

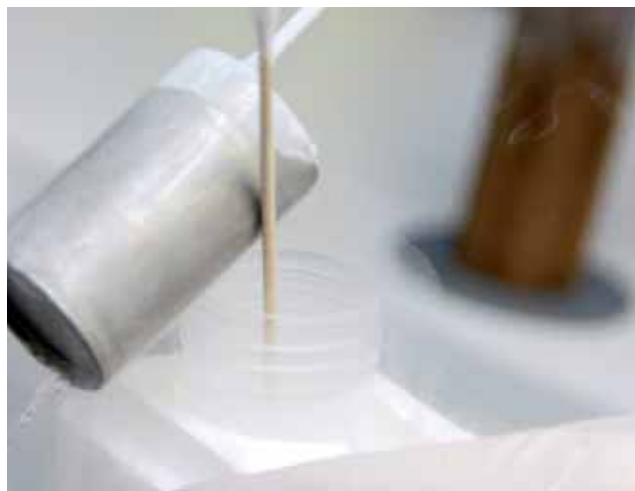
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# Skin cancer

## — surgical and medical management

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Each year, an estimated 60,000 new cases of skin cancer are reported in England and Wales.<sup>1</sup> This article summarises the recommendations for the management of the most common types of skin cancer



Liquid nitrogen being poured from a metal spoon into a pot, for use in cryotherapy. This technique is widely used in skin cancer treatment.

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**S**kin cancer is a significant worldwide health issue. Increasing rates of precancerous and cancerous lesions are being reported — not just in tropical or “sunny” countries, but also in temperate countries such as the UK.

The Australian state of Queensland has the world’s highest incidence of all types of skin cancer.<sup>2</sup> Consequently, the country’s medical services have pioneered a number of good practice initiatives that have influenced the practice standards in other countries. This article will summarise the management of three of the most common forms of skin cancer.

### — Site of care

The way in which patients with skin cancer are reviewed and managed varies widely across the UK.

In general, patients with precancerous lesions or basal cell carcinomas (BCCs) are managed in primary care, while most patients with squamous cell carcinomas (SCCs) or malignant melanomas are managed in secondary or tertiary care. However, this is not always the case and

there is some concern that the level of audit (eg, record keeping) for treatment in primary care is not adequate.

**NCCC guidelines** In an attempt to ensure that all patients with skin cancer in England and Wales are treated to the same standard, and to ensure a complete audit of outcomes, the National Collaborating Centre for Cancer (NCCC) has issued guidelines for the management of patients with skin cancer.<sup>3</sup> These guidelines recognise that some types and stages of skin cancer require treatment by a specialist, whereas others can be treated in general practice.

A structured approach to patient care is recommended, as is the development of cancer networks that comprise two levels of multidisciplinary teams:

- Local hospital skin cancer multidisciplinary teams (LSMDTs)
- Specialist hospital skin cancer multidisciplinary teams (SSMDTs)

The guidelines recommend that LSMDTs should be developed at district general hospitals and link with health professionals working in skin cancer care in the primary sector. SSMDTs should be based at larger hospitals to manage patients with rare or invasive skin cancers, which are associated with greater risk of morbidity and mortality.

The guidelines also say that there must be co-ordination between the two teams to ensure continuity of care and avoid delay in patient treatment. Panel 1 (p48) shows some examples of the cases that the NCCC recommends should be handled by LSMDTs and SSMDTs.

**Australian approach** In Australia, GPs excise more skin cancers than specialists and studies suggest that they treat and refer cases of skin cancer appropriately.<sup>2,4</sup> It has also been noted that GPs are increasingly using complex surgical procedures, especially in Queensland. In recent years, primary care skin cancer clinics have developed, which have been found to have similar diagnostic accuracy to GPs.<sup>5</sup>

### — Initial investigation

As described in the first article of this **Special Feature** (p39), the initial investigation of suspect lesions usually involves visual inspection. The lesion may then be removed if necessary, either to treat the condition or for histological diagnosis.

Dermatoscopy has proved beneficial in distinguishing between malignant and benign lesions, and studies have shown a greater diagnostic accuracy than for ordinary visual examination. However, training is required to interpret dermatoscopy results.

