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An Overview on Basal Cell Carcinoma

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1. Introduction

Basal cell carcinoma (BCC), first described by Jacob in the early 1800(1), is the most common cancer in the general population, accounting for 80% of nonmelanoma skin cancer (2). Worldwide incidence is increasing by about 10% per annum, so the prevalence of BCC will soon equal that of all other cancers combined(3). The average lifetime risk for white skinned individuals to develop BCC is approximately 30 %(4). BCC is uncommon in dark skinned races. Studies have estimated that 1.2% to 4.6% of BCCs arise in black patients (5). BCC is more common in men than in women (ratio of approximately 2:1). BCC most commonly occurs in older than 50 years old (6). Interestingly, women younger than 40 years of age have been found to slightly outnumber men in this age group (7). The increased incidence rates could be attributed to changes in sunbathing behavior in the young and the middleaged, which has changed during the 20th century. Particularly after the Second World War, more people had leisure time for outdoor activities. Also, women's clothing changed allowing larger parts of the body to be exposed to the sun (8).

2. Etiology

The etiology of BCC is still unclear but appears to be of multifactorial origin, resulting from a complex interaction of both intrinsic and extrinsic factors(Table 1).

Extrinsic factors	**Intrinsic factors**
intermittent'' sun exposure during childhood or teenage years	Increasing age
ingestion of arsenic acid (medicine, pesticides),	Positive family history
ionizing radiation	gender (male predominantly)
X-ray and grenz-ray exposure	Fitzpatrick skin type I-type2
low vitamin intake	Red or blond hair
high dietary energy, especially from fats	light eye color (blue or green eyes)
topical nitrogen mustard administration	immunosuppression
thermal burns	Genodermatoses (albinism, xeroderma pigmentosa, Rasmussen syndrome, Rombo syndrome, Bazex–Christol–Dupre syndrome, albinism and Darier's disease, and the naevoid BCC syndrome (Gorlin's syndrome))
Psoralen and UVA (PUVA) treatment	posttransplantation
scars, draining sinuses, ulcers, burn sites and foci of chronic inflammation	

Table 1. Risk factors for basal cell carcinoma.

UV radiation (UVR), and especially UVB, is responsible for the majority of cutaneous damage and is believed to be the primary established risk factor in the development of BCC (9,10). The role of ''intermittent'' sun exposure during childhood or teenage years (periods that are supposed to be critical for tumor development) appears to be of particular importance and has been shown to be a strong risk factor for BCC. The infrequent, intense and intermittent sun exposure during childhood and adolescence, especially before the age of 20, increases the risk of BCC more than if a similar dose was delivered more continuously over the same time period (11). Increased risk of nodular, but not superficial BCC, has been reported in association with occupational sun exposure, Moreover, a strong association has been shown between BCC and skin lesions that are ''objective'' markers of cumulative sun exposure (whether long-term or intense intermittent), such as actinic keratoses and solar lentigines, which result from a combined effect of sun exposure and skin pigmentation characteristics (12, 13, 14). UVR especially prior to the age of 20 years is suggested to initiate a process of basal cell carcinogenesis (15). UVR has two major effects that influence BCC development, namely DNA damage and immunosuppression (16). Exposure to UVR, specifically UVB, induces covalent bonds in DNA between adjacent pyrimidines, generating photoproducts such as cyclodipyrimidine dimers (T /T) and pyrimidine lesions which are mutagenic if not repaired. Unlike UVB, UVA may have more indirect effects in DNA through ROS (17). UVR is also a local immunosuppressant in skin, giving rise to the suggestion that this may compromise local antitumour activity. Exposure to UVR results in a cascade of events including a T-lymphocyte-mediated immunosupression (18). Burning and tanning response of skin (skin type) is important in determining BCC risk. BCCs are more common in males and those with skin types 1 and 2 demonstrate an increased susceptibility with relative risks between 4.0. and 2.1 (19, 20).

In sporadic BCC, DNA repair capacity below the upper 30th percentile was associated with a 2-3-fold increase in BCC relative risk. However, some studies have reported increased repair in BCC patients and so batch variability and the effects of age, family history of skin cancer and current sun exposure may confound results (21).

The incidence rates of BCC are increasing each year. These trends may be due to increases in both acute and prolonged sun exposure (due to altered life style and pro-tanning behavior), and the depletion of stratospheric ozone, together with the increasing aging of the general population (22). Similar to melanoma and in contrast to SCC, sporadic BCC may occur in individuals with intermittent extreme UV exposure behavior (11, 23).

