Nonmelanoma skin cancer (NMSC) is the most commonly diagnosed malignancy in the United States, accounting for 33% to 50% of all the newly diagnosed cancers each year [1–3]. Close to a million new cases are diagnosed in the United States and 3 million in the world every year [1,4]. The incidence of NMSC is thought to be increasing [5]. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) account for the vast majority of NMSC (> 95%). The mortality associated with these cancers is low. It is for this reason they attract relatively little attention from the medical and lay communities; however, they cause considerable functional and cosmetic deformity. The cost of treatment is significant.

Risk factors in skin carcinogenesis

The pathophysiology of NMSC is multifactorial. Relevant causes or associations can be considered in terms of environmental and intrinsic factors. Intrinsic risk factors may include skin type, immune competence, and genetically predisposing syndromes. In contradistinction to a number of other malignancies, the importance of environmental influences is established. Relevant environmental exposures include ionizing radiation and a variety of chemical agents.

Host factors

Phenotype

A significant constitutional risk factor for all skin cancers seems to be skin type and specifically how the skin responds to sun exposure. The variability and genetic susceptibility to skin cancer is related to the melanin content of the skin and the skin’s response to ultraviolet (UV) radiation. The incidence of skin tumors is inversely related to ease of tanning and the content of melanin in the skin [6]. The incidence of NMSC is much lower in nonwhites than in Caucasians.

The Fitzpatrick skin type classification is widely used to classify individuals according to their skin reaction to sun exposure [7]. Many epidemiologic studies have identified that ability to tan is one of the most protective factors. Scandinavians, who have fair complexion but good tanning capacity, have a low incidence of basal cell carcinoma, whereas Irish people, who tan poorly, have a higher incidence [8].

A number of genetic disorders exist that are characterized by an increased incidence of NMSC. In some and perhaps most of these syndromes, a common pathway of reduced protection from or repair of sun-induced damage has been identified.

Xeroderma pigmentosum. This is a rare autosomal recessive disorder (prevalence 1/250,000) [9] characterized by a defect in the normal detection and repair mechanism of the UV-induced DNA damage. Patients have increased photosensitivity, exaggerated sunburn response, and prolonged erythema with early onset actinic changes [10]. A marked increase in incidence of multiple skin neoplasms including mela-
noma (especially superficial spreading type), BCC, and SCC is seen in this disease. This observation supports the role of UV-induced DNA damage in the etiology of cutaneous malignancies (Fig. 1).

The syndrome is usually recognized at an early age, and cutaneous malignancies may develop as early as 5 years of age [11]. Management involves strict avoidance of sun exposure. Neoplasms are treated surgically. Topical 5-fluorouracil and systemic retinoic acid have been used with limited success. The prognosis is poor, with death occurring in the early 20s.

Nevoid basal cell syndrome (Gorlin syndrome).
Gorlin syndrome, or basal cell nevus syndrome, originally described by Gorlin [12], is a multisystemic disorder characterized by the occurrence of multiple BCC often in the hundreds, odontogenic cysts of the jaw, calcification of the falx cerebri, pitting in the palms and soles, and various skeletal abnormalities (bifid ribs, brachymetacarpalism, broad nasal root, and overdeveloped supraorbital rim). BCCs usually develop between the second and third decade and are not aggressive (except in the face), and distant metastasis is rare. There is an autosomal dominant inheritance pattern. The inherited defect seems to be a defect in a tumor suppressor gene located at the long arm of chromosome 9 with 97% penetrance and variable expression (prevalence 1/56,000) [13,14]. Treatment is by prevention (sun avoidance and protection) and removal of the BCC. Life expectancy is normal with good prognosis. The disease can be mutilating and difficult to manage. Other genetic syndromes that predispose to skin carcinoma include (1) albinism (autosomal recessive absence of melanin and increased risk of SCC), (2) porokeratosis (autosomal dominant, 13% chance of SCC formation), and (3) epidermodysplasia verruciformis (autosomal recessive). Patients suffering from epidermodysplasia verruciformis have a diminished ability to resist viral infection (Human papilloma virus 3 and 5). They develop extensive cutaneous viral infections and a tendency for the development of NMSC involving preferentially sun-exposed areas.

