



# New Therapeutic Advances: Skin Cancer and Actinic Keratoses

Update on  
Melanoma

Common  
Nonmelanoma  
Skin Cancers:  
Basal Cell  
Carcinoma and  
Squamous Cell  
Carcinoma

Actinic  
Keratoses: Current  
Approaches to  
Management

5-Fluorouracil  
Therapy:  
Clinical Tips  
and Issues



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# New Therapeutic Advances: Skin Cancer and Actinic Keratoses

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## Accreditation

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## Target Audience

This activity has been developed for dermatologists and other health care professionals who are involved in the treatment of patients at risk for melanoma, nonmelanoma skin cancers, and actinic keratosis.

## Educational Needs

The incidence of melanoma, nonmelanoma skin cancers, and the squamous cell carcinoma precursor, actinic keratosis, is high and has been increasing steadily. Dermatologists must remain abreast of the current recommendations for the diagnosis and treatment of these lesions.

## Learning Objectives

By reading and studying this supplement, participants should be able to:

- Discuss the incidence and risk factors associated with melanoma and nonmelanoma skin cancers as well as the treatment modalities currently available.
- Identify treatment options for various subgroups of patients within the above categories (for example, those who are receiving immunosuppressant therapy after solid organ transplantation).
- Describe the relationship between actinic keratosis and squamous cell carcinoma.
- Explain the role of 5-fluorouracil therapy and the dosing options available to reduce the side effects associated with such treatment.

## Faculty Disclosures

**Dr. Anderson** is on the speaker's bureau of ICN Pharmaceuticals, Inc. She discusses the unlabeled or investigational uses of imiquimod and 5-fluorouracil.

**Dr. Jeffes** is on the speaker's bureau of ICN and has received grant support from, and is a consultant to, ICN and DUSA Pharmaceuticals, Inc. He discusses the unlabeled or investigational use of 5-fluorouracil for treating actinic cheilitis as well as photodamaged skin.

# Update on Melanoma

Nancy J. Anderson, MD

**A**ccording to 2002 statistics from the American Cancer Society, 53,600 new cases of invasive melanoma are diagnosed each year, making melanoma the sixth most common cancer in the United States. Melanoma, which is responsible for more than 80% of all skin cancer deaths, is among the cancers of all types that have the highest increased incidence. Today, the chance of an individual in the U.S. developing

melanoma is 1 in 68. Melanoma has been identified as the leading cause of cancer death in women between 25 and 36 years of age.<sup>1</sup>

Early identification and treatment of these tumors is associated with a better prognosis. The 5-year survival rate for patients with tumors less than 0.76 mm thick is 93%-100%, whereas for those with tumors greater than 4.0 mm thick, the 5-year survival rate is approximately 50%.<sup>2</sup>

## Risk Factors for Melanoma

The highest risk factors for cutaneous melanoma are increasing age, Fitzpatrick skin types I, II, or III, and male gender.<sup>3</sup> All three of these risk factors are, in turn, associated with increased sun exposure. The older an individual is, the greater the accumulated lifetime sun exposure. Individuals with skin type I, II, or III—those with light hair and eyes and fair skin coloring who burn easily and do not tan well—have less inherent sun protection than do individuals with darker skin, hair, and eye coloring. Finally, men are presumably at increased risk because, compared with women, a higher proportion work outdoors.

Additional risk factors that have been identified include numerous normal and/or atypical (or dysplastic) nevi, as well as a personal or family history of melanoma. Intermittent, intense sun exposure also increases risk, particularly in regions that are closer to the equator. Regular use of sun tanning devices (tanning booths) also has been identified as a risk factor for melanoma.<sup>4</sup>

Richert and colleagues<sup>2</sup> note at least a sevenfold increased risk for cutaneous melanoma among Caucasian adults, individuals with a personal or family history of melanoma or with one or more dysplastic nevi, those with acquired (in contrast to congenital) nevi, and individuals with large congenital nevi.

## Melanoma Pathogenesis

It has been demonstrated that 70% of cultured melanoma cells have a defect in the p16 gene. This gene, which is known as the cyclin-dependent kinase inhibitor 2A, is responsible for transcription of the p16<sup>INK4a</sup> protein, a molecule that functions as a tumor suppressor. Approximately 40% of melanoma-prone families demonstrate defects in the p16 gene.<sup>5</sup>

**“Early identification and treatment of [melanoma] is associated with a better prognosis. The 5-year survival rate for patients with tumors less than 0.76 mm thick is 93%-100%, whereas for those with tumors greater than 4.0 mm thick, the 5-year survival rate is approximately 50%.”**

Recent research also has demonstrated the existence of a *BRAF*-protein kinase that mediates a pathway of reticular-activating system signaling.<sup>6</sup> Davies and colleagues<sup>6</sup> found that 60% of melanoma cell lines had mutations in this oncogene. Thus, specific inhibitors of *BRAF*

represent an important potential line of therapy for melanoma.

Histologically, the melanocytes in sun-damaged skin tend to be uniform. Mildly atypical aggregates of melanocytes and architectural atypia in melanocytic nevi lead to dysplastic nevi that can be simply excised, a treatment that yields an excellent prognosis. But with increasing damage, dysplastic nevi (junctional nevi with severe atypia) can form. It is at this stage that early detection and simple excision yield the best prognosis. From these aggregates of atypical cells, early melanoma (melanoma in situ) often results. Thin melanomas, between 1 and 2 mm, also are associated with a low rate of metastasis—approximately 5%. Thicker lesions, between 2 and 3 mm, metastasize in 18% of cases. Thus, the depth (thickness) of the melanoma is critical to prognosis. Other factors include radial versus vertical growth rate, mitotic rate, ulceration, lymph node response, vascular invasion, and tumor cell type.

## Classification and Staging

Melanoma is divided into four classic histologic subtypes: nodular melanoma, superficial spreading melanoma, lentigo maligna melanoma, and acral lentiginous melanoma.<sup>7</sup> Superficial spreading melanoma occurs most commonly, is

associated with the best prognosis, and is most likely to be identified early by the vigilant clinician.

According to the long-used Clark pathology system, Clark level I is an intraepidermal melanoma. Level II indicates a more invasive lesion, extending into the papillary dermis. Level III describes a lesion that fills the papillary dermis. Invasion of the reticular dermis is classified as a level IV melanoma. When a lesion penetrates the subcutaneous fat, it is classified as Clark level V.

