This newsletter contains valuable information on diagnosis and treatment of several conditions commonly seen in practice: actinic keratosis (AK), superficial basal cell carcinoma (sBCC), and external genital warts (EGW). These neoplasms account for a large number of office visits each year, and their sequelae can be significant.

Skin cancer is a growing concern for all patients, regardless of race, gender, or geography. Women have two unique concerns related to skin cancer: as adults, they may be facing personal consequences of years of inadequate sun-exposure protection, and as a health caregiver in their households, they need to remind their family members about the need for sun protection and disease screening. Risk factors for precancerous lesions and skin cancer are the same—frequent or intense sun exposure with greater risk in those with fair skin, light eyes and/or hair, exposure at younger ages, more frequent exposures, a history of skin disorders or damage, and altered immunity.

Dr. Rosen reviews the clinical presentation, diagnosis, and treatment options for AK and sBCC.

Human papillomavirus (HPV) infection is one of the most common sexually transmitted diseases in the United States. Although EGW will not develop in everyone with HPV infection, they are easily transmitted, and most sexual partners are infected by the time of a diagnosis. Dr. Nelson provides a review of HPV infection with emphasis on its role in the pathogenesis of EGW, and discusses multiple treatment options.

The focus for treatment options is the role of imiquimod, a local immune modulator, which when topically applied triggers both innate and cell-mediated immune response. Imiquimod, with its unique mode of action and efficacy against a wide range of skin neoplasias, has shown itself to be a powerful tool in medical practice. Clinical trial data supporting the efficacy and safety of its use in the management of AK, sBCC, and EGW is presented herein.

Imiquimod is indicated for actinic keratosis, superficial basal cell carcinoma, and external genital warts.
Developments in Identifying and Treating Non-Melanoma Skin Cancer

Theodore Rosen, MD

A relatively easy and highly effective preventive counseling opportunity consists of warning patients to limit exposure to ultraviolet (UV) light both from natural (eg, the sun) and artificial (eg, tanning beds) sources. The benefits of judicious limiting of UV exposure are not only cosmetic, such as reduced wrinkling and lentigines (age spots), but also medical, such as lowered risk of skin cancer. Despite our best efforts to educate patients, many do not adhere to recommendations to avoid excessive UV exposure; thus, health care professionals need to be capable of early diagnosis and effective treatment of non-melanoma skin cancer (NMSC) lesions. Fortunately, topical, field-directed treatment options are available that can be administered safely as an alternative to surgical intervention for select lesions.

NMSC lesions include actinic keratosis (AK), superficial and nodular basal cell carcinoma (sBCC and nBCC), squamous cell carcinoma in-situ (SCCIS) (Bowen’s disease), and invasive squamous cell carcinoma (SCC). AK and SCC are part of a disease continuum that includes shared cellular genetic alterations which promote uncontrolled proliferation, morphology, and location. The presence of one or more AK lesions represents “the tip of the iceberg” and should be regarded as “a wake-up call.” To prevent AK lesions from developing into potentially lethal invasive SCC, early treatment is critical.

BCC, the most common form of skin cancer, is characterized by a different pathology and a different set of UV-induced cellular genetic abnormalities. BCC is easily treatable when diagnosed early, but with time can become locally aggressive, damaging surrounding skin and other vital structures in close proximity. Neglected BCC can even invade bone or cartilage, although it rarely metastasizes. UV radiation is a modifiable risk factor for all NMSC lesions.

Diagnosis
A tentative differential diagnosis of NMSC lesions can be made based on appearance, although confirmation of basal and SCCs almost always require biopsy. AK lesions are flat, scaly, and small, often with an underlying redness (Figure 1). Occasionally, AK lesions may be hypertrophic and therefore significantly raised above the skin surface. Nodular BCC lesions are often pearly or waxy with distinct borders and prominent blood vessels on the lesion's surface. Invasive SCC lesions may resemble AK lesions but are thicker, more erythematos, have poorly defined borders, are generally rock hard and may be friable. Superficial BCC exhibits flat, red, scaly surfaces and sharp borders (Figure 2). Sclerotic or morpheoform BCCs are the rarest type and look like depigmented areas or scars. Both of these types of NMSC are much bigger than an AK lesion. Shave biopsy can be used to confirm most suspected NMSC, but punch biopsy is better utilized in order to penetrate the thickness of invasive SCC.