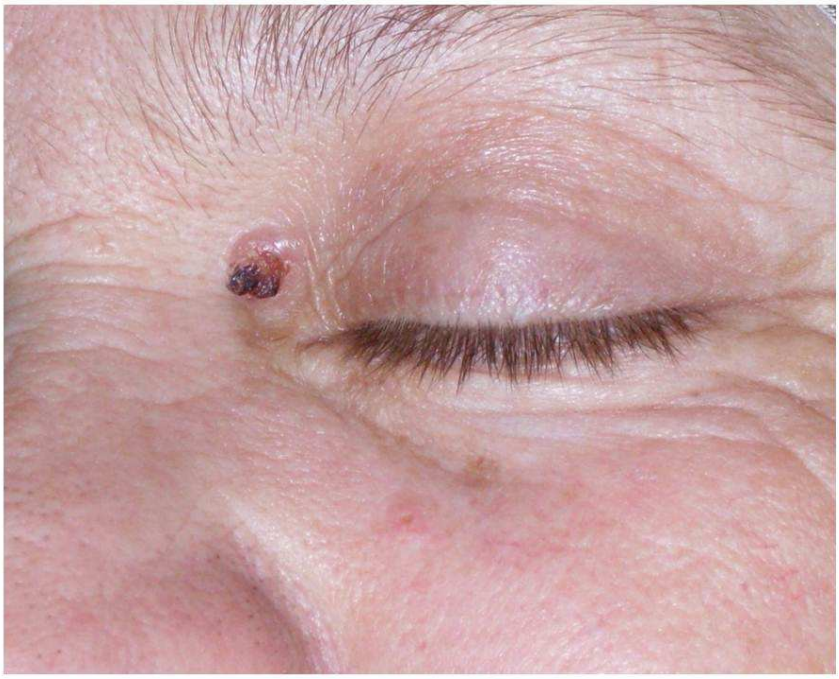
Other extrinsic risk factors, beyond UVR, predisposing to BCC, include ingestion of arsenic acid (medicine, pesticides), ionizing radiation, X-ray and grenz-ray exposure, low vitamin intake, high dietary energy, especially from fats, topical nitrogen mustard administration and thermal burns. Psoralen and UVA (PUVA) treatment, classically for psoriasis, carries a modest increased risk. Constitutional factors include gender, age, immunosuppression and genetic predisposition (a family history of BCC, genetically inherited nucleotide excision repair defects such as xeroderma pigmentosum) . Also, pigmentary traits, such as fair skin, blond or red hair, light eye color, tendency to sunburn and poor tanning ability (skin Type I), have all been associated with a higher risk of BCC (22-24). Fitzpatrick skin type I (always burns, never tans), male gender, red or blond hair and blue or green eyes have been shown to be associated with increased risk of BCC development. Several genodermatoses are associated with the development of BCC, including albinism, xeroderma pigmentosa, Rasmussen syndrome, Rombo syndrome, Bazex–Christol–Dupre syndrome, albinism and

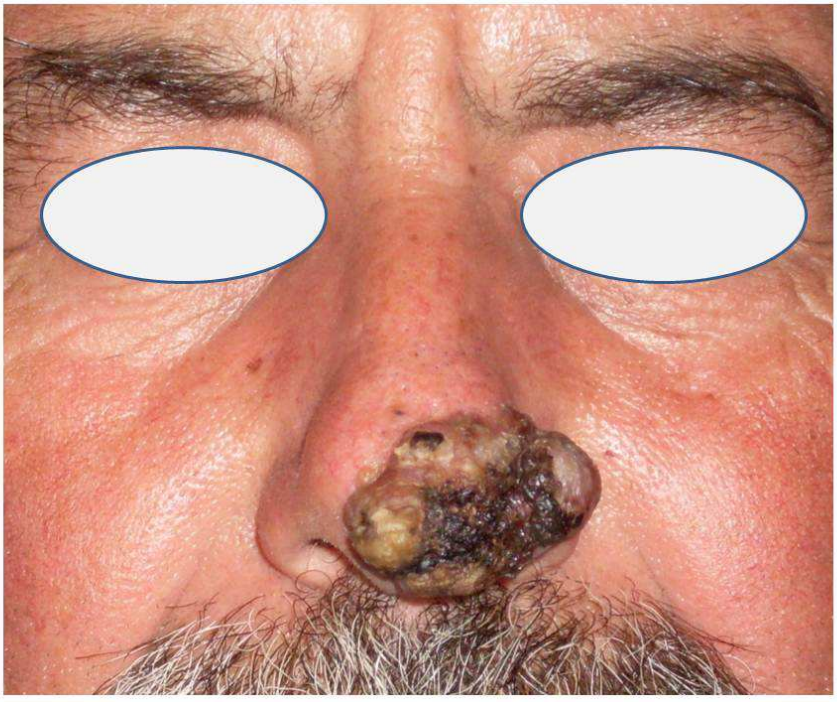
Darier's disease, and the naevoid BCC syndrome (Gorlin's syndrome) (25). These syndromes variably either decrease epidermal pigmentation and thus increase the risk of UV light-induced oncogenic transformation or promote genotypic instability in the epidermis.(26) Nevoid BCC syndrome (NBCCS) is linked to chromosome 9q22, which harbours the PTCH gene where activating germline mutations have been found in BCC tissue (27, 28). Somatic PTCH mutation has also been described in sporadic BCC (29, 30). Dysregulation of the PTCH pathway is thought to be a critical event in BCC development. The tumour suppressor gene (TSG) p53, involved in genome surveillance through the regulation of cell proliferation and death, is frequently inactivated in BCC (31, 32) with up to 56% of tumours displaying mutation in the conserved region of one p53 allele. Indeed, it has been suggested that p53 mutation is a crucial but late event in BCC progression (33).

BCC may, like squamous cell carcinoma, arise in the setting of scars, draining sinuses, ulcers, burn sites and foci of chronic inflammation(15). The incidence of BCC arising from chronic wounds is low, and as few as 2.4% of malignancies develop from chronic leg ulcers(34). The role of immune compromise in provoking an increased risk of BCC may be due to impairment of the immune surveillance of oncogenic viruses. Immunosuppressive therapy also increases risk (ten-16 fold in renal transplant recipients) (35). BCC is the second most common cancer among solid organ transplant recipient(SOTR). The peak incidence rate was 5 years posttransplantation for patients older than 50 and 8 to 10 years for younger patients. Of the various organs transplanted, liver engraftment may bestow greater risk for BCC than others. BCCs in SOTR more often affected younger males and were more likely to present in sun-protected or bizarre locations, such as genitalia, external auditory meatus, and axilla. Lesions developed sooner after heart transplantation (5.7 years) than after renal transplantation (8.1 years). Renal transplant recipients with BCCs were more often younger and male compared to controls. Lesions were more commonly multifocal but not more likely to recur or metastasize. The mean time to tumor development was 10.5 years (36, 37).

