Non-Melanoma Skin Cancers: An Updated Overview

Manal Mohamed El-Sayed, Basma Magdy Elkholy, Maryam Abo-Abdullah Ahmed, Dermatology, Venereology and Andrology and 2 Clinical Pathology Department, Faculty of Medicine, Zagazig University.
Corresponding Author: Maryam Abo-Abdullah Ahmed, Email: Sola65417@gmail.com

Abstract

Background: Non-melanoma skin cancers (NMSCs) are by far the most frequently diagnosed cancers. The most common NMSCs are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), respectively 70% and 25% of NMSCs, although skin cancers could arise from each host cell of the skin. NMSCs show different behavior, growth, and metastatic capability, however, both BCC and SCC have a good prognosis, especially when detected at their initial stages. BCC contributes minimally to the NMSCs mortality rate (MR). Indeed, metastatic BCC shows an incidence of 1 case per 14,000,000 and 2 patients per 14,000,000 who die from locally advanced BCC. Therefore, a MR of 0.02 per 10,000 is to be expected. On the other hand, SCC shows a variable metastatic rate of 0.1–9.9% and it accounts for about 75% of deaths due to NMSCs.

Key words: Non-Melanoma Skin Cancers (NMSCs)

Introduction

The term Non melanoma skin cancers (NMSCs) practically refer to keratinocyte carcinomas, namely basal (BCC), Keratoacanathoma (KA) and cutaneous squamous cell carcinoma (cSCC), since they account for 99% of the tumors in this group (1). Other much fewer common forms of NMSCs include Merkel cell carcinoma, primary cutaneous B-cell lymphoma, Kaposi sarcoma, and dermatofibrosarcoma.

Individuals who develop BCC have an elevated risk of developing new foci of BCC, as well as other types of skin cancer, including melanoma and SCC. Their incidence has increased strongly over time, reflecting also ageing population (2). Actinic keratoses (AKs), considered as the earliest manifestation of SCC, are extremely common, showing a prevalence greater than 40% in the adult population. AKs affect half of the global population, although the prevalence varies according to geographical location and age. AKs occur usually on chronically light-exposed skin (1). AKs share several pathological features with SCC, and they represent a continuum in a multistep process over the years on chronically sun exposed fair skin. Normal-appearing skin that surrounds AKs may develop AKs, because of the UV exposure and expression of molecular alteration, including p53 mutations. This whole area is today known as “field cancerization” (1).

BCC:

BCC is an epithelial tumor that arises from transformed basal cells, which are small round cells found in the lower layer of the epidermis (2).

Epidemiology:

BCC accounts for approximately 80% of all skin cancers, although it accounts for less than 0.1% of patient deaths due to cancer. Its incidence has doubled over the past 25 years. The
estimated lifetime risk for BCC in the white population is 35–40% for men and 20–30% for women, with a male-to-female ratio of 2.1:1 (3).

With the exception of genetic syndromes (i.e., basal cell nevus syndrome, xeroderma pigmentosum, Bazex–Dupre–Cristol syndrome), BCC is rarely observed in patients younger than 40 years of age. However, its incidence increases linearly with age. Although BCC is observed in people of all races and skin types, dark-skinned individuals are rarely affected, and it is most often found in light-skinned individuals, particularly among those with a very fair skin color and red or blond hair (4).

**Pathogenesis:**
BCCs arise from basal cells, which are a layer of cells located at the deepest part of epidermis. Basal cells have recently come to be considered skin stem cells, as they are constantly proliferating and generating keratinocytes, which are continuously pushed to the surface and eventually become a dead layer of stratum corneum. In developing BCC, several risk factors are involved, including Fitzpatrick phototype I and II, sunburns in childhood, family history of skin cancer, immunosuppression, high cumulative UV exposure, and exposure to carcinogenic chemicals, especially arsenic (5).

Among them, UV radiation is thought to be the most important risk factor. Indeed, 80% of BCC arises on sun-exposed areas, especially the head and neck. Regional differences, including hair follicles density, could clarify why the dorsal area of the hands is usually not involved by BCC, despite extensive sun exposure. Contrarily to SCC, BCC is believed to arise de novo (5).

**Genetics:**
A high incidence of TP53 gene mutations is found in BCC. Genetic involvement has been demonstrated on chromosome 9 in patients with familial basal cell nevus syndrome. Such mutation involves the patched (PTCH) gene, a tumor suppressor gene (6). Inappropriate activation of the hedgehog signaling pathway is found in both sporadic and familial cases of BCC. This results in loss-of-function mutations in the tumor suppressor PTCH1 and gain-of-function mutations in Sonic hedgehog, smoothened and Gli (6).