Treatment Options
The goal of treatment for all NMSC is complete removal of the tumor while preserving both function and cosmetic appearance as much as possible. Often overlooked, however, is the potential goal of preventing similar lesions from occurring on contiguous skin. Treatment modalities can be broadly divided into lesion-directed (surgical removal of the lesion only)

To prevent AK lesions from developing into potentially lethal invasive SCC, early treatment is critical.

Figure 1. These lesions on a woman’s cheek are flat and scaly with underlying redness, typical of actinic keratosis.
and field-directed (broad-based topical therapy directed at the lesion and surrounding damaged skin).

The National Comprehensive Cancer Network states that in patients with low-risk sBCC, when surgery or radiation are contraindicated or impractical, topical therapy should be considered. At this time, there are no consensus guidelines for management of AK, although field-directed therapy is becoming a first-line treatment in an attempt to achieve some measure of long-term suppression of carcinogenesis.

Lesion-Directed Treatment: Surgery
Surgical management of NMSC is considered the gold standard of treatment, and is indicated for all invasive tumors. Curettage and electrodesiccation (C&E) is used on low-risk lesions in non-hair bearing sites, is limited to removal of the epidermis and dermis only, and should be accompanied by pathologic confirmation of tumor type. Though widely practiced, C&E can leave residual depressed and/or hypopigmented scars. Excisional surgery with postoperative margin assessment and/or Mohs micrographic surgery with complete circumferential peripheral and deep margin assessment during removal are more extensive forms of surgery indicated for management of deeply invasive tumors, tumors ≥2 cm, incomplete excisions, recurrent neoplasms, and high-risk tumor locations.

Radiation therapy is generally reserved for older patients (>60 years) and is indicated for use in the low-risk regions of the trunk and extremities. It is contraindicated for treatment of the genitalia, hands, and feet; in genetic conditions predisposed to skin cancers; and in patients with concomitant connective tissue diseases.

Cryotherapy consists of rapid freezing of the lesion with liquid nitrogen and may be used for low-risk small, well-demarcated sBCC and AKs. In AK, response to cryotherapy is dependent on freeze times with higher rates of complete response seen in lesions frozen for longer than 5 to 20 seconds. Freeze times for sBCC are substantially longer. An expected outcome of cryotherapy, in addition to local blistering and crusting, is hypo-pigmentation due to destruction of melanocytes during the freezing process. This adverse effect may cause serious cosmetic defects, especially with repeated applications.

Field-Directed Treatment: Topical
Field-directed treatment is best suited for the earliest manifestation of NMSC (AK) and for superficial forms of both BCC and SCC (Table). 5-Fluorouracil is an antineoplastic antimetabolite indicated in topical form for treatment of AK and sBCC. When used for AK, the various formulations are applied twice daily until the inflammatory response reaches the erosion stage.

Table. Therapies for Superficial Basal Cell Cancer and Actinic Keratosis

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<th>Topical/Field-Directed Treatment</th>
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POMA = postoperative margin assessment  
CCPDM = complete circumferential peripheral and deep margin assessment with frozen or permanent section
The efficacy of imiquimod 5% cream was established in AK in two phase III randomized studies of 436 patients with 4 to 8 AK lesions located within a contiguous 25 cm² treatment area on the face or balding scalp. Patients were administered either imiquimod 5% cream or matching vehicle two days per week for 16 weeks followed by an 8-week follow-up period. In both studies, the complete and partial (≥75%) clearance rates were significantly greater with imiquimod.

Notably, 48% of patients treated with imiquimod had an increase in AK lesion count above baseline during therapy with a complete clearance rate of new lesions that was similar to that observed for those present at baseline. The increase in lesion count was attributed to appearance of subclinical lesions that were not visible at baseline. At 8 weeks following completion of treatment, the median percent reduction in the number of AK lesions from baseline was 83.3% in the imiquimod treatment group, indicating that half of patients treated had a least an 83.3% reduction in the number of AK lesions counted in the treatment area at baseline. Local skin reactions were more intense in the imiquimod group and increasing severity was associated with higher clearance rates. After 16 months of follow up, imiquimod continued to provide a long-term clinical benefit in patients with complete AK lesion clearance.

