Basal Cell Carcinoma

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1 Abstract

A basal cell carcinoma (BCC) is a type of skin cancer. BCC is a non-melanoma skin cancer, and is the most common type, 80% of all skin cancer (skin cancer incidence is ¡ 1%) in the UK. BCC are sometimes referred to as 'rodent ulcers'. Basal cell carcinoma (BCC) is a nonmelanocytic skin cancer (ie, an epithelial tumor) that arises from basal cells (ie, small, round cells found in the lower layer of the epidermis). The prognosis for patients with BCC is excellent, but if the disease is allowed to progress, it can cause significant morbidity. This the most common type of skin cancer. About 8 out of 10 skin cancers are basal cell carcinomas (also called basal cell cancers). When seen under a microscope, the cells in these cancers look like cells in the lowest layer of the epidermis, called the basal cell layer.

These cancers usually develop on sun-exposed areas, especially the head and neck. These cancers tend to grow slowly. It's very rare for a basal cell cancer to spread to other parts of the body. But if a basal cell cancer is left untreated, it can grow into nearby areas and invade the bone or other tissues beneath the skin. If not removed completely, basal cell carcinoma can recur (come back) in the same place on the skin. People who have had basal cell skin cancers are also more likely to get new ones in other places.

Basal cell carcinoma (BCC) is the most common skin cancer in humans, yet it accounts for less than 0.1% of patient deaths from cancer. BCC usually appears as a flat, firm, pale area that is small, raised, pink or red, translucent, shiny, and waxy, and the area may bleed following minor injury. Tumor size can vary from a few millimeters to several centimeters in diameter. Basal cells invade the dermis but seldom invade other parts of the body. The deoxyribonucleic acid (DNA) of certain genes is often damaged in patients with BCC; therefore, inheritance may be a factor. Most DNA alterations result from damage caused by exposure to sunlight. (See Pathophysiology.)

Body distribution of BCCs is as follows:

- On the head and neck (most frequently on the face; most common location is the nose, specifically the nasal tip and alae) - 85%
- On the trunk and extremities -15%
- On the penis, vulva, or perianal skin - Infrequent

The anatomic distribution of BCCs correlates with embryonic fusion planes. After adjusting for surface area, BCC occurrence is greater than 4 times more likely on embryonic fusion planes than on other regions of the midface, a finding that supports the possibility of an embryologic role for BCC pathogenesis.

BCC can develop on unexposed areas, and cases of BCC of the prostate have been reported. In some patients, contributing factors are exposure to or contact with arsenic, tar, coal, paraffin, certain types of industrial oil, and radiation. BCC can also be associated with scars (eg, burn complications), xeroderma pigmentosum , previous trauma, vaccinations, or even tattoos.

A skin biopsy (most often a shave biopsy is sufficient) may be necessary to confirm the diagnosis and is often required to determine the histologic subtype of BCC. A punch biopsy may be used to obtain a thick specimen, especially when the clinical suspicion of a BCC is still present after shave biopsy results are negative.

Neglected tumors can continue to grow and lead to significant local destruction and even disfigurement. Surgery, in almost all cases, is the recommended treatment, with treatments varying on the basis of cancer size, depth, and location.

Superficial BCCS have been successfully treated with imiquimod 5% cream, and topical 5-fluorouracil 5% cream may be used to treat small, superficial BCCs. Several studies have shown success in treating small nodular BCCs with imiquimod 5% cream, although this is an off-label indication and patients should be informed of this fact.

2 Introduction

Cancer starts when cells in the body begin to grow out of control. Cells in nearly any part of the body can become cancer cells.

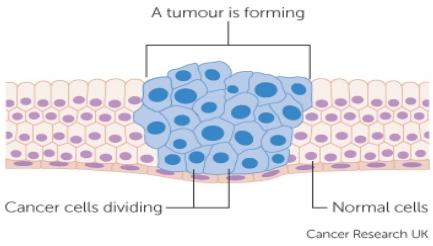
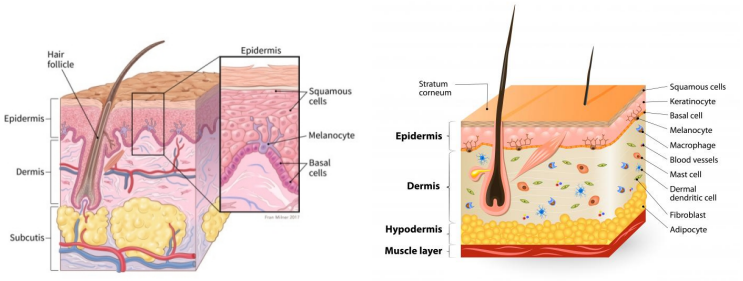


Figure 1: Cancer Cells

There are 3 main types of cells in the top layer of the skin (called the epidermis):

- Squamous cells: These are flat cells in the outer part of the epidermis that are constantly shed as new ones form.
- Basal cells: These cells are in the lower part of the epidermis, called the basal cell layer. These cells constantly divide to form new cells to replace the squamous cells that wear off the skin's surface. As these cells move up in the epidermis, they get flatter, eventually becoming squamous cells.
- Melanocytes: These cells make the brown pigment called melanin, which gives the skin its tan or brown color. Melanin acts as the body's natural sunscreen, protecting the deeper layers of the skin from some of the harmful effects of the sun. For most people, when skin is exposed to the sun, melanocytes make more of the pigment, causing the skin to tan or darken.



(a) (b)

Figure 2: Human Skin

The epidermis is separated from the deeper layers of skin by the basement membrane. When a skin cancer becomes more advanced, it generally grows through this barrier and into the deeper layers.

There are two main types of skin cancer: melanoma and non-melanoma skin cancer. Many people consider skin cancer and melanoma to be synonymous when in fact melanoma is only one form of skin cancer. Melanoma is by far the most aggressive and deadly, and perhaps the most universally known. Melanoma begins in the cells found in the lowest layer of the epidermis referred to as the melanocytes. These cells are responsible for pigment within the skin giving it a brown color. Melanoma most often is found on the skin, even on areas normally not exposed to the sun, and can also start in other parts of the body such as the eyes or mouth. The risk of melanoma increases as people age.

The majority of skin cancer occurrences are non-melanoma with the two most common types being Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC). While they are malignant, they are far less likely to spread to other parts of the body and are more easily treated than melanoma. BCC forms in basal cells found in the middle layer of the epidermis while SCC surfaces in the upper layer in the squamous cells. BCC tends to grow more slowly while SCC has the ability to grow into deeper layers of the skin.

Non-melanoma skin cancers can usually be cured if identified and treated early. “When found early, melanoma is treatable but it is a diagnosis that must be monitored closely for life,” says Dr. Paul S. Dudrick, surgical oncologist with Premier Surgical Associates. “While the risk of recurrence goes down after 5 years, it never completely goes away. Patients must monitor their condition closely and quickly report any changes in skin condition or symptoms that could indicate a tumor.”

3 Pathophysiology

Although the exact etiology of BCC is unknown, a well-established relationship exists between BCC and the pilosebaceous unit, as tumors are most often discovered on hair-bearing areas.

Many believe that BCCs arise from pluripotential cells in the basal layer of the epidermis or follicular structures. These cells form continuously during life and can form hair, sebaceous glands, and apocrine glands. Tumors usually arise from the epidermis and occasionally arise from the outer root sheath of a hair follicle, specifically from hair follicle stem cells residing just below the sebaceous gland duct in an area called the bulge.

3.1 Signaling pathways

The patched/hedgehog intracellular signaling pathway plays a role in both sporadic BCCs and nevoid BCC syndrome (Gorlin syndrome). This pathway influences differentiation of various tissues during fetal development. After embryogenesis, it continues to function in regulation of cell growth and differentiation. Loss of inhibition of this pathway is associated with human malignancy, including BCC.

The hedgehog gene encodes an extracellular protein that binds to a cell membrane receptor complex to start a cascade of cellular events leading to cell proliferation. Of the 3 known human homologues, sonic hedgehog (SHH) protein is the most relevant to BCC. Patched (PTCH) is a protein that is the ligand-binding component of the hedgehog receptor complex in the cell membrane. The other protein member of the receptor complex, smoothened (SMO), is responsible for transducing hedgehog signaling to downstream genes.

When SHH is present, it binds to PTCH, which then releases and activates SMO. SMO signaling is transduced to the nucleus via Gli. When SHH is absent, PTCH binds to and inhibits SMO. Mutations in the PTCH gene prevent it from binding to SMO, simulating the presence of SHH. The unbound SMO and downstream Gli are constitutively activated, thereby allowing hedgehog signaling to proceed unimpeded. The same pathway may also be activated via mutations in the SMO gene, which also allows unregulated signaling of tumor growth.

How these defects cause tumorigenesis is not fully understood, but most BCCs have abnormalities in either PTCH or SMO genes. Some even consider defects in the hedgehog pathway to be requirements for BCC development.

BCC most commonly develops on sun-exposed areas. Zhang et al reported that ultraviolet (UV)-specific nucleotide changes in PTCH, as well as the tumor suppressor gene TP53, are implicated in the development of early-onset BCC.

UV-induced mutations in the TP53 tumor suppressor gene, which resides on band 17p13.1, have been found in some cases of BCC. In addition, frameshift mutations of the BAX gene (BCL2 –associated X protein) have been found in sporadic cases of BCC. A reduction of bcl-2 proteins is observed in the aggressive, infiltrative type of BCC.

