

# A REVIEW OF FREQUENT CUTANEOUS MALIGNANCIES - PART I: NONMELANOMA SKIN CANCERS

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## Abstract

### Keywords:

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Skin cancers are responsible for extensive local tissue destruction, metastasis and even death. The incidence of skin cancers is increasing worldwide, especially those that are highly mortal and those that are associated with an increased morbidity. Basal cell carcinoma, squamous cell carcinoma and cutaneous malignant melanoma accounts for most of skin malignancies. To develop a solid treatment plan one needs to know the epidemiology, biology, etiology, tumor types and clinical behavior. Diagnostic biopsy is important in establishing various treatment options. Principles of reconstruction are briefly described. The article reviews the most frequent cutaneous malignancies in the most important aspects.

### Introduction

Basal cell carcinoma, squamous cell carcinoma and cutaneous malignant melanoma accounts for the majority of cutaneous malignancies<sup>(1)</sup>. This article will cover in part I basal cell and squamous cell carcinoma and in part II cutaneous malignant melanoma. It is estimated that over one million cutaneous malignancies occur in U.S.A. each year. Costs associated with treatment are difficult to estimate, but more than 1 \$ billion were spent for non-melanoma skin cancers alone, worldwide<sup>(2,3)</sup>. Although cutaneous malignant melanoma accounts for a small amount of all skin cancers, it is responsible for 75% of related deaths<sup>(4)</sup>.

The article reviews non-melanoma cutaneous malignancies (part I) and cutaneous malignant melanoma (part II), regarding epidemiology and etiology,

predisposing conditions, tumor biology, clinical types and various treatment options, basis of surgical treatment and general principles of reconstruction.

Basal cell carcinoma (abbreviated BCC), the most common skin cancer, is a malignant epithelial neoplasm of the skin, most often arisen in areas of chronic sun exposure. It is a slow-growing tumor that rarely metastasizes, but if inadequately treated or left untreated, it can cause extensive local tissue destruction and slow death<sup>(5)</sup>.

Squamous cell carcinoma (abbreviated SCC) is the second most common skin cancer, more specific to males and also arising on sun exposed skin of fair complexion<sup>(6)</sup>. In treating SCC, identifying factors that may serve as high risk predictors is paramount<sup>(7)</sup>.

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## Etiology

Predisposing factors include Fitzpatrick skin types I and II, actinic damage in youth that becomes evident in middle age, male sex, personal and family history of others skin cancers<sup>(8)</sup>. Exposure to sun and ultraviolet radiation (abbreviated UVR) is associated with 90% of non-melanoma cutaneous malignancies and 65% of malignant cutaneous melanoma, i.e. UVR A (95% of solar radiation) and UVR B (5% of solar radiation). There are 3 situations of UVR induced skin cancers: mutations with Thiamine substitutions in DNA with alterations of p53 tumor suppressor gene, activated oxygen radicals, Langerhans depletion and T-cells suppression<sup>(8)</sup>. Disorders like Nevus sebaceous of Jadassohn, xeroderma pigmentosum, porokeratosis, albinism, familial atypical multiple melanoma syndrome act through various mechanisms<sup>(8)</sup>. Epidermodysplasia verruciformis, bowenoid papulosis, discoid lupus erythematosus and chronic inflammation (burns, chronic ulcers) are also implied. Immunosuppression associated with transplants also increases the risks<sup>(8)</sup>.

## Epidemiology

Basal Cell Carcinoma is the most common human cancer, with more than 540.000 annual cases in USA by year-end 2010<sup>(5,8)</sup>; the number of cases doubled between 1970 and 1986<sup>(6)</sup>. Most of these carcinomas occur on sun-exposed regions, but also on protected areas like post-auricular sulcus, probably related to embryological closure of skin planes<sup>(9)</sup>. BCC metastasize very rarely. Basal cell carcinomas are stroma -dependent; experimentally transplanted basal cell carcinomas do not survive free of dermal tissue<sup>(10)</sup>. This may explain why these tumors metastasize so rarely, with an incidence of less than 0.1 percent<sup>(11)</sup>.

Squamous cell carcinoma is the second-most common skin carcinoma, occurring especially

in males and on sun-exposed areas<sup>(8)</sup>. It now represents approximately 20% of all skin cancers, approaching epidemic proportions<sup>(12)</sup>. Different from CBC, it does metastasize with an incidence reported between 2-6%<sup>(6,13)</sup>. The incidence rises in light-skinned population and declines with geographic latitude<sup>(14,15)</sup>.

