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Management of nonmelanoma skin cancer in 2007

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SUMMARY

As the incidence of nonmelanoma skin cancer (NMSC) increases, so does the number of modalities used to treat this condition. Surgery is the most frequent approach used to treat NMSC, and clinicians usually perform Mohs micrographic surgery, conventional excision, electrodesiccation and curettage or cryosurgery. The 'gold standard' for treatment continues to be Mohs micrographic surgery, but owing to the time and expense involved with this procedure, it is indicated only in patients with aggressive tumors or those where disfigurement or functional impairment is a risk. Although radiation therapy is effective, its use is limited because of the side effects induced; radiation therapy can be used in certain patients who are not surgical candidates. Newer noninvasive options for NMSC include topical chemotherapeutics, biological-immune-response modifiers, retinoids, and photodynamic therapy, which can be used particularly in patients with superficial tumors. Treatments should be tailored to tumor type, location, size, and histological pattern, and although surgical methods remain the most frequently used, newer noninvasive treatments can be used in select tumors and may reduce morbidity.

KEYWORDS management, Mohs micrographic surgery (MMS), nonmelanoma skin cancer (NMSC), review

REVIEW CRITERIA

The information for this Review was compiled by searching the PubMed database for articles published until 15 December 2006. The search terms used included "Non-melanoma skin cancer" in association with the following search terms: "reviews", "treatment", "Mohs", "curettage and electrodesiccation", "excision", "imiquimod", "photodynamic therapy", "topical chemotherapy", "interferon", "retinoids", "cryosurgery", "radiation therapy", and "immune modifiers". Electronic early-release publications were also included. Only articles published in English were considered. When possible, primary sources have been quoted. Full articles were obtained and references were checked for additional material when appropriate. References were chosen on the basis of the best clinical or laboratory evidence, especially if the work had been corroborated by published work from other centers.

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INTRODUCTION

Nonmelanoma skin cancer (NMSC) is the most common human malignancy and it is estimated that over 1.3 million such cancers are diagnosed each year in the US.[1–3] The incidence of NMSC is difficult to determine, however, as many cases are not reported because the cancer is not typically followed in tumor registries. Although the mortality caused by NMSC is low, 20% of Americans will develop this type of cancer during their lifetime, resulting in an annual cost to Medicare alone of $426 million.[3] The vast majority of NMSC is basal-cell carcinoma (BCC; Figure 1), which comprises 75% of all NMSC cases. Squamous-cell carcinoma (SCC; Figure 2) accounts for 20% of NMSC cases.[1] Treatment options for NMSC include both surgical and nonsurgical modalities. Regardless of the approach used, the goal is to remove the tumor, achieve a high cure rate, preserve the maximal amount of normal surrounding tissue, and provide an optimum cosmetic outcome. The choice of treatment approach depends on the location of the cancer, age and health status of the patient, and risk factors for tumor recurrence.[4]

As clinical diagnosis is not always reliable, a biopsy is usually performed on suspicious lesions, although some clinicians prefer to excise the entire lesion rather than perform an initial biopsy. Lesions that are raised can often be biopsied using a shave technique. If the area is flat or depressed, as with morpheaform BCC, a punch biopsy can be used, as a shave biopsy is unlikely to sample sufficient tumor cells. Sampling to the base of the lesion is especially important with SCC, where the architecture and depth are important diagnostic and treatment parameters.

The most frequently used method for the treatment of NMSC is surgical excision of the tumor. Surgical approaches include conventional excision, Mohs micrographic surgery (MMS), electrodesiccation and curettage and cryosurgery (Figure 3). MMS remains the 'gold standard' for the treatment of a range of NMSCs because this method provides the most complete histologic analysis of tumor margins, the highest cure rate, and

preservation of the maximal amount of normal tissue by removing the tumor with the smallest margin necessary. Various nonsurgical methods for treatment may be suitable in certain patients, because of the potential for disfigurement and functional impairment and the inherent risks associated with any surgical procedure. Radiation therapy has also been used in specific circumstances, and a variety of other relatively new noninvasive options such as topical chemotherapeutics, biological-immune-response modifiers, retinoids, and photodynamic therapy are now available.[4,5]