3.2 Radiation and immunologic origins

Radiation has proven to be tumorigenic by two mechanisms. The first entails the initiations of prolonged cellular proliferation, thereby increasing the likelihood of transcription errors that can lead to cellular transformation. The second mechanism is direct damage of DNA replication, leading to cellular mutation that may activate proto-oncogenes or deactivate tumor suppressor genes.

Immunologically, the mechanism by which prolonged ultraviolet radiation exposure leads to the development of BCC includes suppression of the cutaneous immune system and immunologic unresponsiveness to cutaneous tumors. This local effect includes a decrease in Langerhans cells, dendritic epidermal T cells, and Thy1+ cells. Furthermore, systemic proliferation of suppressor T cells and the release of immunosuppressive factors (eg, tumor necrosis factor-alpha [TNF-alpha], interleukin 1 [IL-1], prostaglandin [PG], interleukin 10 [IL-10]) are believed to be pathogenic to the development of BCC.

3.3 DNA mismatch repair proteins

DNA mismatch repair (MMR) proteins are a group of proteins that physiologically stimulate G2 cell cycle checkpoint arrest and apoptosis. Failure of MMR proteins to detect induced DNA damage results in the survival of mutating cells. MMR protein levels have been found to be higher in nonmelanoma skin cancers than in normal skin, and there is also some evidence of MMR dysregulation.

4 Etiology

The exact cause of BCC is unknown, but environmental and genetic factors are believed to predispose patients to BCC.

4.1 Radiation exposure

Sunlight, particularly long-term exposure, is the most frequent association with development of BCC; risk correlates with the amount and nature of accumulated exposure, especially during childhood. Patient geographic location affects the risk of developing skin cancer. A latency period of 20-50 years is typical between the time of ultraviolet (UV) damage and BCC clinical onset.

The prevalence of BCC increases in areas of higher altitude and in areas of lower latitude. The incidence of BCC is rising, potentially because of atmospheric changes and the increased popularity of sunbathing.

Radiation exposure that contributes to BCC development may also include tanning booths and UV light therapy. Both short-wavelength UVB radiation (290-320 nm, sunburn rays) and longer wavelength UVA radiation (320-400 nm, tanning rays) contribute to the formation of BCC. UVB is believed to play a greater role in the development of BCC than UVA, however, and is the primary agent responsible for most skin cancer.

UVB and UVC can modify unsaturated chemical bonds of nucleic acids, which may lead to mutations. UVC does not penetrate the atmospheric ozone layer. The UVA spectrum is absorbed by melanin and, through free-radical transfer, affects cellular deoxyribonucleic acid (DNA). Mutations caused by UV radiation typically include cytosine (C) to thymine (T), or CC to TT, translocation. This process can cause activation of oncogenes or inactivation of tumor suppressor genes, leading to tumor initiation and progression.

The skin can repair superficial damage, but the underlying cumulative damage remains, including DNA damage. The damage worsens with each successive sun exposure, causing a lifetime progression.

In a 2012 systematic review and meta-analysis of 12 studies with 9328 cases of non-melanoma skin cancer, Wehner et al found that indoor tanning was associated with a significantly increased risk of both basal and squamous cell skin cancer. The risk was highest among users of indoor tanning before age 25. The authors estimate that the population attributable risk fraction in the United States is 8.2% for squamous cell carcinoma and 3.7% for basal cell carcinoma, corresponding to more than 170,000 cases of non-melanoma skin cancer annually caused by indoor tanning. In another 2012 study of 376 patients with basal cell carcinoma and 390 control patients with minor benign skin conditions, indoor tanning was strongly associated with early-onset basal cell carcinoma, particularly in women.

X-ray and Grenz-ray exposure are also associated with basal cell carcinoma formation.

4.2 Gene mutations

Studies have demonstrated a high incidence of TP53 gene mutations in BCC. Researchers speculate that ultraviolet sunlight may play an important role in the genesis of this mutation; yet, genetic involvement has been demonstrated on chromosome 9 only in patients with familial basal cell nevus syndrome (Gorlin syndrome). Such mutation involves the patched (PTCH) gene, a tumor suppressor gene.

Inappropriate activation of the hedgehog signaling pathway is found in both sporadic and familial cases of BCC. This results in loss-of-function mutations in tumor-suppressor protein patched homologue 1 (PTCH1) and gain-of-function mutations in sonic hedgehog (SHH), smoothened (SMO), and Gli.

4.3 Arsenic exposure through ingestion

Arsenic has been used as a medicinal agent, predominantly the Fowler solution of potassium arsenite, which was used to treat many disorders, including asthma and psoriasis. Historically, a contaminated water source has been the most common source of arsenic ingestion.

4.4 Immunosuppression

A modest increase in the lifetime risk of BCC has been noted in chronically immunosuppressed patients, such as recipients of organ or stem cell transplants and patients with AIDS.

Organ transplant patients must be instructed to limit sun exposure and alerted that skin cancer is a serious problem for them. In fact, immunosuppression and sun damage may cooperate to cause skin cancer. The skin cancer incidence is 10-fold higher in transplant patients than in the general population; up to 65-75% of patients with long-term immunosuppression develop skin cancer. Skin cancers can significantly alter and reduce the transplant recipients' quality of life; some patients may develop more than 100 skin cancers per year.

4.5 Xeroderma pigmentosum

This autosomal recessive disease results in the inability to repair ultraviolet-induced DNA damage. Pigmentary changes are seen early in life, followed by the development of basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. Other features include corneal opacities, eventual blindness, and neurological deficits.

4.6 Epidermodysplastic verruciformis

Epidermodysplastic verruciformis is an autosomal recessive disorder characterized by the development of basal cell carcinoma and squamous cell carcinoma from warts (human papillomavirus infection).

4.7 Nevoid basal cell carcinoma syndrome

In addition to basal cell carcinoma, this autosomal dominant disorder can result in the early formation of multiple odontogenic keratocysts, palmoplantar pitting, intracranial calcification, and rib anomalies. Various tumors such as medulloblastomas, meningioma, fetal rhabdomyoma, and ameloblastoma also can occur.

Odontogenic keratocysts, palmoplantar pitting, intracranial calcification, and rib anomalies may be seen. Mutations in the hedgehog signaling pathway, particularly the patched gene, are causative.

4.8 Bazex syndrome

Features of Bazex syndrome include follicular atrophoderma (so-called ice pick marks, especially on dorsal hands), multiple basal cell carcinomas, and local anhidrosis (decreased or absent sweating).

4.9 Previous nonmelanoma skin cancer

Persons who have been diagnosed with one nonmelanoma skin cancer are at increased risk of developing tumors in the future. The risk of developing new nonmelanoma skin cancers is reported to be 35% at 3 years and 50% at 5 years after an initial skin cancer diagnosis.

4.10 Skin type

Albinism has been implicated in BCC. The Fitzpatrick skin-type scale, which ranges from very fair (skin type I) to very dark (skin type VI), categorizes cutaneous sensitivity to ultraviolet radiation. It is based on the individual's tendency to burn and tan and is a good predictor of relative risk among whites.

4.11 Rombo syndrome

Rombo syndrome is an autosomal dominant condition distinguished by basal cell carcinoma and atrophoderma vermiculatum, trichoepitheliomas, hypotrichosis milia, and peripheral vasodilation with cyanosis.

4.12 Alcohol consumption

A study among adults in the United States reports a strong association between excessive alcohol drinking and higher incidence of sunburn, suggesting a linkage between alcohol consumption and skin cancer.

4.13 Hydrochlorothiazide use

The widely used diuretic hydrochlorothiazide (HCTZ) is a potent photosensitizer. Slightly increased risk for BCC (and dramatically increased risk for

cutaneous squamous cell carcinoma [SCC]) was documented in a case-control study that cross-referenced 71,533 cases of BCC and 8629 cases of SCC from the Danish Cancer Registry with data on cumulative HCTZ exposure in these cases with that country's National Prescription Registry. No association was found between nonmelanoma skin cancer and other antihypertensive drugs. [39]

The study results supported a dose-response relationship between HCTZ use and BCC, as follows :

- High cumulative use of HCTZ (50,000 mg) increased the odds ratios (ORs) of BCC by 1.29.
- Patients with the highest HCTZ exposure (¿200,000 mg) had an OR of 1.54 for BCC.
- The association of BCC with HCTZ use was strongest in younger individuals (age 50 years and younger). In these patients, the OR was 1.91. Overall, the proportion of BCCs attributable to HCTZ use was 0.6%.
- HCTZ showed the strongest association with skin cancers on heavily sun-exposed sites such as the lower limbs (versus the trunk).

5 Epidemiology

The American Cancer Society (ACS) reports skin cancer as being the most common cancer in the United States, with basal cell carcinoma (BCC) constituting the majority of cases. The ACS cites an estimate that about 5.4 million basal and squamous cell skin cancers are diagnosed each year in about 3.3 million persons in the US, with about 80% of those being BCCs. Although the number of these skin cancers has been increasing for years, death from them remains uncommon: non-melanoma skin cancers are estimated to cause about 2000 deaths annually, and that number has been decreasing in recent years.

The estimated lifetime risk for BCC in the white population is 33-39% for men and 23-28% for women. BCC incidence doubles every 25 years.

In states near the equator, such as Hawaii, BCC incidence is approaching three-fold that of states in the Midwest, such as Minnesota. BCC incidence also varies globally. The highest rates of skin cancer occur in South Africa and Australia, areas that receive high amounts of UV radiation. Australia has a trend toward increasing BCC incidence, while Finland has a low reported incidence that is approximately one quarter that in Minnesota; BCC incidence in Finland also appears to be increasing, however, especially among young women.

