

Basal Cell Carcinoma

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BOX 6-1 Overview

- Basal cell carcinoma (BCC) is a non-melanoma skin cancer and is the most common type of cancer in humans worldwide.
- A combination of environmental factors, phenotype, and genetic predisposition account for the main etiologic causes of BCC.
- The majority of BCC cases are triggered by DNA mutations produced by UV radiation. The most common mutations are seen in the *patched* (*PTCH1*) gene and in the *p53* gene.
- UV-induced inflammation may also play some role.
- Genodermatoses, such as Gorlin's syndrome (basal cell nevus syndrome) and xeroderma pigmentosum (XP), have BCCs appear prominently in their clinical presentations.
- BCCs have many subtypes that include the following: nodular/noduloulcerative, pigmented, superficial, morpheaform (sclerosing or fibrosing), basosquamous/metatypical, infiltrative, micronodular, field-fire, and giant.
- Treatment via surgical means are standard for BCC removal; however, examples of the variety of treatment modalities used today are simple surgical excision, curettage and electrodesiccation, cryosurgery, radiation therapy, Mohs' micrographic surgery, laser surgery, photodynamic therapy, imiquimod, and 5-fluorouracil.
- Taking preventative measures is absolute key in decreasing the incidence of skin cancer around the world. Abstinence from sun exposure is highly recommended but nearly impossible to comply with. Therefore, appropriate application of sunscreen and protective clothing must be enforced.

INTRODUCTION

The incidence of skin cancer has markedly increased over the past few decades. At this time, between 2 and 3 million non-melanoma skin cancers (NMSCs) and approximately 132,000 melanoma skin cancers occur globally each year. Alarming, one in every three cancers diagnosed is a skin cancer. The Skin Cancer Foundation currently estimates

that one in every five Americans will develop skin cancer in their lifetime due to the ever-decreasing ozone layer, increased recreational exposure to the sun, and more histories of blistering sunburns.¹ Basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma are commonly grouped together under the term "skin cancer." BCC and SCC are the two most common cancers that are distinctly labeled as NMSC.² NMSCs are the most common forms of cancer in the United States³ and account for nearly 90% of all skin cancers diagnosed in the world.⁴ They are not only common in the Caucasian population of the United States,³ but also in Australia.⁵ NMSCs are rising at a disturbing rate in most European nations as well;^{6,7} NMSCs have the highest prevalence at regions and countries nearest to the equator.⁴ Out of the NMSCs, BCC is the most frequently occurring cancer.^{1,4,5,8} BCC is described as an abnormal growth of epidermal keratinocytes immediately above the basement membrane⁹ in the form of indolent malignant neoplasm of the hair follicle.¹⁰ This chapter will primarily focus on the epidemiology, pathogenesis, diagnosis, treatment, and prevention of BCC.

EPIDEMIOLOGY

BOX 6-2 Summary

- BCC is the most frequent type of cancer found in humans; an estimated 75% of all diagnosed skin cancers in the United States are BCCs.
- A definite correlation exists between NMSC's incidence and sun exposure, specifically UV radiation.
- The face, head, neck, arms, and back of the hands are most commonly affected by BCCs. The structures of the head that are most susceptible to BCCs include the nose, scalp, eyelids, ears, and lips.
- Patients with light hair, light eyes, freckles, a fair complexion, Celtic ancestry (Scottish, Irish, Welsh), and Fitzpatrick skin types I and II have an increased incidence of NMSCs.
- Besides sun exposure, other known factors also increase the risk of NMSC such as genetic susceptibility, exposure to chemical carcinogens such as arsenic, tobacco, coal-tar, ionized radiation, asphalt, soot, crude paraffin, anthracene, pitch, organic and inorganic solvents, organophosphatic compounds, burns, scars, and chronic ulcerations.

More than 1 million cases of NMSC occur in the United States every year. Approximately 75% of all diagnosed skin cancers in the United States are BCCs.⁸ The incidence of BCC in the United States, Canada, Australia, and Europe increases roughly by 3 to 6% per year.¹¹ Various epidemiological studies demonstrate that there is a definite correlation between NMSC incidence and sun exposure, specifically UV radiation.^{1,2,5,8,11,12} The incidence of skin cancer has been linked to latitude. The regions closer to the equator have a greater prevalence of NMSC.^{4,13} The state of Hawaii reports an annual incidence of BCC four times more than the incidence of mainland United States.¹³ Nearly 80% of all cases of this cancer arise on areas exposed by the sun, such as the face, head, neck, arms, and back of the hands.¹² The structures of the head that are most susceptible to BCC include the scalp, eyelids, ears, nose, and lips.¹¹ In most cases, sun exposure plays a role in the pathogenesis of the carcinoma, but areas on the body not regularly exposed to UV rays may also be affected by BCC.¹³ These startling incidence rates have started to impose an extreme financial burden in many countries,¹⁴ including the United States. Presently in the United States, NMSCs are the fifth most costly cancer for patients.¹⁵

The patient's race and ethnicity are important factors in determining the incidence of skin cancer.⁴ Patients with light hair, light eyes, freckles, a fair complexion, Celtic ancestry (Scottish, Irish, Welsh), and Fitzpatrick skin types I and II have an increased incidence of NMSCs.^{4,16-18} The phenotypes with red⁷ or blonde hair, blue or green eyes, and Fitzpatrick skin type I (patients who burn the fastest and never tan) have the highest incidence of NMSCs.^{19,20} In a large multicenter southern European study, "Helios," a tendency to sunburn, an inability to tan, and a history of sunburn at youth were warning flags for an increased incidence of BCC.²¹ Individuals with a darker skin tone or African, Asian, and Mediterranean ethnic groups have a lower incidence of skin cancer.⁴ Therefore, melanin, the pigment responsible for darker skin coloring, could possibly protect the skin from these types of cancers.^{4,22} Reports of albinism in Africans show that they have an incidence of BCC comparable with white Caucasians, further supporting the role of melanin as a protective agent against skin cancer.⁴

The incidence of NMSC is on the rise, but fortunately the death rates are declining. The mortality estimate from NMSC is extremely low, with a total 5-year survival rate of greater than 95%.¹⁸ The American Cancer Society believes that approximately 1000 to 2000 people die each year from NMSC. Most of these mortalities are in the elderly, immunosuppressed, and untreated people.⁸ In 1991, it was estimated that a 10% reduction in the ozone layer would cause 12 million extra cases of skin cancer along with 200,000 more deaths in the United States by the year 2050.¹⁸ The rule of thumb is that a 10% reduction in the ozone layer thickness will cause an approximate 20% increase in UV radiation and an overwhelming 40% increase in skin cancers. More specifically, for every 1% decrease in total column atmospheric ozone, an increase of 2.7% in NMSCs should be expected. Only a small change in the thickness of ozone layer makes a big impact on the incidence of skin cancer.²³

People with occupational or recreational outdoor sun exposure and those living at latitudes close to the equator have an increased risk of NMSC. The influence of today's society, culture, and fashion has made a deep impact upon incidence rates of skin cancer. For example, the obsession to obtain deep and dark suntans and its association with higher socioeconomic status has driven skin cancer to epidemic proportions.²³ BCC is no longer exclusively associated with the middle-aged or elderly population. Unfortunately, it has now encroached upon younger age groups because of the dangerous and unprotected levels of sun exposure.⁸

For decades, radiation from the sun and elsewhere has been proposed to have damaging effects. Ultraviolet B (UVB) light, which has wavelengths ranging from 290 to 320 nm, creates carcinogenic mutations in the skin that manifest as cancer at an older age. The UVB light impairs and damages the DNA, as well as leads to suppression of the immune system response. This inhibits the body from detecting the damaged genetic material. The altered DNA goes unchecked and eventually leads to cancer.⁴ BCC incidence is highly related to sun exposure. Other known factors also increase the risk of NMSC such as genetic susceptibility, diet, exposure to chemical carcinogens, tobacco, coal-tar, ionized radiation, asphalt, soot, crude paraffin, anthracene, pitch, organic and inorganic solvents, mineral oils, organophosphatic compounds, burns, scars,

and chronic ulcerations.^{4,6,24} Inorganic arsenic has been proven to induce superficial BCC lesions on areas of the body protected from the sun, such as the trunk.^{4,25} Contact with fiberglass dust and dry cleaning agents also increase the chance of BCC.²⁶ The human papillomavirus (HPV) is currently being researched for having a possible role in triggering superficial BCC.¹¹ Lowered immunity states, such as patients with xeroderma pigmentosum (XP), organ transplantation, and HIV, increase the possibility of developing NMSC.⁴ The immunosuppressive state is conducive to an increased cancer rate for two main reasons.²⁷ First, medications and agents used in transplant and seriously ill patients have a certain degree of toxicity, and perhaps may also be mutagenic.^{28,29} Secondly, the immune system is not optimally functioning because of the patient's health status; therefore, the body's natural defenses are inhibited.^{4,30,31}

Primary (previously untreated) BCCs also have a tendency to recur. Nearly two-thirds of BCCs will recur in the following 3 years after treatment. Between the 5th and 10th year after treatment, about 18% of BCCs will return.³² The American Cancer Society has reported that patients with a single basal cell lesion will develop a new skin tumor within the next 5 years.⁸

PATHOGENESIS

BOX 6-3 Summary

- BCC is the indolent malignant neoplasm of the hair follicle and emerges from keratinocyte stem cells in hair follicles, sebaceous glands, or interfollicular basal cells.
- The radiation from the UV rays induces DNA mutations in certain genes within cells, such as the *p53* gene for BCC and SCC and the *patched (PTCH1)* gene for BCC.
- The most frequent UVB-induced alteration seen is the C → T, CC → TT base substitutions at dipyrimidine sites; these dimers have been named UV signatures.
- UV-induced inflammation via COX-2 plays a role in BCC pathogenesis as well as SCC in the skin.
- The most frequent mutation is associated with the *p53* tumor-suppressor gene; UVB irradiation causes direct alteration to the *p53*, which eventually inhibits apoptosis and the development of skin cancer.
- Alterations of *p53* have been found in nearly 56% of human BCC cases.
- Alterations of *PTCH1* have been found in 30 to 40% of sporadic BCCs.

- Two hereditary disorders, Gorlin's syndrome (autosomal dominant) and xeroderma pigmentosum (autosomal recessive), have indications of *PTCH1* gene mutations. The mutation of the *PTCH1* gene inactivates the suppressor function, leading to uncontrolled cell proliferation and tumor formation.

BCC is the most frequent type of cancer found in humans.^{1,5,8,33,34} Usually, BCCs emerge from keratinocyte stem cells, in hair follicles, sebaceous glands, or interfollicular basal cells.^{33,35} Generally, most BCC cases are sporadic, but BCCs may also appear in genetic disorders such as Gorlin's syndrome (basal cell nevus syndrome) and XP.³³ The majority of sporadic cases are induced by sunlight, specifically UVB rays.^{4,34} The radiation from the UV rays induces DNA mutations in certain genes within cells. The genes that undergo the most substantial mutations are the *p53* gene for BCC and SCC and the *patched (PTCH1)* gene for BCC.³³ UV-induced inflammation in the skin contributes to the pathogenesis of BCC as well as SCC. UV-induced inflammation is mediated by increased prostaglandin synthesis mainly through cyclooxygenase-2 (COX)-2. Erythema and inflammation associated with COX-2 can be inhibited by systemic administration of COX-2 inhibitors. Animal studies have shown that these agents have a chemopreventive effect on already ongoing photocarcinogenesis, and reduce the number of BCC and SCCs in mice.³⁶⁻³⁸

The *p53* and *PTCH1* genes are tumor-suppressor genes.³³ The *p53* gene is responsible for encoding a protein that controls the cell cycle and apoptosis.³⁹ The *PTCH1* gene encodes for a receptor in an inhibitory pathway.³⁵ An alteration to these tumor-suppressor genes leads to their inactivation, triggering mutated cell proliferation.³³

The most frequent UVB-induced alteration seen is the C → T, CC → TT base substitutions at dipyrimidine sites. These unique dimers have been titled as the "UV signature" because of their frequency in photodamaged skin.³³ These signatures are commonly seen in lighter skin compared to darker skin because the greater amount of melanin in darker skin leads to better filtering of radiation, which is more protective.³⁴

The mutation associated with the *p53* gene is more frequent in SCC than in BCC in the skin. UVB irradiation causes direct alteration to the *p53* tumor-suppressor gene, which eventually inhibits

apoptosis and the development of skin cancer. There are *p53* mutations in various BCC lesions including the earliest and smallest ones. Alterations of *p53* have been found in nearly 56% of human BCC cases and the “UV signature” is in approximately 65% of these.^{33,40}

The *PTCH1* gene is a human tumor-suppressor gene that was initially discovered as the gene accountable for the onset of Gorlin’s syndrome. Alterations of *PTCH1* have been found in 30 to 40% of sporadic BCCs and the “UV signature” has been found in 41% of these *PTCH1* altered lesions.^{33,35} This gene is located on chromosome 9q22.3 and is responsible for the repression of genes that direct embryonic cell development, growth, and differentiation, such as the *hedgehog* gene. If this gene and its pathway are abnormally activated, it can lead to various types of tumorigenesis, one type being BCC.^{33,34} The *PTCH1* gene encodes for a large transmembrane glycoprotein that is part of a receptor complex with another transmembrane glycoprotein. The latter transmembrane glycoprotein is the product of the *smoothed* gene (*SMO*),^{33,40} which is a seven-transmembrane-domain protein that has a significant role in the *hedgehog* pathway.⁴¹ The glycoprotein receptor complex is actually the main receptor for *hedgehog*’s extracellular signaling molecule. When this complex binds with specific ligands, it initiates a conformational change within the *PTCH1* gene. This change then activates the *smoothed* gene.^{33,40}

PTCH1 inhibits the *smoothed* repressor function.⁴¹ Abnormal activation of *smoothed* results in an unrestrained, continuous transmission of signals into the nucleus. This activates gene transcription regulated by the *GLI* transcription factor family.^{35,41}