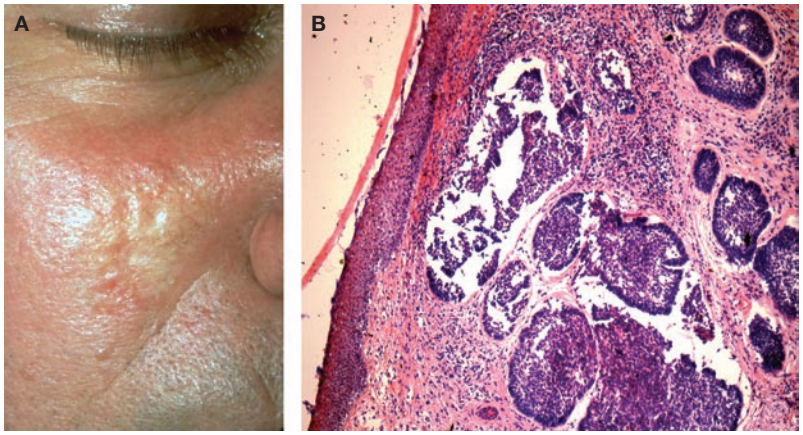

Figure 1 Example of a basal-cell carcinoma in a patient with nonmelanoma skin cancer. (**A**) Nodular basal-cell carcinoma demonstrating typical pearly surface with telangiectasias. (**B**) Histopathology of a basal-cell carcinoma demonstrating basaloid islands with peripheral palisading and clefting.

MOHS MICROGRAPHIC SURGERY

MMS is a technique in which serial horizontal sections of tumor are removed, mapped, processed by frozen section in an enface fashion, and analyzed microscopically. While routine hematoxylin and eosin stain is most commonly used, some surgeons who perform MMS use toluidine blue. The entire peripheral and deep margins are examined by the surgeon and immediate re-excision of the residual tumor region is performed until the area is tumor free. This method provides up to 100% of the excised margin for examination and allows for more-accurate tumor mapping and cancer clearance than standard, vertically-orientated histopathology sections, which assess less than 1% of the tumor margin.[6] MMS is almost universally performed under local anesthesia in an outpatient or office setting by a dermatologist trained in both dermatopathology and cutaneous oncology. Contiguous tumor spread, as occurs in BCC and SCC cancers, is necessary for this technique to be effective. The ultimate goal of MMS is to completely extirpate the cancer while preserving healthy tissue. The majority of skin cancers occur on the face, head and neck where cosmetic outcome is paramount. MMS provides the critical element of tissue preservation that achieves this goal.[7]

MMS is usually more time consuming than conventional excision without frozen section analysis. In addition, there are a limited number of individuals who are fellowship trained in the procedure. For these reasons, and because of the expense involved, the technique is reserved for specific indications. The majority of skin cancers do not require MMS, but certain guidelines have become well-established over time. The use of MMS is indicated in the management of primary tumors in locations associated

