Management of High-Risk Cutaneous Squamous Cell Carcinoma

LORRAINE JENNINGS, MD; CHRYSALYNE D. SCHMULTS, MD
Mohs Micrographic Surgery Center, Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

ABSTRACT

Cutaneous squamous cell carcinoma is an increasing public health concern, representing the second most common cancer in the United States. High-risk cutaneous squamous cell carcinoma represents a subgroup of this disease, where patients are at higher risk of metastasis and death. To date, there are no accepted criteria for defining or managing these patients. This review discusses the current state of knowledge of high-risk cutaneous squamous cell carcinoma and outlines reasonable management strategies based on available data. (*J Clin Aesthetic Dermatol.* 2010;3(4):39–48.)

Cutaneous squamous cell carcinoma (CSCC) is the second most common cancer in the United States, with an excess of 200,000 new cases each year.[1] Although CSCC can usually be cured by a variety of techniques, there are still an estimated 8,000 cases of nodal metastasis and 3,000 deaths in the United States annually, almost wholly attributable to a subset designated as aggressive or high-risk CSCC, which has substantially higher rates of recurrence and metastases.[2,3] Ideal management has not yet been defined for this group, there are no prognostic models that reliably predict individuals at risk for recurrence and metastasis, and there is a lack of randomized controlled trials (RCTs) for the treatment of high-risk CSCC. Subsequently, management of patients is not uniform.[4] The aim of this article is to discuss the current state of knowledge of high-risk CSCC, highlight gaps in this knowledge, and outline reasonable management strategies based on available data.

IDENTIFYING HIGH-RISK PATIENTS

To date, there is no accepted system for defining high-risk CSCC. The potential for advanced or aggressive disease can be attributed to a combination of tumor factors and host factors. Most high-risk tumors will have more than one risk factor present. As prognostic models have not yet been developed, it is unknown how various combinations of risk factors impact risk of recurrence or metastasis. Thus, it remains difficult to estimate these risks for an individual patient and make reasonable treatment recommendations. Development of reliable prognostic models will greatly aid treatment decisions in CSCC. Meanwhile we have summarized the prognostic information currently available. Several tumor factors and host factors have been associated with recurrence, metastasis, and death (Table 1).

TUMOR FACTORS

Location. It is well accepted that CSSC arising in previously injured skin (e.g., a burn site, scar, chronic wound, or ulcer) have an increased risk of metastasis,[2,5–7] with a recurrence rate of 58 percent and an overall five-year survival of 52 percent.[8] However, published data relating to the prognostic significance of anatomic tumor location are conflicting.

Rowe at al[2] published a large review of available data in 1992 examining prognostic factors in CSCC. They reviewed 71 studies that reported local recurrence and/or metastatic rates. Tumors of the ear and lip had elevated risk of metastases, 9 and 14 percent, respectively, as compared to a baseline risk of five percent for tumors on other sun-exposed sites. This is echoed in a prospective study involving 615 patients with CSCC, which found that lesions localized to the ear had a three-fold higher risk for metastasis (hazard ratio 3.6; 95% confidence interval 1.5-8.7).[3] Anogenital SCCs are also associated with a high risk

DISCLOSURE: The authors report no relevant conflicts of interest.
ADDRESS CORRESPONDENCE TO: C. Schmults, MD, Mohs Micrographic Surgery Center, BWH Department of Dermatology, 1153 Centre Street, Jamaica Plain, MA 02130; E-mail: cschmults@partners.org

TABLE 1. Factors associated with increased risk of recurrence, metastasis, and death

TUMOR FACTORS	HOST FACTORS
• Location (ear, lip, anogenital, scars) • Diameter >2cm • Depth >4mm or beyond subcutaneous fat • Perineural invasion • Poorly differentiated tumor • Infiltrative/desmoplastic growth pattern • History of local recurrence	• Immunosuppression Organ transplant recipients (heart/lung>kidney>liver) Chronic lymphocytic leukemia/ lymphoma AIDS • Other: arsenic, psoralen ultraviolet-A (PUVA), radiation exposure, bullous diseases

TABLE 2. Data adapted from Rowe et al,[2] using chi square analysis, to show that location on the lip is significantly associated with metastasis in the data reviewed

	+ METASTASIS	– METASTASIS	TOTAL NUMBER
+ lip location	1,520 (13.7%)	9,574	11,094
– lip location	212 (7.1%)	2,759	2,971

Chi square=93.6, $p<0.0001$

of metastasis, with reported figures varying widely from 15 to 74 percent.[9] Other studies suggesting that tumor location impacts risk of metastasis have only examined CSCCs that have already metastasized to lymph nodes (LN).[10,11]

To accurately determine if location is a significant predictor of metastatic disease, all CSCCs in a patient cohort should be studied and the risk of metastasis evaluated via chi square analysis for location. Table 2 shows such a chi-square analysis for lip location taken from the Rowe data,[2] which show that lip tumors metastasized significantly more frequently than those from non-lip sites. However, it should be noted that these data are taken from case series data rather than cohort data. Such case series data are usually derived from academic centers with specialized patient populations that are different from (and often higher risk than) the population of CSCC patients as a whole. Unfortunately, true cohort studies to date have been few and underpowered (too small) to evaluate the impact of anatomic location on outcomes. Thus, there remains an open question of the impact of location, although location on the ear and lip may confer an increased risk of metastasis, presumably due to close proximity of draining nodal basins.

Tumor characteristics. There is a large body of case series data and a handful of small prospective studies examining the histological features of CSCCs associated with elevated risks of recurrence, metastasis, and death. These features include tumor diameter, depth, extension into subcutaneous tissue, poorly differentiated histology, and perineural involvement,[2,12] especially involvement of named nerves or those larger than 0.1mm in diameter.[13]

Most groups have shown tumors greater than 2cm in diameter to have a high risk of metastasis,[2,6,10] although other studies describe 4cm as a prognostic cut-point[12]; caution should be executed in lesions of the lip and ear, which can metastasize when <2cm in size.[14] Millimeter tumor thickness and tissue level of invasion (e.g., subcutaneous fat, fascia, muscle, bone) are important predictors of metastatic disease, although there are variable reports as to the millimeter depth that confers a higher risk and the magnitude of that risk ranging from >4mm (45.7% risk),[2] >5mm (44% risk for desmoplastic and 17.5% for non-infiltrative CSCC),[15] and >6mm (16% risk).[3] Patients with tumors <2mm thick have minimal risk of metastasis.[3] CSCCs invading beyond subcutaneous fat are strongly associated with disease-specific death.[12]