**Histopathology:**
The term BCC comprises a range of histopathologically and biologically different variants including nodular-cystic, superficial, pigmented, sclerodermiform (morpheic), infiltrating and recurrent BCC as well as nevoid BCC, ulcus rodens and fibroepithelioma of Pinkus. Among these subtypes, ulcus rodens, sclerodermiform, infiltrating and recurrent forms are characterized by a locally aggressive growth pattern (3).

**Clinical-dermoscopic patterns of BCC:**
The first descriptions on the dermoscopic patterns of BCC go back to the very early days of dermoscopy. However, the list of criteria has been continuously updated and renewed. The reported diagnostic accuracy of dermoscopy to recognize BCC ranges from 95 to 99%. (5).
Figure (1): Dermoscopic criteria of basal cell carcinoma. (A) Classical arborizing vessels; (B) fine arborizing vessels; (C) short arborizing vessels; (D) large blue-gray ovoid nests; (E) multiple blue-gray globules; (F) focused dots; (G) concentric structures; (H) spoke-wheel areas; (I) leaf-like areas; (J) ulceration; (K) small erosions and (L) pink-white areas and short white streaks.

The hallmark of nodular-cystic BCC is focused, bright red and branching arborizing vessels. Although sclerodermiform BCC reveals branching vessels, they are usually finer, more scattered and show fewer branches compared with the classic vessels of nodular BCC. In addition, the underlying fibrosis of sclerodermiform BCC results in a dermoscopically whitish background, whereas dermoscopy of nodular BCC typically reveals a translucent pinkish tumor (7).

In contrast to the bright red and focused appearance of the arborizing vessels of BCC, vessels outside of the neoplasm belonging to the normal dermal plexus shining through the thinned skin usually appear blurred and have a darker hue. The difference between tumoral vessels and the vascular pattern of normal skin is useful to estimate the effective lateral extension of BCCs with clinically ill-defined borders (7). The most classical presentation of superficial BCC is that of a reddish plaque with multiple small erosions. In contrast to nodular, cystic and sclerodermiform BCC, superficial BCC lacks classic arborizing vessels. Instead, it usually exhibits, if any, short focused ‘microarborizing’ fine telangiectasias with relatively few ramifications. Multiple small erosions and shiny white-to-red, translucent or opaque structureless areas represent common additional dermoscopic criteria of superficial BCC (8).

Dermoscopy of pigmented nodular and superficial BCCs reveals different pigmentation patterns. Specifically, pigmented nodular BCC exhibits loosely arranged blue-gray globules that differ in size and number, typically combined with arborizing vessels. Instead,
pigmented superficial BCC tends to display translucent light brown to grayish concentric structures, spoke-wheel areas or peripheral finger-like projections (leaf-like areas) (8).

Less-common variants of BCC including Fibroepithelioma of Pinkus (FeP) and nevoid BCC may mimic a range of benign skin tumors such as dermal nevus, skin tag or seborrheic keratosis, which are not routinely excised. As it became a rule to examine almost all skin lesions by dermoscopy, irrespective of whether they look clinically benign or malignant, these rare subtypes of BCC can be, however, easily identified by dermoscopy. This is because they reveal classical BCC-specific vascular or pigmented patterns. Finally, in patients with Gorlin–Goltz syndrome, dermoscopy allows the rapid identification of palmar pits by disclosing dotted vessels (8).

Factors influencing the morphologic patterns of BCC:
There is emerging evidence that the clinical and dermoscopic aspects of BCC are influenced by several factors including histopathologic subtype, location, gender, age and pigmentary trait. There was a higher frequency of superficial BCC on the trunk and lower legs of women, whereas the majority of nodular BCC occur on the head and neck of men. If BCC develops in persons of color, pigmentation is present in more than 50% of the tumors; in striking contrast, only approximately 5% of BCCs in fair-skinned individuals are pigmented. The concept of the signature pattern of BCC has been introduced. This concept refers to the observation that multiple BCC in an individual patient often harbor repetitive clinical-dermoscopic patterns (7).
Prognosis:
The prognosis for patients with BCC is usually excellent with a low risk for metastatic spread; however, if not treated at an early stage, BCC can grow locally aggressive and can result in the destruction of important anatomic structures (6).