Two identical vehicle-controlled studies evaluated the use of imiquimod 5% cream applied 5 times per week for 6 weeks to 364 patients with sBCC. Composite clearance rate (no clinical or histologic evidence or suspicious clinical evidence with no histologic evidence of sBCC at the 12-week posttreatment assessment) and histologic clearance rates were significantly higher in the patients who received imiquimod.

Five-year long-term follow-up in 136 patients has shown continued sustained clearance with 90% of patients clear of sBCC lesions for 4 years, and 87% of patients clear for 5 years. Evaluated in total, the most common adverse events reported in trials of imiquimod in either AK or sBCC consisted of application site reactions. The most commonly reported events were itching and burning, although in selected patients significant erythema and crusting may occur.

Conclusion
While surgery has been the gold standard for treatment of NMSC, field-directed therapies such as imiquimod offer many advantages. In AK, imiquimod...
use is associated with excellent response as a field-directed therapy that addresses not only visible AK lesions but subclinical foci. In sBCC, use of imiquimod 5 times per week produces long-term clearance of lesions.

References


Human papillomavirus (HPV) is now recognized as one of the most common sexually transmitted infections (STIs) in the United States, accounting for more than 33% of new STI cases annually. Incidence and prevalence are difficult to assess because HPV is not reportable, often asymptomatic, and produces antibodies in only 50% of cases. Therefore, prevalence is likely to be significantly underestimated.

Long-term health consequences of infection with high-risk HPV types can be devastating, ranging from precancerous cervical, vaginal, vulvar, and anal dysplasias to invasive squamous carcinoma and adenocarcinoma. One of the earliest clinical manifestations of both high- and low-risk HPV infections is external genital warts (EGW).

Incidence
It is estimated that 500,000 to 1 million new cases of EGW occur in the United States each year, and they account for 600,000 outpatient visits annually. As of 2004, 4% of men and 7.2% of women aged 19 to 59 years reported having a diagnosis of EGW. Rates were highest among white women with higher education and greater income, and multiple lifetime partners also increased the risk.

Clinical Presentations
Genital warts in women can be found on the vulva, perineum, vagina, cervix, urethra, mouth, and larynx. Warts are generally located in areas exposed to friction during sexual activity, such as the posterior fourchette. Symptoms of discharge, itching, burning, soreness, or fissure are rare. Women may note the presence of a mass, and if the warts become very large or superinfected, there may be tenderness, postcoital spotting, or odor.

The classic appearance of condyloma acuminata is a raised, peaked, cauliflower-like lesion. However, they may also be rough or smooth papules or flat lesions (Figure 1). On thickly keratinized skin, they can appear white, grey, or flesh-toned. On mucosal surfaces, low-risk HPV lesions tend to have finger-like projections that blend in color with the surrounding tissue. Flat genital warts can be hyperpigmented, white, or red, depending on local melanocytic involvement.

Differential Diagnosis
The differential diagnosis for EGW in women is extensive. It includes congenital vestibular papillomatosis, in which the vestibule is filled with symmetric, smooth, contoured projections. Close examination can distinguish this disorder because the projections are uniform in size and distribution and consist of many simple cylindrical projections from one surface instead of multiple projections arising from a common base. Other benign conditions to consider include sebaceous cysts, molluscum contagiosum (especially in women with HIV), skin tags, or benign nevi. The differential diagnoses for flat warts include condyloma lata, lichen sclerosis, vulvar hyperplasia, and psoriasis. For all genital warts, the possibility of dysplasia or invasive carcinoma must be considered.

