

Managing  
**NON-MELANOMA  
SKIN CANCER**  
in primary care



**A focus on topical treatments**

*When a patient presents with a suspicious skin lesion the first step is to assess the likelihood of melanoma being present and then to provisionally identify the type of lesion. Surgical excision with histology is the first-line treatment for all skin cancer. It has the highest cure rate among available treatments. Referral, according to local guidelines, to a General Practitioner with a Special Interest (GPSI) in skin lesions, a Dermatologist, a Plastic Surgeon or an ENT Surgeon may be appropriate for patients with large lesions or lesions with an aggressive growth pattern. Patients with superficial basal cell carcinoma or intraepidermal carcinoma (squamous cell carcinoma in situ) may be safely managed with cryotherapy or topical treatments, i.e. fluorouracil or imiquimod creams, when excision is not appropriate because of the location of the lesion or due to cosmetic considerations. Topical treatments should not be considered if the diagnosis is uncertain.*

## **Skin cancer: Causes, risk factors and treatment**

Skin cancer is estimated to account for over 80% of new cancers in New Zealand each year.<sup>1</sup> The majority of these are non-melanoma skin cancers, i.e. basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). However, as BCC and SCC are not required to be reported to the New Zealand Cancer Registry the impact of these cancers on New Zealand communities is difficult to quantify. Non-melanoma skin cancers are rarely fatal, however, they can grow if not treated early and result in substantial destruction of local tissue and disfigurement.

### **Why does New Zealand have high rates of skin cancer?**

New Zealand has one of the highest rates of skin cancer in the world which is reflected in the relatively high rates of melanoma. In 2010, there were 2341 new registrations and 324 deaths due to invasive melanoma in New Zealand.<sup>2</sup> High levels of ultraviolet radiation (UVR) and an outdoor lifestyle combine with four interrelated factors to determine a person's risk of developing skin cancer:

1. Increasing age (the greatest risk factor for developing skin cancer)
2. Individual patterns of exposure to sunlight
3. Skin type and genetic makeup
4. Immune system function

In New Zealand, approximately twice as many males as females die from melanoma. Males aged over 50 years have a higher incidence of melanoma and tend to present with thicker melanomas, which are associated with poorer outcomes.<sup>1,2</sup> Having an outdoor occupation is likely to be one contributing factor for the increased skin cancer mortality rates among males.

### **Ultraviolet radiation and patterns of sun exposure**

Ultraviolet radiation is electromagnetic radiation that, unlike visible light and thermal heat, cannot be detected by the human body.<sup>2</sup> UVR is divided into UVB (290 – 315 nm) and UVA (315 – 400 nm).<sup>3</sup> UVB can cause skin cancer by damaging DNA in P53 tumour suppressor genes, which are involved in DNA repair, or by activating genes that promote cancer (oncogenes).<sup>4</sup> UVA is present in greater amounts in sunlight and penetrates more deeply into the skin than UVB due to its longer wave length.<sup>3</sup> UVA is also able to pass through glass, unlike UVB.<sup>3</sup> UVA radiation has been shown to be involved in the carcinogenesis of skin stem cells.<sup>3</sup> DNA damage due to UVR accumulates over time and the risk of malignancy increases with age.

Differing patterns of UVR exposure are associated with different types of skin cancer in susceptible people. Intermittent, high-dose sun exposure, e.g. during recreational activities, is associated with an increased risk of developing melanoma in younger adults, especially those with many melanocytic naevi (moles) and BCC.<sup>5</sup> Cumulative exposure, which is generally

higher in people with chronic exposure to sunlight, e.g. people with outdoor occupations, is the most significant risk factor for developing pre-cancerous solar keratoses and SCC.<sup>4</sup> Chronic exposure to UVR can also cause slow-growing melanomas to develop on patches of sun-damaged skin in older people.

### Skin type and risk factors for skin cancer

Darker skin pigmentation reduces the risk of developing skin cancer because melanin protects skin cells by absorbing UVB. Skin cancer is rare in Māori and Pacific peoples, but can occur. When Māori or Pacific peoples do present with melanoma they often have thicker lesions and more extensive disease at diagnosis.<sup>6</sup> Māori and Pacific peoples are also more likely than New Zealand Europeans to develop nodular and acral (generally on the soles of feet, palms of hands or under the nails) melanomas, which tend to grow more rapidly and be more difficult to diagnose.<sup>7</sup>

Multiple melanocytic naevi, e.g. more than 100, and more than five atypical naevi (large and unusual looking moles) are risk factors for melanoma. A family history of melanoma approximately doubles a person's risk of developing melanoma.<sup>8</sup>

Features that are commonly associated with a fair complexion are also risk factors for skin cancer, e.g. Celtic ancestry, a tendency to burn easily, blonde or red hair and green or blue eyes.<sup>4</sup>

### The role of the immune system in skin cancer

The immune system plays an important role in preventing skin cancer. This is illustrated by the increased incidence of skin cancer in people who are immunosuppressed, e.g. over 80% of patients who have received a kidney transplant will develop skin cancer within 20 years.<sup>5</sup>

Ultraviolet radiation can cause immunosuppression by: disturbing the way antigens are processed by the immune system, stimulating cytokines that can suppress the immune system and by altering contact and delayed hypersensitivity reactions.<sup>3</sup> UVR therefore initiates and accelerates the progression of skin cancer.