BCC is the least likely cancer to metastasize. BCC differs from squamous cell carcinoma, which accounts for 16% of skin cancers and is more life-threatening.

5.1 Race

Although BCC is observed in people of all races and skin types, dark-skinned individuals are rarely affected, and it is most often found in light-skinned individuals (type 1 or type 2 skin). Those with type 1 skin are very fair and have red or blond hair and freckles; these individuals always burn and never tan. Those with type 2 skin are fair and burn easily while tanning minimally. Whites of Celtic ancestry have the highest risk for BCC. Incidence is low in blacks, Asians, and Hispanics.

5.2 Sex

Historically, men are affected twice as often as women. The higher incidence in men is probably due to increased recreational and occupational exposure to the sun, although these differences are becoming less significant with changes in lifestyle. The current male-to-female ratio is approximately 2.1:1.

For tumors involving the periocular skin, Cook et al reported the incidence of BCC to be equal in men and women. In addition, this investigative team found that the age-adjusted incidence rates for all malignant tumors of the eyelid in men and women, respectively, were 19.6 cases and 13.3 cases per 100,000 population per year. The age-adjusted incidence rates for BCC of the eyelid for men and women, respectively, were 16.9 and 12.4 cases per 100,000 population per year.

5.3 Age

The likelihood of developing BCC increases with age. Data indicate that BCC incidence is far higher (more than 100-fold) in persons aged 55-70 years than in those aged 20 years and younger. Patients 50-80 years of age are affected most often. The median age at diagnosis is 67 years and the mean age is 64 years.

Nevertheless, BCC can develop in teenagers and now appears frequently in fair-skinned patients aged 30-50 years. Approximately 5% to 15% of cases of BCC occur in patients aged 20- 40 years. Aggressive-growth types of BCC are more frequently noted in patients younger than 35 years than in older individuals.

Zhang et al reported an inverse association between body mass index (BMI) and onset of BCC before age 40 years. The multivariate odds ratio for early-onset BCC in obese versus normal individuals was 0.43 for adult BMI and 0.54 for BMI at age 18.

6 Prognosis

The prognosis for patients with BCC is excellent, with a 100% survival rate for cases that have not spread to other sites. Nevertheless, if BCC is allowed to progress, it can result in significant morbidity, and cosmetic disfigurement is not uncommon.

Typically, basal cell tumors enlarge slowly and relentlessly and tend to be locally destructive. Periorbital tumors can invade the orbit, leading to blindness, if diagnosis and treatment are delayed. BCC arising in the medial canthus tends to be deep and invasive and more difficult to manage; this type of BCC can result in perineural extension and loss of nerve function.

Although BCC is a malignant neoplasm, it rarely metastasizes. The incidence of metastatic BCC is estimated to be less than 0.1%. The most common sites of metastasis are the lymph nodes, lungs, and bones.

Although treatment is curative in more than 95% of cases, BCC may recur, especially in the first year, or develop in new sites. Therefore, regular skin screenings are recommended.

6.1 Recurrence

The 5-year recurrence rate is about 5%, but it depends on the histologic subtype and type of treatment; the recurrence rate is less than 1% for primary (previously untreated) BCCs treated with Mohs micrographic surgery. Most reports show that the distance to the closest resection margin is an important predictor of recurrence.

The following is a itemize of treatments and their 5-year recurrence rates for primary (previously untreated) BCCs:

- Surgical excision - 10.1%
- Radiation therapy - 8.7%
- Curettage and electrodesiccation - 7.7%
- Cryotherapy - 7.5%
- All non-Mohs modalities - 8.7%
- Mohs micrographic surgery - 1%

These rates are probably affected by the fact that clinicians use cryotherapy, curettage, and desiccation mostly on smaller and better-demarcated lesions.

Pieh et al reported a recurrence rate of 5.36% after the first excision of the tumor; the rate increased to 14.7% after the second operation, and the rate reached 50% after the third and fourth operations. The highest recurrence, approximately 60%, was seen with lesions arising from the medial canthus. Recurrences usually occur 4-12 months after initial treatment. One meta-analysis

found that the 3-year cumulative risk of devloping a second BCC after an index BCC is about 44%, which is a 10-fold increase over that of the general population. Tumors on the nose or T-zone of the face have a higher incidence of recurrence. Recurrence is most common on the nose and nasolabial fold, but this observation may be secondary to lack of adequate margins obtained in these areas. Infiltrative, micronodular, and multifocal types are more likely than nodular types to recur.

A recurrence of BCC should be suspected when one of the following conditions occurs:

- Nonhealing ulceration
- Tissue destruction
- Scar that becomes red, scaled, or crusted or enlarges with large adjacent telangiectasia
- Scar that slowly enlarges over time (months)
- Development of papule/nodule within a scar

Histologic types of BCC at higher risk for recurrence include morpheaform (sclerotic), micronodular, infiltrative, and superficial (multicentric). Other conditions that contribute to a higher recurrence rate include recurrent tumors that have been treated previously, large tumors (¿2 cm), and deeply infiltrating tumors.

7 Patient Education

Adequate patient education is essential in the prevention of recurrence and spread of basal cell carcinoma. Patients should avoid possible potentiating factors (eg, sun exposure, ionizing radiation, arsenic ingestion, tanning beds). The regular use of sun-protecting clothing (eg, wide-brimmed hat, long-sleeved shirts, sunglasses with ultraviolet [UV] protection) is recommended when outdoors.

Instruct patients to avoid sun exposure particularly during the middle of the day (ie, 11 am to 3 pm), which is the most dangerous time. Also, the sun's rays are especially intense in sunny climates and at high altitudes, and UV radiation can also pass through clouds and water. Patients should be instructed to be careful on the beach and in the snow because sand, water, and snow reflect sunlight and increase the amount of received UV radiation.

During the initial consultation, the patient should be counseled regarding the extent of resection, type of reconstructive procedure, and attendant morbidity. High importance should be attached to adequately preparing the patient regarding the cosmetic and functional result of treatment. During posttreatment follow-up, the patient should be counseled regarding sunlight exposure and the risk of developing additional primary skin tumors.

7.1 Sunscreen

Regular application and reapplication of sunscreen is recommended prior to sun exposure. People who use sunscreens have a 40% reduction in skin cancer incidence versus nonusers.

Note that the sun protection factor (SPF) ratings of sunscreens correspond to the number of minutes required to get the equivalent of 1 minute of unprotected UVB exposure; thus, correctly applied SPF 30 sunscreen permits the equivalent of 1 minute of UVB rays for each 30 minutes spent in the sun. The Centers for Disease Control and Prevention (CDC) recommends use of a sunscreen with an SPF rating of at least 15, [52] while the American Academy of Dermatology (AAD) advises use of a sunscreen with an SPF rating of at least 30. [53] Both organization recommend use of a broad spectrum sunscreen, which will also provide protection against UVA radiation.

Emphasize also that sunscreens must be applied generously, 20-30 minutes before going outside, and reapplied about every 2 hours, more often if swimming or sweating; the AAD recommends use of water resistant sunscreen, which maintains its SPF for 40 minutes of immersion (or, in the case of "very water resistant products, for 80 minutes). For lip protection, a lip balm with an SPF of 15 or higher should be applied.

Instruct parents to protect their children's skin with sunscreen or protective clothing to reduce the risk of BCC later in life. It has been estimated that intensive sun protection before age 18 years can reduce nonmelanoma skin cancer by 78%.

Advise parents not to expose children younger than 12 months to direct sunlight and to cover up children aged 12-24 months with a hat, shirt, and a small amount of sunscreen on the remaining exposed areas. Similarly, for children older than 2 years, instruct parents to consider using sunscreens, covering the child's skin with clothing, and, when possible, restricting the child to shaded areas.

7.2 Self-examination for skin changes

Educate patients on how to recognize any unexplained changes in their skin, especially changes that last for more than 3-4 weeks. Also, educate patients on how to examine their own skin. The knowledge of mole distribution on the skin is helpful.

Tell the patient to first look at the front and back of his or her body in a full-length mirror, using a hand mirror. The patient also should use the hand mirror to look at the back of the neck and scalp, the back, and the breeches. The patient then should turn and look at each side of the body with the arms raised. Next, the patient should bend the elbows and look carefully at the forearms, the back of the upper arms, and the palms. Instruct the patient to sit down and check the backs of the legs and feet, including the spaces between the toes and bottoms of the feet.

The American Cancer Society recommends a dermatologic examination every 3 years for people aged 20-40 years and every year for people older than 40 years.

8 Diagnosis

Given that BCC rarely metastasizes, laboratory and imaging studies are not commonly clinically indicated in patients presenting with localized lesions. Imaging studies may be necessary when involvement of deeper structures, such as bone, is clinically suspected. In such cases, computed tomography scans or radiography can be used.

8.1 Biopsy

Types of skin biopsy that may be used to confirm the diagnosis and determine the histologic subtype of BCC include the following:

- Shave biopsy: Most often, the only biopsy that is required
- Punch biopsy: May be indicated in the case of a pigmented lesion if there is difficulty distinguishing between pigmented BCC and melanoma; ensures that the depth of the lesion can be determined if it proves to be a malignant melanoma

8.2 Histology

Histologically, BCC is divided into the following 2 categories:

- Undifferentiated: When there is little or no differentiation, the carcinoma is referred to as solid BCC; this form includes pigmented BCC, superficial BCC, sclerosing BCC, and infiltrative BCC (a histologic subtype)
- Differentiated: Differentiated BCC often has slight differentiation toward hair (keratotic BCC), sebaceous glands (BCC with sebaceous differentiation), and tubular glands (adenoid BCC); noduloulcerative (nodular) BCC is usually differentiated

9 Management

9.1 Surgery

In nearly all cases of BCC, surgery is the recommended treatment modality. Techniques used include the following:

- Electrodesiccation and curettage
- Excisional surgery
- Mohs micrographically controlled surgery
- Cryosurgery

9.2 Radiation therapy

BCCs are usually radiosensitive; radiation therapy (RT) can be used in patients with advanced and extended lesions, as well as in those for whom surgery is not suitable. Postoperative radiation can also be a useful adjunct when patients have aggressive tumors that were treated surgically or when surgery has failed to clear the margins of the tumor.