3. Clinicopathologic aspects of BCC

The typical BCC is a pearly pink or flesh colored papule with telangiectasia. Lesions may be translucent or slightly erythematous with a rolled border, occasionally accompanied by bleeding, scaling or crusting(Fig. 1). Aggressive growth tumors tend to show more frequent ulceration and large, untended neoplasms can be locally destructive of eyes, ears and nares (38). BCCs are usually slow-growing tumors that only rarely metastasize (39). Growth of BCCs is usually localized to the area of origin; however, some BCCs tend to infiltrate tissues in a three-dimensional fashion through the irregular growth of finger-like projections, which may not be obvious on visual inspection (40, 41). If left untreated, or inadequately treated, the BCC can cause extensive tissue destruction, particularly on the face(Fig. 2). The clinical course of BCC is unpredictable; it may remain small for years, or it may grow rapidly or proceed by successive spurts of extension of tumor and partial regression (42). Thus, early prompt treatment is essential to minimize the morbidity of both cancer and treatment. Eighty percent of BCCs appear on the head and neck compared to 15% on the trunk and 5% on the extremities "larger lesions" are also more likely to be located in areas of the body other than the face where patients do not notice or complain about them as early (43).



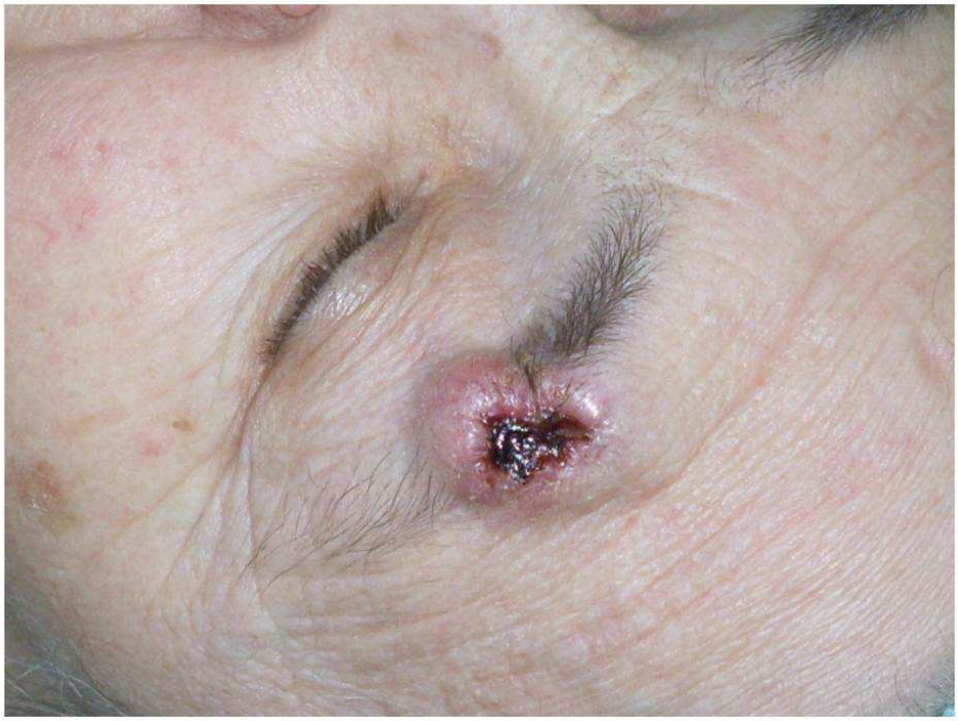


A BCC can usually be diagnosed on the clinical aspect, but histological confirmation is necessary to determine the best treatment option. Although 26 histological subtypes have been described(44), BCC subtypes were categorized based upon the histologic classifications of Lang and Maize(45), Sexton and colleagues(46) and Kirkham(47): (1) those with nonaggressive growth patterns (superficial, nodular, and adnexal, such as follicular) or (2) those with aggressive growth patterns (keratinizing, micronodular, infiltrating, sclerosing, and perineural) or (3) both.

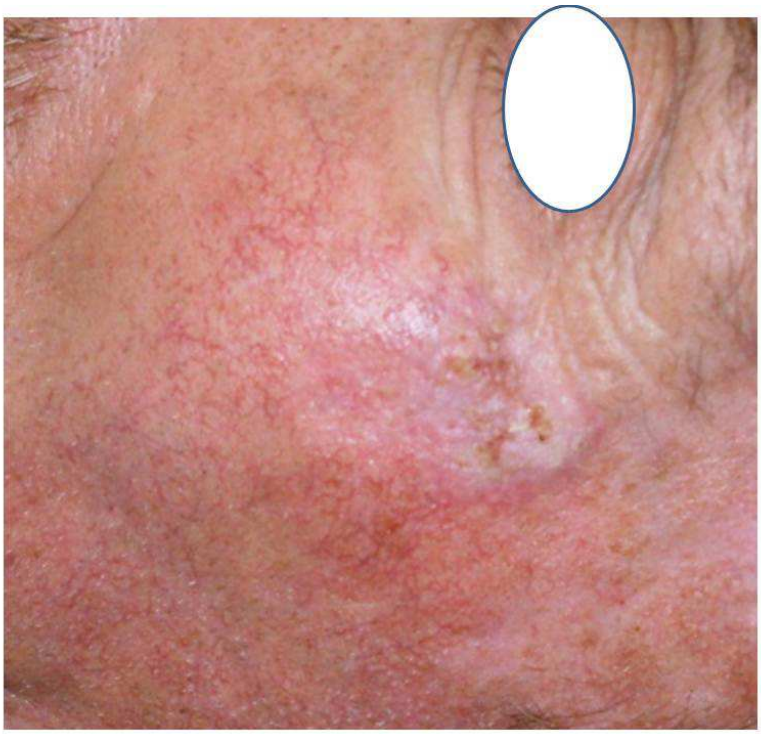
The three most common tumor subtypes are nodular (nBCC), superficial (sBCC), and morpheaform. In a large, retrospective analysis of 13,457 cases of BCC diagnosed at a single center from 1967 to 1996, 79% of BCCs were nodular, 15% were superficial, and 6% were morpheaform In addition, nodular and morpheaform types were most commonly observed on the head region (90% and 95%, respectively), whereas 46% of superficial types were observed on the trunk region. (48)