Histological grade has a marked impact on risk of metastasis and death. A retrospective study estimated a 37-percent cure rate for poorly differentiated tumors, compared with 59 percent for moderate and 88 percent for well-differentiated tumors over a median follow-up period of 2.4 years.[6] Rowe et al[2] reported a 33-percent risk of metastasis in those with poorly differentiated disease. Desmoplastic (also known as infiltrative) CSCCs possess a high propensity for regional metastasis, especially with increasing tumor thickness. One prospective study described infiltrative CSCC as having a six-fold increase in LN metastases (22.7% vs. 3.8%) and a 10-fold increase in local recurrence (27.3% vs. 2.6%) when compared to noninfiltrative CSCC.[15]

Perineural invasion (PNI) has been reported to occur in up to seven percent of cutaneous CSCCs and has been associated with a high incidence of recurrence, metastasis, and death.[2,12,16] Patients may be asymptomatic, with PNI detected only on pathological examination of the surgical specimen, or it may present with cranial nerve deficits, most commonly affecting the fifth and seventh nerves.[17] Outcomes are worse for those with clinical symptoms of PNI. In our retrospective cohort study of 48 patients with perineural CSCC, outcomes were poor for those with involvement of nerves 0.1mm or larger, with a 32-percent risk of disease-specific death; whereas, no deaths occurred in those with invasion of nerves less than 0.1mm ($p=0.003$).[13] Local recurrence is also strongly associated with metastatic disease, specifically distant metastasis; 30 to 50 percent of metastatic CSCC will have had a history of prior local recurrence.[2,18]

HOST FACTORS

Patients who are immunosuppressed have a higher risk of developing skin cancer, and these tumors portend a worse prognosis than is typically seen in immunocompetent

patients. A 13-percent risk of metastatic disease has been described,[2] twice the rate seen without immunosuppression. However, the risk can vary depending upon the type of immunodeficiency. A compromised immune system may result from a wide variety of diseases or therapies. In managing patients with high-risk CSCC, it is important to consider culpable underlying conditions, and, if present, whether immune status can be improved. Table 3 outlines an approach to managing immunosuppressed patients with skin cancer.

Organ transplant recipients (OTRs). It is well understood that OTRs have an increased incidence of CSCCs, with an estimated 65-fold increase compared to the general population.[19] The ratio of CSCCs to basal cell carcinomas (BCCs) is reversed and occurs with a 3:1 frequency.[20,21] Human papilloma virus (HPV), or as yet uncharacterized viruses, has been hypothesized to contribute to CSCC formation in this patient group.[22] Incidence of CSCCs is 2.9 times greater in heart transplant recipients when compared to kidney transplant recipients, attributable to the increased requirement for immunosuppression to avoid rejection of heart transplants.[19] Patients with fair skin and extensive sun exposure are at the greatest risk, with incidence rates as high as 70 percent reported in such patients in Australia.[23] The same study showed that cumulative incidence of developing skin cancer increased progressively with longer duration of immunosuppression; seven percent after one year compared with 45 percent after 11 years and 70 percent after 20 years. A French study of 188 OTRs found that 66 percent of patients will develop a second CSCC within five years of their first.[24] Sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR), has been associated with a lower incidence of CSCC[25] than traditional immunosuppressive agents, as well as producing thinner, less vascularized tumors,[26] likely due to the drug's anti-angiogenic and anti-tumor properties. OTRs present more commonly with high-risk aggressive CSCCs, where tumors are thicker, infiltrative, and poorly differentiated, with a high predilection for metastasis.[27] Veness at al[28] followed 619 heart transplant patients and found that four percent (18/619) developed an aggressive cutaneous CSCC within 10 years of transplant, the majority of which were poorly differentiated (15/18). Sixty-six percent of the cohort died of the disease or had metastasis at two-year follow up.[28] In-transit (local cutaneous) metastases also occur more commonly in OTRs, with an elevated mortality risk when compared to immunocompetent patients (30% vs. 0%, respectively).[29]

Chronic lymphocytic leukemia (CLL) and small-cell lymphocytic lymphoma (SLL). CLL and SLL have been well described as being associated with skin cancer. CSCC is the most frequently reported[30] and is often aggressive, recurrent, and metastatic with high mortality.[31] In a series of 374 CLL/SLL patients, Frierson et al[30] found that three percent developed cutaneous CSCC and more than half met high-risk criteria, with tumor diameters greater than 4cm, PNI, or poorly differentiated histology.[30] Twenty-five percent of tumors recurred or metastasized and a staggering 41 percent of the CSCC patients died of disease. A retrospective, case-controlled study of 28 patients with CLL and CSCC found that the cumulative five-year recurrence rate for CSCC was 19 percent, seven times higher than the control group.[31]

TABLE 3. Managing skin cancer in the immunosuppressed

1. Improve immune status—discuss with prescribing physician options for decreasing immunosuppression or changing agent
2. Clear all invasive CSCC with histological confirmation of clear margins
3. Use field treatments (e.g., curette hyperkeratotic lesions followed immediately by topical 5-FU twice daily for 4 weeks)
4. Close follow up and monitoring: every 3–6 months if patient has AKs or history of CSCC
5. Oral retinoids if continuing to form multiple CSCCs after 6–12 months of approach above
6. Oral 5-FU or epidermal growth factor receptor inhibitors may also be considered

Human immunodeficiency virus (HIV). HIV is not definitively associated with high-grade CSCC, although Nguyen et al[32] described a small case series of 10 HIV patients who developed aggressive CSCC, where 50 percent of patients had died at seven-year follow up.[32] CSCC that develops in patients with acquired immunodeficiency syndrome (AIDS) or poorly controlled HIV should therefore be treated with caution. There is also a well-documented increase in anal and genital CSCC in association with HPV in this patient group.

Other conditions. A variety of other conditions have also been associated with aggressive CSCC and poor prognosis, including arsenic, psoralen-ultravoilet-A (PUVA) or ionizing radiation exposure, and bullous diseases. CSCC is the leading cause of death in recessive dystrophic epidermolysis bullosa, with an 80-percent mortality rate within five years of diagnosis of CSCC.[33] Chronic diseases, such as rheumatoid arthritis and inflammatory bowel disease, are also thought to increase the risk of developing CSCC,[34] possibly related to a combination of immunosuppressive therapy and immune compromise from the disease itself.

