Consensus for Nonmelanoma Skin Cancer Treatment: Basal Cell Carcinoma, Including a Cost Analysis of Treatment Methods

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BACKGROUND Basal cell carcinoma (BCC) is the most common cancer in the US population affecting approximately 2.8 million people per year. Basal cell carcinomas are usually slow-growing and rarely metastasize, but they do cause localized tissue destruction, compromised function, and cosmetic disfigurement.

OBJECTIVE To provide clinicians with guidelines for the management of BCC based on evidence from a comprehensive literature review, and consensus among the authors.

MATERIALS AND METHODS An extensive review of the medical literature was conducted to evaluate the optimal treatment methods for cutaneous BCC, taking into consideration cure rates, recurrence rates, aesthetic and functional outcomes, and cost-effectiveness of the procedures.

RESULTS Surgical approaches provide the best outcomes for BCCs. Mohs micrographic surgery provides the highest cure rates while maximizing tissue preservation, maintenance of function, and cosmesis.

CONCLUSION Mohs micrographic surgery is an efficient and cost-effective procedure and remains the treatment of choice for high-risk BCCs and for those in cosmetically sensitive locations. Nonsurgical modalities may be used for low-risk BCCs when surgery is contraindicated or impractical, but the cure rates are lower.

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Nonmelanoma skin cancer (NMSC) affects 3.5 million people per year in the United States, and basal cell carcinomas (BCCs) comprise of 80% of these cancers.[1–3] In the US population, there are more skin cancers in general and more BCCs in particular than all other cancers combined, with an estimated lifetime risk of 1 in 5.[2] The BCC incidence continues to rise, doubling every 25 years. Although BCCs are generally slow-growing and rarely metastasize, these tumors may insidiously invade the surrounding tissue, causing local tissue destruction, functional impairment, and cosmetic disfigurement. Basal cell carcinoma may also invade nerves and other vital structures such as the eye.

Unlike most other cancers, NMSCs are not regularly recorded in cancer registries, making it difficult to determine accurate incidence rates in large populations. Basal cell carcinoma occurs in all skin types and races. Although the incidence of BCC increases with age, the incidence in young people under 40 years of age is

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increasing as well.[4] Based on a 2006 analysis of population-based claims from multiple US government data sets, including the Centers for Medicare and Medicaid Services (CMS), the total number of NMSC in the US population was estimated to be 3,507,693 and the total number of people treated was estimated at 2,152,500.[1] From 1992 to 2006, the total number of procedures for skin cancer in the Medicare population increased by 76.9% from 1,158,298 to 2,048,517. During this period, the number of procedures for NMSC increased by 16% in the Medicare population. Despite the increasing incidence of skin cancer, the overall mortality from NMSC is decreasing,[5,6] suggesting that early recognition and effective treatment may be altering mortality rates seen from NMSC.

There are many approaches to the management of BCC, and there is no definitive standard of care for the treatment of this tumor. The primary goal of BCC treatment is complete tumor eradication with maximal preservation of normal function and cosmesis. The purpose of this consensus guideline is to assist the physician in choosing a management approach that is best for their patient while being mindful of efficacy, likelihood of cure, cosmetic outcome, functional result, and cost.

Epidemiology

Basal cell carcinoma (BCC) is the most common malignancy in humans. Although BCC occurs in all skin types and races, it is most likely to develop in light-skinned individuals.[7,8] The incidence of BCC is high in white populations of Celtic heritage and low in Hispanics, Asians, and Blacks. The rate of BCC development is 19 times less common in dark-skinned populations than in white populations.[9] The low skin cancer rates observed in dark-skinned populations have been attributed to increased melanin production, which provides a photoprotection factor of up to 13.4.[10,11]

The reported man to woman ratio of those affected with BCC is 1.3 to 1.6:1.[9,12,13] A retrospective record review from 13,457 BCCs in 10,245 patients at a dermatopathology center in France from 1967 to 1996 found the man to woman ratio of 0.92:1.[14] Basal cell carcinoma is rare in children[15] and increases in frequency with age, with a median age at diagnosis of 68 years. In 1 study,[14] the anatomic distribution of BCCs in men was as follows: head and neck (79.6%), trunk (13.4%), upper limbs (3.8%), lower limbs (1.5%), and genitalia (0.1%). In women, the distribution was head and neck (83.9%), trunk (9.4%), upper limbs (2.5%), lower limbs (2.5%), and genitalia (0.2%).[14]

There is great variability in the incidence of BCC worldwide. People living in regions near the equator or with a high ultraviolet-B (UVB) index are at great risk. Australians have the highest incidence, with 2,074 BCC per 100,000,[16] whereas in Finland the incidence is 49 per 100,000. In the United States, age-standardized incidence rates in white populations range from 159 to 407 BCC per 100,000 men and 87 to 212 BCC per 100,000 women.[17] In states near the equator such as Hawaii,[18] the incidence of BCC is 3 times more common than in upper Midwestern states such as Minnesota.[12] The German Cancer Registry showed European age-standardized incidence rates of 80.8 BCC per 100,000 for men and 63.3 BCC per 100,000 for women in 2003.

The incidence of BCC has been steadily increasing.[1,9,19] In Canada from 1960 to 2000, there was an increase from 30.7 to 93.9 per 100,000 in men and 25.7 to 77.4 per 100,000 in women. In Finland, from 1970 to 1995, incidence rates increased from 20.7 to 49.3 per 100,000 in men and 19.3 to 45.0 per 100,000 in women. In the US, the estimated incidence of NMSC increased from 900,000 to 1,200,000 in 1994[20] and to 3,507,693 in 2006.[1] The increased incidence of BCC has been attributed to greater UV exposure as a consequence of ozone depletion,[9] greater sun-seeking behavior and exposure,[21,22] and increased longevity of the population.[23] A recent Mayo Clinic population-based study showed that the BCC incidence in young people (<40 years) is increasing faster in women, from 13.4 to 31.6 per 100,000, than in men, from 22.9 to 26.7 per 100,000. The increased rates of BCC in younger patients are likely due to environmental and behavioral influences, not simply greater lifespan.[4]

Pathogenesis and Etiology

Ultraviolet Radiation Exposure

Chronic sun exposure is the most common risk factor for the development of BCC,[24,25] with a typical latency

period of 15 to 20 years between the time of UV damage and clinical onset. Both UVA and UVB exposure contribute to BCC formation, whether from sunlight, UV light therapy, or tanning booths.[26] Fitzpatrick skin type categorizes patient sensitivity to UV and is a good predictor of relative risk of BCC among whites. Geographic locations with greater UV exposure such as those at higher altitudes and lower latitudes are associated with a higher prevalence of BCC. However, UV exposure is not the only risk factor; in fact, 20% of BCC arise on non–sun-exposed skin.[22] In addition to the cumulative UV dose and skin type, the presence of dysmorphic genes, and the duration and intensity of exposure, particularly in early childhood and adolescence, all play a role in BCC development.[22,27,28]

Ultraviolet radiation exposure induces BCC formation by means of direct DNA damage, indirect DNA damage through reactive oxygen species, and immune suppression. UVB directly damages DNA and RNA with a characteristic C → T or CC → TT transition. UVA is absorbed by melanin and damages DNA indirectly through free radicals. Ultraviolet exposure also causes dose-dependent suppression of the cutaneous immune system, impairing immune surveillance of skin cancer. Cellular immunity is impaired through a reduction in Langerhans cells, dendritic epidermal T cells, and Th1+ cells, and an increase in suppressor T cells. Ultraviolet exposure produces an increase in immunosuppressive cytokines, including tumor necrosis factor alpha, interleukin (IL) 1, IL 10, and prostaglandins.[29–31]

Signaling Pathways

Pathologic alterations in the Hedgehog (Hh) molecular signaling pathway are important in the pathogenesis of sporadic BCC and basal cell nevus syndrome (BCNS), also named Gorlin syndrome. The Hedgehog gene in the Hh signaling pathway codes for the sonic Hedgehog protein (SHH), an extracellular protein that binds to a cell membrane receptor complex.[32,33] On binding, the cell membrane receptor complex initiates a chain of cellular events leading to cell proliferation. The cell membrane receptor complex consists of 2 proteins: the patched (PTCH1) protein and smoothened (SMO) protein. The PTCH1 is the ligand binding site for SHH; SMO is responsible for transducing Hh signaling downstream. In the normal resting state, the PTCH1 holds SMO in the inactive state and inhibits signaling downstream. When SHH binds to the PTCH1, inhibition of SMO is released and results in the activation of transcription factors and the expression of cell cycle regulator genes. The PTCH1 mutations prevent PTCH1 protein from binding to SMO. When SMO is unbound, unregulated cell proliferation occurs. Unregulated cell proliferation may also be associated with overexpression of SHH. The PTCH1 gene mutations occur in up to 70% of people with sporadic BCC; 10% to 20% of people with sporadic BCC have SMO mutations. There is an inherited mutation of 1 allele of the PTCH1 gene in Gorlin syndrome, leading to an autosomal dominant syndrome of predisposition to BCC.

