Basal Cell Carcinomas: An Epidemiologic Analysis

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1 Introduction

The incidence of skin cancer has markedly increased over the past few decades. Basal cell carcinoma (BCC), Squamous cell carcinoma (SCC), and malignant melanoma are grouped under the term “skin cancer”. BCCs and SCCs are distinctly labelled as non-melanoma skin cancers (NMSC). NMSCs are the most common forms of cancer and account for 90% of all skin cancer diagnosed in the world (Garner & Rodney, 2000). Basal cell carcinoma (BCC) is a malignant epithelial neoplasm that originates from the pluripotential cells in the epidermis and hair follicles (Pinkus, 1953). It is the most common skin cancer seen in human population (Jemal et al., 2003). It is often slow growing and may take years to enlarge significantly. But it can cause extensive local tissue destruction and slow death if inadequately treated or left untreated. The mortality rates associated with this cancer is low. However, it causes considerable functional and cosmetic deformity and cost of treatment is significant (Housman et al., 2003).

2 Methods

Our BCC database was reviewed between 1994 and 2012. Variables collected by operating surgeon were the patient’s age, sex, tumor site, size, histologic subtype, surgical margin of excision, multiplicity of lesions, presence of involved margins, recurrence during follow up and the presence of metastasis. All of the pathology specimens were examined and reported by the Department of Pathology at our centre.

3 Results

3.1 Age and Gender

From January 1994 to May of 2012, 518 BCCs were excised from 486 patients. The median age was 65.6 (range, 20 to 93 years), 182 patients were women (37.4%) and 304 were men (62.55%) (Figure 1).

![Figure 1: Gender percentages in BCC patients.](image)

3.2 Anatomical Site

Most basal cell carcinomas were located on the head region (83.8 %). Anatomical distribution were as follows: the nose (25.09%), scalp (15.44%), periorbital region (10.03%), cheek (10.42%), periauricular area (9.65%), forehead (6.17%), upper lip (3.86 %), lower lip (1.15 %), chin (1.15 %) and neck (0.77 %) (Figure 2).
3.3 Diameter of Lesion

294 lesions were smaller than 10 mm (56.7%), 196 lesions were between 10 and 20 mm (37.8%) and 28 lesions were bigger than 20 mm (5.4%). (Figure 3).

3.4 Histologic Subtypes

Among 518 diagnosed BCCs; 358 were nodular (69.11%), 94 were superficial (18.14%), 36 were pigmented (6.94), 18 were morphea like (3.74%) and 12 were basosquamous (2.3%). (Figure 4).
3.5 Tumor Excision

Only 18 patients (3.7 percent) had more than one lesion excised at the same operation. For lesions smaller than 1 cm in diameter we used a 3 mm margin for excision. We increased the excision margin 1 mm for every increase of 1 cm in diameter. We used a safety margin of 4 mm for morpheaform BCC and 5 mm for recurrent BCC. 12 BCCs (2.3%) required re-excision because of involved margins. During follow up we observed recurrence in 16 cases (3.08%). All occurred during the first four years. 8 were in the nose, 4 were in the periauricular area and 4 were in the periorbital area.

4 Discussion

The American Cancer Society reports skin cancers as being the most common cancer in the United States, with over 1 million new cases diagnosed and more than 10,000 deaths estimated yearly. The Skin Cancer Foundation currently estimates that one in every five Americans will develop skin cancer in their lifetime. Basal cell carcinoma incidence increases roughly by 3 to 6% per year (Bastiaens et al., 1998). BCC accounts for 80% of all skin cancers but is the least likely cancer to behave in a malignant fashion and metastasize (Garner & Rodney, 2000). The mortality estimate from BCC is extremely low, with total 5 year survival rate of greater than 95% (Gloster & Brodland, 1996).

The majority of BCCs occur in men, the ratio of male to female in our series is 1.6:1. The higher incidence in men is probably due to increased recreational and occupational exposure to the sun. However, the incidence in women is increasing because of changing fashions in lifestyle. The likelihood of developing BCC increases with age, it is rarely found in patients younger than 40 years. The mean age of our patients is 65.6. The damaging effects of the sun begin at an early age. The results may not appear for 20 – 30 years. Unfortunately, BCCs is no longer exclusively associated with elderly population. It has been encroached upon younger age groups because of the unprotected levels of sun exposure.