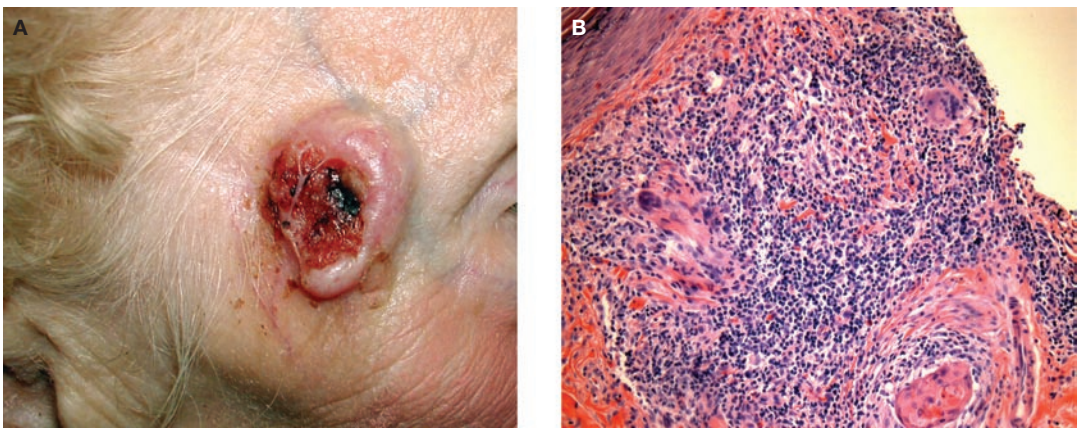

Figure 2 Example of a squamous-cell carcinoma in a patient with nonmelanoma skin cancer. (**A**) Keratoacanthoma, a type of squamous-cell carcinoma, on the temple. (**B**) Histopathology of a squamous-cell carcinoma demonstrating atypical keratinocytes extending into the dermis with inflammation.

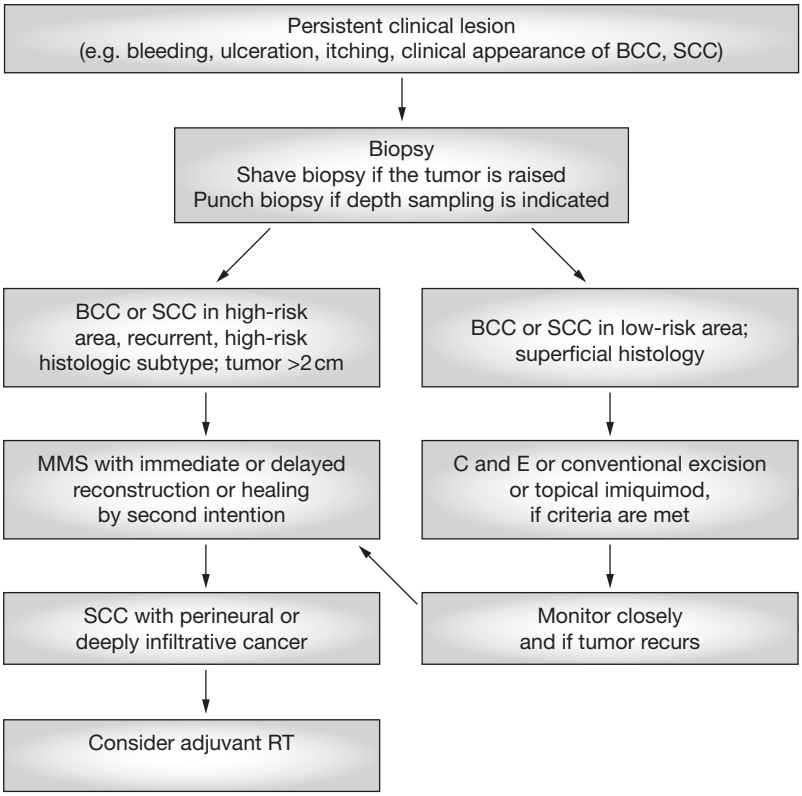

Figure 3 Schematic diagram of the management of nonmelanoma skin cancer. Abbreviations: BCC, basal-cell carcinoma; C and E, curettage and electrodesiccation; MMS, Mohs micrographic surgery; SCC, squamous-cell carcinoma; RT, radiation therapy

with high rates of recurrence including the midface and ears, in tumors greater than 2 cm in size, in tumors with aggressive histological growth patterns (e.g. morpheaform, infiltrative, and sclerosing BCC; Figure 4), in tumors with ill-defined clinical margins, and in recurrent tumors (Figure 5).[5,8] MMS is also the preferred technique to maximize healthy tissue preservation for functionally and cosmetically unique areas such as the nose, lips, and eyelids. MMS is increasingly being used for tumors of the lower extremities where healing can be prolonged and tissue preservation is advantageous.

