Non-melanoma skin cancer: Guidelines for treatment and management in Australia
Clinical Practice Guidelines
Non-melanoma skin cancer: Guidelines for treatment and management in Australia

Prepared by the Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party

Endorsed 24 October 2002
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- fostering and supporting a high quality and internationally recognised research base;
- providing evidence-based advice;
- applying research evidence to health issues thus translating research into better health practice and outcomes; and
- promoting informed debate on health and medical research, health ethics and related issues.

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Disclaimer

This document is a general guide to appropriate practice, to be followed only subject to the clinician’s judgement in each individual case.

The guidelines are designed to provide information to assist decision-making and are based on the best information available at the date of compilation (August 2001).

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EXECUTIVE SUMMARY

- Non-melanoma skin cancer is a major public health problem in Australia causing substantial national health cost and disfigurement resulting from treatment.
- Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) together are the most costly cancers in Australia, accounting for $A232.2 million per year.
- Non-Melanoma Skin Cancer: Guidelines for treatment and prevention in Australia provides evidence-based documentation to assist in sound decision-making. The Guidelines are guides and are neither rules nor are they prescriptive in any way.
- The Guidelines are produced primarily for those practitioners who are providing the majority of care to people with non-melanoma skin cancer (NMSC) in Australia. The data indicate that general practitioners comprise the majority providing this care; hence the Guidelines primarily should be of benefit to them.
- Solar radiation is the major environmental cause of non-melanoma skin cancer.
- Protection against solar radiation is recommended. It is best achieved by seeking shade when outdoors, and by wearing protective clothing. Clothing should be used as the primary means of photo-protection. Broad spectrum sunscreens with an SPF of 15 or greater may be used as an adjunct to sun avoidance and together with other sun protective measures.
- Surgery is prime treatment for non-melanoma skin cancers. Confirmation of complete removal of lesions is required.
- Recurrence is more frequent after excision of ill-defined basal cell carcinomas such as morphoeic and microlobular forms.
- Radiotherapy should be reserved for the small minority of primary BCC and SCC that present peculiar problems for conventional surgery and for cases of persistent, recurrent or advanced BCC and SCC where surgery can be complemented by radiotherapy to improve control rates in this small, poorer prognosis category.
- Cryotherapy, curettage and diathermy treatments have specific advantages and disadvantages, which should be considered and discussed before implementation.
- Other treatments eg, intralesional interferon, imiquimod, photodynamic therapy and laser therapy have limited but definite roles in some selected circumstances.
- Becoming familiar with the clinical features of non-melanoma skin cancer is important in leading to correct diagnosis, effective and efficient treatment, minimal morbidity, better quality of life for affected patients and a reduction of overall cost.
### SUMMARY OF RECOMMENDATIONS AND GUIDELINES

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<tr>
<td><strong>2. EPIDEMIOLOGY</strong></td>
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<tr>
<td>Solar radiation is the major cause of non-melanoma skin cancer.</td>
<td>III-2</td>
<td>4, 12, 13</td>
<td>6</td>
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<tr>
<td>The chances that an individual solar keratosis will develop into an SCC are extremely small; however when one encounters an SCC, the chance that it has arisen in association with solar keratosis is very high.</td>
<td>III-2</td>
<td>14, 33, 36, 39</td>
<td>12</td>
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<td><strong>4. PATHOLOGY</strong></td>
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<tr>
<td>Confirmation of complete removal of the tumours is important. Recurrence from incomplete removal is seen more frequently in clinically ill-defined basal cell carcinomas such as morphoeic and microlobular forms.</td>
<td>III-2</td>
<td>47, 48</td>
<td>26</td>
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<td><strong>5. PROGNOSIS</strong></td>
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<tr>
<td>Higher recurrence rates have been observed for all treatment modalities in the facial region compared with non-facial sites and particularly on and around the nose, eyelids and ears.</td>
<td>IV</td>
<td>24, 56, 57, 62, 63, 68, 69, 70, 71, 72</td>
<td>28</td>
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<td>The estimated prevalence of perineural spread from cutaneous SCC is in the order of 2.5%.</td>
<td>IV</td>
<td>107, 108, 109, 118</td>
<td>31</td>
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<tr>
<td>SCCs of the scalp, ear and vermilion have a higher recurrence and subsequent nodal metastasis rate than SCCs elsewhere, being in the order of 10 to 20% overall.</td>
<td>IV</td>
<td>49, 115, 116, 117</td>
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## 6. SURGICAL TREATMENT

The majority of clinically favourable BCCs can be excised with a margin of at least 3mm with a very high chance of achieving complete excision and long term control.

Patients with BCCs which are large (> 2cm), poorly defined or multiple lesions, unfavourable tumour types, ie infiltrative, ulcerative or morphoeic types or tumours located in sites where the rate of local recurrence is predicted to be high (central face and peri-aural regions) should be considered for referral for specialist care.

Patients with incompletely excised BCC should be considered for re-excision to achieve clear margins. Radiotherapy may be a reasonable alternative for the patient unwilling or unable to undergo further surgery.

Consideration of specialist therapy should occur for patients with an SCC showing perineural spread (See chapter 13). Wide excision is recommended and consideration should be given to post operative radiotherapy.

Patients with recurrent SCC have an increased risk of further local recurrence as well as regional and distant metastases. Excision of the previous treatment site should be undertaken in continuity with the recurrent tumour. Specialist referral is recommended.

Chronically immunosuppressed patients frequently develop multiple SCC which behave aggressively. These patients should be referred for specialist management.

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<td>The prognosis for SCC in chronically immuno-suppressed patients is worse</td>
<td>III-2</td>
<td>16,17,119</td>
<td>34</td>
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<tr>
<td>than in other people. Rates of local recurrence or metastasis are</td>
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<td>increased overall and increase with duration of immunosuppression.</td>
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<td>Patients with BCCs which are large (&gt; 2cm), poorly defined or multiple</td>
<td>IV</td>
<td>3,4,5,6,7,</td>
<td>40</td>
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<td>lesions, unfavourable tumour types, ie infiltrative, ulcerative or</td>
<td></td>
<td>11, 48,58,</td>
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<td>morphoeic types or tumours located in sites where the rate of local</td>
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<td>63</td>
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<td>recurrence is predicted to be high (central face and peri-aural regions)</td>
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<td>should be considered for referral for specialist care.</td>
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<tr>
<td>Patients with incompletely excised BCC should be considered for re-</td>
<td>IV</td>
<td>98,99,100,</td>
<td>41</td>
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<tr>
<td>excision to achieve clear margins. Radiotherapy may be a reasonable</td>
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<td>101, 102,</td>
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<td>alternative for the patient unwilling or unable to undergo further</td>
<td></td>
<td>103, 104</td>
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<td>surgery.</td>
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<td>Consideration of specialist therapy should occur for patients with an</td>
<td>IV</td>
<td>107, 108,</td>
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<tr>
<td>SCC showing perineural spread (See chapter 13). Wide excision is</td>
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<td>109, 144,</td>
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<td>recommended and consideration should be given to post operative radio-</td>
<td></td>
<td>146</td>
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<td>therapy.</td>
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<tr>
<td>Patients with recurrent SCC have an increased risk of further local</td>
<td>IV</td>
<td>11, 147,</td>
<td>45</td>
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<tr>
<td>recurrence as well as regional and distant metastases. Excision of the</td>
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<td>148, 149</td>
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<td>previous treatment site should be undertaken in continuity with the</td>
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<td>recurrent tumour. Specialist referral is recommended.</td>
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<td>which behave aggressively. These patients should be referred for specialist management.</td>
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<td><strong>7. Radiotherapy for Basal Cell Carcinoma &amp; Squamous Cell Carcinoma</strong></td>
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<tr>
<td>Radiotherapy should be reserved for the small minority of primary BCC and SCC that present peculiar problems for conventional surgery and for cases of persistent, recurrent or advanced BCC and SCC where surgery can be complemented by radiotherapy to improve control rates in this small poorer prognosis category.</td>
<td>IV</td>
<td>68,69, 70,71,72, 73, 82,85, 89,94,155,156</td>
<td>49</td>
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<tr>
<td>Radiotherapy for T1 and T2 primary BCC has comparable outcomes (marginally inferior) to specialist surgery.</td>
<td>II &amp; IV</td>
<td>68,70,73,82, 85, 89, 156</td>
<td>54</td>
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<tr>
<td>A radiotherapist’s opinion should be considered for T4 primary, persistent and recurrent BCC.</td>
<td>III</td>
<td>71</td>
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<tr>
<td>Radiotherapy gives comparable control rates as re-excision for incompletely excised BCC and is an alternative to re-excision if further treatment is deemed advisable and re-excision is disadvantageous or not feasible.</td>
<td>IV</td>
<td>101</td>
<td>54</td>
</tr>
<tr>
<td>As the late results of radiotherapy can be poor, it is generally not recommended for patients younger than 60 years with uncomplicated primary SCC anticipated to have excellent outcomes with surgery alone.</td>
<td>III</td>
<td>68,69, 70, 73, 155, 158</td>
<td>57</td>
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<td><strong>8. Cryotherapy, Curettage and Diathermy Treatment</strong></td>
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<td>Cryotherapy achieves high cure rates for primary BCC on trunk and limbs if tumour selection and treatment protocols are optimal.</td>
<td>III &amp; IV</td>
<td>167, 180, 184</td>
<td>62</td>
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<tr>
<td>Cryotherapy for primary BCC on head and neck achieves cure rates equivalent to the other standard modalities if tumour selection and treatment protocols are optimal.</td>
<td>IV</td>
<td>163, 165, 167, 176, 177, 181, 182, 184, 187</td>
<td>62</td>
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<tr>
<td>Cryotherapy achieves lower cure rates for larger BCCs, except for the superficial (non-invasive) type.</td>
<td>IV</td>
<td>165, 167, 176, 178, 179, 183, 185, 186, 189</td>
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<tr>
<td>Cryotherapy achieves lower cure rates for BCCs at high risk facial sites and is not recommended.</td>
<td>IV</td>
<td>94,163,184, 187,183, 186,188</td>
<td>62</td>
</tr>
<tr>
<td>Cryotherapy is contraindicated for ill-defined or morphoeic (infiltrative) BCCs at any site.</td>
<td>IV</td>
<td>165,168, 179</td>
<td>62</td>
</tr>
<tr>
<td>Long term follow up is essential after treatment of BCC with cryotherapy, as late recurrences may occur.</td>
<td>III</td>
<td>60</td>
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<tr>
<td>Cryotherapy achieves consistently high cure rates for solar keratoses.</td>
<td>IV</td>
<td>162,165, 211,212</td>
<td>65</td>
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<tr>
<td>Cryotherapy of Bowen’s disease achieves high cure rates with optimal treatment protocols, but delayed healing may occur on lower limbs.</td>
<td>IV</td>
<td>166,169</td>
<td>65</td>
</tr>
<tr>
<td>Recurrence rates of less than 6% may be achievable if curettage and electro-desiccation is used for appropriately selected BCC.</td>
<td>IV</td>
<td>57, 234</td>
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9. **OTHER TREATMENTS (INTRALESIONAL INTERFERON, IMIQUIMOD, PHOTODYNAMIC THERAPY, LASER THERAPY)**

Intralesional interferon has a limited but definite role in treatment of selected BCCs.                              | III-2             | 2,3,11, 241,243, 249        | 73   |
| Laser therapy offers some treatment advantages for select skin cancers. However, the great majority of tumours are better managed by the less expensive commonly available techniques. | IV                | 224,225, 269,270, 271,272, 273,274, 275,276, 277 | 76   |

10. **PREVENTION (INCLUDING CHEMOPREVENTION)**

Use broad spectrum sunscreens with an SPF of 15 or greater as an adjunct to sun avoidance and other sun protective measures. *Squamous cell carcinoma; there is no evidence for BCC.*  | II*               | 298,299                    | 83   |
| Use clothing, where possible, as the primary means of photoprotection.                                            | III               | 295                        | 83   |
11. METASTASIS OF NON-MELANOMA SKIN CANCER

Response rates have been reported of up to 83% with 37% being complete.

Intralesional 5-FU with epinephrine injectable gel has also been used. More recently, electrochemotherapy which involves intralesional bleomycin and electric pulses locally has achieved response rates approaching 100%.

Clinically suspected lymph node metastases should be confirmed by fine needle aspiration cytology (under radiological guidance if required). Open surgical biopsy should be avoided.

The treatment of metastatic disease to lymph nodes is primarily surgical.

Most regimens are based on cisplatin with the most commonly reported phase II studies using cisplatin and doxorubicin. Other drugs include methotrexate, 5-fluorouracil, bleomycin and vindesine. Objective response rates of > 80% have been reported with complete response rates of around 30%. Patients should be considered for referral to a suitable cancer specialist centre for multidisciplinary care.

Small studies have investigated intralesional cisplatin with epinephrine or 5-fluorouracil with epinephrine gels. Topical 5-fluorouracil has activity in squamous cell carcinoma in small series.

12. FOLLOW UP

There are no data available as yet to underpin a recommendation on the frequency or nature of follow up after the treatment of primary cutaneous non-melanoma skin cancer.

NB: For details regarding levels of evidence, see page 3 of introduction.
1. INTRODUCTION

There have been a number of Guidelines on prevention, early detection and management of cancers produced by the Australian Cancer Network in recent years which have been endorsed by and then become Guidelines of the National Health and Medical Research Council (NHMRC). These have been produced on the basis of need with the primary reasons being identified by the NHMRC* as:

- The size of the health burden
- The cost of the health burden
- Variations in practice
- The existence of available evidence

(*A guide to the development, implementation and evaluation of clinical practice guidelines, NHMRC 1998)

There is no doubt that basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) comprise the commonest cancers in Australia, adding substantially to the cost of provision of health care to the community. There are other non-melanoma skin cancers (NMSCs) apart from these but, despite the fact that they can cause considerable morbidity in those affected, their overall contribution to the size of the public health problem is relatively small. These include Merkel's cell carcinoma and atypical fibroxanthoma. For that reason, these tumours have not been included in these Guidelines. There is no doubt also, even just examining the Medicare Benefit payments, that BCCs and SCCs are being treated by a variety of different medical practitioners in Australia. These include general practitioners, dermatologists, plastic surgeons, general surgeons and radiotherapists. All of these practitioners will have different levels of training and experience and, in many instances, they may have different therapeutic approaches to the tumours. For example, general practitioners may use surgery and on occasion cryotherapy and curettage. Dermatologists use most of the modalities of therapy including surgery, radiotherapy, curettage, cryotherapy and some of the biological response-modifying treatments.

The Guidelines are produced primarily for those practitioners who are providing the majority of care to people with NMSC in Australia. The data indicate that general practitioners comprise the majority providing this care; hence the Guidelines primarily should be of benefit to them.

Although NMSC does not make a large contribution to the mortality figures in Australia, it still has the potential to cause considerable morbidity and require treatment which itself may be associated with some morbidity. It will be clear on reading this report that morbidity due to treatment is a concern. We have reinforced in the text that practitioners who wish to treat them in Australia should be well-trained so that they are competent, as well as feeling comfortable when they do so.
1. INTRODUCTION

It was clear on assessment of the available evidence that there are substantial gaps and questions that need to be answered regarding therapy. Similarly, there has been considerable discussion and debate recently on the terminology of potential precursor lesions for SCC. This is leading to some confusion between the meaning and implication of terms such as solar keratosis, Bowenoid solar keratosis, intra-epidermal carcinoma, Bowen’s disease, in-situ squamous cell carcinoma, and others. This certainly is an area for further work and clarification as there is insufficient agreement as yet amongst pathologists and clinicians. For the purposes of these Guidelines, we have tried to use the traditional terms of solar keratosis and Bowen’s disease, with an explanation in the section on Pathology of the term Bowenoid solar keratosis. The latter term is being used in Australian pathology reporting with increasing frequency. We have deliberately not entered the debate about what is the correct terminology at this stage, but await the outcome of further research in this area. Part of the role of Guidelines such as these being produced is to make recommendations for future research which may provide the answers that the working party has found are necessary and that are currently missing.

In view of the factors mentioned, the Australian Cancer Network initiated a project to develop evidence-based guidelines for the management of non-melanoma skin cancer (NMSC) following the principles outlined in the 1999 edition of the NHMRC Guide to the development, implementation and evaluation of clinical practice guidelines.

A working party comprising representatives from each of the areas involved in NMSC in Australia including general practice, general surgery, plastic surgery, dermatology, radiotherapy, epidemiology, public health and consumers was established to develop the Guidelines. The initial process was for working party members to develop draft documents covering each of the sections outlined in the full document including the epidemiology of the tumours, a brief clinical description, the modes of therapy currently advocated, a public health approach to NMSC prevention and a consumer section indicating concerns of the patients that the treating practitioner might keep in mind. The latter have been written as a series of critical questions that may need to be answered.

It became apparent very early in the process that there are very few, if any, randomised controlled trials related to most of the various forms of therapy that are used for BCC and SCC. Nevertheless, levels of evidence have been presented in the manner prescribed by the NHMRC guide.

The NHMRC designates levels of evidence which have been followed in this document.
1. Introduction

Non-Melanoma Skin Cancer: Guidelines for treatment and management in Australia

Level of evidence ratings

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<tr>
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<tr>
<td>I</td>
<td>Evidence obtained from a systematic review of all relevant randomised controlled trials.</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from at least one properly designed randomised controlled trial.</td>
</tr>
<tr>
<td>III–1</td>
<td>Evidence obtained from well-designed pseudo-randomised controlled trials (alternative allocation or some other method).</td>
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<tr>
<td>III–2</td>
<td>Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.</td>
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<tr>
<td>III–3</td>
<td>Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.</td>
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<tr>
<td>IV</td>
<td>Evidence obtained from case series, either post-test or pre-test and post-test.</td>
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</table>

Within the body of the text, the levels of evidence underlying a recommendation are highlighted.

Another problem that arose in attempting to deal with these tumours was the fact that there may be different therapeutic approaches according to whether or not the treatment is the treatment for a primary tumour or whether it is for a tumour that has recurred. The working party noted that there is some confusion created by the word ‘recurrence’ used to describe where there is residual tumour which may or may not become clinically apparent in the future. For this reason, it was decided to present treatment of the tumours in three categories:

1. Treatment of the primary tumour,
2. Treatment when it is clear at the end of the primary treatment, either clinically or from histopathology (or both), that the treatment has been inadequate and that there is tumour still present (residual tumour),
3. Treatment of clinically recurrent disease which becomes apparent some time (months to years) after the primary treatment in which there was no suggestion, either clinically or histopathologically, at the completion of treatment that there was residual tumour present.

The production of draft Guidelines was the first stage. The second stage was a widespread consultation seeking input from all individuals or organisations who have a stake in the diagnosis and management of NMSC in Australia. Dissemination of this document is part of that process.

It must be stated clearly that the Guidelines are designed as information to assist decision making and are based on the best evidence available at the time of preparation. They are not meant to be prescriptive, being a guide to appropriate practice. They are to be used only subject to the clinician’s judgement in each individual case, taking into account all factors that might influence the decision on which therapy is appropriate for which person.

Finally, the Guidelines are only a first step in a process which aims to improve initially the treating practitioner's knowledge and skill in treating these tumours and, as a result, the outlook for the person with a tumour who requires
treatment. A major requirement of the NHMRC in the development of any Guidelines is also the development of an implementation strategy and an evaluation which shows that they are making a worthwhile contribution. Both of these are important on-going tasks for the working party set up by the Australian Cancer Network following development of the guidelines.

Professor Robin Marks AM
Chairman
ACN Management of Non-Melanoma Skin Cancer Working Party
2. EPIDEMIOLOGY

OVERVIEW

Non-melanoma skin cancers represent a large public health problem among the Australian population in terms of both prevailing health care costs and cosmetic ill effects such as facial disfigurement. Of the 10 most expensive cancers in Australia, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) together are the most costly, accounting for some $A232.2 million per year\(^1\). Skin cancers are avoidable however and these costs potentially could be reduced through primary prevention\(^2\). Because cancer registries do not routinely report skin cancers apart from melanoma, exact incidence rates are not known. National surveys have been conducted however (as part of household market surveys) and these confirm that the incidence rates of skin cancer in people aged 14 years and over are very high. In 1995, the year of the most recent national survey, incidence was estimated to be 788 per 100,000 for BCC and 321 per 100,000 for SCC, with 190,000 people treated for at least one BCC and almost 80,000 for at least one SCC\(^3\). These are the highest reported rates in the world, and represented a rise by some 20% for BCC and over 90% for SCC between 1985 and 1995\(^3\). In 1995, men were more commonly affected by BCC than women were after age 40, and by SCC at all ages. The median age at diagnosis was around 54 years in both sexes\(^3\). In Australia about 200 people die each year from skin cancers other than melanoma\(^2\).

Numerous descriptive epidemiological studies of skin cancer\(^4\) have been highly consistent in confirming that, when sun exposure of skin cells is low or absent, then cancers rarely develop\(^5\). In Australia, this means that the high ambient solar ultraviolet (UV) radiation plays a pre-eminent role in skin cancer causation and that those with white skins are especially susceptible, having the highest known incidence rates. On the other hand skin cancers are exceedingly rare in Aboriginal and Torres Strait Islander Australians. The face is one of the most heavily sun-exposed skin sites and is the site most densely affected by skin cancers in the population\(^5\)—hence their major cosmetic impact. In contrast sites that are virtually never sun-exposed like the buttocks are not affected. Inhabitants of temperate countries who migrate to Australia take on a higher risk of skin cancer than those who do not emigrate\(^6\). Analytic epidemiological studies also point to solar radiation as a major cause of NMSC\(^4\).

A very small proportion of skin cancers in Australia (<1%) is attributable to causative factors apart from solar UV. For BCC these include arsenic\(^7\), ionising radiation therapy\(^8,9,10\) and scars, and for SCC, immune suppression, tobacco, human papilloma virus (HPV) (in patients with epidermodysplasia verruciformis) and chronic ulcers, sinus tracts and scars\(^11\).
Eradication of skin cancer among Australians is unlikely because sun exposure in this country is ubiquitous and because a small proportion of the population is highly susceptible to this disease.

- Primary prevention of the majority of NMSCs is theoretically possible however, through avoidance of excessive sun exposure starting from childhood.
- Skin cancer control could be achieved through national education programs including a national primary prevention campaign, which has been proposed, and would be potentially cost-effective in reducing current expenditure on skin cancer.

**Key point:**

In Australia annual health care costs for non-melanoma skin cancers are around $A232.2 million per year (1993–94) (greater than for any other cancer).

