FEATURE ARTICLE

CE

Nonmelanoma Skin Cancer

Part 1

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DEFINITION

Nonmelanoma skin cancer (NMSC) generally refers to the two most common types, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), which arise from the keratinocytes in the skin. Less common types of skin cancer, such as Merkel cell carcinoma (MCC), dermatofibrosarcoma protuberans (DFSP), and Kaposi sarcoma (KS), are also included in this category.

INCIDENCE

More than one million Americans were diagnosed with a new skin cancer in 2008, accounting for more than 50% of all cancers in the United States (American Cancer Society [ACS], 2008a). Exact statistics are difficult to obtain because most of these cancers are treated in private offices and may not be reported to cancer registries. Some statistics account for individual patients rather than multiple tumors in one individual.

The incidence of NMSC increases with age, and men generally have a 30% higher incidence than women, especially in superficial skin cancers. Recent evidence suggests that the incidence of BCC is increasing in Americans younger than 40 years old, particularly in women who are raised in warmer climates and are exposed to sunlight year-round (National Cancer Institute [NCI], 2007).

Geography also influences the incidence rate. States such as California and Hawaii have twice the incidence of the Midwestern states. Northern European countries, such as Finland, have lower incidence rates, and Australia has the highest incidence of BCC in the world. Ultraviolet (UV) light exposure is the single most important contributing factor in these statistics (NCI, 2007).

Although the rate of new NMSCs continues to rise steadily, most cases have a very high cure rate because they are detected and treated early. Failure of early detection can result in significant destruction of the skin and surrounding structures, including bone.

PATHOGENESIS

In addition to the sun, many other environmental and genetic factors contribute to the development of NMSC. UV radiation (UVR) exposure also can be obtained through artificial sources, as in a therapeutic treatment regimen called phototherapy for psoriasis and other inflammatory disorders of the skin. When further penetration of UV light is enhanced by the administration of Oxsoralen® (Valeant Pharmaceuticals International) through a treatment known as PUVA (psoralen and ultraviolet-A light treatment), the risk of developing skin cancer, especially SCC, increases. Tanning booths are another harmful source of UVR. UVR exposure damages the genetic material, DNA, in cells and interferes with the natural control of how and when cells grow and divide. UVR also affects the cell's ability to repair DNA. If the damage to the genetic structure is severe enough, cancer will develop (Rigel et al., 2005).

Many skin cancers contain changes in one or two genes. When the gene known as *PTCH* is damaged, cell growth is stimulated. If the damage involves the *TP53* gene, then the normal death of damaged cells does not occur, and abnormal cells grow and become tumors.

RISK FACTORS

Ultraviolet Radiation Exposure

Exposure to UVR is the major risk factor for the development of BCC, SCC, and melanoma. UVR exposure probably plays a role in the development of MCC, but the association is not as well understood. The solar

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DOI: 10.1097/JDN.0b013e31822f1f77

UV spectrum is continuous and generally is described in three wavelengths: UVA, UVB, and UVC (see Figure 2-1).

UVA is a long wavelength (320–400 nm) and accounts for 95% of UVR. It penetrates deep in the skin, can penetrate glass and clouds, and is present during all daylight hours, year-round. In the past, this wavelength was not thought to be a major factor in the development of NMSC, but a more recent study supports the fact that UVA causes more DNA damage than UVB (Agar et al., 2004).

UVB is a shorter wavelength (290–320 nm) and penetrates the more superficial epidermal layer of the skin. It is responsible for burning, some tanning, and acceleration of skin aging but does not penetrate glass. UVC (100–290 nm) is the shortest wavelength and is filtered, at least for now, by the ozone layer; therefore, it does not reach the earth's surface.

SCC is strongly associated with cumulative sun exposure. The relationship between UVR and the risk of BCC also is dependent on the time of exposure and the nature and amount of exposure (Armstrong & Kricker, 2001). The risk of developing BCC is increased significantly by recreational exposure to sun during childhood and adolescence. Intense, intermittent exposure is associated with a higher risk of BCC than a similar degree of continuous exposure (Armstrong & Kricker).

Tanning

In any discussion about UV exposure and NMSC, addressing the role of indoor tanning is imperative. In the past, the tanning booth industry was poorly regulated, and the exact amount of UVA and often UVB radiation emitted from the bulbs was not known. Tanning salon owners defended their industry by claiming that their machines emitted only UVA. Because this wavelength is responsible for tanning, this exposure was presumed to be protective and therefore safe. Recent research has shown that UVA is a significant carcinogen and is linked with the development of melanoma and NMSCs (Agar et al., 2004). The current trend of NMSC developing in younger individuals is linked to increased outdoor and indoor tanning.

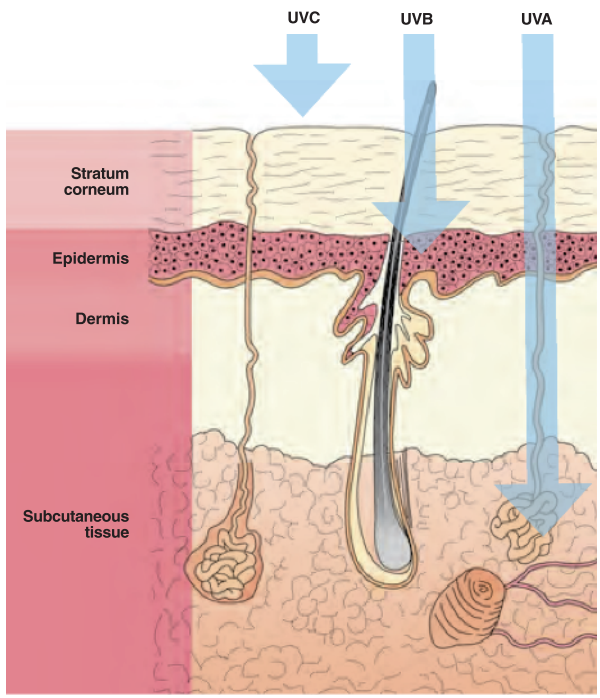


FIGURE 2-1. Three Types of Ultraviolet Radiation.

With the abundance of recent knowledge regarding the deleterious effects of sun exposure, why so many people disregard the evidence and expose themselves repeatedly to the point of burning is difficult to understand. Unfortunately, the current public opinion persists that tanned skin is more attractive. Poorsattar and Hornung (2007) reported that the failure of skin cancer prevention efforts to alter the tanning habits of college-aged students is because of the addictive qualities of UV light, namely the release of endorphins, which further promotes use, thus creating an addiction similar to drugs or alcohol.

In another study, young adults who were regular users of tanning beds reported tanning to help them to relax and found quitting difficult (Feldman et al., 2004). Therefore, if tanning is an addictive behavior, even short-term use of tanning booths to prepare for a trip or to provide a bronze effect for a special occasion can be the beginning of a dangerous cycle. The World Health Organization's recommendation to prohibit the use of indoor tanning booths by minors has received attention from some states, which are beginning to regulate the use of tanning booths by limiting their use to those 18 years of age or older (Sinclair, 2003). However, much more control is needed. The U.S. Senate introduced The Tanning Accountability and Notification Act (2007), or TAN Act, which will require the U.S. Food and Drug Administration (FDA) to determine whether the current labeling requirements for indoor tanning devices, including positioning requirements, provide sufficient information to consumers regarding the risks that the use of such devices pose for the development of irreversible damage to the eyes and skin. Furthermore, the FDA is required to determine if the warning label on tanning beds should be modified to read "Ultraviolet radiation can cause skin cancer" and whether that would more effectively communicate the risk of indoor tanning. Avoiding tanning booths altogether is the best habit to acquire.

Currently, the safest way to achieve a golden glow is with the use of sunless tanners. These products are applied to the skin in the form of lotions or creams containing dihydroxyacetone (DHA), which interacts with the protein on the skin's surface to produce color, which generally lasts several days. Whole body sprays also are available at many salons, but care must be taken to avoid getting the spray in the mouth, eyes, or nose. These

tanners, although cosmetically appealing, provide no protection from UV radiation.

Skin Type

Fair-skinned blonde and red-haired individuals with blue eyes have a much higher risk of skin cancer than darker-skin phenotypes. Therefore, the skin cancer death rates for African American men and women are lower than for Caucasians (ACS, 2007a).

The absence of the protective effects of melanin results in frequent sunburns, which is the primary reason that Australia's skin cancer rate is so high. The major settlers of this continent emigrated from the British Isles and were intended to live in a climate with less UV intensity. Half of all Australians will be diagnosed with skin cancer in their lifetime. Skin cancers make up 80% of all newly diagnosed cases of cancer in Australia. Australia has the highest incidence of skin cancer in the world—four times greater than the rate of skin cancer in the United States. Every year, more than 374,000 people will be treated for NMSC, and 9,500 people will be treated for melanoma (Cancer Council Australia, 2007).

Sex

Historically, BCC and SCC have been more common in men than in women, with SCC occurring three times more often in men. More recently, however, the gender differences in BCC have been less pronounced. Perhaps this is caused by lifestyle issues and styles of dress, but the UV exposure between the sexes is becoming more balanced (Rigel et al., 2005).

Ionizing Radiation

Ionizing radiation exposure, either as a treatment for a disease state, such as acne, or as an accidental environmental exposure, as was seen in World War II, is associated with increased risk of NMSC. Children treated at an early age with radiation for acne and other benign conditions were later found to develop BCC with a latency period of about 20 years. Radiation used to treat childhood cancer produced a 10-fold increase in BCC incidence, all of which occurred within the radiation field (Shaw, 2007b). NMSC, especially BCC, is one of the cancers most strongly associated with the atomic bombings of Hiroshima and Nagasaki (Yamada et al., 1996).

According to one study, radiologists whose hands were exposed to ionizing radiation while treating patients developed SCC in areas of radiation dermatitis (Yoshinaga et al., 2005). Some of this data is compounded by the individual's exposure to UVR as well. Data suggest that exposure to low-dose therapeutic radiation is associated with BCC but not SCC (Karagas et al., 1996).

The development of BCC and SCC seems to be site specific. Most patients who receive low-energy radiation to areas with a high concentration of sebaceous glands, such as the head, neck, and chest, tend to develop BCC. In contrast, patients who receive low-energy radiation to other body sites with a low concentration of sebaceous glands develop SCC (Stern et al., 1984).

Photochemotherapy

PUVA is a commonly used treatment modality. The treatment of psoriasis with exposure to oral psoralen and UVA is known to substantially increase the risk of cutaneous SCC. The risk of BCC was increased only in those patients exposed to very high levels of PUVA or more than 337 treatments (Stern, Liebman, & Vakeva, 1998).

The risk of NMSC must be weighed against the severity of the psoriasis and other possible risk factors such as the concomitant treatment with methotrexate or cyclosporine.

Arsenic

Arsenic, a heavy metal and naturally occurring element, is formed in the earth along with other ores and is a factor for increased risk of SCC. Human exposure to arsenic occurs from natural sources, such as well water. It commonly is seen in agricultural workers and exterminators and is found in the pesticide Paris green. It subsequently is found in drinking water when arsenic leeches out of soil and rocks or the drinking water is contaminated by industrial sources. Although less common in the United States, ongoing epidemics of arsenic-contaminated water poisoning occur in underdeveloped countries. Mining, metallurgy, decorative-glass making, and pressure-treated wood are all sources of arsenic exposure. In the past, arsenical preparations such as Fowler's solution (potassium arsenite) were used to treat syphilis and other conditions (Goldman, 2007). The characteristic skin lesions associated with chronic arsenic exposure are in situ SCC and palmar and plantar keratoses. Arsenical keratoses are discrete, round, wart-like or pointed keratotic projections that resemble numerous small yellow corns on the hands and feet and may appear 20 years after ingestion of arsenic.

Human exposure to arsenic occurs from natural sources such as contaminated ground water and pesticides (U.S. Environmental Protection Agency, 2006). People may also be exposed to arsenic by coming into contact with it in the air, water, and food; by breathing in sawdust or smoke from arsenic-treated wood; by living in an area with high levels of arsenic in rock; or by working in a job in which arsenic is used or made ("Arsenic," 2008).

Immunosuppression

Patients who are receiving immunosuppressive drugs to prevent rejection of solid organ transplants are at increased risk for many cancers. However, the most common are those cancers involving the skin and lips. The interval between transplantation and diagnosis of skin cancer averages eight years for those transplanted at approximately age 40 and three years for those transplanted at age

60. Twenty years post-transplantation, the rate of skin cancer is as high as 80%, and the ratio of BCC to SCC, as seen in the immunocompetent patient, is reversed. SCC occurs 65–250 times more frequently in the immunosuppressed patient than in the general population. BCC occurs approximately 10 times more often (Jensen et al., 1999).

