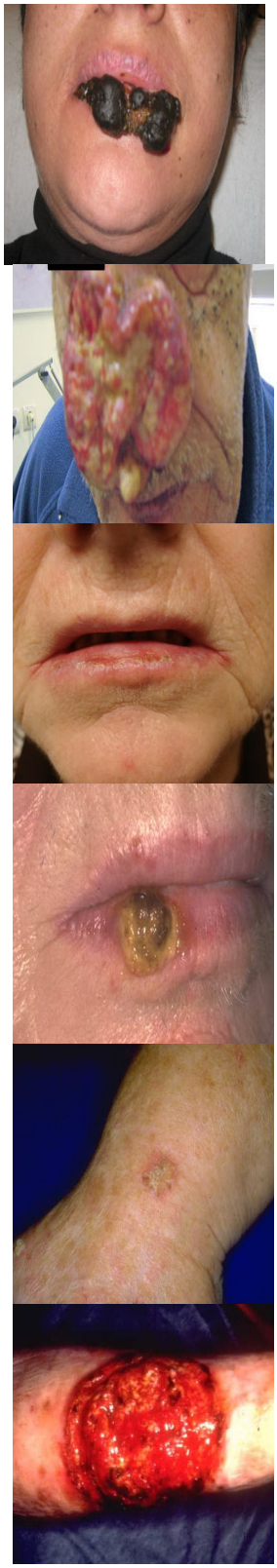

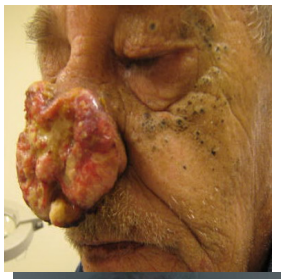

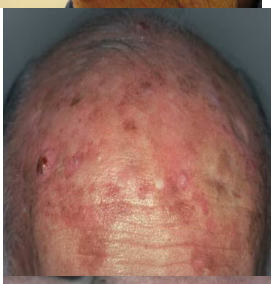

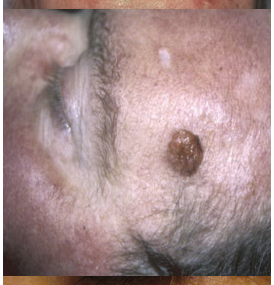

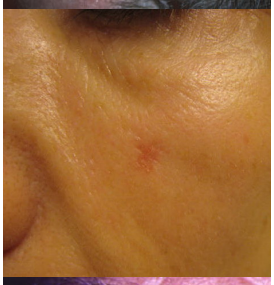

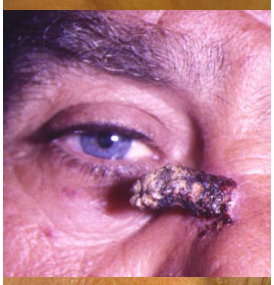

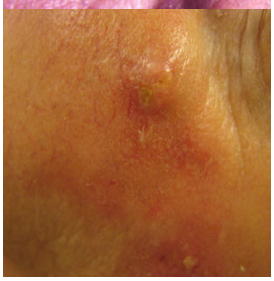

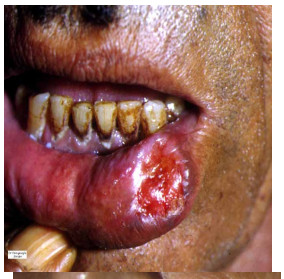

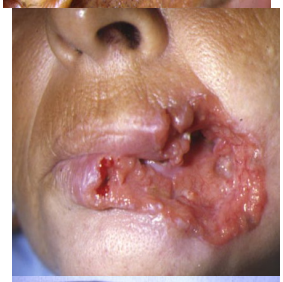

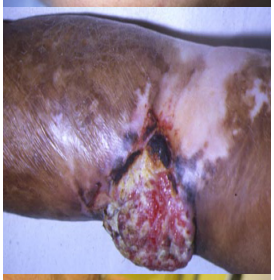

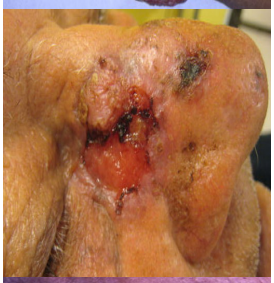

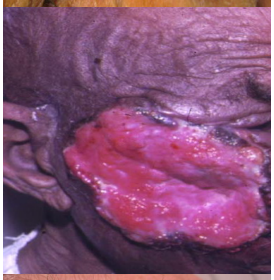

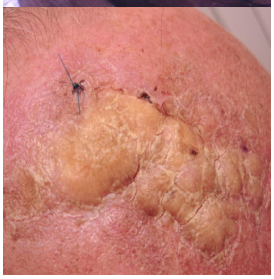

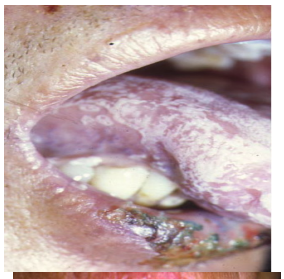

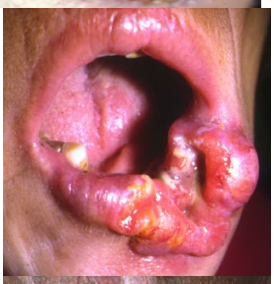

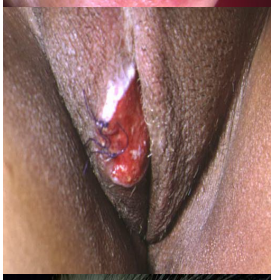

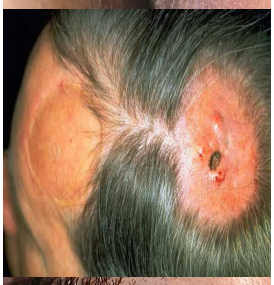

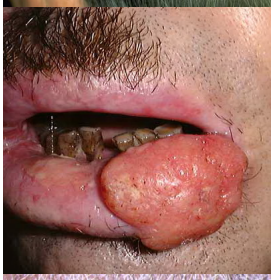

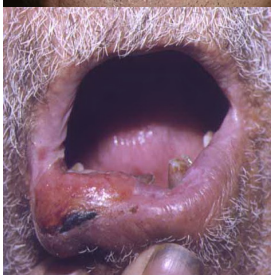

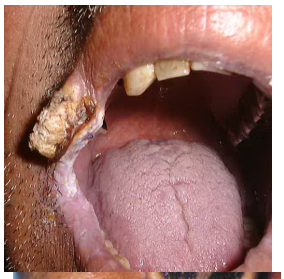

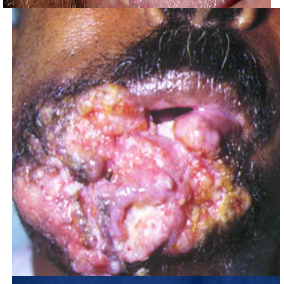

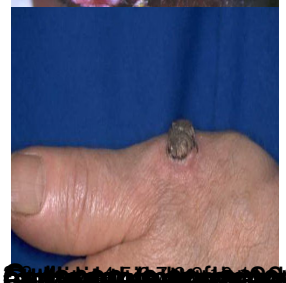

Pathophysiology

Squamous cell carcinoma (SCC) is a malignant tumor of epidermal keratinocytes. Some cases of squamous cell carcinoma occur de novo (ie, in the absence of a precursor lesion); however, some squamous cell carcinomas arise from sun-induced precancerous lesions known as actinic keratoses. Patients with multiple actinic keratoses are at increased risk for developing squamous cell carcinoma.[12] Squamous cell carcinoma is capable of locally infiltrative growth, spread to regional lymph nodes, and distant metastasis, most often to the lungs.

A detailed patient history often reveals the presence of one or more risk factors for squamous cell carcinoma (SCC) (see general risk factors in Background). Most squamous cell carcinomas are discovered by patients and are brought to a physician's attention by the patient or a relative. The typical squamous cell carcinoma manifests as a new or enlarging lesion that concerns the patient. Squamous cell carcinoma is typically a slow-growing malignancy, but some lesions enlarge rapidly. Although most squamous cell carcinoma patients are asymptomatic, symptoms such as bleeding, weeping, pain, or tenderness may be noted, especially with larger tumors. Numbness, tingling, or muscle weakness may reflect underlying perineural involvement, and this history finding is important to elicit because it adversely impacts prognosis.[19]

Actinically derived squamous cell carcinoma