Two hereditary disorders, Gorlin’s syndrome and XP, have indications of *PTCH1* gene mutations. The mutation of the *PTCH1* gene inactivates the suppressor function, leading to cell proliferation and tumor formation. Gorlin’s syndrome is an autosomal dominant disorder characterized by keratocysts, skeletal defects, and numerous BCCs. These patients have a germline mutation of *PTCH1*.³³ XP is an autosomal recessive disorder where the person cannot repair UV-mutated DNA due to the genetic absence of that mechanism. These patients have a higher incidence of skin cancer because of the lack of a repairing mechanism. In XP BCCs, a higher amount of UV-induced alterations of the *PTCH1* gene are found compared to that in non-XP patients. There are also many more “UV signatures.” In half of the

XP BCCs, the *PTCH1* gene and the *p53* gene reveal UV-induced alterations. Since only half of the *PTCH1* genes show UV-induced changes, there is a high probability that another cause unrelated to UV radiation may cause *PTCH1* damage and tumorigenesis.^{33,40,42}

Not only is damage inflicted upon the *PTCH1* gene and the *hedgehog* pathway, but downstream targets such as the *Wnt* gene are abnormally activated as well.^{43,44} Once binding of *Wnt* to its receptor (frizzled) occurs, a signaling intermediate (β -catenin) is dephosphorylated.^{43,45} β -Catenin’s dephosphorylation is significant because it allows this newly altered β -catenin to travel to the nucleus and perform as part of a transcription activation complex so other genes can activate.^{43,46} β -Catenin has been under scrutiny for a correlation with BCC because it is actually a molecule that aids in the bonding of actin bundles, structures necessary for epithelial cell-to-cell adhesion.^{43,47} One immunohistochemical study investigated the distribution of β -catenin in the cells of sporadic BCCs via antibodies directed against β -catenin. The study resulted in surprising confirmation that nuclear β -catenin distribution is a feature of BCC. In this study, atopic dermatitis, psoriasis, and SCC did not have nuclear β -catenin localization, further supporting the theory that nuclear β -catenin distribution is unique to BCC pathogenesis.⁴³

Other genes, besides the ones mentioned earlier, are also speculated to have a part in BCC development. *PTCH2*, on chromosome 1p32.1–32.3, is currently under analysis since alterations of this gene have been found in a case of BCC.^{33,48} The biological role of *PTCH2* is still not understood, but it has been hypothesized to take part in the *hedgehog* pathway at a certain level.³⁵ Another target for research are transcription factors, the *Gli 1* and *Gli 2* zinc finger proteins, which are the activators of the *hedgehog* pathway in mammalian cells. These transcription factors’ genetic material are greatly expressed in BCC lesions. Researchers predict that mutations that lead to a high expression of *Gli 1* zinc finger protein in basal cells are more likely to induce BCC.^{35,49} The transcription factor *Gli1* has an activating function specifically for a platelet-derived growth factor receptor, *PDGFR α* . Scientists have found an elevated *PDGFR α* level expressed in BCCs of mice and humans. A theory has been developed that this growth factor and its receptor play an essential role in the mutation mechanism of the *hedgehog* pathway, thus instigating tumorigenesis.⁴¹

Certain gene polymorphisms have been shown to be associated with certain phenotypic features in BCC patients such as young age, multiple lesions, and lesions on the trunk. Glutathione *S*-transferase and cytochrome P450 genotypes are associated with multiple BCCs.^{50,51} Other known associations include vitamin D receptor (*VDR*) genes and tumor necrosis factor alpha (*TNF- α*) microsatellite polymorphisms.^{52,53}

BCC is classified as a nonendocrine tumor of the skin; however, endocrine cell differentiation within BCC tumors has been discovered. Furthermore, BCC is the first classified nonendocrine tumor to present with endocrine cells.^{54,55} The peculiar endocrine cells in BCCs resemble Merkel cells, the only epidermal endocrine cells. Since true Merkel cells are not present in BCC, these non-Merkel endocrine cells in BCC may contribute to its pathogenesis.⁵⁴

DIAGNOSIS

BOX 6-4 Summary

- Nodular/noduloulcerative BCCs are the most common. Look for pearly, waxy papules or nodules with raised or rolled borders and central small ulcers covered with crust in the latter.
- Superficial BCCs occur more on the trunk and extremities than on the head and neck, and affect younger patients more than do nodular BCCs.
- Morpheaform BCCs may appear similar to a scar. They may grow quite extensively. They have high risk of recurrence and microscopic extension.
- Basosquamous/metatypical carcinoma is more aggressive than is typical BCCs. It shows features of both basal and squamous cell carcinomas.
- Pigmented BCCs mimic pigmented nevi, pigmented seborrheic keratosis, and even melanoma.
- Infiltrative BCCs have an opaque whitish yellow color that may blend with the surrounding skin; this clinical presentation is challenging for clinical diagnoses. These, as well as micronodular BCCs, tend to have high recurrence rates.
- Giant BCCs are at least 5 cm in diameter, and can result from recurrent tumors and neglect.
- Nevoid basal cell carcinoma syndrome is an autosomal dominant disorder that has a mutation of the *Patched1* gene on chromosome 9q22.3. They have numerous BCCs, jaw cysts, skeletal abnormalities, ectopic calcification, and palmar and plantar pits.

As with many dermatologic entities, BCCs can be recognized clinically. A discerning eye is necessary when examining a patient's skin. Although these lesions have typical characteristics, the clinical presentations can vary. A definitive diagnosis cannot be established until a biopsy is taken and proven to be a BCC. A shave biopsy is usually adequate for most BCC lesions, such as the nodular and superficial types. However, if an infiltrative or morphoeform-type is suspected, a punch or excisional biopsy should be taken to verify the diagnosis. Unlike SCCs, BCCs do not have a known precursor lesion; instead, they arise *de novo*. Numerous subtypes of BCCs exist and are usually found on hair-bearing skin; they almost never occur on mucous membranes. They are generally seen in adults, although there are reports of BCCs in children. BCCs, in general, metastasize very rarely. Reports have described a metastasis rate between 0.0028⁵⁶ and 0.1%.⁵⁷ Clinically and histologically, numerous forms can be differentiated, and the most common types are described below.

NODULAR/NODULOULCERATIVE BASAL CELL CARCINOMA

BOX 6-5 Summary

- This form is the most common type of BCC and is commonly found on the head and neck regions. Lesions clinically manifest as pink or red papules, have a pearly or waxy appearance, and have telangiectasias.
- Under microscopic examination, nodular/noduloulcerative BCCs are composed of well-defined, smooth-bordered basophilic staining islands of neoplastic cells. Under higher power, the cells have large homogenous, oval, elongated nuclei with scant cytoplasm. The BCC cells have a high nuclear-to-cytoplasmic ratio and lack well-formed intercellular bridges.
- This subtype of BCC is indolent in growth; however, if left untreated for enough time, this tumor can invade critical structures of the head and neck and increase morbidity.

The most common form of BCC is the nodular/noduloulcerative type. These are most frequently found on the head and neck, and account for 62 to 70% of all BCCs.⁵⁸



▲ FIGURE 6-1 Early BCC papule on the nose.

Clinical Presentation

They usually appear as red or pink papules with raised, rolled borders that slowly enlarge (Fig. 6-1). Typically, they are described as having a *pearly, waxy*, or translucent appearance. Telangiectasias are prominent features on the surface of the tumor that can sometimes present with bleeding (Fig. 6-2). Noduloulcerative BCCs have indurated edges and central painless ulcerations that are covered with crust: “rodent ulcers.”

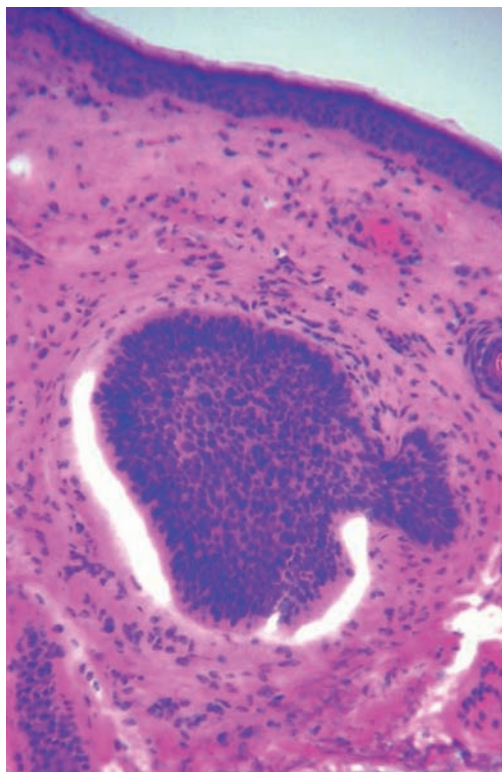
Dermatopathology

Under the microscope with scanning magnification, nodular/noduloulcerative BCC is composed of well-defined, smooth-bordered basophilic staining

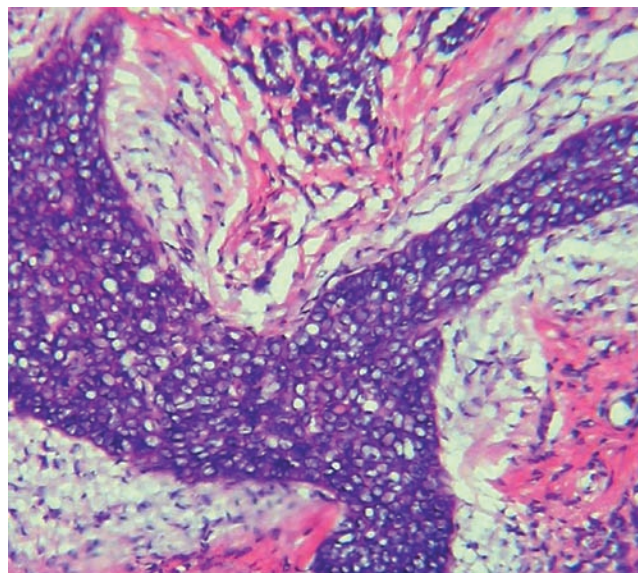
islands of neoplastic cells. BCC islands classically stain much more basophilic than do overlying normal epidermis and normal hair follicle epithelium in H&E-stained sections. These neoplastic islands are made of basaloid cells that show pronounced peripheral palisading of nuclei. Retraction artifacts due to stromal shrinkage in the form of clefts around the tumor islands is a frequent finding^{59,60} (Fig. 6-3). BCCs may arise from normal epidermis, pilosebaceous units, or in conjunction with them (Fig. 6-4). BCC is usually characterized by surrounding stroma with a high content of mucin (Fig. 6-5). Inflammatory response in varying degree usually presents in the surrounding stroma too.



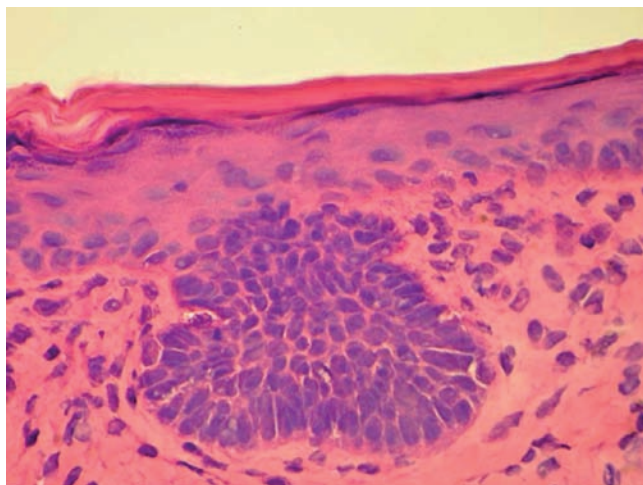
▲ FIGURE 6-2 Typical nodular BCC with rolled borders decorated with prominent telangiectasia.



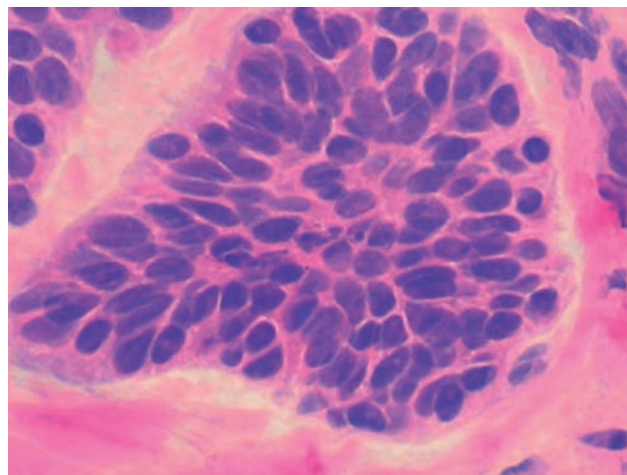
▲ **FIGURE 6-3** Early nodular BCC H&E basophilic nodular BCC tumor island with prominent clefting.



▲ **FIGURE 6-5** BCC with peri tumoral mucinous fibrosis.



▲ **FIGURE 6-4** BCC arising from surface epidermis H&E.



▲ **FIGURE 6-6** BCC with peripheral palisading of the nuclei, basophilic staining neoplastic cells have a high nuclear ratio and show pleomorphism.

In higher magnification, BCC cells have large homogenous, oval, elongated nuclei with scant cytoplasm. These cells have a high nuclear-to-cytoplasmic ratio and are devoid of well-formed intercellular bridges (Fig. 6-6). Even though they are malignant, it is rare for BCC cells to demonstrate atypical mitoses.⁶¹ Necrotic cells and necrosis *en masse* are frequent findings in BCC islands, which the latter reflects itself as ulceration clinically (Fig. 6-7). BCC may show sebaceous, eccrine, apocrine, ductal, glandular, matrical, tricholemmal, squa-

mous, myoepithelial, neuroendocrine, and combined mixed (folliculosebaceous, apocrine/eccrine) differentiations⁶² (Figs. 6-8 to 6-11).

