaform/cicatricial basal cell carcinoma: 2% to 6% of BBCs; an aggressive type with a characteristic white sclerotic plaque and histological appearance.
iv. Infiltrative basal cell carcinoma: again, an aggressive one with distinct deep infiltration.
v. Micronodular basal cell carcinoma: no clinical distinction, micronodular growth pattern on histology.
vi. Superficial basal cell carcinoma (superficial multicentric basal cell carcinoma): about 15% of BBCs; most often found on the chest, back and limbs, and morphologically presents as an erythematous patch mimicking eczema or psoriasis; may enlarge to a big size and is the commonest BCC type recognized in HIV patients.
vii. Pigmented basal cell carcinoma: 6% of all BCCs; resembles nodular BBC but with enhanced melanization/pigment (brown or black); usually seen in Asian people.
viii. Rodent ulcer (Jacobi ulcer): an untreated or neglected lesion can progress to an ulcer.
ix. Fibroepithelioma of Pinkus: lower trunk, thighs and inguinal regions are commonly involved; it can progress to large proportions.
x. Polypoid basal cell carcinoma: identified by nodular exophytic lesions encountered on face, neck and scalp.
xi. Pore-like basal cell carcinoma: seen commonly in male smokers on the nose, nasolabial fold or lower forehead where the skin is peculiarly thick sebaceous, and mimics a large pore or a stellate pit.
xii. Aberrant basal cell carcinoma: when a BCC arises with a lack of any distinct carcinogen or occurs at aberrant/odd locations like the nipple, armpits, scrotum in males and vulva in females.
xiii. Solitary basal cell carcinoma in the young: occurs in facial embryonic clefts and frequently invades deep into the tissues.

8. Staging

The American Joint Committee on Cancer's (AJCC) TNM system is most commonly used for staging [18,21,43].

*8.1. Primary Tumour (T) **

- TX: primary tumour cannot be assessed.
- T0: no evidence of primary tumour.
- Tis: carcinoma in situ.

- T1: carcinoma less than 2 cm in greatest dimension, with fewer than two high-risk features. **
- T2: carcinoma greater than 2 cm in greatest dimension or a tumour of any size with at least two high-risk features. **
- T3: tumour invasion of the maxilla, mandible, orbit or temporal bone.
- T4: tumour invasion of the skeleton (appendicular or axial) or with perineural involvement of the skull base.

* Excludes cutaneous squamous cell carcinoma of the eyelid.
** High-risk features for the primary tumour (T) staging:

- Depth/invasion: >2 mm thickness, Clark level > IV, perineural invasion.
- Anatomic location: primary site ear, primary site non-hair-bearing lip.
- Differentiation: poorly differentiated or undifferentiated.

8.2. Regional Lymph Nodes (N)

- NX: regional lymph nodes cannot be assessed.
- N0: no regional lymph node metastasis.
- N1: metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension.
- N2: metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.
- N2a: metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension.
- N2b: metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension.
- N2c: metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.
- N3: metastasis in a lymph node, more than 6 cm in greatest dimension.

8.3. Distant Metastasis (M)

- M0: no distant metastasis.
- M1: distant metastasis.

Anatomic stage/prognostic groups.

- Stage 0: Tis, N0, M0
- Stage I: T1, N0, M0
- Stage II: T2, N0, M0
- Stage III: T3, N0, M0

T1 to T3, N1, M0

- Stage IV: T1 to T3, N2, M0

T any, N3, M0
T4, N any, M0
T any, N any, M1

9. Diagnosis

Doubtful lesions always need to be biopsied [9]. Initial tissue sampling involves a shave technique for elevated lesions or a 2 to 4-mm punch biopsy of the most abnormal-looking area [11].

Radiology is vital in the evaluation and staging of locally advanced and/or metastatic BCC. MRI is the modality of choice for the assessment of local advancement and for estimating perineural disease and is equivalent or of higher calibre to CT for assessing bony involvement. CT and PET/CT will be of value to elucidate the metastatic workup [44].