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<thead>
<tr>
<th>Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
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<tr>
<td>Solar radiation is the major cause of non-melanoma skin cancer</td>
<td>III–2</td>
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**Basal Cell Carcinoma**

**Incidence and mortality**

General population

In the most recent national survey, the incidence rate of BCC in 1995 was estimated to be 788 per 100,000 in people aged 14 years and over (in men, 955 and in women, 629 per 100,000) and there was a strong inverse association with latitude. Rates in women were higher in younger age groups, while rates in men were higher in older age groups. Compared with 1985, rates of BCC increased by 19% overall, with the increase occurring mostly in men and in the elderly, but there was an apparent decrease in people under 40 years. In Queensland in the Nambour study, age-adjusted annual incidence rates of BCC in men and women aged 25 to 75 years were estimated to be 2,074 and 1,579 per 100,000, respectively in 1992. In the northern city of Townsville estimated incidence rates in 1997 were 2,058 and 1,195 per 100,000 for men and women respectively. Native-born Australians are at higher risk of BCC than migrants.
and, among migrants, age of arrival in Australia is inversely associated with BCC risk\textsuperscript{16}. In people less than 40 years the incidence of BCC was higher in women than men in the national survey\textsuperscript{3} while BCC rates were similar in men and women under 40 in the Townsville study. After 40 years of age, BCC rates in men have generally been found to be progressively greater than in women, with advancing age\textsuperscript{3,15}. When surface area is taken into account highest rates in men and women are found on the face, especially the eyelid, lip and nasolabial fold, followed by ears, nose and cheek\textsuperscript{15}. Very high rates are also seen on the neck, back and shoulders in men and neck, shoulders and outer arms in women\textsuperscript{15}.

**Immunosuppressed patients**

In the follow-up study in Queensland of the 1,158 renal transplant patients with no skin cancer prior to transplantation, 1969 to 1994, BCC was diagnosed as first skin cancer in 35%. 52 patients (19%) developed only BCCs (mean number of BCCs, 2.2), and 50% developed both SCCs and BCCs (mean number of BCCs, 4.3)\textsuperscript{17}. Cumulative incidence of BCCs was approximately 25% at 10 years and 54% at 20 years\textsuperscript{17}. Among the first 455 heart transplant patients in Sydney, the cumulative incidence of BCC was approximately 7% at 5 years and 10% at 10 years\textsuperscript{18}.

**Genetic epidemiology**

Southern European ancestry is strongly protective while people with fair skin, light coloured or red hair\textsuperscript{14}, an inability to tan and a history of childhood freckling\textsuperscript{16} are at significantly raised risk of BCC. This suggests that common variants and mutations in the melanocyte stimulating hormone receptor gene (MC1R) play a role\textsuperscript{19,20}. Xeroderma pigmentosum (XP) patients who inherit a mutation which makes them unable to repair UV-induced DNA damage in their skin cells are highly susceptible to all types of skin cancers including BCC\textsuperscript{21}. Patients with the nevoid basal cell carcinoma (Gorlin’s) syndrome are also highly susceptible to BCC\textsuperscript{22}. Nevoid basal cell carcinoma syndrome is characterised by prominent forehead, jaw cysts, and increased incidence of a variety of tumours. Both XP and Gorlin’s syndrome are rare disorders characterised by early onset and relentless lifelong high frequency of BCCs\textsuperscript{21,22}. The most frequent genetic abnormality in BCC is loss of heterozygosity for the region on chromosome 9 containing the patched gene, and inactivation of this tumour suppressor gene is thought to be a principal cause of both sporadic and familial BCC\textsuperscript{21}. BCCs show p53 mutations and ras mutations, but allelic loss is uncommon apart from the Gorlin locus (in contrast to SCCs)\textsuperscript{22}. BCC case subjects have been reported as three times more likely to have a p53 mutation in normal skin taken from the mirror-image site to the cancer site (excluding face and ears) than normal skin taken from a random site in control subjects\textsuperscript{23}. Frequency of CC to TT mutations (involving codons 247 and 248) did not reflect recalled total UV-radiation exposure however.
Environmental risk factors

The predominant role of solar UV radiation in the aetiology of BCC is supported by the consistent observation that clinical signs of chronic sun damage to the skin are the strongest predictors of BCC, although there is an overall lack of association between BCC and reported chronic sun exposure\(^{14,12}\). Various theories of UV dose-rate dependence have been proposed to explain the apparent differences in dose-response between BCC and SCC, eg, the intermittent UV exposure theory which proposes that pattern of sun exposure rather than the total amount of exposure determines risk of BCC\(^{12}\). It is also speculated that target epithelial cells, maybe highly mitotic, and may require a relatively low threshold of total solar radiation for malignant transformation\(^{13}\) (cf. a higher total dose needed to transform epithelial cells from which SCCs arise). The occurrence of BCC at earlier ages than SCC and on the trunk as well as the face would support this\(^{13}\).

Ultraviolet dose dependence may also vary among the commonest BCC subtypes as suggested by their clinical and histological differences. In particular superficial BCCs appear to differ from the nodular subtype as demonstrated in two large series, one comprising all BCCs diagnosed in a pathology laboratory in Melbourne in a five month period (N=3885)\(^{24}\) and the other, all BCCs diagnosed/treated in a teaching hospital in The Netherlands in an 11 year period (N=2990)\(^{25}\). In both series more of the superficial BCCs diagnosed (49%\(^{24}\) and 62%\(^{25}\)) occurred on the trunk than on any other site while the majority of nodular BCCs (64%\(^{24}\) and 77%\(^{25}\)) occurred on the head and neck. This finding and the younger ages of patients with superficial compared with patients with nodular BCCs suggest that superficial BCCs have a lower threshold for UV carcinogenesis than the nodular subtype. The subtype relation with site is complex however, since nodular BCC predominated over superficial BCCs on the trunk in the Australian series\(^{24}\) and they occurred in similar proportions on the trunk in the Dutch series\(^{25}\).

Other risk factors for BCC are
- exposure to ionising radiation therapy\(^{8}\)
- exposure to arsenic\(^{11,26}\)—this would play a relatively small part in the overall burden of BCCs in Australia
- some dietary factors\(^{27,28}\)

Among immunosuppressed patients, determinants of BCC in immunosuppressed patients in the Queensland follow-up study were a history of previous skin cancer and duration of immunosuppressive therapy\(^{17}\). Level of ambient UV also affects incidence of BCC and other skin cancers after organ transplantation as seen by the far higher rates and earlier times of onset of skin cancer in transplant patients in Australia than in The Netherlands\(^{17}\).
**Key points:**

- When surface area is taken into account, highest rates in men and women are found on the face, especially the eyelid, nonmucosal skin of the lip and nasolabial fold, followed by ears, nose and cheek. Very high rates are also seen on the neck, back and shoulders in men and neck, shoulders and outer arms in women.

- The occurrence of BCC at earlier ages than SCC and its common occurrence on the trunk as well as the face would support the suggestion that BCC requires a lower threshold of total solar radiation before malignant transformation than is required for SCC.

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**Squamous cell carcinoma and related keratinocyte tumours**

**Incidence and mortality**

**General population**

In the most recent national survey of treated skin cancer, the incidence rate of SCC in 1995 was estimated to be 321 per 100,000 in people aged 14 years and over, with a significant latitude gradient: the highest rates are seen in those living at latitudes less than 29°S. Overall SCC incidence had risen by 93% since 1985, but this was mostly in people in the south of Australia (greater than 37°). Surveys in Queensland have confirmed that SCC rates are highest in tropical and subtropical latitudes. In the township of Nambour (26°S), annual incidence rates of SCC in men and women aged 25 to 75 years were estimated to be 1,035 and 472 per 100,000 respectively in 1992. Further north in Townsville (19°S), incidence rates of 1,332 per 100,000 men and 755 per 100,000 women have been reported. The incidence of SCC increases with increasing age and highest rates in both men and women are found on the face, especially the lip region, ears, nose, cheek and eyelid when surface area is taken into account, with neck, dorsa of hands and forearms next most affected. Migrants to Australia have lower risks of SCC than people born in Australia. The mortality rate of non-melanoma skin cancer (predominantly SCC, but could include a small number of deaths from BCC and Kaposi’s sarcoma) in Australia in the years 1995–1998 was 2.0 per 100,000 men and 0.5 per 100,000 women.

There are no published population-based incidence rates of people who develop solar keratoses (SKs) and this would be difficult to calculate given the lability of these lesions. However, it has been found in a follow-up study of 424 volunteer adult residents of Maryborough, Victoria (37°S) who were initially lesion-free,
that 81 (19%) had a prevalent solar keratosis at 12 months. In Queensland, in a population-based prevalence study in Nambour (26°S), 44% of men and 37% of women between the ages of 20 and 69 years had at least one solar keratosis on examination of head, neck, hands and arms, the most common sites of occurrence. Prevalence of SKs is strongly age-dependent reflecting incidence and recurrence rates that exceed rates of regression as people age. A spontaneous remission rate of 10% has been reported based on follow-up after 12 months, though with more intense lesion surveillance, substantially higher rates of remission are seen. On rare occasions a solar keratosis may undergo malignant transformation to SCC, though definitive evidence from a long-term, closely monitored study is lacking. In a medium-term (5-year) study based in Maryborough, Victoria, the rate of malignant transformation was estimated to be less than 1:1000 (though without histological confirmation of the initial lesion, the possibility remains that the lesion was an SCC at the outset). None of more than 1000 SKs in 200 Nambour residents who were followed up every 2 to 6 months for 18 months underwent malignant transformation. In summary, the chances that an individual solar keratosis will develop into an SCC are extremely small. However when one encounters an SCC, the chance that it has arisen in association with solar keratoses is very high.

Relatively little is known about the specific epidemiology of other keratinocyte tumours in Australia. The incidence of keratoacanthoma (KA) was estimated as 36 per 100,000 person-years in a national survey of treated skin cancers in 1990. The incidence rate of seborrhoeic keratoses is not known but the prevalence was recently estimated to be 12% in people 15–25 years; 79% at ages 26–50; and 100% in those over 50 in a volunteer sample of 100 adults in Victoria.

Immunosuppressed patients

In a long-term retrospective follow-up study in Queensland, the risk of skin cancer was evaluated in people who received renal transplants from 1969 to 1994 in that state. Of 1158 Caucasian patients without a history of skin cancer prior to transplantation, SCC was diagnosed as the first skin cancer in 56%; 83 patients (31%) developed only SCCs (mean number of SCCs, 3.9) while 136 (50%) developed both SCCs and BCCs (mean number of SCCs, 12.6). Cumulative incidence of SCCs was approximately 30% at 10 years and 60% at 20 years. In a study of histologically proven skin cancers in the first 455 heart transplant patients in Sydney, the cumulative incidence of SCC was approximately 24% at 5 years and 33% at 10 years.

Genetic epidemiology

Native Australians of southern European ancestry have much lower risk than those of British or northern European origin and, in general, people with fair skin colour who sunburn easily without tanning are at increased risk of SCC and SKs. This is because white skin lacks melanin protection from ultraviolet (UV) radiation. Hair and skin colour are influenced by the common variants of
the melanocyte stimulating hormone receptor gene (MC1R)\textsuperscript{19}, and it is likely that mutations in this gene are linked to risk of non-melanoma skin cancer\textsuperscript{20}. XP patients are highly susceptible to SCC, SKs and KAs\textsuperscript{21}. UV-induced mutations (distinctive mutations especially CC to TT tandem base mutations) in the p53 gene can be found in the majority of SCCs, and there is also a high rate in related keratinocyte tumours. Loss of heterozygosity studies show that allelic loss is common, found in 25–30\% of SCCs\textsuperscript{22}.

Environmental risk factors

The strongest environmental risk factor for SCCs and related keratinocyte tumours is chronic sun exposure and their anatomic site distribution reflects sites of maximal sun exposure. The UV radiation spectral regions of sunlight—the wavelengths 290–320nm (UVB) and 320–400nm (UVA)—are those specifically implicated in carcinogenesis. In studies in Queensland and Western Australia there were strong associations with clinical signs of chronic skin damage, especially SKs\textsuperscript{14,39} and in Western Australia total site-specific sun exposure based on recall was strongly related to risk of SCC\textsuperscript{39}. In the Nambour study population, high levels of occupational exposure and sunburns were strongly and significantly associated with SK prevalence, especially in those people with multiple SKs\textsuperscript{34}. While SKs share many of the same determinants as SCC, they may be a more sensitive indicator of intense sunlight exposure\textsuperscript{40}.

There are other risk factors for SCC including tobacco; HPV (in patients with epidermodysplasia verruciformis); arsenic (in association with arsenical keratoses); polycyclic aromatic hydrocarbons; and chronic ulcers, sinus tracts and scars\textsuperscript{11}. However only a very small proportion of SCCs in Australia would be attributable to these other risk factors compared with solar UV.

Immunosuppressed patients

Determinants of SCC were as for BCC in the Queensland study\textsuperscript{17}. HPV is also believed to play a role\textsuperscript{41}.

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**Key point:**

- The overall incidence rate of SCC in 1995 was estimated to be 321 per 100,000 in people aged 14 years and over in Australia\textsuperscript{3}. There is a significant latitude gradient such that the highest SCC rates (2–4 times the national average) are seen in those living at low latitudes such as Townsville, North Queensland\textsuperscript{15}.  

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The chances that an individual solar keratosis will develop into an SCC are extremely small; however when one encounters an SCC, the chance that it has arisen in association with solar keratosis is very high.
3. CLINICAL FEATURES

INTRODUCTION

The high prevalence rates of NMSC in Australia make it imperative that all clinicians are familiar with its various presentations. Early detection of these lesions is important in minimising morbidity, costs of treatment and mortality associated with these lesions. Clinical examination that is conducted for other purposes, particularly in the general practice context, provides opportunities for screening and early detection of NMSC.

In addition to the clinical features that are evident at any one point in time, clinical history also provides important evidence on which to base diagnosis. NMSCs are changing lesions and the time course of the change is generally evident over a period of months. Many are also symptomatic. These features vary with different skin cancers.

Key point:

• The importance of asking about change and symptomatology in the course of assessing a lesion cannot be underestimated.

Some lesions will be confidently diagnosed on clinical examination and history and others, particularly early lesions with subtle clinical features, will require biopsy. Partial biopsy techniques such as punch, shave and incisional biopsy are considered appropriate in the assessment of NMSCs. Consideration should be given to the role of pre-treatment biopsy in confirming the presence of skin cancer, the type, its growth pattern, prognostic features and the most appropriate modality to maximise the chance of cure and minimise the morbidity of treatment.

Examination for skin cancer should be considered in the general practice context for all patients over the age of 40 and particularly for the elderly. Patients with special risk factors (see chapter 2) should be considered for entry to a regular surveillance program with their general practitioner or dermatologist. A substantial proportion of NMSCs occur on the intermittently exposed parts of the trunk and limbs and it is worthwhile to examine these areas in addition to the head and neck, hands and forearms. The examination should be conducted in a well lit area and magnification may be useful. Atlases are available that illustrate the clinical features of NMSCs.42
Key points:

- Clinical history is important in diagnosis.
- Partial biopsy techniques such as punch, shave and incisional biopsy are appropriate.
- Examination for skin cancer should be considered during physical examination for all patients over the age of 40 and particularly for the elderly.

Basal Cell Carcinoma

Numerous histological types of BCC have been described but most are uncommon and do not have distinctive clinical presentations. There are three common growth patterns of BCC (superficial multifocal, nodular and morphoeic) that have a distinctive clinical presentation. Superimposed on any of these growth patterns may be ulceration or pigmentation. Though these latter features lead to a distinctive clinical appearance, they do not correspond to a specific histological growth pattern and are therefore no longer considered to represent separate types of BCC. Immunosuppression for organ transplantation predisposes to BCC.

Accuracy of clinical diagnosis of basal cell carcinoma

The diagnostic accuracy of experienced dermatologists surveying people selected at random from the general community is around 59% to 65%. This is somewhat lower than would be expected in clinical practice because of the much lower prevalence of skin cancers in the community compared with the clinical setting. No data are available regarding the diagnostic accuracy of clinicians in Australia but in a clinical practice setting in the United States, a diagnostic accuracy of 70% has been reported for university-based dermatologists. These observations indicate that, in spite of the frequency of BCC and in spite of high levels of clinical experience, diagnosis may be difficult.

Superficial

Superficial BCC is a common subtype of BCC occurring in Australians. They generally occur on the trunk or limbs and in younger people more than other growth patterns.

Clinical features

Superficial BCC presents as a bright pink, shiny, usually well-defined erythematous macular lesion. The degree of erythema present may fluctuate greatly and will be increased by stretching or rubbing the lesion. Stretching the
lesion will highlight the shiny surface and may reveal a peripheral, thread-like, pearly rim or islands of pearliness distributed through the lesion.

A minority of superficial BCCs are symptomatic with itching being the most common symptom. Though these lesions are readily eroded by minor trauma, a history of ulceration or bleeding is uncommon.

Causation

Multiple superficial BCCs may occur in the context of arsenic intoxication. Other stigmata of arsenic intoxication include punctate palmoplantar keratoderma, scattered macular hyperpigmentation and longitudinal pigmented bands or horizontal hyperpigmented stripes in fingernails and toenails.

Clinical course

Many superficial BCCs will progressively enlarge over months to years and, if left, may reach 5–10 cm in diameter. Some may be relatively stable and a few will regress. With time areas of nodular and even sclerosing growth pattern may supervene within the original superficial BCC.

Differential diagnosis

Superficial BCC can generally be distinguished from Bowen’s disease by its shiny surface and lack of hyperkeratosis. Superficial BCC has a brighter pink hue than Bowen’s disease (see p19) or amelanotic melanoma. Amelanotic melanoma will frequently show some ill-defined light brown pigmentation. Like Bowen’s disease, solar keratoses will usually be somewhat hyperkeratotic though this may be difficult to distinguish from the scaling seen in some superficial BCCs.

The appearances may suggest an inflammatory dermatosis such as eczema or psoriasis, however, the clinical history is one of inexorable enlargement over months or years. Inflammatory lesions, on the other hand, would generally be more transient.

Nodular

Nodular BCCs are more often found on the head and neck in subjects who are, on average, somewhat older than those with superficial BCC\textsuperscript{24,25}. These findings suggest that they may be more closely tied to chronic cumulative sun exposure than superficial BCC.

Clinical features

Nodular BCC typically presents as a shiny, translucent (pearly), telangiectatic papule or nodule. As the lesion enlarges the pearliness becomes more evident and dilated capillaries may be seen coursing across the surface of the lesion. These are often radially arranged. Recurrent ulceration is frequent and this may lead to central umbilication of the lesion with a more raised, rolled border. Islands of pigmentation may become clinically visible and the lesion may...
become darkly pigmented, suggesting melanoma. Like superficial BCC these may be associated with sensory symptoms in a minority of cases but unlike superficial BCC, nodular lesions will repeatedly ulcerate and bleed.

Differential diagnosis
Nodular BCCs need to be differentiated from SCC and amelanotic nodular melanoma. Nodular BCCs are distinguished by pearliness and horizontal, branching telangiectasia.

Clinical course
Nodular BCCs will progressively enlarge and may raise up over a period of months to years.

Morpheic
Morpheic or sclerosing BCC has a similar body site distribution to nodular BCC. Morpheic BCCs are usually of long standing and tend to be deeply invasive.

Clinical features
As the name ‘morpheic’ suggests, these lesions have a sclerosing growth pattern with fibrosis surrounding areas of BCC. BCCs that are predominantly morpheic present the appearances of a pale scar. These can be clinically difficult to detect and the patient may be unaware of them. Morpheic BCCs constitute an aggressive growth pattern and are often associated with significant tissue destruction. Palpation usually reveals firm induration which may extend more widely and deeply than is evident on inspection. Morpheic changes will frequently supervene in long standing nodular BCCs and these lesions may retain some clinical features of nodular BCC. Morpheic BCCs are frequently asymptomatic. Those with nodular elements may show all the same symptoms as nodular BCCs.

Clinical course
Morpheic BCCs may remain undetected by doctor and patient for many years and may slowly enlarge and deepen to reach a large size before therapy is instituted.

The major differential diagnosis of morpheic BCC is scar and biopsy is frequently necessary to establish the diagnosis.
Key points:

- Superficial basal cell carcinomas present as a bright pink, shiny, usually well-defined erythematous macular lesion.
- Nodular basal cell carcinoma typically presents as a shiny, translucent (pearly), telangiectatic papule or nodule.
- Basal cell carcinomas that are predominantly morphoeic look like a scar.

Squamous cell carcinoma

The majority of SCCs are thought to arise from solar keratoses. The age and body site distribution is therefore similar to solar keratosis. A few develop from chronic ulcers or scars, sites of chronic radiation dermatitis or from infrared irradiation. Immunosuppression for organ transplantation strongly predisposes to SCC.

Clinical features

SCC typically begins as a tender erythematous papule or nodule. This may be surmounted by a variable amount of hyperkeratosis, some producing a keratotic horn. The lesion enlarges over a period of months and becomes increasingly tender. Recurrent ulceration and bleeding may develop. Some, particularly on the scalp and legs may present as an ulcer without a preexisting nodule or surrounding induration.

Accuracy of diagnosis of squamous cell carcinoma

Experienced dermatologists working in a Queensland prevalence study achieved a diagnostic accuracy of 39%, considerably lower than the 59% found for BCC. The clinical diagnosis of early SCC is difficult, particularly to distinguish it from a hypertrophic solar keratosis. It is likely that many early SCCs are treated with cryotherapy based on a clinical diagnosis of solar keratosis. Lesions that are initially considered to be solar keratoses that persist following cryotherapy, enlarge or become tender should be biopsied to explore for the presence of SCC.
Clinical course

The course of an SCC is generally one of progressive enlargement. Ulceration and bleeding become more likely as the lesion enlarges. A few will become locally aggressive with perineural spread. Large lesions have greater potential for metastasis which generally occurs to regional lymph nodes.

Differential diagnosis

SCC may be difficult to differentiate clinically from nodular BCC and amelanotic nodular melanoma. Nodular BCC will generally display a brighter pink colour than the dull red typical of SCC. Pearliness, telangiectasia and islands of pigment are also helpful features of BCC. Amelanotic nodular melanoma may show some light brown pigmentation. Excision and histological assessment may provide the only way to establish the diagnosis.

Key points:

• The majority of squamous cell carcinomas are thought to arise from solar keratoses.
• Squamous cell carcinoma typically presents as a tender erythematous papule or nodule that may show hyperkeratosis.
• Immunosuppression for organ transplantation strongly predisposes to squamous cell carcinoma.
• The clinical diagnosis of early squamous cell carcinoma is difficult.

Solar keratoses

These lesions are usually found on the chronically sun exposed sites of head and neck, dorsae of hands and forearms. They are generally multiple and may be very numerous or confluent.