STAGING

Regional LN exam. All patients suspected of or diagnosed with CSCC should undergo a regional LN exam. Any enlarged nodes should be examined histologically using either fine needle aspiration or excisional biopsy. Tumor-positive nodes should be managed by aggressive surgical resection of all local and regional disease, including LN dissection of multiple nodal basins if indicated. Addition of adjuvant radiation to lymphadenectomy can result in high cure rates, which Veness reported as a 73-percent, five-year, disease-free survival (DFS).[35] Thus, early detection of nodal metastasis may improve outcomes for high-risk CSCC.

Radiological imaging. Radiological imaging represents the standard method to detect subclinical nodal spread. However, the gold standard imaging modality of choice, as well as which patient subsets require imaging, has not been established, as there are few studies of imaging in CSCC. There is a body of data regarding imaging for oro-nasopharyngeal CSCC. In these studies, specificity and sensitivity are widely variable for computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound (USS). It appears that CT and PET have a reasonable sensitivity in picking up subclinical disease, but false-positives are common. The combination of PET-CT increases the sensitivity of CT, but this is an expensive imaging tool and as yet unproven to impact outcomes. In general, CT is superior for detecting central nodal necrosis, extracapsular spread, skull-base invasion, and cartilage involvement, while MRI sensitively detects neurotropic tumors, defines tissue planes, and distinguishes dense connective tissue from muscle.[36,37] Both MRI and CT may be helpful in preoperative planning, especially with tumors suspected of involving LNs or deep structures, such as bone, parotid gland, or major nerves.

The lack of studies of nodal staging in cutaneous SCC leads to uncertainty among physicians regarding which patients require staging and which modality to use. A survey study assessing imaging practices[4] among Mohs surgeons found that, of 117 responders, 35 percent seldom image patients with high-risk CSCC to stage LNs. If imaging was performed, 54 percent of responders preferred CT, 36 percent MRI, 15 percent PET, and five percent had no preference.

The only study comparing accuracy of imaging techniques in CSCC compared preoperative CT versus ultrasound with fine needle aspiration cytology (US-FNAC) in primary CSCC of the vulva.[38] US-FNAC was superior to CT in specificity, sensitivity, negative predictive value, and positive predictive value for detection of LN involvement. The authors concluded that surgical planning was not enhanced with the addition of CT and there was no role for its routine use in managing this group of patients. Therefore, in CSCC, US-FNAC may be a useful screening tool as nodes are usually superficial.

Detection of nodal metastasis by whole body 18F-fluorodeoxyglucose (FDG-PET) is also a sensitive staging tool, although there has only been a single study looking at its effectiveness in CSCC. FDG-PET has the advantage of detecting metastasis in areas of necrosis, fibrosis, and dense scarring secondary to radiotherapy.[39] Cho et al[40] staged nine patients with high-risk CSCC with FDG-PET. LN metastases were detected in 25 percent and distant (lung) metastasis in one case.[40] No completion node dissections were performed, so there was no comparative data on how many nodal metastases PET may miss; therefore, sensitivity and specificity could not be calculated.

Radiological imaging may also be considered to evaluate known perineural invasion, but likely detects only advanced perineural spread. Williams et al[41] found that only 17 of 35 patients with histological perineural CSCC or BCC involving major named nerves (trigeminal nerve or facial nerve) had CT or MRI imaging evidence of nerve involvement. The five-year survival of those with positive imaging was 50 percent compared to 86 percent in the image negative group, indicating that imaging was picking up more advanced disease.

In summary, the role of radiological imaging in CSCC requires further study in sensitivity, specificity, and cost effectiveness in different high-risk patient subsets. Meanwhile, imaging poses little risk to patients and should be considered in those with high-risk CSCC for nodal staging and for preoperative planning if deep or extensive tissue involvement is suspected.

Sentinel lymph node (SLN) examination. SLN examination offers another potential means of identifying LN metastasis in clinically negative nodal basins. Its utility in CSCC is unknown since there have been only case reports and several case series, but no controlled studies. A 2006 review[9] systematically reviewed the English literature for reports of SNL biopsy in CSCC, with clinically negative nodes. The results were divided into nonanogenital and anogenital CSCCs. Of the 85 nonanogenital CSCC patients who had undergone SLN biopsy, 21 percent (n=17) had a positive SLN biopsy. Twenty of the 85 patients underwent completion lymphadenectomy, with a single false-negative detected (5%). Results were similar in the anogenital CSCC group, with 24 percent (139 of 585) having a positive SLN. More patients in the anogenital group underwent completion lymphadenectomy (n=213), with eight of these having positive nodes detected that had been missed on SLN biopsy, producing a false-negative rate of four percent. Most false-negative results were reported in studies from 2000 or earlier in which the combination of preoperative lymphoscintigraphy and blue dye was not used in the SLN localization process. Rates of morbidity were low, and the majority were related to mild local complications. In one study reviewed, all patients underwent total lymph-adenectomy after SLN biopsy with no false-negatives detected.[42] This study employed step sectioning of all SLNs, which identified CSCC in four additional patients who were initially thought to be negative.

SLN biopsy is a minimally invasive staging procedure that may be useful in identifying occult regional LN disease in selected high-risk patients with CSCC. The sensitivity of this procedure can be increased with lymphoscintigraphy (plus blue dye) and step-sectioning techniques. It is unknown whether early detection of LN metastasis will improve outcomes for patients with CSCC. This awaits further study. Fortuitously, unlike melanoma, CSCC with nodal metastasis is often curable so early detection of nodal spread has the potential to prevent distant metastasis and death. Prospective controlled trials are required to assess the utility of SLN biopsy in high-risk CSCC.

TREATMENT

The first step in treating high-risk CSCC is to identify it as such, using the criteria discussed above. However, as

previously mentioned, there are no prognostic models for CSCC so clinicians are currently unable to determine an individual's risk of metastasis and death with accuracy and confidence. This greatly complicates treatment decisions and leads to lack of uniformity in care. Controlled studies are lacking, so no definite standard of care for optimal treatment for CSCC has been established. Despite this, we will review current data available and discuss approaches we currently employ.