Malignancies of all types are more common in heart transplant recipients, probably because of the greater degree of immunosuppression required to prevent organ rejection. An additional risk factor for these patients is a history of significant sun exposure before and after transplantation, especially in those patients who reside at latitudes closest to the equator.

Chronic use of oral glucocorticoids also may be a risk factor for the development of NMSC, primarily SCC, but the same correlation is not true for inhaled steroids (Lim & Stern, 2006).

BASAL CELL CARCINOMA

Epidemiology

BCC is the most common skin cancer in the world, with the highest incidence (726 per 100,000 individuals) occurring in Australia (Lange & Maize, 2005). The overall prevalence of BCC increases with advancing age, especially after age 50, even if damage began early in life. In 2005, the U.S. Centers for Disease Control and Prevention (CDC) published data to support the notion that BCC occurs more often in men than in women and is linked to UVR (Glanz & Saraiya, 2005).

A 2003 review by Housman et al. examined the effect of treating NMSC in Medicare patients. Although not as costly as lung, breast, colorectal, or prostate cancers, the effect was significant, causing it to be the highest cost with the lowest morbidity and mortality. As with melanoma, intermittent intense sun exposure early in life is believed to be a risk factor for BCC. The association of BCC with recreational UV exposure is stronger than with prolonged or occupational exposure (Neale, Davis, Pandeya, Whiteman, & Green, 2007).

In 2007, Neale et al. examined risk factors for the development of BCC. They found a stronger association between sunburns and truncal BCC rather than BCC of the head, leading the authors to postulate that different patterns of sun exposure may be responsible for the etiology of BCC at different sites. In a 2001 retrospective study, Ramachandran et al. (2001) noted that people first diagnosed with a BCC on the trunk went on to develop more BCCs than those who initially presented with BCC on the head.

BCC is the most commonly diagnosed skin cancer among Japanese, Chinese, and Hispanic individuals (Gloster & Neal, 2006). As reported by Halder and Bridgeman-Shah (1995), BCC is the second most common skin cancer, after SCC, diagnosed in Asian Indians. In a 2004 review, Nadiminti, Rakkhit, and Washington (2001) noted that only 1.8% of BCCs occurred in blacks, and those skin cancers were directly correlated to the degree of pigmentation in the skin. The majority of BCCs that occur on ethnic skin are found on sun-exposed areas and develop after the fifth decade. Although very rare in children, BCCs are occurring more frequently in adolescents with low Fitzpatrick skin types (see Table 2-1) who live in sunny climates (Cohen, 2005). Cases of sclerosing or morpheaform BCC, although rare, are reported to arise in early childhood (Paller & Mancini, 2006). When treating children who have known BCC, particularly in areas not exposed to the sun, one should be suspicious of possible underlying causes, such as radiation or arsenic exposure or basal cell nevus syndrome (BCNS). BCNS is an inherited disorder that predisposes the individual to numerous basal cell skin cancers and is discussed in detail later in this chapter.

Genetic risk factors for the development of BCC are related to susceptibility to UVR and include pigmentary disorders such as albinism. Of note, a 2002 study at the Institute for Pigmentary Disorders in Germany found that 100% of 136 Caucasian patients with vitiligo had decreased photo damage and had a lower risk of BCC. This may be caused by increased function of the wild *TP53* gene, which has been found in vitiligo (Schallreuter, Tobin, & Panske, 2002). Genetic syndromes, such as BCNS and xeroderma pigmentosa (XP), are rare. Both are characterized by the development of multiple BCCs and are discussed separately later in this chapter.

BCC is known to arise in nevus sebaceous of Jadassohn, a common, well-circumscribed yellow-orange plaque arising on the head and neck of young children. The etiology of this is unclear, but most cases of BCC appear in patients older than age 40.

BCNS treatment is dependent on regular dermatology screenings, and lesions should be treated as they arise

TABLE 2-1. Fitzpatrick Skin Types

Skin Type	Description
I	Very fair skin. Eyes are blue or green. Hair is red or blond. Always burns; does not tan.
II	Fair, white skin. Burns easily, but gets a minimal tan. Eyes are blue, hazel, or brown. Hair is blond, red, or brown.
III	Skin is somewhat darker; white to olive skin. Sometimes burns, then tans.
IV	Brown skin. Rarely burns. Tans easily and rapidly.
V	Dark brown skin. Very rarely burns. Tans very easily.
VI	Black skin. Never burns.

Note. Based on information from Skin Cancer Foundation, 2008.

to minimize scarring. Prophylactic and early treatment with imiquimod (Aldara®, Graceway Pharmaceuticals) is reported to be useful. Patients with BCNS should be instructed to avoid radiation and repetitive sunlight exposure (Gritsenko, Gordon, & Lebwohl, 2005).

Pathogenesis

On histology, most BCCs arise in the basal keratinocyte of the epidermis and along the adnexal structures (hair follicles, sweat ducts). Academic circles debate whether BCC arises in the adult basal cell or the pluripotential cell (germinative cell). The role of UV-induced epidermal DNA damage as the primary mechanism continues to be corroborated in the literature (Wrone & Stern, 2006). BCC tumors grow by direct extension and are supported by the surrounding stroma (Habif, 2004). The tumor suppressor patched gene (*PTCH*) on chromosome 9 in patients with BCNS is found in one-third of sporadic BCCs and in patients with BCC and XP (Wrone & Stern).

Clinical Subtypes and Presentation

Nodular BCC is the most common form of BCC and is most likely to occur on the head and neck (see Table 2-2). Nodular BCC generally begins as a small, dome-shaped, pink or pearly papule with a translucent appearance. Irregular, torturous, telangiectatic vessels become evident as the lesion grows. With continued enlargement, the structural irregularities become more apparent, causing the surface to become multilobular (see Figure 2-2). The overlying upper layers of the epidermis become thinner, exposing the blood vessels to easy trauma and bleeding. The center of the lesion may ulcerate and a hemorrhagic crust can develop centrally, making the rolled borders more prominent. Although still relatively small, the ulcerated area can heal over with scar tissue, thus giving patients the false assurance that the lesion is resolving. The tumor continues to grow peripherally and deeper, repeating the cycle of ulceration and healing (Habif, 2004). The ulcerated nodular BCCs previously were referred to as "rodent ulcers" because of their large size and ability to destroy surrounding tissue. Occasionally, melanin can be found in BCCs in variable amounts. These pigmented BCCs often have regular globules of brown, blue, or black pigment and need to be distinguished from melanoma in situ or benign pigmented seborrheic keratosis (see Figure 2-3). Telangiectasias and pearly rolled borders may be difficult to visualize in ethnic skin. In fact, BCCs may have a brown-to-glossy black appearance because of the increased presence of melanin, the so-called "black pearly" appearance (Gloster & Neal, 2006). Differential diagnosis of nodular BCC includes intradermal nevus, sebaceous hyperplasia, molluscum contagiosum, syringoma, trichoepithelioma, and ulcer.

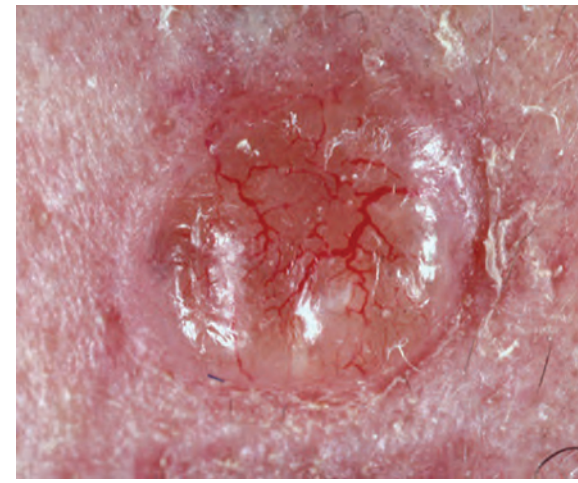


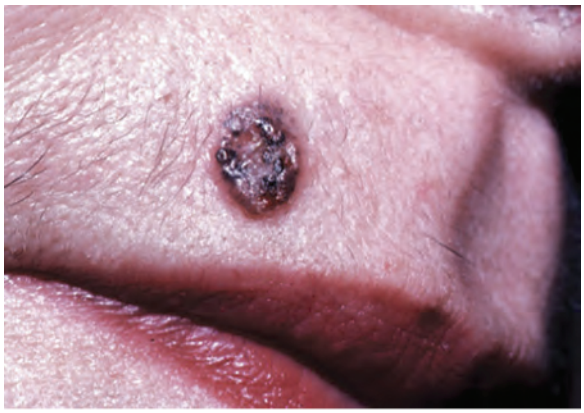
FIGURE 2-2. Nodular Basal Cell Carcinoma. *Note.* Photo courtesy of Suzanne Olbricht, MD, Lahey Clinic Medical Center. Used with permission.

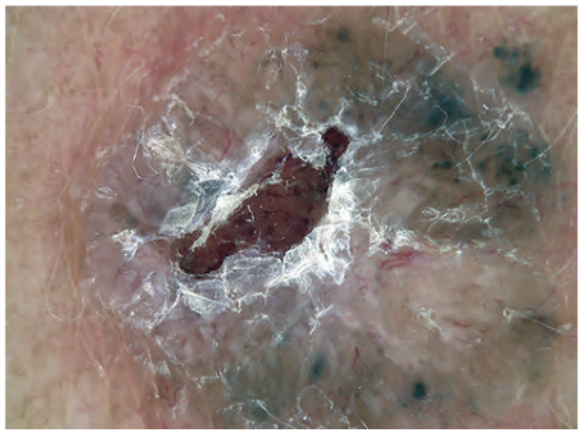
Superficial BCC is most commonly found on the trunk. It also can be seen on the extremities and is found least often on the head and neck. The considerable thickness of the dermis on the back may serve as a barrier and may be the reason superficial BCCs predominate in this region (Lang & Maize, 2005) (see Figure 2-4). It presents as a well-circumscribed, translucent or bright pink-to-red patch, which may contain irregular telangiectasias. The borders may exhibit some scaling or can become slightly rolled in appearance as tension on the surrounding skin increases with the horizontal spread of the lesion. Areas of spontaneous regression can lead to the development of atrophy and hypopigmentation with the lesion. The overall size ranges from several millimeters to centimeters, and with time, the tumor can extend along the hair follicles, and deep invasion can occur. The differential diagnosis for this subtype of tumor includes psoriasis, eczema, discoid lupus erythematosus, and Bowen disease.

Sclerosing or *morpheaform BCC* is the least common form of BCC. It tends to occur on the head and neck and is sometimes found on the trunk. Its name is derived from its resemblance to morphea (localized scleroderma). It appears as a hypopigmented, vague variation in skin texture with a decreased ability to appreciate pores. As the tumor expands, irregular telangiectasias develop, and a slightly shiny, atrophic, scar-like appearance makes the tumor more evident. The ill-defined borders of the lesion make

TABLE 2-2. Basal Cell Carcinoma Clinical Subtypes

Subtype	Most Common Area of Occurrence
Nodular	Head and neck
Superficial	Trunk and extremities
Sclerosing	Head and neck





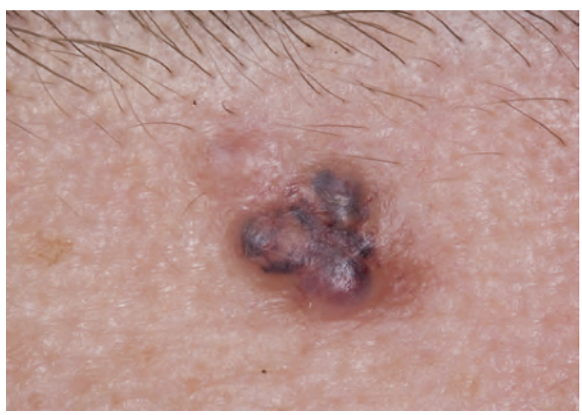


FIGURE 2-3. Pigmented Basal Cell Carcinoma. *Note.* Photos courtesy of Suzanne Olbricht, MD, Lahey Clinic Medical Center. Used with permission.

excising it difficult, as it tends to be locally aggressive, frequently spreading beyond standard 3–4 mm margins, increasing the recurrence rate after routine treatments. The differential diagnoses of sclerosing BCC are morphea, scar, microcystic adnexal carcinoma, and metastatic adenocarcinoma (most commonly from breast cancer) (see Figure 2-5).

