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Basal Cell Carcinoma

Yalçın Tüzün, Zekayi Kutlubay, Burhan Engin and Server Serdaroğlu
Istanbul University, Cerrahpaşa Medical Faculty, Department of Dermatology
Turkey

1. Introduction

Basal Cell Carcinoma (BCC) is the most common malignant tumour of the skin. It is also the most common cancer in humans in some countries. BCC is malignant neoplasm derived from nonkeratinizing cells originating in the basal layer of the epidermis. The histology of the tumour and the surrounding stroma is characteristic.
Basal cell carcinoma was first described in 1824 by *Jacob* who called it "*ulcus rodens*"; its current nomenclature was proposed by *Krompecher* in 1903. It is the most common type of nonmelanoma skin cancer (80% of all skin cancers) and most common malignancy in humans. It is delivered from the basal layer of the epidermis or pluripotent bazaloid cells of adnex and almost seen in the areas of sun exposure and hairy parts of the skin. There are many factors in its etiology including genetic predisposition, immune deficiency and chronic sun exposure (Adisen & Gurer, 2007). Recently published studies major on genetic and molecular aspects of the pathogenesis of basal cell carcinoma. Metastasis is rare in BCC and local destruction and disfigurement are much more common (Sikar et al., 2011). BCC usually appears as a flat, firm, pale area that is small, raised, pink or red, translucent, shiny, and waxy, and the area may bleed following minor injury. Tumor size can vary in diameter. Treatment options include electrodesiccation and curettage, surgical excision, cryosurgery, 5-fluorouracil, 5% imiquimod cream, and superficial radiographic therapy. Electrodesiccation and curettage are the most common treatments. Cure rate in these options is approximately 95%.
Nevoid basal cell carcinoma syndrome or *Gorlin-Goltz* syndrome is an autosomal dominant disorder characterized by multiple basal cell carcinoma, multiple keratocystic tumors, and skeletal anomalies (Bader, 2011).

2. Epidemiology

Frequency of BCC has been increasing in many countries around the world. *The American Cancer Society* reports that it is the most common cancer in the *United States*. Approximately 1 million new cases diagnosed in a year and more than 10,000 deaths occur (2% of all cancer deaths). The observed increase in incidence rates may be because of increased detection and skin cancer awareness in health policy. Increased longevity may also affect the increased incidence of BCC; recent data also suggest that incidence is also increasing in the young population.
Because of its high frequency, the disease has been accepted to be a public health issue. Despite low mortality rates and the rare occurrence of metastases, the tumor may be locally invasive and relapse after treatment, causing significant morbidity. In BCC knowledge of risk factors, early diagnosis and treatment is the major point.

BCC incidence varies all around the world. In states near the equator, such as *Hawaii*, BCC incidence is approaching 3-fold more often than that of states in the Midwest, such as *Minnesota* (Bader, 2011). The highest rates of skin cancer occur in *South Africa* and *Australia.* In these areas exposure to UV radiation is in high dose.
Ramani and *Bennett* reported a significantly higher incidence of BCC in *World War 2* servicemen stationed in the *Pacific* theater than in those stationed in *Europe* (Carucci & Leffell, 2008).
BCC is seen in all skin types, but dark-skinned individuals are rarely affected, and more common in fair-skinned individuals (type 1 or type 2 skin types). People who have *Fitzpatrick* type 1 skin are very fair and have red or blond hair and freckles; these individuals always burn and never tan. People who have type 2 skin are fair and burn easily and tan minimally.
Incidence is low in blacks, *Asians*, and *Hispanics* (Machado et al., 1996). Also it was found that approximately 13 million white non-*Hispanics* living in the USA in early 2007 had at least one non-melanoma skin cancer.
Among to gender men are affected twice as women. The higher incidence in men might be because of occupational exposure to the sun.
BCC frequency increases with age. Except of basal cell nevus syndrome, BCC is rarely found in patients younger than 40 years. Approximately 5-15% of cases of BCC occur in patients aged between 20 and 40 years. Aggressive-growth of basal cell carcinoma (AG-BCC) is more frequently noted in patients younger than 35 years than in older individuals. Aggressive-growth of basal cell carcinoma includes morpheaform, infiltrating, and recurrent BCCs (Bader, 2011).

3. Etiology and pathogenesis

Its etiology is still unclear, but both constitutional and environmental factors and genetic predispotion are accused in BCC etiopathogenesis. The most important risk factor for basal cell carcinoma is exposure to UV-radiation (Bauer et al., 2011). Almost all basal cell carcinomas occur on parts of the body excessively exposed to the sun especially the face, ears, neck, scalp, shoulders, and back. Outdoor workers with a long history of work-related UV-exposure are at increased risk of developing BCC. Other risk factors include light skin phototypes, advanced age, family history of skin carcinoma, light-coloured eyes and blond hair, freckles in childhood and immunosuppression. Behavioral aspects such as occupational sun exposure, rural labor and sunburns at a young age also play a role (Bader, 2011). CYLD is a deubiquitination enzyme that regulates different cellular processes, such as cell proliferation and cell survival. Mutation and loss of heterozygosity of the CYLD gene causes development of cylindromatosis, a benign tumour originating from the skin. *Kuphal* et al. suggested that suppression of CYLD has a significant role in basal cell carcinoma progression (Kuphal et al., 2011).
Between 30% and 75% of the sporadic cases are associated with patched hedgehog gene (PTCH) which is a tumor suppressor gene located in the 9q22 (PTCH1) and 1p32 (PTCH2) location. This gene is almost with all cases associated with basal cell nevus syndrome. Other genetic changes are also described like experiments with activation of the hedgehog signaling pathway in different compartments of the epidermis and on the expression of cytokeratins 5, 14, 15, 17 and 19 with a follicular pattern, which has defined it as a malignant neoplasm of follicular germinative cells (trichoblasts) (Chinem, 2011; Youssef, et al., 2010).

Furthermore, there is an association of BCC with abnormalities of the sonic hedgehog gene (Donovan, 2009). This hypothesis is further strengthened by the rarity of palmoplantar and mucosal lesions, where no hair follicles are found (Betti, 2005; Orsini 2001). *Baskurt* et al. have reported two brothers who have albinism and synchronous developed BCC on their trunk region. That means development of the same malignancy in the same life period at the similar localizations reminds the importance of genetic predisposition (Baskurt, 2011).
BCC can rarely develop on unexposed areas. In some case reports, BCC of the prostate has been reported. Contact with arsenic, tar, coal, paraffin, certain types of industrial oil, and radiation are some factors playing role in BCC etiology (Kwasniak & Zuazaga 2011).
BCC can also be associated with scars (eg, burn complications), xeroderma pigmentosum, previous trauma, vaccinations, or even tattoos (Bader, 2011).
Lee et al. published a case report about expression of RUNX3 (Runt-related transcription factor 3) in skin cancers. They found that higher expression of RUNX3 is seen in several cancers, including basal cell carcinoma. Expression of RUNX3 is reduced in a large number of cancers. As a result they suggest that RUNX3 has an oncogenic potential and does not act as a tumour suppressor in skin cancers (Lee et al., 2011).
Activation of Gli-1 factor, induces the transcription of several oncogenes involved in the development of BCC and other malignancies. An other gene in BCC etiology is SMO gene which is a protein located in the membrane - smoothened -expressed by the SMO gene. *Chinem* et al. reported that mutations in the SMO gene are present in 10-21% of sporadic BCCs and mutations in the p53 gene are present in more than 50% of cases, although the p53 gene is more related to the progression than the origin of BCC (Chinem & Miot, 2011).
Fernandez –Flores reported a case about D2-40 immunoexpression in BCC etiology. They suggested that this immunoexpression was a prognostic connotation in carcinomas of organs other than the skin. In their case rapid grown had been seen over the last few months (Fernandez –Flores, 2011).
Involvement of the trunk and development of multiple BCCs were related to genetic polymorphisms in glutathione S-transferase, NADPH and cytochrome P-450. Also trisomy of chromosome 6 was linked to increased aggressiveness of BCC (Chinem & Miot, 2011).
Kwasniak et al. reported that BCC is one of the cancers most strongly associated with the atomic bombing in Japan. It is reported that residents of *Nagasaki* who were not exposed to atomic bomb radiation, the incidence of BCC was 3.1 per 100,000 while the survivors incidence was 9.4 per 100,000 people per year (Kwasniak & Zuazaga 2011).
Tang et al. reported in their study that topical vitamin D3 treatment of existing murine BCC tumors significantly decreases Gli-1 and Ki-67 staining. Thus, vitamin D3 acting via its *Hedgehog* inhibiting effect may hold promise as an effective anti-BCC agent (Tang et al., 2011).

4. Clinical manifestations

Basal cell carcinoma patients often present with a slowly growing, nonhealing sore of varying duration. The lesions are typically seen on the face (Figure 1), ears (Figure 2), scalp, neck, or upper trunk. Mild trauma initially may cause bleeding. A history of chronic sun exposure is commonly elicited. The early tumours are commonly small, translucent or pearly, raised and rounded areas located on a few dilated, superficial vessels. There are six subtypes of BCC that include nodular, superficial, pigmented, morpheaform, cystic and fibroepithelioma of *Pinkus*.

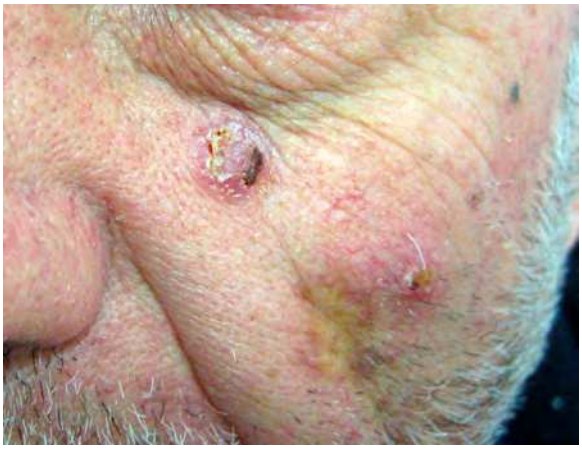

Fig. 1. Basal cell carcinoma as nonhealing sore on face.