Carcinogenesis progress is a multistep process that begins with initiation. Then the genetic mutation occurs<sup>(8,16)</sup>. Promotion results from modifications within the cellular environment. The final step is progression to the final malignant phenotype that materializes with further and definitive genetic alterations<sup>(8)</sup>. All these steps are required for malignant transformation to occur. Exposure to ultraviolet light produces DNA changes that are usually corrected by cellular repair mechanisms. If erroneous sequences are not repaired, propagation continues during DNA replication. Mutations related to ultraviolet light have been associated with mutations of the p53 tumor suppressor gene. In 56% of basal cell carcinomas, mutations occur in both p53 alleles<sup>(17)</sup>; the presence of p53 protein seems to correlate with basal cell tumor aggressiveness<sup>(18)</sup>.

## Diagnosis

**BCC** diagnosis is made by clinical presentation and features, through a logical descriptive and microscopic evaluation made by a dermatologist. Clinical evaluation through naked eye inspection provides the correct diagnosis in two thirds of cases and accuracy is improved by imaging tools as epiluminescence microscopy and serial body photography<sup>(8)</sup>. Tissue biopsy can aid diagnosis in border line lesions.

In **SCC** the most characteristic appearance is that of a raised pink papule or plaque, often scaly or crusted and sometimes eroded or ulcerated, but the tumor may present in a spectrum of appearances<sup>(19)</sup>.

	Low risk	High risk
<b>Clinical risk factors</b>		
• Location, diameter	Under 6 mm	More than 20 mm
• Border	Well defined	Poorly defined
• Primary or recurrent	Primary	Recurrent
• Immunosuppression	No	Yes
• Prior radiotherapy	No	Yes
• Rapid growth	No	Yes
• neurologic symptoms	No	yes
<b>Pathologic risk factors</b>		
• Perineurial or perivascular invasion	No	Yes
• Subtype (BCC)	Nodular or superficial	Morpheaform, micronodular, atypical
• Degree of differentiation (SCC)	Well differentiated	Poor differentiated
• Depth - Clark level (SCC)	Under 4 mm	More than 4 mm (Clark IV or V)

Adapted from *Netscher DT et al. in „Cutaneous Malignancies: Melanoma and Nonmelanoma Types“<sup>(8)</sup>*

**Table 1.** Risk factors in BCC and SCC

Diagnosis is made by clinical impression, microscopic evaluation performed by a dermatologist and tissue biopsy usually performed by a plastic surgeon<sup>(7)</sup>. A dermatopathology examination makes the final diagnosis. Biopsy can be attained by excision, punch or shave and it should be deep enough to distinguish between superficial and deep squamous cell carcinoma<sup>(7,8,21)</sup>.

**Tumoral biology and clinical types**

**Basal cell carcinoma**

**Tumor spread.** As described above, BCC's rarely metastasizes<sup>(8)</sup>; they spread along paths of least resistance (periosteum, perichondrium) until soft tissue is encountered. Reticular dermis seems to be a relative barrier to BCC penetration, and perineurial spread occurs in highly aggressive forms<sup>(20)</sup>. Tumor type is the most important prognostic factor in BCC treatment<sup>(5)</sup>.

**Clinical types.** A descriptive dermatological scheme will aid both diagnosis and consecutive treatment. This may include a primary description (macule, papule, nodule or plaque), a secondary description (scaly, crusted, erosion, ulcerative, smooth), shape (annular, round, diffuse, serpiginous, erythematous), size and measurement, location and fixation to skin layer or deeper tissues. BCC can be considered as circumscribed (nodular solid, nodular ulcerated, adenoid, cystic, keratotic, pigmented) or diffuse (superficial, sclerosing, infiltrative, micronodular)<sup>(5)</sup> - Table 1 describes BCC types. Within this two wide-ranging types, BCC is classified according to type and degree of differentiation and depth of invasion to deep structures<sup>(22,23)</sup>. Although there are multiple types of basal cell carcinoma, the following four types classification will cover most of them<sup>(8)</sup>:

- ✓ **nodulo-ulcerative** - the most frequent one, starting as a small nodule and evolving to an enlarging ulcer with a pearly border
- ✓ **pigmented** - nodular, nodulo-ulcerative or superficial, can be very deceptive
- ✓ **morphea-like** - a yellowish plaque slightly elevated with ill defined borders and intact skin, until ulceration occurs

✓ **superficial**, one or several lesions, with superficial ulceration and crusting.