3.1 Nonaggresive BCC

Nodular BCC is the most common variety and is usually composed of one or a few small, waxy, semitranslucent a flesh-to-pearl–colored papule with a characteristic rolled border that sometimes form around a central depression. Central ulceration and overlying telangiectases are also cardinal features(Fig. 3) (49).



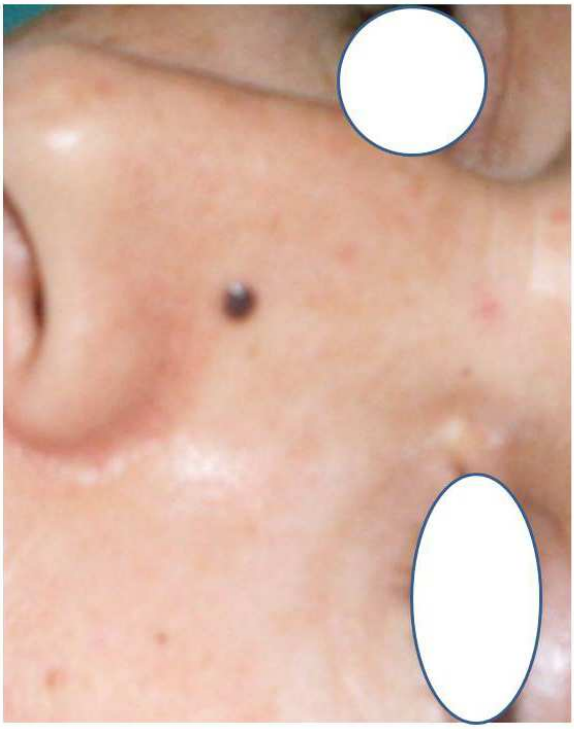
Superficial BCC (sBCC) is often larger than other subtypes and occurs mainly on the trunk where they can be multiple. Superficial BCC may mimic psoriasis, fungus, or eczema. The superficial variant of BCC presents as an enlarging erythematous plaque with mild scale and a scalloped border(Fig. 4).



Pigmented HNBCC are seen more commonly in darkskinned individuals and can mimic a mole or even a melanoma. BCCs may also demonstrate hyperpigmenation, leading to confusion with melanoma in some cases(Fig. 5).
Cystic HNBCC are filled with fluid and may mimic benign cystic lesions, especially around the eye(50).

3.2 Aggressive BCC

This subgroup included BCCs with keratinizing, micronodular, infiltrating, sclerosing, and basosquamous carcinoma (51).
A scar-like or *morpheaform* variant of BCC may appear as depressed, indurated plaque with ill-defined margins.
BCCs with follicular pattern demonstrate basaloid nodular islands of tumor cells in association with a hair follicle; in addition, the tumor epithelium and surrounding stroma form structures reminiscent of follicular germs or contain horn cyst formation resembling a follicular structure or both.



Keratinizing BCCs show nodules of basaloid tumor cells which have a central foci of large horn cysts or pronounced squamous differentiation with keratinization or both; in addition to the undifferentiated basaloid tumor cells, parakeratotic tumor cells with elongated nuclei and slightly eosinophilic cytoplasm may also be present as strands, as concentric whorls, or as cells around the horn cysts.

Basosquamous carcinoma is a subtype of BCC with aggressive behavior and higher tendency for recurrence and metastases. Most authors recognize that basosquamous carcinoma has a nonspecific clinical presentation and the diagnosis is made only after biopsy. The majority of lesions arise on the head and neck (80%) with the central face and perinasal areas being the most common locations (30%). The location of tumors is similar to other types of BCC. The term ''basosquamous carcinoma'' usually implies a BCC with areas of lineage differentiation into squamous cell carcinoma (52). This tumor has areas of BCC and squamous cell carcinoma plus a transition zone between them. The reported incidence of basosquamous carcinoma ranges from 1.2% to 2.7%. Published recurrence rates are 12% to 51% for surgical excision and 4% for Mohs micrographic surgery. The incidence of metastasis is at least 5%. The aggressive biological behavior and clinical course distinguish basosquamous carcinoma from other forms of BCC. Pulmonary metastases occurred in 7.4% of basosquamous carcinomas compared with 0.87% of squamous cell carcinomas. The incidence of perineural invasion was 7.9%. There are no clinical features to distinguish basosquamous carcinoma and the diagnosis is made only after biopsy. It presents in the same locations and with similar clinical characteristics as other BCCs (53).