An important clinical advantage of MMS is that if tumor margins have been determined to be negative, immediate reconstruction can take place. While the majority of surgeons performing MMS reconstruct the tissue during the procedure, in complicated cases a multidisciplinary approach involving head and neck surgeons, oculoplastic surgeons, and plastic surgeons is often helpful. The tissue-sparing technique allows some wounds to heal by second intention.

MMS remains the most-effective method for removing NMSC, with a 5-year recurrence rate of 1% for BCC and 3% for SCC, compared with recurrence rates of 5.3% and 8%, respectively, for standard excision.[5,9] Although the cost of MMS is higher than standard excision, this additional cost might be mitigated by a reduction in tumor recurrence and the costs associated with re-treatment. Disease recurrence occurs more frequently in high-risk sites when treatment modalities other than MMS are used.[10,11] The total cost of MMS is substantially less than the cost of radiation therapy.

EXCISIONAL SURGERY

Excision is the most common therapy for treating NMSC and is useful for treating low-risk tumors because it provides acceptable cure rates and is cost-effective.[5] This method allows for histopathologic examination of the tissue, and while 100% of the margin is not examined, 95% of low-risk tumors will be adequately excised by removal of the tumor with a 4-mm margin. In patients with low-risk superficial tumors, ablative techniques such as curettage and electrodesiccation might provide similar cure rates without limiting physical activity during patient recovery—a frequent requirement following excisional surgery. The cure rates following excision are 95% and 92% for primary BCC and SCC, respectively, and are dependent on the site, size, and pattern of the tumor.[9,12] For recurrent tumors, these cure rates decrease to 83% and 77%, respectively. MMS should, therefore, be used to treat patients with recurrent or poorly-defined lesions because of its higher cure rate.[4,5,9]

RADIATION THERAPY

NMSC can be treated using ionizing radiation as either a primary or adjuvant therapy. Radiation is usually delivered in fractionated doses in the form of superficial X-rays, orthovoltage or deep X-rays, or electron-beam therapy. Fractionation of the dosage allows the normal tissue to recover between treatments; the tumor cells recover more slowly and so fractionation of radiation provides decreased damage to the surrounding tissue, without reducing the effectiveness of the treatment. Radiation treatment is painless and appropriate in debilitated patients. Some patients may suffer from both initial dermatological side effects consisting of alopecia and pruritus, and late effects of depigmentation, atrophy, and telangiectasia. Patients might suffer from radionecrosis

in areas where the skin is thin. Side effects can develop over time, so radiation therapy is best avoided in patients under 50 years of age who have uncomplicated skin tumors.[13] The long-term cosmetic outcome following radiation therapy was reported to be good or excellent by 63% of patients, in contrast to 91% of patients after curettage and electrodesiccation, and 84% after surgical excision.[14] Patients with certain characteristics are not candidates for radiation therapy. Individuals with tumors with ill-defined borders, those with tumors on the lower legs, feet, hands or genitalia, patients with tumors arising in previously irradiated areas, and patients with genodermatoses such as basal-cell-nevus syndrome or xeroderma pigmentosum are unsuitable for radiation therapy. Recurrent and infiltrative NMSC show decreased responsiveness to radiation therapy, but in small tumors (i.e. less than 2 cm), the 5-year cure rates for primary BCC and SCC are 90–93%, which is similar to other treatment methods.[13,14] Radiation therapy is very time-consuming, typically requiring multiple visits to the treatment facility, and is five-to-eight times more expensive than standard excisional surgery.[5] For older debilitated individuals who are unable to tolerate extensive surgery or in circumstances where surgical excision would be extremely disfiguring, radiation therapy may be an excellent choice. This treatment approach can also have a role as an adjuvant therapy to surgery in cases of aggressive SCC with perineural invasion or nodal metastases.[13]