Selection of treatment depends on wart size, number, anatomic site, morphology, adverse effects, provider experience, patient preference, and cost.
Genital warts are routinely diagnosed clinically based on their visual appearance in bright light, occasionally aided by magnification. Biopsies are needed only for suspicious lesions, or when the diagnosis is uncertain (Table). Importantly, there is no place for HPV/DNA typing in routine clinical practice.6

### Treatment

As a virus, HPV is generally protected from serum factors, phagocytosis, and many other elements of the humoral immune system. The cellular immune system has the potential to identify virus-specific antigens on the surface of infected cells, but EGW are protected from these elements because they cannot penetrate into the epidermis. Even if infected cells can be tagged, it is difficult for the immune system to destroy them. Cytotoxic T cells also have only limited access to the epidermis, especially in the absence of inflammation. Therefore, without treatment, EGW can persist for months to years. Selection of treatment depends on wart size, number, anatomic site, morphology, adverse effects, provider experience, patient preference, and cost.6

### Surgical Therapies

Surgical excision under local anesthesia with iris scissors or tangential shave excision with a scalpel is appropriate for isolated, pedunculated condyloma that are attached by a slender stalk. However, surgical excision is generally reserved for very large exophytic lesions.

Ablation can be done using cryotherapy, laser or loop electrical excision procedure (LEEP), depending on lesion site and treatment availability. Care must be taken to limit tissue destruction to the level of the papillary dermis. Cryotherapy of the cervix and vulva is cost-effective, and liquid nitrogen is preferred for urethral warts. The infected cells are destroyed, subsequently liquefying and shedding. Cryotherapy can be repeated every 1 to 2 weeks, provided there is progress in reducing the lesions. Cryotherapy is generally not used in the vagina because it is difficult to control depth of penetration through the vaginal mucosa, and adjacent bowel may be inadvertently injured.

Laser ablation under anesthesia is particularly helpful for treating widespread lesions unresponsive to other therapies. Cervical and vaginal condyloma are also effectively treated with either carbon dioxide or vascular lasers because the depth of thermal damage can be controlled. Cases with more localized involvement can be laser-treated in the office setting. The LEEP is a treatment of choice in many settings for cervical warts and localized exophytic vulvar lesions.

### Medical Therapies

Medical therapy can be used alone or in conjunction with surgery. The CDC’s Sexually Transmitted Diseases Treatment Guidelines, 2006 classified medical regimens into 2 categories: patient-applied and provider-administered.7 Considerations include patient preference, comfort, cost, and duration to clearance of warts. Patient preference is particularly important, as up to 70% of patients have been previously treated.8 Pregnancy status is also important, because some of these agents are contraindicated in pregnancy.9

#### Patient-Applied Treatments

Patient-applied treatments have the advantage of eliminating frequent visits to the health care professional. Direct patient costs of the drug should be balanced against copayments for office visits and the cost of time lost from work and transportation.

Podoflox 0.5% gel is an antimitotic agent that prevents cell division and destroys warts by inducing local tissue necrosis.10 It is applied twice daily for 3 consecutive days for 4 weeks. The treated surface must not exceed 10 cm², and no more than 0.5 mL of the gel should be used per day.9 This treatment provides clearance in 37% of patients.11 Side effects are related to local inflammation. Recurrence has been reported in 4% to 38% of patients, and long-term remission varies from 30% to 60%.12,13

Imiquimod 5% cream is a cell-mediated immune response modifier. It is applied to lesions 3 times a week (alternating nights) for up to 16 weeks. Patients should be advised to rub the cream well into the lesion, and to wash it off 6 to 10 hours after application. Most patients will

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**Table. Indications for Biopsy of EGW**

- Lesions surrounded by thickened skin, ulceration, or pigmentation
- Raised, bleeding, red, or pigmented lesion
- Indurated or fixed lesion
- Lesions >2 cm
- Lesions unresponsive to targeted therapy
- Lesions in high-risk women (HIV, heavy smoking)
develop localized erythema, but fewer than 10% will complain of pain. Those who experience pain can be advised to take a brief “holiday” from treatment. Imiquimod is a category C drug in pregnancy.