In 2002, the American Joint Committee of Cancer's revised classification and staging system for melanoma went into effect.<sup>8</sup> Under this updated TNM system, melanoma prognosis is determined not only by clinical staging (as has been the case under the old system), but also by pathologic staging.

In the new TNM system, in the T classification, Breslow thickness takes precedence over Clark invasion level as a prognostic indicator. Also, ulceration has been included in the T classification in the new system.

The N classification now includes the number of metastatic lymph nodes as the most important factor in determining prognosis, followed by tumor burden and the presence of satellite lesions and in-transit metastases.

Finally, under the M classification, the Committee determined that the site of distant metastases was the most important prognostic indicator. Serum lactate dehydrogenase is also considered in the new system.

## Diagnosis

The basic mnemonic for identifying dysplastic nevi and melanomas is ABCD. Many forms of early melanoma are **as**ymmetrical: a line drawn through the middle would not create matching halves. In contrast, common, benign moles are round and symmetrical. The **b**orders of early melanomas are often uneven and may have scalloped or notched edges. Common moles have smoother, more even borders.

Color is also important to the identification of a lesion as a melanoma. Varying shades of brown, tan, or black are often the first sign of melanoma. As melanomas progress, the colors red, white, and blue may appear. For example, a lentigo (or freckle) often is simply an early sign of sun damage, but when multiple colors appear, lentigo maligna (or melanoma developing from lentigo maligna) should be suspected. Common, benign moles are a single shade of brown.

Diameter is the fourth factor in identifying a melanoma. Early melanomas tend to grow larger than common moles—generally, to at least the size of a pencil eraser (about 6 mm, or ¼ inch).

Most melanomas occur on the trunk in men and the legs in women, but lesions should be inspected wherever they occur. For example, although their coloring tends to protect them from melanoma and the disease is uncommon in African

Americans, this population is at risk for developing malignant melanoma on the palms of the hands and the soles of the feet. Lesions in these locations usually are the acral lentiginous subtype, which has traditionally been considered a more aggressive subtype and is associated with a poorer prognosis. However, this may be attributed to late diagnosis of more advanced disease rather than to a true difference in the biologic nature of the tumor. In addition, melanomas may occur in the nail beds. The nails should be examined for irregular streaking or changes in pigmentation, particularly starting in the proximal nail fold.

An excisional biopsy is generally advised for any lesion that demonstrates the above characteristics. The border should be 1-2 mm, allowing for examination of the full lesion and a more accurate Breslow level report.

## Determining Prognosis

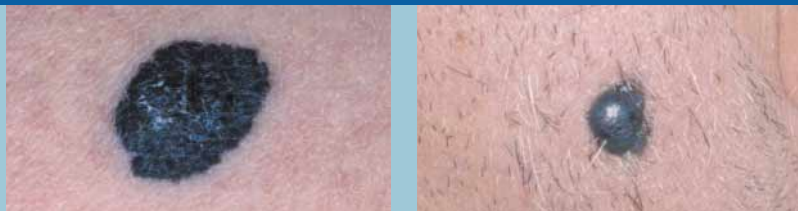
In addition to the Breslow thickness, ulceration is an important prognostic factor. Clark levels are now seen as prognostically relevant for thin melanomas (that is, lesions of 1 mm or less).

Historically, nodal mapping was performed via elective dissection of regional lymph nodes. A new procedure that may obviate the need for elective lymph node dissection is sentinel node biopsy, which is performed in lesions of Breslow stage II or greater.

Sentinel node biopsy, which involves injection of a visible dye and a radioactive tracer in the tumor region, allows identification of involved lymph nodes and tumor spread without the need for biopsy and histologic diagnosis.

The American Joint Committee on Cancer has developed a new version of its tumor/nodes/metastases classification and staging system that incorporates the presence of superficial ulceration as well as information on occult and apparent lymph node metastases in determining prognosis for patients with malignant melanoma.<sup>9</sup>

**Figure 1. Melanoma on the Face**



**Left:** An asymmetrical shape and uneven borders on the facial lesion at left should raise the suspicion for melanoma.  
**Right:** The clinically nodular appearance of the melanoma that developed near this patient's left ear carries a poor prognosis.

## Treatment of Melanoma

Surgical excision is the main treatment, with surgical margins determined by Breslow thickness. For melanoma in situ, the surgical margins should be 5 mm. For lesions less than 1 mm in thickness, the margin should be 1 cm. A 2-cm margin is recommended for lesions with tumor thickness between 1 and 2 mm. For lesions thicker than 2 mm, the surgical margin should be between 2 and 3 cm.<sup>1</sup>

For patients with lesions thicker than 1 mm, surgery should be used in conjunction with nodal mapping to determine tumor stage and any possible need for adjunctive therapy. Patients with thinner melanomas are at low risk for metastatic disease and generally are not considered to be candidates for nodal staging.<sup>1</sup> Patients with positive nodal disease will have stage III or IV disease and are candidates for further treatment after surgical excision with appropriate margins.

Conventional imaging techniques also may be helpful. For example, positron-emission tomography (PET) scanning or combined computed tomography/ PET scanning can localize possible metastatic disease.

Single- and multiple-drug chemotherapeutic regimens are being used for stage III and IV melanomas. Response rates have been reported in the literature ranging from 15%-50%, with average duration of treatment being 4-6 months. However, long-term complete

response rates are less than 2%, and toxicity with conventional chemotherapy is high. Biologic agents currently being used for patients with stage III and IV disease are high-dose interferon alpha-2b (now approved by the U.S. Food and Drug Administration [FDA] for the treatment of stage III melanoma) and high-dose interleukin-2, which is FDA-

**“The American Joint Committee on Cancer has developed a new version of its tumor/nodes/metastases classification and staging system that incorporates the presence of superficial ulceration...in determining prognosis...”**

approved for the treatment of metastatic melanoma.<sup>10</sup> A number of trials of combined biologic and therapeutic agents are under way, and several phase III studies of melanoma vaccines are now in progress at multiple centers throughout the U.S.

## Conclusion

Early detection is crucial, but education of patients may have the greatest effect on reducing the number of melanoma-related deaths. Patients should be taught to do routine self-

examinations. Moreover, patients must be reminded to avoid sun exposure during the peak hours of 10 a.m.-4 p.m., to wear protective clothing (including hats with brims wide enough to protect the ears), and to apply sunscreen every day without fail.