## First, assess for melanoma

When a patient with a suspicious skin lesion presents in general practice the first step is to assess the risk of a melanoma being present. Reassurance should only be given where there is confidence that the lesion is not melanoma. A complete skin examination should be conducted with a good light source and magnification, although another consultation

may need to be scheduled for this. The examination should note the extent of the sun damage and the distribution and morphology of skin lesions.

### 🚩 Red-flags: Is this melanoma?

Approximately half of all melanomas are first identified by the patient themselves and a discussion about the lesion's history will often provide clinically useful information.<sup>6</sup>

**The ABCDE of melanoma** has been developed to help people recognise when they should seek medical advice about a skin lesion:<sup>6</sup>

A = Asymmetry

B = Border irregularity

C = Colour variation

D = Diameter greater than 6 mm

E = Evolution, i.e. change

**“How long has it been there?”** This is the most important question to ask a patient who reports a suspicious skin lesion. If the lesion is new and the patient reports changes over days or weeks then the lesion is likely to be due to inflammation rather than malignancy. Stable lesions that have been present for years can be monitored by observation at the next consultation and their cancer risk reassessed.<sup>9</sup> However, if the patient reports **the lesion has developed and persisted over a period of months then the clinical suspicion of either melanoma or non-melanoma skin cancer should be increased.**

**“Have you noticed any changes in size, shape or colour?”** These symptoms and signs are suggestive of melanoma, particularly if the patient reports change or growth over a period of months. However, they may also be present in benign lesions, e.g. seborrhoeic keratoses (brown warts).<sup>10</sup> Seborrhoeic keratoses usually have a warty or waxy surface with a sharp border and appear stuck on the skin surface. Patients with melanoma may report intermittent itch in and around the lesion.<sup>6</sup> Pain and/or bleeding are rare features of early melanoma but are often reported in advanced or nodular melanoma.<sup>6</sup>

**“Does this mole appear different to others that you have?”** Melanomas stand out as being different from other pigmented skin lesions and are often described as having an “ugly duckling” appearance.<sup>6</sup>

Flat or superficial (Figure 1) are the most common types of melanoma, characterised by an asymmetrical structure


and multiple colours, e.g. black, brown or pink.<sup>6</sup> Areas of depigmentation are also often present and are indicators of regression.<sup>6</sup> Amelanotic melanoma is mostly pink but often has a small focal point of irregular pigmentation on the periphery of the lesion.<sup>10</sup>


Nodular melanoma (Figure 2) is suggested by progressive enlargement, symptoms, e.g. pain and bleeding, and a firm and raised appearance.<sup>6</sup> Nodular melanomas usually have a single colour, e.g. black, steel blue or red, and are usually uniform in shape. They are often misdiagnosed resulting in a disproportionate number of deaths from this type of melanoma.<sup>6</sup>

**Diagnostic excision with a narrow 2 mm margin or referral to an appropriate specialist** should be strongly considered for patients with skin lesions that are unusual, new, changing or difficult to diagnose (see: "Treatments for cancerous skin lesions", Page 14).<sup>6</sup> A second excision with a wider margin will be required if a diagnosis of melanoma is confirmed on histology, and depending on the staging of the melanoma this may need to be as wide as 2 cm.<sup>6</sup>

Observation for one to two months (but no more than three months) may be appropriate for some patients with flat, pigmented lesions where there is clinical uncertainty.<sup>6</sup> This approach is not appropriate for undiagnosed growing nodules. Tumours less than 1 mm thick and without histological evidence of mitoses or ulceration are considered to be at low-risk of metastasis and can be managed in primary care.<sup>6</sup>

Digital imaging is recommended to assist in identifying changes over a short interval, to accompany requests for histology and to request advice from, or make referrals to, other clinicians. Patients with suspected or known invasive melanoma, i.e. lesions that extend deeper than the epidermis, should be urgently referred to specialist care, and prioritised as having a high suspicion of cancer to ensure they receive treatment within 62 days of receipt of referral. Local guidelines may vary for referral to a Surgical Dermatologist, Plastic Surgeon, ENT Surgeon or General Surgeon.

 For further information see: "Detecting malignant melanoma", BPJ 34 (Feb, 2011).