9.1. Dermoscopy

This is a non-invasive, in vivo technique that enhances the diagnostic accuracy of benign versus malignant cutaneous lesions. It helps the distinction between BCC and other pigmented cutaneous tumours like malignant melanoma and seborrheic keratosis [4]. The diagnostic accuracy ranges from 95% to 99% [9]. Dermoscopy structures of BCC comprise three brackets which encompass vascular, pigmentation and nonvascular/non-pigmented. Vascular ones encompass arborizing vessels and short thin telangiectasias whereas pigment-related structures comprise maple leaf or spoke-wheel pattern zones, several bluish-grey nests and globules, and in-focus dots. Nonvascular/non-pigmented structures can be erosions, ulcerations, white streaks, etc. [9]. A diagnostic dermoscopic model has been proposed, depending on (Menzies et al.) the paucity of pigmentation with the appearance of a minimum of one out of six positive morphological traits; positive results on dermoscopy comprise ulcers, multiple bluish-grey globules, leaflike areas and telangiectasia [4].

9.2. Reflectance Confocal Microscopy and Optical Coherence Tomography

The interestingly new non-invasive advancements in diagnosing BCC comprise Reflectance Confocal Microscopy (RCM) and Optical Coherence Tomography (OCT). RCM, working on a near-infrared laser, provides high-magnification pictograms of a lesion at a cellular resolution akin to real-time histology, devoid of the requirement of any (invasive) biopsy [45,46]. The RCM features of BCC are well documented in the literature [47–56]. The most significant RCM features are appreciated at the dermal-epidermal junction (DEJ) or in the papillary dermis. These include dark silhouettes, cleft-like dark spaces, dendritic/plump–bright cells, canalicular vessels and bright tumour islands. Dermoscopy together with RCM enables the diagnosis of BCC subtypes without the need for a biopsy [57]. However, there are certain limitations of RCM such as, firstly, the depth of imaging (250 m) which limits the assessment of the invasion and deep margins of the lesion, secondly, the steep learning curve and, thirdly, the price of the machine [18].

OCT is another non-invasive real-time diagnostic tool that makes use of infrared light to furnish an image based on the summation of multiple light refractions from all the structures of the skin having differing optic characteristics [58]. Studies have evidenced it as 87% sensitive and 80% specific to diagnosing superficial BCC [59]. Furthermore, the combined diagnostic accuracy of OCT with dermoscopy has been reported as 87.4% [58,60]. However, its drawback is that it is difficult to apply to pigmented lesions.

Some of the other non-invasive techniques that can be of help in diagnosing BCC are Raman spectroscopy, high-resolution ultrasonography and terahertz pulse imaging, to name a few [61–64].

10. Management

The prime objective of treatment is to excise the tumour completely. Other treatment modalities include cryotherapy, immunomodulatory drugs, laser treatment or locally applicable chemotherapeutic agents [3]. Management is dependent on factors like the site of the tumour, age, presence of comorbidities and the clinical/pathological variant of the lesion. The importance of the location of the lesion is that the lesions in aesthetically or functionally significant sites such as facial BCC are best managed with the modalities wherein tissues are minimally sacrificed whilst ensuring a total cure [1,3]. Owing to the slow growth of these tumours, in older patients, less invasive therapeutic modalities may be preferred, even though at the cost of greater chances of recurrence. Cystic and nodular BCCs have clearly delineated borders, whereas the morphoeic, micronodular, trabecular, infiltrative and basosquamous types have poorly distinct borders which lend them exceeding virulence. Due to the minimum depth of invasion, topical therapy might work in superficial BCCs (sBCCs) [1].

The following are the common techniques and methods utilized for the management of BCC:

Wide excision, curettage and electrodesiccation, Mohs micrographic surgery, cryosurgery and radiation, while topical application of imiquimod or 5-fluorouracil may provide a response in superficial BCC.

11. Surgical Management

11.1. Standard Excision of Primary BCC with Predetermined Margins

This has been the most common approach used to treat BCC and is regarded as highly effective. Primary tumours are excised with a safe margin of 2–5 mm of healthy skin and about 10 mm or more for recurrent/large tumours. Primary closure may be difficult, particularly in facial lesions requiring grafts or local flaps [1,9]. A frozen biopsy is necessary to substantiate predetermined tumour-free margins [9]. The National Comprehensive Cancer Network (NCCN) recommendation is for a surgical margin of a minimum of 4 mm for low-risk BCC with postoperative margin assessment [65]. For high-risk cases, a wide margin (greater than 6 mm) is recommended. Studies have shown that >95% of small well-circumscribed lesions (smaller than 2 mm) are amenable to complete excision with a margin of 4 mm [18]. According to Boulinguez et al. [66], incomplete excision bears a 24 per cent risk of more aggressive recurrence; the risk is higher for the lesions around the nose, eyes and ears. Thus, the lesion should be excised again as early as possible and radiation has to play a definite role [1,4].