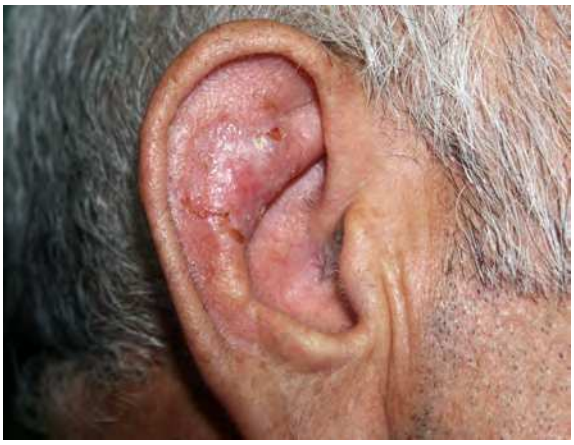

Fig. 2. Superficial spreading basal cell carcinoma located on ears.

4.1 Nodular Basal Cell Carcinoma

Nodular BCC is the most common subtype, accounting for more than 60% of all tumors. Lesions are clinically found on the head and neck regions. BCC can also be seen in sun-protected areas. The nodular form of BCC appears as red or pink papules with raised, rolled borders that slowly enlarge (Figure 3 & 4). Red papules have a pearly or waxy appearance and telengiectasias are seen. On the microscopic examination; BCC is composed of well-defined, smooth-bordered basophilic staining islands of neoplastic cells. Melanin pigmentation of tumor cells and adjacent stromal histiocytes may be seen. Mitoses and individual cell necrosis are uncommon. The surrounding stroma showing myxoid change, is rarely fibrotic and may show calcification in discrete islands of tumour or in adjacent stroma. This subtype of BCC grows slowly; however if left untreated for enough time, it can invade structures and increase morbidity (Miller, 2008; Nouri, 2007 & Schwartz, 2008).

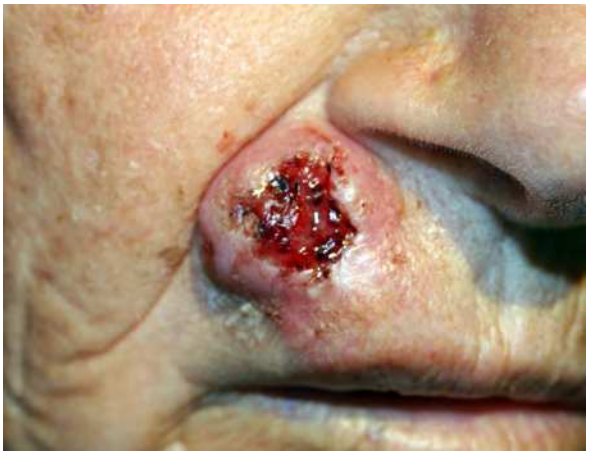

Fig. 3. Rodent ulcer type of basal cell carcinoma

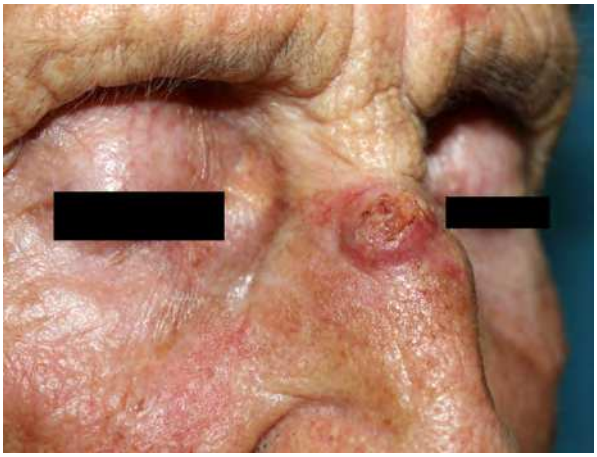

Fig. 4. Nodular type of basal cell carcinoma.

According to some authors multinodular BCC is accepted as an another subtype of BCC. It manifests a plaque-like indurated lesion with poorly demarcated contour. Lesions may be difficult to remove and so have an increased incidence of recurrence. In the pool data, subjects with a micronodular BCC had a mean age comparable with subjects with a superficial BCC but were younger than subjects with nodular or an infiltrative BCC (Betti et al., 2010).

In one study, it was found that nodular BCC is associated with increased hyluronan homeostasis, when compared with normal skin. Also chondroitin sulphate were significantly higher, whereas dermatan sulphate was significantly lower in BCC when compared with normal skin. There may be a relationship between the proliferative activity of tumour cells and the stromal occurrence of hyaluronan and that this proliferative activity differed in the various types of BCC (Tzellos et al., 2010).

4.2 Pigmented Basal Cell Carcinoma

This form of BCC consists of a brown, black, or gray blue color that can present on the head, neck, trunk or extremities. It appears as a hyperpigmented, translucent papule, which may also be eroded (Figure 5). These are usually extremely slow in evolving. This type is seen more frequently in dark-complexioned people such as *Latin Americans* or *Japanese*. Pigmented type constitutes approximately 6% of all BCC. Pigmented nevi, melanoma, pigmented *Bowen*'s disease are the most frequent clinical differential diagnosis for such lesions. Pigmented BCC shows similar histologic features with nodular type but there are large amounts of melanin. In dermoscopy; maple leaf like areas, spoke-wheel areas, large, blue-gray ovoid nests, multipl blue-gray globules, arborizing (tree-like) telangiectasia and ulceration may be seen (Carucci, 2008; Odom, 2000 & Menzies 2002).

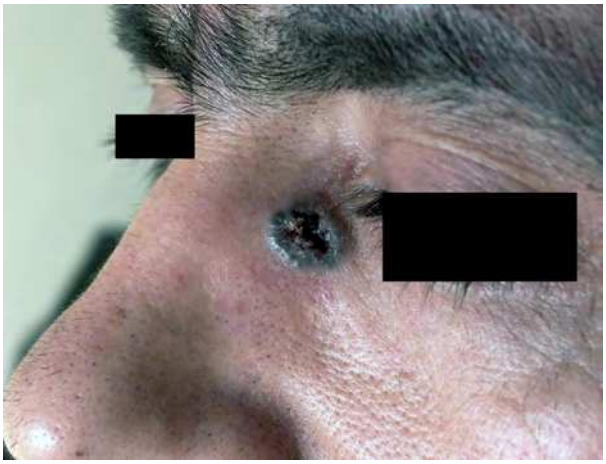

Fig. 5. Hyperpigmented nodular basal cell carcinoma

4.3 Superficial Basal Cell Carcinoma

This subtype is the second common one and seen mostly on the trunk and extremities. Lesions are clinically flat, red to pink, scaly patches with ulcerations and crusting. The borders can be elevated or rolled. This thin threadlike border facilitates distinction from a plaque of *Bowen*'s disease or of psoriasis. It also presents at younger age than nodular type (average age is 57.5 vs 65.5 years). Superficial BCC usually do not extend into the deep dermis, and a nonspecific inflammatory infiltrate may be seen in the papillary dermis. They usually grow laterally, and can reach unstantial sizes. Horizontal growth allows these tumours to extend significantly beyond the clinical borders (Figure 6)..

Superficial BCC is characterized microscopically by buds of malignant cells extending into the dermis from the basal layer of the epidermis. The peripheral cell layer shows palisading. Tumour cells may colonize the hair follicle and rarely the ecrine adnexal structures. Mitoses are infrequent, and apoptotic cells are rare in the atypical basaloid buds. When seen in the setting of a biopsy for suspect superficial BCC, a band-like lymphoid infiltrate should prompt a careful search through multipl levels looking for foci of superficial BCC (Nouri, 2007; Schwartz, 2008 & Tzellos 2010).

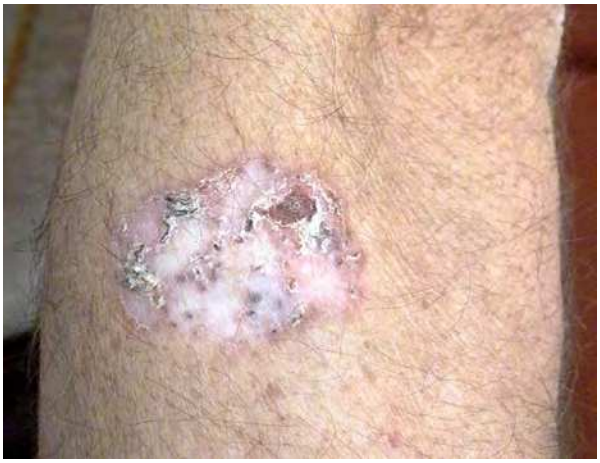

Fig. 6. Slightly elevated borders of superficial type of basal cell carcinoma.

In dermoscopy; according to a study, shiny white to red areas were seen in 100% of the lesions, while approximately 86% revealed short fine telangiectasias; they also described small surface ulcerations or erosions in about 78% of the lesions. Other dermoscopic criteria, such as leaf-like areas, arborizing telangiectasias, blue-gray globules, and large blue-gray ovoid nests, are not strongly associated with the diagnosis of superficial BCC (Scalvenzi et al., 2008).

4.4 Morpheaform Basal Cell Carcinoma

This type of BCC demonstrates waxy white sclerotic plaques occuring in the head and neck region, with a conspicious absence of a rolled edge. The exact margin of the lesion is impossible to define, but palpation reveals a firm skin texture that extends irregularly beyond the visible changes. Ulceration and crusting are also absent, whereas telangiectasia is prominent. The surface is smooth and may be slightly depressed below the normal level. The colour is yellowish, pink or white and may appear as a smooth shiny scar. These lesions are reported to be more frequent on the face in women and may be associated with smoking. The morpheaform BCC tends to develop at a younger age compared with other types, sometimes during adolescence. These lesions are usually misdiagnosed, leading to greater tumour growth and delayed treatment. This is an aggressive growth variant of BCC (Mackie, 2004; Nouri, 2007; Schwartz, 2008 & Tzellos 2010).