 The Ministry of Health will shortly be releasing standards for the provision of services for patients with melanoma, see: [www.health.govt.nz](http://www.health.govt.nz)



**Figure 1 :** Superficial melanoma – the most common type of melanoma. Image provided by DermnetNZ



**Figure 2:** Nodular melanoma – the second most common type of melanoma. Image provided by DermnetNZ



**Figure 3:** Flat pink-red keratoses – suitable for topical treatment. Image provided by DermnetNZ



**Figure 4:** Hyperkeratotic solar keratoses – cryotherapy recommended. Image provided by DermnetNZ

## Pre-cancerous lesions – solar keratoses

Once there is confidence that melanoma is not present the patient can be assessed for the presence of non-melanoma skin cancer. Solar keratoses, also known as actinic keratoses, are frequently encountered, particularly in older patients. These lesions are considered to be pre-cancerous or an early form of SCC and are an indication of chronic exposure to UVR.<sup>10</sup> Solar keratoses appear as multiple, pink-red flat spots (Figure 3), or skin coloured, rough, scaly spots (Figure 4). Sometimes they are more easily felt than seen. Over 80% of solar keratoses occur on the head, neck, back of the hands and forearms.<sup>11</sup> Patients often report tenderness with solar keratoses, but they may cause no symptoms other than being aesthetically undesirable. Keratolytic emollients (Table 1) can be applied to provide symptomatic relief only. The probability of an individual solar keratosis transforming to SCC is unknown; reports range widely from almost negligible to 16% per year.<sup>11</sup>

A Cochrane review found that a wide range of topical treatments were generally comparable in the treatment of solar keratoses, however, there was some evidence that fluorouracil cream may be more effective long-term than cryotherapy.<sup>11</sup> Imiquimod cream is often tolerated better than fluorouracil and may provide better cosmetic results than either fluorouracil or cryotherapy, however, it may cause hypopigmentation and is unsubsidised for this indication.<sup>12</sup> Ingengol gel and photodynamic treatment cause tissue reactions of shorter duration than fluorouracil or imiquimod and have similar response rates. These treatments are not currently available in primary care (Page 14).

**Table 1:** Topical treatment regimens in primary care for solar keratoses<sup>12</sup>

Treatment type	Regimen for solar keratoses
Keratolytic emollients, e.g. urea cream (10%)	Apply to all affected areas, twice daily. Provides short-term symptomatic benefit only.
Cryotherapy	Apply liquid nitrogen in a single freeze for two to five seconds. <sup>13</sup> Repeat in four weeks or as necessary. Cryotherapy can remove approximately 70% of treated solar keratoses, depending on the intensity of treatment. <sup>13</sup> Unsuitable for large or numerous lesions.
Fluorouracil (5%) cream	Apply once or twice daily, for two to four weeks. Monitor weekly.
Imiquimod cream (5%) (unsubsidised for this indication)	Apply two or three times a week for four weeks to six weeks. Assess local response after three weeks and adjust treatment frequency if necessary. Review again after a four week treatment-free interval. Treatment can be repeated if the lesion persists.

Table 1 shows the recommended topical treatment regimens for solar keratoses managed in primary care. If a patient presents with numerous keratoses and it is impractical to treat all of them, target symptomatic, hyperkeratotic (Figure 4) or thickened lesions with cryotherapy as these lesions have a greater risk of transforming to SCC.<sup>10</sup> Treatment of wider areas of skin with fluorouracil cream or imiquimod cream may be appropriate. Ingenol gel or photodynamic therapy is more suitable for flat keratoses or larger areas of sun-damaged skin. It can be useful to freeze thicker, tender lesions two to three weeks before starting treatment as this can increase absorption of topical medicines. Follow-up may be necessary to repeat cryotherapy or biopsy lesions that do not respond to treatment or continue to enlarge. It is important to ensure that persistent lesions are in fact solar keratoses. Seborrhoeic keratoses do not respond to topical treatment.

All patients with solar keratoses should be advised to protect themselves from the sun year-round and to use high protection, broad spectrum SPF 50+ sunscreens when they are exposed to high levels of UVR.

For more detailed information about the topical treatments for non-melanoma skin cancer, see: "Treatment options for cancerous skin lesions", Page 14. For information on diagnosing suspicious skin lesions using dermatoscopy see: "Diagnosing solar keratoses and non-melanoma skin cancer using dermatoscopy, Page 13.

## Non-melanoma skin cancers – basal cell carcinoma

Basal cell carcinoma is the most frequently occurring cancer in humans and, although locally invasive, it rarely metastasises and is almost never fatal. People with a personal history of BCC also have an increased risk of developing melanoma.

Approximately 80% of BCCs occur on the face and neck, but lesions may also be found on the back of the hands, forearms and on the back and lower legs.<sup>14</sup> The classic appearance of a BCC is a "rodent ulcer", which is a lesion with raised pearly edges and central atrophy or ulceration (Figure 5). A pearly (Figure 6), shiny nodule with prominent capillary networks is common. Superficial BCC may also present as an irregular red, scaly patch or plaque with short linear blood vessels (Figure 7). Pigmented forms of BCC may be observed in people with dark skin or people who tan easily.