Treatment:
There are a number of different treatment options for BCC. The choice of treatment should rely on the consideration of the clinical subtype of BCC, location, size and number of lesion(s), as well as on patient’s age, compliance, cosmetic outcome and associated comorbidities. Surgery represents the first choice in treating nodular or sclerodermiform BCC or solitary BCC of any subtype (8).

Follow up:
Persons who have been diagnosed with one BCC are at increased risk of developing further BCC, whereby the chance to develop additional BCC within 5 years is as high as 50%. Accordingly, regular surveillance of patients with a diagnosis of BCC is generally recommended (9).

Keratinocyte skin cancer:
The term keratinocyte skin cancer summarizes different stages in the progression of malignant neoplasms of epidermal keratinocytes showing squamous phenotypic differentiation. Accordingly, it refers to actinic keratosis (AK), intraepidermal carcinoma (IEC) and invasive SCC (10).

Actinic keratosis:
AK, also known as solar keratosis or keratinocytic intraepidermal neoplasia (KIN), is the most common neoplasm within the continuum of keratinocyte skin cancer. They are commonly defined as ‘precancerous’ or ‘premalignant’, but recent molecular and genetical studies suggest that they already present the earliest form of SCC (11).
The process of skin carcinogenesis is still not fully understood. However, several studies have been conducted to better explain the mechanisms that lead to malignancy. On one hand, several of these, such as IF regulatory factor 6 and alpha-2 macroglobulin-like protein 2, play a pivotal role in keratinocyte proliferation and differentiation. On the other hand, other proteins, such as calmodulin-like protein 5, are involved in keratinocyte differentiation. It has been reported that IL-1 beta could modulate the production of keratinocyte proteins in inflammation, leading to a reduction in the expression of both keratinocyte differentiation and motility proteins. Otherwise, IL-1 also affects the synthesis of angiogenetic and anti-apoptotic proteins, leading to a higher expression of both. Therefore, it has been postulated that IL-1 could play a pivotal role in skin carcinogenesis (12).

Epidemiology:
AK represents the most frequent carcinoma (in situ) seen in humans, and its incidence continues to rise. A high occurrence of AK is reported in persons with skin type I–III and in regions with a higher UV exposure. Men are more commonly affected than women; in Europe, 34% of men and 18% of women older than 70 years of age have been found to have AKs. The frequency of AK is highest in Australia, where it has been estimated that 40–60% of the population older than 40 years of age will present with AK (13).
AKs are the most frequent precancerous lesion in humans; they develop usually in fair-skinned people on sun-exposed areas. Between 0.025% and 16% of AKs evolve to iSCC every year. Because every patient shows several AKs, the annual risk of developing iSCC has been reported as between 0.15 to 80%. AK and iSCC have a similar genetic profile, including alterations in the p53 gene. Pathologically, these alterations are described as hyper-chromatic and pleomorphic nuclei with alteration of the nuclear cytoplasmic ratio, loss of polarity, and cellular superposition (12). Cytological atypia at the basal layer of the AK can determine progression to SCC. Nevertheless, not all AKs show this behavior. Indeed, many AKs persist in the same stage, while others will regress, and a few will progress into iSCC. It has been reported that the risk of progression varies up to 16% and the evolution of a particular lesion is unpredictable (11).

AK is the most common precursor of cutaneous iSCC, and it represents a disease continuum. AK can remain stable, regress, relapse or progress. Every AK starts with an atypical basal layer. It has been reported that the progression from AK to iSCC of the skin follows a pathway similar to the ones of cervical cancer (1). However, cutaneous iSCC could also develop from atypical basaloid localized at the epidermal basal layer (AK I). This pathway, known as the differentiated pathway, is the most frequent way that leads to cutaneous iSCC. However, the progression from AK I to AK II and AK III (classic pathway) has been described in several iSCC cases. Therefore, it could be concluded that all AK lesions are potentially invasive (10).

The cell will loss polarity, polygonal shape and cell-cell contacts, and will switch from epithelial to mesenchymal type, with a significant difference in E-cadherin, catherin, vimentin and Ki67, without significant differences in podoplanin (D2-40), p16 and p53 (1). Proliferative AK is a new subtype of AK that exhibits proliferative characteristics both histologically and clinically. Proliferative AK is resistant to standard therapies because of deep migration of abnormal cells along hair follicles and sweat ducts. It has a strong propensity to develop infiltrative SCC and may occur concomitantly with BCC (10). However, it has been also observed that AKs are unlikely to be precursors of SCCs in the Japanese population. Indeed, in a study on Japanese populations, loss of heterozygosis (LOH) was detected in seven of 37 AKs analyzed, but in only one of 14 SCCs evaluated. In addition, microsatellite instability was not detected in all the AK or SCC analyzed specimens (10).