A sunscreen product with a sun protection factor (SPF) of 15 or higher is adequate for patients with most skin types; for those with skin type I, an SPF of 30-45 is advisable. Sunscreens should be applied, in a generous quantity, 30 minutes before sun exposure and 30 minutes after going outdoors; reapplications are advised approximately every 2 hours if an outdoor activity involves perspiring or swimming. Children should be taught these measures early in life.

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**Figure 2. Digital Melanoma**



**A melanoma of the nail bed usually starts at the proximal fold. The nails should be examined for irregular streaking or changes in pigmentation.**

# Common Nonmelanoma Skin Cancers: Basal Cell Carcinoma and Squamous Cell Carcinoma

Nancy J. Anderson, MD, and Edward W. Jeffes III, MD, PhD

**B**asal cell carcinoma (BCC) is the most common cancer in humans, accounting for 1.2 million cancers per year. It is also the most common cutaneous malignancy, accounting for 80% of all nonmelanoma skin cancers, according to the Skin Cancer Foundation. Although the risk for metastases is low, BCC is locally destructive.

*Squamous cell carcinoma (SCC) is the second most common cutaneous malignancy, accounting for approximately 200,000 new cases per year. It has moderate metastatic potential, ranging from 3%-30% as reported in the literature, and it causes approximately 2,000 deaths per year.<sup>1</sup>*

## Risk Factors

The most important risk factor for BCC is an inability to tan. An increased risk for BCC is associated with fair skin, light-colored eyes, red or blond hair, extensive and cumulative sun exposure over a period of years, and an outdoor profession. Skin damage from burns, open and lingering sores, or inflammatory conditions also is associated with an increased risk of BCC. Exposure to radiation and certain chemicals (such as arsenic, once commonly used as an agricultural pesticide) sometimes has been associated with an increased risk for BCC.<sup>2</sup>

The important risk factors for SCC are virtually the same as those described for BCC. Not surprisingly, 80% of lesions occur on sun-exposed areas of the body, including the upper limbs, head, and neck. A history of actinic ker-

atosis also is associated with an increased risk for SCC.<sup>2</sup> The most important risk factors for SCC, however, are cumulative sun exposure and increasing age.<sup>3</sup>

**“...excessive and unprotected exposure to the sun...and skin type have important roles in the development of these nonmelanoma skin cancers. Genetic defects also have been identified that may contribute to the risk.”**

Behavior—that is, excessive and unprotected exposure to the sun—and skin type have important roles in the development of these nonmelanoma

skin cancers. Genetic defects also have been identified that may contribute to the risk. The reported range of mutations in the p53 tumor suppressor gene (TP53) in people with sporadic BCCs is 0%-60%; people with hereditary and sporadic BCCs have been shown to have mutations in the patched tumor suppressor gene.<sup>4</sup>

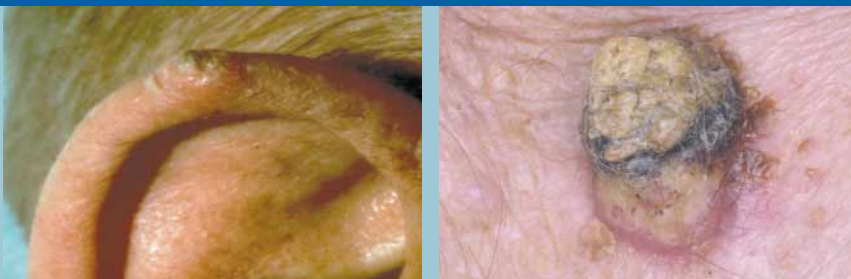
An increased incidence of defects in the TP53 gene also has been found in people with SCCs, and between 10% and 50% of patients with SCCs have mutations in the reticular-activating system tumor oncogene.<sup>4</sup>

## Clinical Presentations of BCC

A persistent, nonhealing translucent or “pearly” lesion is a very common, early sign of BCC. Any open erosion on a pearly papule or photodamaged skin that bleeds, oozes, or crusts and remains open for 3 weeks or more should be biopsied. The index of suspicion should be particularly high when a patient has a history of skin cancer. Patients who have had one BCC are likely to develop another lesion within 3-5 years.

Four clinical subtypes and four common corresponding subtypes of BCC have been described.<sup>2</sup> Both classification systems can be useful in helping to characterize and identify BCCs. The histologic subtypes are nodular (usually a pearly, translucent papule); superficial (a red, scaly plaque); morpheaform (scarlike); and metatypical (also called

**Figure 1. Squamous Cell Carcinomas**



**Left: Squamous cell carcinomas may appear as a wartlike, hyperkeratotic growth. Bleeding and crusting, as this patient experienced, also may occur. Right: When squamous cell carcinoma lesions are neglected, ulceration and infection can occur, as in this patient.**

basosquamous because they have some features that might suggest squamous cell carcinoma). The clinical subtypes—which are closely correlated with the histologic subtypes—are the noduloulcerative BCC; superficial BCC; morpheaform BCC; and sclerosing BCC. Noduloulcerative BCC typically begins as a small papule. Because they often appear on the face, initially they are often thought to be acne lesions. Usually telangiectatic blood vessels appear on the surface. A central irregular ulcer may occur.

A nodular BCC is a shiny, pearly papule that is often pink, red, or white but may also—particularly in dark-haired individuals—be tan, black, or brown. Darker papules may be confused with moles.

Superficial BCCs appear as a reddish patch or irritated area. Such lesions frequently occur on the chest, shoulders, arms, or legs. The patch may be crusty, and the patient may complain that the lesion itches or hurts; at other times, it may persist with no noticeable discomfort. Superficial BCCs are commonly misdiagnosed as contact or irritant dermatitis, and many patients with superficial BCCs initially undergo treatment with a topical corticosteroid. A biopsy is performed when treatment fails to clear the lesion.

Morpheaform, or scarlike BCCs, may be identified as scarlike areas that are white, yellow, or waxy, often with poorly defined borders. Occasionally, the skin itself appears shiny and taut, although this is a less frequent sign. Morpheaform BCCs are especially important to recognize because they are aggressive tumors. An infiltrating histologic component may also exist at the base of noduloulcerative BCCs and may indicate potential aggressive behavior, particularly an increased likelihood of recurrence.

Almost every dermatologist has seen numerous atypical presentations of BCCs—for example, a crusting pyoderma of the scalp or an erosion of the toes that does not respond to appropriate

medical therapy. Shave excision or punch biopsy should be considered for any rash that does not resolve with appropriate treatment.