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## Panel 1: National Collaborating Centre for Cancer recommendations for referring patients with skin cancer

Guidelines from the National Collaborating Centre for Cancer suggest that multidisciplinary teams (MDTs) are set up in district general hospitals to deal with routine skin cancer patients and engage with primary care providers. In addition, MDTs in specialist hospitals should be set-up to deal with more rare or serious skin cancers. This would ensure that resources and expertise are matched with patient need, while allowing low-risk conditions to be managed close to the patient's home.

Patients who could be treated at district general hospitals include those who:

- Develop a squamous cell carcinoma (SCC)
- Develop a basal cell carcinoma (BCC)
- Develop a primary malignant melanoma
- Are suitable for treatment with Mohs surgery (see p51)
- Have a discrepancy between their clinical diagnosis and histopathology

Patients who should be treated at specialist centres include those who:

- Develop a high-risk SCC with possible difficulties in management
- Develop a BCC that has become metastatic
- Develop multiple, malignant melanomas
- Develop a melanoma whilst under 19 years of age
- Are eligible for entry into clinical trials

Biopsy is usually only required if the diagnosis cannot be confirmed after visual inspection, or if a non-melanoma skin cancer (NMSC) is to be treated using a method other than excision.

### — Staging

Cancer staging systems describe how far a cancer has spread through the body. They attempt to group patients who have a similar prognosis and likely treatment plan. Patients with NMSC tend not to undergo formal staging, other than standard diagnostic testing and an examination to determine the presence of regional lymph node involvement.

For patients with malignant melanoma, extensive investigation and staging is necessary.<sup>6,7</sup> The American Joint Committee on Cancer (AJCC) staging system is usually recommended. This system is based on the "TNM" classification, which is explained in Panel 2 (p50). The AJCC staging system is composed of five stages:

- Stage 0 (melanoma is contained within the epidermis)
- Stages I and II (tumour has spread to the surrounding tissue)
- Stage III (regional lymph node or satellite metastases)
- Stage IV (distant metastases)

Tumour thickness is also a key prognostic factor for melanoma and a major indicator of the chance of survival. The effect of tumour thickness on survival rate is outlined in Panel 3 (p50).

Once the stage of the cancer has been determined, the most appropriate treatment can be recommended.

### — Surgical excision

Surgery is the most common method used in the management of BCC, SCC and malignant melanoma. It is considered the "gold standard" treatment against which other treatments are compared.<sup>3,8</sup> This is because surgery offers a high rate of cure with rapid healing, provides a complete specimen for histological examination and diagnostic confirmation, and usually results in an acceptable cosmetic and functional result. However, surgery does carry a risk of causing haematoma, postoperative infection, damage to neurovascular structures or cosmetic deformities (eg, variations in pigmentation, scarring).

To minimise this risk, excisions that are likely to result in cosmetic or functional defects, or those that require specialised reconstructive techniques, should be referred to a skin cancer specialist. The correct technique for performing a surgical excision of a skin tumour is discussed in Panel 4 (p50).

**Margins of surgical excision** To ensure complete excision and optimise cure rates, the tumour is removed along with an area of healthy tissue that surrounds it. The quantity of healthy tissue to be removed is expressed as the margin between the visible tumour border and the incision point of the surgeon's knife. The margin that is used differs according to the type of skin cancer.

For a BCC, a margin of 2–5mm is recommended, with the final decision being based on the type, size and location of the tumour and the experience of the doctor who performs the excision. For small tumours that are not located on the face, a margin of 3–4mm is recommended.

The surgical management of SCCs is similar, but more radical than for BCCs. This is because SCCs are usually more aggressive and have a greater potential for recurrence and metastasis, therefore a total excision should be histologically confirmed.

The recommended margins are 2–10mm — dependant on the size of the tumour. For example, a well differentiated lesion that is less than 2cm in diameter can be successfully excised using a 4mm margin in 95 per cent of cases, whereas a tumour that is larger than 2cm in diameter requires a margin of up to 10mm to obtain a similar cure rates.

Re-excision must be performed if histological examination proves that the initial margins were inadequate.<sup>3,6</sup>

Australian guidelines suggest a minimum margin of 10mm for all invasive melanomas to decrease the risk of local recurrence, although there is no evidence that this minimum will offer any additional chance of survival.

Where tissue flexibility is limited (eg, face, foot or ankle), a skin graft or flap repair is sometimes necessary to repair an adequate margin of removal.

**Indications for excision** BCCs rarely metastasise, so the majority can be cured by excision — the five year cure rate is estimated at 90–98 per cent.<sup>8</sup> Similar cure rates have also been seen for the total excision of SCCs.