3.3 BCC with mixed histology

BCC with mixed histology (BCC-MH) is a cutaneous neoplasm which demonstrates two or more pathologic patterns of tumor within the same malignancy, such as superficial BCC in the papillary dermis and sclerosing BCC in the deeper reticular dermis (1–6). The incidence of BCCs with mixed histology is varied between 11% and 43% (54). BCC with mixed histology is most commonly found on the nose, followed by the ear, cheek, and scalp. This is not surprising as the most frequently reported site for either primary or recurrent BCCs is the nose (55, 56). BCCs with mixed histology (almost 40%) should be treated according to their most aggressive histopathological subtype. Shave/punch biopsy specimens fail to diagnose one of both subtypes in approximately 20% of cases (1).

The different histomorphologic subgroups have their specific clinical correlates. On rare occasions, a lesion manifests tenderness or pain which can be a clue to perineural infiltration in the aggressive growth varieties. Sensorimotor compromise has been reported particularly in lesions of the preauricular and cheek areas (57). Tumor aggressiveness seems to correlate with the presence of perineural invasion that has an incidence of 1% in BCC. Perineural spread is a well-documented feature of cutaneous tumors and may portend a more aggressive course: perineural invasion is associated with larger, more aggressive tumors, and the risk of 5-year recurrence is higher (58). The choice and the selection of the most appropriate therapy depend on many factors, including the size of the tumor, location, whether the tumor is primary or recurrent, histology, and individual patient factors.

Documentation of the specific anatomical location, size in millimeters, and appearance of the cutaneous neoplasm is helpful, as it may be required for later staging. Appearance includes such characteristics as color, margins, symmetry, diameter, and the presence of ulceration. Such features include size greater than 2 cm, location on the central face or ears, long duration, perineural or perivascular invasion, and poorly defined margins. Histologically, morpheaform, metatypical, and infiltrative growth patterns associate with poorer clinical outcomes (59). The ABCD (asymmetry, border, color, and diameter) mnemonic used in melanoma is helpful here too. Many surgeons find photographic documentation of lesions an accurate and speedy means of mapping lesions. Metastatic spread of BCC is very rare, but it is not impossible. Accordingly, palpation of the regional lymph nodes is indeed a mandatory part of the complete workup (60, 61).

4. Metastatic disease

BCCs very rarely metastasize, occurring in 0.0025% to 0.55% of cases (62). Metastatic BCC generally tends to occur on a background of large neglected tumors on the head and neck, mainly in men Metastases most are said to more closely correlate to the size and depth and less so to the histologic subtype of the original tumor. The incidence of metastases and/or death is said to correlate to large tumors greater than 3 cm in diameter in which setting patients are said to have a 1–2% risk of metastases that increases to up to 20–25% in lesions greater than 5 cm and up to 50% in lesions greater than 10cm in diameter. A 'giant' BCC is designated as one that is greater than 5 cm in diameter and has a significant risk of morbidity and mortality. A BCC arising in a young person (ie less than 35 years of age) may have an aggressive clinical course (63, 64).

When metastatic spread occurs, regional lymph nodes are affected first followed by bone, lung, liver and abdominal viscera.. An BCC that metastasizes has an extremely poor prognosis;, the median survival of patients with metastatic BCC is about 10 months. There is

less than 20% survival at 1 year and approximately 10% survival at 5 years (65). Occasionally surgical resection of metastatic disease is possible; cases should be referred to specialist centers for full assessment (66).

5. Other malignancies

The risk of developing a squamous cell carcinoma is increased slightly after developing a BCC (6% risk at 3 years) and there is also a higher risk of developing a malignant melanoma. The relationship of development of other malignancy after development of a BCC is uncertain – some studies have shown a small increased risk with cancer of the lung, thyroid, mouth, breast and cervix and non-Hodgkin's lymphoma, whilst others have shown no association (67).

6. Treatment

The choice for a treatment modality should depend on the site, the size and whether the BCC shows indolent (superficial or nodular BCC) or aggressive growth (infiltrative BCC or basosquamous carcinoma) (5, 8). Careful selection is essential and depends upon individual factors. A biopsy of the lesion prior to definitive treatment can help guide choice. Essentially, the method chosen should take into account the prognostic factors for the tumour under consideration, local facilities available, operator expertise and any comorbidity. Several different modalities are used in the treatment of BCC (1, 50) (Table 2).

Anatomical location	central face or ears
Tumour size	greater than 2 cm
Histological type	morpheaform, metatypical, and infiltrative
Perineural/ perivascular invasion	portend a more aggressive course
Recurrence	scar tissue can cover residual tumour,
Treatment failure	A decrease in resection margin increases the recurrence rate. The optimal resection margin in terms of recurrence is 5 mm
Immunocompromised patients	more aggressive biologic behavior, higher recurrence rate

Table 2. Prognostic factors for BCC

Invasive	**Non -invasive**
Excision	Photodynamic therapy
Mohs' micrographic surgery	Radiotherapy
Curettage and cautery	Chemotherapy :• 5-fluorouracil • imiquimod
Cryosurgery	

Table 3. Treatment options for basal cell carcinoma.

7. Surgery

This method requires that normal tissue surrounding the tumor margins be removed in addition to diseased tissue to ensure that the tumor has been fully excised. BCC lesions are

resected with a preplanned size of surgical margin depending on the surgeon preference, the location, and the size of the lesion. The goal is to safely predict appropriate margins of resection of BCC lesions while sacrificing a minimum amount of healthy surrounding skin. Although surgical excision is a common method for treating BCC, there are important safety and quality of life, Patient age and health status (e.g. immunocompromized) may increase associated risks with a surgical procedure including bleeding and infection. In addition, some patients are afraid of surgery, particularly when treating larger.