Predisposing lesions. A number of skin lesions are associated with the development of NMSC. Understanding the associated risk of malignant degeneration facilitates management of the patient and provides additional clues as to the biology of the malignant transformation.

Nevus sebaceous of Jadassohn. Nevus sebaceous of Jadassohn is a well-circumscribed, raised, yellowish plaque that is present at birth on the scalp and face. Degeneration into BCC is seen in 10% of the cases. Elective excision with clear margins is generally recommended.

Actinic keratoses. Actinic keratosis is the most common premalignant lesion. It develops in 16% of North American Caucasians during their lifetime [15]. Histologically, there is epidermal dysplasia and cellular atypia; however, unlike with SCC, the basal lamina remains intact. The lesions are usually hyperkeratotic and erythematous (Fig. 2). The malignant transformation rate to SCC is between 10% and 13% [16]. Treatment modalities are laser cryotherapy, 5-FU, or retinoids.

Cutaneous horn. The cutaneous horn is a hard keratotic growth that is longer than its base. The treatment of choice is excision. The incidence of an
underlying squamous cell carcinoma is thought to be about 10%.

Immunologic factors

Abnormalities in the host immune system have long been implicated as playing an important role in the development of cancer, although for most malignancies this role has been difficult to prove. In the case of NMSC, the evidence linking defects of the immune system to the pathophysiology of malignant degeneration is clear and generally accepted. Specifically, deficiencies of cell-mediated immunity are correlated with the development of BCC and SCC [17]. Advanced and or extensive NMSCs are associated with low T cell levels and apparent tumor anergy. Chronic sun exposure, an established risk factor for the development of skin cancer, is associated with apparent deficiencies in the cutaneous immune response.

One of the most compelling pieces of evidence invoking a role of the immune system in the development of skin cancer is the observation of a significant increase in the incidence of cutaneous malignancies in the chronically immunosuppressed organ transplant population. Patients receiving chronic immunosuppressive therapy have a 50% risk of developing SCC within 20 years of transplantation [18]; 30% of such cancers are highly aggressive.

Environmental factors

The critical role of environmental influences in the pathophysiology of NMSC has been established. Skin cancer is a rare occurrence in completely normal skin. Exposure to ionizing radiation is probably the most relevant environmental hazard.

UV radiation

The skin is the organ most susceptible to damage by UV light because it is directly exposed. UV exposure of the skin has a number of biologic effects, many of which are detrimental. UV light is part of the electromagnetic spectrum and has wavelengths between 200 nm and 400 nm. The ultraviolet band is further divided into three components: UVA (320–400 nm), UVB (280–320 nm), and UVC (200–280 nm) [19]. Solar UVC is absorbed by ozone in the stratosphere, and its relevance to biologic systems is limited; thus, the division between UVC and UVB was established at 280 nm. The energy carried by each portion of the spectrum is inversely related to its wavelength, so UVC > UVB > UVA. The depth of penetration of UV light into the skin increases with increasing wavelength. Ninety-five percent of the solar radiation reaching the earth’s surface is UVA; the rest is UVB. The peak of UV-induced carcinogenicity has been shown to lie within the UVB portion of the UV spectrum [20]. The amount of UVB reaching the earth’s crust is gradually increasing due to depletion of the ozone layer. This ozone layer depletion has been blamed by some for the increased incidence of melanoma. This trend may allow more UVC to reach the surface of the earth. UVC is more carcinogenic and might be expected to become a more relevant factor in the epidemiology of cutaneous malignancies, including melanoma and NMSC.

The acute response of skin to UV radiation is vasodilatation followed by clinical erythema [21,22]. The time course of UVA erythema in humans differs from UVB, being maximal at 72 hours, compared with 24 to 48 hours for UVB [23]. Adaptive changes are observed in the skin after exposure to UV light. These include increased vascularization, skin thickening (due to epidermal hyperplasia and increased thickness of the stratum corneum), and melanogenesis (tanning) [24,25].

Ionizing radiation

Ionizing radiation causes skin cancer in humans and experimental animal models. The risk is proportional to cumulative dose. Occupation of the patient may be an important factor because radiologists, uranium miners, and airline pilots have a demonstrated increased incidence of skin cancer. Radiation therapy to the face, a practice formerly advocated for the treatment of acne, has been associated with an increased incidence of SCC.