Excision with histological examination of the excised specimen to confirm success is the first-line treatment for malignant melanoma. All melanomas can potentially recur or develop metastases, so the lymph nodes should be examined for evidence of metastases during every follow-up clinic appointment.

### — Alternatives to surgery

The other common treatment options used in the management of skin cancers are:

- Curettage and cauterly
- Cryotherapy
- Topical drug therapy (5-fluorouracil and imiquimod)
- Photodynamic therapy
- Mohs surgery
- Radiotherapy
- Systemic (adjuvant) chemotherapy

**Curettage and cauterly** One technique for removing small tumours involves using a curette (a small, spoon-shaped surgical instrument) to remove the soft material from the tumour. The base of the tumour is then electrically cauterised or burned to destroy any remaining tumour cells.<sup>3,8</sup> This process may need repeating up to three times.

This technique is safe and well tolerated, however, it may be difficult to assess the necessary margins to ensure that the tumour

## Panel 2: TNM classification for staging skin cancers

Skin cancers are classified into stages of development in order to determine a suitable treatment option.

The American Joint Committee on Cancer staging system uses a TNM classification.<sup>7</sup> Within this system:

- T describes the extent of the primary tumour — measured using tumour thickness and the presence of ulceration
- N describes the extent of regional lymph node metastases — measured using the number of regional lymph nodes with metastases and the tumour burden of these nodes
- M describes the extent of distant metastases in other organs — measured using the anatomical site of distant metastases and serum lactate dehydrogenase level

has been completely removed. To ensure optimal results, good technique and specialist training are required.

This technique is not appropriate for use on thin skin (eg, the eyelids, lips or genitalia), and its use on the face is restricted by the risk of unpredictable cosmetic results.

**Indications** Anecdotally, curettage and cautery is regarded as effective for superficial BCCs on the trunk and limbs, especially on the legs of older patients as an alternative to skin grafting. It tends to be used to treat small primary BCCs (less than 10mm in diameter) and solar keratoses. It can also be used on anticoagulated patients and on patients who have multiple lesions.

Curettage and cautery is not considered the treatment of choice for SCC, however there are some data to support the procedure. It is thought that with an increasing number of organ transplant patients developing large numbers of SCCs, the use of this technique may be of value when surgery is impractical.

**Cryotherapy** The destruction of tissue by direct application of a very low temperature agent (eg, liquid nitrogen) is termed cryotherapy. It offers an alternative treatment option for patients who:

- Are elderly
- Are deemed to be at high risk of surgical complications
- Refuse surgery

Cryotherapy is a rapid, widely used and cost-effective technique for the treatment of solar keratoses, Bowen's disease, primary

superficial BCCs and small, primary, well-differentiated SCCs.<sup>8</sup>

It is contraindicated on cosmetic sites (eg, the face in young patients), parts of the body where it is difficult to assess the depth of tumour penetration (eg, head and neck) and in high risk tumours (ie, those that are at high risk of metastasising or recurring).

**Topical 5-fluorouracil** 5-fluorouracil is an antimetabolite that inhibits DNA and RNA synthesis to destroy rapidly proliferating cells.

Clinical response during therapy is indicated at the site of application by the sequential development of erythema followed by vesiculation, tenderness, erosion, necrosis and then epithelialisation. The course of therapy should be discontinued when the reaction reaches the stage of erosion and necrosis or if ulceration occurs.

This sequence may appear unsightly and be uncomfortable for the patient, both during therapy and for several weeks afterwards, and may leave a smooth, pink spot after healing is complete.

The main counselling points for patients who are prescribed 5-fluorouracil cream are outlined in Panel 5 (p51).

Topical 5-fluorouracil is indicated for the treatment of solar keratoses and superficial BCCs, although in most patients other treatments are generally preferred. It should not be applied to easily irritated areas, such as the skin around the eyes.

**Topical imiquimod** Imiquimod is a nucleoside analogue that acts as an immune-response-modifying agent. It stimulates the innate and cell-mediated immune responses to viruses and tumours, ultimately leading to tumour cell destruction.<sup>9</sup> This effect occurs mainly at the site of administration, although some systemic effects have been reported after topical administration.