Basal Cell Nevus Syndrome

BCNS (Gorlin syndrome) is an uncommon autosomal dominant disorder that is caused by a mutation in the human patched gene *(PTCH)*. The disorder has multiple

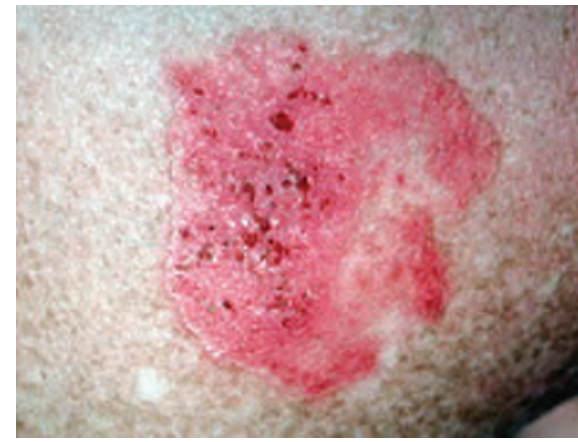
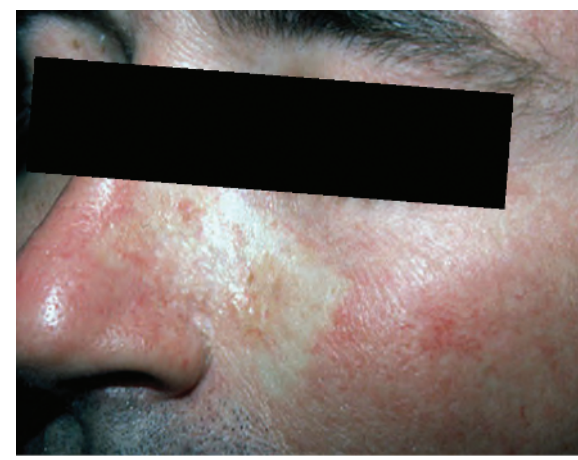


FIGURE 2-4. Superficial Basal Cell Carcinoma. *Note.* Photo courtesy of Suzanne Olbricht, MD, Lahey Clinic Medical Center. Used with permission.

clinical features, the appearance of which vary from patient to patient based on the variable expressivity of the gene mutation. The most common clinical features of BCNS are found in Figures 2-6 and 2-7.

The diagnosis may be difficult to make because of the variability of gene expression. Family history and careful



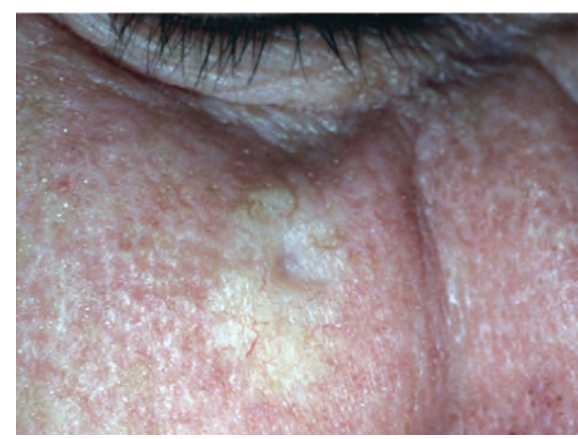


FIGURE 2-5. Morpheaform Basal Cell Carcinoma. *Note.* Photos courtesy of Thomas Habif, MD, Portsmouth Regional Hospital. Used with permission.

- Multiple basal cell carcinomas by a young age, predominantly on the trunk
- Palmar and plantar pitting
- Bone cysts, especially in the mandible
- Skeletal abnormalities of the ribs and spine
- Cleft lip and palate
- Coarse face
- Macrocephaly and frontal bossing
- Ocular defects including hypertelorism, congenital blindness, cataracts, and strabismus

FIGURE 2-6. Common Clinical Features in Basal Cell Nevus Syndrome.

physical examination with radiologic imaging of the jaw, chest, and skull often are diagnostic. The most reliable method of diagnosis if clinical examination is inconclusive is screening of the entire *PTCH* gene for genetic mutations. Histologically, no difference exists between BCNS tumors and traditional basal cell skin cancers. Although exceedingly rare, BCNS has been reported in ethnic patients (Gritsenko, Gordon, & Lebwohl, 2005).

Treatment of BCNS is directed at early intervention to minimize scarring. Prophylactic and early treatment with imiquimod is reported to be useful. Patients with BCNS should be instructed to avoid radiation and repetitive sunlight exposure (Gritsenko, Gordon, & Lebwohl, 2005).

Xeroderma Pigmentosa

XP is a very rare autosomal recessive disorder with a slightly greater prevalence in Japan. It affects males and females with equal prevalence and presents within the first few years of life. Recent advances in the field of genetics have led to the description and clinical identification of eight genetic subtypes of XP. Each genetic subtype exhibits a different defect in the body's ability to repair DNA damage induced by UVR.

The earliest manifestations of XP are acute sun sensitivity with an almost immediate sunburn response, which may manifest as infants crying after minimal sun exposure. The development of pigmented maculae, achromic maculae, telangiectasias, and scaling in photoexposed areas occurs very early in childhood. Severe photo aging and atrophy of the skin can lead to narrowing of the mouth and nares. Unexposed areas are not affected. The skin's inability to repair the damaged DNA soon leads to the development of actinic keratosis and keratoacanthomas. Many of these patients develop NMSC before puberty and have a 1,000-fold increased risk for malignant melanoma. The eyes also are affected with early photosensitivity, conjunctivitis, and telangiectasias progressing to ectropion, corneal opacification, and blindness. Approximately 20% of cases have progressive neurologic degeneration with mental retardation and sensorineural hearing loss (Spitz, 2005).

Prognosis

BCC tends to be a slow-growing tumor that rarely metastasizes through blood vessels or lymphatics. When metastasis occurs, it usually is associated with a rare subtype of BCC called a *basosquamous* or *metatypical* carcinoma. These tumors may be best classified as SCCs "because the more squamoid cells, the greater the potential for metastases" (Lang & Maize, 2005, p. 104). Metastatic BCC is exceedingly rare, representing less than 0.1% of all cases (Gloster & Neal, 2006). When it does occur, the BCC is associated with a long duration, lesions larger than 10 cm, recurrence, and aggressive histologic traits. Metastatic disease has significant morbidity and mortality and can be found in regional lymph nodes, lungs, bone, and skin (Ting, Kasper, & Arlette, 2005).

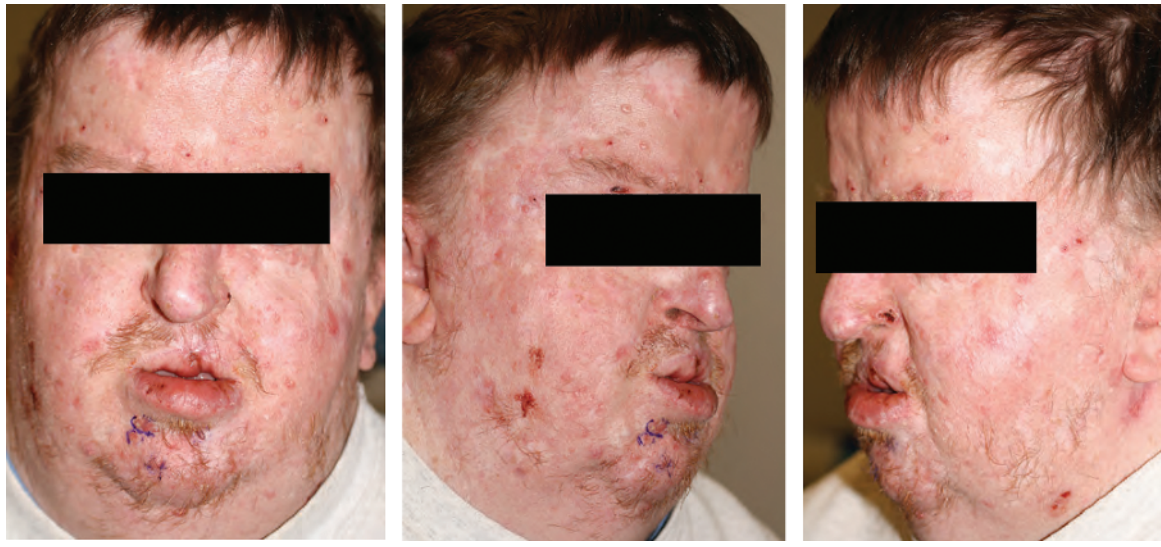


FIGURE 2-7. Basal Cell Nevus Syndrome. *Note.* Photos courtesy of Suzanne Olbricht, MD, Lahey Clinic Medical Center. Used with permission.

The reported slow growth rates of BCCs give them an excellent clinical prognosis. The tumors progress through phases of both growth and regression. The phase that predominates determines the overall rate of growth each individual tumor will experience. BCCs tend to follow the path of least resistance; they can become infiltrative and invade local tissue destroying eyelids, noses, or ears. If left for a long time, the tumor can extend along the nerve (perineural invasion), along the hair shaft (perifollicular invasion), or along embryonic fusion plates. Perifollicular invasion most commonly is found on the scalp, where terminal hair follicles are deeply rooted in the subcutaneous tissue (Lang & Maize, 2005). Perineural invasion can occur in any location of a long-standing tumor; it is a common reason for recurrence. The patient may report new onset numbness, pain, and paresthesia. The objective of treatment is to remove the skin cancer with the best cosmetic and functional result for each patient.

SQUAMOUS CELL CARCINOMA

SCC is the second most common type of skin cancer. It is more likely to metastasize than BCC. Many of the risk factors for SCC and BCC are the same, namely UV exposure, age, geographic location, immunosuppression, and exposure to radiation and other carcinogenic agents. Cumulative lifetime sun exposure is a more significant factor in SCC, whereas intermittent sunburns increase the risk of BCC. As life expectancy continues to rise, the incidence of all skin cancers should increase.

Pathophysiology

SCC is a malignant tumor of the epidermal keratinocytes. It may arise de novo or from a precursor lesion, such as an actinic keratosis (AK), as described in the following section. It can infiltrate locally, invading lymph nodes and nerves, or metastasize distally, especially to the lung (Hess, Schmultz, & Goldman, 2006).

SCC in situ histologically reveals atypical keratinocytes only in the epidermis from the basement membrane to the stratum corneum. Invasive cutaneous SCC penetrates beyond the basement membrane to the dermis and may infiltrate deeper or metastasize beyond. Well-differentiated SCC shows various grades of dysplasia with keratinization. Poorly differentiated SCC shows keratinocytes that are anaplastic with mitosis and carries a higher morbidity risk (Lim & Stern, 2006).

Precursor Lesions

AKs occur as small, superficial, whitish, pink, or brown rough-surfaced lesions with a gritty scale (see Figure 2-8). They often are more easily felt than seen, and the patient may describe them as tender or sensitive when touched. Histologically, atypical keratinocytes are in the lower two-thirds of the epidermis. In these lesions, researchers find mutations in the *TP53* tumor suppressor gene, and when exposed to UVB radiation, further atypical transformation may result. AKs may intermittently improve but tend to persist or remain unchanged for years. Each individual AK has a low rate of progression to SCC, but a large percentage of SCCs arise from AKs or within close proximity to them. Individuals with 10 or more AKs have a 14% probability of developing an SCC within five years (Lim & Stern, 2006).