The most common type of squamous cell carcinoma is the sun-induced type. As such, a history of long-term sun exposure dating back to childhood is frequently elicited. Many patients report having experienced multiple blistering sunburns during their lifetime, while others may have used indoor tanning beds or received UV light therapy (eg, psoralen plus UVA [PUVA] for psoriasis). Patients may have been treated in the past for sun-induced lesions such as actinic keratoses, basal cell carcinoma, melanoma, or squamous cell carcinoma.

Immune suppression

Patients should always be questioned about possible sources of immunosuppression. A history of solid-organ transplantation, hematologic malignancy (particularly chronic lymphocytic leukemia), HIV infection or AIDS, or long-term use of immunosuppressive medications (eg, as treatment for an autoimmune condition) may be elicited.

Marjolin ulcer

This eponym most frequently refers to a squamous cell carcinoma that arises from chronically scarred or inflamed skin; however, malignant transformation to a basal cell carcinoma, melanoma, or sarcoma may also occur.[20] Patients may report a change in the skin (eg, induration, elevation, ulceration, weeping) at the site of a preexisting scar or ulcer. The average latency period is 35 years [21] ; therefore, the diagnosis requires a high index of clinical suspicion. Marjolin ulcers are associated with a high rate of metastasis, estimated at 30%,
[22,23]
and a mortality rate of 33%.
[24]

HPV-associated squamous cell carcinoma

Virally induced squamous cell carcinoma most commonly manifests as a new or enlarging warty

growth on the penis, vulva, perianal area, or periungual region. Patients often present with a history of "warts" that have been refractory to various treatment modalities in the past. A history of previously documented genital HPV infection may be elicited.

Physical

Squamous cell carcinoma (SCC) may manifest as a variety of primary morphologies, with or without associated symptoms. Note the following:

Squamous cell carcinoma in situ

Squamous cell carcinoma in situ is defined histologically by atypia involving the full thickness of the epidermis but without invasion into the dermis. Clinically, lesions of squamous cell carcinoma in situ range from a scaly pink patch to a thin keratotic papule or plaque similar to an actinic keratosis. Bowen disease is a subtype of squamous cell carcinoma in situ characterized by a sharply demarcated pink plaque arising on non–sun-exposed skin. Erythroplasia of Queyrat refers to Bowen disease of the glans penis, which manifests as one or more velvety red plaques.