More than 50% of BCCs have defects in the tumor suppressor gene p53, which resides on chromosome arm 17p.[32–34] The majority of these mutations are UV-specific, suggesting that sunlight plays a causative role in the development of BCC. However, approximately 40% of *PTCH* mutations in BCC are not typical of UV mutagenesis.

Previous Nonmelanoma Skin Cancer

The most common predisposing factor for the development of BCC is a history of BCC or squamous cell carcinoma (SCC). There is at least a 10-fold increased incidence of second BCCs in patients with a BCC history compared with that in patients without a history of NMSC. This risk is reported to be 35% at 3 years and 50% at 5 years after initial diagnosis.[35,36]

Other Exposures and Associations

Basal cell carcinoma may also result from exposure to other external carcinogens such as ionizing radiation. Patients treated with radiation for benign dermatoses, such as eczema, psoriasis, acne vulgaris, and tinea capitis, as well as other x-ray and Grenz ray exposure, developed BCCs decades later in the radiated areas.[37–39] Exposure to arsenic, once commonly used as an insecticide and medicinal ingredient (Fowler solution), is associated with BCC development. Controversy exists as to whether smoking and alcohol consumption increases the risk of BCC.[40,41] Photochemotherapy with

psoralen and UVA (PUVA) increases the risk for cutaneous squamous cell carcinoma, but the role of PUVA in the development of BCC remains unclear.[42] Basal cell carcinomas occur in 30% to 50% of nevus sebaceous lesions,[43] and BCC may develop in chronic scars such as thermal burns and vaccination scars.[44]

Immunosuppression

The lifetime risk of BCC is increased in chronically immunosuppressed patients, including those with AIDS, stem cell transplants, and solid organ transplants, but not to the degree observed with SCC.[45–47]

Genodermatoses and Syndromes

Xeroderma pigmentosum, epidermodysplasia verruciformis, BCNS, Bazex syndrome, and Rombo syndrome are all associated with an increased risk of BCC. More complete information on this topic has been provided in the section "Additional Considerations."

Clinical Features

Although there are many clinical variants of BCC, the most commonly recognized types are nodular, superficial, and morphea-like BCC. The clinical appearance of the BCC can often be misleading with respect to its risk of aggressive behavior. Lesions that have the clinical features of 1 distinct clinical subtype will often be found to contain multiple histologic patterns within the lesion after histologic analysis of the entire specimen.

Nodular BCC

Nodular BCC, the most common clinical form of BCC, presents as a translucent papule or nodule with surface telangiectases. The borders may become rolled or pearly. The size of a nodular BCC may be quite variable; although most are small, they can grow to large sizes if neglected. Local invasion and destruction of adjacent tissue ensues if the lesion is not treated or treated inadequately. Ulceration is common and, if present, is called a noduloulcerative type of BCC. Patients will often give a history of recurrent bleeding and crusting, causing them to seek evaluation. Any chronic nonhealing ulceration should be evaluated by skin biopsy to exclude the possibility of BCC.

Pigmented nodular BCC occurs when melanin pigment is admixed in the tumor mass. Because of its black color, it may be mistaken for a seborrheic keratosis, melanocytic nevus, or melanoma. Pigmented nodular BCCs are more common in dark-skinned individuals and those with brown eyes than in light-skinned individuals with blue eyes.

Superficial BCC

Superficial BCC presents as a pink–red scaly macule or patch, which may contain telangiectases. Portions of a superficial BCC may evolve into nodular BCC over time. Superficial BCC usually presents on the shoulders, back, or chest, and multiple lesions may be present at one time. Because of its similarity in appearance to inflammatory dermatoses such as psoriasis or eczema, one should consider the diagnosis of superficial BCC when confronted with a persistent erythematous scaly patch. As with nodular BCCs, superficial BCC may also be pigmented.

Morphea-like BCC

Morphea-like BCC, often referred to as morphea-form BCC and sometimes as sclerosing or fibrosing BCC, is a distinct clinicopathologic entity. It appears as a flesh-colored-to-pale flat or a slightly elevated plaque with indistinct borders that is indurated and often resembles a scar or localized morphea, hence the derivation of its name. Morphea-like BCC is often not recognized because of its subtle clinical appearance. Ulceration may occur in long-standing lesions. In patients who have a scar or scar-like lesion without a history of trauma or surgery, a biopsy should be performed to rule out morphea-like BCC.

Histopathology

Confirmation of the clinical diagnosis of BCC requires a skin biopsy. Regardless of whether a shave, punch, or excisional biopsy is performed, it is important to include some portion of the dermis in the specimen to differentiate between superficial and other invasive histologic subtypes of BCC. The value in classifying the histologic subtype of BCC is that certain subtypes behave aggressively and are likely to recur if not completely eradicated.[48,49] Although there are 3 main

clinical subtypes of BCC, many tumors have several histologic patterns in 1 lesion.

The characteristic histologic feature seen in all BCCs is groups (or nests) of basaloid cells. Each of these small pleomorphic cells is composed of a basophilic nucleus without a discernible nucleolus and scanty cytoplasm. In general, basaloid cells are nonanaplastic, lacking evidence of cellular atypia, and have low mitotic activity. Retraction artifact between the tumor mass and its surrounding stroma is typically seen on paraffin-embedded sections. Mucin deposition may be present within and surrounding the tumor. Tumor necrosis and ulceration may also be present. The surrounding stroma shows increased numbers of fibroblasts and an increased amount of collagen.

The nodular BCC subtype has round, relatively large masses of tumor cells with peripheral palisading of nuclei at the tumor borders. Tumor nodules can be seen attached to the overlying epidermis and in the dermis. The histologic differential diagnosis may include trichoepithelioma or trichoblastoma. The superficial subtype has small buds of basaloid cells descending from the epidermis. To qualify as superficial, the tumor masses are limited to those attached to the epidermis, with no dermal invasion.

Both nodular and superficial BCC subtypes may have tumor masses with spiky projections. The basaloid cells are arranged as elongated strands with little or no palisading of the peripheral cells. When this occurs, the tumor can be classified as infiltrative in addition to its subtype. Thus one can have a nodular infiltrative BCC or a superficial infiltrative BCC. When most of the tumor nests have spiky projections, the tumor may invade deeply and is referred to as an infiltrative BCC. There may be cells of variable size and shape or foci of squamous differentiation. Clinical ulceration may be present. When BCCs are recurrent, the tumor is embedded in fibrous tissue and frequently there are spiky projections.

The micronodular subtype has histologic features similar to those of the nodular subtype, except that the tumor is composed of multiple small nodules. The morphea-like (morphea-form, sclerosing) subtype is composed of thin strands of basaloid cells that invade the dermis, surrounded by dense fibrous stroma. The histologic differential diagnosis may include desmoplastic trichoepithelioma, microcystic adnexal carcinoma, or metastatic cancer. Basosquamous or metatypical BCC shows features of both BCC and SCC.[51] The exact nature of this lesion is controversial.