## Identifying SCC

As with BCCs, SCCs vary in appearance. An SCC lesion may appear as a wartlike hyperkeratotic growth. Sometimes these SCCs crust and occasionally bleed. Another type of growth may have a central depression that occasionally bleeds. Any persistent, scaly red patch should raise the index for suspicion for SCC. If it persists for 3–4 weeks, and especially if it crusts or bleeds, deep shave or punch biopsy should be performed to establish the diagnosis.

## Treatment Options

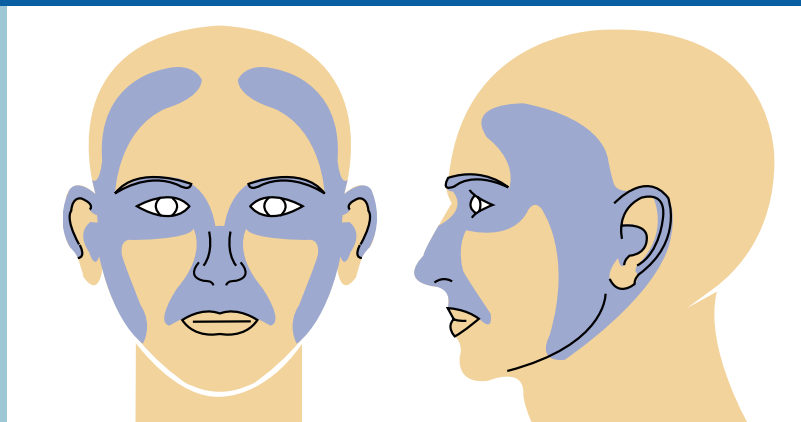
The treatment options for BCC and

SCC are superficial ablative techniques (cryosurgery, electrodesiccation and curettage [E&C]), surgery (simple excision, Mohs' micrographic technique, laser), phototherapy, chemotherapy, and radiotherapy.

## Ablative Techniques

Cryosurgery with liquid nitrogen can be problematic because it requires an aggressive approach, including the use of a probe, to achieve a sufficient freeze. Excellent cure rates are achieved with E&C and this technique is an immediate and definitive treatment. A possible disadvantage—depending on the size and location of the lesion treated—is scarring and/or hypopigmentation. However, it is an attractive alternative for patients who wish to avoid surgery, and many who are alarmed by the diagnosis of skin cancer will accept the cosmetic consequences

**Figure 2. High Risk BCC and SCC Lesions**



**Mohs' micrographic surgery is the treatment of choice for lesions with the following characteristics:**

- **Facial location (anatomic "H" zone: ears, nose, periorbital region, across the temple and forehead, preauricular area)**
- **Recurrent**
- **Large size**
- **Rapidly growing**
- **Ill-defined borders**
- **Histologically poorly differentiated**
- **Show evidence of perineural invasion**

BCC = basal cell carcinoma; SCC = squamous cell carcinoma

Adapted from: Martinez and Otle. *Mayo Clin Proc.* 2001;76:1253-1265.<sup>5</sup>

for the peace of mind that comes with immediate and definitive treatment.

### Surgery

Surgical excision with standard margins—generally, 3-5 mm—is a common and appropriate technique for smaller lesions of the skin, well-differentiated SCC, or BCC (i.e., those that do not have the characteristics listed in **Figure 2** on page 7). Mohs' micrographic surgery—a tissue-sparing technique in which the cancer is mapped as it is removed—is preferred for larger lesions or for those in cosmetically or functionally sensitive areas, such as the nose or face. It is also the treatment of choice for recurrent or high-risk BCC and SCC lesions.<sup>5</sup>

Surgical excision with a laser is used occasionally, but this tool carries no particular advantage over a scalpel for excising SCCs and BCCs except in certain circumstances (in patients on warfarin, for example). The use of carbon dioxide laser or thermal cautery is preferable to E&C for nonsurgical treatment of BCC or SCC lesions in patients with cardiac pacemakers (although some clinicians do not find thermal cautery to be helpful).

### Phototherapy/Chemotherapy

Photodynamic therapy (PDT) involves destruction of cells with the application of a photosensitizing medication, such as aminolevulinic acid,

**Table. BCC and SCC 5-Year Cure Rates for Selected Treatments**

TREATMENT	Cure Rates (%)	
	BCC	SCC
<b>Simple surgical excision</b>	<b>89.9</b>	<b>91.9</b>
<b>Radiotherapy</b>	<b>91.3</b>	<b>90.0</b>
<b>Cryotherapy</b>	<b>92.5</b>	<b>NA</b>
<b>E&amp;C</b>	<b>92.3</b>	<b>96.3</b>
<b>Mohs' micrographic surgery</b>	<b>99.0</b>	<b>96.9</b>

BCC = basal cell carcinoma; SCC = squamous cell carcinoma  
E&C = electrodesiccation and curettage; NA = data not available.  
Adapted from: Martinez and Otley. *Mayo Clin Proc.* 2001;76:1253-1265.<sup>5</sup>

followed by exposure to light to photoactivate the protoporphyrin IX. Use of PDT requires special expertise and equipment.

Topical or intralesional 5-fluorouracil (5-FU) sometimes is used for superficial BCC; it is generally not used for other types of BCC lesions. However, the cure rate with 5-FU is lower than that seen with surgery or E&C. For SCCs, 5-FU can be very useful in resolving small lesions. It also is often used for debulking larger lesions or areas with multiple SCCs prior to surgery.

### Ionizing Radiation

Radiotherapy can be considered as an alternative to surgery, but the long-term consequences of this form of therapy must be considered. As a

result, this form of therapy may be useful in patients over 75 years of age, and radiotherapy may become increasingly utilized as our population ages.

The cure rates for these techniques in BCC and SCC are shown in the **Table**.

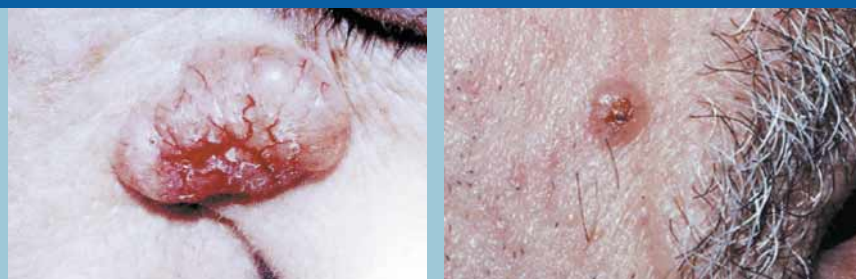
### Conclusion

BCC and SCC are common cutaneous malignancies that are seen most often in sun-exposed areas of patients with fair skin, light-colored eyes, red or blond hair, and extensive and cumulative sun exposure. These lesions are especially common among individuals whose professions require them to be outdoors for extended periods. Treatment is with ablative methods such as E&C; surgery, including laser surgery; phototherapy/chemotherapy; or radiotherapy.