CRYOSURGERY

Cryosurgery uses liquid nitrogen at –196.5 °C to destroy tumor cells through the direct effects of freezing and vascular stasis. Ice crystal formation develops intracellularly and extracellularly, resulting in tissue damage. Rapid cooling produces more intracellular crystal formation and is preferable when treating NMSC because it results in more damage to the tumor cells. To effectively treat NMSC, the tumor tissue must reach a temperature of minus 50–60 °C produced through a series of freeze and thaw cycles administered through a cryogen-spray device. A thermocouple can be inserted into the center of the tumor as it is being treated to ensure that the correct temperature has been reached. Local anesthetic is used as this method is painful and the freezing is nonselective. Patients can develop erythema, vesiculation, edema, exudation, and sloughing as the treated area heals by second intention over a 4 to 6-week period following treatment. Cryosurgery carries a risk of hypopigmentation owing to destruction of the melanocytes by freezing. This method is useful for treating tumors with well-defined borders in elderly or debilitated patients. The reported 5-year cure rates for BCC and SCC treated by cryosurgery are 93% and 96%, respectively.[5,15,16] In general, cryosurgery has been replaced by more definitive approaches that permit margin analysis.

CURETTAGE AND ELECTRODESICCATION

Curettage and electrodesiccation (C and E) is often used to treat superficial NMSC, and relies on the textural differences between tumor cells and the surrounding normal tissue. This method uses a sharp curette to scrape away the friable tumor tissue until normal, firm dermis is felt. The area is first electrodesiccated to cause necrosis of cells. The necrotic debris is then curetted to the base of the wound and the cycle is repeated up to two more times if indicated. In our experience, the best approach is to electrofulgurate (i.e. the cautery tip does not come into contact with the tissue) and gently curette the debris. For superficial lesions, one cycle can suffice followed by gentle fulguration of the base. The area is allowed to heal by second intention, which results in a pink then white stellate scar. The scar can occasionally become hypertrophic. Similar to cryosurgery, this technique does not permit histologic margin analysis. This method of treatment of skin cancer is technique dependent and not appropriate for higher-risk tumors such as morpheaform BCC, but it is cost-effective and rapid to perform. C and E is not suitable for treating recurrent tumors, lesions larger than 2 cm in diameter, tumors extending into the fat, tumors at sites of high risk for recurrence, or lesions with ill-defined borders.[17] The cure rates depend on the site: high-risk locations (i.e. nose, paranasal region, nasolabial fold, ear, chin, mandible, perioral, and periocular regions) have a recurrence rate of 4.5–17.6%, depending on the tumor size. These rates decrease to 3.3% for tumors at low-risk sites of the trunk and extremities.[18] Overall, the 5-year cure rates for primary BCC and SCC treated with C and E are 92% and 96%, respectively.[5,19,20]

TOPICAL CHEMOTHERAPY

The topical chemotherapeutic agent most widely used for cutaneous tumors is 5-fluorouracil (5-FU), which interferes with DNA synthesis in actively dividing cells causing tumor death.[21] Patients self-treat by applying the topical cream

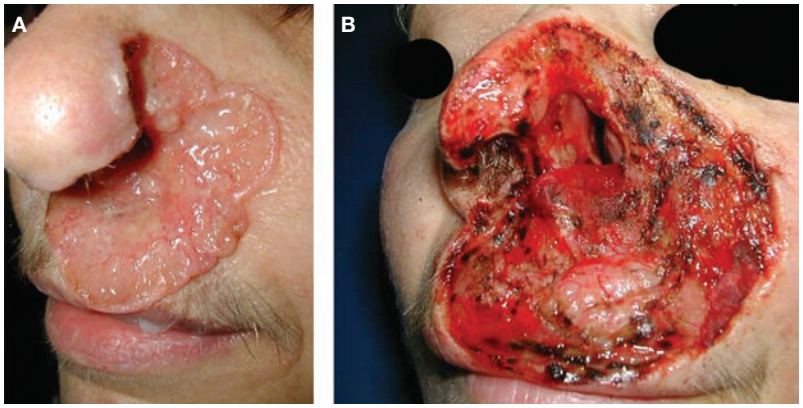

Figure 4 Patient with a basal-cell carcinoma.(**A**) Patient with an aggressive basal-cell carcinoma on the face, which was treated with Mohs micrographic surgery. (**B**) Post-surgical defect after the procedure requiring a multidisciplinary approach to repair the area.