9.3 Photodynamic therapy

Photodynamic therapy (PDT) as an adjunct is a reasonable choice in the following cases:

- Tumor recurrence with tissue atrophy and scar formation
- Elderly patients or patients with medical conditions preventing extensive oculoplastic reconstructive surgery
- Tumor with poorly defined borders based on clinical examination
- Tumor requiring difficult or extensive oculoplastic surgery

9.4 Pharmacologic therapy

Topical agents used in the treatment of superficial BCC include the following:

- Topical 5-fluorouracil 5%: May be used to treat small, superficial BCCs in low-risk areas
- Imiquimod: Approved by the US Food and Drug Administration (FDA) for the treatment of nonfacial superficial BCC
- Tazarotene: Can also be used to treat small, low-risk BCCs
- Oral agents approved by the FDA for advanced forms of BCC include the following Hedgehog pathway inhibitors:

1. Vismodegib (Erivedge)
2. Sonidegib (Odomzo)

10 History

Patients presenting with basal cell carcinoma (BCC) often report a slowly enlarging lesion that does not heal and that bleeds when traumatized. As tumors most commonly occur on the face, patients often give a history of an acne bump that occasionally bleeds.

People who sunburn are more likely to develop skin cancer than those who do not; however, sunlight damages the skin with or without sunburn. Consider BCC in any patient with a history of a sore or skin anomaly that does not heal within 3-4 weeks and occurs on sun-exposed skin, especially if it is dimpled in the middle. These tumors may take many months or years to reach even 1 cm in diameter.

Patients often have a history of chronic sun exposure, including recreational sun exposure (eg, sunbathing, outdoor sports, fishing, boating) and occupational sun exposure (eg, farming, construction).

History of any prior treatment to the index tumor should be elicited, as well as history of any prior non-melanoma skin cancer. In patients with recurrent tumors, deeper invasion should be expected. Recurrence following radiation therapy is often biologically more aggressive.

Occasionally, patients have a history of exposure to ionizing radiation. X-ray therapy for acne was commonly used until 1950. Though not common, patients may have a history of arsenic intake; arsenic is found in well water in some parts of the United States.

11 Physical Examination

Characteristic features of BCC tumors include the following:

- Waxy papules with central depression
- Pearly appearance
- Erosion or ulceration, often central
- Bleeding, especially when traumatized
- Crusting
- Rolled (raised) bordery
- Translucenc
- Telangiectases over the surface
- Slow growing (0.5 cm in 1-2 y)

Basal cell carcinoma occurs mostly on the face, head (scalp included), neck, and hands. It rarely develops on the palms and soles. BCC usually appears as a flat, firm, pale area that is small, raised, pink or red, translucent, shiny, and waxy, and the area may bleed following minor injury. BCCs may have one or more visible and irregular blood vessels, an ulcerative area in the center that often is pigmented, and black-blue or brown areas. Large BCCs may have oozing or crusted areas. The lesion grows slowly, is not painful, and does not itch.

Periocular tumors most commonly involve the lower eyelid (48.9-72.1%), followed by the medial canthus (25-30%), the upper eyelid (15%), and the lateral canthus (5%).

Though a literature review showed all authors agreed that periocular BCC most commonly occurs in the lower eyelid, the remaining anatomical locations and the incidence of occurrence differ among the studies.

Younger patients (¡ 40 y) may have a lower prevalence of BCC on the head and neck and a higher prevalence on the trunk, with greater tendency to superficial BCC, than in older patients. [54] Childhood BCC is exceedingly rare in the absence of other underlying conditions. Only 107 cases of de novo childhood BCC have been reported in the literature, but the majority (90%) occurred on the head and neck, and aggressive subtypes were observed in 20% of the total cases.

Clinical presentation of BCC varies by type. Physical examination of the skin aids in determination of tumor extent, subtype, and involvement of important cosmetic and functional structures. Matted BCCs may indicate deeper tumor invasion and involvement of deeper underlying structures. In patients with recurrent or deeply infiltrative tumors, involvement of the facial nerve or branches of the trigeminal nerve should be investigated. Facial nerve function

can be monitored by comparing facial symmetry during voluntary facial movements with that at rest. Sensory nerve function can be tested and compared to the nonaffected side by means of light touch and pinprick. Orbital invasion can cause diplopia, proptosis, and ophthalmoplegia. Any limitation in ocular movements and/or diplopia should be tested.

BCC seldom causes regional or distant metastasis, with the exception of the metatypical basosquamous type. To evaluate for lymph node metastasis, particular attention should be taken to examine the parotid posterior auricular, suboccipital, and upper cervical groups of lymph nodes.

Several different clinicopathologic types of BCC exist, each with distinct biologic behavior:

- Nodular - Cystic, pigmented, keratotic
- Infiltrative
- Micronodular
- Morpheaform
- Superficial

12 Types

12.1 Nodular basal cell carcinoma

Nodular basal cell carcinoma is the most common type of basal cell carcinoma and usually presents as a round, pearly, flesh-colored papule with telangiectases. More than 60% of BCCs belong to this subtype. As it enlarges, it frequently ulcerates centrally, leaving a raised, pearly border with telangiectases, which aids in making the diagnosis. Fine vessels may bleed, resulting in hemosiderin deposition.

The tumor may present as a cyst, which can be mistaken for inclusion cysts of the eyelid. Cystic BCC is an uncommon variant of nodular BCC and is often clinically indistinguishable from nodular basal cell carcinoma, although it might have a polypoid, cystic appearance. Typically, a bluish-gray cystlike lesion is observed. The cystic center of the tumor is filled with clear mucin that has a gelatinlike consistency. Often, one can see the typical features of a nodular basal cell carcinoma in addition to the cystic features.

Most tumors are observed on the face, although the trunk and extremities also are affected.

12.2 Pigmented basal cell carcinoma

Pigmented basal cell carcinoma (see the images below) is an uncommon variant of nodular basal cell carcinoma that usually has brown-black macules in some areas or affecting nearly the entire tumor, occasionally making it difficult to differentiate from melanoma.

Typically, some areas of these tumors do not retain pigment, and pearly, raised borders with telangiectases that are typical of a nodular basal cell carcinoma can be observed. This aids clinically in differentiating this tumor from a malignant melanoma.

12.3 Keratotic basal cell carcinoma

Keratotic BCC is a variant of nodular BCC and is usually clinically indistinguishable from nodular BCC histologically.

12.4 Infiltrative basal cell carcinoma

With this variant of BCC, tumor infiltrates the dermis in thin strands between collagen fibers, making tumor margins less clinically apparent. Mohs micrographic surgery is the treatment of choice for infiltrative basal cell carcinoma. Because of its growth pattern, electrodesiccation and curettage has a significantly higher recurrence rate when used to treat infiltrative BCC compared to the treatment of nodular BCC; other treatment methods should be sought.

12.5 Micronodular basal cell carcinoma

This aggressive BCC subtype has the typical BCC distribution. It is not prone to ulceration, it may appear yellow-white when stretched, and it is firm to the touch. It may have a seemingly well-defined border.

12.6 Morpheaform (sclerosing) basal cell carcinoma

Morpheaform basal cell carcinoma is an uncommon variant in which tumor cells induce a proliferation of fibroblasts within the dermis and an increased collagen deposition (sclerosis) that clinically resembles a scar. This form accounts for 10% of lesions.

Such lesions appear as flat or slightly depressed, fibrotic, and firm. The tumor appears as a white or yellow, waxy, sclerotic plaque that rarely ulcerates. The morpheaform (sclerosing) type of basal cell carcinoma is often the most difficult type to diagnose, as it bears little resemblance to the typical nodular BCC.

Because the tumor infiltrates in thin strands between collagen fibers, treatment is difficult because the clinical margins are difficult to distinguish from normal, uninvolved skin. Mohs micrographic surgery is the treatment of choice for morpheaform basal cell carcinoma because recurrence is more likely with other treatment modalities.

Ulceration, bleeding, and crusting are uncommon and these tumors are commonly mistaken for scar tissue.

12.7 Superficial basal cell carcinoma

Superficial basal cell carcinomas are seen mostly on the upper trunk or shoulders. This type of BCC grows slowly, has minimal tendency to be invasive, and appears clinically as an erythematous, well-circumscribed patch or plaque, often with a whitish scale. Occasionally, minute eschars may appear within the patch or plaque. The tumor often appears multicentric, with areas of clinically normal skin intervening among clinically involved areas.

A threadlike border is common but not always present. Erosion is less common in superficial BCC than in nodular BCC, although pinpoint areas of hemorrhage or eschar may be present. The papules may mimic psoriasis or eczema, but they are slowly progressive and are not prone to fluctuate in appearance. Numerous superficial BCCs may indicate arsenic exposure. See the images below.