Chemicals

Important hazardous chemicals include the polycyclic aromatic hydrocarbons and arsenic. The former can be found in coal tars, soot, asphalt, paraffin waxes, and lubricating oils. Chronic exposure to arsenic leads to BCC and SCC, usually after a period of 18 to 45 years. Hands are often involved. Education programs and improved industrial safety will limit the number of these types of cases.

Prevention of nonmelanoma skin cancer

Sunscreen

Sunscreens act by absorbing (especially UVB) or by reflecting the UV radiation. Para-aminobenzoic acid is one of the most common active ingredients in sunscreens. This substance penetrates the stratum
corneum and absorbs UV radiation. Titanium dioxide and zinc oxide act as physical barriers and provide the best protection. A sunscreen should have at least a sun protection factor (SPF) of 15. Sunscreens have been shown to decrease the risk of actinic damage and are most effective when started at childhood because the damage is cumulative.

Clothing

Normal light clothing provides limited protection against UV radiation. A plain white cotton T-shirt has a SPF of 10, which decreases when wet. High-SPF clothing and large-rim, closely knit hats are available on the market.

Basal cell carcinoma

BCC is the most common malignancy among whites [26]. This cancer causes considerable morbidity for patients and a financial burden on the health care system. Metastasis and death are rare.

Epidemiology

The incidence of basal cell carcinoma shows clear geographic variation (per 100,000: Northern Europe 40–80; South Wales 114; Minnesota, USA 146; Southern USA 300; and Australia 726–1600) [27,28]. This variation presumably reflects the likelihood of significant sun exposure. Among Caucasians in North America, the incidence has increased at more than 10% a year, leading to a lifetime risk of 30% of developing BCC. The incidence rate continues to increase with the aging population [2]. The incidence of BCC increases after age 40. BCC is more common in men (30% to 80%) and is rare in dark-skinned people. Although 85% to 93% of BCC occurs in the head and neck area, a trend toward involvement of the trunk and extremities has been reported in Australia [29,30]. Patients with BCC have an increased risk of developing a second BCC of the skin (35% at 3 years, 50% at 5 years), which increases with number of previous skin cancers, solar damage, and skin sensitivity [31].

Histologic types

Although various dermatopathologic types of BCC exist, a mixed histology is often seen. These include nodular, micronodular, superficial, cystic, infiltrative, and morpheaform. Histologic subtypes usually match the clinical picture. Histologic type correlates with malignant potential and recurrence and suggests clinical margins of resection [32]. Nodular and cystic lesions are relatively indolent in contradistinction to the superficial, infiltrative, morpheaform, and micronodular subtypes, which are biologically more aggressive [33]. Superficial BCC has an increased risk of recurrence due to an increased tendency of incomplete primary excision. Infiltrative and morpheaform BCCs can be associated with aggressive local invasive behavior, with an increased tendency to recur [34]. Both are characterized microscopically by irregular groups of tumor cells with a spiky appearance. Ulcerative and infiltrative types are more aggressive forms [35].

Clinical types

Nodular basal cell carcinoma

Nodular or nodulocystic BCC is the most common subtype (50% to 55%). It presents as a small solitary nodule or papule on the surface of the skin of the face. It has a shiny, pearly, translucent appearance and often has small or large telangiectatic vessels traversing throughout. The nodule is round or oval, and the depth is usually similar to the width. Over time, the clinical picture may be dominated by ulceration in the center of the nodule surrounded by a rolled pearly border and bleeding, thus masking the nodularity (“rodent ulcer”). Although they are mostly red or flesh colored they may show variable amounts of pigmentation mimicking or even masking melanoma (Fig. 3).

Fig. 3. Pigmented BCC. The presence of pigment may evoke the differential diagnosis of melanoma, particularly the nodular type.
Superficial

Superficial BCC is the second most common type (10%) and presents as an erythematous, flaking lesion frequently containing superficial ulcerations or crusting. The borders are usually round or oval, although they may be irregular. The lesions tend to occur mostly in the trunk. They are indolent and may be confused with a variety of benign disorders, including psoriasis, eczematous dermatitis, and Bowen disease (in situ SCC; see below). Excision may be incomplete because the tumor may extend beyond the clinical margin or because the margin may be obfuscated by erythema arising from associated inflammation. Mohs micrographic surgery (see below) may be a valuable management option. Typically, the tumor is confined to the epidermis, and growth is more radial than vertical.