Typical squamous cell carcinoma

The characteristic invasive squamous cell carcinoma is a raised, firm, pink-to-flesh–colored keratotic papule or plaque arising on sun-exposed skin. Approximately 70% of all squamous cell carcinomas occur on the head and neck, with an additional 15% found on the upper extremities. Surface changes may include scaling, ulceration, crusting, or the presence of a cutaneous horn. Less commonly, squamous cell carcinoma may manifest as a pink cutaneous nodule without overlying surface changes. The absence of surface changes should raise suspicion of a metastatic focus from another skin or nonskin primary site or a different and potentially more lethal tumor such as Merkel cell carcinoma. A background of severely sun-damaged skin, including solar elastosis, mottled dyspigmentation, telangiectasia, and multiple actinic keratoses, is often noted

Periungual squamous cell carcinoma

Periungual squamous cell carcinoma typically mimics a verruca and is frequently misdiagnosed for years as a wart prior to biopsy. Less commonly, lesions may resemble chronic paronychia with swelling, erythema, and tenderness of the nail fold; onychodystrophy also may be noted. Periungual squamous cell carcinomas are frequently associated with HPV.[25]

Marjolin ulcer

This subtype of squamous cell carcinoma appears as a new area of induration, elevation, or ulceration at the site of a preexisting scar or ulcer. Patients with this form of squamous cell carcinoma can have a poor prognosis. The diagnosis of Marjolin ulcer should be considered in any ulcer that fails to heal with standard therapy.

Perioral squamous cell carcinoma

Squamous cell carcinoma of the lip usually arises on the vermillion border of the lower lip. It is sometimes predated by a precursor lesion, actinic cheilitis, which manifests as xerosis, fissuring, atrophy, and dyspigmentation. Actinic cheilitis is analogous to actinic keratosis of the skin. Squamous cell carcinoma on the lip manifests as a new papule, erosion, or focus of erythema/induration. Intraoral squamous cell carcinoma typically manifests as a white plaque (leukoplakia) with or without reddish reticulation (erythroplakia). Common locations include the anterior floor of the mouth, the lateral tongue, and the buccal vestibule.

Anogenital squamous cell carcinoma

Squamous cell carcinoma in the anogenital region may manifest as a moist, red plaque on the glans penis; indurated or ulcerated lesions may be seen on the vulva, external anus, or scrotum. Associated symptoms include pain, pruritus, and intermittent bleeding. These squamous cell carcinomas are also associated with HPV infection.

Verrucous carcinoma

Verrucous carcinoma is a subtype of squamous cell carcinoma that can be locally destructive but rarely metastasizes. Lesions appear as exophytic, fungating, verrucous nodules or plaques, which may be described as cauliflowerlike. Verrucous carcinoma is further subdivided based on its location in the anogenital region (Buschke-Löwenstein tumor), the oral cavity (oral florid papillomatosis), and the plantar foot (epithelioma cuniculatum).

Lymphadenopathy

With any invasive (not in situ) squamous cell carcinoma, regional lymph nodes should be examined. Lymph node enlargement must be further evaluated by fine-needle aspiration (FNA) or nodal biopsy.

Causes

The primary cause of most squamous cell carcinoma (SCC) is cumulative lifetime sun exposure. The frequency of squamous cell carcinoma is increased at lower latitudes, correlating with an increased intensity of ambient light. Other causes of squamous cell carcinoma are discussed below.

UV sunlight exposure

The component of sunlight believed to be most important in cutaneous carcinogenesis is UVB (290-320 nm), which is both an initiator and a promoter of carcinogenesis. In animal models, UV-induced photocarcinogenesis appears to involve the UVB and UVA-2 spectral ranges.[26]

UVB-induced photocarcinogenesis appears to work by suppressing the immune system in several ways. The UVB spectrum inhibits antigen presentation, induces the release of immunosuppressive cytokines, and elicits DNA damage, specifically the generation of pyrimidine dimers in keratinocyte DNA that is a molecular trigger of UV-mediated immunosuppression.[27]

Inactivation of the tumor suppressor gene *TP53* occurs in up to 90% of all cutaneous squamous cell carcinoma lesions.[28] Other tumor suppressor genes found to be mutated in squamous cell carcinoma include *P16* (INK4a) and *P14* (ARF).[29]

Therapeutic UV exposure

UV light treatments used for psoriasis (and other recalcitrant dermatoses) also predispose to the development of squamous cell carcinoma. PUVA is particularly phototoxic and mutations in both *TP53* and the oncogene Ha-*Ras* are present in a large proportion of PUVA-associated squamous cell carcinoma.[30] In addition to being mutagenic, UVA in conjunction with UVB is a potent suppressor of the cutaneous immune system, which likely contributes to its role in cutaneous carcinogenesis.

Fair complexion

Individuals with skin types I and II account for most of the patients who develop squamous cell carcinoma; patients with oculocutaneous albinism are also at risk, and squamous cell carcinomas account for the most common type of cutaneous malignancy in this group. Such individuals lack natural protection from UV-induced carcinogenesis, owing to reduced levels of

the photoprotective pigment, melanin.[31]

Ionizing radiation

Therapeutic ionizing radiation is typically associated with the later development of basal cell carcinomas, but the risk of developing squamous cell carcinomas is also increased.[32] Most patients with radiation-induced tumors have a remote history of x-ray therapy for acne vulgaris, although patients developing squamous cell carcinoma in radiation ports for Hodgkin disease or thyroid cancer treatment is not uncommon.

Chemical carcinogens

Exposure to arsenic is a well-established cause of cutaneous squamous cell carcinoma and internal cancers.[6] Today, the main source of arsenic is contaminated well water, although arsenic may also be found in traditional Chinese medicines. Other carcinogens associated with squamous cell carcinoma include polycyclic aromatic hydrocarbons such as tar, soot, and pitch.