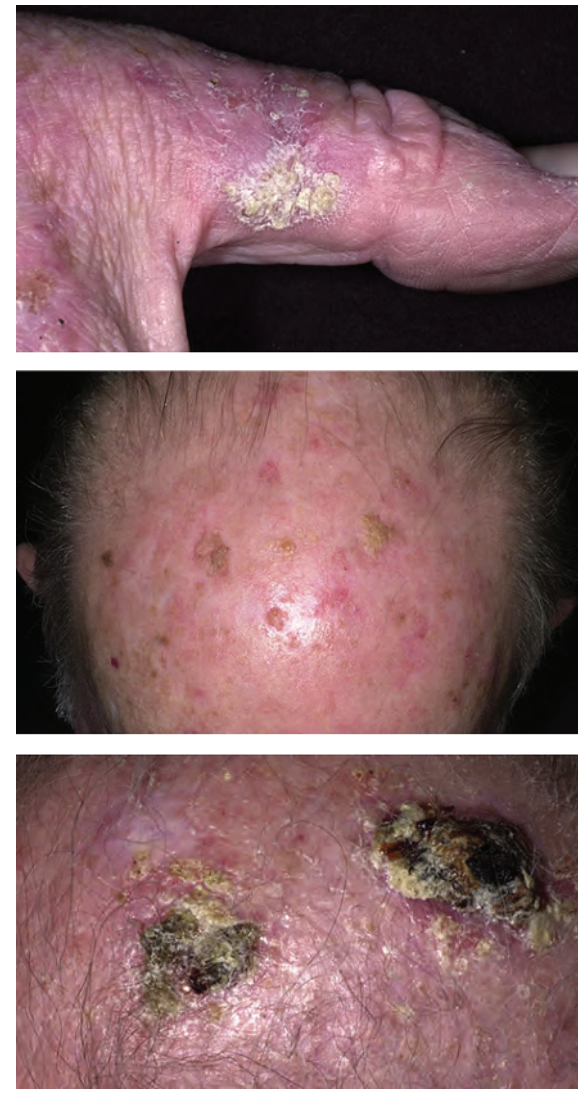


FIGURE 2-8. Actinic Keratoses. *Note.* Photos courtesy of Suzanne Olbricht, MD, Lahey Clinic Medical Center. Used with permission.

AKs usually are treated to prevent transition to SCC. Treatment modalities include cryotherapy, topical treatments such as 5-fluorouracil (5-FU), diclofenac, imiquimod, and photodynamic therapy (PDT).

Cryotherapy or liquid nitrogen often is the treatment of choice for discrete lesions. Liquid nitrogen is applied directly, resolves over a few days to a week, and has an extremely effective cure rate (about 99%) (Shaw, 2007a).

For more diffuse actinic damage with multiple AKs, a topical treatment may be advantageous. 5-FU usually is

applied twice daily as a 2% or 5% cream or lotion for two to three weeks, causing the lesions to become erythematous and crusty. The severity of the reaction typically is related to the amount of sun damage and precancerous lesions present and can be quite uncomfortable and temporarily disfiguring. Imiquimod, an immunomodulator compounded as a cream, is applied nightly two to five times per week for four weeks, causing a similar but less severe reaction and is thought to incur a lower rate of recurrence over time. Reactions also may be seen in areas distant to the application site where no medication was applied directly. This demonstrates a systemic effect, which resolves over a period of weeks. Diclofenac, a topical anti-inflammatory agent, causes less irritation but is applied daily for 90 days. Because of the discomfort associated with these topical treatments, they often are used in smaller, confined areas sequentially, requiring multiple courses to treat the entire face.

Topical retinoids, chemical peels, and PDT also can be used in areas of superficial but widespread sun damage to prevent AK. The best treatment is prevention by avoiding sun exposure and taking appropriate sun precautions.

A *cutaneous horn* is a hard, cone-shaped projection of keratin resembling an animal horn. It occurs on the face, ears, or hands and may become quite long, typically a few millimeters to one centimeter. The base of these lesions may be benign (e.g., seborrheic keratosis, wart), premalignant (e.g., AK), or malignant (e.g., SCC); therefore, a biopsy of the tissue at the base of the lesion is recommended (see Figure 2-9).

Leukoplakia is a premalignant lesion of oral mucosa frequently involving the lips and oral cavity, especially the floor of the mouth, lateral tongue, and buccal vestibule. It also can be seen on the uvula. The transition to SCC is about 17%, and 50% of all oral cancers begin as leukoplakia (Habif, 2004).

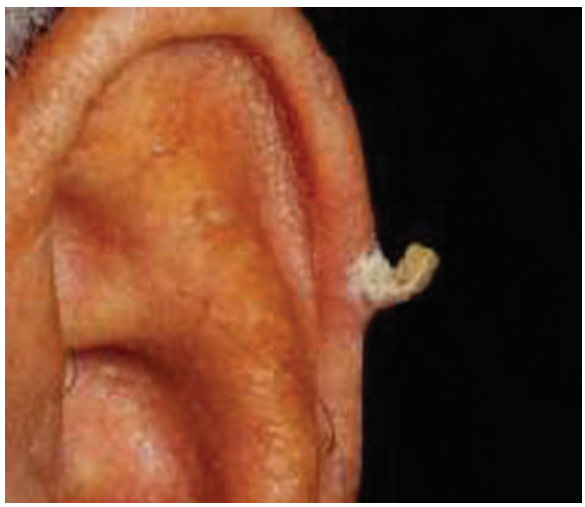


FIGURE 2-9. Cutaneous Horn. *Note.* Photo courtesy of Suzanne Olbricht, MD, Lahey Clinic Medical Center. Used with permission.

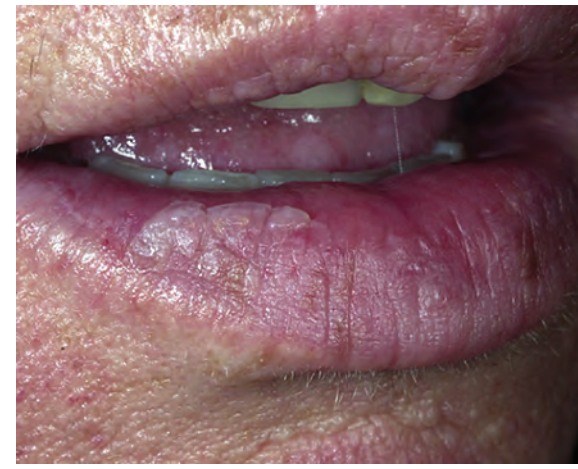


FIGURE 2-10. Leukoplakia. *Note.* Photo courtesy of Suzanne Olbricht, MD, Lahey Clinic Medical Center. Used with permission.

These lesions are fairly nonspecific, are raised, range in color from nearly translucent to white to opaque, and may exhibit some degree of ulceration (see Figure 2-10). They are frequently caused by tobacco use and chronic irritation. Smokers tend to have lesions on the floor of the mouth, whereas smokeless tobacco users have lesions on the edge of the tongue and buccal mucosa. A more aggressive form presents as hyperkeratotic verruciform lesions that are bilateral. Hairy leukoplakia is a variant and often is a hallmark of HIV disease. It is a white lesion with a corrugated surface of papillary projections. The differential diagnosis of leukoplakia includes candidiasis, lichen planus, trauma from cheek biting, and secondary syphilis (Habif, 2004). Smoking cessation alone can cause some of these premalignant lesions to disappear. Biopsy usually is indicated, and treatments include topical 5-FU, laser, or excision.

Keratoacanthoma (KA) is a neoplasm of the skin and mucous membranes that exhibits rapid growth, maturation, and regression (Rigel et al., 2005). KA lesions easily can reach 2 cm in a four- to six-week period and then will regress over a few weeks. They often are painful or tender, skin-colored to red-brown, dome-shaped papules or nodules with a central crater filled with a keratinous plug. They often are described as volcanic-like lesions (see Figure 2-11). Originally, KA was thought to arise from hair follicles, but it also occurs in non-hair–bearing areas, such as the mucous membranes. It usually occurs on sun-exposed areas, such as the nose, hands, ears, and face, and is more common in men and in people older than age 50. KA usually arises as a solitary lesion, but multiple lesions may be seen as in the eruptive type. These lesions can occur as hundreds of papules on the trunk, extremities, and the mouth. They heal spontaneously but can scar if not treated (Sarabi, Selim, & Khachemoune, 2007).

Controversy remains over whether KAs are benign or malignant. Because they grow rapidly in a matter of weeks

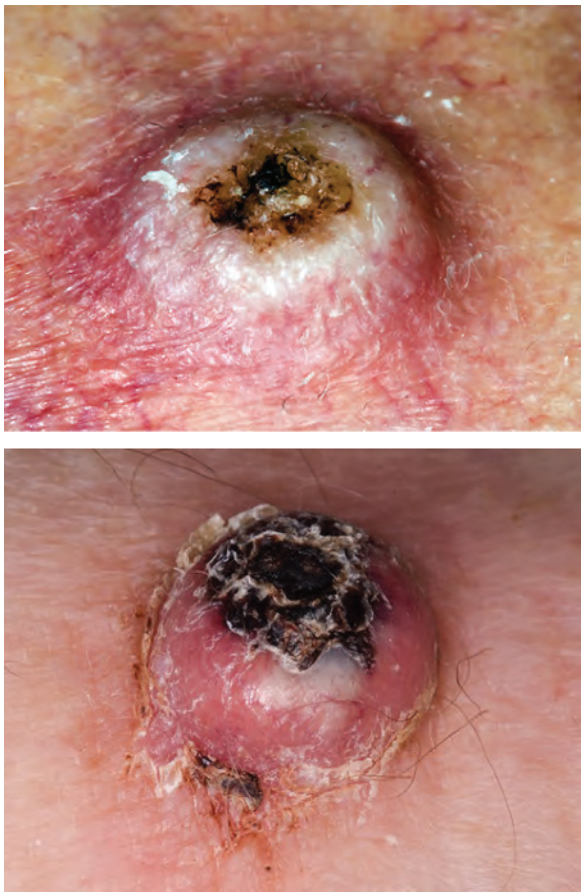


FIGURE 2-11. Keratoacanthoma. *Note.* Photos courtesy of Thomas Habif, MD, Portsmouth Regional Hospital. Used with permission.

and often regress spontaneously, many believe they are benign lesions. However, their biologic behavior is difficult to predict based on clinical appearance alone. Some lesions that appear this way may not resolve and will progress to behave like a SCC with the same risk of metastases. Therefore, the prevailing recommendation is to treat KA as a malignancy with excision, electrodesiccation and curettage (ED&C), cryosurgery, or topical methods.

Human papillomavirus (HPV) is a double-stranded DNA virus of the papovavirus class that infects the squamous epithelial cells of the skin and mucous membranes.

More than 150 types of HPV have been identified and can cause a wide variety of benign clinical cutaneous lesions, such as common warts. The most common presentation of mucosal lesions is condyloma acuminata. Many of these lesions are specific to the virus subtype. HPV has a role in the oncogenesis of cutaneous and mucosal premalignancies, such as SCC in situ (SCCIS) and cervical or anal dysplasia. Invasive malignancies, such as SCC, can be seen in the immunocompromised host, especially individuals with HIV disease or solid organ transplant recipients (Wolff, Johnson, & Suurmond, 2005). HPV types 6, 11, 16, and 18 most commonly are associated with genital warts. Types 16 and 18 most commonly are related to genital cancers, both cervical and anal. HPV can be latent in normal-appearing skin, and infection and transmission can occur unknowingly. Risk factors for anal cancer in men include anal intercourse, HPV infection, and HIV infection. The risk of acquiring HPV infection is reduced with circumcision. Because high-grade atypical squamous intraepithelial lesions are a precursor to invasive anal SCC, ablative therapy is warranted similar to the management of high-grade cervical cancer (Cranston & Palefsky, 2006).

Bowenoid papulosis occurs in the genital area of both men and women and histologically resembles Bowen disease or SCCIS. It is a relatively uncommon condition related to HPV 16 in sexually active adults in their early 30s. The papules are discrete, are flat-topped, range in color from reddish-brown to violaceous, and may coalesce to form larger plaques. They are seen on the glans, foreskin, and shaft of the penis and in the inguinal area in men (see Figure 2-12). In women, they occur on the labia majora, labia minora, clitoris, inguinal fold, and anus. The papules often are bilateral and hyperpigmented. The differential diagnosis includes flat warts, lichen planus, and psoriasis. The lesions typically run a benign course, but malignant transformation has occurred in a few cases. Treatment is similar to that for genital warts and is aimed at being locally destructive and sparing surrounding tissue. Treatment modalities include imiquimod, cryosurgery, electrodesiccation, laser ablation, or excision. Imiquimod has been shown to decrease reccurrence of HPV lesions, possibly by treating surrounding tissue, which may be latently infected with HPV (Habif, 2004).