Although the exact etiology of BCC is unknown, a well-established relationship exists between BCC and the pilosebaceous unit, as tumors are most often discovered on hair-bearing areas. Many believe that BCCs arise from pluripotential cells in the basal layer of the epidermis or follicular structures. These cells form continuously during life and can form hair, sebaceous glands, and apocrine glands. Tumors usually arise from the epidermis and occasionally arise from the outer root sheath of a hair follicle, specifically from hair follicle stem cells residing just below the sebaceous gland duct in an area called the bulge.

Several factors are believed to predispose the patient to basal cell carcinoma. Exposure to sunlight is the most frequent association. Cumulative exposure to sunlight over years is necessary for tumor development (Blum, 1948). There are three types of UV radiation: UVA (320-400 nm), UVB (290 – 320 nm), and UVC (200 – 280 nm). UVB rays are the most carcinogenic, triggering skin cancer via photo-chemical damage to DNA, injury to DNA repair mechanisms, and partial suppression of cell-mediated immunity (Gloster & Brodland, 1996). Patients often have a history of chronic sun exposure. Those at high risk for developing basal cell carcinoma are Fitzpatrick skin types I and II (A. J. J. Emmett, 1988). Because of the climate in our region, most of our patients had a history of chronic sun exposure.

Ionizing radiation exposure may generate BCC by two mechanisms. The first entails the initiations of prolonged cellular proliferation, thereby increasing the likelihood of transcription errors that can lead to cellular transformation. The second mechanism is direct damage of DNA replication, leading to cellular mutation that may activate proto-oncogenes or deactivate tumor suppressor genes. The minimum re-
ported radiation dosage for inducing skin cancer is 4.6 grays (Modan, Baidatz, Mart, Steinitz, & Levin, 1974).

A modest increase in the lifetime risk of basal cell carcinoma has been noted in chronically immunosuppressed patients, such as recipients of organ or stem cell transplants. Immunosuppression alters the immune surveillance mechanism that destroys potentially malignant cells (Strom & Yamamura, 1997). Six of our patients were immunosuppressed after renal transplantation. Organ transplant patients must be instructed to limit sun exposure and alerted that skin cancer is a serious problem for them. In fact, immunosuppression and sun damage may cooperate to cause skin cancer. The skin cancer incidence is 10-fold higher in transplant patients than in the general population; up to 65-75% of patients with long-term immunosuppression develop skin cancer. Skin cancers can significantly alter and reduce the transplant recipients’ quality of life; some patients may develop more than 100 skin cancers per year.

The vast majority of Basal cell carcinomas occur sporadically, but patients with the rare heritable disorder basal cell nevus syndrome (also known as Gorlin Syndrome) have marked susceptibility to develop BCCs. In sporadic BCCs, p53 mutation was essentially the only known molecular abnormality (Ling et al., 2001). However, family based linkage studies of kindreds with basal cell nevus syndrome identified the patched 1 (PTCH1) gene, an inhibitor of the hedgehog signaling, as being mutated (Hahn et al., 1996; Johnson et al., 1996; Klein, Dykas, & Bale, 2005). Biallelic inactivation of PTCH1 results in upregulation of hedgehog signaling, which in turn leads to uncontrolled cell growth and proliferation. Because UV irradiation is a significant risk factor for BCC development, mutations in genes that control the extent of UV-induced DNA damage are associated with an increased risk of developing BCCs. Mutations of the melanocortin 1 receptor gene (MC1R) result in the production of pheomelanin (Rees, 2004). These people with fair pigment are at increased of BCCs.

The anatomic distribution of BCCs correlates with embryonic fusion planes. Recent data indicate that after adjusting for surface area, BCC occurrence is greater than 4 times more likely on embryonic fusion planes than on other regions of the midface, a finding that supports the possibility of an embryologic role for BCC pathogenesis.

