The management of non-melanoma skin cancer

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Non-melanoma skin cancer is an increasingly common problem with a diversity of aetiologies as well as treatments. This article describes the clinical sub-groups and discusses potential management strategies as determined by best clinical practice and patients' individual needs.

The most common human cancers comprise basal cell and squamous cell carcinomata, collectively known as non-melanoma skin cancers (NMSC). Although metastatic disease is unusual, particularly with basal cell carcinoma, both tumour types may cause significant local destruction and disfigurement. Early intervention with effective treatment minimizes complications and maximizes cure rates, cosmetic results and patient satisfaction.

BASAL CELL CARCINOMA (BCC)

BCC is the most common malignancy among caucasians worldwide (Zak-Prelich et al, 2004), but it rarely occurs in dark-skinned races (Wong et al, 2003). The most prominent risk factor for the development of BCC is exposure to ultraviolet radiation (UVR), which causes DNA damage and immunosuppression. A history of childhood exposure is important in determining adult risk of BCC, especially in those who have fair skin, red and fair hair, blue-green eyes and a history of sunburn or freckling at an early age (Kuijpers et al, 2002). Other less common aetiological risk factors include exposure to ionizing radiation (either occupationally or therapeutically) and chemicals such as arsenic – previously found in some medicinal products such as over-the-counter 'tonics'. Rare genetic disorders, such as naevoid basal cell carcinoma syndrome (Gorlin's syndrome, whose features include palmo-plantar pitting, mandibular cysts, cataract formation and multiple BCCs), are also implicated (Kuijpers et al, 2002).

There are several sub-types of BCC. Their clinical appearance is variable and in some cases may cause diagnostic confusion (*Table 1*).

Nodular or nodulocystic BCC ('rodent ulcer') is the most common type of BCC and presents as a pearly telangiectatic papule usually on the

TABLE 1.
Clinical features and differential diagnoses of the various subtypes of basal cell carcinoma (BCC)

BCC tumour subtype	Clinical features	Differential diagnosis
Nodular	Usually presents on the head and neck in those over 60 years. Appears as a pearly, pink, papule or nodule with overlying telangiectasia	Depends on stage of evolution but consider basal cell papilloma, simple inclusion or epidermal cyst, molluscum contagiosum and intradermal naevus
Superficial	Usually truncal in slightly younger age group. Atrophic slightly scaly patch with a vague raised edge	Innocent appearance and lack of symptoms lead to confusion with psoriasis, discoid eczema, fungal infection or Bowen's disease
Morphoeic	A rarer histological subtype which usually occurs on the head and neck. Indurated, flat, yellowish, scar-like lesion with poorly-defined edges	May be mistaken for a simple scar or localized scleroderma
Pigmented	Similar features to nodular and superficial BCC. Small foci of pigment may be noted in a pearly nodule or more diffuse pigmentation may make whole lesion appear brown or black	This type may mimic an intradermal naevus or if darkly pigmented, a basal cell papilloma or malignant melanoma

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head, face or neck (McCormack et al, 1997). Central ulceration creates a rolled edge, which gradually disappears as the tumour invades deeper structures, causing tissue destruction and disfigurement (*Figure 1*). Nodular BCCs may bleed with minor trauma.

Superficial BCC predominantly affects the trunk and upper and lower limbs (McCormack et al, 1997). It appears as a mildly-elevated pink plaque with a raised edge and well-defined boarder and is often multiple (Wong et al, 2003). The patient may not experience any symptoms and this type of BCC may be mistaken for an innocent patch of psoriasis or discoid eczema (*Figures 2–3*).

Morphoeic BCC can occur at any site, although it is more common on the head and neck (Kuijpers et al, 2002). These lesions present as an elevated smooth plaque, which is similar in appearance to a scar. A pearly colour and telangiectasia are important features. Their poorly-defined borders and their aggressive natural history make excision under direct vision technically difficult and there is a higher risk of local recurrence (*Figure 4*) (Wong et al, 2003). Morphoeic BCC can be difficult to diagnose and often present late (Wong et al, 2003).

Pigmented BCC has similar features to the superficial and nodular subtypes, but with a brown or black pigmentation. These lesions may resemble melanoma clinically, but their natural history is much more innocuous (*Figure 5*) (Wong et al, 2003).

Figure 2. Superficial basal cell carcinoma: well demarcated red scaly plaque often with a pearly border.