Assessment of immune status. Assessment of immune status, with thorough history and exam, should be carried out in all patients with high-risk CSCC to rule out any underlying disease, which may place them at high risk for metastasis. This is of particular importance in OTRs whose immunosuppression leads to an elevated risk for recurrent and advanced CSCCs. Out-of-control skin cancer with formation of multiple invasive CSCCs may be a marker of impaired immunity and potentially over-immunosuppression. Reduction in immunosuppression has been associated with a decrease in new CSCC formation and improved outcomes in those with established aggressive disease.[43] Single-agent therapy appears to carry a lower risk than multi-agent immunosuppression. Newer immunosuppressive agents (e.g., sirolimus) are associated with a lower incidence of CSCC development when compared to older calcineurin inhibitors (CNIs) without compromise in graft function.[44,45] In addition, a recent small case series showed that conversion from CNI to sirolimus was associated with reduced vascularization and thickness of post-transplant cutaneous CSCCs,[26] which is consistent with known anti-angiogenic properties of mTOR inhibitors. The authors' own unpublished data indicate that OTRs who do not develop skin cancer were exposed to significantly higher cumulative doses of sirolimus or tacrolimus, indicating that these drugs carry a low risk of cancer formation and may be protective (manuscript in preparation).

Any change in dose or class of immunosuppression in OTRs should be managed by a patient's transplant physician, as changes may be detrimental to graft function or precipitate rejection. A balance must be struck between risks posed by skin cancer and risks of a new immunosuppressive regimen. The role of the dermatologist is to advise the transplant physician of the impact of multiple skin cancers on the patient's quality of life and convey estimates of morbidity and mortality the patient may suffer from skin cancer (Table 2). This will help the transplant physician to take the entire picture into account when considering the immunosuppressive regimen, including the possibility that the patient's skin disease is a sign of systemic immune dysfunction.

In OTRs, the risk of developing CSCC is strongly associated with a high number of keratotic lesions.[46] Thus, efforts to treat actinic keratoses (AKs) and CSCC *in situ* should be a priority. Topical 5-fluorouracil (5-FU), with pretreatment light curettage of hyperkeratotic lesions (to increase medication penetration), may be used to treat field actinic change, with reported clearance of up to 90 percent in immunocompetent individuals.[47]

Photodynamic therapy (PDT). PDT has been shown to reduce the number of AKs in OTRs.[48,49] Although a single study showed PDT to be superior to topical 5-FU,[50] efficacy varies depending upon regimen, and there have been conflicting reports as to whether AK reduction translates into a reduction in the incidence of new CSCC formation.[51,52] PDT has no role in the management of dermally invasive CSCC due to poor long-term cure rates.[53,54]

Surgical clearance. The current mainstay of treatment for high-risk CSCC is complete surgical clearance of the lesion with histological clear margins. Other modalities (curettage, cautery, cryosurgery) have variable outcomes based on the experience of the operator and do not yield histological evidence of adequate margins.[55] These options are more suited to low-risk CSCC and should be avoided in high-risk cases. Available data clearly demonstrate that negative surgical margins are of paramount importance in achieving cure. Tumors that fail to be cleared surgically often recur despite radiation. In contrast, high-risk CSCC with documented clear surgical margins has excellent outcomes when compared to those with unreported margin status (local recurrence 5% vs. 8%, nodal metastasis 5% vs. 14%, distant metastases 1% vs. 7%, and disease-specific death 1% vs. 7%).[56]

Standard excision. Standard excision is generally acceptable in non-high-risk CSCCs, where the tumor is well defined or located in an area where tissue sparing is not critical. A 4mm margin in a well-defined tumor <2cm provides clear removal in 95 percent of cases. However for CSCCs >2cm, or with subcutaneous invasion, a wider margin (e.g., 6mm or more) with definite histological clearance or, preferably, Mohs micrographic surgery is necessary for acceptable cure rates.[57] Tan et al[58] prospectively studied standard surgical excision in CSCCs. Of 480 cases excised with a 2 to 5mm margin, six percent had a positive margin. Lesions on the ear, re-excisions, and invasive lesions were associated with the highest incomplete resection rates. In high-risk CSCC, the proportion of positive margins with standard excision is likely to be higher as tumors are deeper and more infiltrative.

Mohs micrographic surgery. Mohs micrographic surgery is the treatment of choice for high-risk CSCC and those located in cosmetically sensitive or critical areas. Mohs histological sectioning allows for examination of nearly 100 percent of the surgical margin as compared with less than one percent of the margin visualized via standard excision. This is reflected in reported five-year cure rates, with traditional surgical excision reported at 92 and 77 percent for primary and recurrent CSCCs, respectively,[2] while Mohs recurrence rates are 97 percent for primary and 90 to 94 percent for recurrent tumors.[2,59,60] Cure rates decrease for tumors greater than 2cm in diameter and poorly differentiated or recurrent tumors,[2] but still exceed cure rates of standard excision. Mohs is also considered a cost-effective procedure[61–63] and is less expensive than surgical excision with sedation.[63]

To date, there are no direct comparative studies of Mohs

versus standard excision in the treatment of high-risk CSCCs. Data from Rowe et al's[2] systematic review showed that recurrent CSCCs, tumors with PNI, poorly differentiated tumors, and those with diameters greater than 2cm all had lower recurrence rates with Mohs surgery. Although Mohs is considered the standard of care for high-risk CSCC by most American dermatologists, many of these tumors are currently excised by plastic surgeons, head and neck surgeons, or surgical oncologists. A prospective comparative study would help to unify different subspecialties toward a single standard of surgical care for high-risk CSCC.

In CSCC with in-transit metastasis, bone invasion, parotid gland invasion, or intracranial extension along major nerve branches, complete tumor clearance may not be achieved via the Mohs technique. A multidisciplinary team approach provides the best management to these patients, with preoperative imaging and SLN biopsy if indicated. Mohs surgeons may establish the peripheral margin while craniofacial or head and neck surgeons track and remove PNI of major nerves, perform parotidectomy, or remove bone to complete the tumor eradication. In such cases, peripheral margin Mohs under local anesthetic minimizes the time patients must be under general anesthesia and allows the head and neck or craniofacial surgeon to focus on clearance of the deep margin.

Margin interpretation may be difficult in poorly differentiated, highly infiltrative CSCCs or those with subtle PNI. In such cases, the sensitivity of Mohs can be further increased using cytokeratin immunohistochemical stains,[64,65] which can identify individual tumor cells that are otherwise difficult to identify on frozen and paraffin sections stained with hematoxylin and eosin.

