

*Primary Care***CUTANEOUS SQUAMOUS-CELL
CARCINOMA**

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NONMELANOMA skin cancer is the most common cancer in the United States, with over 1.3 million cases expected to occur in the year 2001. Approximately 80 percent of nonmelanoma skin cancers are basal-cell carcinomas, and 20 percent are squamous-cell carcinomas.¹ Squamous-cell carcinoma is the second most common cancer among whites.² Unlike almost all basal-cell carcinomas, cutaneous squamous-cell carcinomas are associated with a substantial risk of metastasis.

INCIDENCE

In 1994 in the United States, the lifetime risk of squamous-cell carcinoma was 9 to 14 percent among men and 4 to 9 percent among women.³ Although it is known that this neoplasm contributes substantially to morbidity and mortality among elderly persons, its incidence and the associated mortality rate cannot be determined precisely.^{4,5} The National Cancer Institute does not collect data on the incidence of or mortality from squamous-cell carcinoma, except for tumors of the genitalia.⁶ However, a sharp rise in incidence during the past two decades has been documented.⁷ According to longitudinal studies in both the United States and Canada, the age-adjusted incidence of squamous-cell carcinoma has grown by 50 to 200 percent over the past 10 to 30 years.⁸⁻¹⁰ In addition, the incidence doubles with each 8-to-10-degree decrement in geographic latitude and is highest at the equator.² The age-adjusted incidence of this neoplasm among whites is 100 to 150 per 100,000 persons per year, and the age-specific incidence among persons over the age of 75 years is approximately 10 times that rate.^{3,9,11-13}

CAUSATION

Table 1 summarizes the risk factors for the development of squamous-cell carcinoma. Exposure to ultra-

TABLE 1. RISK FACTORS FOR THE DEVELOPMENT OF CUTANEOUS SQUAMOUS-CELL CARCINOMA.

Exposure to ultraviolet radiation
Ultraviolet A
Ultraviolet B
Therapy with methoxsalen and ultraviolet A radiation
Exposure to ionizing radiation
Genodermatosis
Oculocutaneous albinism
Xeroderma pigmentosum
Infection with human papillomavirus, especially types 6, 11, 16, and 18
Exposure to chemical carcinogens
Arsenic
Polycyclic aromatic hydrocarbons
Immunosuppression
Organ transplantation
Leukemia and lymphoma
Immunosuppressive medications
Chronically injured or diseased skin
Ulcers
Sinus tracts
Osteomyelitis
Radiation dermatitis
Certain chronic inflammatory disorders, such as dystrophic epidermolysis bullosa
Precursor lesions
Actinic keratoses
Arsenical keratoses
Radiation-induced keratoses
Bowen's disease (squamous-cell carcinoma in situ)
Erythroplasia of Queyrat (squamous-cell carcinoma in situ of the penis)

violet radiation is the most common cause of this type of cancer.^{14,15} Ultraviolet B radiation (wavelength, 290 to 320 nm) from sunlight is principally responsible, with ultraviolet A radiation (320 to 400 nm) adding to the risk.^{2,16,17} Ultraviolet radiation produces mutations in DNA, usually the formation of thymidine dimers in the p53 tumor-suppressor gene. Failure to repair these mutations may result in tumor formation (Fig. 1).¹⁸

Lifestyle changes during the past 50 years have led to increased voluntary exposure to sunlight. Fair-skinned people are at the highest risk for the development of skin cancer.² A history of exposure to sunlight during childhood, particularly a history of sunburns, may be the most important behavioral risk factor.¹⁹ Occupational exposure to ultraviolet radiation has also been implicated.¹ The relative risk of squamous-cell carcinoma is three times as high among people born in areas that receive high amounts of ultraviolet radiation from the sun as among people who move to those areas in adulthood; two to five times as high in