SQUAMOUS CELL CARCINOMA (SCC)

SCC is a skin malignancy which shares aetiological risk factors with BCC, but which is also known to be associated with immunosuppression, especially in transplanted organ recipients, with oral psoralens + UVA (PUVA) therapy and with genetic syndromes, such as oculo-cuta-

Figure 1. A typical nodular basal cell carcinoma with a rolled pearly edge and surface telangiectasia.

Figure 3. Plaque of psoriasis with diffuse silvery scale may mimic a superficial basal cell carcinoma.

sis (AK), the incidence of which reflects that of SCCs (Schmook and Stockfleth, 2003). Typically, AK patients are fair-skinned with a history of excessive sun exposure and AKs are often rough, scaly and more easily palpated than seen (*Figure 7*) (Cockerell, 2003). AK lesions may be multiple and thickened, and may lead to the development of a cutaneous horn or 'hypertrophic' AK (Cockerell, 2003). Any clinical change should prompt biopsy because of the risk of AKs developing into SCC.

Cutaneous SCC *in situ* (Bowen's disease) comprises full-thickness intra-epidermal carcinoma which is typically indolent, grows slowly over a number of years and seldom progresses to invasive carcinoma (SCC). Lesions are usually well-demarcated, solitary and scaly plaques, which may be flat, papular, nodular or verrucous. Lesions can resemble psoriasis, eczema or superficial BCC (*Figure 8*) (Arlette, 2003).

Figure 4. Morphoeic basal cell carcinoma: elevated smooth plaque with poorly-defined pearly border.

MANAGEMENT OF NON-MELANOMA SKIN CANCER

Management of NMSC ranges from simple advice to complex and innovative treatments, such as topical immune-modulating drugs and photodynamic therapy (PDT). In making a choice of therapy, different factors should be taken into consideration, such as histological type and size of the lesion, as well as patient-dependent factors, such as age and the general health of the patient (Kuijpers et al, 2002). All should aim to maximize disease control and minimize patient discomfort and disfigurement (*Table 2*). Occasionally metastasis occurs with SCC. Such cases should be referred to an oncologist for consideration of chemotherapy.

PREVENTION

Sun protection

Although sun protection is essential in preventing NMSC, those who are immuno-suppressed, i.e. organ transplant patients, or those with a previous history of NMSC, should be especially vigilant and should receive strict advice on sun avoidance,

Figure 5. Pigmented basal cell carcinoma with a pigmented rolled border. This may clinically resemble a malignant melanoma.

wearing of protective clothing and the use of high factor UVA and UVB sunscreens on the lips and exposed skin surfaces. Following transplant surgery, annual examination with prompt excision of suspicious lesions is recommended.

THERAPEUTIC INTERVENTION

Surgery

Excision is a safe and effective treatment for NMSC and is the gold standard therapy for SCC and BCC, especially recurrent lesions or those which present on high-risk sites. Surgery provides good cosmetic outcomes and allows excision margins to be examined histologically for tumour clearance and further action taken as required (Kuijpers et al, 2002).

Mohs micrographic surgery (MMS) is a specialized technique which is used primarily to treat morphoeic, nodular and recurrent BCCs. It offers high cure rates for difficult tumours, at the same time allowing maximal preservation of normal tissue (Kuijpers et al, 2002).

MMS is the mainstay of therapy for lesions where there is sub-clinical extension invisible to the naked eye as it involves serial resection and histological examination of tissue until all margins are clear. Overall, 5-year cure rates are estimated at 99% and 95% for primary and recurrent BCCs, respectively (Wong et al, 2003).

Figure 6. Squamous cell carcinoma may present as a keratotic papule on a sun-exposed site.