Mitochondrial DNA (mtDNA) is known to be subject to the loss of a significant proportion of specific sections of genetic code due to exposure to UV radiation and aging. It has been demonstrated in several studies that the mtDNA4977 and mtDNA3895 deletions are more frequent in sun exposed areas. In particular, it has been reported that mtDNA4977 deletion could be an indicator of developing NMSCs. Indeed, mtDNA deletions were related to sun exposure (10).

Infundibular, isthmic, and sub-isthmic atypia have been reported in 25%, 63.6%, 100%, respectively, of iSCC. These findings have implications for identifying patient factors which would be predictive of the progression of actinic keratosis to invasive carcinoma, providing potentially valuable patient screening guidelines. Stem cell quiescence acts as a tumor suppressor in squamous tumors (11).

www.turkjphysiotherrehabil.org
Genetics:
Analysis of chromosome aberrations and gene mutations reveal that AKs, and SCCs have an altered $p53$ gene, bearing signature UV mutations in stem cell-related clones. Further changes in the antiapoptotic gene $bcl2$ are found in AKs and SCCs and altered $p16$ and growth hormone receptor proteins are found in SCCs (14).

Histopathology:
Histopathologically, AKs have been classified according to keratinocytic atypia, mitotic activity, hyperkeratosis, parakeratosis, dermal inflammatory infiltrate and concomitant solar elastosis. Due to its similarity in biological behavior and comparable progression rates with cervical intraepithelial neoplasia, several investigators have proposed the concept of AKs as KINs with subdivision into three histomorphological grades, which correlate to specific clinical and dermoscopic patterns (15).

Clinical-dermoscopic patterns of actinic keratosis:
AKs rarely develop as single lesion; multiple lesions effectively affecting an entire field of chronically actinic damaged skin is more commonly present. This has led to the concept of ‘field cancerization’, which refers to the presence of genetically altered cell clones in normal appearing skin contiguous to fields of neoplastic cells, which have the potential of clonal expansion and thus give rise to locally recurrent skin cancer (7).
A clinical classification for grading AK (grade 1, 2 and 3) was developed; grade 1 describes slightly palpable AK (better felt than seen), grade 2 shows moderately thick AK (easily felt and seen) and grade 3 is very thick, hyperkeratotic and/or obvious. The three different clinical grades of AK correspond dermoscopically to three different patterns (7).

![Figure 3](image.jpg)

Figure (3): Clinical and dermoscopic grading of actinic keratosis. (A & B) Grade 1 actinic keratosis; (C & D) grade 2 actinic keratosis and (E & F) grade 3 actinic keratosis.

Grade 1 AKs are dermoscopically typified by red pseudonetwork patterns and discrete white scales, grade 2 corresponds to an erythematous background intermingled by white-to-yellow, keratotic and enlarged follicular openings (these features are reminiscent of the surface of a strawberry; therefore, this pattern has been termed strawberry pattern). Grade
3 AK exhibits either enlarged follicular openings filled with keratotic plugs over a scaly and white-yellow appearing background or, marked hyperkeratosis seen as white-yellow structureless areas. The diagnostic sensitivity and specificity of dermoscopy in the diagnosis of AK has been reported to reach 98 and 95%, respectively (7).

**Prognosis:**
AK is considered the earliest form of SCC, with the risk of an individual lesion progressing to invasive SCC reported to vary from 0.1 to 20%. Nevertheless, even with a low individual rate of progression, patients with multiple AK (i.e., more than ten) may have a 14% cumulative probability of developing SCC, either within the AK or de novo, within 5 years, underscoring the need of regular follow-up in these patients (16).

**Treatment:**
Treatments for AK can be divided into lesion-directed and field-directed therapy. Lesion-directed treatment aims in the treatment of single lesions, without addressing the problem of actinic damage in the surrounding skin. However, it is particularly helpful in the treatment of grade 3 AKs. Field-directed treatment aims to treat clinically visible and subclinical lesions within the entire field of actinic damage (field of cancerization) (17).