Clinical features

Solar keratoses present as an erythematous macule with superimposed hyperkeratosis. Hyperkeratosis may be gross enough to produce a keratotic horn but the erythematous base of the lesion remains macular and impalpable. There is no underlying induration when the lesion is palpated and they are generally non tender. Solar keratoses may be symptomatic. A variety of sensory symptoms including pricking, burning and stinging may be felt with sun exposure or perspiration.
Differential diagnosis

Pigmented solar keratoses may need to be differentiated from solar lentigines and lentigo maligna. Hyperkeratosis is the most helpful distinguishing feature of solar keratosis. Solar keratoses are smaller and less well defined at the periphery than Bowen’s disease and are also less well defined than seborrhoeic keratoses.

Thickening and tenderness on lateral palpation are signs that a solar keratosis may have developed into invasive SCC.

Clinical course

Only a small percentage of solar keratoses evolve into invasive SCC. One estimate suggests that the rate of malignant transformation is less than one in 1000 per year\textsuperscript{36}. Many SCCs, however, evolve from solar keratoses\textsuperscript{40}.

---

**Key points:**

- Solar keratoses present as an erythematous macule with superimposed hyperkeratosis.
- Only a small percentage of solar keratoses evolve into invasive squamous cell carcinoma.
- Thickening and tenderness on lateral palpation are signs that a solar keratosis may have developed into invasive squamous cell carcinoma.

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**Bowen’s disease**

Bowen’s disease has a predilection for the lower limbs, particularly in females, but may occur at any site.

Clinical features

Bowen’s disease presents as a sharply defined, erythematous, round to oval hyperkeratotic plaque. The degree of hyperkeratosis may vary, some lesions producing a keratotic horn. Hypertrophic Bowen’s disease may show epidermal hyperplasia only without keratin production and present as a raised, moist, juicy plaque or tumour. Bowen’s disease is generally asymptomatic. The clinical history is usually of a long standing, slowly enlarging lesion.

Differential diagnosis

Bowen’s disease may be distinguishable from psoriasis by its long history though the clinical appearances may be very similar. Superficial BCC can be distinguished from Bowen’s disease by lack of hyperkeratosis, the shiny surface
and bright pink colour. Hypertrophic Bowen’s disease may mimic SCC and a biopsy is frequently necessary to distinguish this from invasive SCC. Pigmented Bowen’s disease may mimic superficial BCC or superficial spreading melanoma.

Clinical course
Bowen’s disease will generally enlarge very slowly and will appear to the patient as a stable lesion. The rate of transformation to invasive SCC has not been established but would appear to be low.

Keratoacanthoma
Keratoacanthoma is a well differentiated form of SCC that is characterised by spontaneous resolution. Many of these lesions arise in association with solar keratoses and the age and site distribution is similar to solar keratosis and SCC. The chronically exposed sites of the head and neck, hands and forearms are most commonly affected though multiple keratoacanthomas most often occur on the limbs, particularly the lower limbs.

Clinical course
The most characteristic feature of a keratoacanthoma is its clinical course. These begin as a small papule that rapidly enlarges to form an erythematous nodule with a central keratotic plug. The lesion continues to enlarge over a period of four to eight weeks, remains stable for a period as an asymmetrical, dome shaped erythematous nodule with a central keratotic plug. It may reach a size of several centimetres in diameter. Keratoacanthomas are typically exquisitely tender until regression is well established. The fleshy rim then begins to recede, exposing more of the central keratin plug until there is an erythematous collar surrounding a keratotic horn. The central keratin plug then falls out and the remainder of the lesion resolves sometimes leaving a scar. Rare differential diagnoses include amelanotic melanoma, atypical fibroxanthoma and Merkel cell tumour. Not all lesions with this initial clinical course appearance will resolve and a minority will persist as SCC. Resolution of keratoacanthoma generally takes 6–12 weeks.

Aids to diagnosis
Partial biopsy will generally be unhelpful in differentiating keratoacanthoma from carcinoma. Partial biopsy will almost always be reported as well differentiated SCC because the pathologist requires the architecture of the entire lesion to suggest the possibility of keratoacanthoma.
4. **PATHOLOGY (INCLUDING BIOPSY)**

**HISTOPATHOLOGICAL CLASSIFICATION AND PROGNOSIS**

**Basal cell carcinoma**

BCCs are a group of tumours which are composed of lobules of basaloid cells characterised by hyperchromatic nuclei and scant cytoplasm. These represent pluripotential cells derived or closely related to basal keratinocytes and follicular or epidermal stem cells. Metastases rarely develop from BCC and the main risk is that of recurrence after incomplete removal. Nodular (and nodulocystic) tumours as well as superficial BCCs comprise the majority of tumours. Morphoeic (sclerosing, fibrosing) BCC, infiltrative BCC and microlobular tumours have less well defined clinical margins and are associated with increased rates of recurrence. Although numerous cytological types of BCCs (clear cell, pleomorphic, granular cell, adamantinoid) have been described, most of these are uncommon and these subtypes do not have established prognostic significance.

There may be pitfalls in the histological diagnosis of BCC. BCCs often have recognisable appendageal differentiation, most commonly follicular type, and may need to be distinguished from eccrine or sebaceous carcinomas which have an increased risk of metastases. The distinction between morphoeic BCC and desmoplastic trichoepithelioma as well as sclerosing sweat duct carcinoma may be difficult in small biopsy samples. Similarly some SCCs may have a basaloid appearance (basosquamous carcinoma, SCC with basaloid keratinocytes) and are also associated with increased risk of metastases. The basaloid cells of Merkel cell carcinoma or small cell melanoma may also be mistaken for BCC and have a worse prognosis. In doubtful cases immunohistochemistry may be vital for diagnosis if definite diagnosis cannot be achieved. The appendageal tumours simulating BCC are relatively rare and are not covered in this guideline of non-melanoma tumours.

**Squamous cell carcinoma**

SCCs are a group of non-melanoma skin cancers characterised by lobular proliferation of keratinocytes and intradermal invasion of keratinocytes that show prominent keratin production. The risk of metastases increases with tumour thickness, the presence of clinical immunosuppression and with poorly differentiated tumours. Tumour recurrence is more common with infiltrative and desmoplastic lesions demonstrating spindle or single cell infiltration within a dense connective tissue stroma particularly as initial surgical margins may be
difficult to define as being clear of tumour. Perineural invasion by SCC when close to the excision margins also increases the likelihood of residual tumours. SCCs are usually graded into well differentiated (resembling the differentiation of normal epidermis), poorly differentiated (difficult to diagnose without keratin markers) and moderately differentiated between these two extremes. Acantholytic (adenoid, pseudoglandular) SCCs are associated with loss of cohesion of keratinocytes but the prognostic significance of this variant remains to be determined.

**Solar keratoses**

Solar keratoses represent a potential precursor for invasive SCC and are associated with confluent dysplasia involving the interfollicular epidermis concentrated particularly within basal keratinocytes. Only a small fraction of solar keratoses progress to invasive SCC\(^{31,51}\). The distinction between some hyperplastic solar keratoses and early invasive SCC is not sharp.

**Bowen's disease**

Bowen’s disease (intraepidermal SCC) is associated with full thickness epidermal dysplasia with follicular involvement. The presence of papilloma virus has been found in Bowen’s disease particularly in non sun-exposed sites and on the hands and feet\(^{52}\). This may represent an oncogenic factor. Despite the full thickness epidermal dysplasia the majority of intraepidermal SCC classified as Bowen’s disease have a prolonged in situ phase which may last many years\(^{53}\).

**Bowenoid solar keratoses**

Bowenoid solar keratoses share histological features with both of these precursors and is a term used by some pathologists. Many examples of Bowenoid solar keratoses probably represent true Bowen’s disease particularly when only a small sample is available for diagnosis and follicular involvement cannot be adequately assessed. Solar keratoses that evolve to invasive SCCs may not have progressed to full thickness Bowenoid changes prior to invasion in contrast to the sequence of tumour progression seen in many mucosal precursors. The prognostic significance of Bowenoid lesions induced by the sun as compared to papilloma virus associated lesions remains to be determined.

**Keratoacanthoma**

Keratoacanthoma is usually a spontaneously involuting atypical (dysplastic) squamous proliferation with intradermal invasion which undergoes rapid terminal keratinisation and has a characteristic clinical and histological pattern. The histopathology in some keratoacanthomas may have an infundibulocystic follicular component. Giant keratoacanthomas and centrifugally enlarging lesions
may provide difficulties in diagnosis. Keratoacanthomas may be difficult to differentiate from SCCs particularly in small biopsies, shave biopsies or curette fragments. Immunosuppression may alter the biological behaviour of keratoacanthomas and increased caution in management needs to be used as such lesions in this setting may follow a progressive growth history rather than involuting and represent a SCC.

**Biopsy of Non-Melanoma Skin Cancer**

For the majority of skin cancers primary excision represents the main treatment modality and also provides tissue for definite diagnosis as well as assessing the adequacy of surgery. Preliminary biopsy may be required when a firm clinical diagnosis cannot be made or when the treatment choice may be dictated by the tumour type or pattern of growth. Biopsy is also often obtained prior to undertaking extensive surgery and in order to confirm the diagnosis in cosmetically sensitive areas such as the face. Multiple small 2 mm punch biopsies may be used to define poorly demarcated tumours. For superficial lesions such as for Bowen’s disease or superficial BCC, particularly when the tumour may be multifocal and associated with areas of regression, shave biopsy may be a suitable technique as it maximises the area sampled. This method should be avoided when the aim is to detect the presence of SCC in a setting of solar keratoses as the samples are often too shallow for adequate assessment. Similarly the distinction between SCC and keratoacanthoma cannot always be made on shave specimens. Shave biopsy sites may heal rapidly and may be difficult to locate when the patient returns for further therapy. The site of shave biopsies should be mapped or photographed for future identification. In the majority of deeper tumours an incisional or punch biopsy is a preferable method and allows both pathological diagnosis and assessment of the pattern of differentiation. The technique can also be used to provide a guide to tumour depth particularly prior to using radiotherapy when the biopsy is obtained from the most infiltrated focus.

Curettage specimens are often used for diagnosis when this technique is used for treatment, but are associated with disruption of tumour architecture. Pitfalls in diagnosis with curette specimens may be associated with poor technique, with insufficient material and inclusion of cauterised fragments. Small cell melanoma as well as some appendageal tumours dominated by cells with hyperchromatic nuclei and scant cytoplasm may closely resemble BCC on curettings and mistakes may occur.

When multiple biopsies are obtained these should be carefully marked and sent in separate containers. For excision specimens, a reference suture or other marker should be used for orientation of the specimen so that the site of tumour extension to the margin can be indicated in the histological report.
Histopathological report

In reference to non-melanoma skin cancers, the histopathological report deals with the tumour type, degree of differentiation, pattern of growth, cell morphology and in excisional material the presence or absence of tumour free surgical margins. In order to provide an optimal report the clinician needs to provide patient identification including the age and sex of the patient, exact site of the specimen and a provisional clinical diagnosis. Any history of previous therapy or biopsy of the tumour site should also be included. The presence of a longstanding burn scar, radiodermatitis or ulcer should also be indicated. The final histopathological report should contain the clinical and macroscopic description of each specimen. For specimens containing a reference suture or surgical nick at a specified margin, a diagram indicating the orientation of tissue blocks and colour inks used to identify the cut surfaces should be included in the final report. Individual specimens should be reported separately with their final diagnoses. The measured tumour margins should be included in the report particularly when the tumour extends closer to a border. Measured tumour depth may also be included in the report particularly in biopsies taken prior to radiotherapy. The presence of perineural vascular or lymphatic tumour invasion should also be included in the report.

The validation of tumour clearance margins is partially dependent on the number of tissue blocks and sections examined when the conventional technique of bread loafing the excisional specimen is used. Using this technique infiltrative morphoeic and microlobular subtypes may have undetected extensions to surgical margins. The Mohs’ (see p37,41-2,45-8,61,77) technique which is usually carried out intraoperatively, using frozen sections, samples both the base and all margins and examines the actual surgical marginal planes. This method has less than 1% recurrence rate reflecting its superiority for checking tumour free margins but the technique is not practical for use in all skin specimens submitted for histopathology.

A provisional pathological diagnosis may be issued by a laboratory prior to a final diagnosis particularly when immunoperoxidase markers, further consultation or more rarely ultrastructural studies are needed for definite classification of non-melanoma tumours. The clinician should be aware that these tests may alter the diagnosis and subsequent approach to further management.

Clinical information recommended to be provided on request form:
1. Patient identification.
2. Clinical diagnosis.
3. Any history of previous therapy or previous biopsy of tumour.
4. Diagram of excision specimen with markers for orientation.
5. Specimens from separate sites should be submitted in individual containers.
Keywords with prognostic significance

**Poorly differentiated** refers to tumours in which products of differentiation such as keratin, desmosomal attachments or glandular differentiation are poorly expressed. Immunohistochemistry techniques for keratin subsets are often used to identify such tumours.

**Basosquamous or metatypical carcinoma** are terms used for basaloid tumour which show evidence of squamatisation. These tumours should be viewed as equivalent to squamous cell carcinoma.

**Desmoplasia** refers to tumours which induce sclerotic and extensive fibrous stroma that may be mistaken for a scar. The tumours often present as infiltrative cords of cells that may have ill defined boundaries and are prone to recurrence. Both squamous cell carcinoma and BCC may produce this pattern.

**Large tumour size** particularly in SCC have twice an increased risk of recurrence (tumour greater than 2 cm in diameter 15.2% vs 7.4%) and three times the risk of metastasis (30.3% vs 9.1%) as compared to small squamous cell carcinomas.

**Neural involvement** by tumours takes the form of perineural spread that may extend into the deep tissue and is particularly important in facial lesions. Perineural involvement near the surgical margins is an indication that further measures are required for tumour clearance.

**Dermal lymphatic spread** in satellite nodules may be seen as separate from the primary lesion and represents a poor prognostic sign.

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**Key points:**

- Only a small percentage of solar keratoses progress to invasive squamous cell carcinoma.
- Metastasis rarely develops from basal cell carcinomas.
- The risk of metastasis in SCCs increases with tumour thickness, clinical immunosuppression and in poorly differentiated tumours.

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<table>
<thead>
<tr>
<th>Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmation of complete removal of the tumours is important. Recurrence from incomplete removal is seen more frequently in clinically ill defined basal cell carcinomas such as morphoeic and microlobular forms.</td>
<td>III–2</td>
<td>47, 48</td>
</tr>
</tbody>
</table>
5. PROGNOSIS

Basal cell carcinoma

Key point:
• The endpoint for measuring success of BCC treatment (excluding cosmetic, functional and patient convenience factors) is not universally defined. Survival is a poor measure, and BCC can have a very long history in recurrence pattern (10 to over 20 years being familiar). A chronologically defined local control rate is the best available endpoint. Five year and ten year control rates or recurrence rates are valid instruments.

Introduction

The factors affecting the outcome of both the BCC itself plus the treatment necessary to manage it can be subdivided into:
1. Recurrent tumours
2. Size and depth of invasion (stage)
3. Site
4. Morphological and histological subtype
5. Treatment modality
6. Incomplete excision
7. Perineural spread
8. Naevoid basal cell carcinoma syndrome

1. Recurrent tumours

Recurrent BCC has lower control rates after treatment than primary BCC treatment. In early stage tumours recurrence rates after treatment of previously treated (recurrent) BCC are reported in the range of 15 to 30% compared with previously untreated (primary) BCC of 1 to 10%. However, most series also report still excellent salvage results with radical surgery (or less commonly using radiotherapy). These recurrence figures increase with increasing tumour stage and salvage becomes harder to achieve. Furthermore, control rates are likely to progressively diminish with each successive episode of recurrence and salvage treatment.
2. **Size and depth of invasion (stage)**

Control rates diminish with increasing size. See TNM Staging Appendix 1.

**Overall estimated control rates of treated primary BCC by stage**

<table>
<thead>
<tr>
<th>T stage</th>
<th>Size (maximum diameter)</th>
<th>%Control rates at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>≤ 2 cm</td>
<td>95</td>
</tr>
<tr>
<td>T2</td>
<td>&gt; 2 cm but ≤ 5 cm</td>
<td>88</td>
</tr>
<tr>
<td>T3</td>
<td>&gt; 5 cm</td>
<td>50</td>
</tr>
<tr>
<td>T4</td>
<td>tumour deeply invaded beyond subcutaneous tissues</td>
<td></td>
</tr>
</tbody>
</table>

Cartilage and bone invasion are surrogates of more advanced stage, deeper invasion and/or recurrent BCC. BCC infiltration of cartilage or bone is markedly less controllable, because of the inability to define extent of spread, larger tumour burden, and considerably greater morbidity of radical treatment that may not be possible, acceptable or tolerated by the affected patient.

Rarely very large primary BCC > 10 to 20 cms present due to patient neglect or denial and usually occur on the trunk, where they remain hidden. Due to their large size they are usually deeply invasive and incurable.

3. **Site**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher recurrence rates have been observed for all treatment modalities in the facial region compared with non-facial sites and particularly on and around the nose, eyelids and ears.</td>
<td>IV</td>
<td>24, 56, 57, 62, 63, 68, 69, 70, 71, 72</td>
</tr>
</tbody>
</table>

There is a tendency to a different spectrum of morphological BCC sub-type, occurring on the trunk and limbs compared to head and neck BCC. The face and scalp subcutaneous anatomy is far more complex and critical (posing potentially graver consequences for deep invasion of BCC and greater risk of morbidity from injudicious treatment), than in non-facial sites.
4. **Morphological and Histological Subtype**

Superficial and nodular BCC are usually clinically and histologically well circumscribed and curable with all treatment modalities. Morphoeic, and infiltrative (deeper induration) BCC are harder to macroscopically define and microscopically clear and associated with higher recurrence rates. Basi-squamous (or metatypical) BCC represent 5% of all BCC and are also more likely to recur. However the quality of data supporting these observations is poor.

5. **Treatment Modality**

Surgical excision remains the treatment of choice. Complete excision delivers the highest and most prognostically reliable control rates.

Radiotherapy, curettage with electrodessication and cryotherapy respectively deliver increasingly lower control rates.

Intralesional Interferon, lasertherapy and photodynamic therapy for treatment of BCC should be considered investigational until confirmed and reproducible treatment outcomes are established in prospective trials.

6. **Incomplete Excision**

Incomplete excision is accompanied by a 30% recurrence rate. The risk of recurrence is highest in lesions where both lateral and deep margins are involved. Re-excision or radiotherapy reduces the recurrence rate after incomplete excision to the same rates as complete excision.

7. **Perineural Spread**

This feature is a rare event for BCC and even rarer than in SCC (refer p 31). It occurs in head and neck BCC and specialist opinion on management is advised.

8. **Naevoid Basal Cell Carcinoma Syndrome**

Gorlin's syndrome is a rare inherited disorder with early onset and a relentless lifelong high frequency of BCC. Diminishing reserves of normal skin with increasing age in these patients can eventually compromise control (refer Epidemiology, p 7).

**Squamous Cell Carcinoma**

**Introduction**

The prediction of the biological potential for early SCC and the risk of metastasis can be derived from evidence on the following prognostic indicators covered under seven broad categories. These prognostic findings are frequently multiple in single case scenarios.

1. **Staging T, N, M (Appendix 1)**
2. Local metastatic spread via lymphatics or nerves not embraced by current staging systems and most often associated with recurrent or persistent tumours.
3. Locally recurrent and/or persistent SCC and/or inadequately treated SCC.
4. Histological grade and clinical expressions of growth rate.
5. Anatomic site of primary.
6. SCCs arising from aetiological factors other than ordinary sun exposure in otherwise healthy people.
7. Patient factors … immunosuppression and other patient and skin related co-morbidities.

1. Stage

Staging is a fundamental tool in cancer clinical research for improving outcomes for patients. The application of the generic TNM staging system for carcinoma to SCC of the skin is a poor fit, as a large proportion are classified as T1N0M0. However, until a more sophisticated universal staging system for cutaneous SCC is developed, it remains an interim instrument.

T Stage … Size and Depth of Invasion of the Primary

The size of a primary SCC is three dimensional. The maximum clinical diameter is the most reproducible measurement, but also a reasonable surrogate for depth of invasion and/or tumour burden. The rare exception is Bowen’s disease that can grow to a large area and even be exophytic, but remain insitu.

The T4 staging category identifies advanced (beyond subcutis) clinical invasion and has the poorest prognosis. However, lesser intermediary levels of depth of invasion are not directly accounted for in the T1 to 3 staging system. There is limited evidence in T1 and 2 tumours that shows a rising incidence of nodal metastases with increasing depth of invasion of the dermis or by measuring tumour thickness histologically\(^\text{113,114}\). Other clinical parameters useful for assessing depth of invasion include palpable thickness, diffuse infiltration and induration with poor demarcation of tumour edges and tenderness and inflammation, and are all valid crude signs of a more aggressive tumour.

<table>
<thead>
<tr>
<th>T Stage</th>
<th>5 year disease free survival of treated primary SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>95–99%</td>
</tr>
<tr>
<td>T2</td>
<td>85–60%</td>
</tr>
<tr>
<td>T3</td>
<td>60–75%</td>
</tr>
<tr>
<td>T4</td>
<td>&lt;40%</td>
</tr>
</tbody>
</table>

(see Radiotherapy, p49)
N Stage - Nodal Status\textsuperscript{115,116,117}

The presence of nodal metastasis confers an overall 5 year survival of 40%.

Recurrence in a nodal basin after standard lymphadenectomy (radical node dissection) almost invariably proves fatal.

The risk of regional recurrence after radical lymphadenectomy has been shown to be related to two important factors—histopathologically to the number of nodes containing metastases and the presence of extra-nodal spread (being grossly clinical fixation of node(s)).

The N staging for cutaneous SCC is too simplistic.

In modern oncology practice, the criteria for determining risk of regional relapse and indication for adjuvant therapies is based on the surgical pathology findings, and pre-operative attempts at predicting this on pre-operative clinical and radiological (CT) assessment.

<table>
<thead>
<tr>
<th>No of nodes involved</th>
<th>5 year survival\textsuperscript{79}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49%</td>
</tr>
<tr>
<td>2</td>
<td>30%</td>
</tr>
<tr>
<td>3</td>
<td>13%</td>
</tr>
<tr>
<td>ECE\textsuperscript{84}</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>23%</td>
</tr>
<tr>
<td>Present</td>
<td>47%</td>
</tr>
</tbody>
</table>

M Stage

Once haematogenous metastases have occurred, the patient is no longer curable.

2. Perineural spread

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>The estimated prevalence of perineural spread from cutaneous SCC is in the order of 2.5%</td>
<td>IV</td>
<td>107, 108, 109, 118</td>
</tr>
</tbody>
</table>
The vast majority of cases involve the Trigeminal (IV) and Facia (VII) cranial nerves with the primary site being on the face, lips, ears or perimeter zone of the face.