In 1 study,[48] the most common histologic subtypes of BCC are nodular, superficial, and micronodular. However, a BCC frequently presents with more than 1 histologic pattern. For instance, BCCs may present with both nodular and infiltrative patterns, or nodular and superficial patterns. In the above study,[48] this mixed pattern BCC occurred in 38.6% of lesions, with a mixed nodular-micronodular pattern being the most common mixed presentation. Several BCC subtypes, including morphea-like (morphea-form, sclerosing), micronodular, and basosquamous (also referred to as metatypical or mixed), are considered to be aggressive histologic variants and have a high risk of recurrence.[49,50]

Other less common histologic subtypes of BCC are identified. The adenoid subtype has tumor strands forming gland-like structures. The keratotic subtype contains horn cysts in association with typical basaloid tumor cells without evidence of squamous differentiation. Pigmented BCC results from the presence of melanocytes and melanin admixed with the tumor cells. In clear cell BCC, a portion of tumor cells contains glycogen-filled cytoplasmic vacuoles. Basal cell carcinoma may have tumor cells with sebaceous or matrical differentiation. The fibroepithelioma of Pinkus has anastomosing strands and aggregates of basaloid cells surrounded by a fibrous stroma; occasionally, the basaloid aggregates become very proliferative and infiltrate tissue.

Clinical Risk Factors for Aggressive Tumor Behavior—"High-Risk" BCC

Although BCCs are commonly slow-growing tumors that rarely metastasize, they can infiltrate tissue in any direction and may be clinically imperceptible, leading to extensive tissue destruction, functional impairment, and cosmetic disfigurement. Thus, the treatment goal is complete tumor eradication. To this end, BCC

management is dependent on assessing the clinical risk factors of the individual tumor for aggressive growth, recurrence, and metastasis. Table 1 summarizes these high-risk factors.

Location

Basal cell carcinomas located on the head and neck are more likely to recur than those on the trunk and extremities.[52–54] In a 27-year retrospective review of curettage and electrodesiccation (C&E) of 2,314 primary BCCs at the Skin and Cancer Unit of NYU School of Medicine, modified life-table 5-year recurrence rates were generated based on the anatomic location of the tumors, and showed the following:[55]

1. The high-risk sites correspond to the "mask" areas of the face, including the central face, periocular region, eyelid, eyebrow, nose, perioral, lip (cutaneous and vermilion), chin, mandible, ear, preauricular, postauricular, and temple skin, as well as the hands, feet and genitalia.
2. The cheeks, forehead, scalp, and neck are the intermediate risk sites.
3. The trunk and extremities have the lowest risk of recurrence.

TABLE 1. High-Risk Factors for BCC Recurrence

Tumor factors
Any BCC on high-risk anatomic sites (the "mask" areas of the face, including the central face, periocular region, eyelid, eyebrow, nose, perioral, lip (cutaneous and vermilion), chin, mandible, ear, preauricular, postauricular, and temple skin, as well as the hands, feet, and genitalia)
BCC >1 cm in diameter on intermediate risk sites (cheeks, forehead, scalp, and neck)
BCC >2 cm in diameter on the trunk and extremities
BCC with poorly defined borders
BCC with aggressive histologic patterns (morphea-like, infiltrative, micronodular, metatypical, basosquamous cell carcinoma)
BCC with perineural involvement
Recurrent BCC
Host factors
BCC on sites of previous radiation therapy, burn scars
BCC in patients younger than 40 years
BCC in immunosuppressed patients
BCC in patients with genetic syndromes
BCC in chronic scars, ulcers, sites of inflammation
BCC in patients with a history of aggressively-behaving tumors

Size

The larger the size of the tumor, the greater the risk of recurrence. The authors have adopted the size intervals used by others to distinguish high-risk BCC: (1) tumors in the high-risk areas 6 mm or greater, (2) tumors in the intermediate risk areas 10 mm or greater; and (3) tumors in any area 20 mm or greater.[52,53,56–58]

Borders

Basal cell carcinomas with poorly defined clinical borders have a higher risk of recurrence after primary treatment compared with well-circumscribed lesions.[59–61]

Pathologic Subtype

Basal cell carcinomas with aggressive histologic growth patterns include those with morphea-like (sclerosing), micronodular, mixed infiltrative, or basosquamous features in any area of the tumor. Low-risk histologic subtypes of BCC include nodular, superficial, infundibulocystic, and fibroepithelioma of Pinkus.[62]

Perineural Involvement

Perineural involvement is less common in BCC than SCC, but when present can be associated with a high risk of recurrence.[49,63] An MRI is warranted to rule out musculoskeletal infiltration when any major named nerve involvement is suspected. When extension through foramina is a concern, a CT scan and PET scan with and without contrast may be considered. A PET/CT scan could also be ordered whereby it can be done in 1 sitting and allow excellent localization of any lesion found.

Primary Versus Recurrent

Recurrent tumors demonstrate greater histologic extension than primary ones and are thus more aggressive. Consequently, cure rates are lower with all treatment modalities for recurrent tumors compared with those for primary tumors[64] (Table 2).

TABLE 2. Five-Year Recurrence Rates for Treatment of Primary and Recurrent BCC

Treatment Method	*5-Year Recurrence Rate for Primary BCC (%)*	*5-Year Recurrence Rate for Recurrent BCC (%)*
Mohs surgery	1.0*	5.6†
All non-Mohs surgery methods	8.7*	19.9†
SSE	10.1*, 4.8‡	17.4†, 11.6‡
C&E	7.7*, 13.2§	40.0†, 18.1§
Radiation therapy	8.7*, 7.4‖	9.8†, 9.5‖
Cryotherapy	7.5*	13†¶

*Rowe and colleagues[64] JDSO March 1989.
†Rowe and colleagues[61] JDSO April 1989.
‡Silvermann and colleagues[65] Part III.
§Silverman and colleagues[55] Part II.
‖Silverman and colleagues[66] Part IV.
¶Data less than a 5-year follow-up.

Site of Previous Radiation Therapy

Basal cell carcinomas arising within radiation treatment fields are at greater risk for recurrence or metastasis.[38,39]

Young Age

Less than 15% of BCCs occur in patients younger than 35 years, but clinically and histologically aggressive subtypes occur more often in this group. In a review of 3,381 patients, 38% of women younger than 35 years had morphea-like, infiltrative, or recurrent BCC compared with 9% of women aged 35 years or older. Twenty-five percent of men younger than 35 years had aggressive BCC compared with 11% of men aged 35 years or older.[67]

Immunosuppression

The likelihood of BCC and SCC increases when a patient is immunocompromised,[68–81] such as after an organ transplant and during or after long-term PUVA. Usually, the incidence of SCC is higher than that of BCC in immunosuppressed patients. The literature suggests that there is a high incidence of aggressive tumor behavior and metastasis of SCC in organ transplant recipients, but the data are less clear in the case of BCC. In a recent immunohistochemical study of NMSC in renal transplant and immunocompetent patients, BCC and SCC from the renal transplant patients exhibited increased expression of pro-oncogenic markers compared with tumors from control patients.[68] In addition to solid organ transplants, BCC and SCC occur with increased frequency in hematopoietic cell transplantation patients[77] and in patients with myelodysplasia, acute and chronic leukemias,[78–80] and HIV.[81]

Clinical Evaluation

A complete skin examination is performed by a qualified physician because individuals with a skin cancer often have additional cancers or precancers at other sites and are also at increased risk of developing malignant melanoma.[35] A skin biopsy is performed on suspicious lesions and includes the deep dermis if a clinically appearing morphea-like or nodular lesion is present. Suspicious lesions are often difficult to follow clinically in high-risk patients with multiple skin cancers and precancers. Photographs or digital images are recommended for documenting the location of specific lesions, and there is a low threshold for obtaining skin biopsies in these patients. Preoperative imaging studies may be obtained when there is suspicion of parotid gland, muscle, deep soft tissue, orbital, bone involvement, or perineural invasion.[62]

Selection of Therapy

There are 3 goals of BCC treatment: (1) to remove the tumor completely so that no tumor persists and recurs at a later time, (2) to avert or correct any functional impairment resulting from tumor removal, and (3) to provide the best possible cosmetic outcome, especially because most BCCs are on the face. For a given BCC, the cure rate associated with a treatment modality is the key consideration in choosing the most appropriate therapy.