![Figure (4): Field-directed treatment of multiple actinic keratosis with imiquimod cream.](image)

(A) Baseline reveals numerous, partially grade 3, actinic keratosis; (B) during treatment even clinically normal appearing skin shows significant inflammatory reaction suggestive for field cancerization and (C) significant improvement of the overall aspect of the skin.

**Follow up:**
There is increasing consensus that AK should be interpreted as a biomarker indicating that a patient is at risk of developing skin cancer. Thus, regular surveillance of patients with AK is recommended (18).

**Intraepidermal carcinoma & Bowen’s disease:**
IEC and Bowen’s disease (BD) refer to a SCC in situ (SSCIS) with full-epidermal thickness dysplasia that has the potential for significant lateral spread before invasion. IEC and BD are often named synonymously to describe SSCIS; however, because of some epidemiological, clinical and histopathologic differences between BD and IEC, some controversy exists regarding a common etiologic background and pathogenesis of both subtypes of SSCIS (19).
Epidemiology:
In the light of these controversies in defining BD or IEC and their differential diagnosis from grade III AK/KIN, epidemiological data are rather scarce. In the USA, the annual average rate of BD was reported to be 14.9 cases per 100,000 white individuals. BD is more commonly found on the head and neck in men, and on the lower limbs and cheeks of women (8).

Etiology:
IEC and BD may arise de novo or from a preexisting AK. Its etiology is likely to be multifactorial. BD has been related to human papilloma virus infection, prior arsenic exposure, radiation therapy, chronic immunosuppression and internal malignancies and to UV exposure. Immunosuppressed patients with BD are likely to have multiple and more aggressive tumors (19).

Histopathology:
BD represents a full-thickness anaplasia of the epidermis. Keratinocytes demonstrate morphologic atypia, loss of maturation and disordered arrangement. Apoptotic or dyskeratotic cells, multinucleated keratinocytes and mitoses can be found throughout the epidermis. Extension of the keratinocyte atypia to the follicular epithelium is common. Moderate hyperkeratosis, parakeratosis, acanthosis and a lymphocytic infiltrate of the upper dermis represent additional histopathologic findings. Less commonly, BD displays a pagetoid, upward and laterally extended scatter of large pale keratinocytes with abundant ground-glass cytoplasm (19).

Clinical-dermoscopic patterns of intraepidermal carcinoma and BD:
BD presents as a single lesion in two-thirds of cases, although multiple lesions may be present. Lesions may appear on sunexposed or covered skin. Patients often present with an asymptomatic, slowly enlarging, erythematous, well-demarcated scaly patch or plaque. It may occur anywhere on the mucocutaneous surface. A delay in diagnosis of BD often is encountered because the lesion is asymptomatic; early skin changes may be subtle and overlap with clinical features seen in many conditions (20).

Dermoscopically, BD is typified by the presence of dotted and/or glomerular vessels, white to yellowish surface scales and a red-yellowish background color. Glomerular vessels represent a variation of dotted vessels but are larger in size and characterized by tortuous capillaries. Both dotted and glomerular vessels often appear within the same lesion and are distributed in small, densely packed clusters or groups. In cases of pigmented BD, in addition to the above-described criteria, small brown/black globules arranged either in a patchy distribution or in peripheral lines are seen. Dermoscopy may be also useful for the treatment follow-up of pigmented BD, as disappearance of disease-specific dermoscopic criteria after laser ablation has been related with histopathologic clearance of disease (2).
Figure (5): Dermoscopy of Bowen’s disease and intraepidermal carcinoma. (A) Clinical and (B) dermoscopic features of Bowen’s disease; (C) clinical and (D) dermoscopic features of intraepidermal carcinoma arising from a pre-existing actinic keratosis; (E) clinical and (F) dermoscopic features of pigmented Bowen’s disease.

Prognosis:
If left untreated, BD may progress to invasive SCC, or so-called Bowenoid carcinoma, in 3–20% of cases. Remarkably, Bowenoid carcinoma may metastasize in up to a third of cases, thus conferring a relatively poor prognosis (21).

Treatment:
As suggested in available guidelines for management of BD, there is no single definite ‘right way’ to treat all patients. Choice among a number of different modalities should rely on the consideration of anatomic site, size of the tumor, number of lesion(s), recurrences, ease and availability of the treatment options, as well as on patient’s age, compliance, cosmetic outcome and associated comorbidities (8).

