Basal Cell Carcinoma: An Overview of Tumor Biology and Treatment

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Learning Objectives: After studying this article, the participant should be able to: 1. Describe the epidemiology and etiology of basal cell carcinomas. 2. Understand the biology, histogenesis, predisposing conditions, and syndromes associated with basal cell carcinomas. 3. Have a clear understanding of tumor types and their clinical behavior. 4. Discuss the importance of diagnostic tumor biopsy and treatment options as they pertain to anatomic site, tumor type, and patient age. 5. Understand the basis for surgical management of basal cell carcinomas, the margins of excision, indications for frozen section, and Mohs micrographic surgery. 6. Discuss the value of patient follow-up after treatment of a primary basal cell carcinoma. 7. Review the most recently published literature on this topic and understand new concepts in tumor biology as they relate to diagnosis and treatment options.

Basal cell carcinoma is a malignant epithelial neoplasm of the skin that often arises in areas of chronic sun exposure. This article reviews the epidemiology, etiology, and treatment of basal cell carcinomas. Tumor biology is emphasized to provide a rational basis for specific treatment options. (Plast. Reconstr. Surg. 113: 74e, 2004.)

Basal cell carcinoma, a malignant epithelial neoplasm of the skin, most often arises in areas of chronic sun exposure. It is a slow-growing tumor that rarely metastasizes, but if inadequately treated or left untreated, it can cause extensive local tissue destruction and slow death.

HISTORY, INCIDENCE, AND EPIDEMIOLOGY
Jacob, in Dublin, first reported this slowly destructive, difficult to eradicate lesion in 1827 and coined the term “rodent ulcer.”1 In 1900, Krompecher identified the histologic features of the lesion as an epithelial carcinoma.2 Skin carcinomas are the most common human cancers, with more than 700,000 new cases diagnosed annually; 77 percent are basal cell carcinomas, 20 percent are squamous cell carcinomas, and 3 percent are melanomas and rarer tumors.3 The incidence and mortality rate for these cancers are increasing in the United States. The number of cases of basal cell carcinoma doubled between 1970 and 1986.4

Those at high risk for developing basal cell carcinoma are fair and dry-skinned (oily skin offers some protection) and often have blue or green eyes. The most susceptible people have Fitzpatrick skin types I and II; a history of sunburn, as opposed to tanning, carries a higher risk for development of basal cell carcinoma in this population. Basal cell carcinomas used to be seen in older people but are now seen in younger people and even teenagers due to the popularity of tanning. Most cases in patients younger than 40 years old are found in women. Women are more likely to have a history of cigarette smoking, blistering sunburns, and repeated exposure to tanning beds.6

Race is a factor. People of Celtic heritage are prone to develop skin cancer. The death rate from nonmelanoma skin cancer is 4.4 per 100,000 in Ireland and 2.6 per 100,000 in the United Kingdom, suggesting an increased susceptibility in Celts since the two regions have similar climates.7

Sun exposure and climate are important in basal cell cancer development. The incidence of skin cancer in Australia rises the farther...
Cumulative exposure to sunlight over a 20- to 30-year period is necessary for tumor development. Sun exposure, however, correlates more positively with the distribution of squamous cell carcinoma than with that of basal cell carcinoma. The ratio of basal cell carcinoma compared with that of squamous cell carcinoma in the northern United States versus the southern United States goes from 6:1 to 3:1.

The distribution of basal cell carcinoma across the body varies (Fig. 1). Most of these carcinomas occur on sun-exposed skin, but they are also found in relatively protected areas, such as the postauricular sulcus and nasolabial and inner canthal folds. Occurrence at these sites may relate to bioembryological closure of skin creases or to sebaceous gland distribution. Eighty-six percent of basal cell carcinomas are found on the head, and 7 percent are found on the trunk and extremities. The most common sites are the nose (25.5 percent), cheek (16 percent), periorbital region (14 percent), scalp (11 percent), and periauricular area (11 percent). However, a report from Australia notes a trend toward a greater proportion of trunk and limb lesions (34.3 percent).

Basal cell carcinoma is rare on the hand, penis, and lower lip; malignant lesions at these sites are more likely to be squamous cell carcinomas. When on the hand, basal cell carcinoma is usually dorsal. When near the nailbed, it may be mistaken for a paronychia. The lower lip is more often involved in cutaneous malignancy than the upper lip. Malignant tumors of the upper lip are almost always basal cell carcinomas, and those on the lower lip are usually...
squamous cell cancers. Basal cell carcinoma is the most common malignant eyelid tumor, with 67 percent of lesions occurring on the lower lid and 10 percent at the inner canthus. Squamous cell carcinoma, in contrast, rarely occurs on the eyelids and represents only 2 percent of all eyelid lesions. The ratio of basal to squamous cell carcinoma of the eyelids is 30:1.\textsuperscript{14} The external ear is more frequently affected by squamous than basal cell carcinoma; squamous cell carcinomas account for approximately 60 percent of total tumors of the external ear, contrasted with a 40 percent occurrence rate of basal cell carcinoma and melanoma.\textsuperscript{15} Skin cancers in the external auditory canal are rare, but squamous cell carcinomas outnumber basal cell carcinomas at this site also.\textsuperscript{16}

**HISTOGENESIS**

The factor most often involved in the pathogenesis of basal cell carcinoma is ultraviolet light. The ultraviolet band is divided into C (1 to 290 nm), B (290 to 315 nm), and A (315 to 400 nm). The ozone-rich stratosphere absorbs ultraviolet wavelengths below 290 nm. Ninety-five percent of solar ultraviolet radiation reaching the earth’s crust is ultraviolet A light. The remaining 5 percent is ultraviolet B light, which is responsible for acute sunburn and much of the malignant degeneration that occurs in human skin. Although ultraviolet B rays are more carcinogenic, ultraviolet A rays enhance the carcinogenic effects of ultraviolet B light and exacerbate its damage.\textsuperscript{18} Even people who receive ultraviolet radiation through window glass (which effectively blocks out ultraviolet B light) have premalignant and malignant skin lesions.