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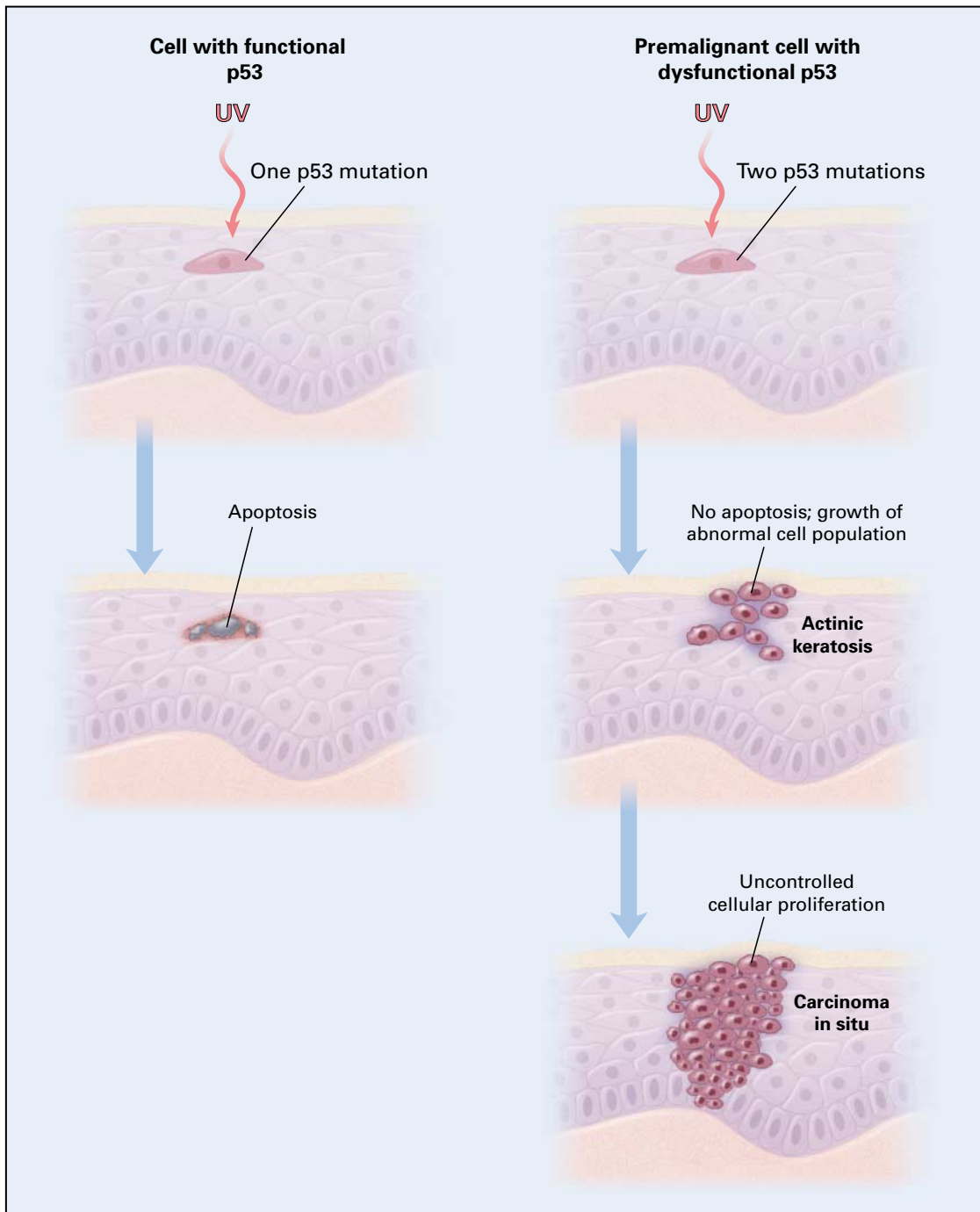


Figure 1. Sequence of Events Thought to Occur after Ultraviolet (UV) Irradiation of the Skin.

Ultraviolet radiation generates specific mutations (the formation of thymidine dimers) in the p53 tumor-suppressor gene. C-to-T transitional changes at pyrimidine sites, including CC-to-TT double-base changes, are the most frequent form of nucleotide-base substitution in ultraviolet-B-damaged DNA sequences. Keratinocytes with one mutation in p53 after ultraviolet irradiation undergo apoptosis. In contrast, keratinocytes with dysfunctional p53 and an additional p53 mutation as a result of irradiation cannot undergo apoptosis and instead undergo clonal expansion, which is manifested clinically as the development of an actinic keratosis. Uncontrolled proliferation of abnormal cells leads to squamous-cell carcinoma in situ and invasive squamous-cell carcinoma.