DNA repair failure

Healthy human skin is constantly repairing UV-induced damage through DNA repair mechanisms. Patients with xeroderma pigmentosum have a deficiency in an enzyme essential for normal DNA repair and are thus prone to the development of innumerable squamous cell carcinomas, and, less commonly, other cutaneous tumors.[33]

Iatrogenic immunosuppression

The use of immunosuppressive medications to prevent rejection in organ transplant recipients is associated with a 65- to 250-fold increased risk of developing squamous cell carcinoma compared with the general population.[34]

The primary risk factor in these patients is cumulative lifetime UV exposure in combination with having Fitzpatrick skin type I or II. This risk also increases with the number of years post-transplantation, presumably because of the cumulative effects of prolonged immunosuppressive therapy.

The greatest risk occurs in heart transplant patients, with diminishing risk seen in recipients of kidney and liver transplants, which correlates with the degree of immunosuppression (ie, number and/or dosage of medications) typically required to prevent rejection in these patient populations.

Pretransplantation end-organ disease may also impact the development of post-transplant squamous cell carcinoma. For example, among renal transplant recipients, the highest prevalence of skin cancer was observed in patients with polycystic kidney disease, while the lowest incidence was seen in those with diabetic nephropathy. Similarly, cholestatic liver disease was associated with a greater post-transplantation risk of skin cancer compared with other causes of liver failure.

Noniatrogenic immunosuppression

In addition to iatrogenic immunosuppression, defects in cell-mediated immunity related to lymphoproliferative disorders (eg, chronic lymphocytic leukemia) predispose to the development of aggressive squamous cell carcinoma. The specific mechanisms by which immunosuppression leads to squamous cell carcinoma development are poorly understood, but diminished immunosurveillance is thought to be critical. $CD8^+$ T cells specific for the tumor suppressor gene *TP53* have been observed in patients with squamous cell carcinoma, suggesting that a functional immune system may target keratinocytes expressing mutated *TP53*.
[35]

Suppression of the immune system would presumably abrogate this response and might be expected to facilitate the development of squamous cell carcinoma.

Human papillomavirus

Infection with specific subtypes of HPV is believed to play a role in the development of anogenital and periungual squamous cell carcinoma. Attempts to definitively link squamous cell carcinoma to HPV have yielded contradictory results, as most squamous cell carcinomas tumors outside of anogenital and periungual sites do not contain HPV. The International Agency for Research on Cancer (IARC; Lyon, France) has determined that current evidence only supports HPV types 5 and 8 as possible carcinogens.[36] However, HPV types 6 and 11 have been associated with Buschke-Löwenstein tumors, whereas HPV type 16 has been frequently identified in both genital and periungual squamous cell carcinoma, suggesting the possibility of genital-digital spread.[37,38] HPV types 5 and 8 have been associated with cutaneous squamous cell carcinoma in the setting of epidermodysplasia verruciformis and some solid organ transplant patients.[39]

Chronic inflammation

Chronic inflammation, irrespective of the underlying etiology, may lead to the development of squamous cell carcinoma. Both noninfectious inflammatory diseases and chronic infections have been associated with squamous cell carcinoma.

Likewise, the Marjolin ulcer variant of squamous cell carcinoma may develop in patients with a chronic scarring condition such as dystrophic epidermolysis bullosa. In fact, the leading cause of death in patients with dystrophic epidermolysis bullosa is metastatic cutaneous squamous cell carcinoma,[10] with an 80% mortality rate within 5 years of diagnosis of squamous cell carcinoma[40] and with two thirds of patients dying from metastatic disease.[41] More recently, evidence suggests that patients with junctional epidermolysis bullosa may also be at increased risk for developing squamous cell carcinoma.[42]

The underlying pathogenesis of such lesions is not understood, but mutations in the *TP53* and *P16* tumor suppressor genes have been described in dystrophic epidermolysis bullosa–associated squamous cell carcinoma.[43]

Conditions that predispose to the development of squamous cell carcinoma

Chronic inflammatory and scarring conditions are as follows:

- Burn scar or thermal injury
- Venous ulcer
- Lymphedema
- Discoid lupus erythematosus
- Erosive oral lichen planus
- Lichen sclerosis et atrophicus
- Mutilating keratoderma
- Necrobiotic lipoidica

Chronic infections are as follows:

- Osteomyelitis
- Acne conglobata
- Hidradenitis suppurativa
- Dissecting cellulitis of scalp
- Lupus vulgaris
- Lymphogranuloma venereum
- Granuloma inguinale
- Chronic deep fungal infection

Genetic syndromes and dermatoses are as follows:

- Dystrophic epidermolysis bullosa
- Epidermodysplasia verruciformis
- Xeroderma pigmentosum
- Oculocutaneous albinism
- Dyskeratosis congenita
- Porokeratosis (Mibelli type, disseminated superficial actinic type, linear type)
- Nevus sebaceous
- KID (keratitis, ichthyosis, deafness) syndrome

Imaging is not routinely indicated for diagnosing cutaneous (SCC). However, radiologic imaging should be obtained in patients with regional lymphadenopathy and/or neurologic symptoms suggestive of perineural involvement, for nodal staging, and for preoperative planning in patients in whom deep or extensive tissue involvement is suspected. CT scanning, MRI, ultrasonography, or positron-emission tomography (PET) scanning may be used depending on the specific question being addressed, although the selection of one modality over another is often based on clinician and institutional preference. Currently, no formal guidelines have been developed regarding the use of radiologic imaging in cutaneous squamous cell carcinoma.

Disease staging workup in high-risk squamous cell carcinoma

Physical examination of lymph nodes

In all squamous cell carcinoma patients, the draining nodal basins should be palpated. If nodes are palpable, a biopsy should be performed using fine-needle aspiration (FNA) or excision. If lymph nodes are clinically negative but the tumor meets high-risk criteria, little data are available to guide what should be done next. Subsequently, management currently varies with regard to further staging.[44] See "High-risk squamous cell carcinoma" in Prognosis.