Prognosis

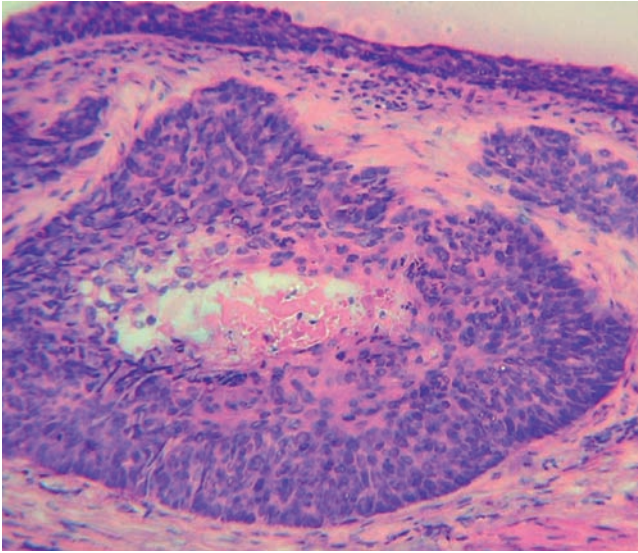
Most nodular BCCs grow at a slow rate and have only limited growth; however, they can invade local structures and cause significant damage. The longer they are allowed to grow, the greater the potential for morbidity and destruction. For example, on the face, nodular BCCs

can invade the nose or eyes to an extent that these structures need to be removed to eradicate the tumor.

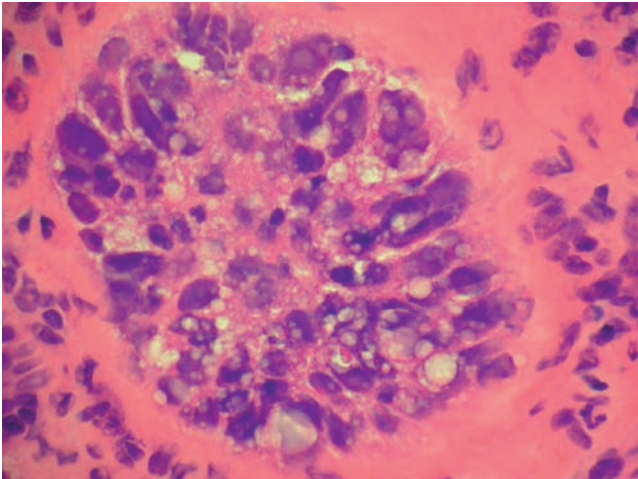
PIGMENTED BASAL CELL CARCINOMA

BOX 6-6 Summary

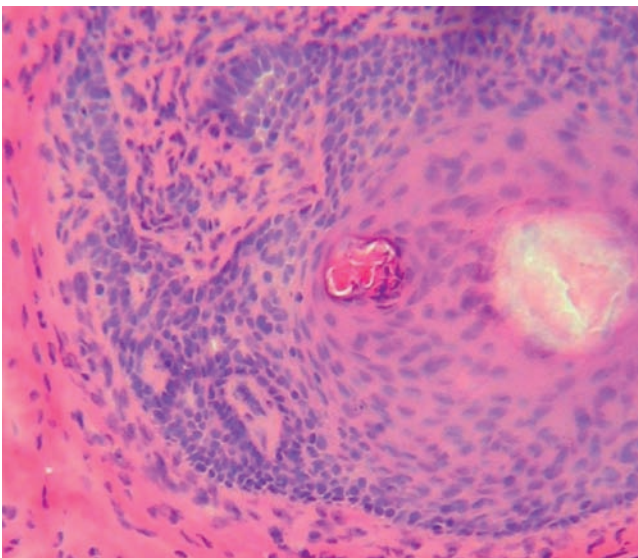
- This form of BCC consists of a brown, black, or gray blue color that can present on the head, neck, trunk, and/or extremities.



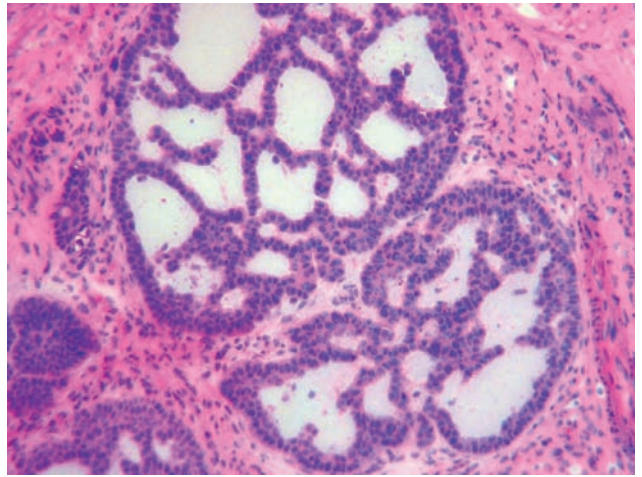
▲ **FIGURE 6-7** BCC on the eyelid with necrosis *en mass*.



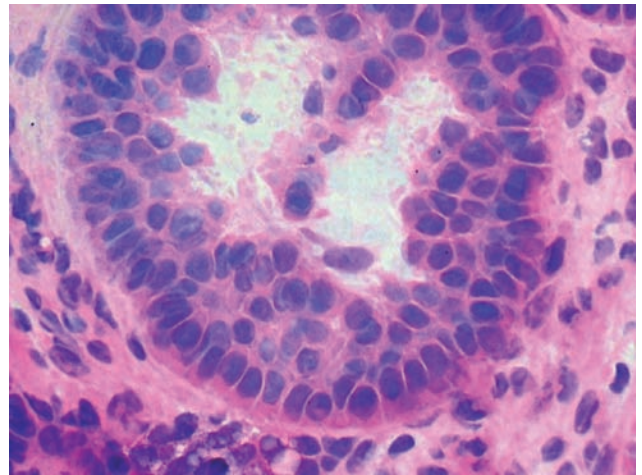
▲ **FIGURE 6-8** BCC with prominent sebaceous differentiation.



▲ **FIGURE 6-9** BCC with squamous differentiation.



▲ **FIGURE 6-10** BCC with glandular differentiation.



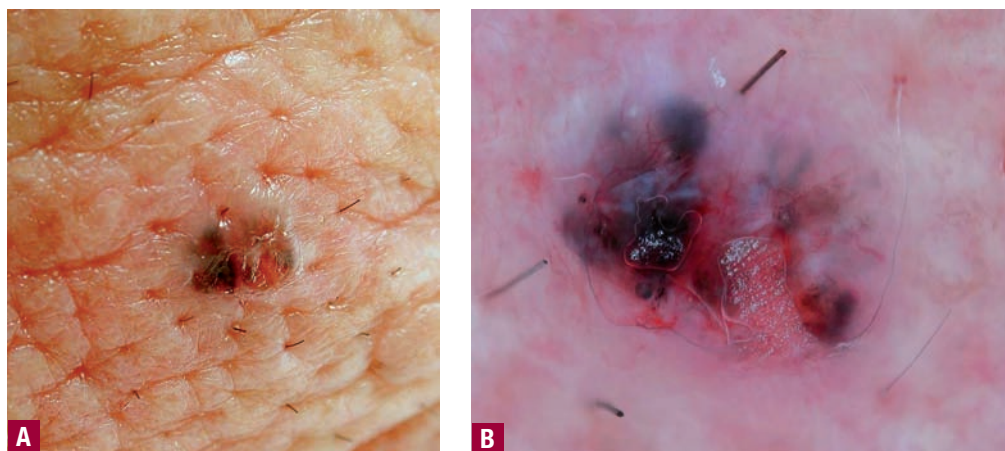
▲ **FIGURE 6-11** BCC with apocrine glandular differentiation.

- Pigmented BCCs can belong to either the nodular/noduloulcerative/micronodular subtype or the superficial multicentric subtype.
- Keep in mind the important differential diagnoses for this type of BCC: pigmented nevi, melanoma, pigmented seborrheic keratosis, and pigmented Bowen's disease.

These BCCs are characterized with brown, black, or grayish blue pigmentation and constitute approximately 6% of all BCCs.

Clinical Presentation

Pigmented BCCs can occur in either nodular/noduloulcerative/micronodular or superficial multicentric clinical types with additional prominent pigmented components (Figs. 6-12 and 6-13). Nodular/noduloulcerative forms frequently are located in the head and neck, whereas the superficial multicentric type can occur often on the trunk and extremities as well. Depending upon the amount and location of melanin present in these lesions, clinical presentation



▲ **FIGURE 6-12** A. Nodular BCC with prominent melanin pigmentation. B. Dermoscopic view of the pigmented nodular BCC.

vary but mostly manifest itself as a pigmented lesion of the skin. Pigmented nevi, melanoma, pigmented seborrheic keratosis, and pigmented Bowen's disease are the most frequent clinical differential diagnoses for such lesions.

Dermoscopy is very helpful in clinical assessment of pigmented BCCs. These lesions are reported to be more often adequately excised with tumor-free margins possibly due to more prominent clinically visible margins secondary to the pigmentation.⁶³

SUPERFICIAL MULTIFOCAL BASAL CELL CARCINOMA

BOX 6-7 Summary

- This subtype of BCC is the second most common and presents more often on the trunk and extremities. Clinically, lesions present as flat, red to pink, scaly patches with ulcerations and/or crusting.
- Under microscopic examination, these BCCs have a single or multiple basophilic staining tumor sheets or buds extending

from the lower part of the epidermis into the papillary dermis.

- These tumors tend to grow laterally and can cause significant damage to local tissue and structures, if not treated.

The second most common form, occurring with a frequency of 9 to 17.5% of all BCCs, is the superficial type.⁵⁸ These lesions are found more on the trunk and extremities compared to nodular BCCs, which are found more often on the face. And patients with superficial BCCs usually present at a younger age than those with nodular types (average age 57.5 vs. 65.5 years, respectively).¹¹

Clinical Presentation

Superficial multifocal BCCs can appear as flat or slightly raised red to pink, scaly,

eczematous patches that can have superficial ulcerations or crusting (Fig. 6-14). The borders can be slightly elevated or rolled. Superficial BCCs can be mistaken for nummular eczema, psoriasis, or Bowen's disease (*SCC in situ*).⁶⁴ This subtype can also present as a pigmented variant with a central brown to black pigmentation from the presence of melanin within the lesion. They initially grow laterally, and can reach substantial sizes. Horizontal growth allows these tumors to extend significantly beyond the clinical borders. As with all BCCs, these lesions are likely to invade local tissues and structures the longer they remain untreated.

Dermatopathology

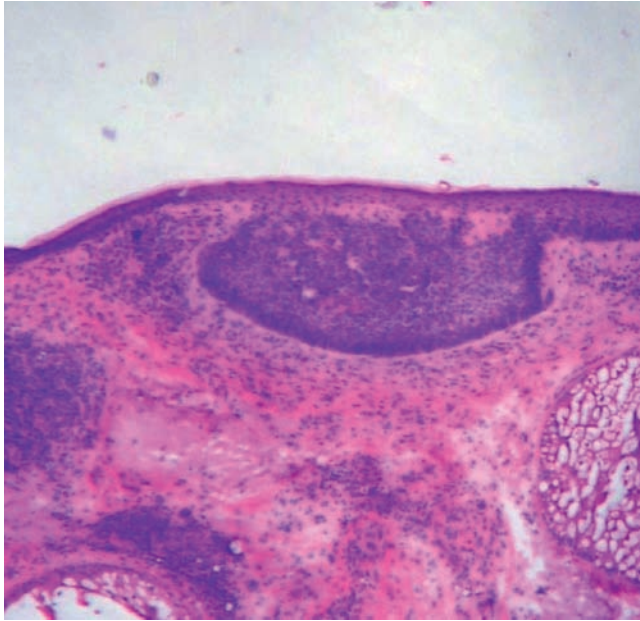
Superficial multifocal BCCs have a single or multiple basophilic staining tumor sheets or buds extending from the lower



▲ **FIGURE 6-13** Pigmented, recurrent infiltrative BCC on the nose.



▲ **FIGURE 6-14** Pigmented superficial multicentric BCC.



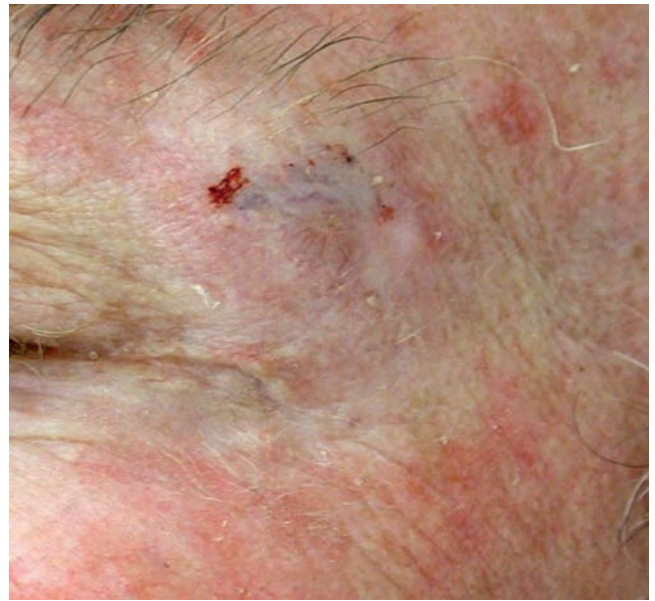
▲ FIGURE 6-15 Superficial multifocal BCC H&E.

part of the epidermis into the papillary (superficial) dermis with pronounced peripheral palisading and spaces of stromal retraction around the neoplastic islands (Fig. 6-15). Superficial BCCs usually do not extend into the deep dermis, and a nonspecific inflammatory infiltrate may be seen in the papillary dermis.⁵⁹⁻⁶¹ Although superficially located, this particular type of BCC needs special attention in diagnosis and treatment, as most of the time the neoplastic islands are discohesive and can be separated by large pieces of normal tissue.

MORPHEAFORM (SCLEROSING OR FIBROSING) BASAL CELL CARCINOMA

BOX 6-8 Summary

- This subtype is not as common and is found on the head and neck region. Morpheaform is also known to be an aggressive type of BCC that is more likely to recur, approximately 60%.
- Morpheaform BCCs present as skin-colored, pink, or white plaques, and may appear as a smooth shiny scar.
- Under the microscope, there is a fibrotic dermis that contains small, linear, and branching collections of tumor cells. It has BCC islands that are not well circumscribed and do not have prominent peripheral palisading of nuclei. Histopathologically, morpheaform BCC cells can reach deep into the dermis.
- Mohs' micrographic surgery is the treatment of choice.