Follow-up:
Considering that most of the treatments have approximately a 10% recurrence risk, a follow-up check for possible recurrence at 6–12 months is recommended. The requirement for long-term follow-up depends on the presence of previous recurrence, highrisk lesions (such as those located perianal), other types of skin cancer and immunosuppression (20).

Squamous cell carcinoma:
Primary cutaneous SCC is a malignant tumor that may arise from the keratinizing cells of the epidermis or its appendages. It is locally invasive and has the potential to metastasize to the regional lymph nodes and to other organs of the body (22).
Xeroderma pigmentosum (XP) is a genetic disorder in which there is a decreased ability to repair DNA damage such as that caused by ultraviolet (UV) light. Symptoms may include
a severe sunburn after only a few minutes in the sun, freckling in sun exposed areas, dry skin and changes in skin pigmentation. Nervous system problems, such as hearing loss, poor coordination, loss of intellectual function and seizures, may also occur. Complications include a high risk of skin cancer, with about half having skin cancer by age 10 without preventive efforts, and cataracts. There may be a higher risk of other cancers such as brain cancers (23).

The disease affects about 1 in 100,000 worldwide. By region, it affects about 1 in 370 in India, 1 in 20,000 in Japan, 1 in 250,000 people in the United States and 1 in 430,000 in Europe. It occurs equally commonly in males and females. Xeroderma pigmentosum was first described in the 1870s by Moritz Kaposi. In 1882, Kaposi coined the term xeroderma pigmentosum for the condition, referring to its characteristic dry, pigmented skin. Individuals with the disease have been referred to as "children of the night" or "moon children" (22).

XP is autosomal recessive, with at least nine specific mutations able to result in the condition. Normally, the damage to DNA which occurs in skin cells from exposure to UV light is repaired by nucleotide excision repair. In people with xeroderma pigmentosum, this damage is not repaired. As more abnormalities form in DNA, cells malfunction and eventually become cancerous or die (24).

Epidemiology:
SCC is the second most common skin cancer after BCC and causes the majority of deaths among the non-melanoma skin malignancies (25).

Etiology:
The majority (70%) of cutaneous SCC occurs on the head and neck, with an additional 15% found on the upper extremities. Tumors of sun-protected skin are more individuals. These tumors carry a higher mortality risk, possibly resulting from delayed diagnosis (6).

Pathogenesis:
UV radiation from sun exposure, occupational exposure, medical treatment (psoralen + UVA [PUVA]), or tanning beds is principally responsible for the development of SCC. Immunosuppression, such as post-transplantation or with chemotherapy also predispose to SCC (24).

Genetics:
DNA mutations, usually in the p53 tumor suppressor gene, have been associated to chronic UV irradiation. This explains why SCC shows a predilection for fair-skinned individuals and chronically sun- exposed body sites (7).

Prognosis:
When detected and treated early, less aggressive SCC has a 95% cure rate. However, if neglected, SCC can cause local tissue destruction and may metastasize. In the latter occasion, prognosis is extremely poor. Furthermore, individuals with a primary SCC possess 18% cumulative risk for developing a second tumor within 3 years, underlying the need for ongoing clinical monitoring. Risk factors for SCC development include fair-skin phototype, male gender, more than 40 years and organ transplantation. Specifically, organ transplant recipients have a 65-fold increased risk to develop SCC, compared with the general population. Interestingly, 22% of SCC in the latter group of patients arises on sun-protected body sites, such as the trunk or lower extremities (26).
**Histopathology:**
Histopathologically, SCC is typified by the presence of nests of atypical keratinocytes, characterized by varying degrees of anaplasia and keratinization. The tumor nests typically arise from the epidermis and extend into the dermis. Several histopathologic subtypes have been described, including spindle cell, pleomorphic, adenoid, acantholytic and clear-cell SCC. Keratoacanthoma is also considered a well-differentiated subtype of SCC. In pigmented variants, an accumulation of melanin in the cytoplasm of keratinocytes is usually detected, while collections of melanophages intermingled with variably dense infiltrates of lymphocytes can be seen in the papillary dermis (26).

**Clinico-dermoscopic patterns of SCC:**
Clinically, SCC usually presents as an indurated hyperkeratotic nodule with or without ulceration, or it may manifest as an ulcer without evidence of keratinization. Since SCC commonly develops on the background of AK, presence of the latter on the surrounding or neighboring skin may be clinically evident. Dermoscopically, SCC is characterized by targetoid appearing follicular openings (white circles) over a structureless white background (7).