The application of imiquimod cream (either five times a week or daily) for six to 12 weeks has shown clearance rates of 79–87

## Panel 3: The effect of tumour thickness on survival rate for melanoma patients

Thickness of tumour (mm)	10 year survival rates
Tumour contained within epidermis	100%
Less than 0.75	97.9%
0.75–1.5	90.7%
1.5–3.0	75.4%
3.0–4.0	55.0%
Greater than 4.0	40.0%

## Panel 4: Correct technique for the surgical excision of a skin tumour

The recommended technique for excision is to remove an ellipse-shaped section of skin from around the lesion with a length-to-width ratio of 3:1 or 4:1.<sup>8</sup> The length axis of the ellipse should be in line with local skin creases or the line of least skin tension.

The skin should be cut with a blade at 90 degrees to the skin. The depth of incision should be sufficient to reach the uninvolved subcutaneous fat that is beneath the tumour.

The wound is then closed with nylon or polypropylene sutures, which are left in place for 5–14 days, depending on the level of skin tension at the suture site. All resected tissue should then be sent for histological evaluation.

per cent in patients with superficial BCCs.<sup>10</sup> However, 10-year cure rates are unknown.

Common side effects following topical administration of imiquimod include local erythema, flaking of the skin, erosion, scabbing and crusting. If these effects are severe or cause discomfort, a rest period of several days may be beneficial. Some patients (less than 10 per cent) experience systemic side effects such as headache, fatigue, myalgia and nausea. The main counselling points for patients who are prescribed imiquimod cream are outlined in Panel 6 (p52).

Imiquimod is indicated for the treatment of external anogenital warts, small superficial BCCs and solar keratoses.

**Photodynamic therapy** The combination of light therapy with methyl aminolevulinic acid cream (a topical photosensitising agent) can be used to treat skin cancer. When activated by light, the photosensitising agent produces reactive singlet oxygen atoms that can destroy tumour cells.

Photodynamic therapy (PDT) has a low incidence of side effects and a good cosmetic outcome.<sup>3</sup> However, it is also expensive and requires the patient to be available for three to four hours to receive treatment. Also, there is currently little information on long-term cure rates.

Treatment consists of two sessions that are delivered one to four weeks apart. Although multiple lesions may be treated at the same time, the decision to treat will depend on the location of the lesion, the patient's pain tolerance and a comparison of cost-effectiveness with other treatment options. The lesion receives an application of cream three hours before it is exposed to the light source.

## Panel 5: Counselling points for the use of 5-fluorouracil cream

5-fluorouracil cream should be applied twice daily, usually for three to six weeks (sometimes up to 12 weeks is necessary).

Patients should wash and dry the affected area before application. The cream should be applied with a cotton-tipped applicator or finger. If the finger is used to apply the cream, the hands should be washed thoroughly after application.

Common side effects include burning and stinging sensations, crusting, oedema, pain and erythema. The pain during and after therapy can be severe, so oral analgesics may be given one hour before light exposure. A local anaesthetic may also be used.

PDT may be used in the management of solar keratoses, uncomplicated SCC and superficial BCC.

**Mohs surgery** Named after Frederick Mohs who first described the technique, Mohs surgery involves the excision of a tumour in stages, with histological examination of the excised tissue after each stage.<sup>3</sup> This examination, which is completed using “frozen section”, mapping and staining techniques, allows the precise location of any residual tumour to be identified before the next stage of excision is performed.<sup>8</sup> This process is repeated until the area is totally free from tumour.

The main advantages of Mohs surgery are that it:<sup>11</sup>

- Ensures total tumour removal while minimising the loss of local tissue
- Has a high cure rate
- Can be performed without the need for a general anaesthetic

However, the technique can take several hours and is more expensive than conventional surgery.

Mohs surgery is typically used to excise tumours that are considered difficult to remove completely using standard surgical techniques or if there is a high risk of recurrence. This typically includes BCCs and SCCs that:

- Are located on the face or around the ears
- Have recurred after previous treatment
- Are large and poorly defined

**Radiotherapy** Reports suggest that radiotherapy has been used successfully to treat all stages of BCC and SCC, with results comparable to those for surgery.<sup>3,8</sup>

The course length for radiotherapy depends on the size of the tumour. For a

tumour that is less than 2cm in diameter, the patient will be required to attend four to twelve sessions of therapy over a period of two weeks. Larger tumours can require up to 30 sessions over three to six weeks.