11.2. Mohs Micrographic Surgery

In Mohs Micrographic Surgery (MMS) or Mohs surgery, tumour excision is examined by microscopic margin control [18]. This is a sophisticated surgical excision technique for skin malignancy having the highest reported cure rates—in primary as well as in recurrent cases [67]. The aim is to spare the local tissues with minimal local relapse rates. It is indicated in primary lesions necessitating maximal sparing of tissues such as nasal, labial or eyelid tumours, or lesions with higher chances of relapse like those on the nose, lips, temporal bones, mucous membranes and penis. Large lesions (>2 cm in diameter), those lacking well-defined borders and those having aggressive histological features (infiltrative, morphologic or perineural infiltrating) are largely suitable for Mohs surgery [21]. It is contemplated as the single most effective modality with high cure rates as well as maximal preservation of tissues [9,19]. Studies have shown five-year disease-free rates of up to 100% in case of primary lesions with up to 96% for recurrent cases [1,4]. Though resource-demanding, it is a systematic, cost-effective modus operandi considered the first-line treatment for high-risk tumours as well as those in aesthetically sensitive areas like the face [11,21,67]. Rowe et al. reported a respective five-year recurrence of one per cent for primary and 5.6 per cent for recurrent tumours with Mohs surgery as compared to 10.1% and 17.4% for standard excision with peripheral margin assessment (SEPMA) [68]. Correspondingly, a ten-year recurrence rate for primary facial lesions was reported as 4.4 per cent for MMS and 12.2 per cent for SEPMA [69]. In addition, utilizing intraoperative frozen biopsy excision with complete circumferential peripheral and deep margin assessment (CCPDMA) is a reasonable option for MMS [65].

11.3. Curettage with and without Cautery

Curettage is another modality employed for the treatment of such lesions. The tumour is scraped off with a curette and its base and margins are electrocauterized for haemostasis and any leftover lesion is extirpated; it can be replicated. The annihilation of margins forbids histologic margin assessment [65]. So, it is recommended to confirm the histopathology prior to surgery. Recurrence rates of 7.7% to 19% at 5 years have been reported with higher rates for recurrent disease, especially facial BCCs [1,18]. So, it is regarded as a contraindication for recurrent tumours [9]. In a study conducted on BCCs excised immediately following curettage and electrocautery, residual tumour was demonstrated in 47 per cent of face, scalp and neck lesions, and 8.3 per cent of limb/torso sites. However, it is an operator-dependent procedure [1]. It is a somewhat time-saving and economical

modality for superficial tumours. The NCCN advocates this technique for properly selected and low-risk patients [16]. The relapse rate ranges from 1 to 15% for small tumours which rises to 50% in tumours > 3 cm since it is very demanding to estimate the deeper extent of the lesion [4,21]. It must be taken into account that such a technique needs to be used with caution at locations with hair such as the scalp, pubis, axillae or the beard area (in men), because of the risk of tumour extension along follicles [18].

11.4. Cryosurgery

Cryosurgery implies 'using liquid nitrogen to destroy tissues' [4,21], employing freeze-thaw cycles to destroy the tumour cells. Though it is quick and low-cost, histological margin assessment is not possible [18]. So, again, we need to determine the histology before the procedure. It is indicated in small-sized BCCs, multiple BCCs and BCCs with well-defined borders, especially when surgical removal is contraindicated [4,21]. So, it finds its applicability in treating superficial lesions and tumours with low-risk, and selected patients with high-risk tumours, either as the only treatment or combining it with curettage [1,70]. It is not recommended for large and recurrent tumours [9]. Also, given the higher recurrence rate as well as poorer aesthetic outcomes, it is better avoided in facial BCCs [1,71]. Overall, it is very much operator-dependent with variable recurrence rates [1]. Some case series have reported cure rates between 94% and 99% [18]. The recurrence rate for small BCCs (<8 mm) is about 8%. Advantages include being an easy, simple and less time-consuming modality. Specific contraindications comprise lesions in the nasolabial fold, ala nasi, tragus and eyelid edges [4,21].