▲ FIGURE 6-16 Morpheaform BCC.

This subtype occurs much less often than do the previous forms, with a frequency of about 2 to 3% of all BCCs diagnosed. They occur mainly on the head and neck.^{58,65} Morpheaform BCCs represent a more aggressive tumor that has a greater tendency to recur. Aggressive behavior in skin cancers has been highly associated with *p53* expression, whereas *Bcl-2* was associated with nonaggressive behavior.⁶⁶

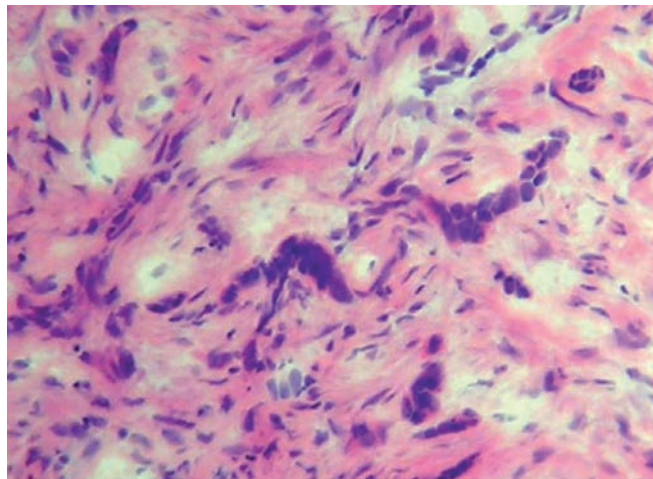
Clinical Presentation

Morpheaform BCC presents clinically as a skin-colored, pink, or white indurated plaque with poorly defined borders. The overall appearance is somewhat shiny and looks like a smooth, firm scar (Fig. 6-16). These lesions are reported to be more frequent on the face in women and may be associated with smoking.⁶⁷ The

underlying tumor may grow quite extensively before the overlying skin begins to ulcerate. Unfortunately, these lesions are often misdiagnosed, leading to greater tumor growth and delayed treatment. The tumor's extension is often underestimated, leading to incomplete excision.

Dermatopathology

Morpheaform BCCs are composed of numerous small cords or clusters of basalioid cells embedded in a dense fibrotic stroma.⁵⁸ The characteristic fibrotic dermis contains small, linear, and branching collections of tumor cells. Unlike the nodular type, morpheaform BCC islands typically are not well circumscribed and do not demonstrate prominent peripheral palisading of nuclei. Morpheaform BCC cells can reach far deeper into the dermis (Fig. 6-17). The lesions can be



▲ FIGURE 6-17 Morpheaform BCC H&E high.

mistaken for other desmoplastic neoplasms such as microcystic adnexal carcinoma and metastatic carcinoma, especially from the breast.^{60,61}

Prognosis

Even though the overall risk is still low, morpheaform BCCs have a greater tendency to be more aggressive and invade into deep layers of the skin more often than do the former subtypes. Recurrence has been reported up to 60% due to frequent microscopic extension beyond the clinical borders.⁵⁹ Since morpheaform BCCs have a higher rate of recurrence and metastasis, Mohs' micrographic surgery (MMS) is the treatment of choice. In general, the larger the tumor size, the greater the subclinical extension and the greater the chance of recurrence.

INFILTRATIVE BASAL CELL CARCINOMA

BOX 6-9 Summary

- Infiltrative BCCs present with an opaque whitish yellow color and blend in with surrounding normal skin.
- BCCs found on embryonic fusion lines are more likely to be the infiltrative subtype.
- Histopathologically, infiltrative BCCs present itself with basophilic staining, and elongated islands and strands of basaloid neoplastic cells with jagged or spiky borders. Usually, the deep or peripheral portions of these neoplasms exhibit more of an infiltrative pattern with no prominent fibrosis in the stroma.
- Mohs' micrographic surgery (MMS) is indicated for these types of tumors and long-term follow-up must be instituted for these patients.

The infiltrative form of BCC is a more aggressive subtype than are some others, and is more likely to recur. The infiltrative subtype can occur solely or more frequently be a component of a mixed-type BCC.

Clinical Presentation

Solely infiltrative BCCs have an opaque whitish yellow color. They do not have a sharp or rolled border; and blend with the normal surrounding skin.⁶⁸ When present as a component of a mixed-type BCC such as nodular, the clinical picture carries both characteristic findings. BCCs on the embryonic fusion lines are reported to be more infiltrative type.



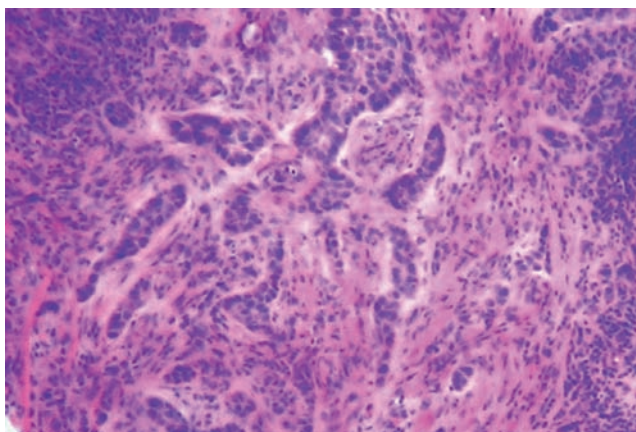
▲ FIGURE 6-18 Infiltrative BCC on inner canthus.

Overall, this type of BCC clinically has less well-defined borders than do nodular types (Fig. 6-18).

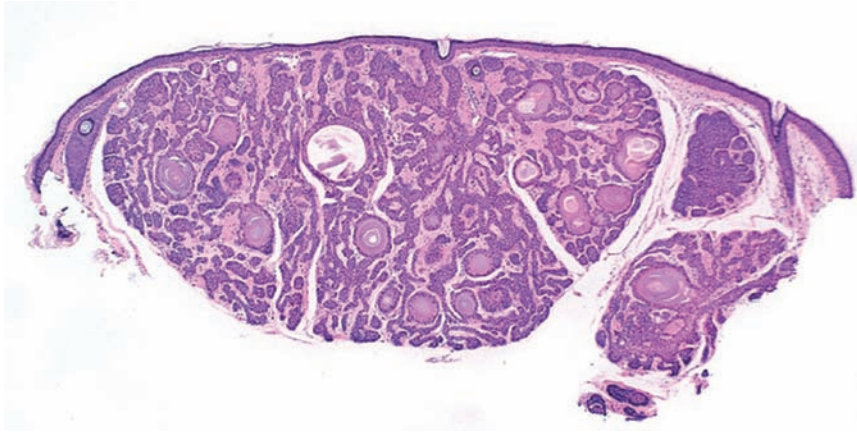
Dermatopathology

In scanning magnification, histopathologically infiltrative BCCs present itself with basophilic staining and elongated islands and strands of basaloid neoplastic cells with jagged or spiky borders. As the neoplastic islands are no longer round or oval, peripheral palisading is also no longer an impressive finding (Fig. 6-19). The neoplastic islands may vary in size and shape, and are also frequently associated with

more nodular, micronodular, or other histological patterns. Generally, the deep or peripheral portions of such neoplasms exhibit more of an infiltrative pattern with no prominent fibrosis in the stroma. This latter finding differentiates infiltrative BCC from morpheaform BCC in which fibrosis in the stroma is an important finding. The surrounding stroma may contain increased acid mucopolysaccharides.⁶⁸ The tumor cells show little cellular differentiation.⁶⁹ Predominant or not, infiltrative growth pattern have to be mentioned in the histopathology report when observed, as implies the high recurrent rate.



▲ FIGURE 6-19 Infiltrative BCC among lymphocytes and coarse collagen bundles.



▲ **FIGURE 6-20** Infundibulocystic BCC H&E.

Prognosis

Infiltrative subtypes tend to show more aggressive behavior than do most of the BCC forms. Also, these tumors have a greater propensity to recur. Following surgical excision, infiltrative BCCs are more likely to have positive margins compared to nodular BCCs. In addition to their infiltrative nature, these neoplasms are usually much larger than they appear clinically. Mohs' micrographic surgery (MMS) is indicated for infiltrative BCCs. Patients should be followed for long-term to gauge any recurrence.^{68,69}

INFUNDIBULOCYSTIC BASAL CELL CARCINOMA

BOX 6-10 Summary

- This subtype was recently categorized as a genuine subtype of BCC and presents as a small, shiny, flesh-colored papule on the head, neck, trunk, and/or extremities. Clinically, this tumor can resemble skin tags.
- Histopathologically, infundibulocystic BCCs have a distinctive combination of follicular differentiation that includes follicular germs and infundibula. With H&E staining, cords and strands of palisading basaloid cells can be demonstrated with scattered infundibular cysts.
- Indolent growth is characteristic of this subtype of BCC; either Mohs' micrographic surgery or nonsurgical treatments are options for therapy.

Infundibulocystic BCC was justified as a true variant of BCC in 1990.⁷⁰ Since then, it has been quite recognized as its own distinct entity and correct identification of this lesion can lead to appropriate treatment and management.

Clinical Presentation

Infundibulocystic BCCs present as small to minute shiny flesh-colored papules on the head, neck, trunk, and extremities of individuals. Ages can vary from adolescents to elderly individuals. In addition, these neoplasms are very slow-growing and may resemble "skin tags."⁷¹

Dermatopathology

It has been reported in the literature that infundibulocystic BCCs have a unique combination of follicular differentiation that includes follicular germs and infundibula.⁷⁰ Under scanning magnification with H&E staining, infundibulocystic BCC demonstrates cords and strands of palisading basaloid cells with few scattered infundibular cysts. Hyperchromasia and rare mitoses may also exist⁷¹ (Fig. 6-20).

Prognosis

Infundibulocystic BCCs grow at a slow pace and are recognized to be a less ag-

gressive subtype.⁷⁰ Treatments such as MMS and nonsurgical management may be successfully used for such neoplasms.⁷¹

GIANT BASAL CELL CARCINOMA

BOX 6-11 Summary

- This subtype of BCC is characterized by its clinical size, diameter of at least 5 cm.
- Tumors appear on the trunk and also have a more aggressive nature.
- Preferred treatment is surgical; however, because of the sheer size, postoperative morbidity needs to be discussed with the patient.

Giant BCCs are defined as tumors of at least 5 cm as their greatest diameter⁷² (Fig. 6-21) and they only make up about 1% of all BCCs.⁷³ These tumors typically appear on the trunk, and display an aggressive behavior, resulting in an increased risk of local recurrence and metastasis.^{74,75} Some of these large tumors are merely the result of neglect,⁷⁶ but others can represent recurrent skin cancers.⁷³ Nonsurgical modalities are relatively ineffective for giant BCCs. However, the surgical operation for an aggressive giant skin cancer may leave the patient with functional loss, major deformity, and serious postoperative complications.⁷²

CONTROVERSIAL ENTITIES

Basosquamous (Metatypical) Carcinoma

BOX 6-12 Summary

- This type of carcinoma has both histopathological features of BCC and



▲ **FIGURE 6-21** Giant BCC on the back, lesion size 5.5 × 4 cm.

SCC; however, it must be noted that this is a controversial category.

- BSC may be even more aggressive than SCC, leading to a higher prevalence of metastasis.
- Clinical presentation can vary from papules to ulcerating tumors and can be found on the head and neck regions.
- Histopathologically, BSC has three components: (1) basaloid components exhibit the features of BCC; (2) cribriform or adenoid growth pattern may be present in this part of the neoplasm as well as Ber EP4 positivity; (3) squamous components show SCC-like features, this part of the neoplasm is expected to be EMA-positive.
- BSCs are likely to recur, have lymph node metastasis, and distant metastasis.
- Mohs' micrographic surgery is indicated for these types of tumors and long-term follow-up must be instituted for these patients to assess for recurrence.

Basosquamous carcinoma (BSC) is reported to constitute approximately 0.4 to 12% of all BCCs.^{77,78} It has also been called basaloid squamous carcinoma, basaloid SCC, and metatypical BCC. Controversy exists as to whether or not this is a unique entity and a form of SCC, or if it is merely a collision of two cancers (BCC and SCC).⁷⁹ The term BSC should be used only to define lesions that bear both typical histopathological features of

BCC and SCC in conjunction with a transitional zone. BCC with keratinization or the cases of simultaneous BCC and SCC on the same site but as two separate neoplasms should not be included into this already not well-defined category.

BSC is reported to have a higher prevalence of metastasis,⁸⁰ even higher than SCCs. In this regard, biological behavior of BSC is much more similar if not more aggressive to SCC rather than to BCC.

True basosquamous/metatypical features in skin neoplasms should be seen as an alarming finding and these lesions are best treated and followed up as carefully as SCCs, in terms of the risk of deep invasion, recurrence, and metastasis.

CLINICAL PRESENTATION These rare tumors occur mostly on the face, neck, and ears.^{78,80} The clinical presentation vary in between flat to slightly raised lesions red papules to large ulcerated tumors⁸⁰ (Fig. 6-22).

DERMATOPATHOLOGY True BSC has three major components: basaloid components exhibit the features of BCC with basaloid, dark staining, well-circumscribed tumor blends that show peripheral palisading and peritumoral clefting. Cribriform or adenoid growth pattern may be present in this part of the neoplasm, as well as Ber EP4 positivity. Squamous components show SCC-like features with larger, lighter stained

cells with a tendency to keratinize consistently with epidermal involvement. This part of the neoplasm is expected to be EMA positive. The intermediate component is the transition zone in between two polar differentiation attempts where the neoplastic cells have neither typical features of BCC nor of SCC but rather in between. Typical strong Ber EP4 or EMA immunostainings diminish in this area. There are cases also associated with undifferentiated spindle cell tumor components that have been reported in the literature^{61,77,81-86} (Fig. 6-23).

PROGNOSIS These tumors have a markedly higher risk for metastases than do BCCs or SCCs alone. BSCs have a propensity for recurrence, lymph node, and distant metastasis,^{78,87} with a metastasis rate reported at 7.4%.⁸⁰ Sentinel lymph node biopsies should be considered for high-risk BSCs that are larger than 2 cm and those with perineural and lymphatic invasion. Predictors of tumor recurrence include male sex, positive surgical margins, lymphatic invasion, and perineural invasion. MMS is appropriate for these tumors and it is important to maintain long-term follow-up to assess for neoplastic recurrence or metastasis.