Morpheaform (sclerosing)

Morpheaform BCC is a rare (2% to 5%) but aggressive variant that presents as a tan, white, or yellowish atrophic plaque with ill-defined borders leading to difficulty in diagnosis and late presentation [36,37]. Inflammatory induration is almost always present. The extent of the tumor is usually not apparent on clinical examination, and the surgical specimen frequently has involved margins. Mohs micrographic surgery is valuable in the management of these lesions. The growth pattern is radial, and ulceration infrequent.

Pigmented

Pigmented BCC is a rare subtype (6%) and may be confused with melanoma (Fig. 6). The pigment is melanin and can render the lesion a variety of colors ranging from tan to black.

Treatment

Surgery

Primary excision. Primary excision is the most common treatment for BCC. The 5-year cure rates should exceed 95% [38,39]. Cure rates approach 99% when surgical margins are negative. Because the goal of surgery is curative, achieving negative margins is important. When planning the excision the size of the tumor, the clinical type, the location, and the ramifications of local recurrence should be taken into consideration.

As margin size increases, recurrence rates decrease. The appropriate margin of resection is not set in stone; rather, the surgeon must balance the risk of recurrence with loss of function or diminished cosmesis. Excision with 5-mm margins has been recommended by numerous authors as a general guideline, although smaller lesions may be managed with a 4-mm margin excision and still have a 95% cure rate [40,41]. Nodular and superficial BCCs are definitively managed with surgical excision in 95% of the cases. The chance of residual tumor in micronodular, infiltrative, and morpheaform are 18.6%, 26.5%, and 33.3%, respectively (positive surgical margins) [33]. With the latter types, up to 1 cm margin excision is recommended. Large lesions may require wider margins because margin positivity and recurrence rates increase with size [42].

Mohs micrographic surgery. Mohs micrographic surgery aims to completely remove the tumor via consecutive excisions 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 [43,44]. The technique is based on the premise that the tumor spreads by contiguous growth and that removal of all tumor cells results in cure. Mohs micrographic surgery provides a higher probability of cure (reaching 99%) and limits the defect size, promoting an improved aesthetic outcome [45]. Indications for Mohs surgery in the management of primary BCC include lesions occurring at sites with high rates of treatment failure (eg, periorbital, preauricular, nasal and nasolabial areas—typically fusion planes), lesions having poorly delineated tumor borders, aggressive malignant features, tumors involving sensitive aesthetic or functional locations (eyelid, canthus), and histologic subtypes associated with increased recurrence rates (morpheaform, sclerosing, infiltrative, basosquamous). Mohs micrographic surgery is useful in the management of the recurrent lesion where the tumor has demonstrated a more aggressive phenotype. Other indications for the technique are evolving. Disadvantages of the technique include expense and time. Large tumors may be managed using a single-stage excision with a modified frozen section technique [46].

Nonsurgical ablation

Destructive methods (eg, electrodesiccation, curettage, cryosurgery, laser) are appropriate methods for the management of smaller lesions that have recurrence rates comparable to primary excision. Electrodesiccation and curettage, when limited to small tumors (<2 mm) and superficial lesions, have a cure rate of ≥95% [42,47]. The cure rates for cryosurgery are similar to electrodesiccation and curettage. Ease of use and generally good cosmetic outcome are compelling advantages of cryosurgery.
Cure rates decrease with increasing tumor size when nonsurgical ablative techniques are used. Another significant drawback is the lack of a specimen for histologic analysis. This can be disastrous in the event that the clinical diagnosis is incorrect.

Medical methods

Surgical ablative methods are in general highly effective, relatively inexpensive, and well tolerated. Nonablative methods therefore must exceed these high benchmarks before being accepted as reasonable alternative therapies. These standards have not been exceeded, and medical methods remain a second choice but one that may be reasonable in certain clinical settings. The use of medications may be particularly germane to the management of some of the hereditary syndromes characterized by the simultaneous occurrence of large numbers of lesions (eg, Gorlin syndrome).