12.8 Gorlin syndrome or basal cell nevus syndrome

Basal cell carcinoma (BCC) is also a feature of basal cell nevus syndrome (ie, Gorlin syndrome), [56] an autosomal dominant inherited condition. The lesions in these patients cannot be distinguished histologically from ordinary BCCs. The gene responsible for this syndrome is located on arm 9q, and chromosome

abnormalities develop in some patients. The number of BCCs in patients with this syndrome may number from one to hundreds. Multiple BCCs begin to appear after puberty on the face, trunk, and extremities. In many cases, the tumors are highly invasive and may involve areas around the eyes and nose.

Other features associated with Gorlin syndrome (fortunately, uncommon) include the following:

- Mental retardation
- Congenital agenesis of the corpus callosum and medulloblastoma
- Odontogenic jaw cysts
- Bifid ribs and pectus excavatum
- Absent or undescended testes
- Mesenteric lymphatic cysts
- Palmar and plantar pits
- Ectopic calcification (particularly of the falx cerebri)
- Ocular and skeletal abnormalities (eg, hypertelorism, shortening of the fourth and fifth metacarpals)

12.9 Other basal cell carcinomas

Other types of basal cell carcinoma include the following:

- Metatypical
- Infundibulocystic
- Follicular
- Pleomorphic

13 Diagnostic Considerations

Although basal cell carcinoma rarely metastasizes, a tumor can extend beneath the skin to the bone, causing considerable local damage due to tissue destruction. This process leads to an ulcer that is sometimes known as ulcus rodens, or a rodent ulcer.

Other medical problems/issues to consider include the following:

- Dermatitis
- Desmoplastic trichoepithelioma
- Eczema
- Intradermal nevus
- Lichenoid benign keratosis
- Ringworm
- Fibroepithelioma of Pinkus
- Adnexal carcinoma (very rare)
- Actinic keratosis
- Sebaceous hyperplasia
- Nevi malignant melanoma
- Keratoacanthoma
- Seborrheic keratosis
- Bowen disease
- Darier disease (keratosis follicularis) [10]
- Cutaneous T-cell lymphoma (mycosis fungoides)
- Metastatic malignancies
- Differential Diagnoses
- Actinic Keratosis
- Bowen Disease
- Fibrous Papule of the Face
- Juvenile Nasopharyngeal Angiofibroma
- Malignant Melanoma

- Melanocytic Nevi
- Molluscum Contagiosum
- Psoriasis
- Sebaceous Hyperplasia
- Squamous Cell Carcinoma
- Trichoepithelioma

14 Workup

14.1 Approach Considerations

Given that basal cell carcinoma rarely metastasizes, laboratory and imaging studies are not commonly clinically indicated in patients presenting with localized lesions. Imaging studies may be necessary when involvement of deeper structures, such as bone, is clinically suspected. In such cases, CT scans or radiography can be used.

14.2 Skin Biopsy

A skin biopsy is often required to confirm the diagnosis and determine the histologic subtype of basal cell carcinoma (BCC). Most often, a shave biopsy is all that is required. Nevertheless, in the case of a pigmented lesion where there may be difficulty distinguishing between pigmented BCC and melanoma, an excisional or punch biopsy may be indicated; this is to ensure that the depth of the lesion can be determined if it proves to be a malignant melanoma.

In most cases, a superficial biopsy specimen that contains dermis is all that is required to confirm the diagnosis of BCC, although it is possible to miss the tumor. For example, an ulcerated BCC may reepithelialize with normal epidermis while tumor is still present at a deeper level. Part or all of the BCC may be sampled, but avoid going beyond the clinical margins if the biopsy is only for diagnostic purposes.

Punch biopsy is an easy method to obtain a thick specimen, but is rarely required. The most suspicious area of a lesion may be sampled, or multiple biopsy samples may be taken if the tumor is large or has a varied appearance in different areas. Avoid punch biopsy if curettage is planned for final treatment.

Occasionally, suspected tumors may require more than a single biopsy to make the diagnosis; therefore, with a high clinical index of suspicion, a second biopsy may be needed to obtain a pathological diagnosis of BCC.

14.3 Cytology

To accurately and definitively diagnose BCC of the eyelid, histological confirmation is required and is most commonly obtained through excisional (shave or punch) biopsy, which provides more information regarding the histological subtype of BCC. Cytology does provide a rapid alternative that may yield and even help confirm a diagnosis during the initial visit, however.

The accuracy of this technique has been reported to be good, but its sensitivity in diagnosing BCC of the eyelid is unknown. It is not considered to be sufficiently sensitive in planning surgical management.

A study by Barton et al showed that for patients who underwent cytology followed by excisional biopsy, cytology had a sensitivity of 92% in diagnosing BCC with a predictive accuracy of 75%. These values were compared to a second group of patients who had incisional biopsy and histological examination

followed by excision with histological confirmation. The second group showed a sensitivity of 100% in diagnosing BCC with a predictive accuracy of 96%.

14.4 Histologic Findings

Several histologic types of BCC exist. Distinctions are important because clinical detection of tumor margins is more difficult with certain histologic types. [60] Usually, BCCs are well differentiated and cells appear histologically similar to basal cells of the epidermis.

Tumor cells of nodular BCC, sometimes called basalioma cells, typically have large, hyperchromatic, oval nuclei and little cytoplasm. Cells appear uniform, and if present, mitotic figures are usually few. The nuclei resemble that of the basal cells of the epidermis, although they have a larger nuclear-to-cytoplasmic ratio and lack intercellular bridges. A mitotic figure is very rarely observed. Nodular tumor aggregates may be of varying sizes, but tumor cells tend to align more densely in a palisade pattern at the periphery of these nests.

Cleft formation, known as retraction artifact, commonly occurs between BCC nests and stroma because of shrinkage of mucin during tissue fixation and staining. Some lobules may have areas of pseudoglandular change, and this is the predominant change in adenoid BCC. In other instances, large tumor lobules may degenerate centrally, forming pseudocystic spaces filled with mucinous debris. These changes are seen in the nodulocystic variant of BCC.

Early lesions usually have some connection to the overlying epidermis, but such contiguity may be difficult to appreciate in more advanced lesions. Increased mucin is often present in the surrounding dermal stroma.

A histopathologic examination of paraffin-embedded sections of BCC usually reveals solid cellular strands, collections of cells with dark-staining nuclei and scant cytoplasm.

The peripheral cell mass is in a palisade arrangement that resembles the basal layer of the epidermis, sometimes with pseudocystic aspects, and with a variable number of mitoses.

The connective tissue stroma surrounding the tumor islands is arranged in parallel bundles and often shows young fibroblasts immediately adjacent to the tumor. The specific histologic pattern of each type of BCC varies in terms of desmoplastic reaction of the morpheaform type and in the stromal islands separated by basal cells strands of the fibroepithelial type. Artificial retraction of the stroma from the tumor islands is frequently observed histologically. Additionally, the stroma is often mucinous. Cells from recurrent BCC often show squamous aspects.

Histologically, BCC is divided into 2 categories: undifferentiated and differentiated. When there is little or no differentiation, it is referred to as solid BCC and includes pigmented BCC, superficial BCC, sclerosing BCC, and infiltrative BCC (a histologic subtype).

Differentiated BCC often has slight differentiation toward cutaneous appendages, including hair (keratotic BCC), sebaceous glands (BCC with sebaceous differentiation), or tubular glands (adenoid BCC). Noduloulcerative

(nodular) BCC is usually differentiated.

When the presence of a dense inflammatory infiltrate obscures the histologic margins of BCC, immunohistochemical stains for cytokeratins can help to identify tumor cells. These stains can be used with fixed or frozen tissue. Such staining with frozen tissue can take as little as 19 minutes, making it practical for use with Mohs micrographic surgery or with standard excision with frozen section margin control.

14.4.1 Nodular basal cell carcinoma

Nodular or noduloulcerative basal cell carcinoma, the most common type, generally consists of large, round or oval tumor islands within the dermis, often with an epidermal attachment. The solid (nodular) type accounts for approximately 70% of all cases. Artificial retraction of the tumor islands from the surrounding stroma is commonly seen. Ulcerations may be seen in large tumors.

14.4.2 Micronodular basal cell carcinoma

Another aggressive variant, micronodular BCC, appears as small, nodular aggregates of basaloid cells. See the image below.

Retraction artifact tends to be less pronounced than in the nodular form of BCC, and subclinical involvement is often significant. Micronodular basal cell carcinoma is similar to the noduloulcerative type, although the tumor islands are small (often ¡ 15 cells in diameter).

14.4.3 Pigmented basal cell carcinoma

In pigmented basal cell carcinoma (BCC), benign melanocytes in and around the tumor produce large amounts of melanin. These melanocytes contain many melanin granules in their cytoplasm and dendrites.

14.4.4 Adenoid basal cell carcinoma

The adenoid type consists of strands of basaloid cells in a reticulate pattern, frequently with prominent stromal mucin. It may occur with the solid type.

14.4.5 Morpheaform (sclerosing) basal cell carcinoma

The more aggressive morpheaform BCCs have growth patterns resulting in strands of cells rather than round nests, within a fibrous stroma. They constitute approximately 5% of BCCs. Morpheaform BCC arises as thin strands of tumor cells (often only 1 cell in thickness) that are embedded in a dense fibrous stroma. The morpheaform basal cell carcinomas exhibit islands of tumor extending into the tissue and may exhibit perineural invasion in 3% of patients. This finding helps classify these 2 histotypes as the most aggressive, with the highest rates of recurrence and positive margins after excision.