Imiquimod’s mechanism of action as a local immune modulator is unique and indirect. It induces local interferon and cytokine release that triggers both innate and cell-mediated immune response, reducing the viral HPV load. Complete clearance of warts is seen in 50% of patients, and more than 80% of women have at least a 50% reduction in wart area. The effects of imiquimod are long term; wart recurrence is lowered in women treated with imiquimod.

**Provider-Applied Therapies**—Podophyllin resin is an antimitotic agent that works in the same manner as podofilox. It is compounded in a 10% to 25% suspension in tincture of benzoin. Like podofilox, it should not be applied to areas greater than 10 mm². Because of possibly serious systemic complications, some experts have recommended against its use in primary care settings. Recurrences following clinical trials have been reported in 23% to 65% of subjects. Podophyllin should not be used in pregnancy.

Bichloracetic acid (BCA)/trichloroacetic acid (TCA) is inexpensive and easy to apply. It denatures and precipitates proteins to kill wart cells. Concentrations vary from 50% to 95%. It must be applied carefully, and rapid drying helps reduce pain. Placing a protective “moat” of lidocaine ointment around the base of the wart can reduce run-off to adjacent tissue and consequent ulceration. Clearance rates of up to 80% can be expected, but multiple applications may be needed at week-long intervals. These agents are not absorbed systemically, and are safe in pregnancy.

**Newer Options**

The FDA has approved sinecatechins, 15%, for topical treatment of EGW. This is a botanical drug extract of green tea leaves. Catechins are a mixture of bioflavonoids, polyphenols, and antioxidants. A 0.5-cm strand of the ointment is applied 3 times a day in a thin layer for up to 16 weeks. In clinical trials, complete clearance was achieved in 53.6% of subjects. The quadrivalent HPV vaccine is not a treatment for genital warts. However, it is particularly effective in reducing the risk of developing EGW by preventing infection with high-risk HPV types 6, 11, 16, and 18.

**Conclusion**

External genital warts represent a cosmetic and often symptomatic problem for patients. Given the wide variety of treatment options, it is more likely that clinicians will be able to design therapies that can meet the needs of individual patients. The patient-applied methods offer many advantages, not only as stand-alone treatments, but also in conjunction with surgical therapies.

**References**


Patient counseling regarding proper use of imiquimod is essential to optimal and safe use. Counseling should be tailored to the patient and the indication, and should include discussion of the risks, benefits, success rates, and recurrence rates of treatment as well as strategies for prevention of further ultraviolet (UV) damage or human papillomavirus (HPV) exposure. Since actinic keratosis (AK) and superficial basal cell carcinoma (sBCC) develop after years of sun damage, these lesions will usually be found in patients older than 40 years of age. Patients with external genital warts (EGW) will generally be in their 20s or 30s, although they can be younger or older. Note that the safety for use in patients younger than age 12 has not yet been established.

Patients often benefit from knowing that imiquimod does not act like any other anti-cancer therapies and is not an antiviral medication. Imiquimod has a unique mode of action and activates the body’s own immune system to fight AK, sBCC, and EGW. All other therapies attempt to either cut out, damage, or poison the lesion. Manage patient treatment expectations by showing them images of before, during, and after treatment, and information on cure and recurrence rates. Consider having simple written materials available to reinforce the information given.

Non-Melanoma Skin Cancer
Imiquimod use should not be initiated until the skin in the treatment area is completely healed from any prior surgery or drug therapy. In patients undergoing treatment of non-melanoma skin cancers, it has been noted that the skin reaction to imiquimod follows a predictable pattern of erythema, edema, erosion and/or ulceration, weeping/exudates, and finally scabbing/crusting. The pattern of skin reactions reflects the inflammatory immune response in the skin. When treating visible AK lesions, imiquimod exposes and treats subclinical AK lesions that are not yet visible before they develop further. The clinical response of imiquimod on AK and sBCC lesions can be seen in Figures 1 and 2.