Micronodular Basal Cell Carcinoma

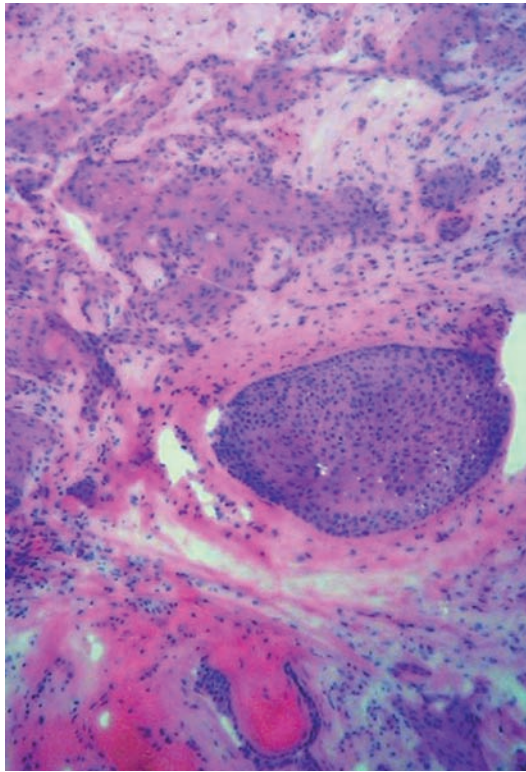
BOX 6-13 Summary

- Micronodular BCCs have a deeper and more subclinical presentation, and therefore, are much larger than they clinically present as.
- Histopathologically, these BCCs have a pattern that consists of round tumor islands less than 0.15 mm in diameter nodules. Also neoplastic islands are present that tend to be round and well circumscribed with peripheral palisading. Retraction spaces may not be as prominent.
- Mohs' micrographic surgery is the treatment modality of choice.



▲ **FIGURE 6-22** Basosquamous carcinoma on the ear helix.

In 1996, the micronodular subtype was reported as a histopathological BCC form that was more difficult to cure than were nodular BCCs, since it was more likely to have positive surgical margins following excision. Micronodular BCC is a histopathological description rather than a distinctive clinical form. Micronodular BCCs may comprise 15% of all BCCs,^{88,89} yet micronodular pattern can also be a component of mixed-type BCC. Micronodular BCCs may have deeper and more subclinical extension



▲ **FIGURE 6-23** Basosquamous Carcinoma H&E.

than do nodular BCCs; therefore, micronodular BCCs are much larger than they appear. Some authors believe that this subtype should deserve the same consideration as the morpheiform and infiltrative forms of BCC.⁸⁹

DERMATOPATHOLOGY Micronodular histopathologic pattern is consistent with round tumor islands less than 0.15 mm in diameter nodules similar to, but smaller than, those in nodular BCC. The neoplastic islands tends to be round, well-circumscribed with peripheral palisading. Retraction spaces may not be as prominent as in nodular BCC. It is not rare to observe two or more types of BCC within one lesion.

PROGNOSIS This type of BCC is reported to be a more difficult form to treat and more prone to recurrence because it tends to stretch beyond its visible clinical borders. The treatment of choice is MMS, because of its ill-defined borders and widespread subclinical extension.⁸⁹

Field Fire Basal Cell Carcinoma

BOX 6-14 Summary

- This type of BCC is a variant of the nodulo-ulcerative subtype and presents as multiple, scarred, crusting, and ulcerating tumors in a single area.

- Lesions extend laterally and can grow to large sizes.
- Incomplete treatment after electrodesiccation and curettage can lead to scarring and recurrence.

Considered a variant of the nodulo-ulcerative type, the “field-fire” BCC presents with multiple tumors in a single area. They appear as a combination of scarring, crusting, and ulceration. These lesions tend to spread laterally and can grow to significant sizes.⁹⁰ This clinical presentation can also be associated with previous and uncompleted treatments of BCCs with modalities such as electrodesiccation and curettage, which lead both to scarring and dis cohesive recurrence.

Fibroepithelioma of Pinkus (FEP)

BOX 6-15 Summary

- These tumors are described as skin-colored, red to pink, smooth, pedunculated nodules on the trunk or extremities.
- Histopathologically, fibroepitheliomas have strands of basophilic tumor cells joining together in a fibrous, edematous stroma reaching from the epidermis into the deep dermis.
- Fibroepithelioma of Pinkus has also been categorized as a fenestrated trichoblastoma rather than as a type of BCC.

CLINICAL PRESENTATION Described by Pinkus in 1953,⁹¹ these lesions are commonly located on the trunk and extremities; fibroepitheliomas can be mistaken for fibromas clinically. They appear as skin-colored red to pink, smooth, pedunculated nodules that are somewhat firm on palpation. FEP is reported to be more common in females and not frequently associated with sun damage.

DERMATOPATHOLOGY Fibroepitheliomas have strands of basophilic tumor cells joining together in a fibrous, edematous stroma reaching from the epidermis into the deep dermis. Hints of follicular bulb and dermal papilla formations can be observed. Bowen et al redefined FEP as a fenestrated trichoblastoma rather than a type of BCC.^{60,92,93}

GENODERMATOSES ASSOCIATED WITH BCC

Nevoid Basal Cell Carcinoma Syndrome (NBCCS)

BOX 6-16 Summary

- NBCCS is an autosomal dominant disorder and is characterized by (1) numerous BCCs at an early age, (2) odontogenic cysts, (3) skeletal abnormalities, (4) ectopic calcification, and (5) palmar/planta pits.
- NBCCS is caused by a mutated *Patched* gene on chromosome 9.
- The most frequent locations for BCCs are on the face, back, and chest. On the face, the BCCs appear around the eyes, on the eyelids, nose, and upper lip.

The nevoid basal cell carcinoma syndrome (NBCCS), also known as basal cell nevus syndrome, Gorlin–Goltz syndrome, and Gorlin’s syndrome, is an autosomal dominant disorder with complete penetrance and variable expression characterized by numerous BCCs. The mutated *Patched* gene is a tumor-suppressor gene found on chromosome 9q22.3. Most are rearrangements that result in the truncation of the *Patched1* (*PTCH1*) protein. Approximately 30% of NBCCS also have mutations in *p53*.⁹⁴ Five features are characteristic of NBCCS⁹⁵:

1. numerous, usually aggressive, BCCs that appear at an early age,
2. jaw (odontogenic) cysts,
3. skeletal abnormalities including the ribs, spine, and skull,
4. ectopic calcification,
5. palmar and plantar pits.

About 0.4% of all BCCs are NBCCS⁹⁶ and 2% of patients under 45 years with BCCs have this syndrome.⁹⁷ NBCCS is estimated to affect nearly 1 in 60,000 people.^{98,99} This condition affects mostly whites, with an equal number of males and females. African Americans typically have many fewer tumors than do Caucasians.¹⁰⁰ The BCCs present in patients between puberty and 35 years, but may occur as early as 2 years of age. The most frequent locations for BCC development are on the face, back, and chest. On the face, the BCCs appear around the eyes, on the eyelids, nose, and upper lip. Milia may be seen among the tumors. The number of tumors may range from only a few to thousands, with sizes from 1 to 10 mm in diameter. Tumor invasion should be suspected when a BCC enlarges or begins to bleed or crust.⁹⁴ Only a few cases of NBCCS have been associated with metastasis; however, it can be associated with other tumors. For example, up to 5% of NBCCS may be associated with medulloblastoma. Patients most affected by medulloblastomas with NBCCS are under 5 years of age. Following radiation treatment, BCCs can become activated and turn progressively invasive within the next 10 years.⁹⁴

Histologically, the carcinomas of NBCCS cannot be distinguished from those of BCCs from patients without the syndrome. Pitting can occur on the hands, feet, or both; it occurs in nearly two-thirds of patients with NBCCS. The pits are from an incomplete lack or total lack of a stratum corneum. These pits can measure 1 to 3 mm deep by 2 to 3 mm in diameter, with some confluent pits even greater in size. Under the microscope, one can see basal cell epitheliomas forming in the epidermis under the pit. These pits are asymptomatic and permanent.⁹⁵

Bazex–Dupr –Christol Syndrome

BOX 6-17 Summary

- This disorder has a dominant inheritance and is linked to Xq24–q27.
- Characteristics of this syndrome are (1) congenital diffuse hypotrichosis, (2) follicular atrophoderma, and (3) basocellular neoforations, including BCCs and basal cell nevi.

Bazex–Dupr –Christol (BDC) syndrome was described by Bazex et al in 1966.¹⁰¹ This disorder is presumed to have dominant inheritance linked to Xq24–q27.⁸⁷

BDC is characterized by congenital hypotrichosis, follicular atrophoderma, and basocellular neoforations, including BCCs and basal cell nevi.¹⁰² Follicular atrophoderma is usually limited to the face, dorsa of the hands and feet, and extensor surfaces of the knees and elbows.¹⁰² Bazex et al originally described the hypotrichosis as diffuse, involving all body parts with hair but without any specific hair shaft abnormality.¹⁰¹ However, patients have been described without hypotrichosis.¹⁰² Microscopically, some hairs demonstrate twisting and trichorrhexis nodosa.¹⁰³

Rombo Syndrome

BOX 6-18 Summary

- Rombo syndrome is hypothesized to be autosomal dominant and is characterized by peripheral vasodilation with cyanosis and follicular atrophy in sun-exposed areas. Manifestations tend to appear between the ages of 7 and 10 years.
- Atrophic skin has a “worm-eaten” appearance termed atrophoderma vermiculatum.
- Histopathologically, irregular elastin patterns with a lymphocytic infiltrate and vascular proliferation is visualized.
- Patients with Rombo syndrome have a greater susceptibility to BCCs, which may develop at about 35 years of age.

Having similarities to the BDC syndrome is the Rombo syndrome. Manifestations of this rare syndrome begin at ages around 7 to 10, with redness in a cyanotic distribution as well as follicular atrophy in sun-exposed areas. Telangiectasias and milia-like papules appear later, and atrophic skin becomes more prominent (some have likened this to a “worm-eaten” appearance called atrophoderma vermiculatum). Patients may also present with vellus hair cysts. Under the microscope, the upper dermis of Rombo syndrome skin demonstrates irregular elastin patterns with a lymphocytic infiltrate and vascular proliferation.¹⁰⁴ These patients have a greater susceptibility to BCCs, which may develop at about 35 years of age. The gene for Rombo syndrome has not been mapped yet, but it may have autosomal dominant inheritance.^{87,104}

TREATMENT

BOX 6-19 Summary

- Surgical excision is one of the most common treatments.

- Excision has a high cure rate for primary BCCs, but has the potential complications of infection and scarring. Excision may require multiple sessions to clear the tumor.
- Curettage and electrodesiccation is another common technique for small (<1 cm), well-demarcated tumors. The C&E cycle is usually performed two to six times; it should not be used for recurrent tumors.
- Cryosurgery lowers the skin's temperature to –50 to –60°C; crystals form within the cell and disrupt the cell membrane. It can be used for single or multiple tumors. Cryosurgery is not advised for aggressive BCCs subtypes.
- Radiation therapy is good for medium-sized tumors in patients of age over 60 years. It is also a good option for patients who are not good surgical candidates or do not want a surgical procedure. Remember the risks of chronic radiodermatitis and the potential for more aggressive cancers to arise at the site of previous irradiation.
- Mohs' micrographic surgery has the advantages of microscopic examination of the clinical borders, as well as being a tissue-sparing technique. It can achieve very high cure rates.
- Mohs' micrographic surgery is the treatment of choice for large tumors (>2 cm), aggressive subtypes (such as morpheiform, basosquamous, micronodular, and infiltrative BCCs), and high-risk anatomic locations.
- Laser surgery and photodynamic therapy have not yet been accepted as primary therapies, but they show promising results in the treatment of BCCs.
- Interferon is a costly method that is a viable nonsurgical alternative, but long-term cure rates are still needed. Interferon can have systemic side effects such as flu-like symptoms, which may decrease patient's compliance.
- Imiquimod recently gained Food and Drug Administration's (FDA) approval for the treatment of superficial BCCs. It is an immune response modifier that promotes a cell-mediated response, and induces the production of numerous cytokines.
- 5-Fluorouracil is a topical chemotherapeutic agent used in low-risk BCCs, especially superficial BCCs. Application-site inflammation, irritation, crusting, and swelling may decrease patient's compliance. It can be used both topically and intralesionally.
- Nonsurgical modalities do not allow for histologic tissue examination.
- Chemoprevention, such as with retinoids and cyclooxygenase inhibitors, is still controversial. More research is needed before this becomes an accepted option.

Once a BCC has been diagnosed, it is time to decide among the various therapeutic options available. Since BCCs can grow to large sizes, invade local tissues and structures, and even metastasize, they almost always need to be treated.¹⁰⁵ When choosing among the numerous modalities, several factors should be considered. Tumor size, location, histologic subtype, morphology, and whether the tumor has invaded any local structures influence the method chosen.¹⁰⁶ Physicians also need to consider a patient's age, health condition, and cosmetic expectations before beginning a procedure. Ideally, a treatment should be cost-effective, convenient, and acceptable to the patient.

Surgical Excision

BOX 6-20 Summary

- Surgical excision is a primary treatment option for NMSC.
- Margins are generally 3 to 6 mm for small and well-delineated BCCs; however, large tumors, clinical extension, rate of growth, and local structures involved need to be considered to merit larger excision margins.
- Surgical defects are repaired with primary closure, flaps, grafts, or are left to heal by secondary intention.
- Surgical excision cure rates range from 90 to 98%.