14.4.6 Infiltrative basal cell carcinoma

This type of BCC accounts for 10% of BCCs. Tumor cells have growth patterns resulting in strands of cells infiltrating between collagen bundles rather than round nests.

The strands of infiltrating BCC tend to be somewhat thicker than those seen in morpheaform BCC, and they have a spiky, irregular appearance.

Infiltrating BCC usually does not exhibit the scarlike stroma seen in morpheaform BCC. Peripheral palisading and retraction are less pronounced in morpheaform and infiltrating BCC than in less aggressive forms of the tumor, and subclinical involvement is often extensive.

14.4.7 Cystic basal cell carcinoma

Cystic basal cell carcinoma consists of large, round or oval tumor islands within the dermis with mucin present in the center of the island. This space is caused by central tumor cell degeneration.

14.4.8 Superficial basal cell carcinoma

Superficial BCC appears as buds of basaloid cells attached to the undersurface of the epidermis. Nests of various sizes are often seen in the upper dermis. The tumor cell aggregates typically show peripheral palisading.

The (multifocal) superficial type (see the image below) is characterized by numerous small nests of tumor cells usually attached to the undersurface of the epidermis by a broad base. Approximately 10-15% of all BCCs are of this type. This is the most common pattern seen in BCCs of the shoulder.

14.4.9 Keratotic basal cell carcinoma

The keratotic type resembles the solid type and its nests of basaloid cells with peripheral palisading. The island centers display keratinization and squamous differentiation. See the image below.

14.4.10 Infundibulocystic basal cell carcinoma

The infundibulocystic type is rare and is usually found on the face. It resembles the keratotic type. Nests are arranged in an anastomosing pattern and lack stroma. Many small, infundibular cyst-like structures with keratinous material are present. Melanin is sometimes present.

14.4.11 Metatypical basal cell carcinoma

Metatypical BCC is rare. In this type, nests and strands of cells mature into larger and paler cells, and peripheral palisading, if any, is less developed than in other types. Prominent stroma, prominent mitotic activity, and many apoptotic cells may be present. This form may be best diagnosed when one evaluates

a BCC with features between those of a nodular BCC and squamous cell carcinoma. These tumors are often aggressive, with an increased tendency for lymphatic and perineural spread.

14.4.12 Basosquamous carcinoma

The basosquamous type is controversial. It has been defined as a basal cell carcinoma (BCC) with differentiation towards squamous cell carcinoma (SCC). It is made up of basaloid cells that are a larger, paler, and rounder than those of a solid BCC. It also consists of squamoid cells and intermediate cells. Some consider the diagnosis of this type most appropriate when one evaluates a tumor with contiguous areas of BCC and SCC. This type is considered to have metastatic potential and is considered an aggressive skin cancer.

14.4.13 Fibroepithelioma of Pinkus

The fibroepithelioma type consists of thin, anastomosing strands of basaloid cells in a prominent stroma.

According to some studies, the so-called fibroepithelioma of Pinkus, considered to be a premalignant skin condition, must be considered as a fenestrated variant of basal cell carcinoma.

14.4.14 Ultrasonography

The use of ultrasonography is controversial. High-frequency (20 MHz) and ultrahigh-frequency (40-100 MHz) ultrasound systems have been used; their accuracy in delineating malignant lesions from benign lesions remains inadequate, however, with a success rate of approximately 20%. Furthermore, the claims of reliable tumor sizing and depth of invasion are promising but still passionately debated.

14.4.15 Laser Doppler

As an adjunct tool, laser Doppler may assist ophthalmologists in distinguishing between benign and malignant adnexal skin lesions and in establishing the tumor margin.

It is reported that cutaneous perfusion to the eyelids is statistically significantly higher than other regions of the body (eg, forearm). Furthermore, the mean perfusion in pretarsal skin has been shown to be 50% greater than that in preseptal skin. In histologically documented basal cell carcinoma of the eyelid, cutaneous perfusion was significantly greater.

14.5 Staging

Basal cell carcinoma rarely metastasizes and is usually not staged, unless the cancer is very large and is suspected of spreading to other parts of the body.

BCC staging may be similar to the staging of squamous cell carcinoma, which is according to the following scheme:

- Stage 0: Cancer involves only the epidermis and has not spread to the dermis
- Stage I: Cancer is not large (ie, ¡ 2 cm) and has not spread to the lymph nodes or other organs
- Stage II: Cancer is large (ie, ¿2 cm) but has not spread to lymph nodes or other organs
- Stage III: Cancer has spread to tissues beneath the skin (eg, muscle, bone, cartilage), and/or to regional lymph nodes but not to other organs.
- Stage IV: Cancer can be any size and has spread to other organs

14.6 High-risk tumors

High-risk BCCs include the following:

- Recurrent or incompletely excised BCC
- Primary BCC with clinically indistinct borders
- Lesions in high-risk (the H, or mask) areas, mainly the embryonic fusion planes (eg, eyelids, nose, ear, nasolabial folds, upper lip, vermillion border, columella, periorbital region, temples, preauricular and postauricular areas, and scalp)
- Lesions that develop in cosmetically and functionally important areas (eg, face, genitals, anal and perianal regions, hands and feet, and the nail unit areas)
- Tumors with aggressive clinical behavior (ie, growing rapidly or ¿2 cm)
- Tumors with aggressive histologic subtype, including sclerosing (morpheaform), basosquamous (metatypical or keratinizing), perineural, periappendageal, or perivascular invasion, infiltrating, adenoidal, or multicentric
- Tumors that develop in sites with previous radiation therapy
- Tumors that develop in immunosuppressed patients

15 Treatment and Management

Approach Considerations According to the National Comprehensive Cancer Network (NCCN), the goal of treatment for basal cell carcinoma (BCC) is elimination of the tumor with maximal preservation of function and physical appearance. As such, treatment decisions should be individualized according to the patient's particular risk factors and preferences

In nearly all cases of BCC, the recommended treatment modality is surgery. [66, 5, 4] The surgical approach varies according to tumor size, depth, and location. Dermatologists may perform nearly all of the therapeutic options in an outpatient setting. Most therapies are well established and widely applied; nevertheless, researchers are studying some additional options (eg, photodynamic therapy with photosensitizers).

Local therapy with chemotherapeutic and immune-modulating agents is useful in some cases of BCC. In particular, small and superficial BCC may respond to these compounds.

Topical 5% imiquimod is approved by the US Food and Drug Administration (FDA) for the treatment of nonfacial superficial BCCs that are less than 2 cm in diameter. Lesions are generally treated once daily, 5 days per week, for a duration of 6-12 weeks.

Likewise, topical fluorouracil is approved by the FDA for the treatment of superficial BCC, administered twice daily for 3-6 weeks. [70] Although no formal restrictions on fluorouracil have been determined based on lesion size or location, it is most commonly used on smaller superficial BCCs on the trunk and extremities. Both imiquimod and fluorouracil may be used topically for prophylaxis or maintenance in patients who are prone to having many BCCs, likely by treating subclinical tumors.

For tumors that are more difficult to treat (ie, infiltrative BCC, morpheaform [sclerosing] BCC, micronodular BCC, and recurrent BCC) or those in which sparing normal (noncancerous) tissue is paramount, Mohs micrographic surgery should be considered and discussed with the patient.

Radiation therapy is a primary treatment option in patients who are not surgical candidates. It may also be used as adjuvant therapy in cases with positive surgical margins. However, radiation therapy is contraindicated in patients with genetic conditions that predispose to skin cancer.

A Hedgehog (Hh) pathway inhibitor can be used to treat patients with locally advanced BCC who are not candidates for surgery or radiation therapy, or whose disease has recurred after surgery or radiation therapy, and those with metastatic BCC. [5] The FDA approved the first Hh pathway inhibitor, vismodegib (Erivedge), in January 2012, and the second, sonidegib (Odomzo), in July 2015. Those agents inhibit Smoothened (SMO), a transmembrane protein involved in Hh signal transduction.

In patients with metastatic BCC resistant to Hh pathway inhibitors, treatment with arsenic trioxide and itraconazole may offer some benefit. Ally and colleagues reported that three of five men with resistant metastatic BC responded to a regimen of intravenous arsenic trioxide 5 days, every 28 days, and

oral itraconazole on days 6 to 28. Although some patients experienced stable disease for 3 months, none had tumor shrinkage; the authors suggest that continuous dosing may be required to fully inhibit the HH pathway and achieve clinical response in such cases.

Surgical Modalities and Guidelines The goal of therapy for patients with BCC is removal of the tumor with the best possible cosmetic result. By far, surgical modalities are the most studied, most effective, and most used BCC treatments. The effectiveness of surgical modalities depends heavily on the surgeon's skills; considerable differences in cure rates have been observed among surgeons. Modalities used include electrodesiccation and curettage, excisional surgery, Mohs micrographically controlled surgery, and cryosurgery.

National Comprehensive Cancer Network (NCCN) guidelines recommend that low-risk BCC in non–hair-bearing areas be treated with curettage and electrodessication. If fat is reached, surgical excision should generally be performed. Standard excision is an alternative, if the lesion can be excised with 4-mm clinical margins and second-intention healing, linear repair, or skin graft. Margins should be assessed postoperatively. High-risk patients should undergo excision with postoperative margin assessment or a Mohs resection.

The American Academy of Dermatology, in collaboration with the American College of Mohs Surgery, the American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery, has developed appropriate use criteria for Mohs micrographic surgery. These include criteria for rating the appropriateness of Mohs micrographic surgery in 69 basal cell carcinoma scenarios.

Some studies suggest that dermato-oncological surgery is associated with a high risk of infection. [38] This risk is greater in patients with diabetes and in those having such surgery in the thigh or lower leg and foot.