Carcinogenesis is a multistep process.\textsuperscript{17} Initiation occurs with genetic mutation. Promotion then results from changes in the cellular environment. Progression to the final malignant phenotype occurs with further genetic alteration. All three steps are necessary for malignant transformation to result. Exposure to ultraviolet light produces DNA changes that are usually corrected by cellular repair mechanisms. If erroneous sequences are not repaired, propagation continues during DNA replication. Mutations related to ultraviolet light have been identified with mutations of the p53 tumor suppressor gene. In 56 percent of basal cell carcinomas, mutations occur in both p53 alleles;\textsuperscript{18} the presence of p53 protein seems to correlate with basal cell tumor aggressiveness.\textsuperscript{19}

As with squamous cell carcinoma, basal cell carcinomas appear to be induced by ultraviolet light, but there may be differences in the mechanisms. Basal cell carcinomas originate in the basal layer of the epidermis; squamous cell carcinomas arise from the malpighian (squamous) layer. The originating cells of basal cell carcinoma are in a deeper zone than those of squamous cell carcinoma, arising from interfollicular basal cells, hair follicles, or sebaceous glands. Thus, exposure to different doses or wavelengths of ultraviolet light may be required compared with the case for squamous cell carcinomas.

While it is well known that the p53 gene is a major target for ultraviolet induction of basal cell carcinoma, it has also been shown that the patched gene (\textit{PTCH}) is a target for ultraviolet light. Mutations in \textit{PTCH} are believed to be responsible for some hereditary basal cell carcinomas in Gorlin’s syndrome, sporadic basal cell carcinomas, and basal cell carcinomas isolated from xeroderma pigmentosum.\textsuperscript{20,21}

Aside from the mutagenic effects of ultraviolet light, ultraviolet radiation may also adversely influence host-tumor relationships, resulting in immunosuppression from depletion of Langerhans cells in the epidermis and stimulation of suppressor T cells and hindering the host from detecting and killing mutated cells.

Collagenase may play a role in the spread of these tumors, which contain increased amounts of type I collagenase.\textsuperscript{25} Nodular basal cell carcinomas produce only type I collagenase. The more aggressive desmoplastic basal cell carcinomas also produce type IV collagenase, which may be responsible for focal gaps in the basement membrane of this tumor subtype, possibly explaining the more aggressive, invasive behavior of this basal cell tumor variant.

Basal cell carcinomas are stroma-dependent; experimentally transplanted basal cell carcinomas do not survive free of dermal tissue.\textsuperscript{27} This may explain why these tumors metastasize so rarely (incidence of less than 0.1 percent).\textsuperscript{28} They can, however, demonstrate aggressive local growth. Understanding the potential for local spread is important in the proper management of basal cell carcinoma. The tumor always follows the path of least resistance. Invasion of bone, cartilage, and muscle is uncommon. When a basal cell carcinoma encounters...
these structures, it spreads along the periosteum, perichondrium, fascia, or tarsal plate.\textsuperscript{29,30} This spread pattern explains in part the difficulty in management and the higher recurrence rate of carcinomas of the eyelid, ear, nose, and scalp. A carcinoma on the nasal tip, for example, may grow along the perichondrium until it encounters an area of articulating cartilages and then extend into the soft-tissue plane that separates the cartilages (Figs. 2 and 3); the tumor, once in this plane, spreads extensively. Embryonic fusion planes are also vulnerable to basal cell tumor penetration. The “tip of the iceberg” phenomenon occurs where there is extensive subclinical tumor spread, including the inner canthus, philtrum, mid-lower lip, nasolabial sulcus, and preauricular and postauricular areas (Fig. 3).

Reticular dermis serves as a relative barrier to tumor penetration. Possibly because of the thick dermis on the back, basal cell carcinomas on the posterior trunk tend to be superficial, although lateral spread in the less dense upper dermis can extend beyond clinically apparent tumor margins.\textsuperscript{30} Perineurial spread is uncommon and found only in highly invasive basal cell tumors.\textsuperscript{30} Because of the planes of tumor spread, the incidence of basal cell carcinoma recurrence in the inner canthus, base of nostrils, and preauricular and postauricular areas is higher than at other sites.\textsuperscript{31} The distribution of recur-

Fig. 2. (Above, left) Basal cell carcinoma of the nasal tip. (Above, right) The basal cell carcinoma had spread along the surfaces of the nasal cartilages (without invading those cartilages) and in the planes between the cartilages, necessitating wide soft-tissue resection, but had left the cartilages intact. Expect wide subclinical tumor spread in areas that involve previous embryonic fusion planes, such as (below, left) the postauricular sulcus and (below, right) the nasal-cheek angle and inner canthus.
rent facial basal cell carcinomas compared with similarly located untreated lesions reported in one study is depicted in Figure 3.31 Furthermore, in these danger areas, excision may be inadequate because tumor excision may be predicated more on the anticipated reconstruction (which may be more difficult at these sites) than on the tumor itself. Recurrences in these four areas are also problematic because spreading lesions have ready access to the cranium and deeper structures.