Surgical excision is one of the primary treatment modalities for NMSC. This option is most appropriate for well-delineated tumors located in less cosmetically sensitive areas such as the extremities. Conventional excision is the method of choice for most physicians when the lesion is less than 2 cm in diameter, is located in a lower risk area such as the trunk or extremities, and is a low-risk subtype such as a nodular or superficial form. The margins required for surgical removal are on the order of 3 to 6 mm for small, well-demarcated BCCs.^{64,107–109} However, this is not a universal rule, as larger tumors, degree of clinical spread, rate of growth, and amount of adjacent skin penetrated may warrant wider margins. Recurrent tumors and those with more aggressive subtypes (i.e., morpheiform, infiltrative, basosquamous, and micronodular) may extend beyond the clinical margins, and therefore, may also require greater surgical margins. Some suggest taking 5 to 10 mm margins for recurrent BCCs.¹⁰⁹

The overall goal of conventional excision is to resect the entire tumor until histologic margins show no residual neo-

plastic cells at the surgical borders. Surgical defects are repaired with primary closure, flaps, or grafts, or are left to heal by secondary intention. Excision can produce good cosmetic results. Excisional wounds tend to heal more quickly than do those after curettage and electrodesiccation or cryosurgery.^{64,110} A further benefit of surgery is the ability to evaluate a lesion histologically (either by frozen or embedded sections) to determine the tumor's subtype and if further treatment is necessary.¹¹¹ Potential drawbacks to conventional surgery include possible infection, scarring, longer procedural time than those of some nonsurgical methods, and more normal tissue removed than with MMS. If margins are still positive after the first surgery, treatment may require multiple sessions.¹⁰⁷

A recent study showed that clinicians might leave positive margins in nearly 16% of patients. Of those still positive, half did not receive any further treatment, which only led to a 3.2% recurrence over 3.6 years. This gives further support to those who believe in a “wait and see” policy.¹¹²

Studies have shown surgical excision to have a very respectable cure rate, typically from 90 to 98%.^{113–115} Overall, in the short term (<5 years), only about 2.8% of primary BCCs recurred after surgical removal. This gives a clearance rate of 97.2%. For the patient, long-term cure rates are most important. At 5 years, clearance rates between 89.9 and 95.2% have been achieved for primary lesions.^{32,116} Proper curettage to better define the BCC's borders prior to excision may increase the cure rate for primary lesions.¹⁰⁹

Previously treated tumors tend to be more difficult to treat. Therefore, there was a higher rate of recurrence found in this group with 11.6% at 5-year follow-up.¹¹⁶ The same study also found that there was a trend toward greater recurrence in men and in aged people. Recurrences at various anatomic sites were compared. BCCs occurring on the head (including the scalp, eyes, periocular area, nose, perinasal area, etc.) had a much higher predilection to recur (6.6%) compared to all other bodily areas such as the neck, trunk, and extremities (0.7%). An evaluation of BCCs on the head revealed a trend toward increasing recurrence rates with increasing BCC diameter.¹¹⁶

A prospective study compared surgical excision with radiotherapy. After 4 years, the surgical group had only 0.7% recurrence, compared to 7.5% with radiotherapy. This is a high cure rate for

excision, and is closer to those reported for MMS. Four years after completing therapy, patients who underwent conventional excision rated their cosmetic outcome higher than those who had radiation.¹¹¹

Curettage and Electrodesiccation

BOX 6-21 Summary

- Curettage and electrodesiccation (C&E) is one of the most commonly used treatment modalities for the removal of BCCs.
- It is appropriate to use this treatment option for small well-demarcated cutaneous tumors. However, this modality is not usually recommended for large-diameter BCCs, aggressive subtypes, or BCC involving high-risk anatomic areas because of the high recurrence rates in these types of situations.
- A C&E wound does not usually require sutures; wounds generally have a satisfactory cosmetic result.

Compared to normal skin, there are significantly fewer desmosomes present in BCC cells. These components are important in mediating cell–cell attachment.^{117, 118} In addition, BCCs have fewer connections to the basement membrane. Hemidesmosomes occupy nearly 45% of the normal basal cell layer, but in BCCs they account only for 7%.¹¹⁹ Therefore, these features allow a curet to separate cancerous cells from the normal surrounding cells in the skin.

Curettage refers to the use of a curet, which has both a blunt and a sharp side for separating and cutting the tumor from the skin. *Electrodesiccation* refers to the use of electrocautery, in which a high-frequency electrical current is directly applied to the tissue. The current obtains hemostasis and may destroy some tumor cells. This modality should be used with caution in patients with pacemakers or implantable cardioverter defibrillators.¹²⁰

The tissue is locally infiltrated with anesthetic prior to the procedure. A sharp curet is essential to properly cut and debulk the tumor. Smaller curets may be used during the initial debulking. The patient's skin should be held taut, to stabilize and hold the operating field firm. During the curetting, the physician should feel a difference between tumor and normal skin. BCCs typically feel soft and easily breakable, but the dermis will feel coarse and more difficult to scrape. The curet begins in the center of the tumor and is scraped in several directions,

continuing throughout the field until the entire area has a gritty feel. Electrocautery is then applied to the entire curetted area. This cycle is typically repeated two to six times in a single visit.¹²⁰

Curettage and electrodesiccation (C&E) is one of the most commonly used treatments for BCCs.¹²¹ It is typically utilized for small (<1 cm), well-delineated cutaneous tumors. This modality may not be appropriate for BCCs with large diameters, aggressive subtypes, or in high-risk anatomic areas such as the mid-face, because of the increased rate of residual tumor and high recurrence rates in these locations.¹²² Also, delicate locations such as the eyelid may not be as amenable to C&E.¹²⁰ C&E does not provide adequate tissue for a histologic examination to ensure that margins are tumor-free.¹¹⁰ Recurrent tumors are not very amenable to C&E, because they are trapped in fibrous tissue. Without the contrast in texture between normal and cancerous cells, curettage of recurrent tumors is difficult.¹²³

C&E is an easy technique to learn; it is cost-effective and convenient.¹²² It can be done rapidly in an outpatient setting and requires only minimal equipment. Also, the C&E wound does not usually disrupt the structure of the underlying dermis or require sutures. Only an experienced physician should perform C&E, as clearance and recurrence rates can vary greatly based on ability.¹²⁴ Recurrence rates also depend on the BCC subtype, anatomic location, and tumor diameter. Subtypes most appropriate for this technique are the superficial and nodular forms.¹²⁰ This procedure usually has a favorable cosmetic result, with minimal scarring and a majority of sites considered to have good or acceptable cosmetic outcomes.^{106,122} However, the wound from this technique may take 4 to 6 weeks to heal—longer than surgical excision. It can also leave a hypopigmented or hypertrophic scar.^{110,125}

C&E achieved a 5-year recurrence rate of 5.7 to 13.2% for primary BCCs; for previously treated (recurrent) BCCs, 18.1% recurred.^{115,122,126} Also, the lesion's diameter is correlated with the chance of recurrence. Generally, the larger the BCC, the greater the recurrence rate. For example, BCCs 0 to 5 mm in diameter had a 5-year 8.5% recurrence rate compared to BCCs with a diameter of 20 mm or more, which had a recurrence rate of 26.1%. In high-risk areas (such as the perinasal, perioral, periocular, and mandibular areas), there was at least a 16.3% recurrence. Fewer BCCs recurred at medium-risk sites (such as the scalp, forehead, and

pre- and postauricular areas) at a rate between 10.7 and 13.4%. Low-risk sites (including the neck, trunk, and extremities) achieved recurrence rates of 9.5% or less with this modality.¹²² Studies have shown that residual BCC may be found histologically in more than one-third of all sites after C&E.^{127,128} The inflammation and proliferative phase of wound healing were not found to have any effect on tumor clearance following C&E, so the exact mechanism of eradication after C&E remains unclear.¹²¹ It is not recommended that C&E be used to treat recurrent BCCs, as this can result in a high recurrence rate of up to 41 to 60%.¹²⁰

There is some controversy over whether C&E may be used to treat BCCs along embryonal fusion lines and in higher risk areas such as the mid-facial region. Some have advocated that this modality is not appropriate for high-risk locations. However, other data supports the possible use of C&E for tumors that are 5 mm in diameter or less. They only had a 4.5% 5-year recurrence rate, compared to those 6 mm and larger, which had a recurrence of 17.6%.¹²²

It seems that all tumors with diameters less than 10 mm in low-risk sites may be treated with C&E. In medium-risk locations, tumors greater than 10 mm should not be cleared with this modality. However, smaller BCCs in these areas can be managed appropriately with this treatment.¹²²

Cryosurgery

BOX 6-22 Summary

- Cryosurgery uses various mechanisms to treat carcinoma by rapidly forming crystals, demonstrating recrystallization patterns as the cells thaw, exposing cells to high electrolyte concentrations in adjacent thawing and nonfrozen fluids, and causing ischemic damage from vascular stasis and destruction.
- Cryosurgery has high cure rates and the overall recurrence rate for primary BCCs is approximately 4.3%.
- Use caution when treating patients with a darker skin tone. This mode of treatment may cause a hyperpigmentation, postinflammatory hypopigmentation, or even a white depigmentation.
- Cryosurgery is a quick, low-cost, and safe treatment option that remains a viable nonsurgical option to treat BCCs.

Cryosurgery employs the use of a cryogen to form an ice ball. Different cryogens are available, including ethyl chloride,

freon, carbon dioxide, and nitrous oxide, but most procedures use liquid nitrogen. This inexpensive cryogen has a boiling point of -196°C and can be readily stored in an insulated container. In an office setting, liquid nitrogen is sprayed from a handheld unit or applied with a cotton-tipped applicator. Numerous nozzles may be used on the handheld unit to change the stream size delivered. Changing the operator's pressure on the applicator controls the freeze depth. Longer durations are associated with a deeper freeze. An ice ball will appear and grow deeper with greater pressure and freezing applied.¹²⁰

Most superficial tumors can be treated with a 10-second freeze, while keeping the BCC frozen and white. The lesion should thaw for approximately 20 to 45 seconds. Cryosurgery should also include a 4 to 6 mm border of normal skin to treat the tumor margins and decrease recurrence.^{120,129} With this quick procedure, typically only two freeze-thaw cycles are required for treatment. As a rule, it is better to freeze quickly and thaw slowly.

Cryosurgery effects tumor clearance through different mechanisms: rapidly forming crystals, recrystallization patterns as the cells thaw, cell exposure to high electrolyte concentrations in adjacent thawing and nonfrozen fluids, and ischemic damage from vascular stasis and destruction. As the skin's temperature is lowered to -50 to -60°C , crystals form within the cell and disrupt the cell membrane.^{120,130}

Cryosurgery is a widely used technique for single or multiple BCCs, but the tumors must be judiciously chosen. Very high-risk BCCs, with aggressive histology or located in critical facial sites, are not appropriate for cryosurgery.¹⁰⁹ Most dermatologists only use cryosurgery for superficial and small nodular BCCs.¹²⁰ High cure rates can be achieved with cryosurgery. The overall recurrence rate for primary BCCs is approximately 4.3%.¹³¹ And on average, recurrent tumors return at a rate 13% after treatment.¹¹⁵ Kuflik¹³² found a cure rate of 94% for primary tumors, and 70% in recurrent BCCs. Another report gave a recurrence rate of 7.6%; notably, this study included morpheiform BCCs.¹³³ Another study of 22 patients with eyelid BCCs saw no recurrences after 5 years, but the authors caution that patient selection was a crucial part of treatment success.¹³⁴ One of the largest studies published the results of 4228 skin cancers (about 92% were BCCs) treated with cryosurgery. With 5-year follow-up, about 97% of the cancers

were cured. Interestingly, most of the recurrences appeared within the first 3 years after therapy.¹³⁵

Cryosurgery can be combined with curettage to achieve a high cure rate on the nose. In one study, a total of 61 BCCs on the nose of at least 10 mm in diameter were first curetted and then treated with cryosurgery. After at least 5 years follow-up, only one tumor recurred. Cryosurgery is typically inadequate to treat lesions on the nose, because this is a high-risk location for recurrence. However, the curettage delineates the tumor's margins and removes the majority of the BCC; the deep freezing eradicates the rest. This technique is not recommended for morpheaform BCCs.¹³⁶

Complications associated with cryosurgery include immediate pain, redness, and edema at the treated site. Throbbing may be felt up to 30 min after the procedure. Within the first day after cryosurgery, the patient may develop a blister, which can be hemorrhagic and scab. Small wounds usually heal within 6 weeks, but it may take 14 weeks or longer for larger wound areas and those found on the trunk or extremities.^{129,130} Caution is required when treating patients with darker colored skin. Cryosurgery may produce a hyperpigmentation, postinflammatory hypopigmentation, or even a white depigmentation, which can be permanent. Infrequently, patients may develop a hypertrophic scar.^{129,137} When using cryosurgery, one must be careful when treating BCCs of the lip, nasal ala, or eyelid because contraction can lead to unfavorable cosmetic results, asymmetry, and free margin retraction.¹²⁹ Nearby structures may be permanently damaged with deep-freezing, such as nerves or the cornea.¹²⁰ Unlike surgical excision, histologic margins are not examined with this method. Overall, cryosurgery is a quick, low-cost, and safe procedure that remains a viable nonsurgical option to clear BCCs.

Radiation Therapy (Radiotherapy)

BOX 6-23 Summary

- Radiation is an appropriate treatment option for patients that are not candidates for surgical procedures or if their skin carcinoma is considered unresectable.
- Recommended locations include facial structures and usually patients are greater than 60 years of age and have medium-to large-sized tumors.
- The most common types of radiation used in dermatologic practices include superficial

X-rays, Grenz rays, contact therapy, supervoltage therapy, electron beam therapy, and radiation from implanted radioactive isotopes.

- Chronic treatment can cause radiodermatitis and cutaneous atrophy.
- Radiation postoperatively should be used in patients with advanced lesions, positive surgical margins, lymph node metastasis, and perineural invasion.