Figure 5 Treatment of a pigmented basal-cell carcinoma using Mohs micrographic surgery (**A**) Patient with a pigmented basal-cell carcinoma on the upper lip. (**B**) Patient with pigmented basal-cell carcinoma after treatment with Mohs micrographic surgery to remove the tumor. (**C**)The area was repaired using an island pedicle flap on the day of surgery. (**D**) At 1 year follow-up, the area is well healed without cosmetic or functional deficits.

for 4–6 weeks, resulting in increasing erythema and superficial erosions at affected sites. These sites typically heal without scarring once the desired inflammatory end point is reached. Some patients can experience pruritus and irritation, and, therefore, require close follow-up during the course of treatment to monitor response to the medication.[22,23]

Although topical 5-FU has been used to treat precancerous actinic keratosis lesions, which may progress to SCC, its usefulness in treating invasive NMSC is hindered by the inadequate depth of penetration of the topical medication into the dermis.[24] Topical 5-FU application has been limited to treating superficial BCC or SCC, because of the potential for persistent, deeper-invasive tumors to remain following treatment, and even then its use is rare.[25]

INTERFERON

Intralesional interferon (IFN) initiates apoptosis of BCC cells via the CD-95 ligand-receptor interaction and the stimulation of interleukin (IL)-2 and IL-10.[21] Treatment with IFN can cause flu-like symptoms including headache, myalgia, and fever, which can be alleviated by taking acetaminophen. Complete response rates of 50–80% have been reported, although these results might not be durable with high-risk tumors.[23] A disadvantage of IFN therapy, aside from the low cure rate, is the need for multiple intralesional injections. A common regimen is 3 injections per week for 3 weeks. This approach is now used only under specific circumstances such as when a patient is not an operative candidate because of their debilitated health or when surgery might result in disfigurement.

IMIQUIMOD

Imiquimod (Aldara, Graceway Pharmaceuticals, Malvern, PA, USA) is a topical immune-response modulator that is effective against superficial BCCs, small nodular BCCs and SCCs *in situ*. The drug is a novel synthetic imidazoquinolone that binds cell surface receptors of Toll-like receptor (TLR)-7 and TLR-8. Imiquimod promotes innate and acquired immune responses via secretion of cytokines (e.g. IFNα, IFNγ, TNFα, IL-1, IL-6, IL-8, IL-10, IL-12), and activation of Th-1 cell-mediated immunity. This cytokine-induced immune response is responsible for the antiviral and antitumor effects of imiquimod. Imiquimod also stimulates natural killer cells and the proliferation of B-lymphocytes. It activates Langerhans cells, the key antigen-presenting cell of the skin, and promotes their migration to regional draining lymph nodes.[26] Responses provide long-term immune memory and could potentially offer future protection against the previously encountered tumor cells. Imiquimod has also been shown to promote the expression of cellular receptors associated with apoptosis.[27,28]

The clinical effects of imiquimod are primarily localized to the skin, and percutaneous absorption into healthy skin is minimal. In addition to its original indication for external genital warts, it has been approved by the FDA for use in actinic keratoses and superficial BCC. The recommended dosing for superficial BCC is 5 days per week for 6 weeks, and studies have demonstrated that this regimen provides an 88% histologic clearance rate.[29,30]

Occasional brisk reactions can occur, and if the patients develop excessive erythema, burning, impetigo or tenderness at the treatment site (Figure 6), rest periods are recommended. The clinical development of local inflammation, however, seems to correlate with the success rate; therefore, some degree of local reaction is desirable. Rare systemic complaints associated with extensive topical application include fatigue, myalgia, arthralgia, and lymphadenopathy.[29,30]