Radiologic staging

Only a few studies have reported on the utility of radiologic imaging in cutaneous squamous cell carcinoma. One study of MRI and CT scanning in patients with histologically proven perineurally invasive squamous cell carcinoma showed that only 20% of asymptomatic patients have positive findings discovered from imaging studies. Thus, CT scanning and MRI appear to be poor in detecting asymptomatic nerve involvement. However, positive imaging findings did correlate with worse outcomes. The 5-year survival rate was 50% if CT scanning or MRI findings were positive, versus 86% if they were negative.[45]

Two studies reported on radiologic imaging for detecting subclinical nodal metastasis.[46] The first, a study of vulvar squamous cell carcinoma, indicated that ultrasonography followed by FNA for suspicious nodes was superior to CT scanning in staging subclinical nodal metastasis, with ultrasound-guided FNA demonstrating 80% sensitivity and 100% specificity. The second is a small study of PET scanning in 9 patients with high-risk squamous cell carcinoma. PET scanning detected subclinical nodal metastasis in 3 of 9 patients.
[47]

Thus, PET scanning and ultrasound-guided FNA may be capable of detecting many cases of

subclinical nodal metastasis.

Sentinel lymph node biopsy

A review of the 85 reported cases of sentinel lymph node biopsy (SLNB) in high-risk, nonanogenital cutaneous squamous cell carcinoma showed that 21% of cases were positive based on SLNB findings. This indicates that SLNB likely can detect many cases of subclinical nodal metastasis. How the sensitivity of SLNB compares with that of PET scanning or ultrasound-guided FNA and whether detection of subclinical nodal metastasis impacts survival are unknown.[48] However, because the 5-year survival rate of patients with nodal metastasis is as high as 73% with aggressive treatment, [17] early detection of nodal metastasis may prove more beneficial in squamous cell carcinoma than in melanoma.

Summary

Little data are available to guide decisions about staging of nodal basins in high-risk squamous cell carcinoma. However, PET scanning, ultrasound-guided FNA, and SLNB all appear to offer a good chance of detecting subclinical nodal metastasis with low morbidity. Thus, nodal staging may be considered in patients with high-risk squamous cell carcinoma. Development of prognostic models that better predict the risk of nodal metastasis will allow for more rational decisions about which patients should undergo nodal staging.

Procedures

Skin biopsy

Although the diagnosis of squamous cell carcinoma (SCC) is often strongly suggested based on clinical findings, a skin biopsy is required for definitive diagnosis. A shave biopsy, punch biopsy, incisional biopsy, or excisional biopsy may be used. The biopsy is routinely performed in the physician's office after the patient is given a local anesthetic.

All skin biopsy samples obtained to diagnose squamous cell carcinoma must reach at least the depth of the mid dermis to allow for a determination of the presence or absence of invasive disease. For high-risk lesions, a larger sample may be helpful to assess for perineural invasion and other histologic features that confer a greater risk of metastasis. Given recent information about depth being an important prognostic factor (analogous to melanoma), a large punch biopsy through the center of the lesion or excisional biopsy may be best, particularly in high-risk lesions or immunosuppressed patients.[3]

Pathologic analyses may be completed by a dermatologist or a general pathologist, but they are preferably completed by a dermatopathologist with extensive experience in squamous cell carcinoma.

Patients with regional lymphadenopathy identified by clinical examination or imaging studies should undergo a lymph node biopsy or FNA for histologic evaluation. SLNB has been used to identify micrometastasis in patients with high-risk squamous cell carcinoma and clinically negative nodes, with 21% positivity.[48] While SLNB appears to be able to detect most subclinical metastasis, whether early detection of lymph node metastasis leads to enhanced survival in squamous cell carcinoma is unknown, because controlled studies have not been conducted. Complete lymphadenectomy of the draining nodal basin has also been suggested for high-risk tumors with an estimated metastatic risk of 20% or greater. However, because prognostic models do not exist, knowing precisely which patients fall into this category is difficult. Thus, when it is feasible, SLNB offers a low-morbidity approach to accurately staging high-risk squamous cell carcinoma.

Histologic Findings

The biopsy report for squamous cell carcinoma (SCC) often carries prognostic implications. Recognizing the implications of the various histologic subtypes of squamous cell carcinoma is important, and the astute clinician uses his or her understanding of histopathology to advantage in planning the appropriate therapeutic intervention.

Squamous cell carcinoma in situ is characterized by an intraepidermal proliferation of atypical keratinocytes. Hyperkeratosis, acanthosis, and confluent parakeratosis are seen within the epidermis, and the keratinocytes lie in complete disorder, resulting in the classic "windblown" appearance. Cellular atypia, including pleomorphism, hyperchromatic nuclei, and mitoses, is prominent. Atypical keratinocytes may be found in the basal layer and often extend deeply down hair follicles, but they do not invade the dermis.

The main feature that distinguishes invasive squamous cell carcinoma from squamous cell carcinoma in situ is invasion of malignant keratinocytes through the basement membrane and into the dermis. Keratinization results in the production of squamous eddies or keratin pearls. The neoplastic cells may demonstrate varying degrees of squamous differentiation and atypia. If the tumor is poorly differentiated, this fact is typically reported by the dermatopathologist because the degree of differentiation has prognostic implications (ie, poorly differentiated tumors have been associated with a higher risk of metastasis).