Clinical Variants of Squamous Cell Skin Cancer

SCCIS is defined histologically by atypia involving the full thickness of the epidermis but not invading the dermis. The keratinocytes appear disorderly with a windblown appearance and may continue along appendages, such as

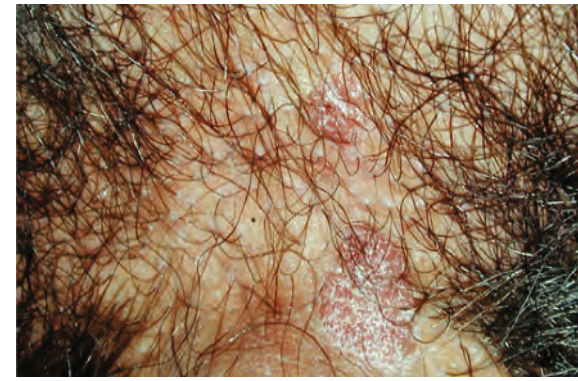


FIGURE 2-12. Bowenoid Papulosis. *Note.* Image reprinted with permission from eMedicine.com, 2008. Available at http://www.emedicine.com/derm/topic919.htm

a hair follicle (Hess et al., 2006). Lesions vary clinically and may resemble AK, a scaly pink patch, or a keratotic papule or plaque. A variant of SCCIS is Bowen disease, which has similar histologic features, but clinically the lesions are well defined, enlarge slowly over years, and rarely develop into a more invasive carcinoma (Bolognia, Jorizzo, & Rapini, 2008) (see Figure 2-13).

SCCIS plaques appear primarily on sun-exposed skin but can be found on mucous membranes. In sun-exposed areas, these lesions may be elevated slightly with surface fissures and well-defined borders. On mucous membranes, especially the glans, vulva, or oral mucosa, SCCIS usually appear as an erythematous fiery patch that can be elevated slightly, be well defined, and have a slight scale.

Erythroplasia of Queyrat is classified as a subtype of SCCIS but originally was described separately. It develops on the glans in uncircumcised males but can be seen on the prepuce or urethral meatus. It is a moist, red, smooth lesion and grows slowly. Erythroplasia of Queyrat is related to HPV infection. Treatment options include topical 5-FU or imiquimod or laser ablation. If the lesion extends into the urethral meatus, excision with Mohs micrographic surgery (MMS) may be indicated (Habif, 2004). *MMS* is the precise excision of a tumor that aims to remove the entire tumor while sparing tissue in critical mass. This procedure will be discussed in greater depth later in this chapter.

The differential diagnosis of SCCIS includes psoriasis, chronic eczema, AK, superficial basal cell skin cancer, seborrheic keratosis, and malignant melanoma.

Invasive SCC is characterized histologically by malignant keratinocytes, which penetrate the basement membrane into the dermis. Clinically, invasive SCC can have a varied appearance. Well-differentiated tumors are flesh-tone to pink in color, may appear as indurated firm plaques, and may be hyperkeratotic or ulcerated. Poorly differentiated SCCs appear as soft, fleshy, and granulomatous papules and plaques. They may have areas of hemorrhage and necrosis, may be friable and bleed easily, and are clinically more aggressive than other types (Lim & Stern, 2006). The more common invasive SCC is a raised, firm, pink keratotic papule or plaque on sun-exposed skin. Surface changes include scaling, ulceration, crusting, and possibly the presence of a cutaneous horn. A subcutaneous nodule with no surface epidermal changes is a less common presentation. It is usually on a background of severely sun-damaged skin with mottled pigmentation, telangiectasia, and multiple AKs. SCC, which is precipitated by UVR, occurs primarily on sun-exposed areas, with 50%–70% occurring on the head and neck. The remaining 30% are found on the dorsum of the hands, forearms, and legs and are more common in men (Hess et al., 2006) (see Figure 2-14). SCC related to arsenic exposure usually occurs on the palms and soles. Tumors associated with radiation therapy (RT) occur at the edges of the radiated sites. Perioral SCC occurs more commonly on the lower lip as the result of more intense sun exposure at the vermillion border. It begins with dryness, fissuring, and depigmentation and can resemble AK. The area may develop a new focus of induration with a firm nodule. The presence of a keratotic plaque on the lip is a sign of potential invasive SCC. *Marjolin ulcers* are an aggressive form of ulcerating SCC that appear in areas of previously traumatized, chronically inflamed, or scarred skin and have a latency period of about 20–30 years (Hess et al.). The typical presentation is a subtle change in the skin of the scar, which may appear slightly more erythematous or feel more indurated. The area may be elevated or weeping. They most commonly arise in areas that sustained scars from thermal burns. If appearing at a site of prior radiation, it is usually at the edge of the treated area. These tumors act more aggressively and warrant definitive treatment, usually with excision (Hess et al.).

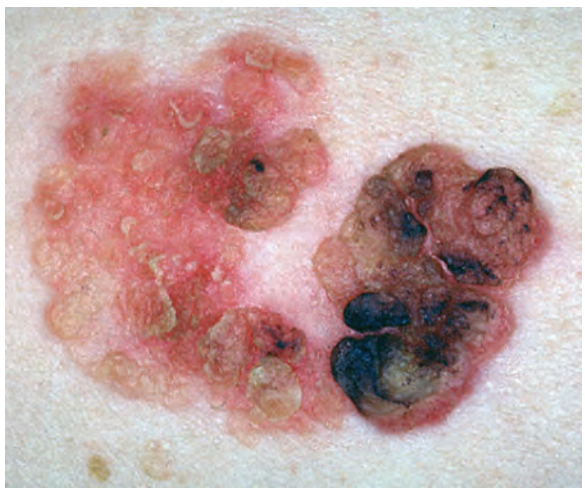


FIGURE 2-13. Squamous Cell Carcinoma in Situ. *Note.* Photo courtesy of Suzanne Olbricht, MD, Lahey Clinic Medical Center. Used with permission.

Verrucous carcinoma (VC) has several distinct variants depending on location. They are locally aggressive, but metastasis is rare. The pathogenesis is not understood completely, but a number of contributing causes have been reported, including inflammatory conditions, such as lichen sclerosis and lichen planus, and environmental factors, such as poor hygiene, lack of circumcision, and chronic irritation. Immunosuppression, HIV, and HPV, especially serotypes 6 and 11, also are implicated. VC subtypes include Büschke-Loewenstein tumor (BLT), oral florid papillomatosis, and palmoplantar epithelioma cuniculatum.

BLT, associated with HPV 6 and 11, is a slow-growing, exophytic, fungating, cauliflower-like or polypoid lesion. Tumors are firm to rock hard, malodorous, and erythematous. Tumors may ulcerate and hemorrhage and can achieve significant size. They most commonly occur on the penis and account for as many as 24% of all penile tumors (Dudelzak, Sheehan, & Sangueza, 2007). Pathology

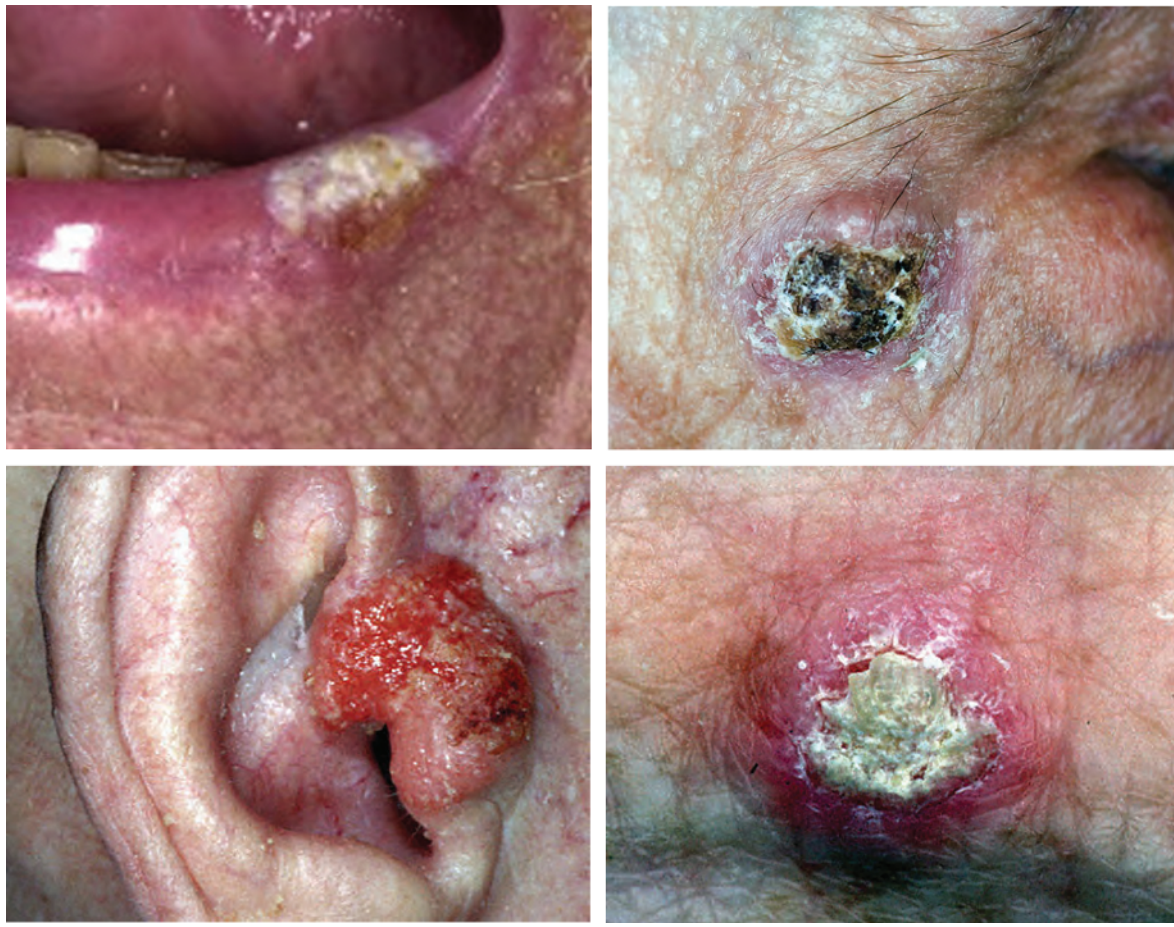


FIGURE 2-14. Squamous Cell Carcinoma, Invasive. *Note.* Photos courtesy of Thomas Habif, MD, Portsmouth Regional Hospital. Used with permission.

resembles benign neoplasms related to condyloma, but condyloma acuminata are superficial and do not grow into underlying tissue. BLT may deeply infiltrate the urethra and anorectal vault. The lesions may be associated with the development of fistulas and abscesses and may lead to infiltration into muscle. Rare reports of metastasis have occurred. Morbidity often is dependent on tumor size. The workup for patients suspected of having BLT should include computed tomography or magnetic resonance imaging if infiltration is suspected. Treatment includes radical excision or MMS with adjuvant therapies. Overall morbidity and mortality are caused by local spread, complications of hemorrhage, cachexia, and peritonitis.

Oral florid papillomatosis is most common in white men age 55–65. Risk factors include tobacco chewing, poor hygiene, and ill-fitting dentures. Lesions can appear as white patches on an erythematous base or as gray-white, warty tumors with a deeply cleaved surface. They are locally aggressive about 53% of the time (Habif, 2004).

Palmoplantar epithelioma cuniculatum affects older men around 60 years of age and usually occurs on the plantar surface of the foot. The lesions are exophytic with ulcerations and often are associated with pain and foul-smelling discharge. Metastasis is rare. Lesions are deeply invasive and difficult to treat. They often are misdiagnosed as refractory warts (Habif, 2004) (see Figure 2-15).

Prognosis

Cutaneous SCC can invade locally by expansion and metastasize via the lymphatics. When they invade,

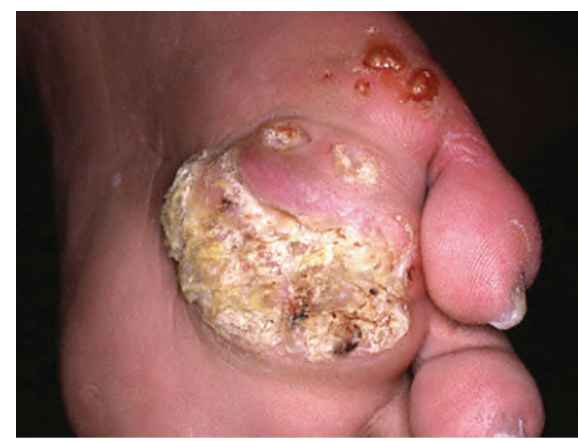


FIGURE 2-15. Palmoplantar Epithelioma Cuniculatum. *Note.* Photo courtesy of Thomas Habif, MD, Portsmouth Regional Hospital. Used with permission.

malignant cells spread until they come in contact with harder or denser cells as in bone, cartilage, and muscle and then spread laterally along these planes. This pattern of invasion occurs particularly in areas of little subcutaneous tissue, such as the ears, nose, and scalp. Conduit spread occurs when the tumor spreads along a nerve or vessel. The rate of metastasis is low in SCC, averaging 2%–6%, and occurs in the more aggressive clinical subsets with an associated poorer prognosis. The highest risk for metastasis occurs from lip and ear lesions. If treated early and appropriately, the cure rate for SCC is greater than 90%. Local recurrence carries a higher risk for metastasis. The presence of regional lymphadenopathy is usually a sign of metastatic disease and carries a poor prognosis. The five-year survival rate with metastases ranges from 25%–35% and depends on the health and immune status of the patient, the size of the tumor, and size of the lymph node. The use of surgery and adjuvant RT increases the survival rate, but RT also increases the risk of developing new SCCs. Metastasis to distant organs remains incurable.