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**Figure 3. Basal Cell Carcinomas**



**Left:** A translucent or pearly lesion is a very common early sign of nodular basal cell carcinoma. **Right:** The ulceration seen in the so-called rodent ulcer is common in nodular basal cell carcinoma because the skin cancer cells are poorly cohesive in these lesions.

# Actinic Keratosis: Current Approaches to Management

Nancy J. Anderson, MD, and Edward W. Jeffes III, MD, PhD

**A**ctinic keratoses (AKs) are the third most frequent reason for dermatologist office visits, accounting for more than 10% of outpatient visits.<sup>1</sup> It has been known for

some time that the presence of AKs identifies patients who are at high risk for the development of other skin cancers, particularly squamous cell carcinoma (SCC).<sup>2</sup>

## Pathogenesis and Natural History

More recently, the relationship between AKs and SCC has become more clearly defined. There is growing acceptance that AKs represent a progression along a spectrum from a benign to a malignant skin lesion.<sup>3</sup> At one end of the spectrum are AKs that represent thin, well-differentiated SCC, followed by thicker, well-differentiated SCC, and finally, the thickest lesions that would be called well-differentiated SCC according to both the current and older terminology. One estimate is that approximately 8% of AKs will progress over a period of 10 years.<sup>4</sup> Some experts maintain that an AK lesion may be viewed as analogous to cervical intraepithelial neoplasia<sup>4</sup> and that AKs should be considered a precursor to invasive, well-differentiated SCC.

In fact, AKs are localized neoplasms limited to the skin. In the strictest sense, there is good evidence to support the view that they are well-differentiated SCC lesions in situ with a good prognosis.<sup>5</sup> Histopathologically, AKs demonstrate a localized proliferation of atypical keratinocytes in the basilar keratinocytes or at the dermal-epidermal junction. When atypia penetrates to more than one third to one half of the dermis, or if it extends through the full thickness of the epidermis, most pathologists would characterize the lesion as an SCC lesion.

Most AKs do not progress to SCC, and many AKs spontaneously regress. The possibility of regression and the fact that not all AKs progress to SCC have

led some insurance carriers to argue that AKs do not require treatment. However, at present, it is not possible to identify with certainty which AKs will regress, which will fail to progress, and which will progress to SCC.

It is the opinion of these authors that hypertrophic or hyperkeratotic

**“More recently, the relationship between AKs and SCC has become more clearly defined. There is growing acceptance that AKs represent a progression along a spectrum from a benign to a malignant skin lesion.”**

AKs are high-risk lesions for progression to SCC or are already well-differentiated SCCs. It is important to note that well-differentiated SCC has a metastatic rate of 0.5%-3% (often quoted as 1%) in healthy, immunocompetent individuals. Poorly differentiated SCCs are uncommon, but they carry a very guarded prognosis because they may be associated with an aggressive course, metastasis, and death.

SCCs that develop in burn or radiation scars or in scars at sites of draining osteomyelitis are associated with a metastatic rate in the range of 10%-30%. Actinic cheilitis—AKs of the mucous membrane epithelium, usually on the lower lip when it converts to

SCC—are at high risk for metastasis, with a reported rate of 11%.<sup>6</sup>

## Epidemiology and Risk Factors

The prevalence of AK is between 11% and 26% in the general population, but prevalence and incidence vary with age and skin type. Individuals with fair skin, light-colored eyes, and red or blond hair are at highest risk for photodamage and the development of AKs. Those with Fitzpatrick skin types IV, V, or VI have intrinsic sun protection equivalent to a sun protection factor rating of 2-3, a level sufficient to prevent most AKs.

The risk for AKs also increases with cumulative sun exposure, and, therefore, AKs are seen more frequently with increasing age. For example, more than 80% of fair-skinned individuals over 70 years of age have AKs.<sup>7</sup>

Accumulating evidence shows that immune status is an important risk factor for the development of AKs. The incidence of AKs is higher in patients who undergo long-term immunosuppression following solid organ transplantation or the long-term use of immunosuppressants, such as cyclosporine, for other reasons. The cumulative increase in risk for skin cancer—mainly SCC—increases with duration of immunosuppression: 7% after 1 year, 45% after 11 years, and 70% after 20 years of immunosuppression.<sup>8</sup> Finally, the inability to repair damaged DNA in the skin cells has been identified as a factor associated with the development of AKs.

## Diagnosis of AKs

Typical AKs are hyperkeratotic scaling papules and plaques. Often, in an area in which a solitary or only a few AKs are visible, a larger field of AKs can be perceived to the touch. The anatomic distribution reflects the expected pattern of sun exposure: More than 80% of AKs occur on the upper limbs, head, and neck.<sup>7</sup> A number of clinical variants to this typical presentation also may be seen, most commonly including hypertrophic AK, pigmented AK, and actinic cheilitis (see **Figure**).<sup>9</sup>

Any erosion on the lower lip (actinic cheilitis) should be biopsied prior to starting therapy. In contrast to a shave excision (which usually is not done to a sufficient depth), a 3-mm punch biopsy at the margins of the ulcer provides an appropriate amount of tissue for examination. Biopsies also should be performed if there is suspicion that an AK has progressed to invasive SCC. The changes that suggest possible evolution of AKs to SCC are pain, erythema, ulceration, induration, hyperkeratosis, increasing size, and cutaneous horn formation.<sup>10,11</sup>

## Treatment of AKs

### Choosing a Modality

Because of the risk for progression to

invasive SCC, the American Academy of Dermatology has issued guidelines that recommend that AKs be eliminated. The factors to consider in choosing therapy include (1) the medical status of the patient; (2) the size, location, number, and duration of the lesions; (3) whether a change has occurred in the growth pattern of the lesions; (4) previous treatment; and (5) the clinician's and patient's experience with a given technique.<sup>12,13</sup>

**"Accumulating evidence shows that immune status is an important risk factor for the development of AKs. The incidence of AKs is higher in patients who undergo long-term immunosuppression..."**

### Commonly Used Treatments

Among the most commonly used treatments are cryosurgery, electrodesiccation and curettage (E&C), and topical 5-fluorouracil (5-FU). Cryosurgery is appropriate for solitary lesions and is associated with a high cure rate and generally acceptable cosmetic results. The

disadvantages of freezing AKs are pain during treatment and the possibility of sensory loss. Hypopigmentation is not uncommon with cryosurgery, so this may not be a good choice for cosmetically sensitive areas such as the face. The risk for hypopigmentation can be minimized by using a freeze-thaw cycle of about 20-30 seconds per lesion to create intercellular ice crystals and avoid damage to melanocytes.