Perineural invasion is identified in two ways with different clinical significance and prognosis.

(i) The earliest indication of perineural invasion is incidentally (asymptomatic) on histopathological examination of a primary SCC of usually a minor dermal nerve. While relatively uncommon, the frequency of this occurrence is unknown as no controlled pathology studies have been undertaken.

The presence of incidental perineural invasion, however, appears to confer a poorer prognosis and on current data requires adoption of a more aggressive management approach (eg wider excision, Mohs’ surgery, postoperative radiotherapy or at the least, an opinion from a specialist skin cancer centre).

(ii) The second, later indication of perineural invasion is symptomatic presentation with either neuralgic type pain, progressive paraesthesia and anaesthesia (due to involvement of various divisions of the sensory trigeminal nerve), a palpable lump along the course of a nerve (eg a lump at a supraorbital or infraorbital notch or mental foramen) or paresis of facial muscles due to involvement of the facial nerve. These symptoms and signs most often occur sometime after seemingly initial successful treatment of the primary SCC and not uncommonly the cutaneous primary SCC is no longer traceable by any means.

While MRI is the imaging modality of choice in diagnosing or assessing perineural spread—in the event of symptoms occurring, a normal MRI does not preclude the diagnosis.

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**Key point:**

- Clinically diagnosed perineural invasion carries a poor prognosis.

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3. Locally recurrent, persistent or inadequately treated primary SCC

These two clinical expressions of ‘uncontrolled SCC at its primary site’ are considered under one category as their pathogenesis, prognosis and treatment are similar.

Locally recurrent SCC is clinically manifest by regrowth of a lump or ulcer at the primary site after initially seemingly clinically adequate treatment (eg complete excision) or clearance of the primary tumour (eg after radiotherapy).
Persistent SCC is a term signifying high histopathological risk of residual SCC due to incomplete excision being reported by a pathologist. Alternatively it can be a clinical observation of macroscopic tumour not completely resolving after treatment.

**Key points:**

- Incomplete excised SCC has a recurrence rate of 50% or more and should be prophylactically re-excised or treated with radiotherapy.
- In the event of recognising recurrent, persistent or inadequately treated cutaneous SCC the prognosis is unequivocally poorer and demands more aggressive clinical treatment, which includes fully advising the patient of its lethal potential in discussion of salvage management options.

4. **Histology and growth rate**

SCCs are graded histologically into well, moderately or poorly differentiated tumours.

Less well differentiated and more infiltrative growth patterns are associated with an increasing risk of recurrence and metastases.

Spindle cell variants are particularly aggressive. Identification of perineural and/or lymphatic infiltration carry a poorer prognosis.

5. **Anatomical site of primary**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCCs of the scalp, ear and vermillion have a higher recurrence and subsequent nodal metastasis rate than SCCs elsewhere, being in the order of 10 to 20% overall.</td>
<td>IV</td>
<td>49, 115, 116, 117</td>
</tr>
</tbody>
</table>

6. **Cutaneous SCCs unrelated to UV irradiation**

SCCs arising in a chronic scar
- Chronic osteomyelitis sinus
- Burns scars—‘Marjolins’ ulcer
- X-irradiation damaged skin
5. Prognosis

The observed latent period of scar presence and SCC development is in the order of 10 to 30 years. They are a particularly poor prognosis group of tumours.

7. Host factors

Immunosuppression

Immunosuppression occurs in a number of clinical situations, including:

1. Long term immunosuppressive therapy (see Epidemiology, p5)
2. Chronic leukaemia, myelodysplasias and lymphomas

The most studied group are organ transplant patients who require long term immunosuppressive therapy. The incidence of skin cancer in transplant patients is twenty-fold the normal rate. The number and risk of more aggressive lesions increases with duration of immunosuppression. Recurrences and metastatic rates are also higher \(^{16,17,119}\).

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>The prognosis for SCC in chronically immunosuppressed patients is worse than in other people. Rates of local recurrence or metastasis are increased overall and increase with duration of immunosuppression.</td>
<td>III-2</td>
<td>16,17,119</td>
</tr>
</tbody>
</table>

General and skin specific co-morbidities

Skin co-morbidity can be site specific related to areas of poor healing—most typically below the knee and pretibial region. In older patients this is heightened by a higher incidence of peripheral vascular disease, varicosities and oedema. No treatment is favourable in this situation where there is a high risk of post treatment chronic benign ulcers or recurrence with compromised treatment. The optimal treatment is surgical excision and skin grafting that can demand several days of strict bed rest in hospital, that patients can be reluctant to undertake with asymptomatic lesions, and that may compound their co-morbidities (such as arthritis, thrombosis, diabetes and fear in the elderly).

Another site-specific co-morbidity occurs in the younger adult (especially women) with facial skin cancers, who seeks unattainable guarantees of perfect cosmetic results from treatment, potentially placing stress on receiving appropriate and timely cancer treatment.

In all these instances careful patient counselling and education on the prognosis and results of treatment are essential.
6. SURGICAL TREATMENT

INTRODUCTION

Surgery is the most common method of management of non-melanoma skin cancer. Compared with non-surgical modalities, surgery has the advantage that it is definitive treatment, provides a complete specimen for histological confirmation of the diagnosis and the adequacy of excision and is associated with a very high rate of local control. Complete excision can be expected to cure the vast majority of patients. Although the overwhelming majority of NMSCs are easily managed by small surgical procedures with excellent functional and cosmetic outcomes, some NMSCs behave aggressively resulting in extensive tissue destruction. Surgery is the primary treatment modality for these lesions which may necessitate extensive surgical resections with less than optimal functional and cosmetic outcomes. At the present time and for the foreseeable future, surgery will remain the gold standard against which all other non-surgical treatments of NMSC should be judged.

OBJECTIVES OF TREATMENT

The objectives of surgical treatment of NMSC are:

- To achieve histologically confirmed complete excision of the tumour with an adequate margin in width and depth.
- To maintain normal function where possible.
- To achieve a good cosmetic result.

For both BCCs and SCCs complete excision of the primary tumour is the goal as recurrent tumours have a higher further recurrence rate which may be associated with a worse cosmetic and functional outcome. In the case of SCC, local recurrence is associated with a higher rate of metastasis to regional lymph nodes and other distant sites.

PRINCIPLES OF SURGICAL MANAGEMENT

The general principles of performing surgical excision of NMSC are:

1. Patients should be informed of the options (surgical and non-surgical) and the risks and benefits as well as the outcome and need for further treatment and surveillance. The treatment should be explained to the patient including what should be expected in the post-operative period and the possible complications as well as the long term outcome including
cosmesis and function. A clear description of the ultimate cosmetic and functional result is essential. The patient should also understand that any tissue removed will undergo pathological evaluation and that further surgery may be necessary to obtain complete removal of the lesion.

2. Familiarity with the clinical features of NMSC is essential in the effective planning of the procedure. Features effecting the margin and depth of the excision (and consequently the risk of local recurrence) in particular should be considered (see below). The mobility of the lesion on underlying tissues should be carefully evaluated as it may indicate deep fixation and the need for extensive surgical procedures.

3. If there is any doubt concerning the clinical diagnosis an appropriate biopsy, eg punch biopsy, should be considered prior to definitive surgical excision. In some cases it may be more expeditious to completely remove a small lesion.

4. The majority of cutaneous NMSC can be excised under local anaesthetic on an outpatient basis.

5. The majority of surgical wounds after excision of NMSC can be closed primarily by simple direct suture.

6. Excision of small clinically favourable lesions located in straightforward sites should be within the skills of general practitioners who are capable and confident in the performance of minor surgical procedures. As the injection of local anaesthetic may distort the tissues, the excision margins should be marked out prior to infiltration (see discussion on width of margins below). The lesion should be excised as an ellipse with a suggested ratio of length to width of 3 or 4 to 1. The long axis of the ellipse should be placed in the line of the local skin creases which is usually the line of least skin tension. In the extremities the long axis should preferably be orientated longitudinally. The skin should be cut vertically with the blade at 90° to the skin. The depth of excision should be through uninvolved subcutaneous fat. Simple interrupted closure with a monofilament suture eg nylon or polypropylene rather than silk is recommended. Thick skin, particularly if there is any tension in the wound, requires a thicker suture such as 3.0. Sutures in sites with significant skin tension eg the back should be left in for up to two weeks. Facial wounds on the other hand deserve a light suture such as 5.0 and the sutures can be removed as early as 5 days.

7. All resected tissue should be sent for pathological evaluation. A careful description of the site of excision is essential as is orientation of the specimen to allow identification of any areas where excision is incomplete. A simple diagram particularly if multiple lesions are removed can be of great assistance to the pathologist.

8. Tumour resections likely to result in cosmetic or functional defects require specialised reconstructive techniques and should be referred for specialist care. Occasionally sacrifice of major structures eg eyelid, tear duct, facial nerve is necessary to achieve complete resection. The skills required for performance of such procedures and the immediate functional
reconstruction are generally only available in specialist tumour centres. Tumours on the face are best treated by trained and experienced practitioners to minimise alteration in function of the eyelids or mouth and ensure a satisfactory cosmetic outcome. Lesions on the nose or ear present specific challenges including the thinness of the subcutaneous tissue, proximity to bone and cartilage and the tightness of the skin envelope which may prevent direct closure of the defect.

9. A knowledge of superficial anatomy is vital in planning even minor skin tumour excisions. Care should be taken with excisions in sites where nerves and other structures may be at risk. Special care should be taken with the temporal branches of the facial nerve which are superficial and may be damaged during excision of lesions which overly the course of the nerve over the zygoma and lateral peri-orbital and temple regions. The Accessory nerve after it emerges from behind the posterior border of the sternomastoid is at risk when excisions are performed in the posterior triangle.

10. Local flap repair providing cover with skin of appropriate colour and texture is the preferred method of closure when direct closure is not possible. Morbidity and post-operative recovery is less and the cosmetic result, particularly achievement of a satisfactory skin colour and texture match, is far superior. At times skin grafting will be necessary and full thickness grafts are used choosing skin from an inconspicuous donor site with similar skin characteristics.

11. Careful planning of surgical procedures based on close attention to the clinical features of the lesion provide very high rates of local control. Similar rates of local control for unfavourable lesions can be approached by attention to the clinical features supported by intra-operative margin control with frozen section. Mohs’ surgery (see below) which also relies on intra-operative margin control also provides excellent and equivalent results for patients with high risk lesions.

**Advantages and disadvantages**

Specific training and expertise are necessary to achieve optimum results. The advantages of surgical excision in treating NMSCs are:

1. An excellent overall cure rate.
2. Pathological evaluation of complete tumour removal.
3. A generally acceptable cosmetic and functional result with rapid healing.

The disadvantages of surgical intervention include the potential complications of:

1. Haematoma, infection, wound dehiscence.
2. Damage to neurovascular and other structures.
3. Cosmetic deformity, variation in pigmentation, hypertrophic scarring. It should be noted that cosmetic results of surgical excision typically improve with time. Delayed scar revision may be helpful.
BASAL CELL CARCINOMA

BCCs are distinguished by the fact they rarely metastasise and can be cured in the vast majority of cases by complete excision. Surgical excision provides excellent five year cure rates estimated at between 90 and 98% for previously untreated tumours.120,121,58

Key point:

- The majority of basal cell carcinomas are clinically favourable ie small, nodular or superficial types, not located in the central face. They can be satisfactorily excised under local anaesthetic with direct primary closure in an ambulatory care setting.

The completeness of the excision (assessed histologically) is the most critical factor in determining the rate of local recurrence and cure. The margins of excision should be wide enough to completely excise the tumour. In evaluating studies of excision margins, the variation in behaviour of BCCs needs to be considered. A number of factors including the experience of the operator, type of BCC, histological features, size and location have been related to higher recurrence rates and need to be considered in the planning of the surgical procedure. These features must be considered in deciding the appropriate margin of excision for a particular lesion. Consequently any recommendations concerning the width of excision must remain a guide only. In reviewing published studies which have attempted to define an appropriate excision margin it is clear that the majority describe patients with small favourable lesions. Recommendations on the width of excision have varied from thin, ie 2 mm, to more extensive margins of 5mm or more122. Careful histological evaluation of excised BCCs demonstrate irregular (and unpredictable) extension of the tumour beyond the macroscopic margins for a variable but usually limited distance.123 This probably explains why as many as one-third of careful excisions may have close or involved margins. The frequency of histologically involved margins decreased in one series from 25% for a margin of 2mm to 5% with a margin of 4mm.124 For small favourable lesions (see below) not located in the central face, a margin of 3 to 4 mm has a high likelihood of complete removal and cure.

The depth of excision has not been as comprehensively studied as the width of excision because the majority of BCCs are thin and with a depth of excision including subcutaneous fat, the deep margin is usually not a problem. In certain situations such as recurrent lesions, BCC in sites such as the ear or nose where the skin is closely applied to underlying cartilage or bone, the depth of excision is critically important and must be considered during the planning of the proposed surgery.
6. Surgical Treatment

Non-Melanoma Skin Cancer: Guidelines for treatment and management in Australia

Guideline
The majority of clinically favourable BCCs can be excised with a margin of at least 3mm with a very high chance of achieving complete excision and long term control.

Level of
IV

Refs
58, 121, 124, 125

It is important to acknowledge that there is considerable variation in the behaviour of BCCs. Factors known to be associated with the development of recurrent disease include:

1. Tumour size and site

Tumour size has been noted to be associated with an increased risk of local recurrence by some but not by all. The effect of tumour size on recurrence is confounded by the location of the lesion. BCCs of the head, particularly the central face and peri-auricular region have a higher rate of local recurrence. Whether this is due to features specific to this site or is related to difficulties in obtaining complete excision due to reluctance or inability to perform a wide and complete excision which may result in significant aesthetic or functional impairment is unknown. It has been suggested that the lack of a barrier to invasion at sites of embryological fusion may explain higher rates of local recurrence in the face although there is little evidence to support this position.

<table>
<thead>
<tr>
<th>Size of lesion</th>
<th>5 year Local Recurrence Rate All Sites (no of cases)</th>
<th>5 year Local Recurrence Rate Head only (no of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5 mm</td>
<td>2.9% (138)</td>
<td>3.2% (123)</td>
</tr>
<tr>
<td>6–9 mm</td>
<td>6.9% (185)</td>
<td>8.0% (130)</td>
</tr>
<tr>
<td>10–15 mm</td>
<td>6.7% (146)</td>
<td>9.0% (127)</td>
</tr>
<tr>
<td>&gt;15 mm</td>
<td>1.9% (128)</td>
<td></td>
</tr>
</tbody>
</table>


2. Tumour type

Several studies have confirmed variation in behaviour of tumours associated with the histologic type of the lesion. BCCs showing histological appearances of sclerosis, ulceration and infiltration which are clinically recognizable as thick, morpheaform or infiltrative types are associated with larger occult extensions with a higher rate of positive margins after excision and a consequent higher rate of local recurrence. The nodular and superficial forms of BCCs which account for the majority of lesions and lack aggressive histological features have a higher rate of complete excision and lower rate of local recurrence.
3. Perineural invasion

Perineural invasion is more frequently associated with SCC although it may occasionally be seen with BCC. The lesions tend to be of a more aggressive histological subtype and located in the head and neck\textsuperscript{131}. (see p29)

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with BCCs which are large (&gt; 2cm), poorly defined or multiple lesions, unfavourable tumour types, i.e. infiltrative, ulcerative or morphoeic types or tumours located in sites where the rate of local recurrence is predicted to be high (central face and peri-aural regions) should be considered for referral for specialist care.</td>
<td>IV</td>
<td>3, 4, 5, 6, 7, 11, 48, 58, 63</td>
</tr>
</tbody>
</table>

4. Incompletely resected BCC are defined as histologically incompletely or inadequately excised BCC

There is considerable debate concerning the most appropriate management of these cases and arguments can be made for any of the three possible options: re-excision, radiotherapy or observation.

Many authors have estimated the rate of local recurrence for persistent BCC to be approximately 30\%,\textsuperscript{132,104} although rates as high as 67\% have been reported.\textsuperscript{97} In evaluating the evidence for a rational management plan the volume of residual disease needs to be but is rarely considered. Tumour within one high power field of a margin was associated with a recurrence rate (12\%) approximately one third that of the rate when the margin was involved with tumour.\textsuperscript{98} The time course to recurrence is of importance when considering an observational policy. Most recurrences occur within 3 years, although cumulative studies show 82\% of recurrences occur in the first 5 years post-treatment and 18\% at 6-10 years.\textsuperscript{60,133} From a practical point of view, diagnosis of recurrent disease can be difficult because normal wound changes are difficult to distinguish from recurrent disease and the recurrence may be initially deep without any obvious superficial features.

Salvage of recurrent BCCs appears to be highly effective although the series are selective and retrospective. Richmond et al reported a 10 year local control rate of 92\% for patients who underwent immediate re-excision versus 90\% for patients undergoing excision of clinically recurrent disease although the 10 year
relapse free rate was 91% versus 40%\textsuperscript{100}. Similar results were reported by Liu et al who managed limited persistent disease with adjuvant radiotherapy\textsuperscript{101}. A cost benefit analysis provided with this study did not support immediate post-operative treatment with adjuvant radiotherapy. In the untreated group 6% of patients developed recurrent disease which was never able to be controlled.

Features predictive of recurrence of persistent BCCs have not been extensively studied. In one series patients with inadequate deep margins had approximately twice the local recurrence rate (33% v 17%) of patients with inadequate lateral margins.\textsuperscript{101}

On the basis that the majority of patients with persistent disease will not develop a recurrence, it has been suggested that incompletely excised BCCs can be followed unless there are unfavourable characteristics including the extent of residual disease, deep as compared to a superficial margin involvement and the histological subtype. At the present time it is not possible to accurately identify patients with minimal residual disease who may benefit from a conservative approach. As recurrent disease is harder to eradicate, subsequent management may involve significant morbidity and occasionally the disease may prove resistant to control, it is prudent to recommend that patients with persistent disease should undergo histologically complete re-excision.

Mohs’ surgery or standard surgical procedures with intraoperative frozen section margin control has been used successfully in the management of persistent disease (see below). The role of adjuvant radiotherapy for persistent disease is unresolved. Limited studies suggest that it probably provides similar rates of control to complete surgical re-excision but is more expensive and inconvenient in many instances\textsuperscript{100}. Generally it should be avoided in younger patients. Most authorities agree that adjuvant radiotherapy for persistent disease is justified for minimal residual disease in patients who are unsuitable for or refuse further surgery or the morbidity of re-excision is not justifiable.

It must be remembered however that many of these patients with persistent BCC are elderly and infirm and further surgery particularly if likely to be major and associated with functional and cosmetic impairment may not be appropriate. Referral to a specialist unit should be considered in this situation.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with incompletely excised BCC should be considered for re-excision to achieve clear margins.</td>
<td>IV</td>
<td>98, 99, 100, 101</td>
</tr>
<tr>
<td>Radiotherapy may be a reasonable alternative for the patient unwilling or unable to undergo further surgery.</td>
<td></td>
<td>102, 103, 104</td>
</tr>
</tbody>
</table>
Recurrent BCC

Among recurrent BCCs, lesions located in the central face and peri-auricular region, large tumours (>2cm), aggressive subtypes (infiltrative, ulcerated and morpheaform) and persistent BCCs are over represented\textsuperscript{101}. The type of primary treatment, ie surgery, radiotherapy, curettage, electro-desiccation for appropriately selected lesions give very high similar rates of local control, however, larger lesions treated by non-surgical techniques are more likely to develop a recurrence\textsuperscript{47}. At least two thirds of recurrences occur within 3 years of initial treatment although up to 20% will recur between 5 and 10 years\textsuperscript{75}.

Recurrent BCCs are associated with a higher risk of further local recurrence, at least 50% higher than previously untreated lesions\textsuperscript{58}. Undetected subclinical extension, aggressive tumour type, irregular invasion of scar tissue and multiple foci of disease have all been suggested as explanations for this higher recurrence rate\textsuperscript{134,135}. Recurrence after non-surgical treatments (radiotherapy, cryotherapy, curettage and electro-desiccation) have been held to be associated with a higher risk of further local recurrence (and metastasis) although there is little objective evidence to support this\textsuperscript{136}. There is no doubt, however, that the changes in the skin such as atrophy, hypo-pigmentation and scarring following non-surgical treatments, make accurate assessment of extent of recurrent tumour difficult. For this reason and because of poor healing due to the previous therapy, particularly radiotherapy, most authorities recommend resection of the scar, macroscopic tumour and all surrounding previously treated skin. Local flap repair rather than primary closure or skin grafting is usually necessary to ensure healing following surgery.

Tumours recurring after previous cryotherapy can be difficult to assess due to treatment related scarring with the possibility that tumour persists deep to an apparently normal dermis. The scarred area should be removed in its entirety to minimise the chance of residual disease.

Tumours recurring after previous curettage and electro-desiccation may also have occult deep extensions not obvious clinically. These deep extensions are particularly troublesome in skin creases such as the naso-labial fold and care must be taken to ensure complete excision.

Frozen section margin control is invaluable in ensuring complete removal of BCCs but does add to the cost and time required for the procedure and should be limited to situations where there is a risk of persistent disease post operatively such as in the management of recurrent BCCs\textsuperscript{137}. It is both highly sensitive and specific in evaluating margins. For small favourable lesions where the risk of positive margins is small, frozen section is not indicated. Alternatively Mohs’ technique is particularly useful in the management of recurrent lesions (see below).
Key point:
- Recurrent BCCs should be considered for referral for specialist management. Complete excision of the lesion with the scar and any previously treated area is usually necessary.

Squamous Cell Carcinoma

The surgical management of SCC is similar to BCC in that the main objective is histologically confirmed complete removal of the tumour. In general, surgical management of SCC is more radical than for BCC because SCCs are potentially more aggressive, have a greater potential for local recurrence and may spread to regional lymph nodes and distant sites. Local recurrence is due to incomplete primary excision (and is therefore preventable). The development of local recurrence is associated with a high rate of subsequent local recurrence (23%) and subsequent metastasis predominantly to the regional lymph nodes (30%) if further local recurrence does occur. Approximately one third of patients who develop regional metastases will die of SCC.

Satisfactory primary excision is therefore mandatory and will result in a high rate of cure in excess of 90%. The recommended surgical margin of excision for SCC varies from 2 to 10mm. Favourable lesions eg well differentiated lesions less than 2cm in diameter will be adequately excised with a 4mm margin in 95% of cases. Tumours larger than 2cm require larger margins up to 10mm to obtain similar rates of local control. For very large lesions even wider margins may be necessary. The depth of excision should be through normal underlying fat. For larger lesions and those predicted to be associated with a higher rate of local recurrence some form of intra-operative margin evaluation is indicated. Frozen section margin control evaluation is generally available only in hospitals and although time consuming and expensive is highly sensitive and specific. Alternatively Mohs’ technique with intra-operative evaluation of the margins if available is an option.