An advantage of surgical treatments is the histological examination of tumor margins to establish clearance. One disadvantage of surgical excision is incomplete margin control. The incidence of incomplete excision of BCC has varied, with reports ranging from 4.7% to 10.8% of treated patients (68, 69). The success of surgical excision can vary depending on the experience of the surgeon, histologic subtype, and excision margin (70). In a retrospective cohort analysis of 1983 BCC cases, significant risk factors for incomplete excision included lesions located on the head and neck ($P < 0.001$), surgeons performing < 51 procedures during the 2- year study period ($P < 0.001$), and patients with aggressive histologic BCC subtypes (e.g. morpheaform and infiltrative) ($P < 0.01$). The study further indicated that curettage before surgical excision of BCC decreased the incomplete excision rate by up to 24% ($P = 0.03$) (71).

A decrease in resection margin increases the recurrence rate. Relative risk of recurrence increases steadily. The relative risks (hazard ratio) for 4-, 3-, and 2-mm margins are 4.2, 6.5, and 10, respectively. It is clear that smaller margins are inherently riskier than larger ones, even if the difference is 1 mm. the reported mean recurrence rates decrease linearly with increasing size of margins until it reaches 5 mm. The optimal resection margin in terms of recurrence is 5 mm.(72)

Consistently, relative risk is inversely proportional to the size of the surgical margin. Using this criterion alone, the best margin in terms of relative recurrence is a 5-mm margin. However, the anatomical constraints require prejudice in choosing the resection margins, especially for lesions of the face. Thus, for those surgeons who desire a minimum 95 percent cure rate, these data indicate that a 3-mm surgical margin can be safely used for BCC lesions 2 cm or smaller. Furthermore, a positive pathologic margin has a mean recurrence rate of 27 percent and thus does not necessarily indicate that a BCC will recur. Thus, when faced with a positive surgical margin, a case-by-case consideration of the risks of observation versus reresection should be applied when determining the next step in management (72).

A study using MMS for excising primary (ie previously untreated BCC) found that for small (<20 mm) well defined tumours 3 mm surgical margins gave tumour clearance rates of 85%, whereas 4–5 mm margins gave clearance rates of 95%. Large and morphoeic BCCs require wider margins to achieve complete histological resection (13–15 mm surgical margins for 95% clearance) (73).

7.1 Mohs micrographic surgery

Mohs micrographic surgery (MMS) is a specialized surgical procedure that is commonly used for patients who present with large (> 2 cm) tumors, high-risk morphea-type BCC tumors, recurrent tumors, or tumors located in cosmetically sensitive locations such as the face (74). But Mohs' micrographic surgery (MMS) is a specialised technique that uses horizontal frozen sectioning to examine serial sections of tissue until all margins are free of tumour. MMS allows for greater tissue conservation and margin control compared with other surgical procedures. This technique histologically maps the margins of the tumor to

more accurately delineate the pattern of tumor infiltration into tissue, while sparing healthy tissue. MMS gives high cure rates for tumours in high-risk sites with maximal conservation of uninvolved tissue. The suggested overall 5-year cure rates for primary and recurrent BCC are 99% and 94.4%, respectively (75, 76).

7.2 Curettage and electrodesiccation

Electrodesiccation and curettage (ED & C) is the most common method used by dermatologists to treat primary nBCC and sBCC tumors < 1.5 cm in diameter. After the tumor is scraped with a curette, the area is then treated with electrosurgery (electrodesiccation or coagulation) to control bleeding and eradicate cancer cells remaining around the wound margins and circumference. Typically two or three treatment cycles are recommended to completely remove the tumor (77). Recurrence rates are varied between 3% to 19%im 5 years (78). Recurrence was higher in nasal, paranasal, and forehead areas (78). Although ED & C appears to have a higher risk for disease recurrence compared with surgical excision, a nonrandomized retrospective chart review suggested that the two treatment modalities are not significantly different (79). If the dermis and the fatty layer is penetrated with ED & C, surgical excision should be performed.Although multiple cycles of ED & C are recommended, there have been reports that single-cycle therapy may reduce the risk of scarri(74). However, a reduction in ED & C treatment cycles may lead to higher recurrence rates. 32(80) Atrophic or hypertropic scar can be develop after ED & C (78). Problematic wounds, with subsequent poor cosmesis, are occasional sequelae.

7.3 Cryosurgery

Cryosurgery is a cytodestructive technique that involves using a liquid nitrogen spray or probe to induce cell necrosis by exposing tissue to low temperatures. Cryosurgery is commonly reserved for tumors with welldefine borders, and two freeze–thaw cycles with a tissue temperature of - 50 °C are recommended. 6. (74) two freeze–thaw cycles of 30 s each are still recommended in the treatment of facial BCC. A systematic review of recurrence rates of studies (≥ 50 patients) published between 1970 and 1997 indicated that cryotherapy in the treatment of primary BCC resulted in a cumulative 5-year recurrence rate of 4% to 17%(81). For treatment of recurrent BCC, the recurrence rate has ranged from 4% (for 56 tumors) to 12% (for 164 tumors), with variable follow-up periods reported (82, 83). Cryosurgery is associated with many adverse events. Shortterm adverse events include perioperative and postoperative pain, tenderness, bulla or vesicle formation, erythema, sloughing of necrotic tissue or eschar formation, and localized edema (84). This procedure can also result in scarring including hypertrophic scarring, local hypopigmentation, and/or peripheral hyperpigmentation (84). When aggressive cryosurgery is used, tumor recurrence may become extensive before diagnosis because of the tumor's concealment by a fibrous scar (74). Cryosurgery should be avoided in areas of hair growth (e.g. scalp or beard area) and in patients with conditions sensitive to temperature, including Raynaud's syndrome, cold panniculitis, and cryoglobulinemia.