When a lesion is not definitively established as an AK by clinical examination, E&C is a good option because it provides a specimen for malignancy testing. It is also associated with a high cure rate. The patient should be cautioned, however, that scarring and hypopigmentation may occur.

5-FU is a pyrimidine analogue that is incorporated into the cells' DNA because of its structural similarity to uracil. The drug interferes with DNA synthesis by blocking conversion of deoxyuridylic acid to thymidylic acid.<sup>14,15</sup> It selectively affects damaged cells associated with clinical and subclinical AKs, sparing healthy tissue.<sup>14,16</sup> The cure rate with 5-FU is highly dependent on the appearance of inflammation.<sup>17,18</sup> A disadvantage of 5-FU therapy is the response of photodamaged skin: erythema, edema, and discomfort. However, inflammation, erythema, edema, erosion, and ulceration are likely necessary for full efficacy. Patients who understand this are more apt to accept the response as a sign of therapeutic efficacy and to be less disturbed by discomfort and the unsightly appearance of the skin during treatment.

5-FU cream and solution are available in a variety of strengths (0.5%, 1%, 2%, and the most often-used concentration, 5%). The response that indicates efficacy, as described above, may be related to the concentration.<sup>17,18</sup>

### Newer Topical Treatment Options

Several other modalities have been studied and are being used to treat AKs. The nonsteroidal antiinflammatory drug diclofenac sodium is now available

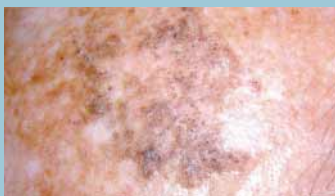
**Figure. Clinical Presentations of Actinic Keratosis**



**A. Typical presentation**



**B. Hypertrophic AK**



**C. Pigmented AK**



**D. Actinic cheilitis**

in topical form, a gel with 3% concentration of the drug. The mechanism of action in the treatment of AKs is unknown. The gel is applied to lesions twice daily for 2-3 months. Lesion healing may not be evident until 1 month posttreatment; up to 47% of patients have shown complete clearance of AKs at 30 days after cessation of therapy.

The results of a phase II study of imiquimod show that application of this topical immune response modifying agent may result in complete clearance of 50% of AKs treated 3 times weekly for 6 weeks. (A phase III study is nearing completion, but no data are yet available.)

Topical retinoids are approved or are expected to be approved soon by the U.S. Food and Drug Administration (FDA) for the treatment of precancerous lesions, to mitigate fine lines, and to increase collagen production. These are applied daily or every other day.

Chemical peeling with 10%-25% trichloroacetic acid or phenol also has been used. Finally, laser surgery—for example, laser resurfacing with carbon dioxide ultrapulse—has shown reduction of precancerous lesions.

### Photodynamic Therapy

In 1999, photodynamic therapy (PDT) with aminolevulinic acid (ALA) and a photosensitizing light source was approved by the FDA for the treatment of AKs. ALA—a precursor to the photosensitizing agent protoporphyrin IX (PPIX)—is applied to lesions on the scalp and face. When the treated skin is exposed to wavelengths ranging from 405-635 nm, the PPIX is photoactivated. Once activated, PPIX generates singlet oxygen and other activated oxygen species that damage cells. For this reason, it is important that ALA be applied directly to the AKs, with normal skin avoided.

Burning and stinging are common during the photoactivation phase, and 71% of patients in clinical trials had scaling and crusting (an expected therapeutic response). However, more than 98% of patients who begin PDT are able to complete the treatment.

**“The cure rate with 5-FU is highly dependent on the appearance of inflammation... inflammation, erythema, edema, erosion, and ulceration are likely necessary for full efficacy.”**

### Conclusion

Actinic keratosis accounts for 10% of dermatologist office visits. In the strictest sense, AKs are considered to be well-differentiated SCC in situ with a good prognosis. AK lesions present as hyperkeratotic scaling papules and plaques. Prevention is best accomplished with sun-protective measures described in the article on melanoma (page 3).

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# 5-Fluorouracil Therapy: Clinical Tips and Issues

Edward W. Jeffes III, MD, PhD

**T**reatment with 5-fluorouracil (5-FU) has been a mainstay of topical therapy for actinic keratoses (AKs) for more than 3 decades. In that time, a large body of literature and countless clinical

encounters have resulted in the development of methods for minimizing side effects, enhancing patient comfort and compliance, and maximizing efficacy.

## Dosing Considerations to Reduce Irritation

The usual dosing schedule for treating AKs on the head and neck is 5% 5-FU cream twice daily for 2 weeks. This leads to significant localized effects and, sometimes, confluent edema. Usually, the first week of treatment is well tolerated by all patients; most of the clinical effects begin by the start of the second week of treatment. During the second week, most patients experience discomfort and are bothered by their appearance due to the inflammatory response. For the first week following cessation of 5-FU applications, appearance is still a significant problem. By the second week after cessation of therapy, most of the scaling and crusting and much of the erythema have resolved.

Controlling the frequency and duration of 5-FU applications allows for improved control of the desired cutaneous reaction. A number of years ago, most clinicians treated AKs with 5% 5-FU twice daily for 4 weeks. The cutaneous reactions resulting from 4 weeks of such treatment are quite severe, commonly leading to confluent crusting and significant burning and stinging. Further, the cosmetic problems associated with this treatment schedule persist throughout therapy and last for at least 3 weeks after cessation of applications of the medication. To decrease the severity of erythema, crusting, and pain, topical corticosteroid creams are commonly used.

In general, the more erythema and crusting the patient can tolerate, the better the clinical response (a decrease in

AKs). A twice-daily schedule of 5% 5-FU applications given for 2 weeks is better tolerated than when the duration is 4 weeks, but the 4-week schedule may be superior to a single 2-week course in eliminating AKs. However, if a 2-week course is repeated a second time, results may occur that are similar to the reaction seen with one 4-week course, thus allowing for greater patient tolerance while yielding the desired therapeutic effect.