those with light skin, hazel or blue eyes, and blonde or red hair as in those with darker features; five times as high among those with outdoor occupations as among those who work indoors; and three to eight times as high among people with severe solar elastosis, freckling, or facial telangiectasia as among others.^{20,21} Use of a combination of oral methoxsalen and ultraviolet A radiation for the treatment of psoriasis is also associated with an elevated risk of squamous-cell carcinoma.^{1,2,22,23}

Ionizing radiation has also been implicated in the pathogenesis of squamous-cell carcinoma. In the 1940s and 1950s, ionizing radiation was used to treat many cutaneous conditions, including acne, dermatitis, and hemangiomas.^{2,24} Workers in certain medical and industrial occupations may also be exposed to radiation.² The risk of squamous-cell carcinoma is directly related to the cumulative total dose of radiation.² The type of radiation associated with tumor development is typically x-rays, but gamma rays and grenz rays may further augment the risk.²⁵ In persons with certain genodermatoses, such as oculocutaneous albinism, squamous-cell carcinomas may develop on sun-exposed areas because there is insufficient protective pigment.²⁶ In those with xeroderma pigmentosum, ultraviolet-radiation-induced mutations in DNA cannot be repaired, and as a result multiple skin cancers may develop at an early age.²⁷

Although the relation is not understood, human papillomavirus infection has been associated with cutaneous squamous-cell carcinoma. Human papillomavirus types 6 and 11 are frequently found in patients with tumors of the genitalia and type 16 in those with periungual tumors. A link between human papillomavirus and squamous-cell carcinomas related to epidermodysplasia verruciformis has also been reported.^{2,28}

Chemical agents have historically been a major cause of squamous-cell carcinoma.² In 1775, Percivall Pott recognized that scrotal cancer in chimney sweeps was caused by exposure to soot. Arsenic, used in various medications in the past, can also stimulate carcinogenesis. Tainted wine and unprocessed well water in developing countries may transmit high levels of arsenic. Metal-ore workers and insecticide handlers may also be at risk. Arsenic exposure produces invasive tumors and carcinoma in situ on the skin, whether or not the skin is exposed to the sun, as well as arsenical keratoses on the palms and soles (Fig. 2). The carcinogenic effects are dose dependent and carry an associated risk of internal cancer.² Polycyclic aromatic hydrocarbons, derived from the combustion and distillation of carbon compounds such as coal tar, cutting oils, and pitch, may also cause cutaneous squamous-cell carcinoma. Cancer of the scrotum was once a common result of exposure to these agents, but changes in industrial practice have made such tumors rare.

Organ-transplant recipients are at increased risk for



Figure 2. Arsenical Keratoses on the Palms.

Punctate erythematous papules and hyperpigmented papules are visible.



Figure 3. Squamous-Cell Carcinoma of the Right Lower Eyelid.

The lesion is 0.3 by 0.4 cm in diameter and has an overlying cutaneous horn. It arose over a period of several weeks in a patient who had undergone cardiac transplantation and was receiving immunosuppressive treatment.

cutaneous squamous-cell carcinoma (Fig. 3),^{1,2} a risk that is potentiated by the use of immunosuppressive medications and by conditions that lead to immunocompromised status.^{29,30} Although much of the published evidence concerns renal-transplant recipients, those who have undergone heart transplantation may be even more susceptible to tumor formation.^{31,32} Squamous-cell carcinoma is up to 65 times as likely to develop in transplant recipients as in age-matched control subjects, with lesions appearing an average of two to four years after the transplantation and increasing in frequency over time.²⁹ In contrast to the general population, transplant recipients have squamous-cell carcinomas more often than basal-cell carcinomas.

Squamous-cell carcinoma is more likely to develop in injured or chronically diseased skin, including skin affected by long-standing ulcers, sinus tracts, osteomyelitis, radiation dermatitis, or vaccination scars.^{2,31,33} Tumors arising at these sites may not be identified for years and, if neglected, carry a substantial risk of metastasis. Certain chronic inflammatory disorders may also predispose patients to the development of tumors; these disorders include discoid lupus erythematosus, lichen sclerosus, lichen planus, dystrophic epidermolysis bullosa, and lupus vulgaris (cutaneous tuberculosis).