Several variants of squamous cell carcinoma can be distinguished by clinical and/or histologic criteria. In some cases, these tumors may be difficult to distinguish from other malignancies based on routine histology findings alone. Therefore, immunohistochemical staining with antibodies to cytokeratins and epithelial membrane antigen is often used to confirm the epithelial (ie, keratinocyte) origin of the tumor. The salient features of keratoacanthoma, spindle

cell squamous cell carcinoma, acantholytic (adenoid) squamous cell carcinoma, and verrucous carcinoma are highlighted in the following table.

Histologic and Clinical Features of Squamous Cell Carcinoma Variants

Staging

Squamous cell carcinoma (SCC) is staged according to American Joint Committee on Cancer (AJCC) guidelines, which use the tumor, node, metastasis (TNM) classification system.[49] This staging system has been updated to incorporate information about tumor factors that impact prognosis. Cutaneous squamous cell carcinoma of the eyelid is excluded from the updated system.

The previous staging system had classified tumor stage based solely on tumor diameter and invasion of deep structures (cartilage, muscle, or bone). Along with tumor diameter, the new system incorporates the following high-risk features:

- Greater than 2 mm thickness or Clark level greater than or equal to IV
- Perineural invasion
- Primary anatomic location on the ear or non–hair-bearing lip
- Poorly differentiated or undifferentiated cellular histology

T1 tumors are those 2 cm or less in diameter and with 0 or 1 high-risk features. T2 tumors are those with diameters exceeding 2 cm or with 2 or more high-risk features. T3 tumors are those involving facial bones (maxilla, mandible, orbit, or temporal). T4 tumors are those with other bone involvement or with perineural invasion involving the skull base.

The new TNM staging system has also revised nodal staging. Previously, the system had only had a single N1 level to signify nodal involvement. The new system has 5 levels. The decision to stage patients according to extent of nodal disease was based on significant findings of several studies, both prospective and retrospective, showing that the number and size of lymph node involvement correlated with patient prognosis.[50,51,52,53,54]

In the new staging system, N1 disease involves a single ipsilateral node 3 cm or smaller in its largest dimension. N2a disease includes cases with a single ipsilateral node greater than 3 cm but less than or equal to 6 cm. N2b refers to those with multiple ipsilateral nodes smaller than or equal to 6 cm. N2c includes cases of bilateral or contralateral involvement less than or equal to 6 cm. N3 disease is reserved for cases with any involved node greater than 6 cm.

In early 2010, Milross et al proposed an alternative nodal staging system (the N1S3), which also stages cutaneous squamous cell carcinoma patients based on the number (single or multiple) and size (< or > 3 cm) of lymph nodes involved, but also incorporates the parotid as one of the regional levels. Stage I disease refers to those with a single lymph node measuring less than or

equal to 3 cm. Stage II includes cases with a single lymph node greater than 3 cm or multiple lymph nodes less than or equal to 3 cm, while stage III is any patient with multiple lymph nodes greater than 3 cm.[55] This system was found to have a significant predictive capacity for locoregional control (*P* <.0001), disease-specific survival (*P* <.0001), and overall survival (*P* <.0001) in a group of 215 patients and was reproduced on external validation in a cohort of 250 patients.

Distant metastases are staged according to the presence (M1) or absence (M0) of metastases in distant organs or sites outside of regional lymph nodes. This remains unchanged from the previous TNM staging system

Stage 0 is equivalent with in situ disease. Disease stages I and II include patients with T1 and T2 tumors, respectively who have no nodal or distant metastasis (N0, M0). Stage III disease includes T3 cases without nodal involvement (N0) *or* cases with N1 involvement. Stage IV includes those with T4 disease, *or* N2 or N3 disease, *or* distant metastasis (M1).

Medical Care

Nonsurgical options for the treatment of cutaneous squamous cell carcinoma (SCC) include topical chemotherapy, topical immune response modifiers, photodynamic therapy (PDT), radiotherapy, and systemic chemotherapy. The use of topical therapy and PDT is generally limited to premalignant (ie, actinic keratoses) and in situ lesions. Radiation therapy is a primary treatment option for patients in whom surgery is not feasible and is an adjuvant therapy for those with metastatic or high-risk cutaneous squamous cell carcinoma. In current practice, systemic chemotherapy is used exclusively for patients with metastatic disease. However, newer, more targeted drugs, such as epidermal growth factor receptor (EGFR) antagonists (eg, cetuximab), have favorable adverse effect profiles and await trails to determine if they are beneficial in high-risk squamous cell carcinoma.

Topical chemotherapy

Topical formulations of 5-fluorouracil (5-FU) are available for the treatment of actinic keratoses and superficial basal cell carcinomas. Successful treatment of in situ squamous cell carcinoma has also been reported.[56] Invasive squamous cell carcinoma should not be treated with topical chemotherapy. An oral form of a 5-FU prodrug (capecitabine), which is approved by the US Food and Drug Administration (FDA) for other forms of cancer, may be considered in patients

with diffuse in situ squamous cell carcinoma over large skin areas, on which topical 5-FU is difficult to apply. However, studies of efficacy have not yet been performed.