Key point:
- The majority of SCCs are small and clinically favourable and can be excised expeditiously under local anaesthetic with direct primary closure as an outpatient.

Factors associated with increased risk of local recurrence and which need to be considered in the planning of surgery include the following:
1. **Tumour size**
The diameter of SCC correlates with risk of recurrence. Tumours less than 2cm in diameter have a 5 year recurrence rate of 7.4% compared with 15.2% for tumours greater than 2cm in diameter.\(^{144}\)

2. **Anatomic site**
Sites associated with a higher risk of local recurrence include the scalp, peri-ocular region, ears, lips and nose. Five year recurrence rates from a large collective review were 18.7% for SCC of the ear, 10.5% for SCC of the lip and 7.9% for SCC at other sites. Rates of metastasis were respectively 13.7%, 11% and 5.2%.\(^{144}\)

3. **Histological features**
   a) Patients with poorly differentiated tumours had twice the risk of local recurrence compared to those with well differentiated lesions.\(^{144}\) The local recurrence rate increased from 7% for well differentiated tumours to 28% for high grade lesions.\(^{145}\) In addition poorly differentiated tumours are more likely to metastasise to regional nodes and other sites.\(^{114}\)
   b) The depth of invasion of SCC has also been reported as a predictor of local recurrence and metastasis. Lesions thicker than 4mm or extending to at least the reticular dermis are associated with a higher rate of local recurrence.\(^{114,146}\) The risk increases with further thickness. In one small series only tumours extending to and beyond the reticular dermis developed local recurrence.\(^{145}\)
   c) Several histological variants of SCC have been reported to be more aggressive and pose a higher risk of both recurrence and metastasis. These include spindle cell carcinoma, acantholytic SCCs and adenosquamous tumours.\(^{114}\)

**Key points:**
- The majority of clinically favourable SCCs less than 2cm can be excised with a margin of at least 4mm with a very high chance of achieving complete excision and long term control.
- SCC of the central face, scalp, lip and ear should also be considered for referral for specialist care in view of the higher risk of local recurrence and the possible need for specialist reconstruction techniques to optimise both cosmesis and function.\(^{49,137,138,141}\).

4. **Perineural invasion**
Perineural invasion is far more common in SCC than BCC complicating the course of up to 5% of all patients with SCC.\(^{143}\) Perineural invasion appears
to be more common in lesions located in the head and neck. Tingling, pain, paraesthesia, reduced sensation or motor function suggest perineural invasion but most patients have no pre-operative symptoms or signs of neural involvement. Intra-operative margin control with frozen section or alternatively Mohs’ surgery can be used to attempt complete excision. Post-operative radiotherapy is an important part of management.

The presence of perineural invasion is reported as posing a very high risk of both local recurrence which may be as high as 50% and distant spread in 35%. The addition of radiotherapy to the site of the primary lesion and the course of the involved nerve in an uncontrolled series was associated with a very high rate of local control and reduced rate of metastasis.

### Guideline

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<thead>
<tr>
<th>Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consideration of specialist therapy should occur for patients with an SCC showing perineural spread. (See chapter 13). Wide excision is recommended and consideration should be given to post-operative radiotherapy.</td>
<td>IV</td>
<td>107,108, 109,144, 146</td>
</tr>
</tbody>
</table>

5. **Previously treated SCC**

SCCs that recur following previous treatment have an increased incidence of further recurrence with approximately one third developing regional metastasis. The rate appears to be higher for SCC of the ear (45%) than lip (32%) or other sites (25%).

### Guideline

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<thead>
<tr>
<th>Guideline</th>
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<th>Refs</th>
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<tbody>
<tr>
<td>Patients with recurrent SCC have an increased risk of further local recurrence as well as regional and distant metastases. Excision of the previous treatment site should be undertaken in continuity with the recurrent tumour. Specialist referral is recommended.</td>
<td>IV</td>
<td>11,147, 148,149</td>
</tr>
</tbody>
</table>

6. **Immunosuppressed patients**

Patients who are chronically immunosuppressed as a consequence of either disease or medication have an increased incidence of cutaneous SCC and these lesions tend to behave more aggressively with a high rate of both local recurrence and metastasis. In an Australian study of patients...
after renal transplantation the incidence of SCC was seen to increase by 5% per year with a 44% incidence after nine years. The fact that each patient had so many aggressive SCCs led to an overall metastatic rate of 13%.

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<th>Guideline</th>
<th>Level of Evidence</th>
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<tbody>
<tr>
<td>Chronically immunosuppressed patients frequently develop multiple SCC which behave aggressively. These patients should be referred for specialist management.</td>
<td>IV</td>
<td>16,17, 119</td>
</tr>
</tbody>
</table>

7. **Aetiology**

A number of pre-existing factors which appear to influence the aggressiveness of cutaneous SCC and the likelihood of both local recurrence and metastasis have been identified. SCCs arising in previously irradiated tissues demonstrated a significant incidence of metastasis (10–30%) and local recurrence. SCCs arising in scars from previous burns, (Marjolin’s Ulcers) not only had a high frequency of regional metastases (35%) but most patients were dead of disease within 5 years. SCC arising in other scars including osteomyelitis and chronic stasis ulcers etc are characterised by similar rates of local and regional recurrence and poor survival.

**Mohs’ Surgery (see pp 37, 41, 42, 45-8, 61, 77)**

An alternative to standard surgical practice is Mohs’ Surgery (also known as micrographically controlled surgery) named after Frederic Mohs, Professor of Surgery from the University of Wisconsin, who first described the technique. His original procedure has been modified to what is now referred to as the fresh tissue technique, using so-called horizontal frozen sections to intra-operatively assess the completeness of the margins of excision.

Mohs’ surgery is generally performed under local anaesthesia. Following excision of the tumour, the whole of the outer layer of excised tissue is examined by frozen section. Mapping and staining of the excised tissue and specialised tissue sectioning enables precise localisation of any residual tumour, which is then excised and examined again by the same process. This is repeated until the margin is free of tumour. The resulting defect is then ready for repair by conventional surgical techniques.

The technique has been found to be particularly suitable for excision of skin cancers which might otherwise prove difficult to excise completely or where a higher than usual recurrence rate might be expected.
**Indications for Mohs' surgery**

Basal cell carcinomas or squamous cell carcinomas which are:

1. Located on the central face or periorificial areas (eyes, mouth, ears).
2. Recurrent following previous treatment.
3. Incompletely excised histologically.
4. High risk histological types, eg micronodular, infiltrating or morphoeic BCCs.
5. Large or ill-defined.

**Advantages of Mohs' surgery**

1. Minimises amount of tissue removed.
2. Has a very high cure rate.
3. Enables defect repair to be carried out with the knowledge that the tumour is likely to have been completely removed.
4. Is performed under local anaesthetic.

**Disadvantages of Mohs' surgery**

1. Time consuming—may take several hours.
2. Expensive.
3. Capital intensive—both in equipment and staff.
4. Requires specific training and expertise.
7. RADIOTHERAPY

INTRODUCTION

Radiotherapy (RT) is the use of ionising radiation to treat cancer and allied disease. Radiotherapy has been used successfully to treat all stages of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) for over 80 years with results comparable to surgery\textsuperscript{68, 69,70,71,72,73,82,85,89,94,155,156}. However, radiotherapy often requires a number of weeks for receiving and then healing from the treatment. The vast majority of BCC and SCC present as small, early lesions amenable to surgery which is commonly simpler, more convenient and expedient for patients, being single episode, highly efficacious (curative with good cosmesis) and delivering a complete specimen for pathology examination. Thus, radiotherapy is seldom used to treat small lesions and is limited to a specialised role in the overall spectrum of the disease.

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<th>Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
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<tbody>
<tr>
<td>Radiotherapy should be reserved for the small minority of primary BCC and SCC that present peculiar problems for conventional surgery and for cases of persistent, recurrent or advanced BCC and SCC where surgery can be complemented by radiotherapy to improve control rates in this small poorer prognosis category.</td>
<td>IV</td>
<td>68,69, 70,71, 72,73, 82,85, 89,94, 155, 156</td>
</tr>
</tbody>
</table>

Ionising radiation (x and $\gamma$ rays \{photons\}, $\beta$ rays \{electrons; particles\}) can be delivered by external beam therapy or brachytherapy. External beam therapy is produced by kilovoltage machines Superficial X-ray Therapy (SXRT), Deep X-ray Therapy (DXRT), teletherapy machines (Cobalt and caesium Units) and linear accelerators (Megavoltage Therapy (MVT) and electron beam therapy). Brachytherapy is the use of sealed isotopes applied directly to the tumour as a surface treatment or implanted into the tumour.

This range of treatment delivery allows the radiation oncologist a very wide selection of precise physical characteristics and radiobiological outcomes to optimally treat the various unique problems skin cancers can present for management. Dermatology ionising radiation practice is limited to SXRT alone, which is low energy, and penetration x-rays, suitable only for small and superficial skin cancers (T1 lesions <0.5cm thick).
Radiotherapy is non-invasive, painless and can be technically tailored to treat skin cancers of any size, or depth of invasion and at any site while minimising damage to adjacent normal tissues. It may also incorporate regions where the skin cancer has spread away from the primary site.

Standard curative dose schedules for treatment of T1 small lesions <2cm usually requires fewer treatments (4–12 attendances over two weeks) than large lesions (15–30 over three to six weeks). In general, more fractionated schedules give superior control rates and cosmesis. However small, early BCC and SCC can be cured with smaller doses than larger lesions and because the treatment areas are smaller, these tumours can be safely given fewer treatments, conveniently reducing the number of patient attendances. Sealed isotopes applied to the surface or implanted into the tumour involve two visits to the radiotherapy department or a short inpatient stay.

**Key point:**
- All BCC and SCC should be confirmed histologically by biopsy prior to radiotherapy treatment.

Normal tissue margins (the perimeter of normal appearing skin adjacent to the skin cancer) can be 0.5cm width for small, well defined BCC and well differentiated SCC, but may need to be more generous, 1–1.5cm for larger, ill-defined BCC and more aggressive SCC. A minimum margin of 1cm will be required when treating with electrons to ensure that the 90% isodose line encompasses the tumour at depth.

**SIDE EFFECTS OF RADIOTHERAPY**

Acute side effects arise two to three weeks after starting radiotherapy and last some days to weeks before completely resolving. These include variably and sequentially, erythema (skin redness), dry desquamation (skin peeling) and finally moist desquamation (patchy or confluent superficial ulceration) due to loss of the epidermis.

Late side effects occur from several months to years and are permanent. All treatments for skin cancer result in scarring. The long term features of radiation damage to the skin include atrophy (thinning), loss of skin appendages (alopecia, loss of sweating), variable change in colour (pallor or pigmentation), variable telangiectasia (fine blood vessels) development, subcutaneous fibrosis and rarely, skin breakdown (radionecrotic ulcer, <2–5% risk). Most importantly, the visible features of late radiation skin damage can change with time. An initial highly favourable cosmetic result can potentially deteriorate with passing years. Thus radiotherapy is not generally recommended for persons under 60 years of age, when surgery gives a better and long term stable cosmetic outcome.
When advanced BCC and SCC invades cartilage (classically the pinna) or bone (eg mandible) the risk of chondro- or osteoradio-necrosis is higher.

Factors affecting cosmesis include how the radiotherapy is given (the number of treatments, the size of the treatment area/volume), the extent of normal tissue destruction by the tumour, idiosyncratic variability of repair response by individuals, past and future sun damage and site of the skin. Convex and concave contoured sites of the face give optimal cosmesis (eg ala nasi, inner canthus, nose, ear and eyelids); flat skin areas (eg forehead, back) and sites of reduced vascularity or greater wear and tear (eg below the knee) lead more often to visible scarring.

Radiotherapy rarely damages nerves or muscle and does not cause major tissue deficit. Radiotherapy may provide a superior functional and cosmetic outcome when anaesthesia (numbness), paralysis or bulk volume tissue loss are planned consequences of surgery for treatment of a (usually larger, more infiltrating) BCC or SCC. Such examples may be facial nerve sacrifice, major anaesthesia of the lip, nasectomy, resection of lip or eyelid commissures.

Based on the limitations and advantages of RT already outlined, the following checklist is useful when considering referral for an RT opinion in treatment of BCC or SCC.

**Relative Indications for Radiotherapy**

1. Older patients where long term scar deterioration is inconsequential.
2. Multiple, especially superficial lesions when impractical to excise.
3. Patients wishing or needing to avoid invasive procedures (eg refuse or unfit for surgery, or anaesthesia, or have anticoagulation problems).
4. Patients prone to keloid formation.
5. When surgery would be mutilating or result in major loss of function (eg nasectomy, resection of lateral eyelid commissure, resection of lip commissure, large superficial lesions with loss of tissue or facial nerve sacrifice).
6. Palliation in advanced neglected inoperable lesions.

**Relative Contraindications for Radiotherapy**

1. Patients younger than 60 years if the lesion is readily excisable.
2. Lesions on freely mobile skin amenable to simple excision.
3. Lesions in hair bearing areas or overlying the lacrimal gland.
4. Advanced lesions invading tendon, joint or bone. Cartilage involvement however, is not a contraindication for RT, it can occasionally be the preferred treatment for the nose or for small lesions of the ear. However RT is best avoided in larger pinna lesions with extensive, inflamed or painful cartilage invasion.
5. Sites of poor vascularity or healing and wear and tear sites (eg pretibial lesions).
6. Previous radiotherapy to the skin lesion in question.
7. Lesions over bony prominences that are prone to trauma tolerate RT poorly.
8. Lesions on the lower limb and upper eye lid tolerate RT poorly.
9. Bony infiltrations. Poor results are achieved with RT alone.
10. Basal cell naevus syndrome (Gorlins Syndrome) and ataxia telangiectasia.

**Basal Cell Carcinoma**

**Primary untreated basal cell carcinoma**

Control rates for BCC ≤2cm (T1) with radiotherapy are 95-99% at 5 years to 93-95% at 10 years.\(^{82,73,70,68,89,85,156}\)

<table>
<thead>
<tr>
<th>Lesion size</th>
<th>T Stage</th>
<th>5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2cm</td>
<td>T1</td>
<td>97%</td>
<td>95%</td>
</tr>
<tr>
<td>2–5 cm</td>
<td>T2</td>
<td>92%</td>
<td>89%</td>
</tr>
<tr>
<td>&gt;5cm</td>
<td>T3</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td>T4 lesions</td>
<td>T4</td>
<td></td>
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</table>

- RT has a limited role in treatment of small primary BCC as complete excisional surgery is more accessible, expedient and convenient with optimal outcomes (control rates and cosmesis).
- RT should be reserved for the minority of T1, T2 and T3 primary BCC when surgery is disadvantageous or not feasible in generally older patients.

**Residual basal cell carcinoma**

Complete clinical resolution of a BCC following curative RT can occasionally take up to 4 months. Most small BCC have disappeared by the time the acute radiation reaction has healed (2 to 8 weeks after finishing RT).

Clinical persistence or progression of a BCC after a standard curative dose of RT should be confirmed in consultation with the treating radiation oncologist, biopsied and treated with excisional surgery by an experienced specialist surgeon.
Radiotherapy for residual BCC after surgery (incompletely excised BCC)

The observed recurrence rate of incompletely excised BCC is on average 33%. As approximately two thirds of incompletely excised BCC do not recur and some authors claim salvage of recurrent lesions gives similar outcomes, the arguments for and against re-excision have been debated in the literature. However, Liu noted 6% were eventually not controlled after salvage. While no statistically significant evidence is available, there is a trend for higher recurrence when the deep margin is involved versus a lateral margin alone, and higher again when both are involved.

Key points:

- If advice for patients regarding re-excision of an incompletely excised lesion is contentious, then the recommendation for RT is equally difficult.
- Immediate re-excision or RT for incompletely excised primary BCC reduces the recurrence rate to less than 9%.

The recurrence rate of one third for incompletely excised BCC applies to the natural presentation incidence spectrum of primary BCC that is vastly small lesions. However, in the very small subset of primary BCC presenting in an advanced state incomplete, close (and anatomically restrained) or inassessible normal tissue margins carry a higher relapse rate. The confidence of adequate treatment margins will be further eroded by perineural spread, micronodular, infiltrative and metatypical (basisquamous) histology patterns and invasion of skeletal muscle, cartilage and bone. In these uncommon cases referral to a specialist skin cancer or head and neck cancer (>75% will be head and neck lesions) clinic for individual assessment and advice re: merit of post-op RT or additional treatment is recommended.

Recurrent basal cell carcinoma

Recurrence can occur at any time after RT but 88–90% of recurrences are reported to occur within the first five years. Recurrent BCC should be treated with excisional surgery including the irradiated tissues by a specialist surgeon, but can also be salvaged with re-irradiation, when surgery cannot be performed. Surgery is preferred to re-irradiation as the risk is higher of more serious late sequelae (radionecrosis of skin and other underlying tissues).
The recurrence rate after recurrence following RT salvaged by surgery is between 14 and 18%. 64, 65, 66, 75, 85, 133

Surgery is the treatment of choice for recurrent BCC and RT is used when surgery is not feasible, incomplete (& further surgery not reasonable) or confidence in surgical clearance is diminished.

Control rates after salvage therapy157 are lower than primary treatment and dependent on the same factors viz. size of the recurrent tumour, number of recurrences and T4 invasion (invasion of skeletal muscle, cartilage or bone).

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy for T1 and T2 primary BCC has comparable outcomes (marginally inferior) to specialist surgery.</td>
<td>II &amp; IV</td>
<td>68, 70, 73, 82, 85, 89, 156</td>
</tr>
<tr>
<td>A radiotherapist's opinion should be considered for T4 primary, persistent and recurrent BCC.</td>
<td>III</td>
<td>71</td>
</tr>
<tr>
<td>Radiotherapy gives comparable control rates as re-excision for incompletely excised BCC and is an alternative to re-excision if further treatment is deemed advisable and re-excision is disadvantageous or not feasible.</td>
<td>IV</td>
<td>101</td>
</tr>
</tbody>
</table>

**Key points:**
- All salvage therapy for recurrent BCC has lower control rates than for primary BCC. 73.
- Adjunctive RT post salvage excision for recurrent BCC should be considered in poorer prognosis cases viz:
  - T4 primaries
  - Larger recurrent lesions
  - Multiple recurrences
  - Poor prognosis histology subtypes
  - Inadequate normal tissue margins
  - Perineural invasion
  - Node positive BCCs

on an individual basis by referral to a specialist cancer centre
Key points:

- Radiotherapy is an alternative curative treatment for primary untreated SCC in a minority of patients when surgery is disadvantageous. Radiotherapy is a more time consuming and inconvenient treatment for primary SCC amenable to surgery where cosmetic and functional outcomes are anticipated to be excellent. Radiotherapy is an alternate efficacious treatment for primary SCC:
  i) when surgery is not feasible eg patient unfit for surgery, patient refuses surgery, anticoagulation poses problems
  ii) when surgery will cause cosmetic or functional morbidity unacceptable to the patient eg naeectomy, loss of function of lips or eyelids, large tissue deficits, multiple lesions
- Radiotherapy is indicated as an adjunct to surgery for incompletely excisable (persistent) SCC or resected locally recurrent SCC to improve cure rates.
- Radiotherapy is important in the management of metastatic SCC (refer Chapter on Metastatic Disease)

Primary untreated squamous cell carcinoma

1. Primary untreated invasive SCC

Radiotherapy for primary SCC has comparable outcomes to surgery. Five year control rates of primary SCC treated with curative doses of radiotherapy are for T1 lesions 93%, T2 lesions 65–85% and T3-4 lesions 50–60%.

2. Residual and recurrent SCC

Incompletely excised SCC carries a local recurrence rate of over 50%. Overall tumour control of all stages of previously untreated primary SCC with radiotherapy is 87%, but the tumour control rate for recurrent SCC treated with radiotherapy is 65%. Recurrent SCC has higher mortality rates than primary SCC. Any SCC residual or recurrent after a standard curative dose of RT should be excised including the accompanying irradiated tissues.
**Key points:**

- Recurrent SCC after radiotherapy should be treated with surgical excision including the irradiated field.
- An incompletely excised SCC can be treated with RT if further excision is not possible or reasonable\textsuperscript{148,149}.

Recurrent SCC despite an initially reported complete excision may be an indication of aggressive biological behaviour. The recurrence and scar should be widely excised. If wide excision is not feasible or local recurrence occurs more than once then RT is recommended.

Local recurrence may be an early manifestation of dermal lymphatic or perineural spread which can continue to arise up to many centimetres, distant from the primary site (see chapter on metastatic spread). If the histopathology report of an excised recurrent SCC reports lymphovascular space invasion or perineural spread, or a poorly differentiated and widely infiltrative pattern, or spindle cell tumour type referral to a specialist centre for opinion regarding further treatment is recommended.

Recurrent SCC should be referred to a specialist skin or head and neck cancer clinic for opinion and management as specialist surgery or combined modality treatment may be indicated.

**Solar keratosis and Bowen’s disease**

Radiotherapy is rarely used as solar keratoses do not require treatment, and are routinely cleared with cryotherapy or 5-fluorouracil (5FU) cream or surgery. These modalities are more convenient and generally less morbid for patients than radiotherapy. Occasionally long-standing Bowen’s disease can grow to a large diameter and not respond to other treatment modalities. Radiotherapy can provide an alternative where surgery for large superficial areas may require grafting.

**Key point:**

- Radiotherapy is rarely indicated for solar keratoses or Bowen’s disease, except for the uncommon long-standing large superficial Bowen’s disease refractory to dermatological care and unsuitable for excision.
**Keratoacanthoma**

Radiotherapy hastens the natural history of resolution of keratoacanthomas with advantages to the patient of shorter lesion duration and less scarring. However, keratoacanthomas can clinically and on incisional biopsy be difficult to distinguish from aggressive primary SCCs and should be excised if doubt exists.\(^{161}\)

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Level of evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>As the late results of radiotherapy can be poor, it is generally not recommended for patients younger than 60 years with uncomplicated primary SCC anticipated to have excellent outcomes with surgery alone.</td>
<td>III</td>
<td>68,69, 70, 73, 155, 158</td>
</tr>
</tbody>
</table>

**Key points:**

- Radiotherapy for primary SCC has comparable outcomes to specialist surgery in a specialist skin cancer clinic\(^ {70,73,69,155}\).
- Incompletely excised SCC is an option with radiotherapy if re-excision is not feasible\(^ {147,148,149}\).
- Radiotherapy is important in the management of recurrent and metastatic SCC (see chapter on Metastatic Disease).
8. CRYO THER APY, CURETTAGE AND DIATHERMY

CRYOTHERAPY

Introduction

Cryotherapy is the destruction of tissue by the direct application of a cryogenic agent such as carbon dioxide snow, nitrous oxide or liquid nitrogen. It is a widely used, rapid, cost-efficient and effective therapy for solar keratoses (SKs). In addition, cryotherapy (cryosurgery) has been employed for more than thirty years for the treatment of selected skin cancers.