11.5. Laser Ablation

Laser ablation is utilized as a management option for BCCs, both as monotherapy and adjunct therapy. It can be acceptable for superficial BCC [4,18,21]. It has been used synergically with curettage for the management of low-risk BCCs [1]. The recurrence rate lies between 3.7 and 15.5% [4,21]. Campolmi et al. found that superficial and NBCC managed with super pulsed CO_2 laser therapy had no recurrence on 36-month follow-up [72,73]. In a retrospective study conducted by Moskalik et al., a recurrence rate of 1.8% was reported for facial lesions managed by neodymium-based (pulsed) laser therapy during a period of 12 weeks to 60 months [74]. The reported undesirable effects include reactive hyperaemia, oedema, scarring and soreness [75].

12. Non-Surgical Management

12.1. Radiotherapy

Radiotherapy (RT) has a crucial role in the treatment of BCC and can be used in the definitive setting, adjuvant setting or both. Patient selection is vital and is best determined in the setting of multidisciplinary care. Tumours in aesthetically challenging locations like the eyelids, nose, central face and ear are usually treated with radiation. This provides for the functional and cosmetic preservation of the tissues wherein surgery might result in functional impairment [16]. However, it is not recommended for upper eyelid lesions due to the risk of keratinization of the conjunctiva or aural tumours because of likely injury to ear cartilage, and the nasal bridge is, in particular, prone to radio necrosis [1,4]. As noted in the above section, it can also serve as a primary modality of management for patients who are not candidates for surgery or those with unresectable tumours [9,18]. Both modalities—teletherapy (external beam RT) and brachytherapy—are being utilized for the management of such lesions [76]. However, it is not to be used in cases with genetic syndromes, like basal cell nevus syndrome, Bazex syndrome, xeroderma pigmentosum, epidermodysplasia verruciformis, BCNS or Gorlin–Goltz syndrome, because of the ionizing radiation potential to induce other malignant tumours [21,77]. Additionally, retreating recurring lesions after prior radiation is also contraindicated [9]. The purpose of postoperative RT after wide local excision of BCC is to reduce the likelihood of local and/or regional recurrence. Generally, in cases wherein the recurrence is almost certain or the salvage procedure is ruled out, RT

(adjuvant) is indicated; furthermore, it has a role following a surgical excision with either positive or too close margins, or when other high-risk variables, like a perineural invasion, bone/nerve invasion or recurring disease, are present [16].

12.2. Topical 5% Imiquimod Cream

Imidazoquinoline amine is a synthetic immune modulator that acts by binding to the toll-like receptor. This produces proinflammatory cytokines such as IFN-α, IL-6 and TNF-α with ensuing cytotoxic T cell-mediated cell death. Imiquimod can be used for a single primary superficial BCC with a diameter of 0.5 to 2 cm. It is not used in periocular, perinasal, perioral or periaural areas. A 6-week application of imiquimod has a cure rate of 70% to 94% [1,4,21]. The effectiveness of imiquimod treatment is reliant on tissue penetration. Because of their shallow depth of invasion, sBCCs may be more amenable to topical treatment. There have been reports that it could be utilized to treat nBCCs as well. The greater depth of these tumours causes partial drug penetration and, thus, poor cure rates. It is a viable option for surgery in cases with superficial lesions of the face, although its lasting efficacy does not reach that of other treatment options. It is contraindicated for recurrent cases but it may be an acceptable choice for older, frail individuals not candidates for surgery [1,4].

12.3. Topical 5-Fluorouracil 5%

5-fluorouracil destabilizes DNA by inhibiting the methylation of deoxyuridylic acid to thymidylic acid. It is occasionally applied on smaller, superficial BCCs and should be used exclusively in low-risk areas. As a result, it is not indicated in facial BCCs [1,4].

Both these (topical 5-fluorouracil 5% cream and imiquimod 5% cream) are approved for the management of superficial tumours, with cure rates going up to 90% [9,18]. At a 1-year follow-up, an RCT found that 5-FU and imiquimod 5% cream had equal efficacy in superficial BCCs [78]. Other publications reported imiquimod as superior with up to 80% clearance rate compared to 68 per cent for 5-FU at 36 months [79]. 5-FU is not advocated for use in nBCC and there are only a few case reports to substantiate it [80,81]. So, such modalities are restricted to superficial/small BCCs located in low-risk sites. Finally, topical applications may lead to adverse effects like erythema, swelling and erosions [18].