Radiation therapy. Radiation therapy is also a primary treatment option for CSCCs; however, outcomes are generally inferior to surgery, tumors can recur quickly after treatment,[66] it is more time consuming and expensive than surgery, and iatrogenic carcinogenesis can occur years later in the radiated area. Thus, radiation as a primary therapy is usually confined to a small subset of early lesions where the cosmetic or functional outcome would be superior to that of surgery[67] or in elderly patients with inoperable tumors. Local control decreases to 80 to 85 percent when used to treat high-risk CSCC with increasing size or deeper invasion.[66] However, in CSCC of the lower lip, radiotherapy has been reported to achieve excellent maintenance of oral function and a comparable cure rate when compared with surgery.[68] It should be used with caution in lower leg tumors, as poor vascularization and peripheral edema may limit effectiveness of treatment and contribute to delayed healing.[69] High-risk CSCC is best approached with surgical excision, combined with adjuvant radiation therapy if indicated. Radiation as a primary treatment for these high-risk tumors is limited by failure to confirm clear margins combined with high propensity for recurrence and metastasis; thus, surgery remains a superior treatment option.

ADJUVANT THERAPY

Radiation therapy. Radiation therapy has been advocated as an adjuvant treatment in certain high-risk groups of CSCC, especially those with PNI, although outcome data for this group are sparse and inconclusive and recommendations are vague as to which patients should be considered. A comprehensive systematic review by Jambusaria-Pahlajani et al[56] analyzed all reports related to outcomes of Ïhigh-risk CSCCs treated with surgical monotherapy compared to those treated with surgery plus adjuvant radiation (ART). The primary outcomes of interest were local recurrence, nodal metastasis, distant metastasis, and disease-specific death. No randomized studies were found. A single, small, underpowered, retrospective study compared surgery versus surgery and ART, while the remaining were case series assessing overall risks of recurrence and metastasis with no comparisons of treatment. Cases treated with surgery and ART had a significantly higher risk of regional (19% versus 10%) and distant metastasis (13% versus 4%) than those treated with surgery alone, although data were not controlled for tumor stage, so those treated with ART likely had more advanced disease. In addition, clear surgical margins were often not documented, so radiation may have been used as salvage therapy, with an inherently higher risk of poor outcome.

It is well described that clear margins prior to ART improve outcomes, even with major nerve involvement[16]; conversely, the risk of local, regional, and distant recurrence is greater when residual microscopic disease is present before radiotherapy.[70] In the Jambusaria-Pahlajani et al[56] review, there was no advantage of ART seen for CSCC with PNI, but the numbers were small and again uncontrolled for tumor stage.[56] CSCCs with advanced PNI have a high risk of recurrence even with clear surgical margins,[13,16,56] indicating that it is difficult to control with surgery alone. Thus, adjuvant radiation is indicated in these cases of advanced PNI involving larger nerves, although its utility has yet to be proven. Patients in whom complete resection of PNI is not possible may do better with salvage radiotherapy, but mortality rates are reported at 30 percent and may be higher.[66]

In summary, the additional benefit of ART is uncertain, especially when clear surgical margins are obtained. However, it may benefit the highest risk patients—those with significant nerve involvement (>0.1mm nerve diameter), those with uncertain or positive surgical margins, or as salvage therapy for inoperable cases or in-transit metastasis. With no clear evidence of benefit, deciding who is an appropriate candidate for adjuvant radiation remains a matter of clinical judgment.

Chemotherapy. Chemotherapy in the management of high-risk cutaneous CSCC remains relatively unexplored. The most extensive research has been in the field of retinoids, which are known to decrease new cancer formation, but do not alter the course of an existing tumor. Their role as prophylactic agents in patients with diffuse actinic damage or recurrent CSCCs is well established, especially in OTRs.[71] Low-dose therapy is usually sufficient

and must be continued indefinitely, as patients usually return to baseline on discontinuation of treatment. Randomized trials of retinoids, either used alone for adjuvant-treatment of established mucosal SCC of the head and neck[72] or in combination with interferon[73] for established CSCC, have shown no benefit. Cisplatin-based combination chemotherapy with 5-FU, methotrexate, bleomycin, and doxorubicin have been used to treat advanced CSCC with variable outcomes and a high incidence of 5-FU-related adverse effects. The oral 5-FU prodrug, capecitabine (Xeloda, Roche Laboratories Inc.), has been designed to be metabolized to 5-FU selectively within tumor tissues, thus producing less systemic toxicity. Used alone,[74] or in combination with subcutaneous interferon,[75] it has produced promising results in small studies of locally advanced CSCC. In the head and neck literature, Phase 1 and 2 trials of capecitabine used with cisplatin or paclitaxel[76,77] or in combination with radiation therapy[78] also showed favorable outcomes.

Epidermal growth factor receptor (EGFR) inhibitors. EGFR inhibitors have been used off label as a novel treatment of CSCC. EGRF is expressed in human epidermis, especially in the basal layers and in epidermal appendages.[79] It may also be overexpressed in primary and metastatic deposits of CSCC,[80] where its activation is responsible for cell cycle progression, proliferation, survival, angiogenesis, and metastasis. Of the EGFR inhibitors, cetuximab has had reported success in several case reports: unresectable CSCC,[81] in-transit recurrent CSCC,[82] metastatic CSCC in epidermolysis bullosa,[83] and in combination with celecoxib.[84] Both Phase 2[85] and 3[86] trials of gefitinib in metastatic mucosal SCC of head and neck failed to show survival benefit. A single case report,[87] however, has reported palliative tumor shrinkage in CSCC.

Despite lack of well-established evidence, chemotherapy, in consultation with oncology, should still be considered as an adjunct therapy in select cases of high-risk CSCC with a high risk of metastatic or locally advanced disease. Many of the available treatments, especially EGRF inhibitors and oral capecitabine, are well tolerated with relatively low risks, so may be considered in highest-risk cases. Meanwhile, further work remains to identify patient subsets likely to benefit from adjuvant chemotherapy and to define optimal regimens.