In histopathology; there is a fibrotic dermis that contains small, linear, and branching collections of basal cells. Morpheaform BCC islands typically are not well circumscribed and do not demonstrate prominent peripheral palisading of nuclei. Individual cell necrosis and mitotic activity are brisk considering the relative tumor volume and the neoplasms themselves are poorly demarcated, showing widespread invasion of the reticular dermis and penetration into the subcutaneus tissue (Nouri, 2007 & Tzellos 2010).

4.5 Cystic Basal Cell Carcinoma

This type of BCC is uncommon. It is usually seen around the eyes. This tumour shows differentiation towards the hair follicle infundibulum. A sebaceous component is usually

absent. It may appear as a blue-gray cystic nodule suggestive of an apocrine hidrocystoma. It has two subtypes. One is small cyst of light blue-gray coloration; other one is variable in size and may be quite large. Both subtypes are interfere with benign cutaneous cysts. It can not be clinically separated from hidrocystoma, as it too has a broad base, fine telangiectasias and a blue tint. Any cyst or inflammatory lesion of the eyelid which does not resolve within a reasonable period should be examined histologically (Braun-Falco, 2000; Nouri, 2007 & Tzellos 2010).

4.6 Fibroepithelioma of Pinkus

This type of BCC was first described by *Pinkus* in 1953. This is an uncommon variant of BCC. Fibroepitheliomas are usually soft pink or flesh-colored nodules or plaques on the trunk, especially the lumbosacral region. They are extremely rare on sunlight-exposed sites and do not ulcerate but erosions may be seen. They may be broad-based flat plaques or pedunculated, tending to be smooth surfaced with a pink or reddish colorationn, and characteristically appear on the lower back. They may be pigmented. They may follow many years after local X-ray therapy.

Histopathologic findings include lacy strands of basaloid cells extending into a fibrous stroma. Some authors regard the fibroepithelioma as a form of fenestrated trichoblastoma, a lesion held to be a benign analogue of BCC that shares many morphological features of BCC but has not to date been shown to manifest PTCH mutations and dominantly affects sun-protected skin (Braun-Falco, 2000; Nouri, 2007 & Repertinger, 2008).

There are other rare clinical types of BCC. These are wild-fire BCC, giant-pore BCC, angiomatous BCC, lipoma-like BCC, and metatypical BCC. In wild-fire type; plaques expands rapidly with crusting, ulceration, and scarring. The giant pore BCC appears on the face as a 2-10 mm orifice, usually skin colored. It could represent a localized follicular abnormality. The angiomatous BCC is bluish or violaceous nodule with a somewhat cystic quality and is exceedingly rare. The lipoma-like BCC displays a remarkable clinical resemblance to the lipoma. Metatypical BCC is very rare and may simply be a subset of BCC that is radiation-resistant. They tend to be large aggressive tumors that usually have been unsuccessfully irradiated. They are seen on the back and nose (Braun-Falco, 2000; Hakverdi, 2011 & Ting, 2005).

5. Biological behavior

5.1 Local Invasion

Local invasion is the most important problem of BCC (Carucci, 2008 & Schwartz, 2008). It grows in a "silent" way into immediately adjacent tissue (Figure 7). It rarely metastasizes. The doubling time is between 6 months and 1 year. There may be irregular intrusions into certain tissues: dermis, fascial planes, periosteum, perichondrium, embryonic fusion planes and nerve sheath (Carucci, 2008). Tumor progression is slow in anatomic fusion planes. BCC located in embryonic fusion planes, periauricular region, tends to be at high risk of deep extension. It has been shown that the highest risk tumors which exhibit extensive subclinical spread are basosquamous and morpheaform BCC found on nose and morpheaform BCC on cheek and those with a preoperative size greater than 25 mm (Batra, 2002 & Schwartz, 2008). The tendency of BCC to spread into the dermis is understandable, because it develops immediately beneath the epidermis. Intradermal invasion may be clinically inapparent and moreover may prove quite asymmetrical, being

several times larger on side of BCC than on the other. Inapparent extensions often result in tumor recurrence after removal (Schwartz, 2008).

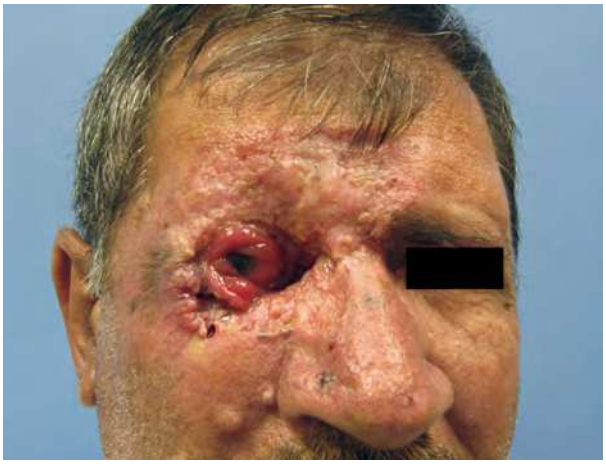

Fig. 7. Advanced and invazive basal cell carcinoma of the right periorbital region.

When BCC penetrates the dermis, additional expansion patterns may ocur (Schwartz, 2008). The biological behavior of the micronodular, infiltrating and sclerosing (morpheaform) variants of BCC are known to be more aggressive than that of the nodular and superficial forms. These three "agressive growth" subtypes are characterized by an infiltrative growth pattern that has poor circumscription (Miller, 2008).
BCC may spread along perichondrium of the nose or ear as the cutaneous and subcutaneous tissues are so thin there. The cartilage of the nose is quite irregular, small pockets of tumor spread in auricular and periauricular region appear to correspond to embryonic fusion planes (Schwartz, 2008).
Stromal reaction tends to be sclerotic rather than fibroblastic or myxoid. The attraction of BCC for connective tissue is well recognized but not well understood. This stromal dependency is one of the basic characteristics of BCC (Miller, 2008).

5.2 Perineural invasion

The reported rate of perineural spread in all BCC is between 0.18% and 3%, and is present more often in deep specimens (Walling et al., 2004). Perineural invasion is more common in the aggressive subtypes of BCC (micronodular, infiltrating and sclerosing variants) (Brown & Perry, 2000).
What is the true incidence of perineural invasion among skin carcinomas? Considering large published series that encompass all 'ordinary' BCCs, it seems rather uncommon, oscillating from 0.19% to 0.49% . Some authors reported an increased frequency of 3.8% in cancers treated by *Mohs*' micrographic surgery (Cernea et al., 2009).
The cancer may extend cylindrically, several cells thick, around the nevre beneath the perineurum (Schwartz, 2008). The low resistance cleavage plane of the perineural sheath may allow rapid and broad tumor extension. 'Skip' areas along nerves are also common, and spread may be proximal or distal along fibers (Walling et al., 2004).

Diagnosis of perineural involvement in many cases requires micrographic analysis, as patients frequently exhibit no neurological symptoms. Those who do demonstrate sensory or motor findings, however, are at particularly high risk of a poor outcome (Walling et al., 2004).

Neurotrophic factors that influence the interaction between cancer cells and nerves are suspected. p75NGFR immunostaining increased detection of perineural invasion compared with H&E. p75NGFR could serve as an alternative to S-100 in the detection of perineural invasion, or as part of an immunostaining panel for perineural invasion detection (Lewis et al., 2006). Usually, however, perineural spread is less extreme but may produce a neuropathy. Rarely, the neuropathy may be the presenting sign of a recurrent skin cancer, with no cutaneous tumor evident (Morris & Joffe, 1983). Involvement of the trigeminal nerve may produce pain; involvement of the facial nerve may cause facial muscle weakness (Schwartz, 2008).

5.3 Metastasis

Despite the large number of primary BCCs diagnosed each year, the rate of metastatic BCC (MBCC) ranges from 0.0028% to 0.5% (Malone et al., 2000 & Soleymani et al., 2008). Since MBCC was first reported in 1894 by *Beadles*, there have been more than 240 cases reported in the literature. Of these cases, 66–85% of MBCCs arise from primary lesions in the head and neck region (Soleymani et al., 2008 & Ting et al., 2005).

The primary tumor must originate from the skin and not the mucosa, metastasis must occur at a site distant from the primary tumor without evidence of direct extension, and the primary and metastatic tumors must have similar histopathology. These are the criteria needed for the true diagnosis of MBCC (Soleymani et al., 2008). Metastases occur in males and females in a 2:1 ratio, most often involving dissemination to regional lymph nodes and hematogenous spread to lungs, bone, and skin (Ting et al., 2005).

Risk factors associated with the rare occurrence of metastasis include tumor size of less than 2cm, multiple primary tumors in the region of the head and neck, significant tumor depth, fair skin, middle age, and male gender (Ozgediz et al., 2008). Mean survival for patients with metastatic disease is 8 months (Snow et al., 1994), although those with spread limited to the lymph nodes alone have an average survival of up to 3.6 years (Soleymani et al., 2008).

There is no consensus as to whether any one histologic subtype of the primary tumor predisposes to MBCC. Nodular, micronodular, morpheaform, metatypical or basosquamous, and infiltrative histologies have all been reported (Soleymani et al., 2008).

In a retrospective review of 5270 morpheaform or invasive BCCs over a 50-year period did not reveal an increased rate of metastasis compared to other histologic subtypes (Soleymani et al., 2008). It is very difficult to predict the metastatic potentiality of BCCs by histopathology (Kinoshita et al., 2005). In a case report it was shown that the tumor cells were bcl-2 negative and positive for Ber-EP4. The negative expression of bcl-2 correlates with the aggressive nature of this tumor and Ber-EP4 confirms the diagnosis of BCC (Richard et al., 2010).