12.4. Photodynamic Therapy (PDT)

PDT incorporates the topical application of a photosensitizing substance, typically aminolaevulinic acid (ALA) or methyl amino levulinate (MAL), with subsequent light irradiation. It is a relatively new method used for the management of superficial or morphoeaform BCC [1,4,21]. Clearance rates are reported between 70 and 90 per cent, but important to note is that the cited trials have limited follow-up durations [82]. Most studies demonstrated high cure rates for the superficial and nodular tumours, with enhanced cure rates for thinner forms of nodular subtype [83–85]. Therefore, it may be indicated in the case of superficial BCCs and thinner nodular BCCs, commonly in individuals with extensive or multifocal disease, or with multiple AKs [18].

12.5. Intralesional Therapy

Several intralesional chemotherapeutic agents, viz., 5-FU, interferons, interleukin-2 and bleomycin, have demonstrated mixed responses when used for the treatment of BCC. Though adverse events are uncommon, these are usually dose-dependent and include injection site local effects as well as flu-like symptoms [76,86]. Intralesional IFN has demonstrated tumour-free rates as high as 96% [21].

12.6. Targeted Therapy—Hedgehog Pathway Inhibitors (HPI)

Vismodegib and sonidegib are the targeted oral medications approved by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for the treatment of basal cell tumours, in cases not pertinent to surgical excision or radiation.

In particular, vismodegib is approved for both locally advanced and metastatic diseases, whereas sonidegib is used in the management of locally advanced diseases only [87–90]. Sonidegib has shown shrinkage of the lesions in >90% of cases with locally advanced BCC. With longer follow-up, it has revealed sustained response in advanced cases [91].

12.7. Electrochemotherapy (ECT)

Electrochemotherapy (ECT) is meant to combine manageable cytotoxic agents with short electric pulses. Being an effective palliative cutaneous therapy, it is a safe and well-tolerated option for multiple/large BCCs, for which conventional treatment is not appropriate. In selected cases of multiple BCCs, a single or two ECT cycles with bleomycin may result in sustainable palliation. Further research into the treatment of locally advanced BCC with ECT is warranted [92].

13. Prognosis and Risk Factors

BCC is considered an indolent tumour that can invade local tissues but usually without distant spread. Spread by chronic local extension is the rule. The first documented case of metastatic BCC was reported by Beadles in 1894. Since then, about 110 cases of true metastases, meeting the diagnostic criteria of Lattes and Kessler, have been reported [12]. BCC accounts for about 0.1 to 2 per cent of all patient deaths due to cancer [4,9].

It usually has a good prognosis; clinically poor prognostic factors include tumour size greater than 2 cm, increased depth of invasion, distribution in the mid-facial region, poorly defined margins, long-standing lesions, recurrent lesions and immunosuppression [3,4]. Additionally, perineural and vascular invasion raises the possibility of metastasis [4]. It should be noted that incidental perineural invasion on pathology has a lower risk of recurrence than clinically evident perineural invasion [16]. Studies are evidence that about one-third of patients will acquire recurrent skin malignancies within 5 years of their initial NMSC diagnosis. A 2002 survey found that 25% of NMSC cases had at least two skin cancers treated the year before [10].

BCC can also be divided into low-risk and high-risk categories based on prognostic factors [16,18]. These prognostic factors (Table 1) include the size of the tumour (larger tumours have a higher risk of recurrence), the clinical margins (poorly defined lesions have a higher risk), the histological subtype (morphoeaform and metatypical subtypes represent high-risk lesions), the histological features (perineural and/or perivascular invasion are markers of higher risk), the recurrence and the tumour site. Regarding the location, high-risk zones are represented by the nose and periorificial areas of the face; intermediate-risk zones are the forehead, cheek, chin, scalp and neck; low-risk zones are the trunk and limbs [16,18]. High-risk BCCs are defined by at least one poor prognostic factor, while low-risk BCCs are superficial BCC, Pinkus tumour (a variant of BCC identified by focal cystic changes), and small nodular BCC on intermediate or low-risk locations [93]. The French guidelines also established an intermediate risk group to differentiate recurrent superficial BCCs from other recurrent BCCs, as well as some nBCCs, based on site and size [94]. Additionally, there is a greater likelihood of recurrence for tumours treated with ablative techniques like lasers, without histopathological control as opposed to surgical excision [16,18].

Table 1. Prognostic groups of BCC according to Dandurand et al. [94].