Treatment of *cosmetic units*—treating different parts of the face or body at different times—is one method of increasing patient comfort with and tolerance of 5-FU treatment. Cosmetic unit treatment is particularly useful with balding men who have numerous

AKs of the scalp and forehead as well as lesions elsewhere on the face and head. I recommend daily or twice-daily applications of the medication on the bald scalp and forehead for 2 weeks. During this time, the treated area can be covered with a hat. The 2-week therapy gives the patient experience with the desired effect before the cheeks and ears are treated (see **Figure**).

*Stepped therapy* is another approach. One would start with once-daily applications of 1% or 2% 5-FU and, after a few weeks, increase the applications to twice daily. After several additional weeks, 5% 5-FU would be substituted for the lower concentration. Alternatively, one could have the patient use

**Figure. Treating Cosmetic Units**



**Treating cosmetic units in 2-week courses of twice-daily therapy allows patients to heal from the effects of 5-FU treatment in one area—such as the scalp and forehead in this patient; before another area is treated.**

**5-FU = 5-fluorouracil**

the low-concentration 5-FU for 2 weeks, allow the skin to heal, and then reinstitute treatment with the 5% concentration. As with the cosmetic unit approach, stepped therapy gives the patient an opportunity to adjust to the effects of 5-FU treatment.

Marrero and Katz<sup>1</sup> reported success with a technique known as fluorhydroxy pulse peel, in which the patient is treated with a 75% glycolic acid peel for 2 minutes, followed immediately by a single application of a 5% 5-FU solution. This regimen is repeated weekly for 8 weeks. Patients experienced transient erythema and scaling. This combination decreased the AK count in this study by 92% at the 6-month follow-up, compared with a 20% reduction in AK count with 75% glycolic acid peel alone.

### Managing Effects of Therapy

Unless 5-FU applications result in significant erythema and crusting, the clinical effects are less than optimal. Patients with the most severe reactions experience not only the most complete AK resolution but also are left with skin that is smoother and less mottled. Thus, rather than side effects, erythema and crusting are more properly referred to as desired effects of treatment.

Patients who are applying 5-FU to the face can be advised to wash the treated area twice daily with a mild antibacterial cleanser such as chlorhexidine gluconate to minimize the occurrence of pustules. Ointments should be avoided, particularly if pustules are present, to prevent occluding these lesions and, possibly, increasing the risk for infection. At the start of therapy, patients can be given a prescription for an antihistamine and an analgesic (such as acetaminophen) to be filled if symptoms require.

Some clinicians give patients a prescription for oral antibiotics (to be filled only when needed). Because 5-FU treatment breaks the skin barrier, it is possible for staphylococci and streptococci to

infect the skin and cause pyoderma or cellulitis. However, infections are not a problem in the vast majority of patients treated with 5-FU. They are seen most commonly in patients who experience the most severe reactions, especially those on 4-week treatment regimens. Patients should be instructed to return for evaluation if they experience symptoms such as unusually severe pain or erythema.

Contact dermatitis occurs very rarely with 5-FU treatment. Contact dermatitis can be difficult to distinguish from the expected photodamaged-skin response to 5-FU. To test for allergic

**"...treating different parts of the face or body at different times is one method of increasing patient comfort with and tolerance of 5-FU treatment."**

contact dermatitis to 5-FU, have the patient apply the medication to a small area of skin that has not been photodamaged—the bathing trunk area is ideal—twice daily for 1 week. A reaction in the test area indicates contact dermatitis.

Periorbital edema may occur during and after treatment with 5-FU on the forehead and scalp. This results from the normal distribution of the transudate that results from the inflammatory reaction. Clinically significant periorbital edema is uncommon and usually resolves rapidly after cessation of treatment.

### Patient Counseling

Patients must be educated about the desired effects of therapy and the relationship between short-term therapeutic response and short- and long-term overall efficacy. Literature provided by product manufacturers can be very helpful,

but usually is not sufficient. Many patients either do not read the brochures or do not fully appreciate the message even when shown photos of the desired response. Consequently, a follow-up visit at 2 weeks after the start of 5-FU applications can be critical to treatment success. At the follow-up visit, patients who are having a more severe reaction than is optimum can be treated. Those whose response is progressing as desired can be reassured that their appearance is what is expected for a good therapeutic outcome, and the expectation can be reiterated that their appearance will improve remarkably within a few weeks after stopping therapy.

### Postmarketing Safety Data

In 2000, 440,000 prescriptions were written for 5% and 2% formulations of 5-FU; 95% of these were for the 5% concentration. A total of 27 adverse events were associated with the use of these concentrations of 5-FU. This is within the range of 25-30 cases of adverse events per year that have been reported for the previous 31 years in which 5-FU has been marketed in the United States. For the first 11 months of 2001 (the last date for which statistics are available), 29 adverse events were reported. With an estimated total of 13.6 million prescriptions, the adverse-event incidence is 1:14,672.

Most adverse events reported in 2000 were inflammatory symptoms, including burning, crusting, erythema, irritation, pain, itching, scarring, and ulceration. These occurred during treatment and usually resolved within 2 weeks after cessation of therapy. Interestingly, most of these are effects that have become recognized as desirable to long-term efficacy.

The theoretical risk for systemic toxicity is low for 5% and 2% 5-FU concentrations with twice-daily application. At most, 5%-10% of topically administered 5-FU is absorbed after application to the face and scalp. Metabolic elimination is rapid, with a

primary half-life of less than 10 minutes. There have been only 7 reports of possible systemic absorption and associated systemic toxicity (mainly bone marrow toxicity) in the 31 years since 5-FU was introduced. In four cases, patients had neutropenia, including decreased platelet counts; two patients had gastrointestinal ulcerations; and one case was reported of neutropenia with gastrointestinal symptoms and dihydropyrimidine dehydrogenase (DPD) deficiency. No deaths have been associated with systemic toxicity. In all cases, the symptoms resolved after 5-FU treatment was discontinued. The postmarketing data suggest that the incidence of systemic toxicity is 1:1.9 million prescriptions.

A new formulation of 5-FU was introduced recently, a 0.5% 5-FU cream in a microsphere delivery system. The product is approved for daily application for up to 4 weeks. The complete response rate after 4 weeks of treatment is reported as 48% (compared with a complete response rate of greater than 80% with the 5% concentration of 5-FU). In the clinical trials, erythema was reported in more than 90% of treated patients and 60% of those in the vehicle-only group. This reaction resolved to baseline within about 2 weeks after the end of treatment in all cases. The theoretical risk for systemic toxicity with this new formulation is very low, with no reports of observed toxicity in the phase III studies; to date, no postmarketing statistics on systemic toxicity are available.