Valid recurrence rates can only be obtained from studies with at least 5 years of follow-up. Less than

one-half of BCC recurrences occur within 2 years after treatment and less than two-thirds occur within 3 years after treatment. In a systematic review of the literature, the average recurrence rates for non-Mohs surgical therapies in studies with less than 5 years of follow-up was 4.2%, compared with 8.7% in studies with a 5-year follow-up. Thus, the short-term studies underestimated the recurrence rate by a factor of greater than 2.

The 5-year recurrence rates for treatment of primary and recurrent BCC have been analyzed in 2 types of studies (Table 2). One type of study was a systematic review that evaluated published studies meeting specific criteria and obtained weighted average 5-year recurrence rates for treatment of primary and recurrent BCC. The recurrence rates for primary BCC[64] were as follows: Mohs surgery 1.0%, surgical excision 10.1%, C&E 7.7%, radiation therapy 8.7%, and cryosurgery 7.5%. The same methodology was applied to published studies with a 5-year follow-up for treatment of recurrent BCC.[61] Recurrence rates were as follows: Mohs surgery 5.6%, surgical excision 17.4%, C&E 40.0%, and radiation therapy 9.8%. The reported recurrence rate for cryosurgery for recurrent BCC is 13%, but the follow-up period was less than 5 years.

The other type of study was from 1 dermatology department (New York University Department of Dermatology) that used comparative data obtained from a retrospective review of the computerized records of 5,755 BCC that were treated at the Skin and Cancer Unit of New York University Medical Center during 1955 to 1982. The 5-year recurrence rates for primary BCC based on the life-table method were: surgical excision 4.8%[55,65] and radiation therapy 7.4%.[66] The recurrence rates for the treatment of recurrent BCC were surgical excision 11.6%,[65] EDC 18.1%,[55] and radiation therapy 9.5%.[66]

These latter studies have a number of limitations. There is no stratification based on location or size of the lesion, which can impact recurrence rates. It is likely that more aggressive tumor types were preferentially treated with surgical excision or Mohs surgery; this would underestimate the recurrence rates for other modalities such as C&E, which are generally reserved for the treatment of small low-risk BCC. Prospective randomized studies of tumors with the same histologic type, location, and size are necessary to more adequately compare the cure rates of the various treatment modalities.

A small low-risk BCC is easily treated, but a high-risk BCC has the potential to exhibit extensive growth beyond the visually apparent tumor, resulting in great local tissue destruction. Such a tumor may invade into parotid gland, orbit, cartilage, bone and, occasionally, even the central nervous system through involvement of peripheral nerves. Mohs surgery is perhaps the most effective treatment for any BCC, but this treatment method is particularly useful for tumors at high risk of recurrence (Table 1).

In addition to the clinical and pathologic tumor characteristics already described, other factors that are evaluated before determining the most appropriate treatment include the patient's general medical condition and psychosocial factors, such as the ability to return for additional treatment, and whether the tumor is in a cosmetically sensitive location. Treatment cost is also a factor because there is a wide range in fees depending on the procedure and the site of service. A more detailed discussion of the cost analysis is provided in section "Cost Analysis."

Surgical Therapy

Surgical treatment of BCC provides the most effective treatment of BCC, based on an evidence-based review of the literature.[82] Surgical techniques include Mohs surgery that offers intra-operative complete, circumferential, and deep margin analysis; excision with postoperative pathologic examination usually done with incomplete margin assessment ("standard surgical excision" [SSE]); and intra-operative frozen section margin sampling,[83,84] which is frequently incomplete.[85]

Mohs Surgery

Mohs surgery, also known as Mohs micrographic surgery, has the best long-term cure rate of any

treatment modality for BCC. It is the treatment of choice for high-risk BCCs and recurrent BCCs because of its high cure rate and tissue-sparing benefit.[59,61,64,86] The high cure rate is achieved because all of the tissue margins are examined, compared with standard vertical sectioning, in which less than 1% of the outer peripheral and deep margins are examined. Thin layers of tissue are taken only in the areas of positive tumor margins, minimizing the wound defect size and enabling a superior cosmetic outcome. In most cases, reconstruction of the defect after Mohs surgery can be performed the same day. In some circumstances, a delay may be required, for example, when a deep wound requires granulation to improve skin graft survival or contour, or when the assistance of a second reconstructive surgeon is necessary. Sometimes, there is a reconstructive delay after Mohs surgery so that paraffin-embedded sections may be examined for better visualization of tumors such as melanoma.

Because the most effective treatment for any BCC is Mohs surgery, it remains the best treatment option for tumors at high risk of recurrence after other treatment modalities. Basal cell carcinomas at high risk for recurrence include (1) primary BCC on high-risk anatomic sites, especially if $\geq$ 0.6 cm; (2) BCCs larger than 1 cm in diameter on intermediate-risk anatomic sites; (3) BCCs larger than 2 cm in diameter on the trunk and extremities; (4) BCCs with poorly defined borders; (5) BCCs with aggressive histologic patterns (e.g., infiltrative, morphea-like, micronodular, metatypical); (6) BCCs with perineural involvement; (7) BCCs in sites of previous radiation therapy; (8) BCCs in patients younger than 40 years; (9) BCCs in immunosuppressed patients; (10) BCCs in patients with BCNS or xeroderma pigmentosum; (11) recurrent BCC; (12) incompletely excised BCC; and (13) BCC in patients with a history of aggressively-behaving tumors Mohs surgery is also the optimal treatment when tumors are located in areas where maximal preservation of normal tissue is preferred or required.

The American Academy of Dermatology[87] in conjunction with the American College of Mohs Surgery, the American Society for Dermatologic Surgery Association,[87] and the American Society for Mohs Surgery recently adopted the first appropriate use criteria (AUC) for Mohs surgery. The AUC included an extensive analysis of the literature that met evidence-based criteria. After this review was completed, 72 case scenarios were created for BCC and voted on for the appropriateness of using Mohs surgery. Those physicians who ranked the case scenarios included not only dermatologists who perform Mohs surgery, but mostly dermatologists who do not perform Mohs surgery. Thus, the ultimate scoring was a blend of both published data and clinical experience. A summary of the AUC guidelines for the treatment of BCC is found in Table 3.

Adverse Effects. Mohs surgery is a very safe outpatient procedure. In a prospective study of 1,358 cases, the overall complication rate was 1.64%.[88] Most surgical complications involved difficulties with hemostasis. No complications were significant enough to involve the assistance of another specialist or to require the hospitalization of the patient.

Advantages. Mohs surgery on average has the highest cure rates for both primary and recurrent BCC. Because Mohs surgery is a tissue-sparing technique, smaller surgical margins are taken initially than with SSE; in addition, with MMS, scarring and functional impairment is often minimized compared with SSE. When used as an adjunct to curettage (as in C&E), electrocoagulation or electrodesiccation can result in atrophic white scars that are rarely seen after second-intention healing after Mohs surgery. Tumor removal and reconstruction are usually performed on the same day, using local anesthesia in an office-based setting. Mohs surgery usually obviates the need for additional visits for delayed reconstruction that are required when side-to-side closure or second-intention healing is not possible with large wound defects after SSE. The 5-year recurrence rates for Mohs surgery are 1% for primary BCCs and 5.6% for recurrent BCCs (Table 1). A systematic review of 298 studies of recurrence rates for primary BCCs, of which only 18 satisfied identified criteria for analysis of treatment modalities, showed that the lowest recurrence rates after 5 years were obtained with Mohs surgery followed by surgical excision, cryosurgery, and C&E.[89]

Disadvantages. The primary disadvantage of Mohs surgery is its expense when compared with C&E, but the cost of Mohs surgery compares favorably with

TABLE 3. Appropriate Use Criteria for Treatment of BCC by Mohs Surgery[87]

Tumor Type	*Area H*	*Area M*	*Area L*
Primary superficial BCC	Mohs appropriate	Mohs appropriate (if ≥0.6 cm) in nonimmunocompromised patient*; Mohs appropriate in immunocompromised patient (any size tumor)	—*
Primary nodular BCC	Mohs appropriate	Mohs appropriate	Mohs (if >2.0 cm) in nonimmunocompromised host; Mohs appropriate (if >1.0 cm) in immunocompromised patient*
Primary aggressive BCC	Mohs appropriate	Mohs appropriate	Mohs appropriate (if >0.5 cm)*
Recurrent BCC or other high-risk features	Mohs appropriate	Mohs appropriate	Mohs appropriate (if nonsuperficial)*

*Mohs surgery is indicated for special patient features, regardless of lesion size or being superficial, including the following: radiation therapy, genetic syndromes, chronic ulcer or inflammation, osteomyelitis, traumatic scar.