FOLLOW UP

Up to 73 percent of CSCCs with nodal metastasis are curable,[35] so high-risk CSCC patients should be followed closely to ensure early detection and treatment of recurrence. A dermatologist review every 3 to 6 months is advised for up to five years, as 95 percent of local recurrences and 95 percent of metastases are detected within this time.[2] Each review should include a total body skin examination, close examination of the tumor site and LN basin, and a neurological exam if indicated. Diligent treatment of AKs and early biopsy of suspicious lesions are also recommended. For aggressive cases, including those with significant PNI or those who are immunosuppressed, repeated radiological imaging of the LN basin every six months may be considered.

CONCLUSION

Management of high-risk CSCC is complex. Lack of prognostic models and treatment guidelines confer an ambiguity regarding the optimal care of these patients. Current best practice stems from clinician experience and predominantly retrospective data. Due to the rarity of nodal disease, metastasis, and death from high-risk CSCC, long-term, prospective, multicenter studies will be required to determine risk factors and best treatment. For now, the key to successful management of these patients is 1) early detection, 2) prompt surgical treatment with clear margins whenever possible, 3) consideration of staging of draining nodal basins, 4) adjuvant therapy when considered appropriate, and 5) close follow up.

REFERENCES

1. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. *J Am Acad Dermatol.* 1994;30(5 Pt 1):774–778.
2. Rowe DE, Carroll RJ, Day CL, Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Dermatol.* 1992;26(6):976–990.
3. Brantsch KD, Meisner C, Schonfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous cell carcinoma: a prospective study. *Lancet Oncol.* 2008;9(8):713–720.
4. Jambusaria-Pahlajani A KK, Hess, SD, Berg D, Schmults CD. Uncertainty in the peri-operative management of high-risk cutaneous squamous cell carcinoma among Mohs surgeons. *Arch Dermatol.* In press.
5. Cherpelis BS, Marcusen C, Lang PG. Prognostic factors for metastasis in squamous cell carcinoma of the skin. *Dermatol Surg.* 2002;28(3):268–273.
6. Mullen JT, Feng L, Xing Y, et al. Invasive squamous cell carcinoma of the skin: defining a high-risk group. *Ann Surg Oncol.* 2006;13(7):902–909.
7. Moller R, Reymann F, Hou-Jensen K. Metastases in dermatological patients with squamous cell carcinoma. *Arch Dermatol.* 1979;115(6):703–705.
8. Edwards MJ, Hirsch RM, Broadwater JR, Netscher DT, Ames FC. Squamous cell carcinoma arising in previously burned or irradiated skin. *Arch Surg.* 1989;124(1):115–117.
9. Ross AS, Schmults CD. Sentinel lymph node biopsy in cutaneous squamous cell carcinoma: a systematic review of the English literature. *Dermatol Surg.* 2006;32(11):1309–1321.
10. Kraus DH, Carew JF, Harrison LB. Regional lymph node metastasis from cutaneous squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg.* 1998;124(5):582–587.
11. Veness MJ, Palme CE, Morgan GJ. High-risk cutaneous squamous cell carcinoma of the head and neck: results from 266 treated patients with metastatic lymph node disease. *Cancer.* 2006;106(11):2389–2396.
12. Clayman GL, Lee JJ, Holsinger FC, et al. Mortality risk from

squamous cell skin cancer. *J Clin Oncol.* 2005;23(4):759–765.
13. Ross AS, Whalen FM, Elenitsas R. Diameter of involved nerves predicts outcomes in cutaneous squamous cell carcinoma with perineural invasion: an investigator-blinded retrospective cohort study. *Dermatol Surg.* 2009;35(12):1859–1866.
14. Dinehart SM, Pollack SV. Metastases from squamous cell carcinoma of the skin and lip. An analysis of twenty-seven cases. *J Am Acad Dermatol.* 1989;21(2 Pt 1):241–248.
15. Breuninger H, Schaumburg-Lever G, Holzschuh J, Horny HP. Desmoplastic squamous cell carcinoma of skin and vermilion surface: a highly malignant subtype of skin cancer. *Cancer.* 1997;79(5):915–919.
16. Goepfert H, Dichtel WJ, Medina JE, Lindberg RD, Luna MD. Perineural invasion in squamous cell skin carcinoma of the head and neck. *Am J Surg.* 1984;148(4):542–547.
17 Mendenhall WM, Amdur RJ, Hinerman RW, et al. Skin cancer of the head and neck with perineural invasion. *Am J Clin Oncol.* 2007;30(1):93–96.
18. Tavin E, Persky M. Metastatic cutaneous squamous cell carcinoma of the head and neck region. *Laryngoscope.* 1996;106(2 Pt 1):156–158.
19. Jensen P, Hansen S, Moller B, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol.* 1999;40(2 Pt 1):177–186.
20. Adamson R, Obispo E, Dychter S, et al. High incidence and clinical course of aggressive skin cancer in heart transplant patients: a single-center study. *Transplant Proc.* 1998;30(4):1124–1126.
21. Ong CS, Keogh AM, Kossard S, Macdonald PS, Spratt PM. Skin cancer in Australian heart transplant recipients. *J Am Acad Dermatol.* 1999 Jan;40(1):27–34.
22. Meyer T, Arndt R, Nindl I, et al. Association of human papillomavirus infections with cutaneous tumors in immunosuppressed patients. *Transpl Int.* 2003;16(3): 146–153.
23. Bouwes Bavinck JN, Hardie DR, Green A, et al. The risk of skin cancer in renal transplant recipients in Queensland, Australia. A follow-up study. *Transplantation.* 1996;61(5): 715–721.
24. Euvrard S, Kanitakis J, Decullier E, et al. Subsequent skin cancers in kidney and heart transplant recipients after the first squamous cell carcinoma. *Transplantation.* 2006;81(8): 1093–100.
25. Campistol JM, Eris J, Oberbauer R, et al. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol.* 2006;17(2):581–589.
26. Rival-Tringali AL, Euvrard S, Decullier E, et al. Conversion from calcineurin inhibitors to sirolimus reduces vascularization and thickness of post-transplant cutaneous squamous cell carcinomas. *Anticancer Res.* 2009;29(6): 1927–1932.
27. Smith KJ, Hamza S, Skelton H. Histologic features in primary cutaneous squamous cell carcinomas in immunocompromised patients focusing on organ transplant patients. *Dermatol Surg.* 2004;30(4 Pt 2):634–641.
28. Veness MJ, Quinn DI, Ong CS, et al. Aggressive cutaneous malignancies following cardiothoracic transplantation: the Australian experience. *Cancer.* 1999;85(8):1758–1764.
29. Carucci JA, Martinez JC, Zeitouni NC, et al. In-transit metastasis from primary cutaneous squamous cell carcinoma in organ transplant recipients and nonimmunosuppressed patients: clinical characteristics, management, and outcome in a series of 21 patients. *Dermatol Surg.* 2004;30(4 Pt 2):651–655.
30. Frierson HF, Jr., Deutsch BD, Levine PA. Clinicopathologic features of cutaneous squamous cell carcinomas of the head and neck in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. *Hum Pathol.* 1988;19(12):1397–1402.
31. Mehrany K, Weenig RH, Lee KK, Pittelkow MR, Otley CC. Increased metastasis and mortality from cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. *Transplantation.* 2006;81(8):1093–100.
32. Nguyen P, Vin-Christian K, Ming ME, Berger T. Aggressive squamous cell carcinomas in persons infected with the human immunodeficiency virus. *Arch dermatol.* 2002;138(6):758–763.
33. Fine JD, Johnson LB, Weiner M, Li KP, Suchindran C. Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986–2006. *J Am Acad Dermatol.* 2009;60(2):203–211.
34. Kinlen LJ. Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. *Am J Med.* 1985;78(1A):44–49.
35. Veness MJ, Morgan GJ, Palme CE, Gebski V. Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: combined treatment should be considered best practice. *Laryngoscope.* 2005;115(5):870–875.
36. Yousem DM, Som PM, Hackney DB, Schwaibold F, Hendrix RA. Central nodal necrosis and extracapsular neoplastic spread in cervical lymph nodes: MR imaging versus CT. *Radiology.* 1992;182(3):753–759.
37. Ginsberg LE. MR imaging of perineural tumor spread. *Magn Reson Imaging Clin N Am.* 2002;10(3):511–525, vi.
38. Land R, Herod J, Moskovic E, et al. Routine computerized tomography scanning, groin ultrasound with or without fine needle aspiration cytology in the surgical management of primary squamous cell carcinoma of the vulva. *Int J Gynecol Cancer.* 2006;16(1):312–317.
39. Bailet JW, Abemayor E, Jabour BA, et al. Positron emission tomography: a new, precise imaging modality for detection of primary head and neck tumors and assessment of cervical adenopathy. *Laryngoscope.* 1992;102(3):281–288.
40. Cho SB, Chung WG, Yun M, et al. Fluorodeoxyglucose positron emission tomography in cutaneous squamous cell carcinoma: retrospective analysis of 12 patients. *Dermatol Surg.* 2005;31(4):442–446; discussion 6–7.
41. Williams LS, Mancuso AA, Mendenhall WM. Perineural spread of cutaneous squamous and basal cell carcinoma: CT and MR detection and its impact on patient management and prognosis. *Int J Radiat Oncol Biol Phys.* 2001;49(4): 1061–1069.
42. de Hullu JA, Hollema H, Piers DA, et al. Sentinel lymph node