8. Photodynamic therapy

Photodynamic therapy (PDT), which uses the intrinsic cellular haem biosynthetic pathway and photo illumination to initiate tumour cell destruction, is a relatively new treatment for superficial BCCs, which is increasingly available for superficial non-melanoma skin cancers.

After topical application, precursor molecules are selectively concentrated in tumour tissue where they undergo further metabolism. After irradiation by visible light of a certain wavelength, these molecules become excited and jump to a higher energy level. Upon release of this energy, reactive oxygen species are released; these cause cellular destruction, and so resolution of the tumour – without scarring. (It is thought that, fundamentally, holes are punched into cellular organelles, especially mitochondria, so the cells can no longer function.). This procedure causes cell death in two ways: through cellular damage and apoptosis. Several studies have indicated that sBCC lesions do not clear with single-treatment PDT The best clearance rate (96% median follow up, 27 months).) is achieved with two exposures 1 week apart. PDT offers patients with large and/or multiple superficial BCCs particular benefits as it gives a low rate of adverse events with good cosmetic results by selectively targeting tumour cells (3).

Although one advantage of PDT is that multiple BCC tumors can be treated simultaneously, PDT is a relatively inconvenient treatment option. Treatment involves a two stage process requiring several office visits. After the topical agent is applied, patients must wait several hours before the light-application phase of the treatment can be initiated. This second-stage of treatment must be performed within a certain time frame after agent application. Furthermore, because single PDT treatments demonstrate poor efficacy in BCC, multiple visits to a healthcare provider's office are required. Increased photosensitivity during the first-stage of treatment provides additional inconvenience because patients must avoid sunlight and bright indoor lighting to reduce the risk of stinging and/or burning sensations from photosensitized skin. Treatment with PDT is typically associated with localized adverse events, including stinging or burning, erythema, and edema (85). Photosensitivity is also associated with this treatment regimen. After application of topical agents, patients should avoid exposure to sunlight or bright indoor light until after controlled exposure to the light source that completes treatment. Treatment with PDT is contraindicated in patients with porphyria, known allergies to porphyrins, and patients with photosensitivity to wave lengths of applied light sources. Further development of PDT for BCC will likely make this a more practical and useful modality (86).

9. Radiotherapy

Radiotherapy is an effective treatment for many BCCs. It has been particularly useful in the treatment of elderly patients and for larger tumors or tumors in difficult-to treat locations. Lower risk areas, such as the trunk and extremities, as well as the genitalia, hands, and feet are usually not treated with this modality. Radiation therapy may be a very useful modality as adjunct treatment for BCC when margins are positive after excision and for extensive perineural or large nerve involvement. The total dose and treatment regimen (e.g. number of fractionated doses) depends on many factors including tumor location, size, type, and depth. A study of BCC irradiated by a 'standardized' X-ray therapy schedule indicated an overall 5-year recurrence rate of 7.4% for primary (n = 862) and 9.5% for recurrent (n = 211) BCC. Radiation therapy is not recommended in younger patients (e.g. < 50 years of age) as less favorable cosmetic outcomes (e.g. late-onset changes of cutaneous atrophy and telangiectasia) may result over time, and there is a risk of developing additional nonmelanoma skin cancers in the radiation field (usually after 10–20 years) (87). Radiation therapy is contraindicated in certain genetic disorders, which predisposes patients to skin cancers (e.g. patients with Gorlin's syndrome, xeroderma pigmentosum, or connective tissue diseases, such as lupus and scleroderma)(88).

10. Chemotherapy of BCC

10.1 Topical 5-Fluorouracil

Topical 5-fluorouracil cream is useful for low-risk tumours on the trunk and limbs, but there is a high incidence of local side effects. 5-Fluorouracil (5-FU) is a chemical ablative agent that inhibits DNA synthesis, prevents cell proliferation, and causes tumor necrosis. Solution and cream formulations of 5% 5- FU administered twice daily for at least 6 weeks have been approved by the FDA in the treatment of sBCC when conventional methods are impractical (e.g. difficult treatment site). 47However, therapy may be required for as long as 10–12 weeks. Because limited data are available, the actual clearance rate for the topical treatment of sBCC with 5-FU is currently unknown. Application of 5-FU causes severe local skin reactions, including pain and burning, pruritus, irritation, inflammation, swelling, tenderness, hyperpigmentation, and scarring. (48)

10.2 Imiquimod

Imiquimod is a member of a newer class of agents called immune-response modifiers. Imiquimod is currently approved by the FDA in the treatment of external genital and perianal warts and actinic keratosis on the face or scalp. The mechanism of action of imiquimod is thought to occur through the activation of macrophages and other cells via binding to cellsurface receptors, such as Toll-like receptor (89). This binding activity induces proinflammatory cytokine secretion (e.g.interferon- α and tumor necrosis factor-α) favoring a type 1 helper T-cell-mediated immune response because of the generation of cytotoxic effector cells Investigators noted a significant correlation between the histologic clearance rate and severity of local skin reactions (i.e. erythema, erosion, and scabbing/crusting) commonly experienced during treatment with imiquimod 5% cream. The data suggested that as the severity of these three local skin reactions increased, there was a greater trend in histologic clearance of sBCC (48).

In addition to sBCC, imiquimod also has demonstrated efficacy in the treatment of nBCC.50,56 (90, 91) Treatment with imiquimod once daily, seven times per week, for either 6 or 12 weeks resulted in nBCC histologic clearance rates of 71% to 76% (90).