**Figure 5:** Nodular basal cell carcinoma (BCC) – excision recommended. Image provided by DermnetNZ



**Figure 6:** Stretching basal cell carcinoma (BCC) reveals a pearly appearance. Image provided by DermnetNZ



**Figure 7:** Superficial basal cell carcinoma (BCC) suitable for cryotherapy or topical treatment. Image provided by DermnetNZ

BCCs are generally slow growing over months or years.<sup>10</sup> Morphoeic (infiltrative with poorly defined edges) or sclerosing (scar-like) BCCs may go unnoticed until they are several centimetres in diameter and have penetrated deeply. Advanced BCCs may appear as large, deep ulcers. BCC located near the eyes, nose and ear can invade the orbital rim, nasal vault and middle ear respectively and may be larger than expected. Consider early referral of any patient with a BCC in these locations to a General Practitioner with a Special Interest (GPSI) in skin lesions, a Dermatologist, a Plastic surgeon or an ENT surgeon.

**Surgical excision with histology is the first-line treatment for BCC**, as this has superior cure rates to topical treatments and histology results can guide the need for further investigation or treatment. Patients with aggressive, recurrent or large tumours, e.g. diameter greater than 6 mm on the face,<sup>14</sup> may require referral to a Dermatologist for consideration of Mohs margin-controlled micrographic surgery (see: "Treatments for cancerous skin lesions", Page 14).

**Superficial BCC, i.e. restricted to the outermost layers of skin**, may be treated topically (Table 2) if the lesion's location, the patient's general health or the presence of co-morbidities mean excision is impractical or associated with an increased risk of complications or poor cosmetic outcome. A punch biopsy may be considered, prior to initiating topical treatments,

for superficial BCC to assess tumour thickness and confirm diagnosis. Non-surgical treatments should not be used if the diagnosis of BCC is unclear.<sup>13</sup>

Cryotherapy delivered in freeze-thaw cycles (Table 2) is effective at destroying malignant cells in superficial BCC because cellular damage occurs both during the freezing process and during the slower thaw, due to the osmotic gradient across the cell membrane. Superficial confirmed BCC can be treated with imiquimod (subsidised under Special Authority criteria) when standard treatment options, including surgical excision, are contraindicated or inappropriate (Table 2).<sup>12</sup> Imiquimod is not indicated for recurrent, invasive, infiltrating or nodular BCC.<sup>12</sup> There is insufficient evidence to compare the effectiveness of cryotherapy with imiquimod for the treatment of superficial BCC. Fluorouracil is not routinely used to treat BCC as there is insufficient evidence to assess treatment effectiveness,<sup>15</sup> however, occasionally it is used to treat small, very superficial BCCs.

Photodynamic therapy is available in some specialist centres for superficial BCC, including BCCs on the face that are unsuitable for surgery. Photodynamic therapy (unsubsidised) can also be used to treat large thin superficial BCCs on the lower leg. Photodynamic treatment for BCC is repeated after one to two weeks.

**Table 2:** Topical treatments regimens in primary care for superficial basal cell carcinoma (BCC)<sup>12,13</sup>

Treatment type	Regimen for BCC
<b>Cryotherapy</b>	Apply liquid nitrogen to the skin for 20 – 30 seconds, allow to thaw for three to five minutes, then refreeze for another 20 – 30 seconds. Unsuitable for facial lesions, due to poor response rates, or distal lower limbs, due to persistent ulceration. Recurrence at the lesion margin may develop following cryotherapy.
<b>Imiquimod cream</b> (Special Authority)	Apply to the lesion and 1 cm beyond, once daily on five days each week, for six weeks. Treatment should be reviewed by at least the third week, to adjust the frequency of application. After a four week treatment break, treatment can be repeated for another six weeks if the response to the first course is incomplete. Imiquimod can cure 70 – 80% of small, superficial BCCs. <sup>10</sup> A punch biopsy should be performed where possible to confirm a diagnosis to qualify for Special Authority subsidy criteria. Imiquimod is indicated for superficial BCC on the neck, chest and distal upper limbs, but it appears to be less effective when used on the distal limbs. Imiquimod can be used to treat facial lesions but as local tissue reaction may be prolonged it may not be a desirable option for all patients.
<b>Fluorouracil (5%) cream</b>	Apply thinly to the affected area, twice daily, for 12 weeks. <sup>10</sup> Not routinely used to treat BCC, however, prolonged courses of treatment are occasionally used to treat small, very superficial BCCs. <sup>10</sup>