Topical immune response modifiers

Imiquimod is an imidazoquinoline that enhances cell-mediated immune responses via the induction of proinflammatory cytokines. It is approved by the FDA for the treatment of genital warts (ie, condylomata acuminata), actinic keratoses, and superficial basal cell carcinoma. Imiquimod cream has also shown effectiveness in the treatment of Bowen disease as monotherapy and in combination with topical 5-FU. However, systemic flulike symptoms and other adverse effects can occur when applied to large surface areas; therefore, using this agent in patients with diffuse in situ squamous cell carcinoma is difficult.[57,58]

Photodynamic therapy

Treatment with PDT involves the application of a photosensitizer (given topically or systemically) followed by exposure to a light source. The resulting photochemical reaction causes inflammation and destruction of the targeted lesion(s). PDT is used primarily to treat large numbers of actinic keratoses in a single session. Squamous cell carcinoma in situ is also amenable to PDT, although a wide range of recurrence rates (0-52%) have been reported. A study of organ transplant recipients with multiple actinic keratoses and field actinic damage showed PDT to be superior to topical 5-FU.[59] A 2009 noncomparative study showed repeated cycles of PDT to be associated with significant reduction in squamous cell carcinoma formation in organ transplant recipients.[60] At this time, PDT is not recommended for treatment of invasive squamous cell carcinoma due to poor long-term cure rates.[61]

Radiation therapy

Primary radiation therapy as a treatment option for squamous cell carcinoma offers the potential advantage of avoiding the deformity and trauma of a surgical procedure. Cure rates for T1 lesions range from 85-95%. However, a number of disadvantages are associated with radiation therapy. For example, radiation therapy is expensive and requires a significant time commitment because treatments are usually given 3-5 times per week for 4-8 weeks. Most patients experience significant irritation at the radiation site, and they frequently develop erythema, erosions, alopecia, and pain, which may require narcotic-level analgesia. Although the initial cosmetic result following radiation is usually good, the long-term outcome is often poor, owing to the development of cutaneous atrophy, dyspigmentation, and telangiectasia in the radiation field. Patients treated with radiation also have a slightly increased risk of developing cutaneous carcinoma (most commonly squamous cell carcinoma) or sarcoma later in life.

Radiation therapy does not involve histologic margin control and has a lower cure rate compared with surgery. For these reasons, as well as those discussed in the preceding paragraph, radiation as a primary therapy is usually confined to a small subset of tumors in which the cosmetic or functional outcome would be superior to that of surgery[62] or in elderly

patients with inoperable squamous cell carcinoma.

In contrast, radiation is routinely used as an adjunct to surgical treatment in cases of nodal metastasis, and the reported 5-year cure rate is 73% for combined surgical and radiation therapy to involved nodal basins.[17] Squamous cell carcinomas with advanced perineural invasion have an elevated risk of recurrence, even when surgical margins are thought to be clear.[44,48,63] Thus, adjuvant radiation may be considered, particularly in cases involving larger nerves, although its utility has yet to be proven. A systematic review analyzing all reports related to outcomes of high-risk squamous cell carcinoma treated with surgical monotherapy compared with those treated with surgery plus adjuvant radiation[64] was unable to show an advantage of adjuvant radiation in the treatment of squamous cell carcinoma with perineural invasion. However, the available studies were uncontrolled for tumor stage and more advanced tumors with a worse baseline prognosis likely received radiation.

In summary, the additional benefit of adjuvant radiotherapy is uncertain, especially when clear surgical margins are obtained. However, it may be considered in patients with multiple high-risk factors, those with significant nerve involvement (particularly named nerves or nerves >0.1 mm in diameter), those with uncertain surgical margins (eg, poorly differentiated, infiltrative, or multiply-recurrent tumors), or as salvage therapy for in-transit metastasis or other tumors which cannot be cleared surgically. A lower threshold for adjuvant radiation should be used in immunocompromised patients with high-risk squamous cell carcinoma.[64]

Systemic chemotherapy

A variety of different chemotherapeutic agents have been used to treat metastatic cutaneous squamous cell carcinoma. Many of the current protocols have been adapted from those used to treat metastatic head and neck squamous cell carcinoma.

Cisplatin-based combination chemotherapy with 5-FU, methotrexate, bleomycin, and doxorubicin have all been used to treat advanced squamous cell carcinoma with variable outcomes.

The oral 5-FU prodrug, capecitabine (Xeloda), has been designed to be metabolized to 5-FU selectively within tumor tissues, thus producing less systemic toxicity. Either used alone, or in combination with interferon alfa, it has shown some efficacy in the treatment of advanced cutaneous squamous cell carcinoma.[65]

More recently, cetuximab, an EGFR inhibitor, has had reported as successful in several case reports.[66,67,68] In the head and neck literature, phase I and II trials of capecitabine, used with cisplatin or paclitaxel[69,70] or in combination with radiation therapy[71] also showed favorable outcomes. EGFR inhibitors are well tolerated with relatively low risks, so they may be considered in cases not amenable to surgery or radiation or as an adjuvant in cases considered to have a high risk of death.

Reduction in immunosuppression

In organ transplant recipients, a reduction in the magnitude of immunosuppression may be an effective adjuvant therapeutic strategy in the treatment of aggressive squamous cell carcinoma. Because a decrease in immunosuppression may increase the risk for rejection of the transplanted organ, this strategy should only be considered in selected high-risk patients and under the careful management of the transplantation physician, who must closely monitor the patient for signs and symptoms of organ rejection.[72]

Newer immunosuppressive agents (eg, sirolimus) are associated with a lower incidence of squamous cell carcinoma when compared with more traditional agents (eg, calcineurin inhibitors), without compromise in graft function.[73,74] Patients on sirolimus also produce thinner, less vascularized tumors, [75] likely due to the drug’s antiangiogenic and antitumor properties. In a study of 182 organ transplant recipients, the mean cumulative doses of prednisone, cyclosporine, azathioprine, and mycophenolate were significantly higher in those with skin cancer. Conversely, the cumulative doses of sirolimus and tacrolimus were significantly lower in those with skin cancer, suggesting that these drugs may be protective.