The distribution of basal cell carcinoma across the body varies. Most of these carcinomas occur on sun exposed areas (Shanoff, Spira, & Hardy, 1967). In our series, 84 percent of basal cell carcinomas are found on head and 16 percent are found on trunk and extremities. The most common site for occurrence is the nose (25.09%)

Patients presenting with basal cell carcinoma (BCC) often report a slowly enlarging lesion that does not heal and that bleeds when traumatized. As tumors most commonly occur on the face, patients often give a history of an acne bump that occasionally bleeds. Patients often have a history of chronic sun exposure, including recreational sun exposure and occupational sun exposure. 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. BCCs may have one or more visible and irregular blood vessels, an ulcerative area in the center that often is pigmented, and black-blue or brown areas. Large BCCs may have oozing or crusted areas. The lesion grows slowly, is not painful, and does not itch.

Several histologic types of BCC exist. Histological diagnostics and classification of basal cell carcinomas (BCCs) are essential for an assessment of the percentage proportions of particular histological groups, risk determination of the recurrence of this illness, and comparison of treatment results. There is no unified and generally accepted classification of BCCs. When classifying BCCs, most authors start from the growth pattern, which gives more information about bio-behavior, and less often from the differentiation of tumors. Usually, BCCs are well differentiated and cells appear histologically similar to
basal cells of the epidermis. BCCs can be divided into several subtypes: superficial, nodular, pigmented, morphea-like and basosquamous.

Nodular BCC is the most common type. It represents 69.11% of our series. It generally consists of large, round or oval tumor islands within the dermis, often with an epidermal attachment. Artificial retraction of the tumor islands from the surrounding stroma is commonly seen. Clinically it presents as well defined translucent pearly nodule that is either round or oval with rolled border and occasional ulceration. Telangiectasias are commonly seen coursing through the lesion. (Figure 5) Most tumors of this kind are observed on the face.

Figure 5: Nodular BCC presents as well defined translucent pearly nodule that is either round or oval with rolled border and occasional ulceration. Telangiectasias are commonly seen coursing through the lesion.

Superficial BCC is the second most common subtype in our series (18%). It is characterized by numerous small nests of tumor cells usually attached to the undersurface of the epidermis by a broad base. Clinically, it presents as slightly elevated plaque or discrete macule that may be scaly (Wade & Ackerman, 1978). (Figure 6) Most often developing on the upper trunk or shoulders. Superficial BCC had the lowest percentage of positive margins after excision (3.6%) (Sexton, Jones, & Maloney, 1990). None of our recurrent BCCs were superficial type.

Figure 6: Superficial BCC presents as slightly elevated plaque or discrete macule that may be scaly.
Pigmented BCC is a rare variant (6.9%). Benign melanocytes in and around the tumor produce large amounts of melanin. These melanocytes contain many melanin granules in their cytoplasm and dendrites. It ranges from brown to blue black and can be mistaken for melanoma (Figure 7). Telangiectases that are typical of a nodular basal cell carcinoma can be observed. This aids clinically in differentiating this tumor from a melanoma.

![Figure 7: Pigmented BCC](image)

Basosquamous carcinomas have both basal and squamous cell differentiations. It has been defined as a basal cell carcinoma with differentiation towards squamous cell carcinoma. It is made up of basaloid cells that are a larger, paler, and rounder than those of a solid BCC. It also consists of squamoid cells and intermediate cells. Some consider the diagnosis of this type most appropriate when one evaluates a tumor with contiguous areas of BCC and SCC. This type is considered to have metastatic potential and is considered an aggressive skin cancer. They have a higher growth rate as well as higher metastatic potential than do other BCCs. It represents 2.3% of all our series.

Morphea like BCC is an aggressive rare variant accounting for 3.7% of all our BCCs. It presents as firm plaques that is yellow or white with ill-defined border (Figure 8). Tumor cells induce a proliferation of fibroblasts within the dermis and an increased collagen deposition (sclerosis) that clinically resembles a scar. The extent of the tumor is usually not apparent on clinical examination. Morphea form BCCs had the highest percentage of positive margins after excision. Thirty three percent of our morphea form BCCs had involved margins after excision. Mohs micrographic surgery is valuable in the management of these lesions.