15.1 Topical Treatments

Several topical creams are used in the management of BCC that is nonrecurring and superficial. NCCN guidelines state that low-risk patients with superficial BCC who cannot undergo surgery or radiation can be treated with topical therapies, although the cure rate may not be as high. Such treatments may also be used in patients with a high risk of multiple primary tumors.

15.1.1 Topical 5-fluorouracil 5%

Topical 5-fluorouracil 5% cream may be used to treat small, superficial BCCs in low-risk areas. It interferes with DNA synthesis by blocking methylation of deoxyuridylic acid and inhibiting thymidylate synthetase and, subsequently, cell proliferation.

In properly selected (eg, thin) tumors, cure rates of approximately 80% have been obtained. The cream is generally applied twice daily and must be used for at least 6 weeks for the treatment of superficial BCC.

Given that 5-fluorouracil can act on BCCs that are too small to be seen with the unaided eye, it may be used in patients with basal cell nevus syndrome or to preemptively treat subclinical tumors. Nevertheless, because not all tumors respond completely, careful patient monitoring is essential.

The use of 5-fluorouracil for other types of BCC is generally not recommended because it may not penetrate deeply enough into the dermis to eradicate all tumor cells. Irritation and crusting are common and expected; significant irritation and discomfort are not uncommon, but scars are unusual. The recurrence rate is very high.

15.2 Interferon

Interferon alfa-2b is a protein product manufactured using recombinant DNA technology. It has shown some success in treating small (¡ 1 cm), nodular, and superficial BCCs. In appropriate BCC tumors, cures rates of up to 80% have been obtained.

Several early studies have shown variable responses of BCC to intralesional interferon alfa. In a small study by Greenway et al, 1.5 million IU interferon alfa-2b injected intralesionally 3 times per week for 3 weeks resulted in the clearing of 3 cases of primary nonrecurrent BCC and 5 cases of primary superficial BCC.

Because larger studies are needed, most practitioners consider this an experimental therapeutic modality. Further data are needed before this treatment modality is recommended for routine ophthalmic practice.

Interferon has not become a mainstay in BCC treatment because of its cost, the inconvenience of multiple visits, the discomfort of administration, and its adverse effects, which include flulike symptoms. Acetaminophen has been administered to alleviate the flulike symptoms associated with this therapy.

15.3 Imiquimod

Imiquimod 5% cream (Aldara) is approved by the US Food and Drug Administration for the treatment of nonfacial superficial BCC. [78, 79] Several studies have shown imiquimod to be curative in all patients with superficial BCC if used twice daily and in 73-82% of patients when used once a day for 6-12 weeks. Smaller studies have shown similar responses for nodular BCC. Studies for other histologic types of BCC are under way.

Treatment is often initiated at 3-7 times per week and the dosage is increased as tolerated to once or twice daily, to maintain mild-to-moderate skin irritation. Patients can titrate the frequency of application to maintain low-to-moderate skin irritation. A 12-week course of treatment is often used, which does not need be contiguous.

In a study of 601 patients with histologically proven superficial basal-cell carcinoma, topical imiquimod cream (once daily, 5 times a week, for 6 weeks) was superior, and topical fluorouracil (twice daily for 4 weeks) was noninferior, to methylaminolevulinate photodynamic therapy (2 sessions with an interval of 1 week). At both 3- and 12-month follow-up, the proportion of patients who

were tumor-free was 72.8% for methylaminolevulinate photodynamic therapy, 83.4% for imiquimod cream, and 80.1% for fluorouracil cream.

15.4 Tazarotene

The receptor-selective acetylenic retinoid tazarotene (Tazorac) can also be used to treat small low-risk BCCs. Tazarotene is thought to cause BCC regression by increasing apoptosis and by decreasing cell proliferation in the skin cancer cells. In one case series, about 70.8% of the BCCs had clinical and dermoscopic regression of more than 50%, and 30.5% healed without recurrence after 3 years; most unresponsive tumors showed keratotic differentiation. The study involved the application of tazarotene 0.1% gel for 24 weeks in 154 small, superficial, and nodular BCCs (109 patients). Changes were followed up by dermoscopy and histologic examination. [83]

In addition to being an off-label indication, another drawback to topical tazarotene for the treatment of BCC is that it requires long-term therapy, for 5-8 months. The only reported adverse effect is dry/irritating skin that is relieved after discontinuation of tazarotene.

15.5 Radiation Therapy

Basal cell carcinomas (BCCs) are usually radiosensitive, and radiation therapy (RT) can be used for advanced and extended lesions and in those patients for whom surgery is not suitable (eg, because of allergy to anesthetics, current anticoagulant therapy, a tendency to form keloids, [84] or facial tumors). In a retrospective analysis of 1715 histologically confirmed primary cutaneous carcinomas (712 BCCs, 994 SCCs, nine tumors with distinct BCC and SCC characteristics) treated with superficial radiation therapy, recurrence rates for BCC at 2 and 5 years were 2% and 4.2%, respectively. Recurrence rates for SCC at 2 and 5 years were 1.8% and 5.8%, respectively. Postoperative radiation can also be a useful adjunct when patients have aggressive tumors that were treated surgically or when surgery has failed to clear the margins of the tumor. The treatment of locally advanced basal cell carcinomas may result in complete remission in approximately 70% of patients.

In the past, RT was a common treatment modality because of its high cure rate (97% for primary tumors). It is now used sparingly, because it is time consuming and extremely expensive. With the advancement in surgical techniques and other treatment modalities, RT is a reasonable treatment choice for recurrent tumors. It may be reserved for primary lesions requiring difficult or extensive oculoplastic surgery. It also eliminates the need for skin grafting when surgery would result in an extensive defect.

RT is contraindicated in young patients because of the high risk of radiodermatitis and scars; in lesions on the trunk and extremities; and in delayed cancer recurrence (eg, especially in patients previously treated with radiation). RT requires multiple visits. Treatment results in radiation damage and, therefore, should be reserved for older patients. RT is less effective for nonfacial tumors.

RT also is contraindicated in patients with connective tissue diseases or genetic conditions predisposing to skin cancer (eg, xeroderma pigmentosum, epidermodysplasia verruciformis, and basal cell nevus syndrome.) This histologic type in conjunction with RT may induce more tumors in the treated area. Radiation adverse effects include dermatitis, keratinization of the conjunctiva, and chronic keratitis.

Cosmetic results are generally good to excellent, with a small amount of hypopigmentation or telangiectasia in the treatment port. This therapy can be less disfiguring than surgical excision. Nevertheless, long-term results after several years can be deforming. Another disadvantage of this technique is that surgical margins cannot be examined. Tumors recurring in previously radiated sites tend to be aggressive and difficult to treat and reconstruct. RT remains an important, feasible option in selected patients with BCC.

The NCCN guideline supports RT for patients whose condition is appropriate, with the reservation that in order to achieve its benefits (high cure rates and good comesis), it must be administered carefully and with attention to algorithm details by well-trained speciaitemizes. Training and proper support are particularly essential to the use of intensity modulated RT as primary treatment. Medical physicists must provide the necessary support and training in this new technology.

15.6 Photodynamic Therapy

Photodynamic therapy (PDT) for basal cell carcinomas (BCCs) has been used for more than 20 years. [87, 88] PDT is the process of using specific wavelengths of light to photoexcite porphyrins that have been applied to neoplastic and preneoplastic cells. This increased energy is rapidly absorbed by adjacent tissue oxygen, causing the formation of singlet oxygen radicals. These radicals rapidly react with adjacent tissue and destroy it. 5-Aminolevulinic acid (ALA-PDT) is the only US Food and Drug Administration approved photoreactive molecule for PDT in the United States, and it is only approved for actinic keratoses. It is photoactivated with blue light for 1000 seconds after 1 hour of incubation.

PDT is administered orally or parenterally, as well as applied topically, and localizes into tumor cells before activation by exposure to light (eg, laser). The efficacy is low, and this treatment is frequently palliative. PDT may cause local edema, erythema, bitemizeering, and ulceration, but the final cosmetic effect is good.

PDT yielded only a 50% cure rate for superficial BCC, versus an 83% cure rate for nodular BCC, in a study by Calzavara-Pinton et al. At present, PDT has no distinct advantage over other well-established therapies for BCC of the eyelid. In a study by Puccioni et al, PDT using methyl aminolevulinate showed notable success and appears to be a viable option in the treatment of BCC of the eyelid in selected patients.

PDT as an adjunct is a reasonable choice in the following cases:

- Tumor recurrence with tissue atrophy and scar formation

- Elderly patients or patients with medical conditions preventing extensive oculoplastic reconstructive surgery
- Tumor with poorly defined borders based on clinical examination
- Tumor requiring difficult or extensive oculoplastic surgery

Although its use is off label, PDT has been used for treatment and prevention of BCCs, including those patients with immunosuppression and nevoid BCC syndrome. Shallow tumors, such as superficial BCCs, respond most consistently. Surgical excision has been shown to be significantly more effective than ALA-PDT in the treatment of nodular BCC.

The strongest support for PDT as a modality for BCCs comes with data on thin lesions treated with methylaminolevulinate (used outside the United States), but at least one long-term follow-up trial has also shown surgical excision to be superior.

Christensen et al reported a 10-year lesion complete response rate of 87% with two sessions of dimetylsulfoxide-supported topical 5-aminolaevulinic acid-PDT and curettage for primary, small BCC. Favourable cosmetic outcomes also were reported for nearly all cases.