In a literature search of cases of black patients with metastatic BCC revealed eight cases. In these cases, the most obvious common predisposing factor seems to be large lesion size, with all of the cases having at least one dimension greater than 5 cm (Saladi et al., 2004).

6. Diagnosis

Diagnosis of BCC is accomplished by accurate interpretation of the skin biopsy results (Carucci, 2008). It should be remembered that the diagnosis of any cancer is always a histologic one; clinical acumen cannot replace histologic documentation (Schwartz, 2008).
The tumor growth pattern is importatnt information that is impossible to determine if only a superficial fragment is submitted to the laboratory. Deep shave, punch, incisional or excisional biopsy can all give sufficient dermis for the evaluation.
A number of non-invasive imaging technologies are being investigated to delineate tumor depth and extent preoperatively and thus guide treatment. Confocal microscopy, infrared spectroscopy and ultrasound are some of them but for the moment they remain experimental.
If a BCC may have been neglected and reached a size such that direct bony invasion occurred a preoperative CT scan should be considered.
Dermoscopy is a noninvasively method that has been reported to be a useful tool for the early and accurate recognition of pigmented lesions of the skin . However, nodular lesions can lack specific dermoscopic criteria being completely or partially featureless in their appearance. Reflectance confocal microscopy (RCM) is an emerging noninvasive diagnostic tool that provides *in vivo* tissue images at nearly cellular histological resolution. In a study four patients with nodular lesions have been examined clinically and dermoscopically equivocal a RCM examination allowed for a rapid and accurate prebiopsy diagnosis (Carucci, 2008 & Schwartz, 2008).

7. Differential diagnosis

A lot of benign appendageal tumors may cause confusion, as may rare malignant appendageal cancers, SCCs, atypical fibroxanthomas, melanocytic nevi, Merkel cell carcinoma and rarely melanoma. A hemispheric nodule clinically indistinguishable from a BCC may be a trichoepithelioma, a benign appendageal tumor. A small yellowish papule with a central dell may be confused with an early BCC; sebaceous hyperplasia is quite common and often displays telangiectasia, additionally reminiscent of the BCC.
Granulomatous lesions may need a distinction from BCC, examples of which include tuberculosis; syphilis; deep fungal infections. Other types of BCC besides the noduloulcerative type expand the list of differential diagnoses. Sclerosing-type BCCs may be mistaken for scars or small plaques of localized scleroderma (morphea) (Table 1) (Schwartz, 2008).

8. Histopathology

BCC have in common proliferations of basaloid keratinocytes in various configurations with a variable fibromyxoid stroma. Epidermal origin is usually evident and an inflammatory infiltrate is variably present (Miller, 2008).
Under the microscope, BCC appears as irregular dermal masses of variable sizes and shapes, surrounded by a layer of peripheral tumor cells with palisading nuclei. The individual tumor cells are usually rather uniform in appearance and lack atypia .When nuclear atypia and multiple mitotic figures are rarely present, this does not alter the clinical course of these BCCs (Schwartz, 2008).

- Nodular basal cell carcinoma:
  - Squamous cell carcinoma
  - Seborrheic keratosis
  - Intradermal nevus
  - Sebaceous hyperplasia
  - Fibrous papule
  - Molluscum contagiosum
  - Keratoacanthoma
  - Scar tissue
- Superficial basal cell carcinoma:
  - Discoid eczema
  - Psoriasis
  - Actinic keratosis (solar keratosis)
  - *Bowen*'s disease
  - Squamous cell carcinoma
  - Seborrhoeic keratosis
- Pigmented basal cell carcinoma:
  - Melanoma
  - Lentigo maligna melanoma
  - Appendegeal tumor
  - Compound nevus
  - Blue nevus
- Morphoeic basal cell carcinoma:
  - Scar tissue
  - Localised scleroderma
  - Trichoepithelioma
- Fibroepihtelioma of *Pinkus*:
  - Skin tag
  - Papillomatous dermal nevus
  - Fibroma

Table 1. Differential diagnosis according to the types of basal cell carcinoma (Carucci, 2008).

Traditionally, BCCs have been classified as solid (or undifferentiated) vs those tumors that manifest specific differentiation features (ie to eccrine, sebaceous or other cell lines). However, the only proven histologic prognosticator of biologic behavior, and therefore a major determinant of what constitutes an appropriate therapeutic approach, is the architectural growth pattern (Crowson, 2006).

The nuclei in basal cell carcinoma as a rule have a rather uniform, nonanaplastic appearance. They usually show no variation in size or intensity of staining and no abnormal mitoses, even in the rare instances of BCC with metastases (Kirkham & Elder 2005). Cellular borders are indistinct and desmosomes are inapparent. Apoptotic cells are common. The fibromyxoid stroma is intimately associated with the tumor islands, often showing increased cellularity (Miller, 2008).

8.1 Special types of histological patterns include

1. Keratotic BCC with parakeratotic stratum corneum
2. Sebaceous differentiation of the sebaceous epithelioma (also called BCC with sebaceous differentiation, a possible marker for *Muir-Torre* Syndrome of multiple sebaceous neoplasms, keratoacanthomas, and multiple low-grade visceral malignancies)
3. Adenoid histologic-type BCC, with its lace-like pattern of interconnected tumor strands, producing a glandlike structure
4. Sclerosing BCC with abundant dense stroma with multiple islands of compressed tumor cells
5. Pigmented BCC with histologic evidence of melanocytes with large amounts of melanin
6. Superficial-type BCC with superficial tumor buds that appear to originate at multiple foci from the overlying attached epidermis
7. Fibroepithelioma, with its long, thin anastomosing tumor cell strands
8. Granular cell–type BCC
9. Signet-ring–type BCC
10. Clear cell–type BCC
11. Cystic BCC, which may mimic other cysts, including inclusion cysts due to penetrating injury, mucoceles, apocrine hidrocystoma, and necrotic metastatic tumors
12. BCC with eccrine differentiation
13. MTC with tumor lobules more irregular and peripheral palisading less pronounced but focally present. Stromal proliferation is more prominent.

Areas of typical BCC may be seen to merge into a metatypical region. The most important histologic finding that confirms the metatypical carcinoma (MTC) diagnosis is the absence of a transition zone between the basal cell and squamous cell types. This is the reason why MTC is not a collision between a BCC and a SCC (Kirkham & Elder 2005; Schwartz, 2008).

8.2 Nodular Basal Cell Carcinoma

The nodular form of BCC is characterized by discrete large or small nests of basaloid cells in either the papillary or reticular dermis accompanied by slit-like retraction from a stroma in which the fibroblasts do not appear to be plump or proplastic . Any of the differentiated elements (eccrine, sebaceous, etc) may be seen in nodular tumors and roughly one-third of cases will show a coexistent superficial component.

The surrounding stroma shows myxoid change, is rarely fibrotic and may show calcification in discrete islands of tumor or in adjacent stroma. Mitoses and individual cell necrosis are uncommon. The presence of abundant slit-like retraction may cause tumor nests to drop out from the stroma during processing yielding empty spaces with a rounded contour in the mid or deep dermis. This is an important clue to the diagnosis in the setting of the nodular and/or infiltrative growth patterns. A significant proportion of BCCs with a nodular component manifests a variable admixture of superficial and/or micronodular morphologies. Melanin pigmentation of tumor cells and adjacent stromal histiocytes may be seen (Crowson, 2006).

In larger tumor islands, central areas of necrosis may develop, leading to the formation of cystic spaces. True cystic or nodulocystic BCCs form on the basis of mucin pools within tumors (Miller, 2008).

8.3 Micronodular Basal Cell Carcinoma

Micronodular BCC manifests a plaque-like indurated lesion with a poorly demarcated contour. They are composed of smaller tumor islands than those of nodular BCC. The

cellular features are similar (Miller, 2008). The micronodular BCC has been reported to have a higher incidence of local recurrence and may penetrate more deeply into the reticular dermis and/or subcutis (Crowson, 2006).

8.4 Infiltrative growth Basal Cell Carcinoma

Infiltrating BCC is poorly circumscribed with jagged, irregular contours and tumor strands which may invade beyond the dermis. Peripheral palisading is absent, inflammation is minimal, and the surrounding stroma is often fibrous. There is evidence that many of these multifocal buds connect in a net-like pattern, so most are not truly multifocal (Miller, 2008). Infiltrative tumors, in particular, have been found to have a relatively higher growth fraction as ascertained by Ki-67 immunohistochemistry (Walling et al., 2004).

8.5 Keratotic Basal Cell Carcinoma

Also known as pilar BCC as it appears to differentiate along pilosebaceous lines, the keratotic BCC manifests large basaloid tumor nests that are rounded and show central keratinization and degeneration. The central cysts typically lack a granular cell layer and are filled with keratin and parakeratotic debris; a granular cell layer is present in some cases and the cysts may show central calcification surrounded by the basaloid tumor cells.True hair production is absent (Crowson, 2006). Infundibulocystic BCC may appear similar but usually has a more anastomosing pattern of tumor nets (Miller, 2008). Keratotic BCC shares with trichoepithelioma the presence of horn cysts, and it is sometimes difficult to decide whether a lesion represents a keratotic BCC or a trichoepithelioma (Kirkham & Elder 2005).

8.6 Morpheaform Basal Cell Carcinoma

Morpheaform or sclerosing BCC is characterized by columns of basaloid cells one to two cells thick enmeshed in a densely collagenized stroma containing proplastic fibroblasts (Crowson, 2006). A peripheral palisaded pattern of tumor cells is absent and stromal retraction is also frequently not evident (Miller, 2008 ; Walling et al., 2004). Individual cell necrosis and mitotic activity considering the relative tumor volume and the neoplasms themselves are poorly demarcated, showing widespread invasion of the reticular dermis and penetration into the subcutaneous tissue (Crowson, 2006). Morpheaform BCC has been associated with greater subclinical depth of extension , and morpheaform and infiltrating BCC are associated with a greater rate of recurrence (Walling et al., 2004).