![Figure 8: Morphea–form BCC](image)
Regardless of the appearance of the lesion, we perform a histologic confirmation and typing. The histologic characteristics influence clinical behaviour, recurrence, and metastatic potential. Shave biopsy with a scalpel is a simple method removing the epidermis and a portion of the dermis. Since this tumor arises from the basal layer of the epidermis, shave biopsy will provide sufficient material for histological diagnosis and classification. Approximately 75.9% accuracy rate has been found with shave biopsy (Russell, Carrington, & Smoller, 1999). We don’t prefer this type of biopsy in pigmented BCC’s that are difficult to differentiate from the melanomas. Punch biopsy garners a full-thickness specimen. The punched out defect may be sutured or may heal secondarily. The accuracy rate with punch biopsy is 80.7% (Russell et al., 1999). We only prefer using this type of biopsy when a large lesion of uncertain diagnosis exists. Excisional biopsy, is the biopsy type that we usually prefer. We advise excisional biopsy for small lesions that enable primary closure afterwards that does not cause distortion of the environmental tissues. Otherwise, an incisional biopsy may be done before the definitive treatment.

Once the pathologic diagnosis of BCC is confirmed, the next step is to plan for tumor eradication by correlating tumor characteristics with patient’s age, skin history, medical history, social history, and cosmetic expectations. Treatment options include standard surgical excision, Mohs micrographic surgery, nonsurgical ablation and topical chemotherapy.

Surgical excision is the preferred method in our centre. We generally perform excision under local anaesthesia or in the outpatient surgery settings. Our excision margins usually change according to the size, type and location of the lesions. We use the minimal safety margins in areas like the periorbital region and send the tumor for frozen section examination during the operation to ensure complete removal of the tumour. For lesions less than 1 cm in diameter we use a 3mm margin for excision. We increase the excision margin 1 mm for every increase of 1 cm in tumor diameter. We use a safety margin of 4 mm for morpheaform BCC and 5 mm for recurrent BCC. The safety margins may well be increased according to the degree of destruction of tissues in recurrent BCCs. In areas where there is no delicate structure nearby such as the back region, we prefer to use a wider excision margin in our excision spectrum. It is certainly better not to leave any residual tumour after the first operation as long as the surgical result is not compromising the aesthetic result. Frozen section examination or Mohs surgery may be used anywhere any suspicion about the completeness of removal arises. Proper curettage to better define the BCC’s border prior to excision may increase the cure rate for primary lesions (Telfer, Colver, Morton, & British Association of, 2008). The wound may be left for secondary healing, closed primarily, skin grafted or closed using a flap. The specimen is sent to the pathology laboratory with results transmitted within a few days. The final surgical decision is made on the basis of these results. A flap is used only after the final margins are negative.

Mohs micrographic surgery aims to completely remove the tumor via consecutive excision of the tumor, spatially orienting the specimen, histologically examining the margins, re-excising the residual tumor, and repeating the cycle until the area is tumor free. It is based on the principle that the tumor spreads by contiguous growth. The cure rates for primary BCCs < 2 cm treated with MMS approach 99%. Recurrent BCC cure rates range from 94 to 96% (Lawrence, 1999; Shriner, McCoy, Goldberg, & Wagner, 1998). Mohs micrographic surgery is indicated for the treatment of recurrent BCC, primary BCC occurring at sites with high rates of recurrence (e.g., periorbital, periauricular and nasolabila areas), histologically difficult BCC (i.e., morphelike), and BCCs in which conservation of tissue is critical (e.g., on the nose and ear).

Destructive methods like curettage and electrodesiccation (C&E), cryosurgery and laser are appropriate methods for the management of smaller lesions that have low recurrence rates. Due to unacceptably
high recurrence rates, poor cosmetic outcomes and lack of histological control, it is generally not accepted as a first line therapy for BCC in our centre.