Most BCCs are sensitive to doses of radiation therapy that can be endured by normal surrounding skin.¹³⁸ This modality is indicated for patients who are not candidates for surgery or who have skin cancers deemed unresectable.¹³⁷ Radiotherapy may be appropriate for primary BCCs of the head and neck¹³⁹ as well as for recurrent ones. Most high-risk tumors can be managed with MMS, but this option is not desirable or available to all patients.¹⁴⁰ It has also been recommended for medium-sized tumors in older patients (>60 years of age).¹⁴¹ Suitable locations to consider X-ray radiation include the eyelids, ears, nose, and lips, where surgery could be disfiguring. These areas retain excellent functional and cosmetic results after treatment.^{138,140} Cosmetic outcomes may not be as favorable for tumors of the trunk and extremities.¹³⁸ With higher doses used, there is a greater risk of damaging normal skin and having worse cosmetic results.¹³⁹ The most common types of radiation used in dermatology include superficial X-rays, Grenz rays, contact therapy, supervoltage therapy, electron beam therapy, and radiation from implanted radioactive isotopes.¹³⁸ During irradiation, protect sensitive structures nearby, such as the eye or lacrimal gland. Protective materials used include lead, gold, or tungsten.¹³⁹

When conventional surgery was compared to radiation, surgical excision was preferred for its better cosmetic results and lower recurrence rates.¹¹¹ Radiotherapy is a good option for patients with physical or psychological impairments and can be used concomitantly with most medications. Patients also benefit from this procedure being painless and performed on an outpatient basis without anesthesia. Radiotherapy can be useful for incompletely excised tumors and those inadequately removed by C&E. Some disadvantages of the technique are the inability to histologically examine the treated tissue, potential threat of a radiation-induced malignancy in the future, and possibly increased surgical complica-

tion and difficulties if the radiotherapy is not successful.¹³⁹ Tumors that recur following radiation tend to be more aggressive, invasive, and difficult to treat than are the primary lesions. Side effects include cutaneous atrophy, telangiectasia, and dyspigmentation of the treatment area. Redness, skin necrosis, and hair loss can also be seen.¹²⁹

Contraindications include tumors arising from burns, scars of chronic ulcers, or osteomyelitis scars. Additional radiation treatments should not be performed on skin cancers in the location of chronic radiodermatitis. For patients who are especially prone to developing multiple cancers (i.e., basal cell nevus syndrome, XP, etc.), irradiating the tumors may actually induce new cancer formations.¹³⁸ However, recent evidence suggests that select basal cell nevus syndrome patients may benefit from superficial radiotherapy.¹⁴²

It is important not to forget the danger of chronic radiodermatitis with X-ray therapy. After total therapeutic doses of 40 to 60 Gy, the associated skin can become intensely erythematous while sloughing and oozing. This acute radiodermatitis is generally not painful, and slowly heals in 3 to 6 weeks but can remain noticeable for many years. Radiation therapy can also induce a slow cutaneous atrophy after 3 to 24 months.¹³⁸ This treatment may not be as appropriate for younger patients with the potential decline in cosmetic appearance following treatment.¹³⁹

Radiotherapy should be spread over 2 to 6 weeks for better results. Overall cure rates are usually greater than 90% for primary BCCs.^{138,139,143} Previously treated tumors recur at a rate of approximately 82%.^{139,143} Up to 89% of eyelid, nose, and ear skin cancers can be locally cured.¹⁴⁴⁻¹⁴⁶ The cure rates are comparable with conventional surgery. Radiation can even be used for larger (>2 cm), more clinically advanced tumors with a reported 13% recurrence.¹⁴⁷ Caution is required when treating larger lesions, as the amount of radiation required approaches levels that can harm nearby tissue.¹⁰⁹ But more aggressive forms, like morpheaform BCCs, may still have high recurrences.⁶⁶

Postoperative radiation should be used in patients with advanced lesions, positive surgical margins, lymph node metastasis, and perineural invasion.¹³⁹ Radiation therapy is appropriate for patients who are in poor health, elderly, or have large facial tumors.⁶⁶ X-ray irradiation, when performed properly and with appropriate precautions, can be a safe and efficacious BCC therapy.¹³⁸

Mohs' Micrographic Surgery

BOX 6-24 Summary

- Mohs' micrographic surgery is the treatment modality that has the highest cure rates along with the best tissue conservation and patient's satisfaction record.
- Dr. Frederic E. Mohs developed this surgical technique that currently consists of a fresh-tissue technique with precise microscope-guided excision.
- Mohs' micrographic surgery is indicated for NMSCs and a variety of other rare and aggressive skin lesions.
- Overall Mohs' micrographic surgery 5-year cure rates are greater than 99% and 96% with primary BCC and recurrent BCC, respectively.

Currently, Mohs' micrographic surgery (MMS) is the technique that offers patients the lowest cancer recurrence rates. In addition to its high cure rate, MMS has the highest tissue conservation rate, has a higher patient satisfaction rate, and is a safe procedure that is primarily performed in an outpatient setting.³ Dr. Frederic E. Mohs, who developed the MMS, stumbled upon his technique as a medical student in 1932. Mohs discovered that zinc chloride paste was an ideal way to chemically fix a tumor's architecture *in situ*. The idea of fixation *in situ* combined with microscope-aided excision was the basis of all future improvements in this surgical practice.¹⁴⁸⁻¹⁵⁰

Presently, the majority of MMS is a fresh-tissue technique, which incorporates the use of a local anesthetic (preferably 1% lidocaine solution combined with epinephrine 1:100,000), as opposed to the old fixed-tissue technique that used zinc chloride paste. Mohs also incorporated the use of horizontal tissue sections as opposed to vertical layers or "bread-loading." This method of cutting the tumor lets the surgeon visualize tumor margins more effectively.^{151,152} The tumor must be contiguous for MMS to be completely successful.¹⁵²

MMS is principally used for the treatment of aggressive BCCs and SCCs, but it has successfully treated a variety of other aggressive and rare cutaneous cancers.¹⁵³ Since BCCs are the most common type of skin malignancy in the United States,^{154,155} the majority of MMS cases are for BCC (Table 6-1).^{152,156} Overall MMS 5-year cure rates of greater than 99 and 96% are achieved with primary BCC and recurrent BCC, respectively.^{152,157-159} In contrast, 5-year

Table 6-1
BCC Histologic Subtypes Most Amenable to Mohs' Micrographic Surgery

Morpheaform/sclerosing/fibrosing
Infiltrative
Micronodular
Metatypical/basosquamous

cure rates achieved with other treatment modalities are not as successful.^{152,160,161}

Cure rates rely upon BCC subtype, location, size, and whether the lesion is primary or recurrent (Table 6-2).¹⁵² MMS is indicated for the more aggressive histologic subtypes of BCC, which include morpheaform, infiltrative, micronodular, and basosquamous.^{152,156,162}

Morpheaform BCCs are more likely to have elongations of tumor cells leading to subclinical, silent spread; therefore, MMS is indicated.^{152,156} In a series of 51 morpheaform BCCs, the average length of tumor extension from the clinically apparent cancer was 7.2 mm.¹⁶³ The infiltrative BCCs are capable of deep tumor infiltration, upon rare occasions even leading to perineural invasion. Thus, MMS is indicated for such an aggressive tumor that has the potential to destroy such delicate and essential structures.^{152,156} Micronodular BCCs are found to have significant tumor extensions as opposed to its counterpart, the nodular BCC.⁸⁹ Although superficial BCCs can be successfully treated with traditional surgical excision, these lesions may exhibit extensive subclinical spread^{152,156} with follicular involvement. MMS is indicated in these complicated cases because of its precision with tumor margins and unprecedented tissue conservation.¹⁵⁶

MMS is strongly recommended for the above BCC variants. These aggressive histologic subtypes of BCC are dangerous because they are more likely to have significant silent spread, high recurrence rates, and a potential to metastasize.

Table 6-2
Locations Most Amenable to Mohs' Micrographic Surgery

Nose
Medial and lateral canthi
Preauricular and postauricular areas
Philtrum
Lip
Eyelids
Digits
Anogenital region
Other areas that require ultimate tissue conservation

Laser Surgery

BOX 6-25 Summary

- Laser therapy is a fairly novel option for the treatment of BCC and has not been widely studied.
- Lasers that have been tested are the 585-nm pulsed-dye laser (PDL), the Nd:YAG laser, and the CO₂ laser with inconclusive results.
- Lasers may prove to be effective in the future; however, more clinical studies are warranted to test the efficacy of lasers alone and in combination with other therapies.
- Presently, lasers are still not a well-accepted primary treatment for basal cell carcinomas.

Lasers are used to treat a variety of conditions, such as port-wine stains, hemangiomas, and telangiectasias. They are relatively new options for NMSCs, and have not been widely used in the treatment of BCCs. But they offer the potential benefits of being less invasive than are surgical alternatives, and more selective, affecting only the laser-treated area and sparing surrounding tissues. A 585-nm pulsed-dye laser (PDL) has been attempted, but the recurrence and cure rates were unacceptable in comparison to other more commonly used treatments such as Mohs' or excisional surgery.¹⁶⁴ Operating at 585 nm, this laser selectively targets hemoglobin in vessels. The PDL is a nonablative laser that operates on the theory of selective photothermolysis; this leads to a microvascular thrombosis within the targeted vessel.¹⁶⁵

A small number of patients have been treated with a neodymium:yttrium, aluminum, garnet (Nd:YAG) laser. The Nd:YAG heats the skin to cytotoxic levels above 41 C to kill the cancerous cells. With a 3- to 5-year follow-up, 97.3% of BCCs were cleared; only 1 of the 37 lesions recurred (2.7%).¹⁶⁶

Another laser used is the carbon dioxide (CO₂) laser, which emits infrared light at a wavelength of 10,600 nm. This is an ablative laser that targets water in the skin to create a localized thermal injury. Laser ablation can have significant side effects such as hypertrophic scarring, crusting, bleeding, and dyspigmentation. Another potential drawback is that there is no histologic tissue evaluation after the procedure to assess therapeutic efficacy.¹²⁹ It has been tried in large BCCs and in basal cell nevus syndrome in which surgery was either contraindicated

or undesirable.¹⁶⁷ Some suggest treating superficial BCCs along with a 4-mm border of normal skin. The resulting wound is allowed to heal by second intention.¹⁶⁸

Controversy exists over the efficacy of this modality. A study of 370 superficial BCCs showed that the CO₂ laser combined with curettage achieved complete eradication with no recurrence after an average follow-up period of about 20 months.¹⁶⁹ Another study of 61 BCCs used the CO₂ laser and found a 97% cure rate, with a mean follow-up of 41.7 months.¹⁷⁰ In contrast, when 24 lesions were treated, 50% recurred by the end of the first year.¹⁷¹ Compared to conventional surgery, the CO₂ laser was faster and more cost-efficient.¹⁷² Good candidates for laser surgery include patients with multiple or large BCCs on the trunk or extremities. Basal cell nevus syndrome and immunosuppressed patients may not be candidates for conventional surgery, where removal of every lesion may not be possible. Finally, lasers are a noninvasive method that may appeal to elderly patients with many medications and concomitant afflictions.¹⁷⁰ Lasers may prove to be efficacious in the future, most likely in combination with other therapies. But they are still not well-accepted primary treatments of BCCs.

Photodynamic Therapy (PDT)

BOX 6-26 Summary

- Photodynamic therapy is a treatment option for select patients with BCCs in areas where tissue loss or scarring might be functionally or cosmetically unfavorable.
- Superficial BCCs have the highest cure rate with this treatment modality, approximately reaching 79 to 100%.
- The most successful treatments have been seen in superficial BCCs less than 2-mm thick.

Photodynamic therapy (PDT) utilizes a photosensitizer like 5-aminolevulinic acid (5-ALA) to make the tumor more susceptible when treated with a light source. 5-ALA may be used alone or with a substance such as dimethylsulfoxide to enhance tissue penetration. The methyl ester of 5-ALA, methyl aminolevulinate (MAL), may offer greater permeation into a lesion due to its increased lipophilic nature and its enhanced predilection for neoplastic cells.¹⁷³

5-ALA is a precursor to the photosensitizer protoporphyrin IX (PpIX) in the

heme biosynthetic pathway. When 5-ALA absorbs light, it is converted into PpIX. This generates oxygen singlet species and radicals to induce cell death.¹⁷⁴ Numerous light sources and lasers have been attempted, including UV, blue, and red lights.^{173,175} PpIX has absorptions near 410 and 635 nm. Blue lights do not penetrate deeply enough to be effective, but red light irradiation targets the second peak and effects greater tissue penetration.¹⁷⁶ PDT works because the photoactive derivative, PpIX, accumulates more in the mitochondria of rapidly dividing tumor cells than in the surrounding normal skin cells.¹⁷⁴ The process results in localized tissue destruction, while preserving adjacent tissues. This may be a good option for BCCs in areas where tissue loss or scarring might be functionally or cosmetically unfavorable. Compared to cryotherapy, PDT had a shorter healing time, less scarring, and a superior cosmetic outcome.¹⁷⁷ Elderly patients and others who may not be good surgical candidates or do not desire surgery may consider this noninvasive option. Large areas and multiple tumors, such as in basal cell nevus syndrome, have been treated successfully with ALA-PDT.¹⁷⁸ Side effects include a localized burning or stinging sensation, pain, redness, crusting, and photosensitivity in the days or weeks following treatment. MAL-PDT may be less painful than ALA-PDT.¹⁷⁹

Even though it is convenient and leaves an excellent cosmetic result, the recurrence rates after a single PDT session can be unacceptably high. PDT appears to be more effective in superficial BCCs than in the nodular subtype.¹⁸⁰ Clearance rates typically range from 79 to 100% for superficial BCCs.^{176,181-184} Nodular BCCs, which tend to be thicker and deeper, may not allow the photosensitizer to penetrate as well or reach as deep into the tumor. The response rate is between 10 and 75%, but may improve to 100% after multiple treatments.¹⁸⁴⁻¹⁸⁷ Recurrence rates range from 2 to 43%, with many of the higher recurrences in studies that include nodular and morpheaform BCCs.¹⁷⁶

When MAL-PDT was compared to surgery in nodular BCC eradication, the two methods did not differ significantly. However, the MAL-PDT had better cosmetic outcomes, but did trend toward having a higher recurrence rate.¹⁸⁸ When treating recurrent lesions, PDT cured 82% of previously treated BCCs, although most required multiple treatments.¹⁸⁹

Long-term cure rates for PDT have been disappointing, and treatment may require multiple sessions to increase the clearance rate. This modality may still prove to be a good option for select patients. Since the photosensitizers may have limited penetration and diffusion, BCCs should be of the superficial subtype and less than 2-mm thick to increase the chances of successful tumor treatment. Consider this treatment when patients have large and numerous superficial tumors. PDT is not recommended for the treatment of more aggressive subtypes (i.e., morpheaform, etc.). More studies are needed before PDT becomes a primary treatment. Until then, it will remain an adjunctive addition to the current treatment armamentarium for BCCs.