procedure is highly accurate in squamous cell carcinoma of the vulva. *J Clin Oncol.* 2000;18(15):2811–2816.
43. Otley CC, Maragh SL. Reduction of immunosuppression for transplant-associated skin cancer: rationale and evidence of efficacy. *Dermatol Surg.* 2005;31(2):163–168.
44. Abou Ayache R, Thierry A, Bridoux F, et al. Long-term maintenance of calcineurin inhibitor monotherapy reduces the risk for squamous cell carcinomas after kidney transplantation compared with bi- or tritherapy. *Transplant Proc.* 2007;39(8):2592–2594.
45. Schena FP, Pascoe MD, Alberu J, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation.* 2009;87(2):233–242.
46. Bouwes Bavinck JN, Euvrard S, Naldi L, et al. Keratotic skin lesions and other risk factors are associated with skin cancer in organ-transplant recipients: a case-control study in The Netherlands, United Kingdom, Germany, France, and Italy. *J Invest Dermatol.* 2007;127(7):1647–1656.
47. Pearlman DL. Weekly pulse dosing: effective and comfortable topical 5-fluorouracil treatment of multiple facial actinic keratoses. *J Am Acad Dermatol.* 1991;25(4): 665–667.
48. Dragieva G, Hafner J, Dummer R, et al. Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients. *Transplantation.* 2004;77(1):115–121.
49. Dragieva G, Prinz BM, Hafner J, et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. *Br J Dermatol.* 2004;151(1):196–200.
50. Perrett CM, McGregor JM, Warwick J, et al. Treatment of post-transplant premalignant skin disease: a randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. *Br J Dermatol.* 2007;156(2): 320–328.
51. Willey A, Mehta S, Lee PK. Reduction in the incidence of squamous cell carcinoma in solid organ transplant recipients treated with cyclic photodynamic therapy. *Dermatol Surg.* 2009 Nov 4 [Epub ahead of print].
52. de Graaf YG, Kennedy C, Wolterbeek R, et al. Photodynamic therapy does not prevent cutaneous squamous cell carcinoma in organ-transplant recipients: results of a randomized-controlled trial. *J Invest Dermatol.* 2006;126(3):569–574.
53. Fink-Puches R, Soyer HP, Hofer A, Kerl H, Wolf P. Long-term follow-up and histological changes of superficial nonmelanoma skin cancers treated with topical delta-aminolevulinic acid photodynamic therapy. *Arch Dermatol.* 1998;134(7):821–826.
54. Calzavara-Pinton PG. Repetitive photodynamic therapy with topical delta-aminolaevulinic acid as an appropriate approach to the routine treatment of superficial non-melanoma skin tumours. *J Photochem Photobiol.* 1995;29(1):53–57.
55. Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. *Br J Dermat.* 2002;146(1):18–25.
56. Jambusaria-Pahlajani A, Miller CJ, Quon H, et al. Surgical monotherapy versus surgery plus adjuvant radiotherapy in high-risk cutaneous squamous cell carcinoma: a systematic review of outcomes. *Dermatol Surg.* 2009;35(4):574–585.
57. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. *J Am Acad Dermatol.* 1992;27(2 Pt 1):241–248.
58. Tan PY, Ek E, Su S, Giorlando F, Dieu T. Incomplete excision of squamous cell carcinoma of the skin: a prospective observational study. *Plast Reconstr Surg.* 2007;120(4): 910–916.
59. Lawrence N, Cottel WI. Squamous cell carcinoma of skin with perineural invasion. *J Am Acad Dermatol.* 1994;31(1): 30–33.
60. Leibovitch I, Huilgol SC, Selva D, et al. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia I. Experience over 10 years. *J Am Acad Dermatol.* 2005;53(2):253–260.
61. Seidler AM, Bramlette TB, Washington CV, Szeto H, Chen SC. Mohs versus traditional surgical excision for facial and auricular nonmelanoma skin cancer: an analysis of cost-effectiveness. *Dermatol Surg.* 2009;35(11):1776–1787. [Epub ahead of print] 2009 Sep 8.
62. Cook J, Zitelli JA. Mohs micrographic surgery: a cost analysis. *J Am Acad Dermatol.* 1998;39(5 Pt 1):698–703.
63. Rogers HW, Coldiron BM. A relative value unit-based cost comparison of treatment modalities for nonmelanoma skin cancer: effect of the loss of the Mohs multiple surgery reduction exemption. *J Am Acad Dermatol.* 2009;61(1): 96–103.
64. Zachary CB, Rest EB, Furlong SM, et al. Rapid cytokeratin stains enhance the sensitivity of Mohs micrographic surgery for squamous cell carcinoma. *J Dermatol Surg Oncol.* 1994;20(8):530–535.
65. Cherpelis BS, Turner L, Ladd S, Glass LF, Fenske NA. Innovative 19-minute rapid cytokeratin immunostaining of nonmelanoma skin cancer in Mohs micrographic surgery. *Dermatol Surg.* 2009;35(7):1050–1056.
66. Kwan W, Wilson D, Moravan V. Radiotherapy for locally advanced basal cell and squamous cell carcinomas of the skin. *Int J Radiat Oncol Biol Phys.* 2004;60(2):406–411.
67. Veness M, Richards S. Role of modern radiotherapy in treating skin cancer. *Australas J Dermatol.* 2003;44(3): 159–166; quiz 67–68.
68. Veness MJ, Ong C, Cakir B, Morgan G. Squamous cell carcinoma of the lip. Patterns of relapse and outcome: reporting the Westmead Hospital experience, 1980–1997. *Australas Radiol.* 2001;45(2):195–199.
69. Veness MJ. The important role of radiotherapy in patients with non-melanoma skin cancer and other cutaneous entities. *J Med Imaging Radiat Oncol.* 2008;52(3): 278–286.
70. Cox J, ed. *Radiation Oncology: Rationale, Techniques, Results.* 8th ed. Philadelphia, PA: Mosby; 2003.
71. Harwood CA, Leedham-Green M, Leigh IM, Proby CM. Low-dose retinoids in the prevention of cutaneous squamous cell