Curettage refers to the use of a curet for separating and cutting the tumor from the skin. Electrodesiccation refers to the use of electrocautery, in which a high-frequency electrical current is directly applied to the tissue. The current destroys tumor cells and obtains hemostasis. During the curetting, the physician should feel the difference between tumor and normal skin. Tumor tissue feels soft and easily breakable, whereas normal dermis is difficult to scrape and feels coarse. After curettage, electrocautery is applied to the entire curetted area. This cycle can be repeated in a single visit (Orengo, Katta, & Rosen, 2002). C&E is an easy technique to learn and requires only minimal equipment’s. However, the wound may take 6 weeks to heal leaving a hypopigmented or hypertrophic scar. Recurrence rates can be as high as %13 depending on BCC subtype, anatomic location and tumor diameter (Rowe, Carroll, & Day, 1989; Silverman, Kopf, Grin, Bart, & Levenstein, 1991). We recommend avoiding C&E in BCCs along the embryonic fusion lines.

Cryosurgery uses various mechanisms to treat carcinoma by forming crystals, demonstrating recrystallization patterns as the cells thaw, exposing cells to electrolyte concentrations in adjacent thawing and nonfrozen fluids, causing ischemic damage from vascular destruction (Giuffrida, Jimenez, & Nouri, 2003). Liquid nitrogen is the most common used cryogen. High risk BCCs with aggressive histologic subtype or BCCs in critical facial sites are not appropriate for cryosurgery. The recurrence rate for primary BCCs treated with cryosurgery is 4.3% (Thissen, Neumann, & Schouten, 1999). Immediately after application, pain, redness and edema are observed at the treated site. Within the first days after cryosurgery blisters may develop. It may take several weeks for wounds to heal. Cryosurgery may produce permanent hyperpigmentation or hypopigmentation.

Laser therapy is a novel option for the treatment of BCCs. However, long term results have not been determined yet and more clinical studies are warranted. Treatment with a combined 585 nm pulsed dye laser (PDL) and 1,064 nm Neodymium Yttrium Aluminum Garnet (Nd:YAG) laser was found effective in reducing tumor burden in patients with BCC (Jalian, Avram, Stankiewicz, Shofner, & Tannous, 2013). Lasers are still not well accepted primary treatment of BCCs.

Photodynamic (PTD) therapy is administrated by application of photosensitizer to the target area. When these molecules are activated by light, they become toxic, therefore destroy the target cells. Long-term cure rates for PDT have been disappointing, and treatment may require multiple sessions to increase the clearance rate. This modality may still prove to be a good option for select patients. Since the photosensitizers may have limited penetration and diffusion, BCCs should be of the superficial subtype and less than 2-mm thick to increase the chances of successful tumor treatment.

Most BCCs are sensitive to doses of radiation therapy (RT) that can be endured by normal surrounding skin. RT of tumors < 2 mm has a cure rate of 90% for BCC (Leshin, Yeatts, Anscher, Montano, & Dutton, 1993). However, larger lesions have a much lower success rate. We reserve radiation for elderly patients who are poor surgical candidates or for patients having residual or recurrent tumors. RT is contraindicated in young patients because of the high risk of radiodermatitis and scars; in lesions on the trunk and extremities; and in delayed cancer recurrence. RT requires multiple visits. Treatment results in radiation damage and, therefore, should be reserved for older patients. RT is less effective for nonfacial tumors. RT also is contraindicated in patients with connective tissue diseases or genetic conditions predisposing to skin cancer (e.g., xeroderma pigmentosum, epidermodysplasia verruciformis, and basal cell nevus syndrome.) This histologic type in conjunction with RT may induce more tumors in the treated area. Radiation adverse effects include dermatitis, keratinization of the conjunctiva, and chronic keratitis.
Topical treatment using 5-fluorouracil may be used to treat small, superficial BCCs in low-risk areas. It interferes with DNA synthesis by blocking methylation of deoxyuridylic acid and inhibiting thymidylate synthetase and, subsequently, cell proliferation. In properly selected tumors, cure rates of approximately 80% have been obtained. The recurrence rate is very high. It is not in our routine. Retinoids are derivatives of vitamin A, and are essential to maintaining cellular differentiation. When present in physiologic to supra-physiological levels, retinoids can impede the progression of epithelial carcinogenesis. Oral retinoids may be indicated for multiple BCCs, such as basal cell nevus syndrome. Others include organ transplant recipients and patients with greatly sun-damaged skin.