The risk of metastasis is determined by patient and tumor characteristics. Tumors occurring on the lips or ears, in the anogenital region, or in scar tissue are considered high risk. In addition, large tumor size, greater than 2 cm in diameter and invading deeper than 4 mm, has a greater risk of metastasis. The presence of invasion into subcutaneous fat and other structures, poorly differentiated histologic appearance, and perineural spread also contribute to the level of risk. Intrinsic patient factors include organ transplant recipients, especially heart and kidney, hematologic malignancy, chronic immunosuppression, and HIV infection. Marjolin ulcers also metastasize, which may be related to delayed diagnosis. Perineural invasion occurs in 2%–14% of cases, most commonly in older adult men with tumors of the head and neck. Involvement of a major nerve increases risk of metastasis (Hess et al., 2006).

DIAGNOSIS AND WORKUP OF NONMELANOMA SKIN CANCER

When skin cancer is suspected clinically, biopsy confirmation is essential. Biopsy is a simple procedure performed with various techniques depending on the size, location, type of lesion, and clinical suspicion. Histologic confirmation may help to direct treatment by identifying the depth of involvement, histologic variation, and any aggressive features, such as neural invasion.

Shave biopsy is the simplest option. It may be superficial or deep, does not require sutures, and may be used for superficial lesions, such as BCC where the pathology is confined to the epidermis.

A punch biopsy is performed with a cone-shaped instrument that penetrates down to subcutaneous fat. This often is used when the pathology is thought to invade into the deeper dermis, such as SCC. Sutures are optional but often afford a better cosmetic result and more rapid healing. If the clinical suspicion for skin cancer is high and complete excision is inevitable, suturing may not be necessary.

Excisional biopsy is recommended for most pigmented lesions, especially if malignant melanoma is suspected. If the lesion is small, then the entire lesion may be removed with a punch excision. If the lesion is larger, elliptical excision is recommended and sutures are necessary.

In addition to conventional histologic analysis, *confocal microscopy* is a less-invasive technique that allows for in vivo imaging of certain tumors of the skin. This technique is similar in principle to ultrasonography but uses reflective light from a laser instead of ultrasound. The advantages over conventional biopsy are that it is faster and the skin site can be imaged repeatedly to evaluate dynamic changes, such as response to therapy. Morphologic characteristics have been defined for BCC, imaging is noninvasive and painless, and the tissue is not altered by processing. Data are collected in real timewith AK and SCC. Although not widely used at present, this technique holds great promise as a diagnostic tool and as an adjunct to surgery (Gonsalves, Nierneyer, & Torres, 2005).

Physical examination is an important part of the workup, with careful examination of lymph nodes if SCC is diagnosed. The patient also should be observed for any possible nerve involvement in the affected area.

Once the diagnosis of NMSC is confirmed, the method of treatment is decided considering multiple factors, including the potential for the lesion to recur or metastasize and whether the lesion is primary or has already recurred. If the lesion is a recurrence, the presence of scarring will be a factor in determining treatment method. Histologic variation of the tumor and aggressive biologic behavior, such as size, depth of invasion, and involvement of surrounding structures such as nerves must be considered. The patient's immunocompetence, age, general health, convenience, and overall wishes determine the ultimate decision.

STAGING

Because most NMSCs do not metastasize, staging seldom is needed. When appropriate, the tumor staging system of the American Joint Committee on Cancer is used and can be helpful to plan appropriate treatment and monitor a patient's progress. However, this system often is inadequate when staging SCC because the system does not assess critical values, such as perineural invasion, depth, differentiation, and clinical subtype. Recently, the role of sentinel lymph node biopsy (SLNB) in the staging of NMSC has been studied because of its usefulness in staging melanoma and breast cancer. In a retrospective study, Sahn and Lang (2007) sought to determine the reliability and usefulness of SLNB in patients with high-risk SCC. They determined that the predictability of metastasis to regional lymph nodes in SCC is far less than in melanoma. Likewise, no specific characteristics have been shown to predict a positive SLNB. They concluded that the small number of cases studied and low yield did not justify the

routine use of this procedure. In a review of English medical literature, Ross and Schmults (2006) found that SLNB in patients with cutaneous SCC accurately diagnosed lymph node metastases with few false negatives. They concluded that more controlled studies were needed to demonstrate whether early detection of subclinical nodal metastasis would lead to improved overall survival for patients with high-risk SCC.

TREATMENT OF NONMELANOMA SKIN CANCER: BASAL CELL CARCINOMA AND SQUAMOUS CELL CARCINOMA

The objective of NMSC treatment is to remove the skin cancer with the method that achieves the best cosmetic and functional result for each patient.

The selection of a method of treatment is based on the potential of the lesion to recur or metastasize. Limitations of each treatment are tempered by several factors in addition to the skill of the provider and the cosmetic results and include (Drake et al., 1993)

- Primary or recurrent tumor
- Perineural invasion (indicated by the presence of pain or paresthesia)
- Aggressive biologic behavior (i.e., size > 1 cm, rapid growth, ulceration, depth, or invasion into deeper tissue)
- An immunocompromised host
- Occurrence in previous inflammatory or degenerative process or scar
- Convenience to the patient, the patient's wishes, and the patient's general health.

Early diagnosis of SCC and BCC and consideration of the chances of a lesion recurring or metastasizing provide the best opportunity for cure. Currently available treatment options for localized disease are discussed below and include the following methods.

- Surgical excision
- MMS
- Cryotherapy
- ED&C RT
- Topical chemotherapy (e.g., 5-FU, interferon, retinoids)
- PDT
- Systemic chemotherapy
- Laser therapy

Surgical Excision

Surgical excision is the treatment of choice for the majority of cutaneous cancers. It is well tolerated, can be performed in an outpatient setting under local anesthesia, and allows full visualization and examination of the tumor.

The advantage of excision over destructive methods like cryotherapy or ED&C is that adequacy of treatment may be achieved through histologic examination of the margins of the excised tissue. Recommendations for surgical margins vary depending upon the risk of local recurrence (Brodland & Zitelli, 1992). Tumors that are well defined, small (< 2 cm in diameter), and rendered a low risk require a 4 mm margin of normal tissue around the visible tumor border and result in complete removal of primary tumor mass in 95% of cases. Moderately to poorly differentiated SCCs should be excised with 6 mm margins. Narrower margins are more likely to leave residual tumor. Poorly defined primary SCCs that are large (> 2 cm in diameter), are in high-risk locations (e.g., ear, lip, scalp, eyelids, nose), or extend into subcutaneous tissue require a 6 mm or larger margin. For more aggressive tumors, MMS is recommended to achieve similar histologic cure rates (Motley et al., 2002). For BCCs larger than 2 cm in diameter with an aggressive histologic pattern, or for recurrent BCCs, a 5 mm margin is recommended.

In addition, curettage of the tumor to determine clinical margin prior to excision is an important step in improving the cure rate. Following surgical excision, SCCs have a five-year recurrence rate of 8.1%. Recurrent SCCs treated with surgical excision have a much greater five-year recurrence rate of 23.3% (Rowe, Carroll, & Day, 1992).

Patients with recurrent tumors, incompletely excised tumors, tumors arising within chronic ulcers or radiation sites, or SCCs with perineural extension need more extensive procedures. These high-risk tumors are better treated by MMS, if possible (Chartier & Stern, 2006).

The advantages of excision of BCC and SCC over other therapies include shorter duration of the procedure, lower cost (if frozen sections are not required), complete healing within one to two weeks, and microscopic assessment of the margins. Excision is suitable for BCCs involving all sites, and long-term (> 10 years) cosmetic and functional results are usually superior.

The major disadvantage of surgical excision is the risk of false-negative margins caused by the traditional "bread loaf" technique of sectioning. This typically results in evaluation of less than 1% of the tumor margin and a greater amount of normal tissue removed than is required for complete tumor eradication (Hess et al., 2006).

Mohs Micrographic Surgery

Dr. Frederick Mohs at the University of Wisconsin developed MMS in 1936. He recognized that microscopically monitoring the surgical margin during excision would ultimately improve the overall clearance of the tumor and result in lower rates of recurrence.

With the precise excision of tumors, normal tissue is spared, ensuring preservation of vital structures, simplification of wound repair, and improvement in cosmetic results. Although Mohs' original technique has progressed from a fixed method to one of fresh tissue removal, the concept has endured, and the long-term results have been proved over time. Most defects are repaired with primary intention, and healing generally is complete within two

weeks. Potential complications associated with general anesthesia and sedation are avoided because MMS requires only local anesthesia (Rigel et al., 2005).

MMS is the preferred treatment for the following high-risk skin cancers.

- Large, invasive BCCs and SCCs (diameter > 2 cm)
- Morpheaform and infiltrating BCC (These are aggressive subtypes that consist of sclerotic plaques with often poorly defined borders that can extend beyond clinical margins. These tumors rarely ulcerate or bleed and are often mistaken for scars [Ramsey, 2008].)
- High-risk SCC without nodal disease
- Poorly differentiated, ill-defined, recurrent, or incompletely treated tumors
- BCC and SCC in high-risk areas
- Areas where maximal tissue preservation is mandatory (e.g., penis, digits)
- Areas of high recurrence (e.g., lips, ears, nose, central face)
- Recurrent or incompletely excised BCC

Five-year cure rates are 95%–99% for primary BCCs. The average five-year recurrence rate for primary cutaneous SCC treated with MMS is 2%–5%, depending on tumor location; for recurrent SCC, the five-year recurrence rate is 10%. MMS can be used for removing tumors from any part of the body, including eyelids, lips, nose, ears, fingers and nail beds, and genitalia. The MMS procedure is the same for BCC and SCC and also is used for removal of MCC and DFSP (Rigel et al., 2005).

A dermatologist trained in this surgical procedure performs MMS in an outpatient setting. Using local anesthesia, the surgeon acts as pathologist and reads the histology as the procedure progresses. Patients generally tolerate the procedure well, but it can be lengthy, sometimes two to four hours or longer for more complicated cases. In addition to a small rim of clinically normal-appearing tissue, the tumor is excised at an oblique angle, which allows for histologic evaluation of 100% of the peripheral margin, compared with 1% of the peripheral margin when standard excision is used (Rigel et al., 2005) (see Figure 2-16).

The surgeon processes and examines the tissue. Histologic findings are correlated with the lesion using a Mohs map, which the surgeon draws after excising the tumor to depict the exact location of the tumor. If tumor is seen in any of the microscopic margins, the location is noted on the Mohs map, and another specimen from only this area is taken. The tissue is processed and evaluated microscopically again. This process is repeated until all margins are clear of tumor cells. Once the tumor is removed completely, the defect is closed immediately using primary side-to-side closure, local flap, graft, or distant flap, or the defect is allowed to heal by secondary intention (Rigel et al., 2005).

The disadvantages of MMS are the length of time required for the procedure and its cost. Defect repair can take one hour or more. Histologic preparation and examination consume a significant amount of the total procedure time. While specimens are processed and analyzed, patients are temporarily bandaged and may wait in the waiting room.

MMS is more expensive than standard surgical excision, and its cost-effectiveness is controversial. Some consider MMS cost-effective because of the lower rates of local recurrence; however, others disagree because of low recurrence rates associated with standard excision (Rigel et al., 2005).

MMS provides higher cure rates than any other treatment option for both primary and recurrent BCC and SCC. All recurrent tumors are potential candidates for MMS. It is useful in cosmetically sensitive or functionally critical areas (e.g., periocular, periauricular, perioral areas, nose and perinasal areas, lips, ears), as well.

When treating patients with BCNS, especially patients with numerous lesions, it may be impossible to obtain clear lateral margins without creating an unmanageably large defect. Depending on the tumor location, the surgeon may decide to achieve clear, deep margins and follow the patient or use less-invasive treatment modalities to manage the remaining epidermal component (Rigel et al., 2005).