Various protocols have been followed to achieve varying levels of success—increasing incubation time, increasing occlusion time, and using longer and/or deeper-penetrating wavelengths of light (eg, red light or pulse-dye laser). Many patients continue to prefer PDT because of its short healing time, excellent cosmesis, and relative affordability.

Also see the British Association of Dermatologists Therapy Guidelines and Audit Subcommittee's clinical guidelines summary, Guidelines for topical photodynamic therapy: update.

15.7 Systemic Retinoids

Although several clinical trials have shown some efficacy for available systemic retinoids in chemotherapy and chemoprevention, the long-term toxicity of these agents generally excludes them as treatment choices for most patients. [94] Studies are exploring their value as cancer preventive agents in patients at high risk for developing multiple tumors.

15.8 Hedgehog Pathway Inhibitors

15.8.1 Vismodegib

Vismodegib (Erivedge) is the first FDA-approved drug for advanced forms of basal cell carcinoma (BCC). It selectively inhibits Smoothened (SMO), a key transmembrane protein involved in hedgehog signal transduction of cancerous epithelial cells. In a phase I dose-ranging study by Von Hoff et al, 18 of 33 patients showed an objective response. Two of the 18 had complete response, and the remaining 16 showed a partial response. [95] FDA approval was based

on a single, international, open-label trial (n=104). Of the 104 participants, 96 were evaluable. Of those with metastatic BCC (n=33), 30.3% had partial response, but none had complete response. With locally advanced BCC (n=63), 22% showed a partial response and 20

15.8.2 Sonidegib

A second Hedgehog pathway inhibitor, sonidegib (Odomzo), was approved by the FDA in 2015. Approval was based on the BOLT trial. Eligible

patients had locally advanced BCC not amenable to curative surgery or radiation or metastatic basal cell carcinoma. Patients were randomized in a 1:2 ratio to receive 200 mg or 800 mg oral sonidegib daily, stratified by disease, histological subtype, and geographical region. For the 66 patients in the 200 mg group, the overall response rate was 58%; 3 patients (5%) achieved a complete response and 35 (53%) achieved a partial response. The duration of response ranged from 1.9 to 18.6 months, and in approximately half of the responding patients, the tumor shrinkage lasted at least 6 months.

16 Recurrence

The following is a itemize of treatments and their 5-year recurrence rates for primary BCCs:

- Surgical excision - 10.1%
- Radiation therapy - 8.7%
- Curettage and electrodesiccation - 7.7%
- Cryotherapy - 7.5%
- All non-Mohs modalities - 8.7%
- Mohs micrographic surgery - 1.0%

These rates are probably affected by the fact that most clinicians use cryotherapy, curettage, and desiccation mostly on smaller and better-demarcated lesions.

16.1 Prevention

Avoid possible potentiating factors (eg, sun exposure, ionizing radiation, arsenic ingestion, tanning beds). The regular use of sun-protecting clothing (eg, wide-brimmed hat, long-sleeved shirts, sunglasses with ultraviolet [UV] protection) is recommended when outdoors. Instruct patients to avoid sun exposure particularly during the middle of the day (ie, 11 am to 3 pm), which is the most dangerous time. Also, the sun's rays are especially intense in sunny climates and at high altitudes, and UV radiation can also pass through clouds and water. Patients should be instructed to be careful on the beach and in the snow because

sand, water, and snow reflect sunlight and increase the amount of received UV radiation.

Researchers are investigating chemoprevention with systemic administration of retinoids as cancer preventive agents in patients at high risk for developing basal cell carcinoma; the efficacy of these agents will take several years to evaluate, however.

The American Cancer Society recommends a dermatologic examination every 3 years for people aged 20-40 years and every year for people older than 40 years. The US Preventive Services Task Force determined that insufficient evidence exists to make a recommendation on asymptomatic adults receiving skin cancer screenings from a clinician.

16.2 Consultations

Ideally, treatment options for the patient with basal cell carcinoma should be evaluated jointly with a surgeon, dermatologist, and radiotherapist and based on histologic diagnosis.

Although early basal cell carcinoma can be treated adequately by means of local excision, advanced and recurrent tumors are best managed by a multidisciplinary approach involving head and neck surgical oncologists, Mohs micrographic surgeons, reconstructive plastic surgeons, pathologists, prosthetists, and radiation oncologists.

16.3 Long-Term Monitoring

Mc Loone et al found that patients who are diagnosed with BCC have a 35% chance of developing another tumor within 3 years and a 50% chance of developing another (not recurrent) BCC within 5 years. The NCCN guidelines state that 30-50% of patients will develop another nonmelanoma skin cancer within 5 years. These patients are also at an increased risk of developing cutaneous melanoma. Therefore, regular skin screenings are recommended.

Fewer than 1% of BCCs spread to another site in the body; nevertheless, after treatment, which is curative in more than 95% of cases, BCC may develop in new sites. Recommend appropriate prolonged or lifelong follow-up care.

Tumors occurring after radiotherapy tend to be more aggressive and infiltrative than other tumors. Metastasis is rare but has been reported with rates of 0.01-0.1%. Metastases most often originate from large, ulcerated tumors. Metastases usually occur in regional lymph nodes. Follow-up visits are scheduled 3 months after therapy and every 6 months to 1 year thereafter for the life of the patient.

17 Causes

The commonest cause is too much exposure to ultraviolet (UV) light from the sun or from sun beds. Basal cell carcinomas can occur anywhere on your body, but are most common on areas that are exposed to the sun, such as your face, head, neck and ears. It is also possible for a basal cell carcinoma to develop where burns, scars or ulcers have damaged the skin. Basal cell carcinomas are not infectious.

Basal cell carcinomas mainly affect fair skinned adults and are more common in men than women. Those with the highest risk of developing a basal cell carcinoma are:

- People with freckles or with pale skin and blond or red hair.
- Those who have had a lot of exposure to the sun, such as people with outdoor hobbies or who work out of doors, and people who have lived in sunny climates.
- People who use sun beds.
- People who have previously had a basal cell carcinoma.

Are basal cell carcinomas hereditary?

Apart from a rare familial condition called Gorlin's syndrome, basal cell carcinomas are not hereditary. However some of the things that increase the risk of getting one (e.g. a fair skin, a tendency to burn rather than tan, and freckling) do run in families.

18 symptoms

Most basal cell carcinomas are painless. People often first become aware of them as a scab that bleeds occasionally and does not heal completely. Some basal cell carcinomas are very superficial and look like a scaly red flat mark: others have a pearl-like rim surrounding a central crater. If left for years, the latter type can eventually erode the skin causing an ulcer – hence the name "rodent ulcer". Other basal cell carcinomas are quite lumpy, with one or more shiny nodules crossed by small but easily seen blood vessels.

Approximately 85% of BCCs occur on the face, head (scalp included), and neck; others appear on the trunk or extremities; rarely, they may occur on the hands. Other characteristic features of BCC tumors include the following:

- Waxy papules with central depression
- Pearly appearance
- Erosion or ulceration: Often central and pigmented
- Bleeding: Especially when traumatized
- Oozing or crusted areas: In large BCCs
- Rolled (raised) border
- Translucency
- Telangiectases over the surface
- Slow growing: 0.5 cm in 1-2 years
- Black-blue or brown areas

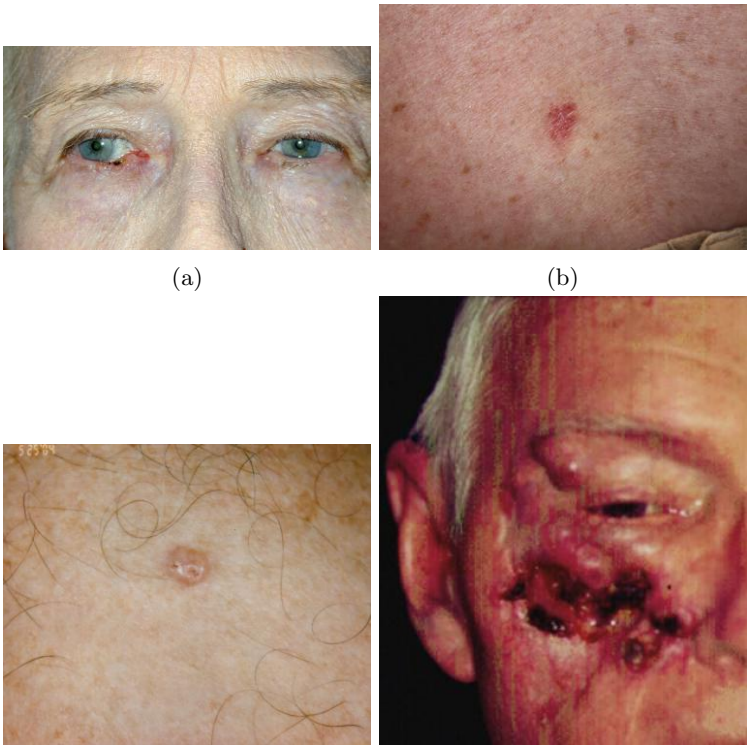
Periocular tumors most commonly involve the following:

- Lower eyelid: 48.9-72.1%
- Medial canthus: 25-30%
- Upper eyelid: 15%
- Lateral canthus: 5%

19 Diagnosing

Sometimes the diagnosis is clear from its appearance. If further investigation is necessary a small area of the abnormal skin (a biopsy) or all of the lesion (an excision biopsy) may be cut out and examined under the microscope. You will be given a local anaesthetic beforehand to numb the skin.

20 Samples



(a) (b)

(c) (d)

Figure 3: BCC