## Squamous cell carcinoma (SCC)

Squamous cell carcinomas (SCC) develop from the flat, scale-like (squamous) cells that form the outermost layer of the epidermis. When a SCC is limited to the epidermis it is referred to as intraepidermal carcinoma (IEC – also known as SCC in situ, Figure 8). The term Bowen's disease is no longer used. IECs are generally flat, but can be several millimetres in thickness and slow-growing over months or years. There are usually multiple irregular orange-red or brown plaques with variable scaling or crusting. SCC will often be tender and will rarely go unnoticed. The presence of chronic leg ulcers and infection with human papillomavirus (HPV) increase the risk of developing SCC.<sup>10</sup> Chronic leg ulcers may progress into aggressive ulcerating SCC, referred to as Marjolin's ulcer.<sup>10</sup> Smoking increases the risk of developing SCC on the lip and genitalia and is likely to be a risk factor for developing SCC in other sites.<sup>10</sup> People with a history of SCC also have an increased risk of developing malignant melanoma.<sup>10</sup>

Approximately 80% of invasive SCCs develop on the face and neck, but lesions may also be found in other areas exposed to the sun.<sup>14</sup> The clinical characteristics of invasive SCC are dependent on the keratin producing cells within the tumour. Well differentiated SCC appear as firm slow-growing skin-coloured nodules with scaling or a protruding horn (Figure 9).<sup>10</sup> SCC that are less differentiated grow more quickly and have an irregular crusted plaque that is often ulcerated (Figure 10).<sup>10</sup> Keratoacanthoma appear as symmetrical nodules with a central crater or keratin core. They grow rapidly, reaching a diameter of 2 cm in few weeks. Keratoacanthoma can cause an immune reaction and resolve within months, but may be indistinguishable from aggressive tumours and should be excised.

SCC will metastasise in approximately 5% of cases, but this risk is higher if the lesion is large or deep, or is located on the ear, lip, genitals or on mucosal surfaces, or involves nerve fibres.<sup>10,14</sup> Metastasis of SCC is also more likely if the immune system is suppressed, e.g. in people with chronic leukaemia or people who have received an organ transplant.<sup>14</sup>

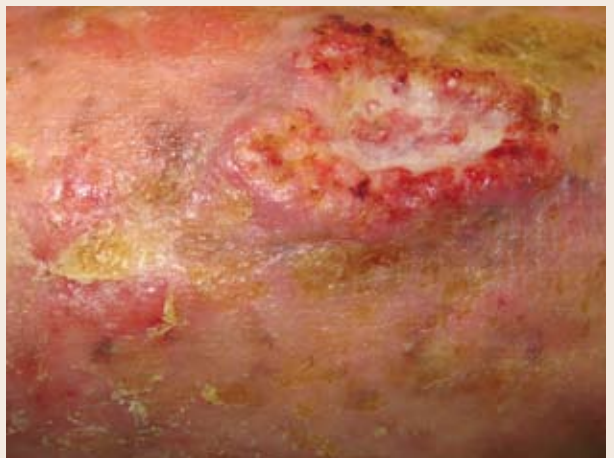
**A regional lymph node examination should be considered whenever invasive SCC is suspected.**<sup>14</sup> Nodal metastasis is more likely to occur in patients with SCC with poor differentiation and perineural invasion.<sup>14</sup> Symptoms such as pain, burning, stinging, anaesthesia, paraesthesia, facial paralysis, diplopia and blurred vision are suggestive of neurological involvement. The role of sentinel node biopsy in the investigation of suspected SCC is uncertain.<sup>14</sup>



**Figure 8:** Typical red crusted plaque of intraepidermal carcinoma (IEC). Image provided by DermnetNZ



**Figure 9:** Cutaneous horn suitable for excision. Image provided by DermnetNZ



**Figure 10:** Poorly differentiated and ulcerated squamous cell carcinoma (SCC) for wide excision. Image provided by DermnetNZ



**Surgical excision is the first-line treatment for SCC** and is indicated for all invasive SCC. For clinically well defined, low risk tumours that are less than 2 cm in diameter, a 4 mm margin of unaffected tissue around the tumour is sufficient to completely remove 95% of all primary SCCs.<sup>16</sup> At least a 6 mm margin of unaffected tissue should be removed, or referral to a Plastic Surgeon, ENT Surgeon or Dermatologist for Mohs margin-controlled micrographic surgery is recommended for tumours that have one or more of the following features:<sup>16</sup>

- Greater than 2 cm in diameter
- Classified as moderately or poorly differentiated
- Extending into subcutaneous tissues
- Present on the ear, lip, scalp, eyelid or nose
- Recurrent

**Cryotherapy or fluorouracil** can be used to treat IEC where the diameter, location or number of lesions make surgery unsuitable (Table 3). A skin punch biopsy may be considered, if practical, before beginning topical treatment for IEC to assess tumour risk and confirm diagnosis. A Cochrane review found that there was insufficient evidence to compare the effectiveness of cryotherapy with fluorouracil in the treatment of IEC.<sup>17</sup> Imiquimod is not registered for the treatment of IEC in New Zealand and there is a lack of quality studies investigating its effectiveness for this condition. However, many clinicians report that imiquimod is useful for treating IEC.