8.7 Fibroepithelioma of Pinkus

Described by Pinkus in 1953 the fibroepithelioma typically arises above the natal cleft or on the lower trunk as a pink or flesh colored nodule with a constricted inferior margin suggesting a seborrheic keratosis. In this tumor, elongated basaloid epithelial strands manifesting slit-like retraction from stroma are enmeshed in a myxoid matrix or a background of proliferating spindle cells with abundant collagen (Crowson, 2006 & Miller, 2008). Peripheral palisading is less prominent, as is peritumoral retraction.

Only rarely will one find areas of the tumor with more classic findings for BCC. Some consider fibroepithelioma as a benign tumor while others view it as very low-grade of BCC (Braun-Falco et al., 2000). In differential diagnosis ecrine syringofibroadenoma and reticulated seborrheic keratosis should be considered (Miller, 2008).

8.8 Subtypes according to histopathological growth pattern and potential for aggression

Less aggressive

- Superficial
- Nodular

More aggressive

- Infiltrative
- Micronodular
- Morphoeic

Other types (uncommon)

- Basosquamous (metatypical) – BCC with squamous differentiation. Probably more aggressive with a greater chance of metastasis than other forms of BCC.
- Adenoid
- Cystic
- Pigmented
- Cornifying/keratotic
- Fibroepithelioma
- Follicular/infundibulocystic

9. Treatment

For basal cell carcinoma, the goal of treatment is elimination of the tumor with maximal preservation of function and physical appearance according to the 2011 National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. As such, treatment decisions should be individualized according to the patient's particular risk factors and preferences. Evaluating all of the cases, the recommended treatment modality for basal cell carcinoma is surgery. Treatments vary according to cancer size, depth, and location on the body. Dermatologists may perform nearly all of the therapeutic options in an outpatient setting. Most therapies are well established and widely applied; nevertheless, researchers are studying some additional options (photodynamic therapy with photosensitizers etc and awaiting further reports.

Local therapy with chemotherapeutic and immune-modulating agents is useful in some cases of BCC. In particular, small and superficial BCC may respond to these compounds. Topical 5% imiquimod is approved by the US Food and Drug Administration (FDA) for the treatment of nonfacial superficial BCCs that are less than 2 cm in diameter. Likewise, topical fluorouracil is approved by the FDA for the treatment of superficial BCC. Both imiquimod and fluorouracil may be used topically for prophylaxis or maintenance in patients who are prone to having many BCCs.

For tumors that are more difficult to treat (infiltrative, morpheaform, micronodular, and recurrent BCCs) or those in which sparing normal (noncancerous) tissue is paramount, *Mohs* micrographic surgery should be preferred.

For metastatic BCC, the 2011 NCCN guideline recommends clinical trials of systemic chemotherapy, particularly platinum-based combination therapy. Clinical trials of investigational biologic modifiers such as hedgehog pathway inhibitors are also recommended (Bader, 2011).

9.1 Mohs Micrographic Surgery

Mohs micrographic surgery (MMS) is a procedure based on the principles of microscopic margin control and tissue sparing (Alam et al., 2010). *Mohs* micrographic surgery was first reported in 1941 by *Mohs* (Samarasinghe et al., 2011). At first the tumor tissue is removed at an angle of about 45°, and then tumor tissue is instantly frozen and cut horizontally from the base to the surface, and all margins, especially lateral and basal margins, examined histologically whether tumor cells are still present or not. If the tumor cells detected, additional excisions are performed until all the tumor tissue has been disappeared (Wetzig et al., 2009). This method almost requires local anesthesia (Telfer et al., 2008).

This specialized surgical procedure is commonly used in a patient with large (> 2 cm) tumors, high-risk morphea-type BCC tumors, recurrent tumors, or tumors located in cosmetically sensitive locations (Ceilley Del & Rosso, 2006). There are three important matter for compliance with the method of *Mohs* micrographic surgery for BCCs: i) location and size, ii) histology, iii) pre-treatment preferences. If BCC lesion is located on the head and neck, if some of the histological types are present (shown in Table 2) and if the lesion is previously untreated, MMS is preferable. The most common indication for MMS is BCC located on the head and neck. Because these sites of the body are the most cosmetically sensitive regions and also recurrence risk is considerably high. BCC lesions in some parts of the body such as eyelids, lips, ears, nose, H-zone, genitalia, fingers and toes are generally treated by *Mohs* micrographic surgery (Wood & Ammirati, 2011). Aggressive histological subtypes of BCC include metatypical, morpheaform, micronodular, and infiltrative have a higher risk for recurrence, for this reason MMS is recommended in the treatment of these lesions with this certain histology (Cumberland, 2009). The indications for Mohs micrographic surgery are shown in Table 3 (Telfer et al., 2008).

Most of the methods of treatment except MMS do not include microscopic evaluation of tumor margins, such as curettage and desiccation, cryosurgery, radiation therapy and topical chemotherapy (Cumberland, 2009). The advantages over other surgical procedures this surgical procedure enables for greater tissue conservation and margin control (Ceilley Del & Rosso, 2006). *Muller* and his colleagues have shown that MMS is more tissue sparing compared to surgical excision (Muller et al., 2009). Also the 5- year recurrence rate is approximately 1% and 6-10% for primary BCC and recurrent BCC, respectively (Ho & Byrne, 2009). In another study conducted in recent years, very low recurrence rates and excellent cure rates have been reported in both primary and recurrent BCC by *Wetzig* et al (Wetzig et al., 2010).

• BCC with poorly defined clinical margins
• Syndromic multiple BCCs
• Large and deeply penetrating BCC
• Basosquamous (metatypical) BCC
• Morphea-form, sclerotic, micronodular, infiltrative, recurrent BCC
• BCCs with local invasion (perichondral, perivascular, periosteal, and perineural invasions)
• Superficial multicentric BCC
• BCC arising within a scar
• BCC within an existing lesion

Table 2. MMS is preferred in the treatment of some specialized subtypes (Wood & Ammirati, 2011).

In recent years, high-resolution ultrasound has been used for some tumoral lesions before Mohs micrographic surgery and is indicated for small lesions of BCC (Marmur et al., 2010). It is a non-invasive technique and it can detect how deep tumors spread into the skin (Wood & Ammirati, 2011).
Also in recent years immunostaining techniques have been used to detect tumor cells when histological features are nonspecific or is masked histologically by dense inflammation. Sometimes immunostaining can increase the efficacy of the margins evaluation but it is very expensive (Cumberland, 2009).
Complications of Mohs micrographic surgery include postoperative bleeding, scarring, wound infection, flap or graft necrosis (Samarasinghe et al., 2011).

- Tumor site cosmetically sensitive locations (especially central face, around the eyes, nose, lips and ears)
- Undefined tumor margins
- Tumor size (any size, but mainly > 2 cm)
- Histological subtype (especially morpheaform, infiltrative, micronodular and basosquamous subtypes)
- Recurrent lesions
- Local invasions (perineural or perivascular involvement)

Table 3. Indications for Mohs micrographic surgery (Telfer et al., 2008).

9.2 Standard surgical excision

Surgical excision is the main treatment modality for basal cell carcinoma and is usually applied as a standart method (Rogers & Bentz, 2011). This method is one of the most commonly used techniques in the treatment of nodular BCC and superficial BCC. Tumor tissue plus surrounding normal tissue area should be excised in this method (Ceilley Del & Rosso, 2006). A four millimeter excision margin is currently recommended for small, well demarcated BCC's (Sherry et al., 2010). The deep margins should contain the fascia (forehead), the perichondrium (ear, nose), or the periosteum (scalp) (Dandurand et al., 2006). Then, whether the presence of tumor cells in extracted material margins, should be verified by histopathological examination. Nevertheless, the incidence of incomplete excision can be increased up to 10% approximately. Some factors such as experience of surgeon, histologic subtypes and excision margins play an important role in the success of the operation (Ceilley Del & Rosso, 2006).
Its effectiveness is quite higher for primary BCC and also cosmetic results are usually well. Peripheral excision margins for primary BCC of 3–5 mm and 5-10 mm for recurrent BCC have been suggested. Due to high recurrence risk excision should be wider in recurrent BCC (Telfer et al., 2008). In contrast to small primary BCCs, morphoeic and large BCCs require wider surgical margins, between 5-15 mm, for complete histological resection (Pua et al., 2009). *Gulleth* et al. reported that 3-mm surgical margin can be safely used for nonmorpheaform basal cell carcinoma lesions 2 cm or smaller (Gulleth et al., 2010).
The cure and recurrence rates are variable. *Wetzig* et al. reported high cure rates for primary and recurrent BCCs, 99,5% and 97,1% respectively, at the end of 5-year follow-up (Wetzig et al., 2010). *Szeimies* et al. reported that clinical lesion response 99,2% and cosmetic outcome 59,8% 3 months and 12 months after surgical excision for superficial basal cell carcinoma, respectively. 12 months after surgical excision, reccurence has not been reported (Szeimies et

al., 2008). *Rhodes* et al. found that surgical excision is more effective than photodynamic therapy for the treatment of nodular basal cell carcinoma as a result of 5-year follow-up and recurrence rate was reported as 4%. (Rhodes et al., 2007). In 2008 a randomised controlled study of surgical excision versus fractionated 5-aminolevulinic acid-photodynamic therapy by *Mosterd* et al. found that 88 primary nodular BCC excised with 3 mm margins, the cumulative incidence of failure was 2,3% after 3-years of treatment (Mosterd et al., 2008).
There are some disadvantages of this method such as scars, bleeding and risk of infections (Szeimies et al., 2008). Also incomplete excision is another complication of the surgical excision which is correlate with the cure and recurrence rate, the patients morbidity and/or mortality, and the overall cost of treatment. *Pua* et al. reported that the overall incomplete excision rate was 1,54% (Pua et al., 2009). For this reason, surgical excision should be done by experienced surgeons (Szeimies et al., 2008).