CLINICAL PRESENTATION

The principal precursor of cutaneous squamous-cell carcinoma is actinic keratosis.^{7,34-36} Actinic keratoses are scaly lesions, typically 2 to 6 mm in diameter, that are more easily felt than seen; they may be the same color as the skin, pink, or brown. They can involute or persist, and affected persons usually have many lesions, some of which may evolve into squamous-cell carcinoma (Fig. 4). Among persons with multiple actinic keratoses, the cumulative lifetime risk of having at least one invasive squamous-cell carcinoma is substantial, possibly 6 to 10 percent.¹¹ Estimates of the annual rate of progression per lesion range from 0.025 percent to 20 percent, but the cumulative risk depends on the number of lesions and the length of time they persist.^{34,37}

Actinic keratosis has been described as a type of carcinoma in situ — in this case, carcinoma involving only the epidermis — since on histologic examination actinic keratoses and invasive squamous-cell carcinomas exhibit a spectrum of neoplastic changes.³⁸ From



Figure 4. Actinic Keratoses on the Scalp, One of Which Has Become an Invasive Squamous-Cell Carcinoma.

There are multiple erythematous, scaling patches and a central erythematous plaque with a thick overlying scale.



Figure 5. Bowenoid Papulosis of the Pubic Region, Penis, and Scrotum.

Diffuse hyperpigmented papules are present.

a therapeutic standpoint, it may be impractical and unnecessary to treat each individual keratotic lesion, but patients with many lesions should be followed closely so that evolving squamous-cell carcinomas can be detected and treated expeditiously.^{39,40} Options for treating actinic keratoses include cryosurgery, electrodesiccation and curettage, topical fluorouracil, dermabrasion, and laser resurfacing.

Other precancerous conditions that may evolve into squamous-cell carcinoma include bowenoid papulosis and epidermodysplasia verruciformis.^{1,2} Patients with bowenoid papulosis (Fig. 5), which is often associated with human papillomavirus types 16 and 18, present with hyperpigmented papules that have histologic features identical to those of Bowen's disease, a type of squamous-cell carcinoma in situ.⁴¹ Epidermodysplasia verruciformis consists of widespread, flat warts that may degenerate into carcinoma in situ or invasive squamous-cell carcinoma.

Squamous-cell carcinoma in situ may progress to invasive disease if not treated completely.^{2,35} The most common forms of squamous-cell carcinoma in situ are Bowen's disease and erythroplasia of Queyrat. Patients with Bowen's disease present with sharply demarcated, erythematous, velvety, or scaly plaques on sun-exposed areas (Fig. 6). Erythroplasia of Queyrat is less common and occurs on the glans penis of uncircumcised men as red, smooth plaques.

Most invasive squamous-cell carcinomas occur on the head and neck; the next most common site is the trunk.^{2,9} The lesions are papules or plaques that are firm, skin-colored or pink, and smooth or hyperkeratotic. Ulceration may be present.³⁵ Patients may describe their lesions as itchy or painful nonhealing wounds that bleed when traumatized.



Figure 6. Squamous-Cell Carcinoma in Situ (Bowen's Disease) on the Right Temporal Region of the Scalp. This erythematous plaque is 3.0 by 3.0 cm in diameter and has sharply demarcated borders.

Keratoacanthoma resembles squamous-cell carcinoma (Fig. 7)⁴² and tends to grow rapidly to form a crateriform nodule. On histologic examination, keratoacanthoma may be difficult to distinguish from squamous-cell carcinoma. However, experienced dermatopathologists can distinguish them histologically in about 85 percent of cases.⁴³ Tumors that are not readily classifiable should be treated as squamous-cell carcinomas.

Verrucous carcinoma is a less common variant of invasive squamous-cell carcinoma (Fig. 8).^{2,35} The indolent, cauliflower-shaped tumors resemble large warts and are locally aggressive but are less likely to metastasize. Adequate local excision generally results in complete cure.