Photodynamic therapy is also a treatment option for large flat areas of IEC on the face, neck and lower legs, however, this treatment is unsubsidised and unregistered for this indication and not available in primary care.

## Follow-up of patients treated for non-melanoma skin cancer

Patients with a history of pre-cancerous or cancerous skin lesions should be advised that the risk of treated lesions becoming recurrent, or new lesions developing, is increased if they are exposed to excessive UVR. Encourage regular self-examination of the skin, using a mirror or involving their partner or carer. Any new or changing lesions should be reported, particularly if they stand out as being different, or are growing, crusting or bleeding. Photography of the lesions may help patients and clinicians with surveillance and follow-up.


It is particularly important that “sun smart” behaviour is encouraged in people with a history of skin cancer. The Metservice sun protection alert for each centre in New Zealand is available online. This informs people of the time of day when there is a risk of being harmed due to UVR, i.e. the ultraviolet index (UVI) is greater than three, and the following measures should be taken:

- Slip into a long-sleeved shirt
- Slop on broad-spectrum (SPF 30+) sunscreen 15 minutes before going outdoors
- Slap on a hat with a wide brim
- Wrap on a pair of wrap-around sunglasses

 The Metservice sun protection alert is available from: [www.metservice.com/national/home](http://www.metservice.com/national/home)

**Table 3:** Topical treatments regimens in primary care for intraepidermal carcinoma (IEC)<sup>12, 13</sup>

Treatment type	Regimen for IEC
<b>Cryotherapy</b>	Apply liquid nitrogen in a single freeze to the skin for five to ten seconds
<b>Fluorouracil (5%) cream</b>	Apply thinly to the affected area, once or twice daily, for an initial duration of three to four weeks. Treatment can be applied for eight weeks, or longer. An occlusive dressing should be used to increase penetration if tissue reaction is minimal.
<b>Imiquimod (5%) cream</b> (unsubsidised and unregistered for this indication)	Apply to the lesion and 1 cm beyond, once daily on five days each week, for six weeks. Treatment should be reviewed by at least the third week, to adjust the frequency of application. After a four week treatment break, treatment can be repeated for another six weeks if the response to the first course is incomplete.

 The Sunsmart skin cancer awareness programme has information available on how patients can reduce their risk of developing skin cancer.

Available from: <http://sunsmart.org.nz/being-sunsmart>

### Follow-up of non-melanoma skin cancer

Patients who have been treated for non-melanoma skin cancer require follow-up every six to 12 months.<sup>13</sup> It is reported that between one-third and one-half of all patients with a non-melanoma skin cancer will develop another malignancy within five years.<sup>14</sup> Surveillance in the two years following treatment for SCC is particularly important as 70 – 80% of recurrent SCC develops within this time period.<sup>14</sup> Patients with a history of skin cancer who are immunosuppressed are at increased risk of developing further malignancies and a follow-up schedule for these patients should be discussed with an appropriate specialist, e.g. a Dermatologist.<sup>14</sup> Patients who have a history of invasive skin cancer should also be taught to regularly self-examine their lymph nodes.<sup>14</sup>

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### Diagnosing solar keratoses and non-melanoma skin cancer using dermatoscopy

Dermatoscopy can provide more confidence in discriminating between benign lesions that can be left untreated and malignancy that should be excised. A dermatoscope with strong polarised light and ×10 magnification is used to assess the symmetry of pigmented structures, e.g. lines, dots, circles and clods, and their patterns, e.g. reticular, dotted or without structure. Lack of symmetry of colour and structure, i.e. chaos, indicate a high suspicion of malignancy, once seborrhoeic keratosis has been excluded.

On dermatoscopy:

- Solar keratoses may contain small, irregular white circles. Facial keratoses may contain a “strawberry pattern” of concentric red and white rings.
- Basal cell carcinoma will show a loss of normal skin features and asymmetry of structure and colour. Microerosions may also be present. Pigmentation tends to be at the edge of the lesion in the form of irregular light brown, grey or blue structures. The blood vessels of BCC appear as branched lines. Polarised dermatoscopy of BCC shows white lines without a pigmented network.
- Intraepidermal carcinoma shows light pigmentation in a linear array. The blood vessels appear as groups of irregular large, red dots and coils.



# Treatments for non-melanoma cancerous skin lesions

When considering potential treatments for skin cancer it is important to discuss patient preference as well as the effectiveness of the treatment. For example, an older patient with multiple co-morbidities may prefer not to have a slow growing BCC removed.

**Surgical excision with histology is the first-line treatment for all skin cancers.** This will generally completely remove the tumour as well as guide the need for any further investigations or treatment once the histology is known. Superficial non-melanoma skin cancer should only require a single excision if an adequate margin of normal skin is removed with the tumour (see below). Excision also has the advantage over topical treatments of being a one-off treatment that does not rely on patients adhering to a dosing regimen. An increased risk of bleeding should always be considered in patients taking medicines such as aspirin, clopidogrel, ticagrelor, dabigatran or warfarin. The use of antithrombotic medicines does not greatly increase the risk of complications due to minor surgery, however, in individual patients, e.g. a patient taking warfarin with an elevated or unstable INR, non-surgical treatment may be preferable.