Multicentric basal cell carcinomas, or “field fire” lesions, do not exist. Although histologic examination may demonstrate what appear to be multiple separate islands of tumor, as in so-called superficial multicentric basal cell carcinoma, computerized three-dimensional reconstructions confirm that basal cell carcinomas are unicentric in origin. A solitary tumor has multiple microscopic extensions32 that must be completely removed at the time of surgical excision.
PREDISPOSING CONSIDERATIONS

X-irradiation [(including fluoroscopy) used for epilation in tinea capitis and to treat hirsutism or acne] may generate basal and squamous cell carcinoma development. The minimum reported radiation dosage for inducing skin cancer in humans is 1000 rads, but it may even be as low as 450 rads. DNA damage probably plays a role. There is usually a long latency period for the development of radiation-induced skin cancer. The anatomic site of irradiation correlates with the tumor type that develops. Basal cell carcinomas most often arise after irradiation of the head and neck, and squamous cell cancers appear more often on irradiated extremities.

Arsenic ingestion (sources include well water, insecticides, medications, mining and smelting operations, and sheep dipping) can cause both basal and squamous cell cancers and Bowen’s disease. Arsenic-induced cutaneous lesions are usually multiple and are usually found on the trunk. Arsenical keratoses may occur on the palms and soles. The latency period for the development of skin cancers caused by arsenic is long.

The incidence of basal cell carcinoma is much higher in patients whose immune responses are suppressed by steroids and other drugs following organ transplantation; the overall incidence of skin cancers in the immunosuppressed transplant population is 20.6 times that of the general population, and it is common to have multiple cutaneous malignancies in a single patient. The ratio of basal to squamous cell carcinomas is 4:1 in the general population; among immunosuppressed transplant patients, however, the ratio is 1:1.7, suggesting that immune suppression plays a larger role in the pathogenesis of squamous cell cancers than in that of basal cell carcinomas. Basal cell carcinomas have also been reported in patients with acquired immune deficiency syndrome.

Exposure to psoralens and sunlight predisposes individuals to development of skin cancers, a finding important to those with psoriasis and other dermatologic conditions who undergo treatment with psoralen plus ultraviolet A light. Psoralen/ultraviolet A treatment may act as a carcinogen or a cocarcinogen, decreasing the number of Langerhans cells in the skin and impairing induction of cutaneous delayed hypersensitivity. This impairment of cellular immunity may account for the short latency period associated with psoralen/ultraviolet A-induced neoplasms.

A single definitive injury (trauma) is rarely associated with the subsequent appearance of a basal cell carcinoma. Basal cell carcinomas may occasionally arise in scars or burns; these lesions usually occur in older patients who have evidence of damage from chronic sun exposure. Basal cell carcinomas rarely originate from smallpox vaccination scars and even less frequently originate from chicken pox scars.

PREDISPOSING DERMATOLOGICAL CONDITIONS

Nevus sebaceus of Jadassohn presents at birth as a slightly raised yellow-brown plaque and is quiescent during childhood. The most common affected site is the scalp, although the face, the neck, and, more rarely, the trunk and limbs may be involved. The lesion gradually enlarges, becoming more noticeable at puberty and taking on a yellow, cobblestone appearance. It may be darkly pigmented in African Americans. A hamartomatous conglomerate of sebaceous glands associated with heterotopic apocrine glands and hair follicles, the nevus sebaceus is also called an organoid nevus because it involves the entire skin organ. In 10 percent to 20 percent of patients, nevus sebaceus evolves into basal cell carcinoma. Excision before puberty is recommended.

Porokeratosis is a group of hereditary conditions characterized by disseminated annular plaques with sharply raised horny borders. Approximately 13 percent of these lesions transform into basal and squamous cell carcinomas. Two of the at least five distinct varieties of porokeratosis have premalignant potential. Mibelli porokeratosis is the most common type. The lesions of disseminated superficial actinic porokeratosis are smaller than those of Mibelli porokeratosis, and the frequency of malignant transformation is not as high. Lesions in disseminated superficial actinic porokeratosis occur mainly on sun-exposed areas of the body.

Basal cell nevus syndrome, or Gorlin’s syndrome, is inherited in an autosomal dominant manner with low penetrance (Fig. 5). It is caused by a mutation in the tumor suppressor gene located at chromosome 9q23.1-q31. Typical nevi are reddish brown, papular, and variously sized; they appear after puberty in most patients and may number from several to thousands. Lesions become invasive basal cell
carcinomas in approximately 76 percent of patients. Principal syndrome features include multiple scattered basal cell carcinomas, mainly on the face and back; jaw cysts; skeletal abnormalities such as bifid ribs, scoliosis, and brachymetacarpia; overdeveloped supraorbital ridges, a broad nasal root, and hypertelorism; palmar and plantar pits; calcification of falx cerebri; and occasional neurologic abnormalities, including mental retardation and medulloblastoma.

Bazex syndrome is an inherited X-chromosome–linked dominant trait consisting of follicular atrophoderma with multiple basal cell carcinomas, hypotrichosis, hypohidrosis, and “ice pick” marks on the extremities.