A question has been raised regarding the safety of 5-FU in patients with DPD deficiency. Because DPD is the major enzyme employed to degrade 5-FU, a deficiency in the major pathway for 5-FU degradation logically would lead to the expectation that blood levels of the drug would be higher and that systemic toxicity might be a risk. As noted above, one

such case in a patient with DPD deficiency has been reported in the 31 years of experience with 5-FU. In this case, the patient was being treated for basal cell carcinoma. After 1 week of treatment, the patient experienced abdominal pain associated with bloody diarrhea and vomiting, as well as fever and chills. He was treated with broad-spectrum antibiotics and total parenteral nutrition. He gradually improved and recovered.

**“Patients with the most severe reactions experience not only the most complete AK resolution but also are left with skin that is smoother and less mottled.”**

Johnson and Diasio<sup>2</sup> demonstrated that the association between DPD deficiency and severe toxicity is not clear in cancer patients treated with 5-FU intravenously at concentrations greatly exceeding those used with topical 5-FU therapy. In this study involving 103 patients with cancer—44 with DPD deficiency and 59 with normal DPD—Johnson found that the severity and rate of unexpected toxicity (including mucositis, granulocytopenia, and diarrhea) was comparable in the two groups. A slightly greater death rate was noted in the DPD-deficient group, for reasons that were not established. Thus, even at chemotherapy blood levels, DPD deficiency alone (either homozygous or heterozygous) does not predict severe toxicity.

The frequency in DPD deficiency in the general population is known: 3%-5% for heterozygous state and

0.1%-3% for homozygous state. One can assume that since 13.6 million prescriptions for 5-FU have been written, this represents approximately the same number of patients.

## Conclusion

Topical 5% 5-FU is an effective treatment for AKs. Treatment is associated with crusting, edema, and other inflammatory effects that are associated with efficacy. The greater the inflammatory response, the more effective the therapy. However, consideration should be given to minimizing patient discomfort by using the strategies discussed here.

Topical 5-FU has a 31-year history of use, and the postmarketing surveillance data demonstrate that the risk for systemic toxicity is slight. Regarding the question of 5-FU therapy in patients with DPD deficiency, based on the data on the incidence of DPD deficiency in the general population cited above, 13,600 homozygous and 680,000 heterozygous DPD-deficient patients would have been treated in 31 years. Since only seven cases of systemic toxicity have been reported, the data suggest that DPD deficiency secondary to topical application of 5-FU probably is not a major problem. However, until the issue regarding the role of DPD in 5-FU toxicity has been resolved, it may be advisable to avoid the use of this drug in patients with DPD deficiency.

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## New Therapeutic Advances: Skin Cancer and Actinic Keratoses CME Post-Test and Program Evaluation

### Instructions for CME credit.

The University of Kentucky College of Medicine designates this educational activity for a maximum of 1 hour in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit actually spent in the educational activity. There is no fee to participate in this activity. Please mail the CME Post-Test and Program Evaluation form by **February 28, 2004** to: **Attn: Distance Education, University of Kentucky Chandler Medical Center Continuing Education, One Quality Street, Ste 600, Lexington, KY 40507-1428, 859-257-5320 Ext 80345.**

**INSTRUCTIONS:** For each question or incomplete statement, one answer is correct. Check the most appropriate response. Seven of ten correct responses are required for credit.

- The 5-year survival for melanomas greater than 4.0 mm thick is approximately \_\_\_\_\_.
  - 30%
  - 50%
  - 70%
  - 90%
- Of the four histologic subtypes of melanoma, \_\_\_\_\_ is the one that occurs most frequently and is associated with the best prognosis.
  - Acral lentiginous melanoma
  - Lentigo maligna melanoma
  - Nodular melanoma
  - Superficial spreading melanoma
- The most important risk factor for basal cell carcinoma is:
  - Extensive and cumulative sun exposure over a period of years
  - Inability to tan
  - Open and lingering sores
  - Skin damage from burns
- A history of actinic keratosis is associated with an increased risk for:
  - Basal cell carcinoma
  - Squamous cell carcinoma
  - Both A and B
  - Neither A nor B
- The preferred technique for treatment of recurrent or high-risk nonmelanoma lesions is:
  - Chemotherapy with 5-fluorouracil (5-FU)
  - Electrodesiccation and curettage
  - Mohs' micrographic surgery
  - Surgical excision with margins from 2-5 mm
- Topical or intralesional treatment with 5-FU may be useful in all but which one of the following clinical circumstances?
  - Debulking larger nonmelanoma cancer lesions
  - Reducing the size of squamous cell carcinomas prior to surgery
  - Treating nodular basal cell carcinoma
  - Treating superficial basal cell carcinoma
- Which one of the following is *not true* of actinic keratoses (AKs)?
  - AKs are localized neoplasms limited to the skin.
  - AKs demonstrate a localized proliferation of atypical keratinocytes at the dermal-epidermal junction.
  - Many AKs spontaneously regress.
  - Most AKs progress to squamous cell carcinoma.
- An increased risk for development of AKs is definitively associated with all but which one of the following?
  - Blond hair
  - Cumulative sun exposure
  - Inability to repair damaged DNA in skin cells
  - Light-colored eyes
- In the 31 years since topical 5-FU has been available, a total of \_\_\_\_\_ reports of possible systemic absorption and associated systemic toxicity have been documented.
  - 7
  - 70
  - 700
  - 7,000
- Toxicity to 5-FU in patients with dihydropyrimidine dehydrogenase deficiency \_\_\_\_\_ .
  - Has been associated with 7 deaths
  - Has been established by Johnson in studies of intravenous 5-FU
  - Is not clear
  - Is lower with lower concentrations of 5-FU

### EVALUATION FORM

We would appreciate your answering the following questions to help us plan for other activities of this type.

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	Excellent	Good	Fair	Poor
Text	_____	_____	_____	_____
Photographic images	_____	_____	_____	_____
Post-Test	_____	_____	_____	_____
- How would you rate the clinical relevance of the material?
 

_____	_____	_____	_____
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_____	_____	_____	_____
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- Do you believe such materials, supported by educational grants from industry, are appropriate and useful? Please rate from 0 (not appropriate/useful) to 10 (very appropriate/useful).
 

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- Other comments:
 

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Please indicate amount of time spent on this activity: \_\_\_\_\_ hrs \_\_\_\_\_ min (maximum 1 hour) spent on activity.

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