During and following treatment, all patients diagnosed with any type of AK or skin cancer should be reminded to practice simple skin cancer screening and prevention strategies. For screening in patients who have had a skin cancer, the National Comprehensive Cancer Network (NCCN) recommends self examinations and skin evaluations every 6 to 12 months for life (as in other situations, the US Preventive Services Task Force has more conservative recommendations). For prevention, patients should always wear a broad-spectrum sunscreen that blocks both UVA and UVB with a sun protection factor (SPF) of at least 15. Sunscreens that block both UVA and UVB include metal oxides, avobenzone (Parsol), and mexoryl (Anthelios, currently only available with SPF15 in the United States). They should be instructed to apply sunscreen to dry skin 30 minutes before exposure, reapply 30 minutes after beginning exposure, and reapply after 2 to 3 hours of outdoor activity. Wearing protective clothing, especially hats, sunglasses, and coverings for the arms, legs, and abdomen, is important as well. Tanning beds should not be used.

External Genital Warts
Treatment of genital warts should begin with a discussion of the natural history of HPV. After diagnosis, patients often have little understanding of the disease process and high levels of anxiety related to the disease. Their initial expectations are usually centered on “cur-ing” the disease with minimal pain, lifestyle changes, or health care visits. With time, these concerns often shift to treatment of lesions, impact on pregnancy, and long-term treatment efficacy. Effectively educating patients and addressing their concerns are vital for defining realistic treatment goals and achieving higher levels of patient satisfaction.

Explain to patients that HPV genital infection is sexually transmitted and common among sexually active adults. Also, clarify that treatment of genital warts may not reduce the risk of infecting current or future partners, nor does it protect against recurrence. Women with genital warts or those whose partners have been treated should be reminded of the importance of regular cervical cancer screening.

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Explain to patients that when imiquimod is applied to the wart, activated immune cells travel to the area and work to eliminate the HPV-infected cells that are causing the warts. This helps the warts to clear. Note that imiquimod is pregnancy category C. It is indicated for use only on external HPV infections, and it is contraindicated for use on occluded mucus membranes or on the uterine cervix. The response of EGW to imiquimod can be seen in Figure 3.

**Dosing of Imiquimod**

The dosing parameters for imiquimod differ for AK, sBCC, and EGW. Patients undergoing treatment with imiquimod should be given directions for use and be advised of the importance of applying the cream in a safe manner. They should also be made aware of possibility of an intense local reaction. Dosing instructions are as follows:

**Actinic Keratosis**
- Apply imiquimod 2 times per week to an area of skin approximately 25 cm² for 16 weeks. Imiquimod may be applied to the face (eg, forehead or cheek) or scalp but not both simultaneously.
- Rest periods of several days may be necessary in the event of an exaggerated local skin reaction. However, the total treatment period should not be extended beyond 16 weeks due to missed doses or rest periods.

**Superficial Basal Cell Carcinoma**
- Apply imiquimod 5 times per week (eg, Monday through Friday) for 6 weeks.
Target tumors should have a maximum diameter of 2 cm and be located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet). The treatment area should include a 1 cm margin around the tumor.

If there is clinical evidence of tumor following treatment, a biopsy or alternative intervention should be considered.

External Genital Warts

- Apply imiquimod 3 times per week until there is total clearance of external genital/perineal warts or for a maximum of 16 weeks. When applied to the treatment area, it should be gently rubbed in until it is no longer visible.
- Imiquimod cream should be applied prior to bedtime and left on the skin for approximately 8 hours (6 to 10 hours for EGW), then removed by washing the area with mild soap and water.
- Describe to patients the exact area to be treated, and explain that the area should be washed with mild soap and water and be allowed to dry thoroughly before applying imiquimod. After applying imiquimod cream, patients should wash their hands.
- Only one packet at a time of imiquimod should be used.

Explain that local skin reactions (redness, burning, flaking, or crusting) in the treatment area are common. Patients should be instructed to contact you if reactions affect their daily activities or do not go away. A rest period of several days may be needed. Patients undergoing treatment for AK or sBCC should avoid sun exposure. Patients undergoing treatment for EGW may use non-occlusive cotton gauze dressings or cotton undergarments. Imiquimod should not be used in the vagina.

Because imiquimod is indicated for several conditions, be sure patients know which condition is being treated, possible side effects, and when to call you if needed. Imiquimod’s noninvasive regimen is a good alternative to surgery and most patients will appreciate the ease of treatment.

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References