Surgical Care

Most squamous cell carcinomas (SCCs) are readily treated in the physician's office by surgical or destructive methods, with a high expectation of cure. The treatment of squamous cell carcinoma must take into account multiple patient- and lesion-specific factors. The standard modalities available for the treatment of localized (primary) invasive squamous cell carcinoma are described below. Because squamous cell carcinoma is a lesion that can recur, metastasize, and cause death, and, because recurrent squamous cell carcinoma carries a worse prognosis, every opportunity should be taken to effect complete tumor extirpation at first presentation.

Cryotherapy

Cryotherapy with liquid nitrogen is a safe and low-cost procedure for the ablation of selected in situ squamous cell carcinomas. The 5-year cure rate for squamous cell carcinoma can be 95% or greater with proper tumor selection and technique. In the United States, cryosurgery is routinely used for in situ disease and actinic keratoses. It is not often used for invasive squamous cell carcinoma because deeper portions of the tumor may not be eradicated by this technique and because the development of scar tissue at the site of cryotherapy might obscure a recurrence. The risks associated with cryotherapy include transient pain, edema, and blistering. Hypopigmentation and alopecia are also common and may be permanent, so treatment of hair-bearing areas and in darkly pigmented individuals is generally not recommended.[76]

Electrodesiccation and curettage

Electrodesiccation and curettage (ED&C) is a simple technique that can be used to treat low-risk squamous cell carcinoma on the trunk and extremities. The tumor indications are similar to those of cryotherapy. In addition, ED&C can be used to treat superficially invasive

squamous cell carcinomas without high-risk characteristics. However, the thick scars that often occur after ED&C can delay the diagnosis of cancer recurrence. Subsequently, ED&C should be used with caution in invasive squamous cell carcinoma. It is not appropriate for certain anatomic locations (ie, eyelids, genitalia, lips, ears).

The technique is based on the delineation of tumor margins with a curette because tumor tissue is generally more friable than the surrounding normal tissue. ED&C is known to be very technique dependent, and cure rates improve with a practitioner's experience. The main disadvantage of ED&C is a lack of histologic margin control, and most dermatologic surgeons believe the actual long-term cure rate for invasive squamous cell carcinoma is much lower than that quoted in the literature. Tumor recurrence may result from failure of ED&C treatment to eradicate atypical cells residing deep in the hair follicles or in the dermis. Nonetheless, the procedure is fast, minimally invasive, well tolerated, and effective for properly selected lesions.

Excision with conventional margins

Standard excision with conventional permanent (ie, paraffin-embedded) tissue sections is an excellent, highly effective, and well-tolerated therapy for primary squamous cell carcinomas that lack high-risk features and are located in areas where tissue sparing is not critical. Cure rates following simple excision of well-defined T1 lesions may be as high as 95-99%. The generally accepted 5-year cure rate for primary squamous cell carcinoma treated with standard excision is 92%; this rate drops to 77% for recurrent squamous cell carcinoma.

A 4-mm margin of healthy tissue is recommended for lower-risk lesions (<2 cm, well-differentiated, without subcutaneous fat invasion) on the trunk and extremities. For lesions larger than 2 cm, invasive to fat, and in high-risk locations (ie, central face, ears, scalp, genitalia, hands, feet), a 6-mm margin of healthy tissue is recommended. Given the cosmetic and functional impact of these wider margins, tumors in this latter category are often removed via Mohs surgery (see below) to achieve high cure rates while sparing normal tissue. The depth of an excision should always include a portion of the subcutaneous fat.

One pitfall of standard excision is that histologic margins can be reported to be negative when they are, in fact, positive (false negative) because the traditional bread-loaf method of tissue sectioning typically results in evaluation of less than 1% of the specimen’s margins. More commonly, a greater amount of healthy tissue is removed than is necessary for complete tumor extirpation. Therefore, simple excision is most valuable in the treatment of small primary squamous cell carcinomas on the trunk, extremities, or neck, where tissue sparing is less essential.[77]

Mohs micrographic surgery

Mohs micrographic surgery (MMS) is a specialized technique for removing many forms of skin cancer, including squamous cell carcinoma. Because of its many advantages, MMS is the procedure of choice for squamous cell carcinoma in which tissue preservation is needed, for ill-defined squamous cell carcinoma, recurrent tumors, and for high-risk squamous cell carcinoma. The main advantage of MMS over simple excision is the ability to histologically

examine nearly 100% of the surgical margins (as compared with <1% of the margin visualized via standard histologic sectioning) and to carefully map residual foci of invasive carcinoma. This residual tumor is removed in a step-wise fashion until clear margins are obtained.

MMS provides the best available cure rates (94-99%) for squamous cell carcinoma and has been of particular value in curing squamous cell carcinoma associated with perineural invasion. In a comprehensive historical review, Rowe et al[78] noted that local recurrences are less frequent when squamous cell carcinoma is treated with MMS compared with all non-Mohs modalities. This local recurrence rate differential in favor of MMS was observed in primary squamous cell carcinoma of the skin and lip (3.1% vs 10.9%), for locally recurrent squamous cell carcinoma (10% vs 23.3%), for poorly differentiated squamous cell carcinoma (32.6% vs 53.6%), and for squamous cell carcinoma with perineural involvement (0% vs 47%).

MMS offers the added benefit of preserving healthy tissue, thus facilitating reconstruction and optimizing cosmetic and functional outcomes. It is performed in an outpatient setting with local anesthesia and is therefore a safe and cost-effective procedure[79,80] , and MMS is less expensive than surgical excision with anesthesia in a hospital setting.
[79,80]

As a result of the fellowship training programs in Mohs surgery overseen by the American College of Mohs Surgery and the new Accreditation Council for Graduate Medical Education (ACGME)–accredited Procedural Dermatology Fellowship programs, MMS has become widely available throughout the United States.[81,82]