RECURRENCE AND METASTASIS

Invasive squamous-cell carcinoma has the potential to recur and metastasize. The five-year rate of recurrence of primary cutaneous lesions is 8 percent, and the five-year rate of metastasis is 5 percent.^{31,44,45} Table

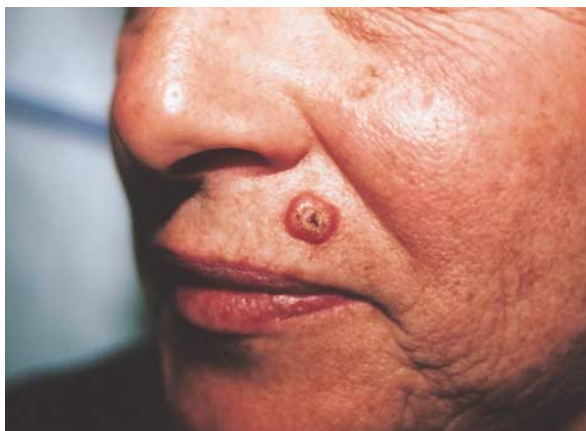


Figure 7. Keratoacanthoma above the Left Upper Lip.

The lesion is 1.0 by 1.0 cm in diameter and has a central keratotic plug. This lesion may be difficult to distinguish from a well-differentiated squamous-cell carcinoma.



Figure 8. Verrucous Carcinoma on the Distal Aspect of a Finger. This lesion resembles a viral verruca.

2 summarizes the risk factors and relative risks associated with tumor recurrence and metastasis. Chief among the factors affecting risk are the size and location of the tumor. Large lesions (>2 cm in diameter) recur at a rate of 15 percent, which is twice that of smaller lesions, and they metastasize at a rate of 30 percent, three times that of smaller lesions.³¹ The five-year rate of cure in patients with large tumors is 70 percent, regardless of the treatment chosen.² Squamous-cell carcinomas of the lip and ear are also aggressive lesions (Fig. 9), with rates of recurrence and metastasis ranging from 10 to 25 percent.^{31,46} Other sites associated with a high risk of recurrence and metastasis are the scalp, forehead, temple, eyelid, nose, mucous membranes, dorsal surface of the hands, penis,

TABLE 2. RISK FACTORS FOR RECURRENCE AND METASTASIS OF CUTANEOUS SQUAMOUS-CELL CARCINOMA.

VARIABLE	APPROXIMATE RELATIVE RISK*	
	RECURRENCE	METASTASIS
Clinical features		
Rapid growth	—	—
Size >2 cm	2	2
Site		
Lip	2	3
Ear	2	3
Immunosuppression	—	2
History of radiation treatment	—	—
History of treatment for squamous-cell carcinoma	3	4
Histologic features		
Tumor depth >4 mm or to Clark level IV or V†	2	5
Poorly differentiated appearance	2	3
Infiltrative deep or peripheral margins	—	—
Spindle-cell features	—	—
Acantholytic features	—	—
Perineural invasion	5	5

*A relative risk of 1 is defined as the likelihood of recurrence or metastasis of a small primary squamous-cell carcinoma. Dashes indicate an association with increased risk, but one for which there are insufficient data to estimate the relative risk.

†Clark level IV indicates a lesion that involves the reticular dermis, and level V indicates invasion into subcutaneous fat.

scrotum, and anus.^{1,2,35,47} Squamous-cell carcinomas arising in injured or chronically diseased skin are associated with a risk of metastasis that approaches 40 percent.^{31,48}

Other clinical features associated with recurrence and metastasis include rapid growth and local recurrence of the tumor, as well as immunosuppression.^{2,29,49} Rapidly growing lesions on the eyelid or ear may metastasize in up to one third of cases.⁵⁰ In transplant recipients with long-term immunosuppression, tumors develop two to three decades earlier than in other, immunocompetent patients; in the former group, the overall rate of metastasis per patient exceeds 10 percent.³¹ Locally recurrent squamous-cell carcinomas metastasize at rates that range from 25 percent for most cutaneous lesions to 30 to 45 percent for ear and lip tumors.^{2,31}

Histologic features that are predictive of recurrence or metastasis include a depth of more than 4 mm, involvement of the reticular dermis or subcutaneous fat, or penetration into fascia, muscle, bone, or cartilage. In a study by Rowe et al.,³¹ poorly differentiated squamous-cell carcinomas recurred at a rate of 28.6 percent, and the five-year rate of cure after treatment was 61.5 percent; in contrast, well-differentiated tumors had a local-recurrence rate of 13.6 percent, and the five-year rate of cure was 94.6 percent.



Figure 9. Squamous-Cell Carcinoma of the Right Ear.