Compared with surgery, the disadvantages of radiotherapy are:

- The time taken to complete treatment is longer, due to the need for several sessions of treatment
- The lesion takes longer to heal
- The technique yields no specimen for histological examination

Radiotherapy can also cause several side effects, which are either acute or long-term. Acute side effects include erythema, dry desquamation (skin peeling) and subsequent moist desquamation — due to a loss of epidermal cells. These effects occur two to three weeks after starting treatment and may take several days to resolve.

Long-term (permanent) effects may take months or even years to develop. These include atrophy, alopecia, loss of sweat-gland function, changes in skin colour and subcutaneous fibrosis. In rare cases, skin breakdown may result in the formation of a radionecrotic ulcer.

**Indications** Radiotherapy is generally not recommended in patients under 60 years of age, because the visible side effects can vary with time. Therefore, an initially favourable cosmetic result can potentially deteriorate. Surgery is preferred in these younger patients because it produces a more stable cosmetic result. Also, most patients with BCC or SCC present when the lesion is still small and therefore can be easily removed by surgery.

Radiotherapy may be considered for patients with multiple, superficial lesions that are impractical to excise, or for palliative care patients. It may also be considered for patients who wish to avoid surgery or where surgery would be mutilating or result in unacceptable loss of function.

Experimental and clinical studies indicate that melanoma is responsive to radiation, although higher doses are required to achieve successful response rates. Radiotherapy has a limited role in the management of primary melanoma, but may be useful in patients with lentigo maligna or to treat symptomatic metastases.

### Submitting articles to Hospital Pharmacist

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**Intralesional interferon** Interferons have antiproliferative, cytotoxic and immunostimulating effects, which are believed to be the basis of their antitumour activity.<sup>8</sup>

The use of intralesional interferon to treat NMSCs has been reported since the 1970s, but there are few randomised studies and it is not considered a first-line therapy.

Common side effects include mild “flu-like” symptoms, and swelling and erythema at the injection site. The concomitant use of oral paracetamol and the application of cold compresses may prevent or relieve these effects.

Intralesional interferon may be used to treat well defined, nodular or superficial BCC in patients who reject (or who are considered unsuitable for) surgery or radiotherapy due to the location of the tumour or the possibility of a poor cosmetic result.

In this scenario, the most effective regimen of interferon alpha-2b is 1.5m IU given three times weekly for three weeks.

**Adjuvant chemotherapy** Chemotherapy is often used for patients with metastatic melanoma in addition to other treatments, but no adjuvant therapy has been shown to increase overall survival in these patients.<sup>7</sup>

Interferon alpha seems to protect patients from recurrence during the treatment period and prolonged therapy seems to improve disease-free survival.<sup>12</sup> One study using high-dose interferon demonstrated an improvement in overall survival, but the follow-up period was short. The same improvement was subsequently not demonstrated in a follow-up study.

In the management of metastatic disease, systemic chemotherapy has not shown significant activity. Dacarbazine is considered the most active monotherapy, producing response rates of 12–20 per cent.<sup>13</sup> Other drugs used include cisplatin, the vinca alkaloids, temozolamide and fotemustine. Trials with these drugs are ongoing.

## Future developments

Evidence has shown that melanoma cells may be immunogenic, which has prompted research into the potential development of an antimelanoma vaccine.<sup>14</sup> So far, results are encouraging, but do not show clear-cut improvements in overall survival. Continuing research is seeking more specific antigens and better immunologic adjuvants.

Future developments in staging systems for the management of malignant melanoma are likely to involve the use of sentinel node biopsy (SNB).<sup>15</sup> This involves the removal and histological examination of the first lymph node that the by-products of a tumour drain into. SNB is likely to become the standard staging system for primary cutaneous melanoma.

## Panel 6: Counselling points for the use of imiquimod cream

Patients should make sure the affected area is clean and dry before the cream is applied. The application area consists of the lesion and a 1cm margin of surrounding skin. A thin layer of cream should be applied to the area and not washed off for six to 10 hours. The hands should then be washed thoroughly.

The cream should be applied once a day, on five consecutive days per week for six weeks. The response to treatment is then assessed after regeneration of the affected skin (usually six to 12 weeks after treatment is completed).

Imiquimod cream is supplied in single dose sachets. Anecdotally, some doctors recommend that any unused portion of the sachet can be retained for the next application. However the manufacturer recommends that the unused portion of the sachet is discarded. Patients should protect the treated area from sunlight and avoid using sunlamps. If a dressing is required, it should be non-occlusive.

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