Immunotherapy. Recognition of the relevant role of the host immune system in the development of NMSC has suggested a potential indication for immune modulators as a therapeutic modality. Alpha interferon is a naturally occurring antiviral biologic that may act by stimulating a T-cell–mediated antitumor immune response. Intra- or peritumoral injection of interferon has been associated with complete regression rates of 50% to 80% [49,50]. The more aggressive forms of basal cell carcinoma do not seem to have a durable response to interferon, and recurrence rates are high [51].

Imiquimod 5% is an exciting, novel, topically applied immune agent with a variety of potential anti-viral and anti-neoplastic indications. Imiquimod is associated with lesion regression rates between 70% and 100% [52]. Superficial tumors seem to respond better than the nodular type, although long-term recurrence rates have not been assessed.

Chemotherapy. Topical treatment using 5-fluorouracil may be used to treat multiple superficial BCC on the trunk and limbs but seems to be ineffective for the invasive subtypes [53]. Chemotherapy administered systemically is reserved for the rare inoperable or metastatic BCC. Temporary regression and palliation can be achieved using cisplatin.

Radiation. Basal cell carcinomas are sensitive to radiation, and a cure rate of 92% may be expected [42]. Radiation is a noninvasive method usually reserved for elderly patients who are poor surgical candidates or for patients having residual or recurrent tumors. Disadvantages include expense, time, and radiation-related complications [54].

Incompletely excised basal cell carcinoma. A positive surgical margin suggests incomplete excision. Recurrence rates vary between 33% and 67% after presumed incomplete excision [55,56]. Recurrence rates are higher with a positive deep margin compared with positive lateral margins (33% versus 17%) [57]. Fifty-four percent of the re-excised scars show residual tumor [58]. Treatment options for patients having a positive margin include observation, reexcision, and radiation.

Although supported by some authors, observation alone may be a poor choice. Patients may not be compliant with appropriate follow-up. It may be difficult to differentiate clinically between recurrent tumor growth and normal post-surgical induration. Considerable tumor regrowth may occur by the time that the recurrence is clinically accepted. Most authors advocate early re-excision for the management of patients having positive margins [58,59]. Radiotherapy can be a second-line option in the event that re-excision is not desired [60].

Recurrent basal cell carcinoma

Although the results of primary excision overall are excellent, recurrences of BCC occur, and their management can be challenging. Recurrence rates as high as 25% may be observed in certain anatomic locations, especially in periorbital, perinasal, and periauricular regions. There is thought to be something unique about these embryonic fusion planes [56]. Recurrence rates vary with the clinical subtype. Infiltrative, morpheaform, and superficial types have the highest recurrence rates. It may be difficult to differentiate between an exuberant scar and recurrent tumor. Recurrence rates also vary with size of the primary. Recurrence of small lesions are less frequent (4.3% for lesions < 9 mm compared with 13.7% for lesions > 10 mm) [61]. Ulceration, bleeding, or erythema may be signs of recurrence. The time to recurrence may be protracted. Cumulative recurrences of 30%, 50%, and 66% are observed within 1, 2, and 3 years, respectively [62]. Approximately 20% occur between 5 and 10 years later, underscoring the need for long-term follow-up. Recurrence rates after primary surgical ablation are lowest for Mohs surgery (1%) compared with standard surgical technique. Mohs surgery is the most reliable technique for the management of recurrent lesions with respect to recurrence [63].
Metastatic basal cell carcinoma

Metastasis of BCC is rare (less than 0.1%). Metastases may occur via lymphatic and hematogenous routes. Regional nodes, lungs, and bones may be sites of involvement [64,65].

Differential diagnosis of basal cell carcinoma

The differential diagnosis of BCC includes trichoepithelioma, desmoplastic trichoepithelioma, eccrine epithelioma, and microcystic adnexal carcinoma. These latter lesions are relatively uncommon.

Microcystic adnexal carcinoma is a locally invasive tumor mostly found on the lip, nose, and periorbital area. Histologically, it may resemble BCC. Perineural invasion and recurrence are common. Wide local excision or Mohs surgery is the treatment of choice [66].