The tumour margin should be identified before administering local anaesthetic. As a general rule the margin of normal skin around the tumour should not be less than 3 – 4 mm. Margins that are smaller result in increased rates of recurrence, especially of BCC, which can be difficult to remove. Shaving, curettage (scraping out the malignant tissue) and cautery may be appropriate for thick solar keratoses, some IEC and small, well defined nodulocystic or superficial BCC. A deeper incision with simple or complex wound closure, e.g. use of skin flaps, is likely to be necessary for larger lesions or lesions that have been confirmed on histology to be incompletely excised. The cosmetic outcome of sutured wounds is improved if they are covered with an occlusive dressing for at least four days.<sup>9</sup>

Mohs margin-controlled micrographic surgery is generally performed by a specially trained Dermatologist. This involves removing horizontal sections of skin tissue, examining them

under a microscope, colour coding specimens and then creating a map to locate remaining cancer cells. The cure-rate for Mohs margin-controlled micrographic surgery can be as high as 99% for primary skin cancer and 95% for recurrent skin cancer.<sup>10</sup> This procedure is mainly used for facial lesions and is useful for:<sup>10</sup>

- Recurrent or incompletely excised BCC and SCC
- BCC and SCC without clearly defined borders
- Areas where sensory function is important, e.g. eyelids, nose, ears and lips
- BCC and SCC that is larger than 2 cm in diameter or rapidly growing
- High-risk or aggressive SCC, e.g. infiltrative histology or poorly differentiated

**A punch biopsy should be considered for suspicious non-melanocytic skin lesions that will not be surgically removed** to confirm a diagnosis and guide treatment.<sup>10</sup> However, this is not necessary for low-risk tumours with classical features seen on dermatoscopy (see: “Diagnosing solar keratoses and non-melanoma skin cancer using dermatoscopy”, Page 13). When performing a punch biopsy, stretch the skin perpendicular to the direction of least skin tension as this will allow for an elliptical wound that is easily closed with a single suture or steri-strip. The biopsy site should be on the wound margin so as to include tissue from the tumour and surrounding, non-affected skin.<sup>18,19</sup> The use of forceps should be minimised when handling the sample as this may crush tissue, making histological analysis difficult.

 For further information on punch biopsy and other surgical procedures see:

<http://dermnetnz.org/doctors/lesions/procedures.html>

**Cryotherapy using liquid nitrogen is widely used in general practice** to treat solar keratoses, low-risk superficial BCC or IEC less than 1 cm in diameter on the trunks and limbs.<sup>13</sup> Spray devices have the advantage of allowing the freeze to be controlled using different applicators. If a spray device

is not available a cotton-tipped stick can be dipped into a flask of liquid nitrogen. The disadvantages of this technique are: contamination, rapid thaw, inadvertent drip, inaccurate application and under or over-treatment. Some degree of hypopigmentation is inevitable following cryotherapy and this may be more noticeable in people with darker skin.

Liquid nitrogen is applied for a length of time dependent on the type, diameter and thickness of the lesion. Superficial lesions, i.e. solar keratoses and IEC, can be removed with a freeze lasting a few seconds, however, superficial BCC requires longer and repeat applications aiming for a cumulative tumour freeze-time of approximately 60 seconds. Within a few hours the patient will develop a clear, red or purple blister. Generally, these do not require special attention, but should be kept clean and intact. Dressing is recommended if the area is likely to be rubbed, e.g. the neck, or knocked, e.g. the hand, or where discharge onto clothing is a concern.<sup>10</sup> Eschar (scabs) on the face often peel off after five to ten days, hands may take three weeks to heal and eschar on the lower leg may remain for up to three months.<sup>10</sup> Due to the longer healing rates cryotherapy is not suitable on the lower leg for patients with impaired circulation.<sup>13</sup> Caution is recommended when applying liquid nitrogen to the back of hands as damage to the extensor tendons can occur. Infection following cryotherapy is rare.<sup>10</sup> If freezing occurs over a sensory nerve, e.g. the sides of the fingers, numbness may result with normal sensation generally returning over weeks to months.<sup>10</sup>

**Fluorouracil (5%) cream is indicated and fully subsidised for the treatment of pre-cancerous and superficial malignant skin lesions.**<sup>12</sup> It is toxic to dividing cells as it is incorporated into DNA and RNA; stopping the cell cycle. The area of skin being treated should not be larger than 22 × 22 cm.<sup>12</sup>