Interferon

BOX 6-27 Summary

- Treatment with interferon is an adjuvant therapy that can be recommended in certain situations.
- Intralesional treatment is most effective with superficial and nodular BCCs, and clinical improvement may take up to 16 weeks to visualize.
- Interferon treatment may induce side effects such as flu-like symptoms that may lead to decreased patient's compliance.
- This treatment modality is expensive and requires a major time commitment from the patient. As of now, cure rates are not comparable to other established treatment modalities; however, long-term clinical studies are warranted to justify its use as a primary treatment.

Interferons (IFNs) are additional therapies for BCCs. These natural glycoproteins are secreted in response to different inducers, including viral infections. IFN- α induces BCC cells to express FasR. Since FasL is also still expressed, the neoplastic cells are subjected to the FasR/FasL-mediated apoptotic pathway.^{190,191} Intralesional IFN- α generally achieves cure rates between 70 and 100%,¹⁹²⁻¹⁹⁵ and is effective for both nodular and superficial BCCs. Clinical improvement can be seen after about 8 weeks, with the greatest difference at 16 weeks. When the tumor appears cured clinically, this usually correlates with histologic clearance as well.¹⁹⁶ But the cure rate becomes dismal with more aggressive, unresponsive forms such as morpheaform and recurrent tumors. With these tumors, the clear-

ance rate falls to only 27%.¹⁹⁷ A study combining INF- α 2a and INF- α 2b found the combination to be no more effective than each IFN by itself.¹⁹⁸ IFN- β 1a had a similar cure rate at 67%.¹⁹⁹

Side effects of systemic IFN are flu-like symptoms (i.e., fever, headache, fatigue, chills, anorexia, and arthralgias), which may cause decreased patient's compliance.^{174,195} Giving IFN is not only expensive, but also time-consuming since frequent visits are needed for multiple injections. Cure rates are not equivalent to other treatments.

IFN is minimally invasive and does not leave a large scar. If positive margins exist after surgery, IFN has been used successfully to control the remaining neoplasm. It is still an investigational treatment with long-term cure rates lacking. This may be another nonsurgical alternative to contemplate in patients not suitable for surgery.^{109,195}

Imiquimod

BOX 6-28 Summary

- Imiquimod is a recently approved topical immune response modifier for superficial BCCs.
- Patients who are appropriate candidates for this treatment include the elderly, nonsurgical candidates, those with lesions on areas prone to scarring if surgically treated, and patients who do not favor a surgical option.
- This topical medication is approved by Food and Drug Administration (FDA) only for superficial BCCs as large as 2 cm in diameter located on the neck, trunk, or extremities.
- Local side effects of this medication include erythema, hardened skin, edema, vesiculation, erosion, ulceration, scabbing, and flaking. Systemic effects of this medication include headaches, gastrointestinal disturbances, nausea, and vomiting.
- Cure rates for nonaggressive subtypes of BCC have ranged from 60 to 100%.

Previously indicated only for genital and anal warts, in 2004, imiquimod cream gained Food and Drug Administration's approval as a treatment for superficial BCCs. Indications include elderly patients who may not be surgical candidates, superficial BCCs in areas where scarring may be problematic, and for patients who simply do not favor surgery. After using the cream, patients typically experience very little to no scarring. This cream is only approved

for biopsy-proven superficial BCCs up to 2 cm in diameter located on the neck, trunk, or extremities.

Imiquimod is a type of immune response modifier, which promotes a cell-mediated response. Binding to Toll-like receptor-7 on macrophages and dendritic cells induces the production of interferon (IFN)- α , tumor necrosis factor- α , and interleukins 1, 5, 6, 8, 10, and 12. Imiquimod upregulates the body's IFN to remove tumors.^{200,201} The neoplastic cells also become more apoptotic, as imiquimod decreases the expression of Bcl-2.²⁰¹

Even though only approved for superficial BCCs, studies show imiquimod also to be effective for nodular subtypes.²⁰⁰ Cure rates for these nonaggressive subtypes range from 60 to 100%, depending on the dosing schedule and tumor size treated.²⁰¹⁻²⁰⁶ It has been used even in some aggressive forms such as infiltrative BCCs.²⁰¹ Transplant recipients²⁰⁷ as well as patients with basal cell nevus syndrome²⁰⁸ and XP²⁰⁵ have also benefited from this noninvasive therapy.

This medication is not always a benign treatment. It can have systemic effects such as headache, gastrointestinal disturbances, nausea, and vomiting. Local side effects include erythema, hardened skin, edema, vesiculation, erosion, ulceration, scabbing, and flaking. These are generally well tolerated by patients, and do not cause patients to stop therapy.²¹⁰ Even though this modality's cure rates are not as good as destructive methods, this may still be a desirable nonsurgical alternative for some patients. Also, it is generally prescribed for at least 6 weeks, and compliance might be a concern. The local irritation, erythema, other possible side effects, and weeks of therapy must be weighted against a single surgical intervention.

5-Fluorouracil

BOX 6-29 Summary

- 5-Fluorouracil is a topical agent that is used to treat low-risk superficial BCCs, particularly on the face.
- Cure rates have been reported to be 95% with superficial BCCs.
- Application site irritation, inflammation, crusting, and swelling may occur during treatment sessions.

Treatment of BCCs with 5-fluorouracil (5-FU), a topical chemotherapeutic agent, is usually used in cases of low-

risk BCCs (e.g., those not on the nose, ears, and central zone of the face), especially superficial BCCs.¹⁰⁹ However, this compound is not strong enough to eliminate tumors with extensive invasion or involving a patient's follicles. Since this treatment can be easily applied by the patient and spread on relatively large areas, 5-FU can be used for multiple BCCs on the trunk and extremities,¹⁰⁹ but it is not indicated for nodular BCCs.²¹¹ 5-FU is an analog of thymine and inhibits thymidylate synthetase, which disturbs DNA synthesis and leads to cell death. It can cure up to 95% of superficial BCCs.¹²⁹ Results can be improved if the lesion is curetted before starting topical therapy.²¹² The final cosmetic outcome is very good. However, during treatment, patients may experience considerable tenderness as well as application-site irritation, inflammation, crusting, and swelling, which may decrease patients' compliance.¹²⁹

5-FU can also be injected directly into the lesion. This procedure is safe and effective in superficial and nodular BCCs. This may clear 80 to 90% of lesions, which makes it a viable, noninvasive alternative for treatment.²¹³

Chemoprevention (Retinoids and COX-2 Inhibitors)

BOX 6-30 Summary

- Oral retinoids is suggested to be an appropriate chemopreventative agent for patients that are predisposed to multiple NMSCs.
- Studies have shown that retinoids supplementation is connected to reduced and delayed skin carcinoma formation. However, this outcome diminishes over a few months span once supplementation is terminated.
- Topical retinoids, such as tazarotene, may have beneficial effects in treating BCC; however, preliminary results are inconclusive.
- Known side effects of excessive retinoids are osteoporosis, ligament and tendon calcification, and liver abnormalities. Retinoids are also teratogenic during pregnancy, and isotretinoin has a possible link to depression.

Many of the studies performed in chemoprevention of NMSCs have focused on actinic keratoses and SCCs. However, studies are emerging to determine the effects of these compounds on BCCs.

RETINOIDS

Retinoids are derivatives of vitamin A, and are essential to maintaining cellular differentiation. They also play a role in cell growth and apoptosis. When present in physiologic to supra-physiological levels, retinoids can impede the progression of epithelial carcinogenesis. The chemopreventative effect may be exerted at the retinoic acid receptor (RAR) level. Mice models of cancerous skin cells had decreased RAR expression during tumor malignancy progression. Retinoids, at supra-physiological levels, may be able to increase the expression of RARs, and offset the negative tumor-promoting effects.²¹⁴

Oral retinoids (such as acitretin and isotretinoin) may be indicated for those with predilections for multiple NMSCs, such as XP and basal cell nevus syndrome.^{110,215,216} Others include organ-transplant recipients and patients with greatly sun-damaged skin.^{110,215} These supplements have been associated with reduced and delayed tumor formation while taking the drugs, but the favorable effects diminish within months of completing therapy.²¹⁵ However, some studies have found isotretinoin to have no significant effect in the prevention of BCCs when compared to placebo or retinol.^{217,218} In addition, dietary retinoids in 73,000 female nurses and 43,000 male health care professionals failed to show any association between dietary intake and BCC development risk.^{219,220}

Topical retinoids, such as tazarotene, may have beneficial effects in treating BCCs.²²¹ After 24 weeks, 76.7% of superficial and nodular BCCs had regressed by more than half. Of these, 46.7% were completely cleared with no recurrence for 2 years. The antitumor effect was likely from increased apoptosis and increased RAR expression, similar to oral retinoids.²²²

The current evidence does not support the use of retinoids, either natural or synthetic, in the treatment of NMSC. There may be some indications where these substances may be useful, such as in patients with high susceptibility to skin cancer development. But patients should be warned and monitored for signs of adverse events similar to excessive vitamin A intake such as osteoporosis, ligament and tendon calcification, and liver abnormalities.^{223,224} Other potential complications include the known teratogenic risks of retinoids during pregnancy and isotretinoin's possible link to depression.²²⁴

CYCLOOXYGENASE INHIBITORS

BOX 6-31 Summary

- Drugs that are considered to be in this group are aspirin, piroxicam, and indomethacin. These drugs are known as nonsteroidal anti-inflammatory drugs (NSAIDs).
- Selective COX-2 inhibitors, such as celecoxib, have been shown to prevent UV-induced skin cancers in animal models.
- A growing need for an effective and safe chemopreventive agent warrants more long-term clinical trials to justify this agent to be used for chemoprevention.

Cyclooxygenase (COX)-1 and -2 are enzymes involved in the conversion of arachidonic acid to prostaglandins. COX-2 gene expression is increased and even overexpressed in some cancers of the esophagus, stomach, colon, breast, and lung. Drugs such as aspirin, piroxicam, and indomethacin nonselectively inhibit both COX-1 and COX-2 enzymes. Collectively, these medications are known as nonsteroidal anti-inflammatory drugs (NSAIDs).³⁶ Several studies have even shown that regular NSAID usage decreases the risk of death and incidence of breast and colorectal cancers.^{225–229} Selective COX-2 inhibitors like celecoxib are thought to avoid the unwanted gastrointestinal side effects associated with nonselective agents.

Interestingly, COX-2 upregulation may contribute to the promotion and progression of skin cancers.²³⁰ A number of animal models show that use of both selective and nonselective cyclooxygenase inhibitors may be able to prevent UV-induced skin cancers.^{36,231–234} However, it remains to be seen if these results will translate into a treatment and preventative measure for human skin cancer. Also, when using these drugs, remember the possible link between selective COX-2 inhibitors and increased heart disease risk.²³⁵

PREVENTION

BOX 6-32 Summary

- Prevention is the most critical measure one can take to decrease the risk of developing skin cancer.
- Avoid sun exposure between the hours of 10 a.m. and 4 p.m.
- Sunscreen that protects against UVA and UVB rays should be applied liberally everyday.

- Wearing sunscreen, with a protective factor index of at least 30 or higher, may decrease the risk of NMSCs.
- Protective clothing is essential such as long-sleeved shirts, long pants, and wide-brimmed hats.
- Preventative education must be implemented to encourage patients to be proactive against skin cancer.

Prevention is the most critical measure one can take to decrease the risk of developing skin cancer. Avoiding extreme and unnecessary sun exposure is imperative, especially between the hours of 10 a.m. and 4 p.m. when the sun is brightest. Wearing sunscreen, with a protective factor index of at least 30 or higher during the first 18 years of life, may decrease the chance of NMSCs by 78%. Consumers should take care when choosing a sunscreen. Most sunscreens in the past protected only against UVB rays, and UVA protection was rarely included. Presently, sunscreen manufacturers are including protection against both types of rays.^{3,236} UVB is mostly associated with skin cancer. UVA rays are emitted year-round, and cause lines and wrinkles by destroying collagen and elastin in the dermis. UVB rays are most intense during the summer and are the main cause of sunburn.³ Sunscreen and protective clothing are essential. Whenever possible, one should wear long sleeves and long pants while outdoors.^{3,4} Wide-brimmed hats are also advised because they can provide complete coverage of the head, neck, and face.⁴ Even sunscreen incorporated into special clothing has been manufactured for maximum protection. SPF 30 or higher is available in various clothing and accessories.²³⁷ Tanning beds are extremely hazardous and should be avoided at all costs.

Because NMSC is so common, and various treatments can be expensive, it is predicted that the cost to manage BCC is on the rise. Although mortality is not high in NMSC, the frequency of the cancer is a burden upon insurance companies. To reduce financial problems, the public must be educated about skin cancer because it is, for the most part, preventable.¹⁵ Physicians must implement preventative education measures along with routine physical exams. Patients should know how to distinguish skin cancers and be more prudent toward the subject of skin cancer.³ Physicians must insist on a follow-up every 3 to 6 months for the first year after treatment.

Subsequently, 6 months is an adequate interval for a routine checkup. Physicians and patients should note scars that thicken or alter in color or texture. These observations could justify further examination and possibly may prevent a recurrence of the cancer.⁴ With public awareness, liberal use of sunscreens, and protective clothing, the BCC epidemic can be reduced and controlled.

FINAL THOUGHTS

BCC is by far the most common cancer in the world and is the main cause of the skin cancer epidemic we are now facing. Fortunately, the majority of BCC cases are also preventable due to the chief etiologic factor, UV radiation. An ever-increasing amount of evidence, linking the dangers of UV radiation to cancer, is discovered and imposed upon the health care field and the general public. With this evidence in hand, it is the job of physicians to reinforce and educate patients until the message is understood. Many treatment modalities are also becoming available, including topical regimens. It is necessary to explore these newer agents with large clinical trials to prove their efficacy to have them available in the near future for our patients. With new treatment options and preventative measures in hand, the BCC crisis may be finally under control.

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