Xeroderma pigmentosum (Fig. 6) is a genodermatosis characterized by an autosomal recessive defect in which the DNA repair mechanism for fibroblast ultraviolet light–induced damage is impaired. The defect is in the endonuclease, an enzyme that excises segments of DNA containing ultraviolet light–induced thymine dimers.
The skin and eyes of patients with xeroderma pigmentosum are intolerant of ultraviolet light. The skin of an infant with xeroderma pigmentosum appears normal at birth, but the earliest exposure to sunlight results in an exaggerated clinical sunburn reaction. Repeated sun exposure leads to pigmentary changes appearing as intensely pigmented freckles. The skin subsequently dries and thickens, ultimately leading to cutaneous and subcutaneous atrophy, particularly around the eyes, nose, and mouth. The eyes are painfully sensitive to light and tear excessively. In more severe cases, progressive neurologic deterioration results in “xerodermic idiocy.” Many patients develop multiple malignant epithelial tumors (basal and squamous cell carcinomas and melanomas) in the first decade of life. Patients

![Fig. 5. Patient shows the characteristic facial appearance and skin lesions of basal cell nevus syndrome. Photographs courtesy of Don Gard, M.D.](image1)

![Fig. 6. (Left) Multiple cutaneous pigmented lesions of xeroderma pigmentosum. (Right) This patient developed a malignant melanoma, but squamous cell cancers and basal cell carcinomas occur more frequently. Photographs courtesy of Don Gard, M.D.](image2)
usually die in the second decade. The prognosis for children with xeroderma pigmentosum is dismal since there is no specific treatment. Use of sun-protective clothing and topical sunscreens and an indoor lifestyle are the best preventive measures. A child with the disease must be monitored frequently to detect and treat malignant cutaneous lesions quickly.

Rombo syndrome, albinism, and linear unilateral basal cell nevus are other inherited conditions that carry an increased risk for the development of basal cell carcinoma.

CLASSIFICATION OF BASAL CELL CARCINOMAS

Basal cell carcinomas are classified by both clinical appearance and histologic characteristics. They have traditionally been classified according to degree of differentiation, that is, adenoid, keratotic, pigmented, and so forth, although tumor type and degree of differentiation hold no prognostic significance in many cases. From the perspective of providing the clinician with information helpful in planning the optimum therapeutic procedure, the histologic growth pattern is more relevant than the type of differentiation (Fig. 7). Jacobs et al. differentiated between nodular, ulcerative, and infiltrative histologic types of basal cell carcinomas, but it is perhaps more helpful to distinguish primarily between circumscribed and diffuse lesions and then secondarily within these two large groups to classify basal cell carcinomas according to type and degree of differentiation (Table I).

Lesions that masquerade as basal cell carcinoma do exist. Ulcerative lesions may be factitious, and biopsies will differentiate them from basal cell carcinoma. Trichoepithelioma may be solitary or numerous and usually occurs on the face. It may be confused with basal cell carcinoma both clinically and histologically (with cells of origin from the root sheath of hair follicles) (Fig. 8). Eczema, actinic keratoses, psoriasis, and fungal infections may be confused with superficial keratotic basal cell carcinomas (Fig. 9, above, left and right, and below, left). Nevi are well-defined maculopapular lesions of variable size. They may resemble nodular, pigmented basal cell carcinoma, but the latter are invariably firm and cannot be indented by a blunt cotton-tipped swab (Fig. 9, below, right). Histologic analysis may be required to make the distinction.
mous cell carcinomas was ambiguous. A lesion that falls in this category is either a keratotic basal cell carcinoma, which shows horn cyst formation and represents an attempt at hair follicle production, or a small cell squamous carcinoma. Basal cell carcinomas with squamous differentiation behave no differently than pure basal cell carcinomas and do not represent an intermediate step toward squamous cell carcinoma. The premalignant fibroepithelial tumor of Pinkus is a variant of basal cell carcinoma and is composed mainly of large aggregates of basaloid cells without adnexal differentiation. Cells are uniform in size with large nuclei. Desmosomes are present, as demonstrated by electron microscopy and immunohistochemistry, and can be detected in as many as 60 percent of cases with light microscopy alone. Cells at the periphery of islands of aggregated basaloid cells align parallel, in contact with the basement membrane and with the cell apex pointing inward to the island’s center, in a picket fence arrangement called palisading. Nodular basal cell carcinomas are clinically well-defined, flesh-colored lesions with multiple telangiectatic surface vessels. While the solid (nodular) basal cell carcinoma is histologically poorly differentiated, its growth pattern is circumscribed, and it presents as a dome-shaped lesion with defined borders. If these clinically well-circumscribed lesions ulcerate, then they are called nodular ulcerative basal cell carcinomas.

**Diffuse Basal Cell Carcinomas**

Diffuse basal cell carcinomas are plaque-like, spread horizontally, and have poorly defined margins. They tend to have a higher recurrence rate than circumscribed lesions because they extend insidiously in the dermis beyond the clinically visible or palpable border, making it difficult for the clinician to gauge accurately the amount of normal-appearing tissue around the tumor that must be sacrificed to achieve total removal. Basal cell carcinomas with diffuse growth patterns may be treated either by conventional excision or with Mohs micrographic surgery; both techniques provide a tissue specimen that can be examined microscopically to ensure that all of the tumor has been removed. Diffuse carcinomas include superficial basal cell carcinomas, morpheaform or sclerosing lesions, infiltrating lesions, micronodular basal cell tumors, and eccrine and apocrine epitheliomas.

Superficial basal cell carcinoma has been called superficial multicentric basal cell carcinoma because multiple discrete foci appear to be present on two-dimensional microscopic sections. Three-dimensional computer-generated reconstructions reveal, however, that ap-
parent multiple foci are all interconnected. “Multicentric” is a misnomer. The superficial variant occurs most often in the upper trunk, especially the shoulder area. Lesions should not be thought to be easily treated. They are reported to have the highest recurrence rate of all basal cell carcinomas because they extend peripherally beyond their clinically apparent borders. Superficial carcinomas are scaly, crusted, erythematous, and flush with the skin surface; they may be ringed by a raised “pearly” border that slowly expands over time. They may be confused with eczema, actinic keratosis, psoriasis, or fungal infection.