Several studies have shown that imiquimod can also be effective against nodular BCC, requiring application at least 5 times per week for 6–12 weeks, although the clearance rates are low at 71–76%. Imiquimod monotherapy for nodular BCC produces lower clearance rates than other modalities such as excisional surgery, MMS, or C and E;[31–33] however, when imiquimod is used after initial treatment with curettage or with C and E, the clearance rates are greater.[34,35]

Imiquimod has demonstrated promise in off-label use for other types of NMSC including Bowen's disease, a type of SCC *in situ* that presents as a slow growing, well-demarcated erythematous plaque. In one study of 16 patients with Bowen's disease located on the legs and shoulder, a 93% clearance rate was achieved.[35] Patients were treated with the same imiquimod regimen as was used for superficial BCC.[36] Two studies report the successful treatment of *in situ* SCC lesions on the penis using imiquimod The treatment regimen used in the first study involved 11 days of therapy repeated in 2 cycles, while imiquimod was given 3 times a week for 12 weeks in the second study. No clinical recurrence at 18 months after therapy was noted.[37,38]

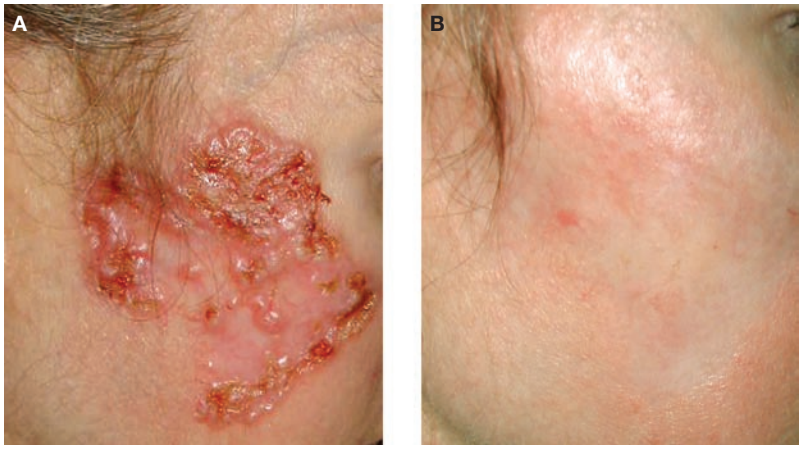

Figure 6 Treatment of a basal-cell carcinoma with imiquimod. (**A**) A young woman being treated with imiquimod for a superficial basal-cell carcinoma on the cheek. (**B**) Six months after treatment the erythema within the area has cleared with no residual tumor and leaving a cosmetically acceptable result.

PHOTODYNAMIC THERAPY

Photodynamic therapy involves the application of a photosensitizing compound to the skin that preferentially accumulates within the tumor cell and is then activated by a light source. Photodynamic therapy is effective in treating SCC *in situ* and superficial BCCs. Compounds used in this manner include the photosensitizing porphyrin 5-aminolevulinic acid (ALA) and the methyl ester of ALA (mALA), both of which are converted to protoporphyrin IX once absorbed into the skin. Protoporphyrin IX is an endogenous photosensitizer that accumulates in the intracellular membranes of organelles, such as lysosomes and mitochondria, after an incubation period of several hours. Protoporphyrin IX becomes activated to a higher energy level by exposure to a light source in the 450–750 nm wavelength range. Reactive-oxygen species including singlet oxygen are then generated, causing apoptosis and damage to tumor cells.[39,40] Patients experience stinging, burning, and itching, and the treated areas become erythematous, scaling, and crusted after light activation of the photosensitizer. Since the tumor cells of epithelial origin are preferentially photosensitized, the damage to surrounding tissue is limited, and cosmesis after healing is usually excellent.