**Squamous cell carcinoma**

Unlike BCC, SCC has premalignant precursors and presents in a spectrum of appearances, the most characteristic is that of a raised papule or plaque, scaly or crusted that sometimes gets eroded or ulcerated<sup>(19)</sup>. Most lesions are diagnosed early, under 1,5 cm., but this is not always the case<sup>(7)</sup>. The SCC is almost always preceded by premalignant lesions, that can be very similar in appearance. The diagnosis is made only by biopsy which identifies atypical cytology and invasive component<sup>(8)</sup>.

Tumor spread of SCC is mainly by local invasion and destruction, but they can also metastasize in the primary regional lymphatic drainage and hematogenous<sup>(8)</sup>.

Prognostic factors for SCC are based on the following factors:

- ✓ Broder grades of differentiation: grades with no differentiation are likely to recur and metastasize<sup>(24)</sup>.
- ✓ Location: ear, lips, nose, genitalia and scalp are at high risk<sup>(6,25)</sup>.
- ✓ Tumor size and depth: size over 2 cm and Clark level V are more likely to recur and metastasize<sup>(26)</sup>.
- ✓ Perineurial invasion is associated with 47% local recurrence, 35% regional node metastasis and 15% distant metastasis<sup>(27)</sup>.
- ✓ Rapid growth and recurrence<sup>(8)</sup>.

Clinical types are very similar between in situ and invasive lesions; the biopsy is what identifies between them<sup>(8)</sup>:

1. Squamous cell in situ, that is confined to epidermis<sup>(28)</sup>:
  - a. actinic keratosis is the most common premalignant lesion and develops in 20% of cases to invasive carcinoma.
  - b. Bowen disease represents dysplasia at all epidermal levels, with 10% becoming invasive after many years<sup>(29)</sup>. When on glans penis it is called erythroplasia of Queyrat. Invasive SCC is more virulent and metastases develop in 33% of cases.

BCC dimension	1 cm	1 - 2 cm	More than 2 cm	Recurrence, morphea-form, critical locations, high risk of recurrence
Surgical margins	2 mm	3-5 mm extending in subcutaneous fat	1 cm	MOHS surgery, more than 1 cm
SCC stratification	Low risk	High risk	Recurrence, morphea-form, critical locations, high risk of recurrence	
Surgical margins	4 mm	6 mm	MOHS surgery	

Adapted from Netscher DT et al. in „Cutaneous Malignancies: Melanoma and Nonmelanoma Types“<sup>(8)</sup>

**Table 2.** Surgical excision margins for BCC and SCC



**Figure 1. Nodular ulcerated CBC (Dr. Jecan personal photo archive)**  
**1a - Ulcerated, nodular CBC of the zygomatic area, with marked skin excision at 1 cm.**  
**1b - Post - excision defect with planned Limberg flap**  
**1c - Aspect afetr flap inset**

2. Invasive SCC presents invasion into dermis through the lamina basale. The common forms are:  
 a. Invasive SCC associated with actinic keratosis.  
 b. De novo invasive SCC.  
 c. Keratoachantoma.  
 d. Adenoid SCC.

When treating and developing a surgical plan for BCC and SCC, one must stratify the lesions in "low-risk" or "high risk" categories and adapt the plan accordingly<sup>(8)</sup>.

**Management and Treatment** of the BCC and SCC should consider the following aspects and principles<sup>(8)</sup>:

✓ **Tumortype.** Well demarcated tumors can be treated by surgery, curettage, cryosurgery and radiation all with good cure rates. Superficial BCC can be managed with electrodesiccation, avoiding morbidity associated with surgery. Ill defined tumors require Mohs micrographic surgery. Tumors under 2 cm are best treated with surgical excision and Mohs micrographic surgery<sup>(8)</sup>.

✓ **Patient age** should not defer treatment, unless serious associated conditions exist.

✓ **Number of lesions.** Isolated lesions benefit from surgical excisions. Multiple lesions, especially superficial, benefit from electrodesiccation or cryosurgery.