Although the results of primary excision are excellent, recurrences can occur. Recurrence rates are higher in the inner canthus, base of the nostril and preauricular and postauricular areas (A. J. Emmett & Broadbent, 1981). This can be attributed to the scarcity of tissue, proximity to vital structures and cosmetic considerations that must be taken into account in treating lesions on these locations. Recurrence rates are also increasing with increasing lesion size. We observed recurrence in 16 cases (3.08%). All occurred during the first four years. 8 were in the nose (Figure 9), 4 were in the periauricular area and 4 were in the periorbital area.

Figure 9: Recurrent BCC in the nose

The incidence of incomplete excision of BCC reported in retrospective studies is in the range of 6.3 to 25 percent (Bogdanov-Berezovsky et al., 2001; Dieu & Macleod, 2002; Griffiths, 1999; Hauben, Zirkin, Mahler, & Sacks, 1982; Hussain & Earley, 2003; Mak et al., 1995; Richmond & Davie, 1987; Rippey & Rippey, 1997; Schreuder & Powell, 1999; Sussman & Liggins, 1996). In our series, 12 BCCs (2.3%) reported to have involved margins. The anatomic distribution of lesions with involved surgical margins were as follows; 6 lesions in the nose, 4 in the periauricular area and 2 in the periorbital area. In these cases, we prefer re-excision because reported recurrence rates for incompletely excised basal cell carcinomas can be as high as 86% (Pascal, Hobby, Lattes, & Crikelair, 1968). The hedgehog pathway inhibitor, Vismodegib, represents a new opportunity for the treatment of such patients with involved margins. Vismodegib has approval from the United States Food and Drug Administration for treatment of
metastatic BCC, locally advanced BCC recurring after surgery, and BCC that is not treatable via surgery or radiation (Bayers, Kapp, Beer, & Slavin, 2013; Sobanko, Okman, & Miller, 2013).

The prognosis for patients with BCC is excellent, with a 100% survival rate for cases that have not spread to other sites. Nevertheless, if BCC is allowed to progress, it can result in significant morbidity, and cosmetic disfigurement is not uncommon.

Although basal cell carcinoma is a malignant neoplasm, it rarely metastasizes. The rate of metastasis is below 0.1% (Goldberg, 1997). This low rate can be explained by BCCs connective tissue stroma dependent growth. Experimentally transplanted BCCs will not survive without dermal tissue (Grimwood, Ferris, Mercill, & Huff, 1986). Size, depth of invasion and histological type are important predictors for metastasis (Randle, 1996). Favoured sites of metastasis include regional lymph nodes, liver, lung, bone and skin. This rare metastasis is twice as common in males as in females.

Adequate patient education is essential in the prevention of recurrence of basal cell carcinoma. Avoiding extreme sun exposure is imperative. Wearing sunscreen, with a protective factor index of at least 30 or higher may decrease the chance of BCCs. Presently, sunscreen manufacturers are including protection against both types of rays. Whenever possible, one should wear long sleeves and long pants while outdoors. Wide-brimmed hats are also advised. Patients should avoid other possible potentiating factors. Patients should be educated on how to recognize any unexplained changes in their skin, especially changes that last for more than 3-4 weeks.

For those without a history of skin cancer, a dermatologic examination is recommended every 3 years for persons aged 20-40 years and every year for persons older than 40 years. The American Cancer Society recommends a dermatologic examination every 3 years for people aged 20-40 years and every year for people older than 40 years.

5 Conclusion

BCC is by far the most common cancer in the world and is the main cause of the skin cancer epidemic we are now facing. Fortunately, the majority of BCC cases are also preventable due to the chief etiologic factor, UV radiation. An ever increasing amount of evidence, linking the dangers of UV radiation to cancer, is discovered and imposed upon the health care field and the general public. With this evidence in hand, it is the job of physicians to reinforce and educate patients until the message is understood. Many treatment modalities are also becoming available, including topical regimens. It is necessary to explore these newer agents with large clinical trials to prove their efficacy to have them available in the near future for our patients. A large body of information serves as a foundation for oncologic principles, diagnosis methods, surgical excisions, follow up protocols and reconstructive methodologies that are currently in use. Surgical ablation remains the mainstay of treatment.

References