Trichoepithelioma is a benign, flesh-colored lesion that resembles BCC [67]. Desmoplastic trichoepithelioma are benign lesions occurring mostly in women. Excision is appropriate. These lesions may be confused with morpheaform BCC histologically [68]. Eccrine epithelioma mimics BCC in clinical behavior with aggressive local invasion. It tends to occur in the scalp, and the treatment is wide local excision and possible Mohs surgery because recurrence is common [69].

Squamous cell carcinoma

SCC is the second most common skin cancer after BCC. SCC usually arises in damaged skin and is often preceded by sun damage, leukoplakia, actinic keratoses, or radiation damage. SCC may occur in chronic or unstable wounds and should be considered in the differential diagnosis of any chronic wound.

Epidemiology

The incidence of SCC seems to be increasing. Incidence rates in Australia increased by 51% from 166 per 100,000 people in 1985 to 250 per 100,000 in 1990 [52]. Whether this represents increased awareness and therefore an acquisition bias or reflects changing environmental risks remains speculative.

Histologic types

Histologically, SCC is characterized by varying degrees of keratinocyte dysplasia. Classically, keratin pearls and intercellular bridging are seen. The grade of the tumor is determined by the degree of differentiation. High-grade tumors are marked by increased cellular atypia and loss of keratinization. High-grade tumors are biologically more aggressive and are associated with a worse prognosis.

Clinical course

SCC presents as a painless, erythematous, poorly defined lesion with elevated borders (Fig. 4). They may resemble an actinic keratosis. Compared with BCC, these tumors are more aggressive, and nodal metastases are more common.

Treatment

The mainstay of treatment is surgical resection. Surgical margins are determined according to size of the primary, location, grade, depth of invasion, and patient factors (age, general health, aesthetic considerations, etc.).

Wide local excision

Definitive surgical margins for the management of SCC are unclear and dependent on tumor and host characteristics. For lesions smaller than 2 cm, a 4-mm margin is probably adequate, whereas lesions larger than 2 cm may be better managed with a 1-cm margin [70,71]. The size of the margins may be modified depending on the differentiation, size, and the invasion of surrounding structures. Some authors advocate wider margins (3.5-cm margin for a 3-cm tumor) to achieve a 95% cure rate [72]. The excision
should be into the subcutaneous fat. Early re-excision is recommended in the event of positive resection margins. The goal is to minimize risk of recurrence and metastasis. In general, local recurrence rates are around 5%.

Mohs surgery

Mohs surgery may be an appropriate surgical option particularly in the management of recurrent tumors or tumors in locations where preservation of function or aesthetic concerns are paramount. The cure rate for Mohs micrographic surgery of SCC is ranges from 94% to 97% (well-differentiated primary tumors) [72]. Advantages of this technique include maximum healthy tissue preservation, lower recurrence rates, and potential tumor-free borders.

Destructive techniques

In SCC, destructive techniques such as laser, cryosurgery, and electrodesiccation and curettage are mostly recommended for small, superficial lesions at noncritical locations. These modalities are associated with higher local recurrence [73].

Radiation

Radiation therapy may be appropriate front-line treatment for some primary SCCs of the skin. Local control rates are comparable with surgical resection for early tumors, with cure rates up to 90% [74]. The administered radiation dose and regimen varies according to the size of the tumor. The treatment course may require several weeks. The treatment is more expensive and involves the risk of radiation-associated complications and is therefore best reserved for patients and who are poor surgical candidates. Adjuvant radiotherapy may be indicated after regional lymph node dissection when there is concern about extracapsular nodal extension or evidence of residual microscopic disease. Radiotherapy renders effective palliation of metastatic disease.

Chemotherapy

Topical 5-FU is most appropriately used for the treatment of actinic keratoses and is not generally as effective in the treatment of established SCC. Systemic chemotherapy is indicated in the management of metastatic disease. Indications for chemotherapy in the adjuvant setting are less clear.

Recurrent squamous cell carcinoma

Predictors of recurrence after surgical ablation include degree of differentiation, depth of invasion, and perineural invasion. The likelihood of recurrence in well, moderately, and poorly differentiated SCCs are 7%, 23%, and 28%, respectively [75]. The risk of recurrence increases with depth of invasion of the primary. Perineural invasion with or without clinical symptoms (eg, paresthesias, pain, tingling, numbness) suggest increased recurrence rates, which may be as high 10%. For recurrent tumors or where the primary excision was inadequate or showed perineural invasion, wide excision under histopathologic control (microscopically controlled surgery, Mohs technique) may be reasonable.