Morpheaform, or sclerosing, basal cell carcinoma (Fig. 11) is a firm plaque surrounded by “scar” tissue. Ulceration is rare and skin elevation is minimal. It is difficult to treat because the precise definition of margins by clinical inspection or palpation is impossible. Spread may extend 7 mm beyond the apparent tumor border. Thin strands and nests of cells are surrounded by dense, fibrous stroma, which precludes treatment by curettage. Peripheral palisading is not prominent or may be absent. Morpheaform basal cell carcinoma infiltrates deeply into the dermis and is the most aggressive of all the clinical subclasses.

Infiltrating basal cell carcinoma invades both peripherally and deeply and is characterized by a very aggressive course. It lacks a central cohesive mass, consisting of elongated islands of atypical basal cells widely separated by mucinous, edematous, or fibrotic stroma. Tumor nests are often angulated and may be oriented almost perpendicular to the skin surface. Palisading is poorly developed, and the lesion is macroscopically plaque-like and poorly marginated.

Micronodular basal cell carcinoma shares with other infiltrating basal cell carcinomas the propensity for dispersion of nests of epithelial cells, small, round aggregates with well-developed palisading. Clinically, these lesions are poorly defined and flat, with the capacity for deep invasion. A feature unique to this type of basal cell carcinoma is that the deepest cell nests often appear to be lying free in the tissue without surrounding stroma. It is hypothesized that these deepest cell clones may have acquired their own autonomy, unlike solid basal cell tumors in which the epithelial component is intimately dependent on the connective tissue stroma for its propagation.

Eccrine epitheliomas commonly occur on the scalp. They are well differentiated and exhibit follicular or sebaceous differentiation, but they tend to recur, as do other basal cell

Fig. 9. (Above, left and right, and below, left) Superficial keratotic ulcerative basal cell carcinomas on nose, forearm, and forehead show the characteristic surface scaling epithelium with ulceration. (Below, right) Pigmented basal cell carcinoma.
carcinomas with diffuse growth patterns. Apocrine epitheliomas are rare but pursue an aggressive clinical course requiring radical surgical extirpation.\textsuperscript{60}

**CLINICAL IDENTIFICATION**

If the clinician follows a scheme of descriptive dermatology by having appropriate terminology, this will aid in both diagnosis and treatment. A logical way to accomplish this might include some or all of the following descriptors: (1) primary description: macule, papule, nodule, or plaque; (2) secondary description: scaly, crusted, lichenified, erosion, ulcerative, or smooth; (3) shape: annular, round, irregular, serpiginous, diffuse, or erythematous; (4) size, measurements; (5) location: specific, truncal, sun-exposed, previous surgery site, and so on; and (6) fixation: fixed to deeper tissues or overlying skin fixed to lesion.

For practical purposes, despite the multiple types of basal cell carcinoma, most can be classified into four types: (1) nodulo-ulcerative, which is the most frequent type, starting as a small nodule with a few surface telangiectasias, increasing in size and undergoing central ulceration, then representing the typical rodent ulcer with an enlarging ulcer surrounded by a pearly rolled border; (2) pigmented; (3) morphea-like, which is a slightly elevated, firm, yellowish plaque with an ill-defined border over

\begin{figure}[h]
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\includegraphics[width=\textwidth]{fig10.jpg}
\caption{(Above, left) Adenoid cystic lesion on the back has a circumscribed growth pattern with well-defined clinical borders. (Above, right) Adenoid cystic basal cell carcinoma of the nose. (Below) Classic nodular ulcerative basal cell carcinomas of the forehead (left) and lower eyelid (right), with well-defined clinical margins and “pearly,” raised tumor edges with tiny telangiectasias.}
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\begin{figure}[h]
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\caption{Morpheaform (sclerosing) basal cell carcinoma of the medial canthus.}
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which skin remains intact until ulceration finally occurs; and (4) superficial, which is one or several erythematous, scaling, slightly infiltrating patches surrounded by a fine border, psoriasiform or eczemoid in character, with superficial ulceration and crustings. This simple classification has served us well in the treatment of most basal cell carcinomas.

**TREATMENT**

Treatment of a basal cell carcinoma has four goals: (1) total lesion removal, (2) preservation of normal tissue, (3) preservation of function, and (4) optimal cosmesis. The most important goal is ridding the patient of the tumor; if this goal is not met, the other three cannot be accomplished. The importance of removing all of the tumor is illustrated in a study which found a high recurrence rate of basal cell carcinoma in young women because cosmetic concerns took precedence over definitive treatment.

Because these carcinomas grow slowly and rarely metastasize, they are often not given sufficient respect. Plastic surgeons often think only in terms of surgical ablation dictated by their training. In choosing an appropriate treatment modality, clinicians should consider not only those methods in which they are most skilled but also those that are most appropriate to the type and location of the lesion.

Definitive diagnosis requires biopsy and histologic examination. Excisional biopsy can be carried out if the lesion is small (<0.5 to 1.5 cm, depending on the site). Larger lesions should receive either full-thickness incisional biopsy or punch biopsy, and histologic confirmation should be obtained before major ablation. Prior incisional biopsy does not adversely affect the natural history of the tumor, provided the lesion is excised as soon as the histologic diagnosis is confirmed.