Figure (6): Dermoscopy of squamous cell carcinoma. (A) Clinical and (B) dermoscopic features of early invasive squamous cell carcinoma showing targetoid follicular openings characterized by a inner yellow globules and an outer white rim (white circles); (C) clinical and (D) dermoscopic features of invasive squamous cell carcinoma displaying central masses of keratin surrounded by linear coiled vessels; (E) clinical and (F) dermoscopic features of invasive squamous cell carcinoma showing polymorphous vessels consisting of linear and glomerular vessels.
Additional features that are commonly seen are amorphous masses of white-yellow keratin (often located in the center) and polymorphic vessels consisting of peripheral hairpin, dotted/glomerular and/or linear-irregular vessels. This variability of vascular structures, along with more recently described criteria related to keratinization, may be useful to discriminate invasive SCC from in situ variants (AK and BD) (25).

In detail, according to a recently proposed model, progression from AK into invasive SCC is characterized by a dermoscopically evident increase in vascularization and keratinization structures. The former is reflected by the development of initially dotted/glomerular vessels and later, hairpin and linear/irregular vessels. Instead, keratinization is characterized by the early appearance of diffuse yellow-whitish opaque scales, followed by the development of white structureless areas or a central mass of keratin, associated with ulceration (7).

**Figure (7):** Progression model of keratinocytes skin cancer: dermoscopy reveals different features at different stages in the progression of keratinocyte skin cancer.

In addition, keratin masses and white circles surrounding follicles have been recently proposed to specifically predict the diagnosis of SCC or KA among nonpigmented tumors. Similarly, a whitish background and keratin have been suggested to discriminate invasive SCC from amelanotic melanoma, which commonly exhibits a polymorphic vascular pattern associated with a pinkish background hue (7).

Taking all the above into consideration, white structures and keratin represent valuable dermoscopic clues for diagnosis of invasive SCC. It should be noted that well-differentiated SCC often presents as a rapidly growing nodule, which dermoscopically exhibits structureless white areas, central masses of keratin and elongated peripheral vessels that remind to the arborizing vessels of BCC. Instead, poorly differentiated SCC lacks signs of keratinization both dermoscopically and histopathologically and often presents as ulcerated plaque (endophytic growth) showing only polymorphous vessels (7).
Figure (8): Side-by-side comparison between well-differentiated and poorly differentiated squamous cell carcinoma. (A) Clinically, well-differentiated squamous cell carcinoma often shows exophytic growth and (B) dermoscopic signs of keratinization. Instead, poorly differentiated squamous cell carcinoma often grows endophytically (C) and lacks dermoscopic signs of keratinization (D).

**Staging:**
The American Joint Committee on Cancer recommended an updated TNM system for SCC classification, depending on the tumor size and depth, the presence of nodal or distant metastasis and the degree of histopathological differentiation. The latter staging system has been criticized because of its failure to encompass several of the well-known prognostic factors for SCC (24).

High-risk criteria for recurrence and overall patients survival include tumor location (i.e., lips, ears, anogenital region, within a scar or chronic wound), size greater than 2 cm, invasion to subcutaneous fat, poorly differentiated cells, recurrent tumor and perineural involvement. In addition, immunosuppression represents a powerful predictor of untoward outcomes in SCC (25).

**Treatment:**
Conventional surgical excision followed by histopathological assessment of margins represents the treatment of choice for invasive SCC. Mohs micrographic surgery should be considered for the management of high-risk SCC, particularly at difficult sites where wide surgical margins may be technically difficult to achieve without functional impairment (27).

Radiation therapy has been reported to achieve comparable results and may be considered a reasonable alternative treatment choice for SCC of special locations, such as lip, nose and ear, as well as when surgical morbidity would be unacceptably high. Curettage and cryosurgery may also be used by experienced clinicians, but data on response and recurrence rates of invasive SCC with these techniques are inadequate. Imiquimod has also been reported to be effective in rare cases (8).

**Follow up:**
Since 95% of local recurrences and 95% of metastases are detected within 5 years, it is reasonable for the patients with a high-risk SCC to be kept under observation for recurrent disease for this period of time. In general, ultrasound sonography of the regional lymph nodes every 4–6 months is recommended. Furthermore, considering that SCC usually develops on severely actinically damaged skin, long-term follow-up is also recommended (25).
References