Cryotherapy

Cryotherapy is the treatment of choice for many small (< 1 cm in diameter) cutaneous tumors in areas at low risk for recurrence. This technique is quick and easy to perform, requires minimal anesthesia, and has few disadvantages or contraindications. Small (< 1 cm in diameter) well-defined, well-differentiated, and superficially invasive SCCs are appropriate for cryotherapy (Nordin, 1999). Cryotherapy is a widely accepted therapeutic modality for BCC, with cure rates as high as 97%–99% and excellent cosmetic results. Successful treatment is dependent on provider skill and proper tumor selection (Kuflik & Gage, 1991).

In cryotherapy, liquid nitrogen (–195.8°C) is applied to the tumor and a surrounding rim of normal-appearing skin, usually a margin of at least 3 mm. The frozen area is allowed to thaw, unaided. For SCC, a rapid tissue freeze to –50°C and slow thaw is needed for tissue destruction. In most cases, the tumor is refrozen to complete two freeze-thaw cycles. For Bowen disease, a single freeze-thaw cycle may be sufficient (Holt, 1988). Tumor cell death is caused by the formation of intra- and extracellular ice crystals, hypertonicity, disruption of the phospholipid membrane, and vascular stasis (Kuflik, 1994).

Following treatment, the patient usually will experience moderate to severe swelling, pain, and oozing that resolves over days to weeks. The treated area eventually will slough off and produce an ulceration that heals over four to six weeks. This may result in residual hypopigmentation, permanent alopecia, and/or hypertrophic scarring, which usually resolves over 8–12 months. Treated areas on lower

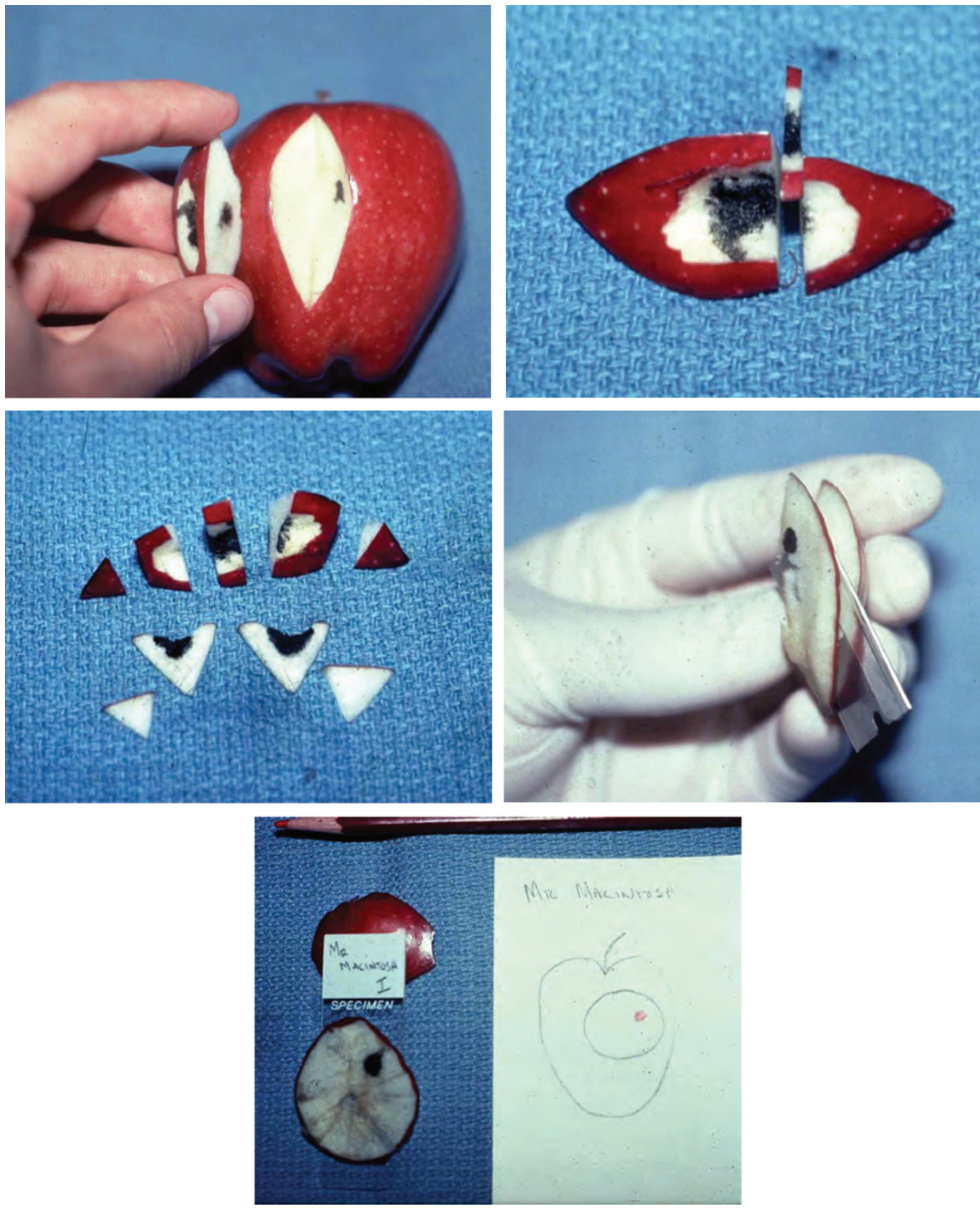


FIGURE 2-16. Mohs Micrographic Surgery. *Note.* Photos courtesy of Suzanne Olbricht, MD, Lahey Clinic Medical Center. Used with permission.

extremities may take longer to heal, and hypopigmentation can persist for many years (Chartier & Stern, 2006).

Cryotherapy is not indicated for recurrent, large, deeply invasive, poorly defined, and other high-risk cutaneous SCCs because of the increased risk of local recurrence and/or metastatic spread. The risks associated with cryotherapy include transient pain, edema, and blistering. Hypopigmentation and alopecia may be permanent; therefore, treatment of hair-bearing areas and darkly pigmented individuals generally is not recommended. The five-year cure rate for SCC can be 96% or higher with proper tumor selection and technique.

The many variables involved in treatment, such as method of application (spray versus cryoprobe), freeze-thaw time, number of freeze-thaw cycles, and temperature of tumor base, will interplay in the successful eradication of

the tumor. For these reasons, five-year recurrence rates are believed to be approximately 8% and 13% for primary and recurrent BCCs, respectively (Chartier, 2006).

Cryotherapy is not indicated for BCC tumors deeper than 3 mm or those with indistinct margins. The main disadvantages are a hypopigmented scar, prolonged healing, pain during the procedure, and the risk of recurrence (Tung & Vidimos, 2002).

Of note, cryotherapy can be considered for patients with high-risk tumors who are unable to tolerate MMS, excision, or the frequent visits necessary for RT (Chartier & Stern, 2006).

Electrodesiccation and Curettage

ED&C is a relatively quick, well-tolerated office procedure with a low complication rate that spares adjacent healthy tissue and usually gives favorable cosmetic results. ED&C is useful for small, superficial, well-defined cutaneous SCCs and BCCs that are located in noncritical, low-risk sites, such as the trunk and proximal extremities. The recurrence rate for nonmelanoma skin cancer following ED&C in these areas is much lower than in other areas treated with ED&C (Rigel et al., 2005).

Cutaneous SCCs and BCCs have a distinctive type of tissue that feels different and is more friable than surrounding healthy tissue. By alternately curetting away tumor and then electrodesiccating the base and a firm rim of surrounding normal skin, cure rates of 96% or better have been reported (Honeycutt & Jansen, 1973; Knox, Lyles, Shapiro, & Martin, 1960; Rowe et al., 1992; Whelan & Deckers, 1981). Other studies have indicated higher recurrence rates, closer to 10%–20%, particularly for Bowen disease (Sturm, 1979; Whelan, 1967). As with cryosurgery, the main disadvantage of ED&C is the lack of histologic confirmation of the tumor margins, thereby limiting its use to small, well-defined primary (nonrecurrent), low-risk tumors. The following routine precautions are recommended when using electrosurgery in patients with pacemakers and implantable cardiac devices (ICDs).

1. Use short bursts of energy less than five seconds in duration.
2. Keep power settings as low as possible.
3. Avoid the use of cutting current.
4. Avoid use on skin around the pacemaker or ICD.

According to Bolognia et al. (2008), no cases of interference to a pacemaker or an ICD in a dermatologic setting have been reported to date.

The cosmetic result following ED&C and excision is site dependent. ED&C on the trunk and extremities often leads to a flat, white macula or patch but may leave a raised or depressed oval scar or occasionally a long-standing keloidal scar. The ED&C sites remain pink and elevated for a period of months before improving (Rigel et al., 2005). On the face, ED&C sites may heal with a fine white patch or macula; however, they often are depressed and heal with a firm, rope-like scar caused by wound contraction. In general, excision or MMS with repair leads to a better aesthetic scar than ED&C does (Rigel et al.).

ED&C is inappropriate for tumors that invade into or beyond the subcutaneous tissues, where the expected discriminating feel of the more friable cancerous tissue is lost. ED&C should be avoided on the midface (e.g., midnose, nasal alae and sulci, medial canthi, nasolabial folds), as these areas do not provide a firm surface for curettage. If tumors are partially treated, healing skin can bury residual tumor beneath scar tissue. By the time a recurrence is clinically evident, the tumor can be large, and curative treatment may be more difficult to achieve.

Curettage Alone for Treatment of Basal Cell Carcinoma

According to Barlow et al. (2006), electrodesiccation is associated with poor cosmesis, in particular postoperative hypopigmentation and hypertrophic scarring, and it has the potential to interact with ICDs and to delay healing. Reports of similar cure rates and better cosmesis for patients treated with curettage alone have been documented. In their study, Barlow et al. used "a single disposable 4–6 mm curette from the center to the periphery, including a 2–5 mm peripheral margin, of biopsy-confirmed BCCs" (p. 1040). After thorough curettage was performed in at least three directions, the base was wiped clean, and hemostasis was achieved with 20% aluminum chloride. Monsel solution (ferric subsulfate solution) and 30% aluminum chloride are associated with delayed wound healing, and both contribute to tissue necrosis, which could increase wound depth and result in higher cure rates. When hemostasis is achieved with pressure following curettage alone, recurrence rates are slightly higher.

Patients were followed for five years; five-year cure rates were 96.3% for tumors treated with curettage alone, nearly identical to an estimated 95.3% five-year cure rate for BCCs treated with traditional ED&C (Barlow et al., 2006).

According to the authors, tumor location, size, and histologic subtype were not predictive of recurrence (Barlow et al., 2006). Operator experience affects cure rates and is found to be an independent risk factor for recurrence. Two important factors in preventing recurrence when treating with curettage alone or traditional ED&C are "meticulous technique and the ability to recognize a normal dermal base" (Barlow et al., p. 1043). Meticulous technique includes several firm passes across the entire base of the tumor plus 2–5 mm margins in all directions (Barlow et al.; Honeycutt & Jansen, 1973).

Radiation Therapy

RT is beneficial for patients unable to tolerate outpatient surgery and for older adult patients with large tumors and a life expectancy of less than 15 years. It should not be

used for SCC in patients younger than 55 years of age because of long-term cosmetic morbidities and the potential risk of SCC developing within the treated site. A lag time of 20 years is typical for SCC arising in irradiated skin.

RT is an important option for treatment of primary or recurrent BCC and as a primary or adjuvant treatment for SCC. On average, five-year cure rates for primary, previously untreated BCC are 91%–93%; 96% for low-risk, small primary BCC; 86%–91% for large and/or locally advanced BCC; and 86%–91% for recurrent BCC. Five-year cure rates for primary SCC average about 90%. RT alone for larger or more deeply invasive tumors yields good cosmesis and functional outcomes (Rigel et al., 2005).

RT usually is delivered in a fractionated schedule, which divides the total dose and delivers it over a period of several days. BCC and SCC generally are treated with a total dose of 40–50 Gy delivered over a period of one to seven days, depending on the size and thickness of the tumor. For some patients, frequent visits are a problem. Other disadvantages include the lack of histologic margin control, high cost compared to other modalities, and short- and long-term side effects. Recurrent BCCs that initially were treated with RT behave more aggressively than those that recur after surgical procedures and have higher rates of second recurrence and distant metastasis (Rigel et al., 2005).