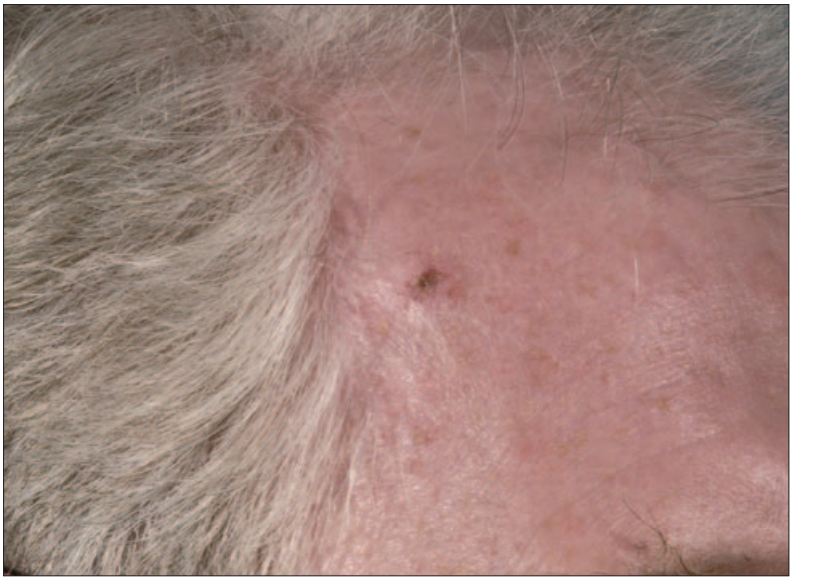

Figure 7. Actinic keratoses are often rough and scaly. They are more easily palpated than seen.

Ablative treatment

Cryotherapy with liquid nitrogen is a quick, easy and inexpensive procedure which is useful for small numbers of low-risk lesions such as AKs and Bowen's disease. It is also effective in the treatment of superficial BCCs and may be used in

TABLE 2.
Therapeutic options for non-melanoma skin cancer

Treatment	Indications	Limiting Factors
Preventive		
Sun avoidance and topical sun blocks	All patients	Patients' understanding of aetiological factors and compliance with recommended measures
Annual skin inspection	Transplant recipients on immunosuppressive treatment	
Interventional		
Surgical		
Excision	SCCs, all BCCs particularly in high risk sites and recurrent BCCs	Gold standard, but scarring inevitable
Mohs micrographic surgery	Morphoeic, nodular or recurrent BCCs particularly in high risk sites	Mohs technique not widely available, expensive set up
Ablative		
Cryotherapy curettage	Superficial or small nodular BCCs, AKs and Bowen's disease	Not suitable for high-risk sites such as central face. Difficulty in interpreting histology if tumour curetted
Topical	Superficial BCCs, AKs and Bowen's disease	Local inflammation/ulceration may limit duration of compliance
Other		
Photodynamic therapy	Single or multiple superficial BCCs, AKs or Bowen's disease	Time-consuming and may cause local discomfort
Radiotherapy	Useful as adjuvant therapy or if surgery contraindicated	Radiation dermatitis
Chemotherapy	Consider in presence of metastases	

AK = Actinic keratosis, BCC = Basal cell carcinoma, SCC = Squamous cell carcinoma

small, low-risk nodular BCCs with remission rates reaching 70% (Schmook and Stockfleth, 2003). Unfortunately, it may damage surrounding healthy tissue and the cosmetic effect is therefore dependent on the skills of the operator. Short-term side effects include pain and blistering but, in the long term, there may be pigmentary changes, ulceration, scarring and permanent loss of hair at treated sites (Kuijpers et al, 2002). Cryotherapy may be suitable for those for whom surgery is contraindicated or unacceptable.

Curettage and cautery is suitable for small, low risk tumours, such as superficial BCC, AK and Bowen's disease, but are generally unsuitable for SCC. This treatment involves scraping away tumour bulk under local anaesthesia and arresting bleeding with electrocautery. Advantages include the avoidance of surgical repair, especially if lesions are large, or if patients are frail debilitated or unlikely to tolerate surgery. Cosmetic outcomes with this method are generally good and tend to improve with time (Kuijpers et al, 2002). Curettage is not recommended for lesions at high-risk sites, such as the central face, and perhaps its main disadvantage is the inability to interpret tumour margins histologically by virtue of the tissue damage sustained during treatment.

Figure 8. Bowen's disease is usually a well demarcated solitary scaly plaque.

Topical agents

Topical therapy is well suited to the treatment of low-risk, multiple, superficial BCC on the trunk and limbs and for AK. These agents are less widely used than surgical procedures, but offer an alternative to surgery in some patients.

A topical anti-metabolite, 5-fluorouracil (Efudix®, 5-FU), is a cream which can be used in the management of multiple superficial BCCs on the trunk and limbs where it is up to 95% effective. However, it is less effective in other types of BCC and in AK (Bader, 2004). Use of 5-FU may be limited because of tumour recurrence (Bath et al, 2002). The dosing regimen can be variable, but it is usually used twice a day for 2 weeks with a rest period of 2 weeks, and then repeated again for another 2 weeks. Results can vary widely and use is not recommended on the head or neck. Local effects include pain and ulceration.