This lesion is 1.2 by 0.7 cm in diameter. It was treated with Mohs' micrographic surgery because of its location at a site associated with high risk and its history of rapid growth.

Perineural invasion is also an ominous finding.⁵¹ Neurotropic spread results from contiguous movement of tumor cells along nerve fibers. Invasion of the nerves may not be clinically or histologically apparent until the tumor has spread extensively.^{2,35} Although perineural spread occurs in only 5 percent of squamous-cell carcinomas, it does confer a high risk of recurrence and metastasis.^{2,35} Most patients with perineural invasion die of the disease within five years after presentation.

SCREENING AND DETECTION

A complete history taking and physical examination are indispensable. Information should be elicited about sun exposure beginning in childhood, occupational exposure to ultraviolet light or carcinogenic chemicals, previous radiation treatment, and potential causes of immunosuppression. If the patient has a history of skin cancer, the type, location, and dates of treatment should be noted. A total-body examination of the skin is the only screening test available for cutaneous squamous-cell carcinoma. Since early disease is highly cur-

able and metastatic disease carries a grim prognosis, prompt detection is potentially lifesaving. Physicians who believe they lack the clinical skills to identify skin cancers should consider referring patients with signs of disease to a dermatologist.

Particularly among patients who have previously had skin tumors, screening is necessary to monitor for recurrence or persistence of the tumors and for the presence of new lesions. There is a 30 percent risk of having a second primary squamous-cell carcinoma within five years after treatment for the first tumor.⁵² Since about 90 percent of recurrences and metastases occur during the first five years after treatment, screening during this period may be adequate.⁵³⁻⁵⁵ Organ-transplant recipients should undergo regular screening examinations regardless of whether they have any history of skin cancer.⁵⁶

According to commonly accepted guidelines, patients who have a history of nonmelanoma skin cancer or who have predisposing conditions should undergo screening once or twice yearly.^{35,37} Screening may be performed every 18 to 24 months in patients at lower risk. Self-examination and the use of sunscreens should be encouraged. If metastasis is suspected, biopsy specimens should be obtained from palpable lymph nodes for histologic examination, and appropriate imaging and laboratory studies should be performed to detect distant metastases.

PROGNOSIS

Most patients with primary cutaneous squamous-cell carcinoma have an excellent prognosis. For those with metastatic disease, however, the long-term prognosis is extremely poor.^{1,58} Ten-year survival rates are less than 20 percent for patients with regional lymph-node involvement and less than 10 percent for patients with distant metastases. If metastasis does occur, regional lymph nodes are involved in approximately 85 percent of cases; approximately 15 percent of cases involve distant sites, including the lungs, liver, brain, skin, and bone.^{1,2,36,59}

TREATMENT

Appropriate use of electrodesiccation and curettage, excision, or cryosurgery can eliminate up to 90 percent of local tumors with a low risk of metastasis — specifically, small (≤ 1 cm in diameter), well-defined primary lesions on the neck, trunk, arms, or legs.² Cryotherapy and electrodesiccation and curettage are relatively inexpensive to perform. Surgical excision and Mohs' surgery are more costly but can offer significantly lower rates of recurrence and metastasis for patients with high-risk tumors.

With electrodesiccation and curettage, the tumor and a surrounding margin of clinically unaffected tissue are destroyed by cauterization, and the area is scraped with a curet.³⁵ The process is repeated several times to maximize the probability of complete removal

of the tumor. A disadvantage of this approach is that no specimen of margin tissue is available for evaluation. Nevertheless, five-year rates of cure in patients with small, primary squamous-cell carcinomas who are treated with electrodesiccation and curettage may be as high as 96 percent.^{31,60,61} Cure rates in those with high-risk tumors who undergo treatment with this technique are much lower.⁶²

Indolent primary tumors can be locally excised. Surgical excision, as compared with electrodesiccation and curettage, offers the advantages of allowing histologic verification of tumor margins, rapid healing, and improved cosmesis. Disadvantages include the risks of hematoma, seroma, infection, and wound dehiscence. Surgical excision involves the use of the traditional "breadloafing" method of histopathological processing,⁶³ which allows less than 1 percent of the complete margin of the surgical specimen to be viewed. For this reason, cure rates in patients with squamous-cell carcinoma who undergo excision do not differ significantly from cure rates in those who are treated with electrodesiccation and curettage.³¹