SSE when the cost of pathology, the savings of re-excisions to obtain clear margins, and fewer recurrences are factored in.[90] Mohs surgery is significantly less expensive than SSE with frozen section margin control in an ambulatory care center or hospital setting. Mohs surgery is also a time-consuming technique because of its comprehensive laboratory examination of the excised tissue.

Standard Surgical Excision

Standard surgical excision consists of surgical excision followed by postoperative pathologic analysis with permanent sections. For well-circumscribed tumors with diameters less than 2 cm, 4-mm margins are adequate most of the time.[91] Larger margins should be considered (4–6 mm) for re-excision of low-risk primary BCC if positive margins were obtained after the initial excision. For tumors larger than 2 cm in diameter on low-risk locations (trunk and extremities), 10-mm margins are recommended. Thus, in some cases, large margins are required to increase the likelihood of complete tumor removal with SSE, and thus SSE may result in a larger surgical defect and a larger scar than those with Mohs surgery.

Adverse Effects. The risk of infection and hematoma formation is low.

Advantages. Unlike destructive or topical modalities, there is histologic analysis of the excised tissue specimen. If the BCC is excised in 1 procedure in an office setting, the cost may be less than for Mohs surgery. Standard surgical excision has faster operative time than Mohs surgery, but Mohs surgery has a higher cure rate. For sutured wounds, SSE has a faster healing and requires less postoperative care than C&E wounds.

Disadvantages. Repair of SSE defects before permanent-section histologic confirmation of negative margins is performed with side-to-side closure if possible, because tissue rearrangement (skin flaps) can make locating positive margins, if found on permanent sections, difficult. In situations where skin grafting or tissue rearrangement will be required for closure, Mohs surgery is preferred because it will usually preclude the need for a staged procedure. The lack of complete surgical margin assessment accounts for the higher recurrence rates observed with SSE than those with Mohs surgery.

Destructive Modalities and Nonsurgical Therapies

Alternative treatment approaches for BCC include curettage alone or followed by electrodesiccation (C&E), radiation therapy, cryosurgery, topical medications, and photodynamic therapy (PDT). Nonsurgical modalities may be considered for superficial low-risk BCC, although the cure rate may be lower than that with surgical treatment.

Curettage and Electrodesiccation

Curettage and electrodesiccation[92–94] is used for low-risk BCC but is not recommended for high-risk BCC because of unacceptably high recurrence rates. There are multiple techniques described for curettage with or without electrodesiccation. Evidence from long-term data indicates that as a technique, C&E can yield varying cure rates based on the experience of the clinician performing the procedure.[55] For appropriately selected tumors, curettage alone has been shown to have a cure rate equal to that of C&E, with better healing.[94] Curettage and electrodesiccation should not be used for tumors present on terminal hair-bearing skin because of the risk of tumor extension along follicular structures. If the subcutaneous layer reached during the curettage or the biopsy result obtained from the curettage reveals a high-risk BCC subtype, SSE or Mohs surgery is recommended. Curettage and electrodesiccation is a reasonable treatment option for small superficial and nodular primary BCCs with nonaggressive histology, particularly in those patients unable to undergo a more extensive surgical procedure or radiotherapy.

Adverse Effects. Basal cell carcinomas treated with C&E are left to heal by second intention and often leave a white atrophic scar that can be cosmetically disfiguring; BCCs treated with curettage alone have a lower risk of hypopigmentation and scarring.[94]

Advantages. Curettage and electrodesiccation is the least expensive and fastest method to treat BCC.

Disadavantages. Curettage and electrodesiccation produces wounds that require more wound care and have slower healing than sutured wounds. Curettage and electrodesiccation often produces white, atrophic scars that can be cosmetically unacceptable to many patients and results in recurrence rates that are excessively high for high-risk BCC. Curettage alone produces much less hypopigmentation.[94] Healing after curettage is primarily dependent on wound depth; deep wounds are likely to leave a persistent depression, especially on the nose. There is no histologic confirmation of complete tumor clearance.

Radiation Therapy

Radiation therapy is used as the primary treatment or as an adjuvant therapy for NMSC. Three methods are currently used for radiation therapy of NMSC.[95–98] Orthovoltage or superficial x-rays range from 75 to 125 kV and are used for lesions less than 5 mm in thickness. Megavoltage electron beam technology, now more commonly used, penetrates tissue up to 6 cm and uses electron beams 6 to 20 MeV in strength. Brachytherapy is a third method, where the radioactive source is applied on the surface of the tumor (as a mold) or is placed interstitially. Brachytherapy produces less injury to the surrounding uninvolved tissue than electron beam radiation. Radiation therapy is used less frequently than surgical modalities for the treatment of NMSC and is generally reserved for patients over 50 years of age because of the potential adverse long-term sequelae.[83]

Adverse Effects. Adverse effects include desquamation, alopecia, atrophy, telangiectasia, pigmentary alteration, fibrosis, ectropion, parotitis, mucositis, soft-tissue or bone necrosis, radiodermatitis with nonhealing ulcerations, ocular damage, hearing loss, and secondary skin malignancies decades after treatment.[99]

Advantages. Radiation therapy is sometimes preferred by patients who wish to avoid surgery. Radiation therapy is occasionally recommended as a primary treatment when surgery will compromise function or for tumors that are surgically unresectable. Radiation may be used in the patient for whom surgery is contraindicated for medical reasons. Radiotherapy is also used as adjuvant therapy when further surgery could sacrifice major nerves or other vital structures, or there is perineural invasion by cancer cells.

Disadvantages. Radiation therapy is an expensive BCC treatment method and requires 15 to 30 patient visits because radiation doses must be fractionated to minimize poor cosmetic results. Radiation therapy is contraindicated in patients with BCNS and xeroderma pigmentosum because of their risk of developing ionizing radiation–induced malignancies as a result of impaired DNA repair mechanisms.[97,100,101] Recurrence rates are significantly higher after radiation therapy than those after

Mohs surgery for both primary and recurrent BCC. Commonly, the BCCs that recur after radiation therapy tend to be highly infiltrative and aggressive. Cosmesis at a 4-year follow-up was better for lesions treated with surgery compared with radiation therapy in 1 randomized study.[102] There is no histologic confirmation of complete tumor destruction with radiation therapy.

Cryotherapy

Cryotherapy involves the controlled application of liquid nitrogen to the clinically visible tumor and a small surrounding margin of normal-appearing skin.[103] For accurate temperature control, a temperature probe may be inserted at a lateral tumor margin and pushed obliquely so its thermostat tip is just below the tumor. Application of liquid nitrogen is continued until a temperature of −60°C is reached. Cryosurgery may be considered for small low-risk BCCs and is not recommended for high-risk lesions because of their high recurrence rates. Cryosurgery may also be combined with curettage, also called curettage and cryotherapy.

Adverse Effects. Patients experience pain and swelling after the treated area thaws. An eschar usually develops after treatment and persists for approximately 4 to 6 weeks. Permanent pigment loss, atrophy, and hypertrophic scarring are common. Motor and sensory neuropathies are infrequent complications.

Advantages. Cryosurgery is a low-cost procedure that is used rarely for small, well-defined low-risk BCCs when surgery is contraindicated and patients are unable to undergo radiation.

Disadvantages. The success of the procedure is operator-dependent, and the overall recurrence rates are high for primary and recurrent BCC.[61,64] Cryosurgery has longer healing times than sutured wounds. Scarring is unpredictable and may be severe. There is no histologic confirmation of complete tumor clearance.