Whereas plastic surgeons generally think in terms of incisional, excisional, or pinch biopsy to make a histologic diagnosis, the dermatologists have taught us that a shave biopsy may be as accurate as a punch biopsy in making the diagnosis of basal cell carcinoma, since the tumor arises from the basal layer of the epidermis and so a shave biopsy will encompass a representative tumor sample. The advantage of a shave biopsy is that when the diagnosis is in doubt and the histologic report proves to be benign, a better cosmetic result from one biopsy will result. A punch biopsy is also said to possibly preclude certain types of future treatments for a biopsy-proven basal cell carcinoma. For example, if the “dermal sling” is violated, treatment with curettage and electrodesiccation may be prevented or at least rendered less effective.

A counterpoint position has also been taken in the dermatologic literature that cautions against using shave biopsies for all lesions. A shave biopsy might be considered on most suspected basal cell carcinomas to establish a diagnosis. However, it is well known that basal cell carcinomas may be histologically heterogeneous. A clinically nodular carcinoma may have a more aggressive histologic subtype (for example, micronodular or infiltrating) deep to the main nodular mass, and this would be missed on routine shave excision. Thus, punch biopsies are necessary for larger, indurated, or more aggressive lesions.

**VARIABLES TO CONSIDER IN THE MANAGEMENT OF BASAL CELL CARCINOMA**

Patient age, number of lesions, lesion size, distinctness of tumor borders, primary versus recurrent carcinoma, and anatomic location are variables to consider when managing basal cell carcinoma.

**Patient age.** Physicians used to assume the elderly were not candidates for surgery but should be treated by radiation therapy. Elderly people, however, should not be denied definitive surgery, because most can tolerate even a difficult Mohs resection under local anesthesia. Because aged skin is more forgiving than young skin, curettage and electrodesiccation of a lesion can yield a good cosmetic result in an older patient; the same treatment of a similar lesion might produce a hypertrophic scar in a younger patient. Radiation therapy is generally reserved for older patients, for larger lesions.

**Number of lesions.** Excision of multiple carcinomas may not be the most practical or even the best treatment. Cryosurgery or curettage may be the most realistic treatment approach for a patient with multiple superficial carcinomas of the trunk, and it will likely yield excellent cosmetic results. Multiple excisions with postoperative tension on adjacent suture lines in thick skin, particularly on the back, can transform initial fine line scars into ugly spreading ones.

**Lesion size.** Curettage and electrodesiccation or cryosurgery may be the treatment of choice for a large-diameter (5 cm or larger) superficial carcinoma on the back, since excision and
skin grafting may produce a suboptimal cosmetic result. Size is a determinant of curability. As a general rule, the incidence of tumor recurrence increases significantly when a basal cell carcinoma is more than 2 cm in diameter, probably because of the greater degree of subclinical peripheral tumor spread. Surgical excision and Mohs micrographic surgery are the treatments of choice with larger lesions (other than superficial basal cell carcinoma), although radiation may also be suitable, again in older patients.

Distinctness of tumor borders. Well-demarcated, exophytic basal cell carcinomas are characterized by a circumscribed nodular histology and can be managed by curettage and electrodesiccation, cryosurgery, radiation, or surgical excision, with an expected high cure rate for all approaches. Lesions with ill-defined or plaque-like edges have extensive subclinical spread and a correspondingly higher recurrence rate; they may be best managed with Mohs micrographic surgery.

Primary versus recurrent basal cell carcinoma. The treatment cure rate for recurrent carcinomas is significantly lower than that for primary lesions. Mohs surgery, with its exacting histologic control, may offer the best likelihood of cure for recurrent lesions, since these tumors are usually poorly defined and embedded in a sclerotic matrix with extensive subclinical spread. Radiation therapy may not be advisable for recurrent carcinomas because of the difficulty in determining how wide a margin to include in the treatment field. Curettage and electrodesiccation are not suitable for recurrent lesions because removal of tumor nests embedded in scar is difficult.

Anatomic location. Even insignificant looking basal cell carcinomas with a nodular growth pattern may demonstrate extensive subclinical spread, deep extension, and biologically aggressive behavior in high-risk areas such as the nasal ala, the preauricular and postauricular areas, and the medial canthus. Most basal cell carcinomas at these sites, with the possible exception of the most superficial lesions, may best be managed by Mohs micrographic surgery or at least by surgical excision with frozen-section determination of margin adequacy.

Aside from mode of spread, other characteristics of a particular anatomic site may make a specific treatment unsuitable. Mobility of tissues of eyelids or lips, for example, makes effective curettage of lesions in these areas difficult. Basal cell carcinomas in areas rich in pilosebaceous units, such as the scalp and nasal tip, may bud off hair follicles and escape the curette. Deep dermis on the distal nose is so dense that tumor islands may not be adequately removed by curettage. Invasive basal cell carcinomas of the scalp are generally not treated by cryosurgery because the scalp's rich vascularity makes obtaining an adequate freeze difficult.

Many clinicians elect not to re-excite a basal cell carcinoma when pathologic examination shows involved resected margins, since residual tumor is found in only 50 percent of re-excised specimens. This statistic may, however, mean that residual tumor was undetected because of “incomplete” histopathologic examination of the re-excised tissue.

Some have reported a recurrence rate for incompletely excised basal cell carcinomas as high as 86 percent, although it is generally accepted to be approximately 35 percent. Since recurrent basal cell carcinomas often behave aggressively and are difficult to manage, most surgeons recommend reexcision if margins are involved, as soon as the initial surgical site is healed. Patient compliance and reliability in returning for follow-up examinations are other factors in deciding whether to re-excite an incompletely excised carcinoma.