carcinomas in organ transplant recipients: a 16-year retrospective study. *Arch Dermatol.* 2005;141(4):456–464.
72. Toma S, Bonelli L, Sartoris A, et al. 13-cis retinoic acid in head and neck cancer chemoprevention: results of a randomized trial from the Italian Head and Neck Chemoprevention Study Group. *Oncol Rep.* 2004;11(6):1297–1305.
73. Brewster AM, Lee JJ, Clayman GL, et al. Randomized trial of adjuvant 13-cis-retinoic acid and interferon alfa for patients with aggressive skin squamous cell carcinoma. *J Clin Oncol.* 2007;25(15):1974–1978.
74. Cartei G, Cartei F, Interlandi G, et al. Oral 5-fluorouracil in squamous cell carcinoma of the skin in the aged. *Am J Clin Oncol.* 2000;23(2):181–184.
75. Wollina U, Hansel G, Koch A, Kostler E. Oral capecitabine plus subcutaneous interferon alpha in advanced squamous cell carcinoma of the skin. *J Cancer Res Clin Oncol.* 2005;131(5):300–304.
76. Hitt R, Jimeno A, Rodriguez-Pinilla M, et al. Phase II trial of cisplatin and capecitabine in patients with squamous cell carcinoma of the head and neck, and correlative study of angiogenic factors. *Br J Cancer.* 2004;91(12):2005–2011.
77. Bentzen JD, Hansen HS. Phase II analysis of paclitaxel and capecitabine in the treatment of recurrent or disseminated squamous cell carcinoma of the head and neck region. *Head Neck.* 2007;29(1):47–51.
78. Kim JG, Sohn SK, Kim DH, et al. Phase II study of concurrent chemoradiotherapy with capecitabine and cisplatin in patients with locally advanced squamous cell carcinoma of the head and neck. *Br J Cancer.* 2005;93(10):1117–1121.
79. Nanney LB, Magid M, Stoscheck CM, King LE, Jr. Comparison of epidermal growth factor binding and receptor distribution in normal human epidermis and epidermal appendages. *J Invest Dermatol.* 1984;83(5):385–393.
80. Shimizu T, Izumi H, Oga A, et al. Epidermal growth factor receptor overexpression and genetic aberrations in metastatic squamous-cell carcinoma of the skin. *Dermatology.* 2001;202(3):203–206.
81. Suen JK, Bressler L, Shord SS, Warso M, Villano JL. Cutaneous squamous cell carcinoma responding serially to single-agent cetuximab. *Anticancer Drugs.* 2007;18(7):827–829.
82. Bauman JE, Eaton KD, Martins RG. Treatment of recurrent squamous cell carcinoma of the skin with cetuximab. *Arch Dermatol.* 2007;143(7):889–892.
83. Arnold AW, Bruckner-Tuderman L, Zuger C, Itin PH. Cetuximab therapy of metastasizing cutaneous squamous cell carcinoma in a patient with severe recessive dystrophic epidermolysis bullosa. *Dermatology.* 2009 May 13. [Epub ahead of print].
84. Jalili A, Pinc A, Pieczkowski F, et al. Combination of an EGFR blocker and a COX-2 inhibitor for the treatment of advanced cutaneous squamous cell carcinoma. *J Dtsch Dermatol Ges.* 2008;6(12):1066–1069.
85. Cohen EE, Rosen F, Stadler WM, et al. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2003;21(10):1980–1987.
86. Stewart JS, Cohen EE, Licitra L, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *J Clin Oncol.* 2009;27(11):1864–1871.
87. Baltaci M, Fritsch P, Weber F, et al. Treatment with gefitinib (ZD 1839) in a patient with advanced cutaneous squamous cell carcinoma. *Br J Dermatol.* 2005;153(1):234–236.