9.3 Chemotherapy

Chemotherapy is generally used in two conditions: i) for the management of uncontrolled local disease, ii) for patients with metastatic BCC. Both conditions are extremely rare and are rapidly fatal position.
Various drugs can be used in metastatic BCC, including cyclophosphamide, etoposide, 5-fluorouracil, methotrexate, bleomycin, doxorubicin, and cisplatin but their effectiveness is variable. Cisplatin is the most effective chemotherapeutic agent in the treatment for patient with metastatic or locally advanced BCC, alone and/or combined. *Carneiro* et al. reported that a case of BCC metastatic to the lungs treated with the combination of carboplatin and paclitaxel (Carneiro et al., 2006). Also *Jefford* et al. observed that this treatment regimen was less neurotoxic effect and could provide rapid symptomatic relief (Jefford et al., 2004).
Paclitaxel, which is a chemotherapeutic agent, shown to be effective in a patient with nevoid BCC syndrome. Most of the aggressive BCC lesions of the patient which had not responded to treatment with intravenous cisplatin healed after 19 cycles intravenous paclitaxel treatment (Russo, 2005).
Snipes et al. reported that there was improvement with systemic 5-fluorouracil(5-FU) in a 52-year-old male patient with nodular BCC (Snipes et al., 2006).

9.4 Curettage and desiccation

Electrodesiccation and curettage (ED&C) is the most common method used by dermatologists to treat primary nodular and superficial BCC tumors < 1,5 cm in diameter (Ceilley Del & Rosso, 2006; Jefford et al., 2004). Initially tumor tissue is curetted and then the area is treated with electrosurgery (electrodesiccation or coagulation) to control bleeding until clinically normal tissue is appeared and all of tumor cells are eliminated. This method is repeated two or three times for achieving the success (Ceilley Del & Rosso, 2006). The wound heals within 4-6 weeks by secondary intention (Ho & Byrne, 2009).
While electrodesiccation and curettage are generally used for the treatment of low-risk lesions, they are generally contraindicated for the treatment of high-risk lesions because of their high recurrence risk (Telfer et al., 2008). This method can be applied in selected cases whom patients with multiple, superficial tumors on the trunk. Nevertheless, this method is contraindicated for facial tumors and in high-risk lesions (Wetzig et al., 2009). Disadvantages of this treatment option include to leave residual tumor tissue which may be demonstrated with histopathological examination and to develop hypertrophic scarring at

lesion site (Wu et al., 2006). There is a risk of development of hypertrophic scarring or white scar tissue formation after the procedure and this probability increases with the number of treatment cycles (Ceilley Del & Rosso, 2006). Some complications such as ulceration, hypopigmentation, blistering, edema, pain, secondary infection and recurrence can be seen immediately after the treatment or a later period (Dixon, 2005). Despite all of these possibilities cosmetic outcomes are usually pleasurable (Murchison et al., 2011).
The cure rates for primary basal cell carcinoma were reported between 88%-99% (Murchison et al., 2011). Also *Barlow* et al. reported that results of curettage alone were successful for nonaggressive basal cell carcinomas (Barlow et al., 2006).

9.5 Cryosurgery

The aim of this method is destruction of tumor cells using liquid nitrogen spray or probe. Cryosurgery is usually suitable for BCC lesions with well-defined borders (Ceilley Del & Rosso, 2006). Liquid nitrogen has a boiling point of -195^{o}C, making it a very effective cryotherapy agent (Moesen et al., 2010). Two freeze-thaw cycles (30 seconds each cycle duration) with a tissue temperature of -50 ^{o}C are recommended (Ceilley Del & Rosso, 2006). While double freeze-thaw cycles are generally suggested for the treatment of facial BCC, superficial truncal lesions may need only one treatment cycle (Telfer et al., 2008). At first the diagnosis should be confirmed by biopsy. Preliminary curettage may be done before cryosurgery except superficial basal cell carcinoma. Thermocouple needles are useful to measure the temparature inside the tumor. When the desired temperature was achieved within the tumor, freezing process is interrupted until the frozen ring is resolved, and then freezing-thawing cycle was repeated (Kuflik, 2004). The success rate increases when the procedure used the treatment of correct lesions by the experienced people (Telfer et al., 2008). One of the advantage is that this method does not require local anesthesia. Other advantages are outpatient, inexpensive and no requirement of patient sedation (Murchison et al., 2011).
Some factors include rate of temperature fall, speed of tissue thaw, solution concentration, time of subzero temperature exposure, lowest temperature achieved in the target tissue and the number of freeze–thaw cycles can change the degree of tissue destruction. If the freezing occurs quickly, further tissue damage happens according to slow freezing (Murchison et al., 2011).
Two distinct technique, open also known as spray and closed also known as probe or contact, are preferred for malignant lesions. Some sensitive areas, e.g. eyelids, the use of probes is quite favorable, because periocular structures can be damaged with spray technique. Therefore, when using the spray technique, it should be noted to avoid damage to unaffected areas by the dermatologists (Murchison et al., 2011). In the treatment of primary periocular BCCs, cryosurgery with nitrous oxide probe may be an alternative treatment modality in the absence of appropriate surgical procedures. The disadvantage of this procedure is higher recurrence rate, approximately 8%, compared with other treatment modalities (Moesen et al., 2010). But *Emanuel* and her colleagues reported that 5-years cure rate and 30-years cure rate for basal cell carcinoma after cryosurgery were 99% and 98,6% respectively (Kuflik, 2004). This noninvasive method was compared with topical methyl aminolaevulinate photodynamic therapy, recurrence rates were similar but cosmetic results were worse than photodynamic therapy (Basset-Seguin et al., 2008).
Adverse events such as peri/postoperative pain, tenderness, vesicle and/or bullae, erythema, sloughing of necrotic tissue or eschar formation, localized edema, scarring,

hypo/hyperpigmentation may occur during or after the procedure (Ceilley Del & Rosso, 2006). Posttreatment pain may require the use of narcotic drugs especially within the first few days (Murchison et al., 2011). Severe edema may occur in some locations such as periorbital region, around the temples and on the forehead and therefore the patients should be warned (Wetzig et al., 2009).
Cryosurgery should be avoided in areas of hair growth and in patients with conditions sensitive to temperature, including *Raynaud*'s syndrome, cold panniculitis, and cryoglobulinemia (Ceilley Del & Rosso, 2006). Some body sites such as hair-bearing scalp, nasolabial fold, tragus, retroauricular groove, upper lip and distal portion of the lower leg are relatively contraindicated locations. Cryotherapy is not recommended for sclerodermiform BCC (Wetzig et al., 2009).

9.6 Topical treatment of Basal Cell Carcinoma

9.6.1 Imiquimod cream

Topical imiquimod 5% cream (Aldara 3M Pharmaceuticals, St Paul, MN) is a Toll-like receptor agonist that acts as an immune-response modifier (Raasch, 2009 & Robinson et al., 2003). Imiquimod 5% cream is approved by the United States Food and Drug Administration (FDA) for the treatment of external genital and perianal warts; nonhyperkeratotic actinic keratosis and superficial BCCs mostly in patients in whom surgery is not an option. Imiquimod promotes the innate immune response and the cell-mediated immune pathway, potentiating its antiviral, antitumoral, and immunoregulatory properties (Amini et al., 2010). The mechanism of action of imiquimod is thought to occur through the binding to cell surface receptors, such as Toll-like receptor 7 which leads to activation of macrophages and other cells (Ceilley Del & Rosso, 2006). Toll like receptor 7 (TLR-7) is found on dendritic cells and monocytes (McGillis & Fein, 2004). Binding to TLR-7 receptor induces proinflammatory cytokine secretion (e.g.interferon-alpha and tumor necrosis factor-alpha, IL-1, IL-12, IL-6, IL-8, and IL-10) that favors type 1 helper T-cell-mediated immune response (Robinson et al., 2003). These cytokines play role in the activation of the adaptive immune response toward the TH-1 or cell-mediated pathway and inhibit the TH-2 pathway. By this immunmodulation, imiquimod is believed to be important for control of tumors (Navi & Huntley, 2004). Data have shown that imiquimod 5% cream may induce Fas (CD95) receptor (FasR) mediated apoptosis in BCC cells (Berman et al., 2003). Normally in BCC cells FasR expression is not seen so cell apoptosis via a FasR–Fas ligand interaction is prevented (Ceilley Del & Rosso, 2006). *Berman* et al. demonstrated that BCC cells in 3 of 4 patients treated with imiquimod 5% cream applied five times per week for up to 2 weeks were positive for FasR, leading to an infiltration of T lymphocytes (i.e. suggesting cell apoptosis), while all 5 vehicle-treated patients had FasR negative BCC cells at the end of the treatment period (Berman et al., 2003). Therefore, imiquimod 5% cream acts by inducing FasR in the treatment of BCC.
Imiquimod has been approved in the United States by the FDA for the treatment of superficial BCC (sBCC) in immunocompetent adults with tumors >0.5 cm^2 in area and <2 cm in diameter located on the trunk and extremities (Krown, 1991). Initial trials of imiquimod 5% cream for the treatment of skin cancer focused on sBCC. In a multicenter 6-week dose-response trial, complete histological clearance was seen in 87.9 % (29/33) of patients in the once-daily three-times-per–week regimen, 73.3 % (22/30) of patients in twice-daily three-times-per-week regimen, and 69.7 % (23/33) of patients in the once-daily, three-

times-per-week regimen. The median duration of treatment for complete clearance was 10-16 weeks (Marks et al., 2001).

Patients with sBCC were enrolled in a randomized, double-blind,vehicle-controlled study to determine the efficacy of longer treatment regimens and treated with imiquimod for 12 weeks once daily seven times per week (n =31), once daily five times per week (n =26), or once daily three times per week (n =29) (Geisse et al., 2002). In this study, histologic clearance rates in the three groups were 87%, 81%, 52%, respectively. These histologic clearance rates for imiquimod were similar to those reported in the 6-week study (Marks et al., 2001), suggesting that an additional 6 weeks of treatment may not be necessary for efficacy.