Topical Therapy

Topical 5-fluorouracil (5-FU) is approved by the Food and Drug Administration (FDA) for treatment of superficial BCC, but there are no long-term studies evaluating its efficacy. One study using 25% topical 5-FU in petrolatum under occlusion for 3 weeks found a 5-year cure rate of 79% for superficial BCCs.[104]

Imiquimod 5% cream was approved by the FDA for treatment of superficial BCCs of the face, neck, trunk, and extremities in 2004. Imiquimod may stimulate innate and acquired immunity by inducing transcription of interferon alpha and gamma, and tumor necrosis factor alpha after binding to toll-like receptor 7. In several randomized controlled studies evaluating the efficacy of imiquimod for BCC, 1 year cure rates have varied from 52% to 100% for superficial BCCs,[105–108] and 42% to 70% for nodular BCCs.[109,110] There are no published reports with long-term follow-up greater than 2 years and no data on the use of imiquimod for morphea-form BCC. Therefore, the use of imiquimod for nodular and morphea-form BCC should be avoided if possible.

Adverse effects. Application site reactions are common, dose-dependent, and include pruritus, erythema, edema, pain, hyperpigmentation, hypopigmentation, bleeding, crusting, and erosions. Rarely, with imiquimod, systemic reactions occur and include flu-like symptoms, arthralgia, myalagia, fatigue, and lymphadenopathy.

Advantages. 5-fluorouracil or imiquimod can be used for superficial BCCs in patients who are poor surgical candidates and is a good option for patients with multiple superficial BCCs. 5-fluorouracil is relatively inexpensive, and thus the cost of treatment is inexpensive.

Disadvantages. 5-fluorouracil and imiquimod cream have slow treatment times compared with surgery or destructive approaches and frequently produce local side effects lasting several weeks. Although the amount of imiquimod cream needed to treat a single BCC is generally small, because of the way it is packaged the cost of treatment with imiquimod is comparable with surgery and the cure rates with either cream are lower than surgical methods. There is no histologic confirmation of complete tumor clearance.

Photodynamic Therapy

Photodynamic therapy involves the application of a photosensitizing agent on the skin followed by irradiation with a light source.[111] Photodynamic therapy using 20% topical aminolevulinic acid (ALA) in combination with a blue light source and PDT using the methyl ester of ALA (MAL) in combination with a red light source are approved by the FDA for the treatment of actinic keratoses. There are multiple studies using a wide variety of treatment regimens evaluating the efficacy of PDT for treatment of NMSC. The cure rates range from 62% to 91% for superficial BCC and 50% to 92% for nodular BCC.[112] In 1 randomized study of BCC treated with PDT using MAL combined with red light, the complete response rate at a 5-year follow-up was 76% for PDT versus 96% for surgical excision, but the cosmetic outcome was better with PDT.[113]

Adverse Effects. There is pain and burning during treatment with PDT. Erythema and edema develop immediately after treatment and may last for 1 week. Other side effects include crusting, blistering, weeping, and bleeding.

Advantages. The cure rates for PDT are lower than those with surgery, but the reported advantage over surgery is better cosmesis. Broad areas of the skin or multiple BCCs may be treated in 1 session when a "field effect" is suspected.

Disadvantages. Patients remain photosensitive for a period of 24 to 48 hours after treatment. Tumor clearance rates are lower than with other treatment modalities. There is no histologic confirmation of complete tumor clearance.

Synthesis of Literature Regarding Treatment of BCC

The analysis of the different treatment options for BCC took into account selected published cure rates (Table 1) and the advantages, disadvantages, and adverse effects of each treatment type. An algorithm that reflects these parameters and is consistent with the AUC guidelines is shown in Figure 1.

Follow-up

Patients who have had 1 BCC are likely to develop additional primary lesions over time, many of which may go unnoticed. In a 5-year prospective follow-up study of 1,000 patients after treatment for BCC, 36% developed new primary BCCs and 20% of patients with very fair skin types and frequent sun exposure went on to develop multiple BCCs. The reported 3-year cumulative risk was 44%.[36] The risk of recurrence of BCC also increases over time.[61,64] Less than one-third of recurrences are seen within the first year after treatment, and 50% develop during the first 2 years after treatment. Eighteen percent of recurrences occur between 5 and 10 years after treatment. Based on these data, patients with a history of BCC should have long-term, even lifetime, follow-up, particularly those with high-risk or multiple tumors. The main reasons for follow-up include (1) early detection and treatment of tumor recurrence; (2) early detection and treatment of new lesions; and (3) reinforced patient education, especially regarding sun protection.[114]

Metastasis

It is possible for BCCs to metastasize, but the metastatic rates are much less than 1%.[50,115] Tumor characteristics seen in metastatic BCCs are the same as those associated with recurrent BCCs, that is, tumors with aggressive histologic subtypes, high-risk anatomic locations, large size, perineural invasion, or a history of previous exposure to ionizing radiation, and other host factors (Table 1). It has been reported that the mean interval from presentation of the initial BCC to discovery of metastasis is 9 years. Not surprisingly, most metastatic BCCs originate in the head and neck region, where the bulk of BCCs develop, and spread to regional lymph nodes, bone, lung, liver, and skin. Involvement of salivary glands, brain, and the spine has also been reported. The prognosis of metastatic BCCs is poor, with mean survival times ranging from 1 to 4 years.

Understanding the molecular genetics of BCC development has provided new opportunities for molecular therapy of this cancer by targeting Hh and other signaling pathways. GDC-0449, an orally active small

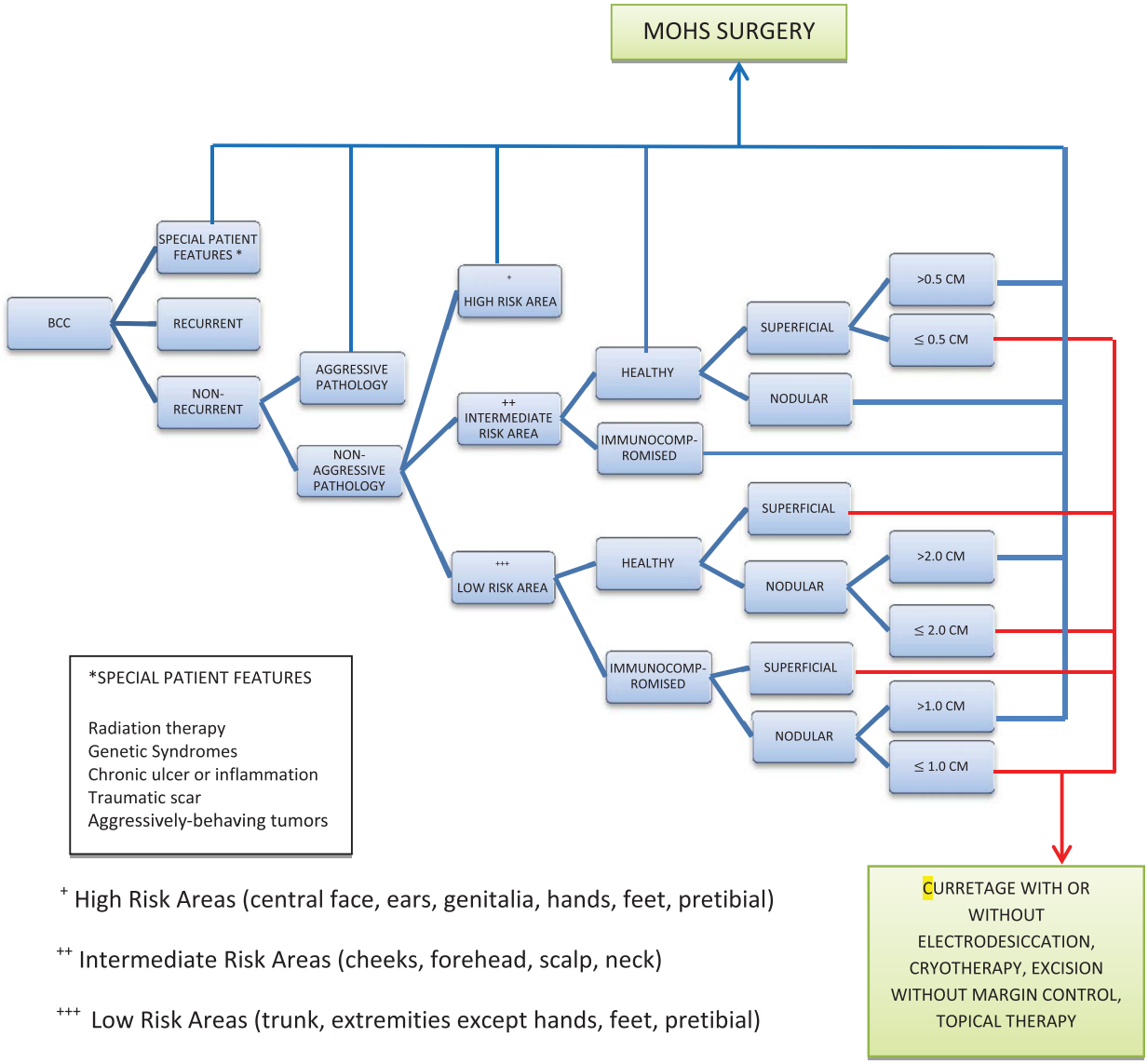

Figure 1. Algorithm for BCC treatment on appropriate use criteria.