In general, the technique is most ideal for low risk primary tumours with well-defined margins on the trunk or limbs viz. Bowen’s disease (intra-epidermal squamous cell carcinoma), primary superficial or small papular basal cell carcinomas (BCCs), keratoacanthomas (KAs) and small primary well-differentiated squamous cell carcinomas (SCCs).

It is often combined with initial curettage to provide a specimen for histological analysis.

Cryosurgery may offer special advantages for elderly high-risk surgical patients especially those with a pacemaker or coagulopathy, for those who refuse surgery and for sites where scar contracture is best avoided eg digits.

Occasionally, in certain areas, cost and accessibility to surgical care may make cryotherapy the preferred treatment option.

Alternative forms of treatment, especially surgical excision, are indicated for large nodular, morphoeic or ill-defined BCCs, moderately to poorly differentiated SCCs, recurrent tumours and for certain high risk facial sites.

Nevertheless, many studies attest to the efficacy and acceptable cosmetic results achieved by cryosurgery in specialist clinics, even for difficult cancers.

If used for invasive tumours, a biopsy giving histological confirmation of the tumour is mandatory before treatment, or if there is evidence of residual tumour following treatment.
Rarely, cryosurgery may be used for palliation of incurable cancers to lessen tumour bulk or pain and reduce malodorous discharge\(^{194}\).

**Key point:**

- Cryotherapy is a simple and effective form of therapy for solar keratoses. If treatment protocols are optimal, cryotherapy achieves high cure rates for select low risk BCCs and SCs on the trunk and limbs. Acceptable cure rates, comparable to other standard treatment modalities, may be achieved for higher risk tumours in specialist clinics\(^{162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,94}\).

**Basal Cell Carcinoma**

Basal cell carcinomas may be successfully treated by cryosurgery with many large series by specialist clinics demonstrating cure rates equivalent to other treatment modalities\(^{94, 164,165,166,167,168,176,177,178,179,180,181,182,186,187,188}\). The importance of careful tumour selection is emphasised to achieve acceptable results\(^{95,166,184,187}\). Histological confirmation of the BCC and analysis for high-risk features is strongly recommended\(^{166,195,196,197}\). Cryosurgery is most effective for primary well-defined lesions of non-aggressive type at sites away from the head and neck\(^{167,176,178,180,184}\).

In general, it would be contraindicated for morphoeic or ill-defined BCCs\(^{163,166,177,178,182,187,188}\) and relatively contraindicated for high-risk facial sites such as lips\(^{184,192}\), alar creases\(^{192}\), inner canthus\(^{192,196}\) and periauricular regions\(^{196}\).

Repeated freeze thaw cycles with 3–5mm margins are recommended\(^{166,184,198,196,199,200}\). Thermocouple needles may be used to monitor the temperature at the base of lesions. However, several clinical parameters correlate well with adequate depth freeze and are more routinely employed\(^{192,201,198,202,196,197,199}\). Curettage is often combined with cryosurgery and may help improve the cure rate\(^{177,182,185,190,199,200}\).

Cure rates for BCC by cryosurgery are technique dependent. The aim of therapy is to produce a selective volume of tissue necrosis equivalent to that removed by simple excision. Cure rates consistently exceed 95% in specialty clinics where optimal selection and treatment protocols are used\(^{160,163,164,166,167,176,178,180,181,182,184,185,187,188}\). Suboptimal cryotherapy technique results in unacceptably low clearance rates\(^{94}\). One extensive review of multiple series reported a 5 year recurrence rate for cryosurgery of 7.5%, comparable to other standard treatment modalities\(^{60}\).
Most large series utilise liquid nitrogen in an open spray technique with repeated freeze-thaw cycles. However, superficial BCCs have been successfully treated with single freeze-thaw cycle cryotherapy achieving cure rates of 96%. Thermocouple needle monitoring of the temperature produced at the base of tumours (-40 to -60 degrees centigrade) may be employed.

Histological confirmation of all invasive tumours by pre-treatment biopsy is mandatory. Certain microscopic features are associated with a greater depth of invasion and a higher risk of recurrence.

Curettage provides a sample for histology, facilitates cryotherapy of larger tumours by reducing the tissue volume to be ablated, and may offer some advantages at sites such as nose and ears to define the full extent of tumour growth prior to cryosurgery.

Clinical features are fundamental in choosing those BCCs suitable for cryosurgery. Primary BCCs constitute the great majority of tumours treated in reported series. In general, such tumours are well-defined and non-morphoeic in type. Most series exclude ill-defined or fibrosing basal cell carcinoma in their selection criteria due to unacceptably high recurrence rates.

The size of a BCC also determines its response to cryosurgery. In general, the greater the diameter of a tumour, the lower the cure rate.

Recurrent BCCs respond less well to cryosurgery with lower cure rates, and Mohs’ surgery (see pp 37, 41–2, 45–8, 77) is the preferred treatment for such lesions.

Site criteria are also essential in selecting BCCs suitable for cryosurgery. Tumours on the trunk and limbs respond with consistently high cure rates of greater than 97%. Less optimal results are achieved for sites on the head and neck, although acceptable cure rates have been reported for selective cancers in experienced specialist clinics.

Routine follow up is essential for all patients treated by cryosurgery. Most recurrences will become evident within 5 years and many within 2 years. However, some BCCs have recurred as late as 10–12 years after treatment.
Guidelines | Level of Evidence | Refs
---|---|---
Cryotherapy achieves high cure rates for primary BCC on trunk and limbs if tumour selection and treatment protocols are optimal. | III & IV | 167, 180, 184
Cryotherapy for primary BCC on head and neck achieves cure rates equivalent to the other standard modalities if tumour selection and treatment protocols are optimal. | IV | 163, 165, 176, 177, 181, 182, 184, 187
Cryotherapy achieves lower cure rates for larger BCCs, except for the superficial (non-invasive) type. | IV | 167, 165, 176, 178, 179, 183, 185, 186, 189
Cryotherapy achieves lower cure rates for BCCs at high risk facial sites and is not recommended. | IV | 94, 163, 184, 187, 183, 186, 188
Cryotherapy is contraindicated for ill-defined or morphoeic (infiltrative) BCCs at any site. | IV | 165, 179, 168
Long term follow up is essential after treatment of BCC with cryotherapy, as late recurrences may occur. | III | 60

SQUAMOUS CELL CARCINOMA AND RELATED KERATINOCYTE TUMOURS

Squamous cell carcinoma

Squamous cell carcinomas (SCC) of low risk type can be similarly treated by cryosurgery. It may be indicated for small, primary, well-defined and non-ulcerated tumours on the trunk and limbs and acceptable cure rates have been reported\(^{164,166,167,176,178,179}\). In general, less-well differentiated SCCs, recurrent SCCs and those on the head and neck are treated by surgical excision\(^{164,176,177,138,203}\).

Repeated freeze thaw cycles with a minimum of 5mm margins are recommended\(^{176,190,204}\). Curettage may be used initially to debulk the lesion and is followed by cryosurgery\(^{177,204}\).

Histological confirmation and analysis for high risk features is essential prior to cryosurgery\(^{195}\).
Fewer SCCs are treated by cryotherapy than BCCs relative to their prevalence, implying that most published studies employ strict selection guidelines\(^{164,166,176,178}\).

In general, **low risk tumours** are selected. The criteria for such SCCs include:

- primary tumour\(^{176,180}\)
- small size\(^{164,176}\)
- well defined\(^{164,176}\)
- clinically and histologically well-differentiated\(^{164,176,177,180}\)
- on trunk or limbs\(^{166,175,180}\)

Cure rates of greater than 95% are consistently achieved if selection criteria are strict and optimal treatment protocols are employed\(^{164,165,166,167,174,175,176,177,178,180,181}\). The risks of recurrence and metastasis are increased at certain facial sites especially lips, ears, periocular regions and perhaps scalp\(^{49,205}\).

One retrospective Australian study on deaths from SCC of the skin found that 76.5% originated from the head and neck\(^{205}\).

Even with strict selection criteria in experienced clinics, some recurrences occur following cryosurgery for head and neck lesions\(^{163,165,166,176}\), in contrast to the very rare recurrences for those on the trunk and limbs\(^{166,175}\).

Management of SCC on the head and neck with cryosurgery should generally limited to specialist clinics with the full range of treatment options available.

Residual or recurrent SCCs are better removed surgically as cryosurgery leads to unacceptably low cure rates\(^{167}\).

**Solar keratoses**

Solar (actinic) keratoses are common skin lesions displaying different clinical and histological features. They represent both markers of solar damage and potential precursors of SCCs\(^{206}\).

A continuum of clinical and histological dysplasia occurs from SK to in-situ SCC (Bowen’s disease) and invasive SCC. However, not all SKs progress to SCC and some can regress spontaneously\(^{31}\), or following routine use of sunscreen application\(^{207,208}\). No clinical feature of SKs allows identification of those which will become malignant. However, early progression to SCC may be indicated by increased erythema, thickening, alteration or change in size\(^{209}\).

The diagnosis of SKs is usually made clinically but biopsy may be indicated to exclude malignancy.

SKs may be treated for cosmetic reasons, due to irritation, or because of the potential for developing SCC. This risk may be greater for immunosuppressed patients\(^{210}\).
Topical 5-fluorouracil cream may be used initially to highlight subclinical keratoses prior to cryotherapy treatment.

Successful clearance of SKs with cryotherapy with good cosmetic results requires accurate diagnosis and adequately timed treatment protocols. A single freeze-thaw cycle is usually recommended. Cure rates of greater than 98.8% have been reported.

Hyperkeratotic or suspicious SKs may be better treated by curettage alone, or curettage followed by cryotherapy, electrodessication or laser cautery to the base. These techniques provide a specimen for histological confirmation.

Widespread SKs may be treated by cryopeels but are more efficiently dealt with by field techniques, such as topical 5-fluorouracil cream, Masoprocol cream, chemical peeling, dermabrasion or laser resurfacing. Alpha-hydroxy acid or retinoid formulations may be used topically to reduce signs of photodamage including SKs.

Long term follow-up, education and prevention are an integral part of the care of patients with SKs.

Discrete SKs are cleared by single freeze cryotherapy achieving cure rates of 98.8% and 100% in two major studies. Individual lesions were mapped and followed up for signs of recurrence for periods ranging from 6 months to 8.5 years. Both series employed open spray liquid nitrogen with total freeze times based on the palpable thickness of SKs.

Extensive confluent SKs on the face may be similarly cured by cryotherapy, and can be made visible by 10 days of pre-treatment with topical 5-fluorouracil cream.

SKs are clinically graded (especially by palpable thickness) to determine treatment parameters. The great majority of lesions are treated by single freeze cycle cryotherapy, but some thicker SKs may require double freeze-thaw cycles of treatment.

Sites of treatment predominately involve face and upper limbs in the reported series with no difference in response rates. SKs of the periocular area responded equally well with no recurrences in a single study.

**Bowen’s disease**

Bowen’s disease is SCC confined to the epidermis. Bowen’s disease has been treated successfully with cryosurgery with many studies reporting greater than 95% cure rates and reasonable follow up periods. Non-optimal treatment protocols produce less satisfactory results. A pre-treatment biopsy is usually recommended.
A single freeze-thaw treatment cycle of 30 seconds with a 3mm margin is advised\textsuperscript{166,169}. Slow healing was reported for lesions greater than 20mm in diameter and for those on the lower legs\textsuperscript{172,231,232}.

Cure rates greater than 99\% are achieved with optimal cryotherapy\textsuperscript{166,169}. That is, liquid nitrogen used in an open spray technique with a single freeze cycle of 30 seconds or greater, achieving a minimal 3mm freeze halo around the marked lesion.

Cure rates vary from 66\% to 97\% with less aggressive protocols\textsuperscript{164,167,169,171,172,173}. Body site appears to make no difference in response to cryotherapy, but delayed healing was reported for lesions on the lower limbs\textsuperscript{172}.

Size does not adversely affect response and large lesions can be managed with overlapping treatment fields\textsuperscript{170,172}.

**Keratoacanthoma**

Keratoacanthomas can also be treated with cryotherapy achieving cure rates equivalent to curettage plus electrodessication, simple excision or radiotherapy\textsuperscript{163,166,175,176,178,179,191,233}. Larger lesions are often removed by curettage (providing a specimen for histology) followed by double freeze-thaw cycle cryotherapy to the base of the lesion.

Limited studies exist on cryotherapy of KAs\textsuperscript{163,166,175}. A **cure rate** of 87.5\% was achieved in one series of 5 lesions on the head and neck and 3 lesions on the trunk and limbs\textsuperscript{166}. Double freeze-thaw cycles of 30 seconds or more with 3 to 5mm treatment margins were used\textsuperscript{163,166,175}.

Site differences in response to cryotherapy have not been noted in the small series reported\textsuperscript{166}.

Size appears to have been a factor in the choice of cryotherapy with almost all lesions treated less than 20mms in diameter. One large KA responded to cryotherapy after initial shave excision\textsuperscript{175}.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Level of evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryotherapy achieves consistently high cure rates for solar keratoses.</td>
<td>IV</td>
<td>165, 162, 211, 212</td>
</tr>
<tr>
<td>Cryotherapy of Bowen's disease achieves high cure rates with optimal treatment protocols, but delayed healing may occur on lower limbs.</td>
<td>IV</td>
<td>166, 169</td>
</tr>
</tbody>
</table>
Key points:

• Cryotherapy is not often used for keratoacanthomas, but may represent reasonable treatment for smaller lesions. If the diagnosis is in doubt after biopsy, then treatment should be as for SCC\textsuperscript{163,166,175}.

• Cryotherapy produces cure rates equivalent to other standard treatment modalities for low risk SCCs on the trunk and limbs\textsuperscript{166,175,176,180}.

• SCC on the head and neck are high risk tumours. Cryotherapy in specialist clinics achieves acceptable cure rates if tumour selection and treatment protocols are optimal\textsuperscript{166,168,174,176,177,181}.

• Cryotherapy is contraindicated for recurrent SCC\textsuperscript{167}.

Relative Indications

1. Elderly patients, especially those with medical disorders less tolerant of surgical procedures, eg with pacemakers, coagulopathies.
2. In geographic areas with poor access to surgical facilities.
3. At body sites with higher risk of cicatricial scarring from other treatment modalities eg digits, penis.
4. At body sites with increased risk of keloid scars from other treatment modalities eg upper arms and upper trunk.
5. Solar keratoses at any site if discrete and non-suspicious.
6. Bowen’s disease especially on trunk or limbs.
7. Keratoacanthomas if small and at low risk sites.
8. BCCs and SCCs of low-risk type especially on the trunk and limbs.

Relative Contraindications

1. Cosmetic sites especially face and neck in younger patients.
2. High risk body sites especially on face and neck ie sites where it is difficult to ascertain depth of tumour penetration, or where deep recurrence poses greater potential risks.
3. High risk tumour categories ie. moderately to poorly differentiated SCC, and ill-defined or morphoeic BCC.
4. Recurrent cancers—surgical excision with histological confirmation of clear margins is essential.
CURETTAGE AND DIATHERMY

Curette and diathermy (C & D) is a specialized technique used in the management of basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, and Bowen’s disease.

To achieve the cure rates described, both careful lesion selection and critical attention to technique are required. It is considered that specialist training is necessary before using C & D.

**Mechanism**

The dermis surrounding skin cancers appropriate for C & D is gelatinous by comparison to normal dermis and can be easily enucleated using a curette. The curette makes no further progress when it reaches the surrounding healthy dermis and thus the operator can differentiate between normal and cancerous tissue. It follows from this that, if the lesion penetrates through into subcutaneous fat, the technique loses its selectivity, as fat is not able to resist the curette like healthy dermis. It is therefore not appropriate for lesions penetrating to the depth of the dermis. It also will not be effective in the treatment of cicatricial lesions which do not have a gelatinous stroma, e.g., morphoeic BCC.

The technique varies slightly between operators but essentially involves 1–3 cycles of curettage each followed by the application of diathermy to the base. Some operators now use CO2 laser in place of the diathermy.

The procedure is not appropriate on very thin skin such as eyelids, lip, or genitalia where tearing of tissue would allow the curette to break through to the subcutaneous layer.

**BASAL CELL CARCINOMA**

Curettage and diathermy is anecdotally regarded as effective for superficial BCCs on the trunk and limbs. It is useful in the treatment of BCCs on the legs of older patients as an alternative to skin grafting. Unpredictable cosmetic results restrict use on the face to situations where the cosmetic result is not a high priority. It has the advantage of being rapid to perform, tissue conserving, and not contra-indicated in anti-coagulated patients.
## Control rates for BCC treated by serial curettage by diameter\textsuperscript{57,67,75}

<table>
<thead>
<tr>
<th>Lesion: Size/type/location</th>
<th>Cure rate at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1cm all sites</td>
<td>98.77%</td>
</tr>
<tr>
<td>&lt; 1cm nose</td>
<td>93.55%</td>
</tr>
<tr>
<td>&gt; 2cm all sites</td>
<td>84%</td>
</tr>
<tr>
<td>&gt; 2cm ears</td>
<td>67%</td>
</tr>
<tr>
<td>All sizes not head</td>
<td>&gt; 96%</td>
</tr>
<tr>
<td>&lt; 1cm cheek, forehead &amp; temple</td>
<td>94.7%</td>
</tr>
<tr>
<td>&gt; 1cm as above\textsuperscript{166,169}</td>
<td>77.3%</td>
</tr>
<tr>
<td>&lt; 0.5cm nasal, paranasal, periorbital, lips, chin, jawline and ears\textsuperscript{166,169}</td>
<td>94.7%</td>
</tr>
<tr>
<td>&gt; 0.5cm as above</td>
<td>77.3%</td>
</tr>
</tbody>
</table>

As indicated by the above data, lesion selection by site and size is critical. Higher recurrence rates have also been noted with previously treated lesions\textsuperscript{57,67,75}. Morphoeic BCCs are not treated as they are not curettable due to the lack of a gelatinous stroma. Excisional data does confirm that histological type is a significant factor in recurrence; morphoeic and other infiltrating types of BCC characterised histologically by small cell clumps, showing higher recurrence rates\textsuperscript{75}.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Level of Evidence</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence rates of less than 6% may be achievable if curettage and electrodesiccation is used for appropriately selected BCC.</td>
<td>IV</td>
<td>57, 234</td>
</tr>
</tbody>
</table>
Key points:

Curettage and diathermy:

• Is not used on high-risk areas (nasal, paranasal, lips, chin, jawline and ears) or at least not for lesions larger than 5mm at these sites\(^57\).
• Is not used on lesions larger than 10mm on middle risk sites (face forehead, temples and scalp)\(^57\).
• Is used for all sizes of lesion on low risk areas (neck, trunk and limbs)\(^57\).
• Is not used on morphoeic lesions\(^75\).
• Is not used for recurrent lesions\(^57,67\).
• Is carried out by operators with appropriate supervised training in the procedure\(^57\).

Squamous cell carcinoma and related keratinocyte tumours

Squamous cell carcinoma

The use of curettage and diathermy in the management of SCC is subject to differences of opinion.

There are some limited data in the literature to support the procedure. One study demonstrates a cure rate of 96% in a group of 48 patients followed for 5 years and 98% in a group of 101 patients observed over 4 years. In both groups selection was based on a lesion size of less than 2 cm and ‘unusually invasive, destructive, or sclerosing lesions were treated by irradiation or surgery’\(^158\).

With the increasing number of organ transplant patients developing very large numbers of SCCs, the use of curettage and diathermy in selected tumours can be of value where surgical excision may be impractical.

Bowen’s disease

Curett and diathermy is one of a number of modalities used by dermatologists in the management of Bowen’s disease on exposed areas.

As mentioned previously the technique requires that the skin can be stabilised by stretching to provide a firm base against which to curette. It is also important that the dermis will not allow the curette to break through to the deeper tissues. This precludes the use of the technique on eyelids or the genital area and lip.
many cases occur on the legs of elderly women this method has the advantage of not requiring reconstruction.

Published data are limited to retrospective, uncontrolled studies with inadequate follow-up. These studies report recurrence rates ranging from 6.25% to 20%\textsuperscript{171,235,236}.

**Keratoacanthoma**

Keratoacanthoma is regarded as a benign tumour and commonly treated by dermatologists using the technique of curettage and electrodesiccation. The cosmetic results are anecdotally regarded as good\textsuperscript{237,238}.

Published studies show acceptable cure rates but are compromised by follow-up times of less than 5 years\textsuperscript{237,238}.

Curettage of keratoacanthoma involving the nail bed is controversial\textsuperscript{239,240}.

Curettage seems an acceptable procedure for keratoacanthoma provided that:

- It has not been previously treated.
- It is not on the ear or lip.
- It is less than 1 cm in diameter on other parts of the head.
- It strictly satisfies the clinical diagnostic criteria for keratoacanthoma.
- The curette is used to obtain the largest and deepest single piece of tissue possible for histology and the report is consistent with the diagnosis.
- Close follow-up can be achieved with immediate excision at the first sign of recurrence.
- It is carried out by operators with appropriate supervised training in the procedure.
9. OTHER TREATMENTS (INTRALESIONAL INTERFERON, TOPICAL IMIQUIMOD, PHOTODYNAMIC THERAPY, LASER THERAPY)

**INTERFERON**

**Introduction**

Interferons are proteins synthesised by leukocytes, fibroblast and lymphocytes in response to microbes, tumours and antigens. Acting as cytokines via interaction with cell surface receptors, these proteins have antiviral, antimicrobial, antitumour and immunomodulatory actions. Antitumour effects of interferons may be direct (antiproliferative, cytotoxic or enhanced cell surface receptors) or indirect (partly immune system activation).

Apoptosis can be induced by CD95 receptor ligand interactions.

Systemic (subcutaneous) interferon α, b, d have been successfully utilised in the management of Kaposi’s sarcoma, cutaneous T-cell lymphoma, viral papilloma and malignant melanoma. Subcutaneous interferon α-2a combined with oral retinoids may be useful for multiple lesions of Bowen disease. The following recommendations apply to the use of *intralesional* interferon for basal cell carcinoma and squamous cell carcinoma.

**BASAL CELL CARCINOMA**

Intralesional injection of interferon α-2b as the treatment for nodular and superficial basal cell carcinoma has been reported as having response rates of 24–100%, reflecting dose regimens, technique and duration of followup.