RT generally is not used for tumors on the trunk and extremities. Because these areas are subjected to greater trauma and tension, they are more prone to ulcerate from atrophy or poor vascularity of irradiated tissue. In addition, pigmentary changes and telangiectasia are more likely to occur (Rigel et al., 2005). Although uncommon using modern techniques, RT has the advantage of sparing cosmetically and functionally important structures. It is noninvasive and painless, and it can be used for patients who are not surgical candidates or who have incompletely excised tumors. Beneficial cosmetic results may deteriorate over time, and treatment-related cancers may develop. For this reason, RT should be considered a last resort for recurrent, previously irradiated tumors and should never be used in patients with BCNS because it could induce hundreds of difficult-to-manage skin cancers.

Short-term cutaneous complications include erythema, edema, scaling, vesicles, bullae, erosions, ulceration, pain, and occasionally infection. Healing occurs three to four weeks after the final treatment. Less common short-term side effects include "comedo reaction," a benign condition characterized by the appearance of large, open comedones at the periphery of the treated area in sites on the nose, cheeks, and ears; appearance of pseudorecidives, which are keratosis-like nodules that develop within the irradiation field that develop several weeks after treatment and spontaneously resolve several months later with no long-term sequelae; nail shedding; and, very rarely, gangrene (Rigel et al., 2005).

Long-term sequelae include cataracts, chronic radiation dermatitis, delayed radiation necrosis, permanent alopecia within the radiation field, secondary cutaneous malignancies, thyroid cancer, and infertility. Some complications (e.g., chronic radiodermatitis, alopecia) are common, predictable, and generally avoidable. Others (e.g., cataracts, infertility, thyroid cancer) are uncommon but predictable and can be avoided with proper shielding (Rigel et al., 2005).

Delayed radiation necrosis may appear months to years after RT and is characterized by spontaneous breakdown of the skin within the irradiated field with erythema, erosions or ulcerations, crusting, and discomfort. Often, delayed radiation necrosis is precipitated by trauma, infection, or exposure to cold or sun and is caused by poor vascularity and atrophy within the irradiated area. Permanent alopecia usually occurs within the treatment field when using doses to treat cutaneous malignancies. Chronic radiodermatitis appears months to years after treatment and is characterized by permanently mottled areas of hypopigmentation and hyperpigmentation; dry, hyperkeratotic, atrophic, shiny epidermis; telangiectasias; and dermal fibrosis.

Radiation-induced cutaneous malignancies include both BCC and SCC. Usually they develop within irradiated sites that also are exposed to UVL and can develop 5–65 years after RT. Radiation-induced BCC and SCC frequently behave aggressively, with a higher likelihood of subclinical extension. Radiation-induced SCC has a greater risk of metastasis and death. More rarely, RT-induced malignancies include fibrosarcoma and melanoma. Higher radiation doses, larger radiation fields, sun-exposed sites, fair skin, and early age at radiation exposure increase the risk for secondary cancers (Rigel et al., 2005).

Topical Chemotherapy

Topical 5-FU and imiquimod are approved by the FDA for topical treatment of superficial BCC (sBCC) and AK.

5-FU interferes with DNA synthesis by inhibition of thymidylate synthetase. 5-FU is available as 1%, 2%, or 5% creams and solutions. More concentrated formulations and a sustained-release intralesional preparation have been tested but are not standardized or FDA approved. Only 5% 5-FU is suitable for treatment of sBCC and will not eradicate invasive BCC or those with follicular involvement. If used to treat invasive BCC, the superficial component may be eliminated, but the deeper component may be buried below scar tissue and continue to grow until it becomes a subdermal mass with extensive subclinical spread (Rigel et al., 2005).

5-FU has been used and studied over the past four decades. Its role mainly is confined to sBCC in noncritical locations. If used for properly selected sBCC, 5-FU cream demonstrates cure rates as high as 95%. Treatment of nonsuperficial, recurrent, or other high-risk BCCs yield lower cure rates and therefore is contraindicated. 5-FU is

especially useful for patients with BCNS, who develop numerous BCCs at a young age. This treatment is suggested as prophylaxis for this population (Rigel et al., 2005).

Topical 5% 5-FU cream should be applied twice daily for 3–6 weeks or sometimes for 10 weeks, depending on clinical response. Adequate response depends on the concentration and vehicle, frequency of application, use of occlusive dressing, clinical and histologic features of the tumor(s), patient skin type, and degree of sun exposure before and during treatment.

Curettage before applying 5-FU under occlusion is more effective than topical 5-FU with occlusion only. Because topical 5-FU can conceal unsuspected deep foci of BCC, it should be used in patients for whom no other treatment is practical (Rigel et al., 2005).

Topical 5-FU causes a brisk inflammatory reaction that develops in treated sites during therapy. Before starting therapy, patients need education about anticipated side effects, including burning, stinging, pain, erythema, edema, erosion, ulceration with serous oozing, and possible secondary infection. Discomfort can be severe enough to temporarily or permanently discontinue therapy. Patients commonly limit or avoid social outings during treatment because of the undesirable cosmetic effects. Special care must be taken when applying 5-FU to areas of increased sensitivity (e.g., around eyes, lips, nose), and patients should avoid prolonged sun exposure during treatment. Intense inflammation is ameliorated by temporarily stopping treatment, decreasing the concentration, and applying emollients or midpotency topical steroids. This inflammatory reaction is an indication of the efficacy of topical 5-FU. Absence of an inflammatory reaction should prompt a change in treatment regimen, such as increasing concentration or application frequency or applying under occlusion or in conjunction with a topical keratolytic agent or retinoic acid. Changing to a different treatment modality ultimately may be necessary.

After stopping 5-FU, healing occurs over two or more weeks. During this time, residual erythema and sometimes hyperpigmentation are present, which eventually fades. Long-term favorable cosmetic results are an advantage over other treatment modalities.

Disadvantages of topical 5-FU and imiquimod include lack of FDA approval for all types of cancers, post-treatment pigmentary changes, treatment-associated photosensitivity, and the tendency to conceal deep, residual tumor nests.

The mechanism of action of imiquimod in treating sBCC is unknown. Small studies show that imiquimod increases infiltration of lymphocytes, dendritic cells, and macrophages into the tumor; however, the significance of these findings is unclear (Rigel et al., 2005). Imiquimod cream should be applied to biopsy-proven sBCC with 1/3-inch margin of normal-appearing skin daily, five days a week, for six weeks. Skin reaction is similar to that seen with topical 5-FU treatment and includes redness, swelling, formation of sores, itching, or burning.

Intralesional Interferon

Interferon (IFN) alfa-2b and IFN gamma have been injected into superficial and nodular BCCs. IFN gamma lacks efficacy, but IFN alfa is associated with complete clinical and histologic response rates of 80%–100%. Various dosing regimens have been used; all require multiple injections. According to one study, 1.5 million IU of IFN alfa per injection, three times per week for three weeks, achieved response rates of 80% or more. However, in the only placebo-controlled trial, the one-year recurrence rate was 19% (Rigel et al., 2005). Failure rates for treating aggressive BCC with IFN alfa approach 73% (Rigel et al.).

Side effects with IFN alfa intralesional injections include fever, malaise, rheumatic symptoms, altered psyche, chills, transient decreased white blood cell count, pain, and itching at the injection site. In addition to mediocre cure rates, side effects, and multiple visit requirements, this procedure is costly.

Photodynamic Therapy

PDT combines three elements: oxygen, light, and a photosensitizing chemical, such as porphyrin, to activate reactive oxygen species within targeted tissues. When this occurs, cancer cells are destroyed without damaging healthy tissue (Rigel et al., 2005).

The photosensitizing agent, most commonly aminolevulinic acid, is applied either topically or systemically where it is absorbed by both normal and abnormal tissue. The topical formulation generally is preferred for cutaneous disease because systemic porphyrin administration is associated with prolonged photosensitivity.

Reported cure rates are variable with PDT, ranging from 46%–100% for superficial SCC; however, long-term efficacy is uncertain (Chartier & Stern, 2006).

Disadvantages associated with PDT include the methods of photosensitized chemical administration, variability in types and methods of light exposure, and definition of recurrent disease (clinically detected versus histologically assessed), in addition to the high number of treatments required and associated treatment discomfort.

Currently, PDT is used primarily to treat large numbers of AKs in a single session with a strong evidence base of efficacy (Rigel et al., 2005). Hyperkeratotic lesions can be curetted prior to administration of the photosensitizing agent. PDT has been used to treat SCCIS; however, efficacy in these lesions is uncertain.

In the treatment of BCC, the greatest therapeutic promise is for sBCCs, particularly large, numerous BCCs and those not amenable to other forms of surgical therapy. However, because studies are not complete in addressing long-term recurrence rate and potential long-term carcinogenic effects, PDT should be considered investigational

for treatment of BCCs and not standard treatment at this time (Chartier, 2006).

Retinoids

Limited research is available on the use of oral retinoids (e.g., isotretinoin, acitretin) in the management of BCC (Micromedex, 2004). Most existing data come from the use of these agents to prevent BCC development in patients with BCNS. In most cases, oral retinoids yield partial BCC regression; however, at high doses, oral retinoids appear to have preventive effects. Many patients cannot tolerate the required dose, 1.5 mg/kg/day of isotretinoin, for long periods of time. Relapse occurs when medication is discontinued. Side effects of oral retinoids include depression, osteoporosis, joint and lower back pain, elevated cholesterol/triglyceride levels, gastrointestinal upset, liver problems, pseudotumor cerebri, increased intracranial pressure, hearing loss, impaired ability to see in the dark, and decreased red and white blood cell counts (Rigel et al., 2005). *Pseudotumor cerebri* is an idiopathic form of intracranial hypertension that causes chronically elevated intracranial pressure (ICP) and papilledema, which can lead to progressive optic atrophy and blindness (Goodwin, 2006).

Systemic Chemotherapy

Both metastatic BCC and uncontrolled local disease are managed with chemotherapy. Metastatic BCC has a poor prognosis when disseminated disease is present. Some patients live for years, but most survive 10–20 months following diagnosis (Rigel et al., 2005).

Chemotherapy traditionally is used for primary treatment of inoperable SCC or as a last option after failing surgery and RT (Rigel et al., 2005). Systemic chemotherapy occasionally is given before surgery and/or RT to decrease tumor volume and increase cure rates. If BCC metastases are confined to lymph nodes, then surgery with or without RT may be successful (Rigel et al.). With disseminated metastases (e.g., skeletal metastases), systemic chemotherapy with or without RT is recommended (Rigel et al.).

Cisplatin, bleomycin, cyclophosphamide, 5-FU, vinblastine, and doxorubicin most commonly are used to treat SCC and disseminated metastatic BCC; cisplatin appears to be most effective with higher rates of long-term survival (Micromedex, 2007a; Rigel et al., 2005). Common side effects of systemic chemotherapy include hair loss, mouth sores, low blood counts, easy bruising, bleeding, loss of appetite, nausea, and vomiting. The side effects vary in frequency and severity based on the drugs used and what, if any, other treatments are used in combination, including RT and surgery (ACS, 2008b).

In advanced or unresectable BCC, cisplatin and doxorubicin with or without RT provide excellent palliation. This regimen is moderately well tolerated and yields higher response rates with prolonged disease control (Rigel et al., 2005).

PROGNOSIS FOR NONMELANOMA SKIN CANCER: BASAL CELL CARCINOMA AND SQUAMOUS CELL CARCINOMA

BCCs rarely metastasize, but they do grow locally without stopping. Tumors can impinge on vital structures, resulting in loss of function but rarely death. Most BCCs can be treated successfully before serious complications occur.

Cutaneous SCC is an elusive malignancy. MMS continues to be the gold standard for margin control and tissue sparing with local disease. For macroscopic regional spread, the standard of care is surgery and RT.

Primary BCCs recur at a rate of 1% with MMS, and as often as 10% with other treatment modalities. Smaller tumors are less likely to recur. Primary SCC recurs at a rate of 2.3%–5.3% with MMS, and 18.7% with other treatment modalities (Rigel et al., 2005).

Close follow-up is important, and follow-up frequency depends on the severity of the tumor(s), the extent of actinic damage, and the frequency and quantity of the development of new cancers and AKs. Highest rates of recurrence occur within five years of treatment; a small number of tumors recur more than five years after treatment (Rigel et al., 2005).

In addition to screening for recurrence, routine follow-up visits are important for detecting new tumors; 42% of SCC metastases occur along with persistence or recurrence of the primary tumor. Between 20% and 33% of patients develop a new BCC within one year of being treated for an initial BCC. Within five years of treating an initial BCC, 45% of patients develop another BCC, and 20% of patients with skin type I or II (see Table 2-1) develop one or more BCCs (Rigel et al., 2005). ■

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