molecule that targets the Hh, seems to have antitumor activity in locally advanced or metastatic basal cell carcinoma.[32,116] This agent is now termed vismodegib. GDC-0449 or vismodegib (Genentech, South San Francisco, CA) is a small-molecule inhibitor of the SMO protein. In a recently reported Phase I study, 18 of 33 patients with BCCs that could not be treated with surgery, radiation, or other systemic therapy had a response to the drug on the basis of imaging, physical examination, or both. There were 2 complete responders and 16 partial responders, defined as a 50% reduction in visible or palpable tumor.[117] In another open-label, multicenter 2 cohort Phase II study, 43% of patients with locally advanced BCC and 30% of patients with metastatic BCC showed improvement from baseline. Side effects included muscle spasms, hair loss, altered taste sensation, weight loss, fatigue, nausea, decreased appetite, and diarrhea.[118] Phase 2 trials of this drug and other targeted molecular inhibitors in BCNS are ongoing.

It should be emphasized that the current data on vismodegib are very preliminary. The chosen parameters to assess the success of this drug are subjective rather than histopathologic. Subjective parameters, such as visible tumor reduction either clinical on the patient or in radiologic tests are usually assessed by oncologists with internal cancers. Dermatologists, however, would

like to think of improvement in histopathologic terms—the lack of tumor on post-treatment biopsies. Biopsies after vismodegib treatment are not reported in the current published studies. Further, long-term (5 years) follow-up is not yet available in the patients studied and the cost of the drug (US $9,000/month × 3–6 months) may be difficult to justify except in extreme cases where radiation and surgery cannot be used.

Cost Analysis

Skin cancer has reached epidemic proportions in the US and is presently the most common malignancy with an incidence equaling that of all other cancers together. Because physicians face increasing pressure to deliver cost-effective care, it is vital that they understand the total cost of different skin cancer treatment modalities, in addition to their relative risks and benefits, to determine which modality yields the best value for the patient.

Much of the cost analysis in the literature does not differentiate between BCC and SCC but lumps them into the categories of NMSC, because the costs of the procedures are identical. Published studies evaluating the cost-effectiveness of the various treatment modalities demonstrate that the cost of C&E (US $392–US $652) is approximately 50% to 60% of either SSE or Mohs surgery.[119–124] However, some nonsurgical treatments such as imiquimod (US $931–US $959) are comparable in cost with SSE and Mohs surgery.[1] Because of the unacceptably high recurrence rates documented with destructive methods, including C&E, cryotherapy, and nonsurgical treatments, these therapies are reserved for low-risk BCC, as defined in this consensus guideline. Furthermore, destructive modalities, such as C&E and cryotherapy are not appropriate for the treatment of tumors in cosmetically sensitive areas, where they can leave permanent disfiguring scars.

Some authors advocate fractionated radiation as first-line therapy in the treatment of BCC, particularly in those patients in whom health concerns preclude surgical treatment, but there are very few health conditions that do not allow a patient to undergo office-based surgery with a local anesthetic. Radiation therapy has higher recurrence rates than Mohs surgery for primary and recurrent tumors, requires approximately 15 to 30 treatment visits, and costs 2 to 4 times that of Mohs surgery or surgical excision (US $2,559–US $4,558).[119,123,124]

The data presented in this consensus guideline demonstrate that SSE and Mohs surgery remain the most effective modalities to treat BCCs. Mohs surgery is the standard of care for the treatment of high-risk, invasive, or recurrent tumors, and tumors in areas that require maximal preservation of uninvolved tissue to maintain function or cosmesis. There is a general misperception that Mohs surgery is costlier than SSE. However, published reports analyzing the relative costs of the various treatment options for NMSC demonstrate that the outlays for SSE and Mohs surgery are comparable.[119–124] In 2006, the CMS reduced the relative value units for Mohs surgery treatment of NMSC on the trunk and extremities, and the CMS reversed the multiple surgery reduction exemption associated with Mohs surgery in 2008. As a result of these changes in reimbursement, the cost of Mohs surgery in 2009 is 17% lower than in 1998[124] and is often less than that of excision and repair.[123,124]

Mohs surgery remains the most cost-effective method of treating high-risk BCC because the excision, pathology, and repair can all be performed in the office setting, and usually on the same day. With Mohs surgery, small (≈2–3 mm) margins are taken peripherally and deep, often resulting in shallow small wounds, of which a large percentage (18%–30%) is permitted to heal by second intention.[123,124] Standard surgical excision requires margins of 4 to 10 mm, resulting in larger deeper defects and more expensive repairs. There are fewer future costs after Mohs surgery than those after SSE because of the low recurrence rate, lack of local regional extension and destruction, and rare metastasis. Standard surgical excision also results in greater workforce costs because of the necessity for multiple surgeries when the lack of immediate margin confirmation results in incomplete tumor removal.

Payment is made to a single physician for Mohs surgery procedures. When a patient is treated for skin

cancer by facility-based excision, increased (often exorbitant) reimbursement is spread out to the operating room, surgeon, pathologist, anesthesiologist, and laboratory and paid by 2 different arms of Medicare, Parts A and B, which are never reconciled. Because the charge for the skin cancer excision is only generated by the surgeon, the unexpected result is that the cost for excision mistakenly seems much lower than for Mohs surgery and is more difficult for insurers to track. Furthermore, hospitals have recently been charging facility fees for surgeons in procedure rooms that are less equipped than ambulatory surgery centers; in effect, this is hospital-based office surgery for which there is an office charge. Thus, performing surgery in an outpatient hospital setting adds tremendously to the cost of Mohs surgery and SSE.

Rogers and Coldiron[123] performed a cost analysis on a variety of treatment modalities and surgery settings for a single variably sized BCC on the cheek and SCC on the forearm, based on the 2008 RVU values. For a single BCC on the cheek, the average cost of C&E was US $471. The average cost of topical treatment with imiquimod (US $959) was equivalent to office-based excision with permanent sections and immediate repair (US $1,006). At smaller lesion sizes (0.6 cm), excision with immediate repair (US $807) was less expensive than imiquimod but became somewhat more expensive as the lesion size increased. Office-based excision with permanent sections, and delay of repair until confirmation of negative margins, increased the cost to US $1,170. Mohs surgery with repair was relatively equivalent to office-based SSE with an average cost of US $1,263 and has the advantage of margin analysis at the time of surgery, minimizing the need for additional surgeries. The average cost for radiation therapy of a BCC on the cheek was US $2,591 to US $3,460. A comparable analysis was performed for the treatment of an SCC on the forearm and yielded similar results.

The greatest differential in expenditure, however, lies not within the type of treatment method chosen but in the treatment setting. In their analysis,[123] Rogers and Coldiron found the average cost of excision and repair or Mohs surgery in the office setting for a single BCC on the cheek was US $1,006 to US $1,263, compared with when the same surgery was performed in an ambulatory surgical center (ASC) (US $2,334) or in a hospital setting (US $3,085). In another study,[123] Mohs surgery for an average NMSC (US $805) was the least expensive modality compared with SSE in the office setting (US $1,026–US $1,200) and SSE of the same tumor in the ASC (US $2,507).