A large placebo controlled study utilising interferon α-2b 1.5 million units 3 times weekly for 3 weeks revealed tumour free rates at 1 year in 81% of interferon treated patients compared to 20% of placebo treated patients.

Aggressive (morphoeiform and recurrent) subtypes of basal cell carcinoma treated with the above regimen do poorly with surgical excision at 2 months revealing no residual tumour in only 27%.

Side effects with the above dose regimens are universal with most patients suffering mild flu-like symptoms. Fever and myalgia are common, chills and arthralgia are observed and swelling and erythema often noted at the injection site.
The cost effectiveness of interferon has been considered by Shiell\textsuperscript{250}. Interferon may be cost-effective in some patients who would otherwise be hospitalised for treatment of their basal cell carcinoma.

**Indications\textsuperscript{242}**

For the vast majority of patients surgery and radiotherapy are the preferred modes of treatment for basal cell carcinoma. Interferon therapy may be considered for patients with well defined nodular or superficial basal cell carcinoma who fulfil the following criteria:

1. Those who reject surgery or radiotherapy.
2. Whose tumours are considered problematic for surgery or radiotherapy because of functional location or cosmetic reasons.
3. Those with or without potential wound healing disorders.

**Contraindications\textsuperscript{244}**

1. Poorly defined or aggressive histological basal cell carcinoma subtype.
2. Organ transplant recipients (including renal, corneal, cardiac, other)—increased risk of transplant rejection\textsuperscript{244,251}.
4. Elderly patients, particularly with cardiac, renal and/or liver disease.
5. Multiple sclerosis.

**Treatment regimen**

1. The diagnosis of basal cell carcinoma and histological subtype should be confirmed by a small punch biopsy taken under local anaesthetic.
2. Indications and contraindications assessed as above.
3. Informed consent obtained from the patient, including adverse effects, efficacy, treatment course and need for prolonged follow-up.
4. 1.5 million IU of interferon α-2b drawn into tuberculin syringe with integrated 30 gauge needle: 0.15 ml using ten million unit 1cc diluent.
5. Except in large lesions the 0.15 mls is injected via a single site, using a fan approach to distribute the interferon throughout the tumour.
6. The most effective regimen appears to be 1.5 million IU given three times weekly for three weeks—total dose 13.5 million IU\textsuperscript{245}.
7. Systemic side effects may be reduced by the use of paracetamol prior to and following injections. Cool compresses may reduced local adverse effects\textsuperscript{242}.
8. Clinical follow-up to ensure resolution of tumour and absence of recurrence should continue for 5 years\textsuperscript{242}.
Squamous cell carcinoma

Intralesional interferon has been used since 1975\textsuperscript{252}. There is a very significant difference between intralesional and systemic interferon proving that local antitumour effects are the important factors. There are no randomised studies assessing the use of interferon as local therapy for squamous cell carcinoma\textsuperscript{242}. Small doses of interferon can be used when injecting intralesionally which reduces the systemic toxicity (eg 1.5 million units into the lesion 3 times a week for 3 weeks). Short and medium term studies of the effect of intralesional interferon on primary invasive and in-situ squamous cell carcinoma show moderate to good response rates\textsuperscript{244,253,254}. One pilot study assessing lip squamous cell carcinoma revealed a complete response of only 17%. In another study injecting 33 lesions the response in squamous cell carcinoma was 97.1% with a complete response rate of 88.2%.

Systemic side effects included fever, headache, myalgia and flu like symptoms but were only severe in 10% of patients. Using much lower doses (eg 100,000 units per ml at each injection yielded lesser response rates)\textsuperscript{244,254}. Long term, follow-up after use of human natural leukocyte interferon suggests reduction in the recurrences\textsuperscript{254}.

In patients with squamous cell carcinoma unsuitable for surgical therapy and at low risk of metastatic disease intralesional \(\alpha\)-2b may be considered but long term and detailed follow-up is mandatory. The role of interferon as adjuvant therapy for patients with progressive or metastatic squamous cell carcinoma remains uncertain.

Interferon and retinoids

Vitamin A derivatives slow growth of squamous cell carcinoma in preclinical studies.\textsuperscript{118} Thirteen cis retinoic acid can be given orally daily and combined with subcutaneous interferon \(\alpha\)-2a daily for two to three months. It can be considered for severe or extensive squamous cell carcinoma in situ\textsuperscript{218}. Response rates of up to 69% have been reported with complete response rates of 25%\textsuperscript{243,255}. The likelihood of response depends on the extent of disease. The major toxicity was cumulative fatigue which is not uncommon with such biological agents.

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<tr>
<th>Guideline</th>
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<td>Intralesional interferon has a limited but definite role in treatment of selected BCCs.</td>
<td>III–2</td>
<td>2,3,11, 241, 243, 249</td>
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</table>
9. OTHER TREATMENTS

TOPICAL IMIQUIMOD*

Imiquimod is an immune response modifier that induces cytokines related to cell mediated immune responses including interferon-α (IFN-α), IFN-γ, and interleukin. It has been approved for use in the treatment of external and perianal genital warts. Because of the efficacy of intralesional interferon in the treatment of BCC, it was believed that a topical interferon inducer may be of therapeutic value in these tumours.

Topical imiquimod 5% cream has been reported to have clinical efficacy when used in the treatment of BCC, both nodular and superficial. A double-blind placebo controlled trial evaluated different dose frequencies until 2 weeks after clinical resolution or to a maximum of 16 weeks. The medium application time was between 10 and 16 weeks for the lesions that cleared. A total of 35 patients (7 nodular BCC, 28 superficial BCC) were included in regimens including twice per day, once per day, three times per week, twice per week and once per week. There was a dose response with 100% tumour clearance in those dosed twice daily, once daily and three times weekly; a 60% clearance in those dosed twice weekly, and a 50% clearance in those dosed weekly compared with a 9% clearance in those treated with the vehicle.

In a larger phase II dose response study imiquimod 5% cream was studied at different frequencies for a fixed duration of 6 weeks in the treatment of superficial basal cell carcinoma. There was a 100% clearance in those treated twice daily; 87.9% clearance in a once every day regimen; 73.3% clearance in a twice daily three times per week regimen; and 69.7% clearance in a once daily three times per week regimen. The twice daily regimen was used on only three patients as that arm of the study was stopped early as a result of intense inflammatory skin reactions at the site of application. Application site reactions were common in the studies reported and were dose related.

Sixteen patients with Bowen’s disease (carcinoma in situ) were treated in an open-label study with once daily application of imiquimod 5% cream for a designated 16 weeks. A complete response rate of 93% was seen in 15 of the patients who completed the study. One patient died of unrelated intercurrent illness before a biopsy specimen could be obtained and therefore was not included in the analysis. Once again, local skin reactions were common with six patients ceasing treatment between four and eight weeks.

Further studies are ongoing to assess the value of imiquimod 5% cream in the treatment of solar keratoses.

* R Marks and S Kossard have participated in clinical studies of imiquimod 5% cream initiated by and supported with grants from 3M Pharmaceuticals, St. Paul, Minnesota.
Key point:
- Imiquimod 5% cream, a topical interferon inducer, potentially offers another treatment option in the management of basal cell carcinoma and other keratinocyte tumours. Its exact role awaits the results of further studies.

Photodynamic therapy

A broad range of procedures is covered under the definition of photodynamic therapy (PDT). The practicality of PDT is still in the stage of evolution with multiple clinical trials being conducted to develop suitable agents, light sources, etc, to obtain optimal tumour clearance with optimal cosmetic outcome. The principle of cutaneous PDT involves:

1. Exposure of the skin lesion to a photosensitising chemical either by systemic or topical application.
2. Absorption of this chemical into the tumour that is being treated.
3. Exposure of the lesion to a light source that is capable of photoactivating the sensitiser and penetrating the depth of the tumour.
4. Destruction of the tumour as a result of this photoactivation process via the generation of reactive oxygen intermediates that irreversibly destroys essential cellular elements and pathways.
5. Selective sparing of the normal cell lines within and adjacent to the tumour being targeted. In an ideal state the normal cells would be spared.

Potentially, PDT can result in excellent cosmetic outcomes. Scarring can occur following treatment in some body sites. The area reacts initially in a similar manner to cryotherapy with some peeling and occasionally blistering to the treated tumour area.

PDT has some advantages in patients who have bleeding disorders, pacemakers, have multiple lesions or who are physically frail where standard surgical intervention poses difficulties.

At present, the most suitable tumours to treat are those that are superficial including solar keratoses (80% or greater response rate) and superficial basal cell carcinomas (BCCs) (85–90% response rate). Bowen’s disease (intraepidermal squamous cell carcinoma) has also been reported to have high cure rates in the order of 90–100%.

More invasive tumours such as nodular BCCs have had lower response rates in the order of 60–85% cure. The same applies to squamous cell carcinomas with long term cure rates in the order of 40–70%.267,268
Key point:
• Photodynamic therapy potentially offers another treatment option in the management of non-melanoma skin cancer being most suitable for patients who have superficial tumours. Its exact role awaits the results of further studies.

LASER THERAPY

Introduction
Lasers have been used within dermatology in the treatment of skin cancers for more than 10 years [269]. Nevertheless they remain largely a specialist tool due to costs and specific training required for their applications. They may be employed as laser scalpels for cancer excisions [270], or more routinely for laser cautery following curettage [271] or shave excision [272]. While offering some advantages in the precision of tissue removal, they are impractical for widespread usage.

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<td>Laser therapy offers some treatment advantages for select skin cancers.</td>
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<td>However, the great majority of tumours are better managed by the less</td>
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<td>expensive commonly available techniques.</td>
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Although various laser formats have been employed for the superficial destruction of cutaneous lesions or skin resurfacing, including Argon [272], YAG [274, 278, 279], or more recently Erbium [280]. Carbon Dioxide lasers (CO2) have proved to be the most useful and versatile [269, 270, 271, 224, 225, 273, 275, 276, 277]. CO2 lasers produce infrared monochromatic light with a wavelength of 10,600 nanometers. This wavelength delivers heat energy to tissue resulting in its vaporisation. The effect on target tissue depends on the rate of energy delivery per unit area per unit of time (energy fluence = joules per second per centimetre squared). If laser energy is delivered as a single focused pulse then a defined well of tissue is vaporised. If delivered in a continuous or repeat pulse manner then a precise incision is achieved by a focused beam (laser scalpel technique), or a broader area of depth ablation by a defocused beam (paintbrush technique). Most applications involve delivery of variable energy fluences for precise removal of
layers of tissue to predictable depths. Good visual control is achieved as bleeding points are automatically cauterised\textsuperscript{270,281}. The laser may be used as a sole ablative tool or as an adjunctive therapy after initial curettage\textsuperscript{271} or shave excision\textsuperscript{272}. In the latter respect it is used as a laser cautery similar to electrodessication, electrofulguration or hot wire cautery. Laser ablation following tumour debulking has some theoretical advantages over other modalities of treatment in terms of the precision and control of marginal and deep tissue removal. Laser light may also be used to activate the photosensitising agent in the treatment of skin cancer by photodynamic therapy\textsuperscript{261,55}.

**Basal cell carcinoma**

Cure rates equivalent to other modalities can be achieved for superficial or nodular BCCs if laser technique is optimal\textsuperscript{271,278,277}. Clearance is increased by more laser passes\textsuperscript{271,275,276}, or by the addition of curettage\textsuperscript{271}. It is especially useful for large or multiple lesions over the trunk or limbs\textsuperscript{271}. Its speed of operation may offer advantages in the occasional patient with extensive numbers of superficial BCCs requiring treatment in one session\textsuperscript{277}.

Good haemostasis and a dry surgical bed are achieved with a laser scalpel for advanced cancers\textsuperscript{270} and for Mohs' surgery\textsuperscript{281}.

**Key points:**

- Serial laser ablation achieves high cure rates for superficial and nodular BCCs\textsuperscript{271,275,277}.
- Large numbers of BCCs may be removed rapidly in single session\textsuperscript{277}.
- Laser ablation may be followed by light curettage to increase the cure rate\textsuperscript{271}.

**Squamous cell carcinoma and related keratinocyte tumours**

**Squamous cell carcinoma**

Squamous cell carcinomas of low risk type may be similarly removed by curettage combined with laser ablation of further tissue at the base and margins. This is analogous to curettage plus electrodessication or cautery\textsuperscript{203,193}.
Key points:

- Laser ablation is highly effective for removal of widespread solar keratoses and in-situ malignant changes on the lower lip (laser vermilionectomy) or face (laser resurfacing)\textsuperscript{55,224,225,223,261,282}.
- Bowen’s disease may be successfully treated by laser ablation. This may be especially advantageous at difficult sites eg digits\textsuperscript{224,225,273}.
- Keratoacanthomas and low risk SCC may be similarly removed by laser therapy. Initial debulking by curettage or shave excision may improve cure rates\textsuperscript{272}.
- The laser scalpel may offer advantages of better haemostasis in Mohs’ surgery or for excision of advanced SCCs on the face\textsuperscript{270}.

Solar keratoses

Individual solar keratoses (SKs) can be removed by laser therapy with some possible cosmetic advantages\textsuperscript{225}, but it remains impracticable for the great majority of lesions, and cryotherapy and 5-fluorouracil cream are the preferred treatments\textsuperscript{162,215}.

Potentially the greatest application for laser therapy is in regard to field skin resurfacing for reducing extensive solar keratoses and other signs of photodamage\textsuperscript{224,225,282}.

The success and long-term benefits of procedures designed to ablate the epidermis and papillary dermis such as dermabrasion\textsuperscript{283,219,222}, chemical peeling (trichloroacetic acid or phenol)\textsuperscript{222,217,284}, manual sanding with or without added chemical peels\textsuperscript{285}, cryopeeling\textsuperscript{212} and laser resurfacing\textsuperscript{224,225,223,282,286} have been well documented. One significant recent study on laser resurfacing demonstrated sustained improvements in the epidermis and dermis at two years follow-up\textsuperscript{223}. Compared to pre-treatment biopsies, the epidermis remained thickened with normalised basal cell polarity and absent dyskeratosis, while the dermis demonstrated thickening of the grenz zone, increased collagen fibres and reduced solar elastosis. Laser ablation offers some advantages of predictable depth ablation, accessibility to difficult sites and safety compared to other methods of skin resurfacing. The whole subject of cutaneous laser resurfacing has been recently reviewed\textsuperscript{286} and the histologic changes summarised\textsuperscript{287}.

Actinic cheilitis may be successfully treated by laser vermilionectomy\textsuperscript{269,55,261,288,289}. This technique removes extensive solar keratoses, leukoplakia and other signs of photodamage from the lower lip. Good cosmetic and functional outcomes with a
lower risk of complications than standard surgical vermilionectomy have been reported\textsuperscript{261,55}.

**Bowen’s disease**

Bowen’s disease may be removed by carbon dioxide laser therapy and several treatment series give high cure rates\textsuperscript{224,225,275,231}. It is especially useful in difficult areas where maximal tissue preservation is desired eg digits\textsuperscript{273,280,232}.

Extensive experience has been obtained in removal of genital leukoplakia and intraepithelial squamous cell carcinomas\textsuperscript{291,292}.

**Keratoacanthomas**

Keratoacanthomas can be successfully removed by laser ablation\textsuperscript{272}. Initial curettage or shave excision may simplify the procedure and improve the cure rates\textsuperscript{233}. If any doubt exists after initial biopsy, then tumours should be treated as SCC\textsuperscript{293}.
10. PREVENTION (INCLUDING CHEMOPREVENTION)

PREVENTION

Exposure to sunlight is strongly associated with the development of non-melanocytic skin cancer. Within Australia and other countries such as the USA, the incidence of non-melanocytic skin cancer is highest in areas of low latitude (i.e., closest to the equator) and it occurs more frequently on parts of the body that are habitually exposed to sunlight. In particular, squamous cell carcinoma (SCC) rarely occurs on parts of the body that are not habitually exposed. SCC and the other main type of non-melanocytic skin cancer, basal cell carcinoma (BCC), appear to differ in their relationship to sun exposure. SCC is related to total lifetime exposure to the sun, but not to the pattern of exposure (intermittent exposure versus more continuous exposure as occurs in outdoor workers). Outdoor workers appear to have the highest risk. In contrast, recreational and intermittent exposure may be more closely related to BCC than the total amount of exposure, with indoor workers possibly having higher risk than outdoor workers.

A randomised trial of adults in Queensland showed that sunscreens reduced the risk of SCC, but not BCC. Two randomised trials of sunscreens showed that they reduced the prevalence of solar keratoses, which are closely related to SCC.

Studies of immigrants to Australia indicate that sun exposure during childhood and adolescence is very important in causing both BCC and SCC. There is also more direct evidence of the importance of exposure early in life for SCC. These findings indicate that particular emphasis should be placed on protection from excessive sunlight exposure in childhood and adolescence. However, skin cancer itself is rare before puberty and there may be a long latent period, usually many years, from the initiating sun exposure to the time a skin cancer (especially an SCC) becomes clinically apparent. Furthermore, while childhood sun exposure is very important in the development of skin cancer, exposure in adult life is also important. Therefore, everyone should be advised to use sun protection measures throughout their life. This is considered advisable despite lack of conclusive evidence of reduced incidence of skin cancer resulting from current sun avoidance practice.

The Cancer Council Australia does not distinguish between melanoma and non-melanoma in its recommendations on prevention of skin cancer, which relate to sun protection. It recommends avoiding the sun in the middle of the day, staying in the shade whenever possible, wearing a wide-brimmed hat and clothing to cover exposed skin, and using sunscreen. These strategies are discussed in more detail below.
The most effective strategy to prevent skin cancer is to avoid exposure to ultraviolet radiation (UV) from the sun and to plan outdoor activities before 10am and after 2pm (before 11am and after 3pm Daylight Saving Time). Sixty per cent of the day’s harmful UV occurs between these hours. Skin will burn more quickly around midday than earlier or later in the day.

In addition:

Hats and clothing

Always encourage the wearing of broad-brimmed or legionnaire hats (those which cover face, neck and ears reduce the UV exposure to the face and eyes) and comfortable clothing that protects the arms, legs, body and neck from the sun. Choose closely woven fabrics that can’t be seen through when held up to the light. (The Australian Standards Association has a system for the rating of the protection factors of fabrics to help consumers select fabrics with a high protection factor rating, if they want.)

Shade

Seek shade. Whenever possible, choose activities which can be conducted in or moved to shady areas. But it is possible to get burnt in the shade by reflected UV rays so use clothing and sunscreen as well.

Sunscreen

Use sunscreen. Apply a sunscreen of SPF15 or greater to all exposed areas of skin as the last line of defence. All recommended sunscreens should be broad spectrum with protection extending as far as possible into the UVA range. Sunscreen should not be relied on as the only form of protection. Apply 20 minutes before going outside and reapply at least every two hours. For specific circumstances such as swimming, a water-resistant sunscreen should be selected. (The Australian Standards Association permits labelling of the sun protection factor of a sunscreen up to 30+) 

Sunscreens should not be used to extend the duration of sun exposure, such as prolonging sunbathing. Using sunscreen to extend exposure to the sun may increase the risk of developing melanoma.

Sunglasses

Wear sunglasses. There are a wide range of sunglasses available which are effective and inexpensive—check the label to make sure they meet the Australian Standard AS 1067.

Window glass

Three millimetre window glass is equivalent to SPF 14 sunscreen in filtering UVB. It does not filter UVA.

Advice should be given regarding the potential risk of UV damage from sunbeds, tanning booths and tanning lamps.
**Guidelines**

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<tr>
<td>Use broad spectrum sunscreens with an SPF of 15 or greater as an adjunct to sun avoidance and other sun protective measures.</td>
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<td>298, 299</td>
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<tr>
<td>* Squamous cell carcinoma; there is no evidence for BCC.</td>
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<tr>
<td>Use clothing, where possible, as the primary means of photoprotection.</td>
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**Recommendations**

- Stay in the shade whenever possible during daylight hours
- Avoid the sun in the middle of the day (i.e., during the two hours either side of solar noon)
- Wear a broad-brimmed hat when outdoors
- Provide children with appropriate sun protection for outdoor activities
- Advise against the use of sunbeds, tanning booths, and tanning lamps

**Chemoprevention**

**Synthetic retinoids**

Organ transplantation

Both cardiac and renal transplant recipients have been shown to have a greatly increased risk for the development of non-melanoma skin cancer. This has been shown to affect 25% of Australian renal transplant recipients by 5 years and 44% by 9 years post transplantation. The most dramatic increase in incidence occurs in squamous cell carcinoma though there is also an increase for basal cell carcinoma. A greater proportion of the squamous cell carcinomas occurring in this context show aggressive growth patterns and poor prognostic features. Aggressive squamous cell carcinomas contribute to substantial numbers of deaths in the Australian organ transplant population. Human papilloma virus infection is more common in the transplant population and prolific warts may develop. High frequencies are seen of the human papilloma virus Types 5 and 8 that are associated with cutaneous malignancies in the condition epidermodysplasia verruciformis. These may play an aetiological role in the development of squamous cell carcinomas. UV exposure is also an important risk factor in this population.

Four studies of retinoid chemoprophylaxis of skin cancer have been undertaken in renal transplant recipients. All have shown a significant reduction in rates of
squamous cell carcinomas during treatment\textsuperscript{306,307,230,308}. In one study patients were observed following cessation of retinoid chemoprophylaxis and skin cancer suppression was not maintained, suggesting that these agents act at a late stage in tumour development.

Because of the need for long term therapy it is recommended that retinoids be instituted only when patients begin to suffer from numbers of squamous cell carcinomas that are causing significant morbidity or threatening life. The long term benefits must be weighed against the short and long term adverse effects of retinoids. The major long term adverse effect is calcification of tendons and ligaments and spinal hyperostoses\textsuperscript{309}.

**Xeroderma pigmentosum**

A trial using isotretinoin in 7 patients showed a 63\% reduction in skin cancers compared with the 2 year period before treatment\textsuperscript{310}.

**Naevoid basal cell carcinoma syndrome**

Several trials of retinoids have demonstrated effective chemoprophylaxis of basal cell carcinoma in this context\textsuperscript{120, 311,312}.

**Betacarotene supplementation**

Two trials of betacarotene in the chemoprevention of skin cancer have failed to demonstrate a beneficial effect\textsuperscript{120,313,298}. 

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84 Non-Melanoma Skin Cancer: Guidelines for treatment and management in Australia
11. METASTASIS FROM NON-MELANOMA SKIN CANCER

BASAL CELL CARCINOMA

Lymph node metastases

Basal cell carcinomas rarely metastasise to lymph nodes. Most commonly the patient has a long history extending over many years of multiple recurrences or an uncontrolled primary lesion. Other factors including a history of prior radiotherapy, large primary tumours and head and neck lesions have also been noted.314,315

Regional control can usually be achieved with lymphadenectomy. Post operative radiotherapy may be indicated for patients with a high risk of recurrence ie. extensive disease, multiple involved nodes, extra capsular extension, close/involved surgical margins.316,317 Radiotherapy alone is a reasonable alternative to surgery for the poor operative candidate or the patient with inoperable disease requiring palliation. Survival after development of regional disease is short due mainly to failure to control the primary lesion.