In addition to sBCC, imiquimod also has been demonstrated efficient in the treatment of nBCC (Shumack et al., 2002). One such study was a Phase II clinical trial comparing efficacy of various dosing regimens in a 6-week study in *Australia* and *New Zealand* and a 12-week study in *United States*. In both studies histological examination of lesion site on 6-weeks post-treatment showed the highest clearance rate in the once daily for 7 days per week groups, with 71% of patients in the 6-week study and 76% of patients in the 12-week study having complete response following treatment. The authors pointed out that these response rates were lower than the nearly 88% response rates seen in studies of superficial BCC lesions (Shumack et al., 2002).This type of treatment modality applies better for those patients in which surgery, radiotherapy, or cryotherapy are not an option.

The side effects from use of imiquimod are mainly local site reactions. In a phase II study, the most common local skin reactions were erythema, crusting, flaking, and erosion (Marks et al., 2001). 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. *Torres et al*. have reported on a randomized, double-blind, vehicle-controlled phase II study (n = 72) of imiquimod 5 days per week for 2–6 weeks before excision with MMS in the treatment of sBCC and nBCC. 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 (Torres et al., 2003).

9.6.2 Topical 5- Fluorouracil

Fluorouracil (5-FU) is an antineoplastic pyrimidine analog which decreases cell proliferation and induces cellular death, particularly in cells with high mitotic rates, through inhibition of thymidylate synthetase, which interferes with DNA synthesis. Evidence suggests that 5-FU used as a topical chemotherapeutic agent in NMSC has been effective for the treatment of superficial BCC, insitu SCC, and AKs. Due to lack of penetration through the dermis, 5-FU is generally not recommended for invasive BCCs and SCCs (Chakrabarty & Geisse, 2004). Published studies have indicated that 5-FU monotherapy has low clearance rates compared with other modalities. In a small study, 44 sBCC tumors were treated with a high concentration of medication, administered as a 25% fluorouracil paste, with occlusion that was changed once weekly for 3 weeks (Ebstein, 1985). This treatment regimen resulted in a 5-year recurrence rate of 21%. Although rigorous data are lacking, reports of 5-FU in combination with curettage or cryotherapy have suggested that combination therapy may be more effective than monotherapy (Ebstein, 1985; Tsuji et al., 1993). In the same study, 51 light curettage of 244 sBCC tumors before the 25% fluorouracil regimen resulted in a 5-year

cumulative recurrence rate of 6%, compared with the above-noted 21% for the fluorouracil regimen alone. Because limited data are available, the actual clearance rate for the topical treatment of sBCC with 5-FU is currently unknown.
In another study,superficial BCC treated with fluorouracil, thirty-one tumors were treated twice daily for an average of 11 weeks. A 90% clearance rate was observed on the basis of histologic evaluation results 3 weeks after treatment. No clinical follow-up was provided (Gross et al., 2007).
Application of 5-FU causes severe local skin reactions, including pain and burning, pruritus, irritation, inflammation, swelling, tenderness, hyperpigmentation, and scarring (Ebstein, 1985).

9.7 Radiation Therapy

Radiation therapy (RT) has been a useful alternative to surgical treatments. Radiotherapy (RT) can be effective for primary BCC, recurrent BCC or as adjuvant for incompletely excised BCC in patients where further surgery is neither possible nor appropriate (Samarasinghe et al., 2011). It has been particularly useful in the treatment of elderly patients and for larger tumors or tumors in difficult-to treat locations, such as the eyelids or pinna of the ear. Lower risk areas, such as the trunk and extremities, as well as the genitalia, hands, and feet are usually not treated with this modality (Ceilley Del & Rosso, 2006). RT is a complex mixture of different techniques including superficial RT (generated at up to 170 kV) which is suitable for lesions up to ~6 mm in depth, electron beam therapy (generated at higher energies) which penetrates deeper tissues, and brachytherapy which is useful for lesions arising on curved surfaces (Telfer et al., 2008). The total dose and treatment regimen (e.g. number of fractionated doses) depend on many factors including tumor location, size, type, and depth (Ceilley Del & Rosso, 2006). Radiotherapy is contraindicated in radiotherapy recurrent BCC, genetic syndromes predisposing to skin cancer and connective tissue disease. Significant side effects are radionecrosis, atrophy, and telangiectasia. Skin cancers can arise from radiotherapy field scars and should be avoided in younger age groups (Samarasinghe et al., 2011).
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 (Silverman et al., 1992).
Surgical excision (91% with frozen section margin control) of 174 primary facial BCCs < 4 cm in diameter has been compared with RT (mix of interstitial brachytherapy, contact therapy and conventional RT) for 173 lesions (Avril et al., 1997). The 4-year recurrence rates were 0-7% (surgery) and 2-5% (RT).
Radiation therapy is contraindicated in certain genetic disorders, which predispose patients to skin cancers (e.g. patients with *Gorlin*'s syndrome, xeroderma pigmentosum, or connective tissue diseases, such as lupus and scleroderma) (Ceilley Del & Rosso, 2006).

9.8 Photodynamic Therapy

Photodynamic therapy (PDT) is performed by topical application of the prodrug 5-aminolaevulinic acid (ALA) or methyl aminolaevulinic (MAL) to the BCC lesion. The prodrug is converted intracellularly into a potent photosensitizer, protoporphyrin IX (PpIX), and, when exposed to oxygen and an appropriate light source, a cytotoxic reaction via oxygen radicals occurs within cells containing these precursors.(Ceilley Del & Rosso, 2006;

Samarasinghe et al., 2011). The light source is usually either 410nm blue light or 630nm red light to match the absorption peak for PpIX. Red light may be preferred with the lipophilic MAL for deeper tissue penetration (Samarasinghe et al., 2011). PDT induces intense inflammation through the release of cytokines, chemokines and other immunological proteins by the injured and apoptotic cells. PDT has also been demonstrated to act as a biologic response modifier (Oseroff, 2006). In addition to damaging target cells directly, PDT, through upregulated cytokine production, enhances the innate and adaptive immune responses in immunocompetent individuals (Oseroff, 2006).

In a study of 95 patients with sBCC, the primary response rate with ALA PDT was 86%, with a 44% recurrence rate after a median follow up of 19 months and a projected disease-free rate of only 50% (Fink-Puches et al., 1998). In a long-term study of 350 sBCC and nBCC lesions treated with methyl 5-ALA PDT, 89% of lesions cleared with an overall cure rate of 79% after a mean follow-up of 35 months (Soler et al., 2001).

For nodular BCC a study comparing MAL PDT with surgical excision in 101 patients showed a MAL PDT cure rate of 76% compared to 96% for surgical excision. Cosmetis result was better for PDT with 87% of patients rated as good cosmetic outcome in comparison to 54% for surgery (Rhodes et al., 2004).

When undergoing PDT, patients often complain of stinging, burning, and itching at the site of treatment. Erythema, scaling, and crusting may be evident after treatment, but usually the area heals with no evidence of scarring (Neville et al., 2007).

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. Because single PDT treatment demonstrates poor efficacy in BCC, multiple visits to a healthcare provider's office are required. 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 (Ceilley Del & Rosso, 2006).

9.9 Immunotherpy

9.9.1 Intralesional Interferon

Interferon (IFN) works by binding to receptors located on target cells. The exact mechanism of action of these cytokines remains unclear, but interferons are known to have many important effects for the treatment of skin cancer, including antiproliferative effects (i.e., inhibition of mitosis and growth factors, activation of pro-apoptotic genes, and promotion of antiangiogenic activity) and upregulation of the immune system in the skin (Amini et al., 2010).

The mechanism by which IFN causes regression of BCCs has also been investigated. In IFN-treated BCCs, a considerable increase in the number of CD41 T cells infiltrating the dermis and surrounding the BCC nests was observed. As CD41 T cells have been shown to be capable of inducing apoptosis in their target cells via the CD95 receptor–CD95 ligand interaction, the expression of this ligand and receptor was subsequently analyzed in IFN-treated BCCs. In untreated patients, BCCs were found to express the CD95 ligand but not the receptor. In IFN-treated patients, BCCs expressed both the CD95 ligand and CD95 receptor, indicating that this signaling pathway may be capable of inducing apoptosis within these tumors by CD95 interactions with CD95 ligand (Buechener et al., 1997).

Intra- and perilesional IFN represent effective nonsurgical alternatives to treat BCCs, obtaining clearance rates between 70 to 100% (Telfer et al., 1999; Tucker et al., 2006). Its use is limited by its cost, safety profile, and the inconvenience of returning to a physician's office for multiple injections. A multicenter randomized controlled trial where IFN-α2b was used to treat 172 patients with biopsy proven BCC found the optimal dose to be 1.5 million IU intralesionally administered 3x/wk for three weeks. Significant clinical and histological clearance was obtained when compared with placebo (Greenway et al., 1986).
Twenty BCCs received treatment with intralesional IFN-α2b 3x/wk for three weeks at a dose of 1.5 million IU for lesions less than 2cm in diameter and three million IU for lesions 2cm or greater in diameter. More than half of lesions completely responded clinically and histologically at eight weeks of follow up. In those lesions that completely responded, only one recurrence was reported at five years of follow up (Bostanci et al., 2005).
Treatment with IFN can cause flulike symptoms including headache, myalgia, and fever, which can be alleviated by taking acetaminophen (Neville et al., 2007).
Even though several studies have demonstrated IFN's biologic potential for the treatment of BCC, it is not an established treatment option for BCC. This is because the clearance rates (approximately 70%) do not approach those achieved with surgical interventions, and it is also time consuming and costly to perform, as injections have to be administered by a healthcare professional up to five times per week. In addition, there have been no definitive large-scale studies that have determined the initial and long-term efficacy of this treatment option (Gaspari & Sauder, 2003).