Patients applying fluorouracil must avoid exposure to the sun as this can make adverse effects worse; it is best used during the winter months.<sup>10</sup> Patients should avoid contact with eyes and mucous membranes while using fluorouracil.<sup>12</sup> The use of gloves and/or cotton-tipped applicators when applying the cream is also recommended and hands should be washed thoroughly after application if these are not used. Hyperkeratotic lesions being treated with fluorouracil should be covered with an occlusive dressing, but this is not necessary on thin flat lesions on facial skin.<sup>12</sup> Topical use of fluorouracil should be expected

to cause local irritation and photosensitivity and may result in permanent hyperpigmentation and scarring. Erythema multiforme may also occur.<sup>12</sup> Inflammation is likely to last for one to two weeks after treatment has finished.<sup>13</sup> Patients can be reassured that the greater the inflammatory reaction, the more effective the treatment is likely to be, but pain can be substantial and treatment is often discontinued early.<sup>12</sup> Severe discomfort that is associated with an inflammatory response may be treated with a topical corticosteroid and analgesia.<sup>12</sup> Patients should be advised to store fluorouracil safely so it will not be inadvertently used by other members of the household.

Fluorouracil is contraindicated in women who are pregnant or breast feeding and in people with a dihydropyrimidine dehydrogenase deficiency, which slows the rate at which uracil is metabolised. The prevalence of this deficiency is reported to be approximately 3%, however, people who are severely affected by this deficiency are likely to display neurological symptoms, e.g. seizures or intellectual disability.<sup>20</sup> Adverse effects due to uracil toxicity following topical application are extremely rare and estimated to occur in one in 100 000 people.<sup>20</sup> Fluorouracil should be used with caution in patients with inflammatory skin conditions, e.g. eczema, as adverse reactions may be more severe.<sup>12</sup> Dermatitis may also occur in patients with no history of sensitive skin.

**Imiquimod (5%) cream is subsidised under Special Authority criteria for the treatment of confirmed superficial BCC** when standard treatment options, including surgical excision, are contraindicated or inappropriate.<sup>12</sup> Imiquimod is an immune modifier that causes the removal of skin cells by inducing local cytokine production. Imiquimod causes local irritation and should not be applied to broken skin. The cream is provided in packs of 12 sachets and each sachet can treat an area of skin up to 25 cm<sup>2</sup>. The cream is well absorbed and should be left on the treated area for eight hours (typically over night), then any residue washed off with a mild soap and water.<sup>12</sup>

Skin treated with imiquimod may become inflamed, itchy, ulcerated and flaky. Painful erosions can occur on mucous membranes and cream should not be applied within 1 cm of the eyes, nose and lips. Inflammation may vary between patients and treatment should be monitored.<sup>10</sup> Occlusion of the treated lesion is not necessary. Advise patients that because

imiquimod activates the immune system locally, inflammation is an expected result which indicates that the cream is likely to be effective. Reassurance can be given that the inflammation will settle leaving an acceptable cosmetic result. The patient should be advised to stop treatment if black coloured ulceration or systemic flu-like symptoms occur.<sup>10</sup> Topical steroidal cream may reduce treatment efficacy and should not be used to treat reactions.<sup>13</sup> Imiquimod is also effective for treating locally occurring subclinical lesions. Patients with mild symptoms following treatment with imiquimod can be treated with paracetamol.<sup>10</sup> Assess the patient's response 12 weeks after they have completed the regimen to determine if there is a need for further treatment.<sup>12</sup>

### Treatment options generally not used in primary care

**Photodynamic therapy** is performed by private providers and in some hospital clinics. It can produce good cosmetic results, but it is painful and can be expensive. Treatment involves the application of methyl aminolevulinate (16%) cream thickly to the lesion and a 1 cm margin. This is occluded for three hours and then exposed to a wavelength of light that matches the absorption spectrum of the active component within the cream and penetrates to the required depth. Sunlight can be used to treat the skin as this contains multiple wavelengths of light. After absorbing light the active component reacts with O<sub>2</sub> to form destructive single oxygen atoms that destroy the lesion.<sup>20</sup>

Photodynamic therapy has a relatively short treatment duration (approximately 15 minutes) and may also reduce other visible signs of photo-damage.<sup>20</sup> Adverse effects of treatment may include discomfort and intense inflammation; in these patients pain and pruritus may be reported during exposure. Local anaesthetic, analgesia or breaks in treatment may be required. After treatment a tissue reaction may persist for one to two weeks.

**Ingenol mebutate gel** is an extract of milk weed (*Euphorbia peplus*) that has been shown to be useful in the treatment of superficial skin cancers and solar keratoses.<sup>10</sup> This medicine was registered in October, 2013, and is expected to be available (unsubsidised) in New Zealand in February, 2014. Ingenol gel (0.015%) is applied to the face and scalp once daily, for three days. Ingenol gel (0.05%) is applied on the trunk and extremities once daily, for two days.<sup>10</sup> The reaction to treatment is variable and will last one to two weeks.

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