Dellon recommended an alternative approach when surgical margins were involved. He demonstrated in a prospective study that 93 percent of incompletely excised basal cell carcinomas recurred when most (>25 percent) of the palisade layer was irregular, compared with no tumor recurrence after 5 years in lesions with minimal (<25 percent) irregularity of the peripheral palisade. He proposed that very irregular lesions be re-excised and that slightly irregular lesions be observed, in addition to recommending that lesions with intermediate histologic characteristics and poor lymphocytic infiltration be re-excised.

Another study found that incompletely excised basal cell carcinomas of superficial or nodular subtype that were less than 1 cm in diameter, located anywhere except the nose or ears, with less than 4 percent marginal involvement on the initial inadequate excision, had no evidence of tumor persistence.

Thus, for a small group of select patients, close clinical follow-up may be indicated if the risk of recurrence is very low. However, there is general agreement that in the majority of pa-
tients for whom the initial tumor resection is histologically incomplete, immediate reexcision or Mohs micrographic surgery should be performed.

**PREFERRED TREATMENTS**

Preferred treatments (ranked in order of author preference and from literature review) for basal cell carcinomas, based on subtype and anatomic location, are summarized as follows:

- Nodular basal cell carcinoma less than 1 cm in diameter, not in high-risk area: curettage, cryosurgery, excision.
- Nodular basal cell carcinoma greater than 1 cm in diameter, not in high-risk area: excision, cryosurgery (for lesions <2 cm, probably to be combined with curettage), Mohs surgery (lesions >2 cm).
- Nodular basal cell carcinoma in high-risk area: Mohs surgery, excision with frozen section.
- Superficial basal cell carcinoma: shave excision with curettage, curettage and electrodesication, cryosurgery, excision (poor choice for multiple lesions or large trunk lesions).
- Morpheaform basal cell carcinoma, any location: Mohs surgery, excision with frozen section.
- Basal cell carcinoma with aggressive growth pattern, any location: Mohs surgery, excision with frozen section.
- Recurrent basal cell carcinoma: Mohs surgery, excision with frozen section.
- Incompletely excised basal cell carcinoma: reexcision and use of frozen sections if original carcinoma was diffuse, Mohs surgery.

**TREATMENT MODALITIES**

Curettage and electrodesication are the most common method of treating basal cell carcinomas. Tumors less than 2 mm in diameter are eradicated 100 percent of the time, and those measuring 2 to 5 mm have an 85 percent cure rate; the cure rate for tumors greater than 3 cm in diameter is only 50 percent. Although the experienced surgeon can “feel” tumor extensions traced through the curette, curettage is essentially a blind procedure, since no tissue is submitted to the pathologist for confirmation of margins. Even the most avid proponents of this technique reserve it for primary lesions of less than 1 cm in diameter, although some report excellent results (97 percent cure rate with 5-year follow-up) for larger lesions. Trunk and extremity lesions are more amenable to this treatment than lesions on the head and neck.

Cryosurgery for basal cell carcinomas requires a cryoprobe or a liquid nitrogen spray unit. Cotton disks and cotton-tipped swabs dipped in liquid nitrogen are not suitable for treating even superficial basal cell carcinomas. Indications for cryosurgery include nodular or ulcerated basal cell carcinomas (tumors with well-defined borders); most tumors overlying bone or cartilage, including the nasal tip (may be frozen down to the periosteum or perichondrium); and selected eyelid lesions.

The overall cure rate for cryosurgery has been reported to be 97 percent, although most cryosurgically treated lesions measure less than 2 cm in diameter. The morbidity rate associated with cryosurgery is high, and cosmetic results are unpredictable. Treatment-related complications include a long period of edema, permanent loss of pigment, atrophic and hypertrophic scars, and neuropathy from adjacent nerve injury, particularly on the digits or around the elbow. An inherent disadvantage to cryosurgery is the lack of microscopic verification of complete tumor eradication. Contraindications for cryosurgery include morpheaform tumor, basal cell carcinoma of the scalp or at high-risk sites (nasolabial fold, preauricular and postauricular areas), basal cell carcinoma at the lip vermilion border or eyelid free margin, lesions greater than 3 cm (except superficial basal cell carcinoma), basal cell carcinomas fixed to underlying bone or cartilage, and recurrent tumors.

Surgical excision offers a greater than 90 percent overall cure rate (Figs. 12 and 13). Use of loupe magnification in tumor excision allows more accurate visual assessment of tumor borders. The tumor border and tumor margins are marked before injection of local anesthetic, because injection distorts the tumor and prevents accurate palpation of the borders.

A 2-mm margin yields a cure rate of 94 percent in small (<1 cm) nodular lesions. Margins of 3 to 5 mm around a tumor and extending deeply into subcutaneous fat are recommended for primary lesions less than 2 cm in diameter. Lesions greater than 2 cm in diameter tend to have more widespread subclinical extension and require margins of approximately 10 mm. Tumors with aggres-
sive histologic growth patterns and the so-called superficial multicentric basal cell carcinomas also require margin resection of up to 10 mm because of more extensive subclinical spread.