**Figure 2. Ulcerated CSC located in posterior torso (Dr. Jecan personal photo archive)**  
**2a - Planned excision at 1 cm**  
**2b - Post - excision defect**  
**2c - Excised tumor with marked cranial pole**  
**2d - Defect closed after local skin flap advancement**



**Figure 3.** Recurrent CBC of the naso-genian junction (high-risk area) (Dr. Jecan personal photo archive)  
 3a - Clinical aspect of the tumor  
 3b - Post excision defect  
 3c - frontal view after 9 months, reconstruction with naso - genian flap with composite skin graft  
 3d - Worm-eye view after 9 months, reconstruction with naso - genian flap with composite skin graft

✓ **Anatomical location.** High risk areas, i.e. fusion lines in the face, may require frozen-section margin determination.

✓ **Primary versus recurrent tumor.** Mohs surgery can yield better results in well defined, recurrent tumors<sup>(6)</sup>.

✓ The concepts of “low risk” versus “high risk” factors for recurrence of BCC and SCC must be understood and incorporated in the surgical plan - **Table 2** (adapted from **David T. Netscher et al. in “Cutaneous Malignancies: Melanoma and Nonmelanoma Types”**). SCC margins of excision for low-risk lesions are 4 mm and for high risk lesions 6 mm, including underlying fat<sup>(8)</sup>.

**Treatment** options for BCC and SCC include the following types.

**Electrodesiccation** and **cauterage** is common for tumors less than 2 mm. being eradicated 100% and for 2-5 mm. tumors with an 85% success rate<sup>(30,31)</sup>. Tumors larger than 1 cm. should be treated otherwise. The cosmetic aspect is inferior to surgical excision<sup>(32)</sup>.

These options does provide material for pathological examination but no tissue to confirm margins; so if SCC is suspected, a biopsy is warranted<sup>(8)</sup>.

**Topical therapies** offer comfort to the patient, in the treatment of large areas with generally good cosmetic outcome. The trade-off is a long treatment time and the need of excellent patient compliance<sup>(8)</sup>. Imiquimod is F.D.A. approved for superficial BCC<sup>(8)</sup>, Bowen disease<sup>(33)</sup>, invasive SCC and lentigo maligna melanoma<sup>(34)</sup>. Topical 5-fluorouracil is indicated in diffuse actinic keratoses.

Non responsive lesions may harbor foci of squamous cell carcinoma<sup>(35)</sup>.

**Surgical excision** provides material for histological examination and may be planned with standard margins, frozen excision with standard margins, excision with frozen-section margin evaluation and MOHS micrographic surgery<sup>(8)</sup>. Standard margins identification is aided by loupe magnification. For BCC under 1 cm. a 2 mm. margin is indicated; 3-5 mm. margins extending in subcutaneous fat are recommended for lesions under 2 cm. Lesions greater than 2 cm. or recurrent ones require margins of 10mm - Figure 1. For SCC “low risk” the margins are at 4 mm., and for “high risk” a 6 mm. margin is advocated<sup>(8)</sup> (table 2).

Frozen sections are recommended for lesions greater than 2 cm., morpheaform or in critical anatomical locations<sup>(8)</sup>.

MOHS micrographic surgery technique involves horizontal frozen sections of the undersurface of the tumor and microscopic examination. It is indicated for recurrent lesions, poor margins, critical cosmetic locations or anatomical areas with high risk for recurrence<sup>(8)</sup>.

**Radioterapy** is reserved for older patients with BCC or SCC and has a good overall cure, of 92%<sup>(36)</sup>.

**Cryotherapy** is indicated for tumors less than 2 cm<sup>(37)</sup>.

**Sentinel node biopsy** may be indicated in some selected cases of “high-risk” SCC<sup>(38)</sup>.

### Principles for reconstruction

Reconstruction after surgical excision of the tumor is established using general principles

of defects reconstruction. Spontaneous healing, suture, skin grafts, local flaps and microsurgical flaps can be used, according to the size, location and composition of the defect, age of the patient and general health status<sup>(39)</sup> - Figures 2, 3.

### Follow Up

For BCC and SCC recurrences appear up to 4 years, so follow-up should be at least 3 years, on a yearly basis, more frequent for multiple BCCs<sup>(5)</sup>. Clinical signs can be indicators of recurrence (scaling, erythema, crusting). New lesions can be observed early, especially for type 1 and 2 skin patients<sup>(40)</sup>.

### Conclusions

Basal cell and squamous cell carcinoma can be locally invasive and disfiguring and on occasions can prove fatal (especially SCC). Early diagnosis is important; along with understanding the cellular pathology, types of tumors and clinical behavior can lead to proper management. Mohs micrographic surgery, with margins control, can help in high-risk lesions. A multidisciplinary board is appropriate in complex cases<sup>(7)</sup>.

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