Table 4 summarizes the published data on cost-comparisons for surgical treatment of NMSC in different practice settings—office-based surgery, ASC, or the hospital operating room. Office-based surgery, including Mohs surgery (mean cost, US $895.50), is 2 times less expensive than ASC-based surgery (mean cost, US $1,698.52) and 4.5 times less expensive than the same procedures performed in the hospital operating room (mean cost, US $4,188.17). Although facility fee data are not shown in this table, it is the authors' experience that when hospitals charge these fees that the costs are comparable or even higher than those of an ASC.

Because health care costs escalate and insurers attempt to contain costs and decrease health care use, it is important to realize that nonhospital-based office procedures, such as C&E, SSE with permanent-section margin control, and Mohs surgery are the most affordable options. Physician-owned office settings provided the lowest cost per treatment episode (US $492 per episode)[120] and are the dominant setting for NMSC care. Dermatologic surgeons manage most NMSCs and use a wider range of treatment options compared with other specialists. Legislative or regulatory measures that attempt to restrict or limit the use of Mohs surgery or office-based surgery will only result in higher overall costs.

Additional Considerations

Genetic Propensity for NMSC

Patients with NMSC frequently report a family history of NMSC. However, it is not clear if this represents a genetic propensity or is simply related to the similarity of skin type between the parent and the child. The only truly established genetic link is in patients with a well-defined syndrome.

TABLE 4. Effect of Surgery Setting on Cost of NMSC Surgery

Date	*Study*	*Authors*	*Office-Based Surgery*	*ASC-Based Surgery*	*Hospital OR–Based Surgery*
1998	Mohs micrographic surgery: A cost analysis	Cook and Zitelli[119]	US $1,270	US $1,973	N/A
2001	Cost of NMSC treatment in the United States	Chen and colleagues[120]	US $492	US $1,043	US $5,337
2004	Mohs micrographic surgery versus traditional surgical excision	Bialy and colleagues[121]	US $970	US $1,399	N/A
2006	Treatment patterns and costs of NMSC management	John Chen and colleagues[122]	US $500	US $935	US $4,345
2008	A RVU-based cost comparison. Effect of the loss of the Mohs multiple surgery reduction exemption	Rogers and Coldiron[123]	US $1,131	US $2,334	US $2,680–US $3,085
2012	Cost analysis: Mohs micrographic surgery	Ravitskiy and colleagues[124]	US $1,010	US $2,507.10	N/A
Average cost			US $895.50	US $1,698.52	US $4,188.17

Basal cell nevus syndrome[125–127] is an autosomal dominant disorder with a prevalence of 1 in 57,000, complete penetrance, and variable expressivity. A genetic mutation on transmembrane receptor protein PTCH on chromosome 9 is found in 60% of patients with BCNS.[128,129] Major associated features include odontogenic keratocysts of the jaw, glabrous skin pits, calcification of the falx cerebri and bifid, fused or splayed ribs. Childhood medulloblastoma is seen in 1% to 5% of patients with BCNS. The BCCs in BCNS behave similarly to sporadic BCCs with rapidly increasing numbers seen starting in puberty. Treatment is the same as for sporadic BCCs, except that the large number of lesions seen requires frequent follow-up visits to keep up with new lesion development. Ionizing radiation is contraindicated because these patients tend to quickly develop new BCCs in the irradiated field.

Xeroderma pigmentosum is an autosomal recessive disease that results in the inability to repair UV-induced damage to DNA. By age 2, almost all children with xeroderma pigmentosum develop freckling of the skin in sun-exposed areas (such as the face, arms, and lips) and hyperpigmentation, followed by BCC, SCC, and malignant melanoma. Other features include corneal opacities leading to blindness and neurological deficits. Epidermodysplasia verruciformis is an autosomal recessive disorder characterized by the development of BCC and SCC from human papilloma virus infection.

Other rare syndromes associated with BCC include the following: (a) Rombo syndrome,[130] an autosomal dominant disorder associated with milia, atrophoderma vermiculatum, acrocyanosis, and trichoepitheliomas; (b) Bazex–Dupre–Christol syndrome,[131] an X-linked dominant disorder associated with hypotrichosis, hypohidrosis, and follicular atrophoderma on the dorsal hands; (c) Brooke–Spiegler syndrome, an autosomal dominant disorder associated with cylindroma, trichoepithelioma, and spiradenoma; and (d) Schopf–Schultz–Passarge syndrome, either autosomal recessive or dominant and associated with ectodermal dysplasia, hidrocystomas, palmoplantar keratoses, and hyperhidrosis.

Immunosuppressed Patients and BCC

Patients who are immunosuppressed because of disease (hematopoietic malignancies, HIV) [78–81, 132] or medication (anti-rejection meds, such as cyclosporine, azathioprine, corticosteroids etc), have an increased incidence of NMSC.[75–77,133] Transplant patients with skin cancers require very close monitoring (often monthly skin examinations) and prompt and

aggressive treatment of their skin cancers because the cancers tend to grow very quickly and metastasize early. Strict avoidance of sun exposure is important. A dermatologist should be an integral part of the transplant team. The goal is that the patient be on the lowest possible dose of immunosuppressive medications (especially anti–T-cell drugs). For patients who can tolerate oral retinoids, such as isotretinoin or acitretin, these medications have been shown to reduce the rate of new skin cancer formation.[134–136] However, reducing or stopping the retinoid leads to a rebound in new skin cancer growth that may be difficult to manage. Imiquimod can be used as part of the patient's treatment regimen because it does not seem to have an adverse effect on the transplanted organ.

Treatment of the Challenging Patient

The patient's medical, mental, and functional status needs to be taken into consideration when recommending treatment. Because the majority of skin cancers are treated under local anesthesia, there are very few instances in which surgery under local anesthesia poses a sufficiently high risk. The pros and cons of surgery need to be weighed in patients that are not mentally competent to give informed consent and/or who are not able to cooperate with the procedure. In such cases, the patient's guardian must be brought into the discussion and if the decision is made to proceed with surgery, it may be done under a higher level of sedation or general anesthesia.

The age of the patient should not be a consideration whether or not to proceed with surgery. However, the patient's health level, functional state, mental state, life expectancy, and willingness to undergo the proposed procedure should be weighed against the aggressiveness of the tumor and the likelihood that the tumor will affect the patient's quality of life or life expectancy. For example, a small primary BCC on the trunk in a patient with advanced Alzheimer disease may not warrant treatment.

X-ray treatment is a reasonable alternative for some tumors in infirm patients. However, the need for 15 or more visits may be more difficult for the patient and their caregivers than a 30-minute procedure in the dermatologist's office. Partial or incomplete treatments such as topical 5-fluorouracil for morphea-form BCC should be avoided, because they give the patient a false sense that the problem has been addressed, while the tumor continues to grow under the surface only to require more extensive surgery in the future.

Patients with multiple skin cancers in 1 anatomic area ("field effect") can be challenging to manage. Such patients should be treated in stages, removing the more aggressive BCCs first, and allowing the surgical sites to heal before proceeding to remove the less aggressive BCCs. This will prevent the patient from being overwhelmed, and limiting the number of healing sites will minimize patient discomfort and the risk of infection, dehiscence, and necrosis.

Conclusion

The incidence of BCC is increasing significantly, with over 2.5 million new cases per year in the United States. Basal cell carcinomas rarely metastasize but if left untreated will cause localized tissue destruction, cosmetic deformities, and functional disability. There are multiple modalities to treat BCC, but the cure rates, patient morbidity, cosmetic outcome, and costs vary, sometimes widely. Optimal results for high-risk BCC are achieved with surgical approaches, with Mohs surgery offering the highest cure rates and maximal preservation of tissue, function, and cosmesis. Mohs surgery remains the treatment of choice for high-risk tumors, and because it is performed in the office setting often times with immediate repair, it is highly efficient and cost-effective. Low-risk BCCs may be treated with a variety of surgical and nonsurgical modalities, for which costs, cure rates, and cosmesis vary.

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