Frozen sections of tumor margins are expensive and not recommended for every suspected basal cell carcinoma or for every patient. They are generally not necessary for well-circumscribed lesions of less than 1 cm in diameter, for lesions in noncritical areas in a location where wide surgical margins can be taken safely, or for lesions where repair requires only direct suture closure and does not involve rearrangement of local tissues or skin graft application. The surgeon can safely excise the lesion and await the pathologist’s interpretation of the permanent sections. If microscopic margins are found to be involved, reexcision will not adversely affect the likelihood of cure.

Frozen sections of margins are recommended for any basal cell tumor in a high-risk area, for any morpheaform basal cell carcinoma, and for lesions greater than 2 cm in diameter.

Frederick Mohs developed the micrographic surgery technique (Fig. 13). The confidence with which adequacy of surgical excision can be predicted depends not only on the width and depth of the excision but also on the thoroughness with which the surgical margin is examined histologically. Current fresh tissue modifications of the original technique no longer involve use of a fixative. Horizontal frozen sections of the entire undersurface of the excised tissue are made and examined microscopically. Cure rates with the Mohs micrographic technique are as high as 99 percent for primary basal cell carcinomas and 95 percent for recurrent basal cell lesions.

Indications for Mohs micrographic surgery include recurrent basal cell carcinomas; basal cell tumors with poorly delineated margins, either morpheaform or arising from scar tissue; lesions in anatomic sites with relatively high rates of treatment failure, specifically periorbital, periauricular, and paranasal areas; critical locations, such as the eyelid, in which maximum preservation of uninvolved tissue is desired; and lesions greater than 3 cm in diameter.

Chemotherapy with topical 5-fluorouracil or with retinoids does not offer acceptable cure rates for general use in the treatment of basal cell carcinomas. Imiquimod 5% cream holds promise as a topical treatment for superficial basal cell carcinoma. Imiquimod is an immune response modifier that induces cytokines, including interferons. A topical agent is of particular advantage for treatment of superficial carcinomas because of their frequently large size and location on the trunk. In addition, there are increasing health and economic burdens in many countries for the treatment of basal cell carcinoma. In Australia, for example, nonmelanoma skin cancers consume the largest proportion of the health budget from all the cancers treated in the whole country.

Thus, there is significant potential economic benefit of having a patient-administered topical treatment option for superficial carcinoma.

Radiation therapy, usually reserved for older patients with basal cell carcinoma, has an overall cure rate of 92 percent and requires specialized equipment (Fig. 14). It is a safe, noninvasive treatment method in selected patients, such as those with basal cell tumors in areas where negative margins are difficult to obtain (nasal, periauricular, and periorbital regions). Potential complications of radiation therapy are dry eye, xerostomia, epilation, lacrimal duct scarring, and skin necrosis.
Other, less frequently used methods of treatment are interferon-alpha therapy (which may be effective for nodular ulcerative and superficial basal cell carcinomas), laser excision (which shows no clear advantage over other methods), and phototherapy (a new treatment modality for basal cell carcinomas that holds some promise for patients with widespread disease, such as Gorlin’s syndrome).

**FOLLOW-UP**

Since most basal cell tumor recurrences appear 1 to 4 years after treatment, follow-up should continue for at least 5 years. Features associated with increased risk for basal cell carcinoma recurrence are long-time presence of the lesion, location of the lesion in a high-risk area (midface, ear), large tumor size, and a lesion with aggressive clinical and histologic features (morpheaform, perineural invasion, neglected tumor, inadequately treated or recurrent lesion, or history of radiation exposure). The frequency with which patients should be seen in follow-up depends on the severity of the cancer treated.

Recognition of recurrent basal cell carcinoma can be difficult. Clinical signs that may be indicators of recurrence include scaling, erythema, crusting, or intermittent ulceration within previous scar; scar enlargement with an increase in telangiectasias; development of papules or nodules within a scar; and frank tissue destruction causing damage such as loss of eyelashes or progressive elevation of the nasal ala.

An additional benefit of observing patients for tumor recurrence is that many first-time patients later develop new lesions of which they are often unaware. Twenty percent to 33 percent of basal cell carcinoma patients will develop a new lesion within 1 year of having been treated for the initial lesion, and by the fifth year, 36 percent of patients will develop another basal cell carcinoma. Posttreatment surveillance is particularly important for patients with skin types I and II who incur frequent sun exposure.

The risk of developing subsequent nonmelanoma skin cancers was extensively evaluated by meta-analysis of 17 previously published reports. The 3-year cumulative risk of a subsequent squamous cell carcinoma after an index squamous cell carcinoma is 18 percent (10-fold increase compared with first tumor incidence). For basal cell carcinomas, the 3-year cumula-

Fig. 13. This sclerosing preauricular basal cell carcinoma is best excised using Mohs micrographic techniques.
The risk of developing a basal cell carcinoma in patents with a prior squamous cell carcinoma is about equal to that risk among persons with a prior basal cell carcinoma, but the risk of developing a squamous cell carcinoma in persons with a prior basal cell carcinoma is low (6 percent).

Since early detection of a smaller basal cell carcinoma may reduce scarring and disfigurement, and since more than 80 percent of basal cell carcinomas occur on the face and neck (sites easily monitored by the patient), patient and family education and a yearly complete skin examination are essential for detecting new basal cell carcinomas not yet noticed by the patient. Patients with a history of multiple basal cell carcinomas would benefit from more frequent follow-up examinations. The need for continued surveillance of patients with basal cell carcinoma who have remained tumor-free after 3 years is limited. Because of the greater clinical importance of squamous cell carcinoma and these patients’ high rate of both subsequent squamous and basal cell carcinoma, annual follow-up examinations for at least 3 years and education with self-examination are especially important.

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REFERENCES


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