Because imiquimod promotes an inflammatory reaction to treat the tumor, treatment is generally associated with mild to- moderate local skin reactions, with severity related to frequency of application (92, 93). In a phase II study, the most common local skin reactions were erythema, crusting, flaking, and erosion (92). However, these dose-related side-effects were generally well tolerated, and none of the patients discontinued because of local skin reactions.

In addition to monotherapy, imiquimod 5% cream may also be useful as adjunctive therapy in the treatment of BCC. Treatment with imiquimod significantly reduced the size of the target tumor and thereby resulted in a smaller cosmetic defect from the MMS excision compared with vehicle. Adjunctive therapy with imiquimod reduced the frequency of residual tumor with ED & C compared with ED & C alone and also appeared to improve cosmetic appearance. These studies suggest that imiquimod 5% cream may be useful as adjunctive therapy in the treatment of nBCC (48).

11. Issues in the treatment of BCC

BCC treatments have many advantages and disadvantages, which depend on many factors, including tumor type, tumor location, cosmetic considerations, and physician and patient

convenience. Surgical procedures such as MMS and surgical excision have the lowest 5-year recurrence rates (Table 4). However, effective clearance of BCC tumors with surgical procedures is highly dependent on tumor margins and the skill of the healthcare provider. Thissen *et al*. (81) recommend that surgical excision is preferred over common procedures such as cryosurgery and ED & C, provided surgery is not contraindicated. With PDT, there is limited tissue penetration (i.e. depth), a critical requirement when treating invasive tumors. Mohs micrographic surgery is recommended for larger BCC tumors in high-risk areas of the face and head and for tumors with aggressive growth patterns (81).

Treatment option	**Description**	**5-year recurrence rate, %**
Surgical excision	Surgical excision of diseased and surrounding healthy tissue	Complete excision: 3–14 Incomplete excision: 26–42
Curettage and electrodesiccation	Multiple cycles of diseased tissue excision and electrodesiccation to control bleeding and eradicate cancer cells in surrounding margins	3–19
Mohs micrographic surgery	Specialized surgical procedure to maximize excision of diseased tissue and minimize loss of healthy tissue	Primary BCC: 1 Recurrent BCC: 6–10
Cryosurgery	Multiple cycles of cytodestruction (i.e. cell necrosis) of diseased tissue with liquid nitrogen	4–17
Radiation	X-rays or high-energy particles administered in fractionated doses to kill tumor cells	7–10
PDT	Multiple cycles of 2-stage process (photosensitization via topical agent and light exposure) creates cytotoxic reaction in tumor cell	Single cycle: 21–50* Double cycle: 4†

BCC = basal cell carcinoma; PDT = photodynamic therapy; ALA = aminolevulinic acid.
* Projected overall cure rate based on median follow up of 19–35 months.
† Study of 26 lesions with median follow up of 27 months. Data and table from 48th reference.

Table 4. Treatment options and recurrence rates of BCC

12. Recurrency of BCC

The likelihood of BCC recurrence may be influenced by one or more factors(Table 2). In addition to fthe tumor's treatment, the cancer's biologic behavior and the patient's immune status are related to the incidence of tumor recurrence. For example, in immunosuppressed individuals, BCCs not only demonstrate more aggressive biologic behavior but also have a significantly higher recurrence rate as compared with this malignancy in patients who have an intact immune system (94).
The histologic subtype of BCC influences the biologic behavior of the tumor. Recurrent BCCs are commonly associated with a primary cancer that has an aggressive histologic subtype (95-98).

Also, BCCs with aggressive histologic patterns require more aggressive treatment; in addition, when the Mohs micrographic surgical technique is used, a greater number of stages are required to achieve tumor free margins as compared with BCCs without aggressive tumor growth patterns (99).

Inadequate treatment of BCCMH may represent an unsuspected etiology for recurrent skin cancer. For example, an unexpected aggressive pathologic pattern of BCC may not be detected after a superficial biopsy. Subsequently, the cancer may recur if the initial treatment for the diagnosed nonaggressive tumor subtype is inadequate for the undiscovered aggressive carcinoma. Clinical recurrence of cancer results when there has been persistence of the original tumor secondary to inadequate eradication (54). The recurrence rate for BCC lesions with positive margins calculated from the aggregated data is 27 percent (72). The reported percent of BCC recurrence varies depending on the treatment modality (54).

Recurrent BCC (rBCC) is known to be a high-risk tumour with a worse prognosis than primary BCC (50, 59, 76, 100). This may be due to the fact that scar tissue can cover residual tumour fields or because the appearance of basaloid tumour cells in recurrent tumours is frequently squamified, lacy and morpheaform, which may be easily missed in scar tissue (76). The only RCT investigating treatment modalities in rBCC showed that after 5 years of follow-up MMS is the preferred treatment for facial rBCC because of statistically significant lower recurrence rates (101).

Besides tumour characteristics, patient characteristics are of importance when choosing a treatment for an individual. In a few cases where surgery is impossible or undesirable, it may be advantageous to treat a patient with a different, possibly less effective, treatment. Particular management difficulties are posed by recurrent tumours. In general, they are best treated by Mohs' micrographic surgery in high-risk sites and excision elsewhere.

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The book Skin Cancer Overview is divided into three sections to cover the most essential topics in skin cancer research: Etiology, Diagnosis and Treatment, and Prevention. Due to the complexity of skin cancer, this book attempts to not only provide the basic knowledge, but also present the novel trends of skin cancer research. All chapters were written by experts from around the world. It will be a good handbook for researchers with interests in skin cancer.

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