Metastatic squamous cell carcinoma

SCC has the propensity to metastasize most frequently to the regional lymph nodes and then systemically (ie, to the lungs, bone, and brain). Phenotypic correlates include location, depth of invasion, differentiation, and size of the tumor [74]. Identified factors that may increase the risk of metastasis include a tumor > 2 cm, depth of invasion > 4 mm, poor differentiation, scar carcinoma, perineural invasion, immunosuppression, and history of previous treatments (Fig. 5). Lesions on the face and dorsum of hand metastasize more commonly (10% to 20%) than lesions on the trunk and extremities (2% to 5%) [76,77]. The 5-year survival rate for patients having metastatic cutaneous SCC is 34% [74].

Squamous cell carcinoma variants

Squamous cell carcinoma associated with long-standing wounds, irritation, or inflammation

Long-standing wounds have a 2% risk of harboring a SCC [78]. Originally described in the setting
of burn wounds (Marjolins ulcer), malignant degeneration may occur in any chronic wound including venous stasis ulcers, decubitus ulcers, hidradenitis, and chronic osteomyelitis (Fig. 6). The possibility of malignancy should be considered in any chronic wound, and a biopsy should be performed. Wound- or scar-associated SCC is generally more aggressive than its UV-induced counterpart and metastases more frequently (from 20% to 30%) [79,80]. The overall prognosis for patients with metastatic disease is dismal [81].

**Bowen’s disease**

Bowen’s disease is a SCC in situ with epidermal and follicular involvement. Only 10% of cases become locally invasive; the rest remain localized for long periods. The lesion is erythematosus with sharp and irregular borders (Fig. 7). There may be superficial scaling and crusting. Lesions involving glans penis are termed erythroplasia of Queyrat.

**Verrucous carcinoma**

Verrucous carcinoma is a well-differentiated variant of SCC so named due to its wart-like appearance (Fig. 8). Local invasion is common. Underlying bone involvement may occur; however, metastases are rare. Involvement of the palmar and plantar skin is common. Surgical excision is appropriate. Because recurrence after primary resection is common, Mohs surgical technique may be appropriate. Radiotherapy is not advocated because it may induce anaplastic transformation [82].

**Differential diagnosis of squamous cell carcinoma**

Keratoacanthoma is a noninvasive, benign lesion histologically resembling SCC. It presents as a 1- to 2-cm, raised solitary mass with a central plug. The clinical course is marked by rapid growth over several months followed by a spontaneous regression that occurs in a similar time interval. Although watchful waiting may be an option, early complete excision confirms the diagnosis, rules out the possibility of a more worrisome squamous cell carcinoma, and often results in a cosmetically more acceptable scar than would follow spontaneous regression.

Pseudoepitheliomatous hyperplasia is a benign disease often arising from sites of chronic inflammation and mimicking verrucous carcinoma clinically.

Bowenoid papulosis is a benign disease that resembles SCC on histology. Clinically, it presents as small papules coalescing to form large plaques. Some types of human papilloma virus (especially HPV-16) have been implicated in the development of this disease. The treatment is conservative because the lesions behave in a benign fashion.
Other skin tumors

Merkel cell carcinoma

Merkel cell carcinoma is one of the most aggressive primary malignant tumors of the skin. It usually arises after the sixth decade and presents as a solitary nodule on a sun-exposed area (up to 75% in the head and neck area). It originates from the pluripotent basal cells in the epithelium. Aggressive excision with 3- to 5-cm margins is the treatment of choice because it is highly aggressive, locally invading subcutaneous planes, fat, lymphatics, and blood vessels. This malignancy metastasizes early. The utility of sentinel node mapping and biopsy followed by selective lymphadenectomy has been documented [83–85].

Summary

Each year, there are as many cases of NMSC as all other cancers combined. Although there is relatively low attributable mortality, the morbidity and expense of treatment is significant. Unlike many other malignancies, host and environmental factors relevant to the pathophysiology have been clearly demonstrated. Surgical ablation remains the mainstay of treatment.

References