The depth of penetration of the photosensitizing agent can limit its effectiveness against thicker tumors. Photodynamic treatment of nodular BCC using mALA has demonstrated complete responses in 90% of patients, with 74% remaining clear after 2 years.[41] In a second study examining the use of photodynamic therapy in Bowen's disease, 88% of patients had a complete response and 82% remained disease-free after 1 year.[42] Although the cosmesis of areas treated by photodynamic therapy was favorable compared with surgical excision, careful long-term follow-up is necessary because of the higher recurrence rates.

Photodynamic therapy can be a useful nonsurgical treatment of superficial NMSCs although the recurrence rate with this technique is high. One review showed immediate clearance rates of up to 100% for superficial BCC and SCC *in situ*; the reported recurrence rates were 0–31% for superficial BCCs and 0–52% for SCC *in situ*.[39] Photodynamic therapy is limited by the depth of penetration of the topical photosensitizers and should not be used to treat thick tumors, tumors with certain aggressive histologic subtypes (e.g. morpheaform BCC) or recurrent cancers. When the compound is activated by red light, pain can be a limiting factor, and the treatment modality does not offer histologic margin control.[43]

RETINOIDS

Systemic retinoids that are derivatives of vitamin A have a proven chemopreventative effect in reducing the risk of developing SCC and BCC. The mechanism of action is thought to occur via induction of apoptosis, impedance of tumor proliferation, or stimulation of differentiation during the tumor-promotion phase of carcinogenesis.[44] Oral retinoids might decrease the morbidity associated with multiple primary tumors and might reduce the risk of death in patients with high-risk cancers. It is often prescribed for transplant patients who develop numerous SCCs due to immunosuppression.[45] Systemic acitretin has been shown to decrease actinic keratoses in renal-transplant patients;[46] however, one study of 26 renal-transplant recipients showed a similar number of malignancies in patients taking a maintenance dose of 0.2 mg/kg/d acitretin, despite a decrease of almost 50% in actinic keratoses.[47] Acitretin can cause side effects such as cheilitis, hair loss, and xerosis, and patients should, therefore, be started on a low dose of the medication and the dose increased gradually according to the patient's tolerance. A suggested regimen is an initial 10 mg daily dose of acitretin, which is increased every 2 to 4 weeks until the patient is on a maintenance daily dose of 25 mg. If the patient develops significant side effects, maintenance on a lower dose of the medication is recommended.[45] Hyperlipidemia can be a limiting factor in many patients. The chemopreventative effect ceases upon discontinuation of the medication and tumor burden may return to pretreatment levels. The adverse effects of retinoids and the necessity of laboratory monitoring limit their use to only high-risk patients. These agents are typically not effective in treating existing tumors.[21,45]

CONCLUSIONS

NMSC continues to increase in prevalence. Treatment options employed should be tailored to the type of tumor, tumor location, size of tumor, and histologic pattern. Surgical methods remain the 'gold standard' although alternatives to surgery are appropriate in certain tumors if considerable disfigurement or functional impairment might result from surgery. In addition to longstanding nonsurgical options such as radiation therapy and cryosurgery, the newer additions of biologic immune response modifiers (e.g. imiquimod) and photodynamic therapy can be used in select tumors and can reduce morbidity.

KEY POINTS

- The incidence of nonmelanoma skin cancer (NMSC) continues to increase, and it is estimated that 20% of Americans will develop this type of cancer during their lifetime
- The 'gold standard' for treating NMSC is Mohs micrographic surgery, although other surgical modalities such as excision or curettage and electrodesiccation are often very effective, less expensive, and can be the treatment of choice in certain circumstances
- Radiation therapy is an effective treatment option, although side effects of this method and the cost limit its usefulness to cases involving nonsurgical candidates
- Newer immune-modulating agents such as imiquimod have proven effective for treating superficial variants of NMSC and can be used in instances when other methods would be difficult to perform or where cosmesis is important
- Photodynamic therapy is an emerging treatment for superficial NMSC, although it should not be used for thicker tumors

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JA Neville has declared associations with Graceway Pharmaceuticals. See the article online for full details of the relationship. The other authors declared no competing interests.