For some well-differentiated tumors — those that are 2 cm in diameter or smaller; do not occur on the scalp, ears, eyelids, lips, or nose; and do not involve the subcutaneous fat — a margin of 4 mm around the clinical border of the lesion has been recommended to achieve a 95 percent chance of clearance. For tumors that occur at anatomical sites associated with a high risk of recurrence or that are larger than 2 cm, a 6-mm margin is recommended.⁶⁴ Recurrence rates after the excision of low-risk lesions range from 5 percent to 8 percent.³¹ Tumors larger than 2 cm recur at a rate of 15.7 percent after excision, whereas those 2 cm or smaller recur at a rate of 5.8 percent.³¹ Poorly differentiated lesions recur at a rate of 25.0 percent after excision, as opposed to well-differentiated lesions, which recur at a rate of 11.8 percent.³¹

Cryotherapy may be used to treat small squamous-cell carcinomas. With this approach, liquid nitrogen is used to cool the lesion to tumoricidal temperatures.³⁵ Patients with bleeding disorders or contraindications to surgery may be candidates for cryotherapy. Graham and Clark⁶⁵ reported a cure rate of 97.3 percent in a study of 563 primary squamous-cell carcinomas, the majority of which were between 0.5 and 1.2 cm in diameter. Recurrences generally become evident within two years after treatment.

Fractionated radiation treatment may be preferred for patients who are unable to tolerate surgery or who have inoperable tumors and may provide favorable functional and cosmetic results.^{2,35} Radiation may also be used in combination with other types of therapy to treat aggressive or recurrent lesions.³⁵ The disadvantages of radiotherapy include its high cost and the need for multiple visits.^{2,66} Furthermore, tumors that recur after radiotherapy are likely to be highly aggressive.²

Tumors that are associated with a high risk of re-

currence or metastasis must be treated definitively to maximize the chance of cure. If local excision is the chosen method of treatment, a 6-mm margin of surrounding normal tissue should be removed to allow a 95 percent chance of cure.⁶⁴ Patients with potentially aggressive local tumors may be considered candidates for prophylactic irradiation of the regional lymph nodes after surgery.³⁵

The treatment that offers the highest rates of cure for patients with high-risk primary or recurrent squamous-cell carcinoma is Mohs' micrographic surgery.^{1,46,51,64,67,68} Mohs' surgery can be performed in stages on a single day, and Mohs' technique of horizontal frozen sectioning provides a view of 100 percent of the peripheral and deep margins of each specimen, so incomplete excision is much less likely than with standard pathological processing.⁶³ Mohs' surgery affords a five-year rate of local control of 96.9 percent in patients with primary cutaneous squamous-cell carcinoma at any site except the lips or ears; in contrast, the five-year rate of local control is 92.1 percent with other forms of treatment.³¹ In patients with recurrent squamous-cell carcinoma, Mohs' surgery is associated with five-year cure rates of 90 to 93.3 percent, in contrast to cure rates of 76.7 percent for recurrent tumors treated with standard excision.³¹

Treatment of nodal disease may involve radiation, lymph-node dissection, or both. Regional disease is most effectively treated with these two techniques in combination, an approach that offers a five-year rate of cure of 30 to 40 percent.³¹ Treatment of metastatic squamous-cell carcinoma may include systemic chemotherapy or treatment with biologic-response modifiers, but the efficacy of these methods in the treatment of distant metastatic disease has not been established.⁶⁹⁻⁷¹

CONCLUSIONS

Most cutaneous squamous-cell carcinomas are easily treated, and the rate of cure is high. A substantial minority, however, may recur or metastasize. Obtaining a complete history and performing a total-body skin examination will help to identify tumors at high risk for recurrence or metastasis as well as those that may be more easily treated. Since the prognosis is poor for patients with tumors with regional or distant spread, lesions that are considered likely to metastasize should be treated promptly.

Nonmelanoma skin cancers, including squamous-cell carcinoma, are largely preventable. Unfortunately, changing leisure habits involving greater exposure to sunlight have resulted in epidemic increases in the incidence of cutaneous squamous-cell carcinoma. Physicians should emphasize to their patients the prophylactic benefits of sun avoidance and protection from sunlight, beginning in childhood, to minimize the risk that this potentially life-threatening cancer will develop.

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