Low-Risk BCC	Intermediate-Risk BCC	High-Risk BCC
Superficial primary BCC	Superficial recurrent BCC	Morphoeaform or poorly defined
Nodular primary BCC when: <1 cm in intermediate-risk area <2 cm in a low-risk area	Nodular primary BCC when: <1 cm in a high-risk area >1 cm in intermediate-risk area >2 cm in a low-risk area	Nodular primary BCC when: >1 cm in a high-risk area
Pinkus tumour		Histological forms: aggressive Recurrent forms (apart from superficial BCC)
High-risk zones are the nose and periorificial areas of the head and neck; intermediate-risk zones are the forehead, cheek, chin, scalp and neck; low-risk zones are the trunk and limbs.		
Aggressive histological forms include micronodular, morphoeaform and metatypical basosquamous forms.		
The perineural invasion also seems to be a histological sign of aggressiveness.		

A class of aggressive BCCs that are both histologically and clinically aggressive is known as aggressive-growth basal cell carcinoma (AG-BCC). This group includes morphoeaform, infiltrating and recurrent BCCs. Aggressive growth BCC is more likely to be seen in young patients below 35 years. Among patients under 35 years of age, 38% of women and 25% of men had AG-BCC compared with 9% of women and 11% of men in the older age group [95].

The 5-year recurrence rates for primary BCCs after surgical excision is 10.1%; radiotherapy, 8.7%; curettage and electrodesiccation, 7.7%; cryotherapy, 7.5%; all non-Mohs modalities, 8.7%; and Mohs micrographic surgery, 1%. Recurrences typically happen 4 months to 1 year after initial treatment and the likelihood of acquiring a second lesion within 36 months is around 44 per cent which is ten times higher than the likelihood in the general population [96,97]. Recurrence rates are higher for tumours on the nose or T-zone of the face. Recurrence occurs most commonly on the nasolabial fold and the nose. Compared to nodular types, infiltrative, micronodular and multifocal types have a greater recurrence potential. Metastasizing basal cell carcinoma is very uncommon (0.02 to 0.55 per cent). The most common sites of metastasis reported are the lymph nodes, lungs and bones. Diagnosed cases of BCC have a 35 per cent risk of recurrence at the same site within 36 months and a 50 per cent chance of developing another (not recurrent) BCC within 60 months [98].

14. BCC Prevention

Although early diagnosis and prompt treatment are indispensable to improve outcomes, the implementation of preventive measures may play a pivotal role, especially when initiated in early life (before adolescence) [18]. Prevention includes lifestyle modifications like refraining from tanning beds, desisting from sunburn and keeping away from prolonged direct sun exposure as well as shade seeking, sunscreen application, and physical barrier methods such as protective clothing, hats and sunglasses [99]. Regular sunscreen application from childhood seems more beneficial than when started at a later age (adulthood) [100].

To date, the only BCC prevention medication includes the oral intake of a water-soluble vitamin B3 derivative, nicotinamide (NAM), which is found in edible items such as meat, fish, legumes, mushrooms, nuts and grains [101,102]. NAM is regarded as a cutaneous immunity normalizer as it offsets UV-induced immune suppression. NAM restricts keratinocyte injury, by modifying several activities like limitation of DNA damage and optimization of DNA damage response [103]. Therefore, NAM (500 mg twice daily) should be contemplated as a rational choice for BCC prevention, especially secondary prevention in high-risk individuals with pre-existing BCC [18]. Other studies propose that pharmacological inhibition of COX-2 may limit epithelial neoplasms and that daily use

of celecoxib might curtail the risk of developing BCC [104,105]. High-risk people with a positive history of past BCC can benefit from celecoxib treatment. However, literary evidence is poor and the results are too inconsistent to advocate for chemoprevention [106].

In general, routine screening for skin cancers is still debatable. The U.S. Preventive Services Task Force cites literary evidence as inadequate to recommend for or against routine whole-body skin examination to screen for cutaneous malignancy [11]. The NCCN guidelines recommend a whole-body skin examination every 6–12 months for the first 2 years following BCC diagnosis and then at least annually for life [107]. However, patients are encouraged to practice active self-monitoring [18].

15. Conclusions

Clinically, BCCs have an indolent course and possess very little metastatic potential. Recurrences do occur depending on the location as well as the histological type of the lesion. So, preoperative risk assessment may be of great rescue. For all subtypes, surgical excision is the gold standard. However, other modalities do have their role depending on the multiple factors as described. Also, preventive majors will hold promise in reducing the incidence.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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