Imiquimod (Aldara®) cream is an emerging immuno-modulating agent originally approved for the treatment of genital and peri-anal warts and now for small superficial BCC. It stimulates both the innate and adaptive arms of the immune system, enhancing immune function and providing a useful therapeutic option for the management of selected cutaneous malignancies, particularly superficial BCCs (Miller et al, 1999). Although not yet approved for the treatment of AK, there are promising results for the management of 'field cancerization', where multiple AKs are indistinguishable from one another and must be collectively assessed as a complete area of cancer (Schmook and Stockfleth, 2003).

Imiquimod is also useful for superficial BCC lesions occurring on sites where slow healing or surgical closure may be a problem. Adverse effects include inflammation, crusting and redness at the site of application, but this settles within a few days of treatment withdrawal. Although unpublished interim results of ongoing clinical trials have demonstrated high-sustained rates of clinical and histological clearance of superficial BCC with imiquimod (93% after 1 year) (Gollnick et al, 2003), long-term follow-up studies and future clinical trials are needed to establish clearance rates beyond this.

Diclofenac sodium (Solaraze®) gel is licensed for the treatment of AKs. Patients should be advised to apply treatment for 60–90 days and therapeutic benefit may not be evident until after stopping.

Other treatments

PDT is suitable for the treatment of superficial BCC, AKs and Bowen's disease. PDT is a relatively new treatment comprising a 2-step process: the application of a light-activated substance (delta-aminolevulinic acid or its methyl ester, Metvix®), followed by exposure to a red light source which stimulates its activation. Delta-aminolevulinic acid is a precursor for the formation of protoporphyrin IX (PpIX), a photosensitizer produced in larger quantities by tumour than by normal tissue. When cells containing PpIX are irradiated with red light in the visible spectrum, cytotoxic singlet oxygen is formed and cell death follows. The technique is non-invasive and yields an excellent cosmetic result (Kuijpers et al, 2002).

Although results for superficial BCCs, AKs and Bowen's disease are promising, its utility may be limited by local pain, stinging or burning (Schmook and Stockfleth, 2003). It is also time-consuming as the cream must be left on the area to be treated for 3 hours before exposure to the light source (Schmook and Stockfleth, 2003). PDT is a relatively recent development and, as there is a lack of prospective clinical trials and standardized treatment protocols, its response rates cannot be compared with cure rates for other treatment modalities (Kuijpers et al, 2002).

Radiotherapy is an established treatment which can be used to treat BCC and SCC, but is now not routinely used, except in treatment failures or as an adjuvant therapy for tumours with perineural extension where recurrence rates are likely to be high. Local side effects include radiation dermatitis and alopecia (Kuijpers et al, 2002; Schmook and Stockfleth, 2003).

CONCLUSIONS

The rapid rise in incidence of NMSC is becoming an increasing problem for an already overstretched health-care system. The first priority in the battle against skin cancer should always be primary prevention, and patient education should always play a key role in any management strategy for the disease. While surgery remains the gold standard of treatment for many NMSCs, as patients are now tending to develop multiple lesions at younger ages (Kuijpers et al, 2002), the future is likely to see an increasing demand for effective non-surgical treatments. Although more evidence for the long-term clearance rates of these new treatments, such as PDT and imiquimod is still needed, they are likely to play a growing role in the management of NMSC. HM

Conflict of interest: Dr Gupta has served as a consultant and received honoraria from 3M pharmaceuticals. In addition, he has received support from 3M and Galderma for ongoing clinical trials.

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KEY POINTS

- The incidence of non-melanoma skin cancer is increasing worldwide and, although mortality rates are low, there is considerable associated morbidity.
- The single most important aetiological risk factor is ultraviolet radiation exposure, and all possible steps should be taken to increase public awareness and to encourage sun avoidance.
- Basal cell carcinoma is the most common human cancer, but developments in the field of transplant surgery have led to an increase in squamous cell carcinoma in organ recipients receiving long-term immunosuppressive therapy.
- Management of lesions is directed at achieving maximum cure rates with minimum cosmetic disfigurement.
- Choice of treatment is dependent on tumour type, site of involvement and the individual needs of each patient.
- New topical agents appear promising and may obviate the need for invasive surgery.