9.10 Special management issues

9.10.1 Incompletely Excised Basal Cell Carcinoma

Various prospective and retrospective reviews of incompletely excised BCC suggest that not all tumours will recur. Studies using approximately 2–5 years of follow up have reported recurrence rates following histologically incomplete excision of 38%, (Richmond & Davie, 1987) and 41% (De Silva & Dellon, 1985). Patients should undergo re-treatment of incompletely excised lesions especially when they involve critical midfacial sites, where the deep surgical margin is involved, the surgical defect has been repaired using skin flaps or skin grafts and where histology shows an aggressive histological subtype (Mackie & Quinn, 2004). If the decision is made to re-treat rather than observe, re-excision (with or without frozen section control) or MMS are the treatments of choice. Patients should be treated at the time of diagnosis, because delay will likely result in increased local tissue damage. Patients should be evaluated for XRT if they are unable to undergo re-excision (Carucci & Leffell, 2008).

9.10.2 Neurotropic Basal Cell Carcinoma

Perineural invasion is not a common finding in basal cell carcinomas, with an estimated incidence that, depending on the series, varies between 0.17% and 3.8% (Ratner et al., 2000). The frequency is higher in more aggressive histological subtypes and in recurrent tumors. Due to the high risk of local recurrence, basal cell carcinomas with perineural invasion require specific management. The majority of authors agree on the use of *Mohs* surgery as the treatment of choice for this type of tumor; however, the use of other therapeutic options, such as adjuvant radiotherapy, or performing an additional Mohs stage after obtaining negative margins (Leibovitch et al., 2005), continues to be a subject of debate. Patients with gross perineural invasion manifesting neurologic symptoms would benefit from

preoperative magnetic resonance imaging to assess extent of tumor spread (Carucci & Leffell, 2008).

9.10.3 Metastatic Basal Cell Carcinoma

While the lifetime risk of basal cell carcinoma is high, it is well known to physicians that metastasis is relatively rare. Studies have indexed a metastasis rate of 0.0028% to 0.5% (Von Domarus & Stevens, 1984). In a review by *Randle*, tumors with any of the following characteristics should be considered high-risk for metastatic potential: long duration, location in the mid face or ear, diameter larger than 2 cm, aggressive histological subtype, previous treatment, neglected, or history of radiation (Randle, 1996). There is a 2% incidence of metastasis for tumors larger than 3 cm in diameter.

Increased tissue invasion and extension of the tumor into adjacent anatomical structures also enhance metastatic potential (Snow et al., 1994). Immunosuppression and evidence of perineural spread or invasion of blood vessels have also been implicated as risk factors for metastasis (Robinson & Dahiya, 2003).

For patients with metastatic disease, morbidity and mortality remain exceedingly high. The biggest risk factors for metastasis are tumor size, depth, and recurrence, despite optimal treatment. Primary basal cell carcinoma metastasizes usually via lymphatics, although it also spreads hematogenously. Metastasis most commonly occurs in regional lymph nodes, lung, and bone.

If nodal disease is suspected on surgical examination, lymph node biopsy and imaging studies, as well as evaluation by medical and surgical oncologists, are indicated. Platinium-based chemotherapy has been used with modest results in treatment of metastatic BCC; however rapid clinical response was reported using a combination and paclitaxel (Carucci & Leffell, 2008).

10. Course and prognosis

The prognosis of basal cell cancer is very good. Patient's survival rate is 100% without metastasis. However, rare in advanced cases can lead to serious morbidity and cosmetic problems.

The incidence of basal cell carcinoma is increasing with each passing day, consequently increases in the rate of metastatic BCC (MBCC). Therefore, the prognosis is important for early detection and treatment of cases of BCC.

Metastatic BCC is extremely rare. Rates reported in the literature of metastatic BCC are between 0.0028% and 0.5% (Berlin et al., 2002; Cotran, 1961; Malone et al., 2000). Criteria for the diagnosis of metastatic BCC were first described in 1951 by Lattes and Kessler. These are as follows:

1. Primary tumor is originated from the skin and not from mucous membranes or other glands
2. Metastasis occurred to a distant site from the primary tumor and could not result from direct extension
3. Both metastatic and primary tumors have identical histopathology
4. No squamous cell features may be present (Ozgediz et al., 2008).

BCC metastases could be occured by lymphatic, hematogenic, or direct infiltration of subcutaneous tissue (Von Domarus & Stevens, 1984).

The most common areas of metastasis are lymph nodes, lungs, bone, skin (Berlin et al., 2002), and parathyroid glands (Wadhera et al., 2006). 85-90% of metastatic BCC is due to head and neck region (Wadhera et al., 2006). More than 300 cases of metastatic BCC have been reported in the literature (Spates et al., 2003).
The median age of the first sign of metastasis has been reported as 59, with the interval from onset of primary tumor to the time of metastasis ranging from <1 to 45 years.
A limited number of reviews have elucidated several possible risk factors for developing MBCC (Table 4).
The prognosis of metastatic BCC is usually very poor. The median survival time was 8 months after the first metastasis, although it has been reported in patients with longer survival time (Boswell et al., 2006). Only those with lymph node metastasis have limited survival time as 3.6 years (Pfeiffer et al., 1990).
The risk of metastasis increases with the size of primary tumor. Those with primary tumor size greater than 3 cm, 2% increases the risk of developing metastasis, 25% for those greater than 5 cm in, 50% for those greater than 10 cm in diameter (Snow et al., 1994).

- Size of tumor > 2 cm
- Head and neck locations
- Tumor recurrence refractory to treatment
- Previous radiation therapy
- Multiple primary tumors
- Increased depth of tumor
- Invasion of perineural space and blood vessels
- Fair skin
- Male

Table 4. Generally Accepted Risk Factors of Metastatic Basal Cell Carcinoma.

Some BCC species and locations are more likely to metastasize. Today, very large size attained is reported cases of BCC. Giant BCC is rarely seen and constitute 1% of all cases of BCC. Rates of local invasion and metastasis of making Giant BCC is higher (Varga et al., 2011). Early diagnosis and treatment can not be done in cases of localized BCC. Periorbital BCC may lead to blindness as a result of orbit propagation. Cases of BCC in the medial region of cantus deep seated and tend to be invasive. BCC cases of this type of may lead to perineural invasion and neural dysfunction (Bader, 2011).
Poor prognosis could be avoided by early diagnosis and treatment, various patient's self sufficient treatments and sun protection (Wong et al., 2003). Oral retinoid therapy may prevent or delay the development of new BCC lesions in patients with a high degree of actinic damaged skin, Gorlin syndrome patients and renal transplant patients (Hodak et al., 1987).

11. Recurrence

5-year recurrence rate of BCC is approximately 4-5% (Kyrgidis et al., 2010). Tumour localization, T-stage, histologic subtype (Pieh et al., 1999) and the choice of treatment are significant predictors of the risk of recurrence. The relapse rate for primary basal cell carcinomas on the T-region of the face and nose is highest. T2 and T3 tumours show a 2- and

3-fold increased relapse rate, respectively, compared with T1 basal cell carcinomas. Patients with chronic skin diseases have a 50% lower risk of relapse than healthy patients. Recurrent basal cell carcinomas have a higher relapse rate than primary lesions. Patients treated in a specialized skin cancer unit have a 6,4-fold higher cure rate compared with those treated by less experienced physicians (Bogelund et al., 2007). Recurrence 5-year rate due to various treatments is summarized in the following table 5.

- Surgical excision - 10.1%
- Radiation therapy - 8.7%
- Curettage and electrodesiccation - 7.7%
- Cryotherapy - 7.5%
- All non-Mohs modalities - 8.7%
- Mohs micrographic surgery - 1%

Table 5. Recurrence rate according to the treatment choices

Reported rates of incomplete excision of basal cell carcinoma (BCC) range from 5% to 25% (Farhi et al., 2007; Su et al., 2007). Incomplete excision and repeated surgical excisions are increased recurrence rate. A positive pathologic margin has an average recurrence rate of 21-32,2 percent (Santiago et al., 2010).

Following BCC patients after their treatment procedure, the probability of occuring the new tumor in their first 3 years is 35%, and in 5 years that ratio is 50% (Mc Loone et al., 2006). The median time free of second primary tumour was 7 years, while the median time free of recurrence was 12 years (Kyrgidis et al., 2010). For that reason, following up BCC patients after their treatment procedure is very important (Mc Loone et al., 2006). Recurrence of incompletely excised BCC was significantly higher in younger patients, in aggressive histological types and in localizations like postauricular and nasogenian folds (Santiago et al., 2010).

A 3-mm surgical margin can be safely used for BCC to attain 95% cure rates for lesions 2 cm or smaller (Gulleth et al., 2010). Issued as a clean surgical magrin, recurrence develops in approximately 1% in cases of BCC. Average 36.6 months of development time to recurrence is needed after surgery (Wetzig et al., 2010).

Located on the face of recurrent BCC and aggressive subtypes of the best treatment is Mohs surgery (Mosterd et al., 2009). 5-year recurrence rate after Mohs surgery for recurrent BCC is approximately 5.6%. This rate is 4 times more than the other treatment modalities (surgical excision, radiotherapy, cryotherapy, curettage and electrodesiccation) (Rowe et al., 1989).

A recurrence of BCC should be suspected when one of the following conditions occurs:

- Nonhealing ulceration
- Tissue destruction
- Scar tissue that becomes red, scaled, or crusted or enlarges with large adjacent telangiectasia
- Scar tissue that slowly enlarges over time (months)
- Development of papule/nodule within a scar

Histologic types of BCC at higher risk for recurrence include morpheaform (sclerotic), micronodular, infiltrative, and superficial (multicentric). Other conditions that contribute to a higher recurrence rate include recurrent tumors that have been treated previously, large tumors (>2 cm), and deeply infiltrating tumors (Bader, 2011).

In immunocompromised patients, the risk of developing BCC is 10-16 times higher than the normal population. The risk of BCC in patients with renal transplant recipients is approximately 15% and female patients are at greater risk of BCC development. Recurrence rate after surgery is 10% (Mertz et al., 2010). However, placement and choice of treatment in these patients revealed no difference in terms of the normal population and does not seem to act more aggressively (Lott et al., 2010).

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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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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821