Distant disease

Metastatic disease from BCC is an extraordinarily rare event. Lung and bone are the commonest sites. Reported experience with only a handful of patients indicate that cisplatin based regimens appear to be the most effective. Response rates of up to 83% have been reported with a median duration among responders of 24 months.318 Radiotherapy may be useful in palliation of distant metastases.

Chemotherapy

(i) Systemic treatment:

Rarely systemic chemotherapy is used in metastatic basal cell carcinoma or for locally advanced disease. Most regimens include cisplatin. Only small groups of patients have been reported with response rates up to 83% with 37% being complete responses.319,320,321,322,323,324,325

(ii) Local treatment:

Local chemotherapy has been employed in the treatment of basal cell carcinoma. Most commonly reported is the topical application of 5-flourouracil creams.326,118,327,255 Intralesional 5-FU with epinephrine injectable gel has also been used. More recently, electro-chemotherapy which
involves intralesional bleomycin and electric pulses locally has achieved response rates approaching 100%\[328\].

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<td>with 37% being complete.</td>
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<td>Intralesional 5-FU with epinephrine injectable</td>
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<td>gel has also been used. More recently, electro-</td>
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<td>chemotherapy which involves intralesional</td>
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<td>achieved response rates approaching 100%.</td>
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**Squamous Cell Carcinoma**

**Lymph node metastases**

The incidence of lymph node metastases from SCC occurring in sun affected skin is very low (less than 1%) but may be considerably higher in certain situations including\[49,329\]:

1. SCC occurring at sites of mucosal-squamous cell junction including lip, anus and vulva
2. Immuno-suppression
3. Previous radiotherapy
4. SCCs arising in chronically inflamed/irritated lesions.

Primary lesions located in the head and neck, in particular the lip and ear, are responsible for the majority of lymph node metastases from SCC.

Among patients developing regional recurrence, specific tumour factors related to the development of regional recurrence include\[49\]:

1. Tumor Size. SCC greater than 2cm are twice as likely as smaller lesions to develop regional recurrence.
2. Tumor Site. Lesions located on the ear and lip have a higher rate of local recurrence than cutaneous SCC elsewhere.
3. Tumor Grade. Poorly differentiated SCC have double the recurrence rate of well differentiated lesions.
4. Tumor Thickness. SCC greater than 4mm in thickness recur three times more commonly than thinner lesions.
5. Recurrent SCC. Recurrent lesions are twice as likely to recur.
6. Peri-neural Invasion. The most serious predictor of regional recurrence with up to 50% developing regional recurrence.

The time to development of regional disease is short, usually within 12–24 months after initial treatment of the primary lesion.

**Key point:**
- Regional lymph node spread of SCC is uncommon but is often associated with metastasis to distant sites and a poor outcome.

Any clinical suspicion of node metastases warrants investigation by CT scanning + ultrasound. The diagnosis of nodal metastases should be confirmed by fine needle aspiration cytology (FNAC). Occasionally image guided FNAC or core biopsy may be necessary. Open incision biopsy of a suspicious lymph node for diagnosis is not advised: it potentially increases the risk of dermal lymphatic involvement, compromises further management, reduces the efficacy of subsequent lymphadenectomy and usually requires an avoidable general anesthetic.

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<td>Clinically suspected lymph node metastases should be confirmed by fine needle aspiration cytology (under radiological guidance if required). Open surgical biopsy should be avoided.</td>
<td>IV</td>
<td>330</td>
</tr>
</tbody>
</table>

Although cutaneous SCC is the obvious primary for a regional lymph node metastases, this is not always the case, especially in the head and neck the commonest site of regional metastases. Patients may have had numerous previous skin cancers of the head and neck and may also be at increased risk for other upper aero-digestive tract mucosal primary SCCs as the source of the SCC nodal metastasis. A thorough examination of the upper aero-digestive tract by an experienced clinician is necessary if any doubt as to the site of the primary lesion exists.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
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<tbody>
<tr>
<td>The treatment of metastatic disease to lymph nodes is primarily surgical.</td>
<td>IV</td>
<td>49, 117, 329, 331</td>
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</table>
Given the complexity of treatment for patients with regional metastases specialist referral is indicated. Lymphadenectomy for disease in the axilla or groin is straightforward. Occasionally lymph node metastases occur at unusual sites including the epitrochlear region and popliteal fossa. For cervical lymph nodes most authorities recommend a selective neck dissection. The extent of the lymphadenectomy is determined by the site of the primary lesion and the involved node(s) and the extent of the disease. Generally the accessory nerve and sternomastoid muscle can be preserved which reduces the morbidity of the procedure.

Post-operative radiotherapy is recommended for patients with a high risk of recurrence including:

- Parotid node metastases
- ≥ 3 nodes positive in the neck
- ≥ 4 nodes positive in the axilla or groin
- Significant extra nodal extension
- Close or involved surgical margins
- Skin infiltration
- Recurrent nodal metastases, salvaged surgically
- Node metastases in unusual sites, viz posterior triangle neck / SCF / occipital nodes (from primary cutaneous SCC of posterior scalp, upper trunk), epitrochlear and popliteal nodes
- Node metastases accompanied by local relapse.

For patients with extensive disease, eg very large nodes, multiple nodes, bilateral nodes and involvement of overlying skin or fixation of nodes, multimodality treatment is indicated. In these instances, or if any doubt exists on the extent or integration of treatment, pre-operative assessment and opinion from a multidisciplinary team is recommended. A head and neck surgeon, reconstructive surgeon, dental oncologist, surgical oncologist, radiation oncologist and medical oncologist may need to be involved in complex cases.

Recurrence of nodal disease is associated with a very poor prognosis. While no randomised trials exist to support the role of post-operative RT in cutaneous SCC, evidence extrapolated from mucosal related metastatic SCC is strongly supportive.

Curative RT alone for nodal metastases is indicated if lymphadenectomy is not possible due to the patient being unfit for surgery or refusing surgery. Salvage surgery is sometimes possible if complete or durable control is not achieved with RT alone. Palliative RT is appropriate for inoperable, advanced regional metastases to treat pain, stave off skin ulceration, and reduce bleeding. It is unlikely to prolong survival.

Survival after lymph node metastasis is poor with only one third surviving 5 years. Half of these patients die of uncontrolled regional disease without distant metastases. For patients with regional spread from SCC of the lip, survival may be twice as high.

Survival after lymph node metastasis is poor with only one third surviving 5 years. Half of these patients die of uncontrolled regional disease without distant metastases. For patients with regional spread from SCC of the lip, survival may be twice as high.
Dermal lymphatic spread (in transit metastases)

This is a very uncommon condition and may be seen in association with regional spread and or locally recurrent disease. Wide surgical excision is indicated followed by adjuvant radiotherapy. Further recurrence is not uncommon.

Perineural spread

Perineural spread may be incidental or symptomatic. Incidental implies early spread is asymptomatic and is recognised only after complete pathological examination of the specimen. No further intervention is indicated if the lesion has been completely excised. Radiotherapy treatment recommendations are found in the Chapters on surgery and RT for SCC. (Chapters 6 & 7)

Symptomatic perineural spread is late or established spread of SCC away from the primary SCC site along an involved nerve and carries a very poor prognosis. The vast majority occur in head and neck cutaneous SCC.

Surgical resection of the involved nerve, which is usually followed by adjuvant radiotherapy, is appropriate. Alternatively, high dose RT with palliative or curative intent covering the entire course of the nerve back to its origin from the CNS is acceptable. Treatment invariably causes major morbidity. Relief of symptoms occurs in >50% of cases with variable durability.

Metastatic squamous cell carcinoma

Distant metastases from SCC are uncommon. They rarely precede the development of regional metastases or occur in isolation from regional metastasis. The time to occurrence after presentation with the original primary lesion is short, usually within 2 years. The commonest sites of spread are the lung and liver but bone and brain may also be involved. Radiotherapy is effective in controlling symptoms and delaying local progression of disease. Cisplatin based chemotherapy protocols appear to be the most effective but other agents with some efficacy include 5-flurouracil, bleomycin and vindesine. Survival despite treatment is poor with few patients surviving more than 2 years. Specialist referral is indicated.

Chemotherapy

(i) Systemic treatment:

Systemic chemotherapy has been used for metastatic squamous cell carcinoma of the skin. It can be used alone or as part of multimodality therapy. Most regimens are based on cisplatin with the most commonly reported phase II studies using cisplatin and doxorubicin. Other drugs include methotrexate, 5-fluorouracil, bleomycin and vindesine. Objective response rates of > 80% have been reported with complete response rates of around 30%.
(ii) Local treatment:

Local chemotherapy has been used in the treatment of metastatic squamous cell carcinoma. Small studies have investigated intralesional cisplatin with epinephrine or 5-fluorouracil with epinephrine gels\textsuperscript{327, 255}. Topical 5-fluorouracil has activity in squamous cell carcinoma in small series\textsuperscript{252,328,335,336}.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Level of Evidence</th>
<th>Refs</th>
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</thead>
<tbody>
<tr>
<td>Most regimens are based on cisplatin with the most commonly reported phase II studies using cisplatin and doxorubicin. Other drugs include methotrexate, 5-fluorouracil, bleomycin and vindesine. Objective response rates of $&gt; 80%$ have been reported with complete response rates of around $30%$. Patients should be considered for referral to a suitable cancer specialist centre for multidisciplinary care.</td>
<td>III</td>
<td>118, 319, 320, 321, 322, 323, 324, 325, 326</td>
</tr>
<tr>
<td>Small studies have investigated intralesional cisplatin with epinephrine or 5-fluorouracil with epinephrine gels. Topical 5-fluorouracil has activity in squamous cell carcinoma in small series.</td>
<td>III</td>
<td>252, 255, 327, 328, 335, 336</td>
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</table>
12. FOLLOW UP

No study has assessed the possible benefit from regular medical review for patients who have been treated for a non melanoma skin cancer in comparison with observation by the patient themselves.

There are three reasons to undertake follow-up for such patients:

DETECTION OF FURTHER PRIMARY TUMOURS

Many studies attest to the higher incidence of subsequent non-melanoma skin cancers in patients who have been treated for one. It is likely that these will be detected earlier by regular medical follow-up thereby minimising the morbidity associated with the disease and its treatment.

At each follow-up visit all of the skin surface that has been chronically or intermittently sun exposed should be examined. Good lighting is important.

The frequency and duration of follow-up should be varied according to risk factors for further primary tumours. Patients in special risk groups such as organ transplant recipients may require three monthly follow-up by a specialist. For others annual follow-up by their general practitioner may be sufficient.

LOCAL PERSISTENCE OF THE PREVIOUSLY TREATED TUMOUR

Follow-up after treatment for a primary tumour for local persistence (clinical local recurrence) of the primary tumour should be considered if:

(a) A treatment modality has been used that is associated with a high rate of locally persistent disease.

(b) There is uncertainty about the completeness of removal with previous surgery.

(c) The primary tumour has clinical and/or histological features that are associated with high risk of locally persistent disease.

(d) The tumour has been treated at a site where extensive locally persistent disease would be difficult to treat.
EARLY DETECTION OF METASTATIC DISEASE

Published studies suggest that frequency of metastatic disease from primary squamous cell carcinoma of the skin may be as much as 1–2%, although this is likely to be the upper limit for the vast majority of tumours. The rate is higher from lip and ear. Metastasis from squamous cell carcinoma generally presents in the regional lymph nodes. It has been suggested that six monthly follow-up for a two year period would be sufficient for most squamous cell carcinomas.

Tumours with factors that increase the risk of metastatic disease (e.g., large volume lesions, lip lesions, transplant recipients) should be considered for more frequent follow-up over a longer period. At each follow-up visit the patient should be examined by the doctor, palpating both regional and distant lymph node sites in addition to examining the skin for local persistence of the primary tumour and further primary tumours.

Following treatment of a primary tumour all patients should receive counselling about their risk for further primary tumours, local persistence of their previous primary tumour and for metastatic disease. As much as possible these risks should be quantified. The patient should be advised about ways in which these problems might present and how they should go about assessing themselves for these possible eventualities.

<table>
<thead>
<tr>
<th>Conclusion and Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
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<tbody>
<tr>
<td>There are no data available as yet to underpin a recommendation on the frequency or nature of follow-up after the treatment of primary cutaneous non-melanoma skin cancer.</td>
<td>0</td>
<td>Nil</td>
</tr>
</tbody>
</table>
13. **WHO TREATS AND PROBLEMS TO REFER**

**INTRODUCTION**

The pivotal position occupied by general practitioners (GPs) in the Australian health scene accounts for the fact that they diagnose and manage most suspicious skin lesions in Australia, particularly in rural areas. Morbidity studies highlight the very high incidence of NMSC in Australia and thus the significantly high workload and decision making for skin cancer management by the general practitioner. Raasch and others raise questions about the current practice of 'excising suspicious skin lesions as informal screening for skin cancer'. A recent study in the Townsville area of Queensland which addressed this issue confirmed the general understanding that excision biopsy is the standard preferred management for clinically diagnosed NMSC and the lesions that were diagnosed as clinically benign were not excised or biopsied. The study also found that there was a relatively high proportion of correct clinical diagnoses for NMSC.

It is sobering to realise that NMSC is responsible for the death of 200 Australians each year. Difficulty in managing many of these tumours is 'due to atypical or unusual presentations as well as a poor understanding of their histological variants'. This highlights the importance of appropriate training and skills acquisition for the GP. As Marks points out, with this background GPs should be able to treat a large proportion of skin cancers.

**TO TREAT OR TO REFER**

The decision influencing treatment depends on many factors including the experience and skills of the doctor of first contact, geographical location, local facilities including availability of radiotherapy and in particular available specialists whether surgeons or operative dermatologists.

The actual decision to refer for specialist management can be difficult. However rural GPs especially those in remote areas may proceed directly to excision biopsy with confidence in their own skills while GPs in busy city practices are inclined to refer to specialists trained in skin surgery.

The most appropriate practitioner to manage the uncomplicated small tumours is the adequately trained GP who can simply remove most of these by an elliptical excision with a 3 mm margin. Early presentation and diagnosis facilitates the
process and the more experience that the GP acquires, which largely comes from hands on treatment, the better the management process. It should be emphasised that there is a wide variation in skills, training and confidence of GPs with some, particularly rural GPs or those with surgical training in hospitals, possessing skills to manage more complex skin tumours. The treating GP should have an appropriate treatment room with adequate sterilisation facilities, correct instruments and good lighting.

GPs should be prepared to excise most tumours at first contact because it makes economic sense. They should also be able to learn and undertake basic skin biopsy techniques (punch and shave) to establish a diagnosis.

GPs should also be aware of the variety of treatment modalities for NMSC including surgical excision, cryotherapy, curettage and radiotherapy. Each management decision has to be tailored to the particular lesion in that individual patient but generally simple surgical excision with primary closure is the treatment of choice for most skin cancers.

Cryotherapy is a useful and relatively simple option in appropriately trained GPs for the treatment of low risk superficial BCCs, but histological diagnosis is essential before such destructive forms of therapy. Obvious or suspected solar keratoses are an exception.

A review of Health Insurance Commission data on services provided for excision of skin tumours reveals that along with specialists such as dermatologists and plastic surgeons, Australian GPs excise a substantial proportion of these lesions on the face and body, not just tumours less than 10 mm, but also including those 10–20 mm in size.

GPs need to be aware of the limitations of their skills and should be prepared to refer to an appropriate specialist.

**Problem areas requiring experience and care**

The education of GPs on the management of NMSC should include basic information on the anatomical pitfalls awaiting surgical excision. The following summarises potential or real problem areas:

- The face—for cosmetic reasons
- The face—for potential nerve damage eg temporal branch of facial nerve
- The lips and helix of the ear—because of malignant potential
- The eyelids
- The inner-canthus of the eye with close proximity to the nasolacrimal duct
- Mid sternomastoid muscle area where the accessory nerve is superficial
- Fingers where functional impairment may be a concern
- Lower limb below knee where healing, especially in the elderly, will be a problem
There are specific lesions where it is appropriate to refer to a specialist and this may apply to the experienced GP. In many instances it is comforting for both the patient and their GP to have a technically difficult problem managed by a specialist.

Referral should be considered for:

- uncertainty of diagnosis
- any doubts about appropriate treatment
- tumours larger than 1cm
- multiple tumours
- recurrent tumours, despite treatment
- incompletely excised tumours especially when complete excision may be difficult
- recommended treatment beyond the skills of the practitioner
- anticipation of difficulty with technique or anatomy where an appropriate specialist should be consulted
- squamous cell carcinomas on the lips and ears
- infiltrating or scar-like morphoeic BCCs, particularly those on the nose or around the nasal labial fold—as there may be a problem in determining the tumour’s extent and depth
- cosmetic concerns such as lesions of the upper chest and upper arms where keloid scarring is a potential problem
- areas where palpable regional lymph nodes suggestive of metastatic spread of squamous cell carcinoma viz head & neck, axilla and groin
- large lesions which may require complicated methods of closure such as grafts and flaps—where the GP is inexperienced in these techniques
- when the GP will be unavailable for regular follow up especially for an SCC

Key point:

- Operative specialists should be given the opportunity to deal with the lesion in its entirety.

Although complete excision of a skin cancer with a narrow margin may not effect outcome it is better to avoid two procedures for the one lesion.

The first opportunity for treatment is the best opportunity to achieve cure.
Follow up

All patients treated for NMSC whether by the GP or specialist require follow-up for evidence of recurrence, metastasis and/or any new primary skin cancers. The patient’s GP is ideally placed for such review and can liaise with any treating specialist regarding particular concerns.

Opportunistic screening

Screening for NMSC should be considered during the general examination of patients presenting with another medical problem or for a routine examination. Although the majority of cancers appear on sun exposed areas where they are most clearly visible it is important to keep in mind that a significant number of NMSCs occur on the trunk and limbs hence the relevance of a total body cutaneous examination not only in those at greater risk (family history, past personal history and skin type) but in all patients. Such an examination should be a feature of the annual check-up.

Education of GPs

All graduating doctors should have had the opportunity to become familiar with skin disorders in particular malignant skin tumours. This of course is the responsibility of those in medical schools who are responsible for the curriculum. A good undergraduate foundation complemented in particular by clinical exposure to patients in dermatology clinics or general practice seems to be imperative.

Vertical integration of this education with substantial postgraduate education and training in the general practice training program is important to achieve a well informed practitioner. Diagnostic and management skills should be assessable during this program.

Education of the patient

One of the important health promotion and educative tasks of the GP is education of their patients about prevention and management of skin cancer. Video programs, wall charts and patient education material in the waiting room is one method, as well as opportunistic education of patients through preventive advice. Clear explanation of the tumour, management plan and reason for any referral is simple good sensible medical care.

Summary

The patient’s general practitioner is the first to be confronted with a suspicious skin lesion. Hence the importance of providing optimal training from undergraduate through to graduate for GPs with a heavy emphasis on recognition of skin cancer. Correct diagnosis and appropriate management are linked.
For most clinically obvious or suspicious NMSCs the best management is excision with a 3mm margin followed by primary closure and then histological confirmation.

It is imperative that GPs be aware of their limitations and refer where appropriate. Such guidelines for referral to a specialist with training in skin surgery and other treatment modalities are presented in this paper.

**Key points:**
- GPs play a pivotal role in the early detection and management of NMSC.
- Uncomplicated small tumours are best removed by an elliptical excision with a 3mm margin.
- The first opportunity for treatment is the best strategy to achieve cure.
- Caution should be used in the management of NMSCs on the face, including the ears.
- It is important to be aware of guidelines for referral.
- Specialists should be given the opportunity to deal with a problematic lesion in its entirety.
- Opportunistic screening with a total body cutaneous examination on all patients should be practised.
- Young patients with sun damaged skin need regular review.
Table 1  Tumour features that indicate a high risk (after R Rosen)  

**Basal cell carcinoma**
- Recurrent
- Incompletely excised
- Larger than 2cm
- Poorly defined
- Morphoeic, infiltrating
- Micronodular, perineural
- Special sites:
  - Nose
  - Eyelids
  - Temple
  - Pre and post auriculae
  - Lower legs

**Squamous cell carcinoma**
- Recurrent
- Incompletely excised
- Larger than 2cm
- Deeper than 6 mm
- Primary mucosal SCC
- Poorly differentiated SCC
- Perineural
Suspect NMSC

Skills, location, facilities, experience

Not NMSC

See suspicious skin lesion

Uncomplicated

Excise

Not excise

Biopsy

Not biopsy

Monitor

Not monitor

Refer

Complicated*

Treat

Not treat

Monitor

Refer

Inadequate/ complications

Adequate

Early detection

No NMSC

Delayed treatment

No NMSC

Missed NMSC

No NMSC

8. Prevention

*Tumour >1cm, 'recurrent tumours', incompletely excised tumours, recommended treatment beyond skills of GP, anticipated difficulty with technique or anatomy, suggestion of metastases, follow-up uncertain or unavailable.

Figure 1 Pathway for management of NMSC—GP focus (courtesy of B Raasch)
ECONOMICS OF THE PUBLIC HEALTH PROBLEM DUE TO NON-MELANOMA SKIN CANCER IN AUSTRALIA

NMSC is by far the most common malignant neoplasm in Australia, with an incidence of 282,825 cases in 1996\(^{349}\) (Table 4.2). However, many of these cases are amenable to cure and hence not life-threatening. For this reason, the public health problems of NMSC measured in terms of disability-adjusted life-years (DALYs) is not as large as the incidence of the disease would suggest. The estimates of the public health problem in Australia in terms of DALY’s constructed by Mathers, Vos and Stevenson\(^{349}\) (Table 5.3) show the rank of the DALY disease load for males is 71 out of 75 leading causes of the public health problems, while for females it fails to rank in the top 75 leading causes.

Mathers et al\(^{1}\) (Table 2) estimate that the total direct cost of NMSC in Australia in 1993–94 was $232.3 million. This is considerably larger than an earlier estimate of the annual direct cost of NMSC of $50 million although the authors of the 1985 study stress that they believe it is a minimum estimate\(^{350}\). These estimates suggest a small to moderate disease liability arising from NMSC when viewed in the context of the total health system costs for disease and injury in 1993–94 of $31,397 million\(^{351}\) (Table 6.20).

Mathers et al\(^{1}\) (Table 11) estimate that the treatment cost per case of NMSC in Australia is $750. This figure is within the range of treatment costs for basal cell carcinoma in an Australian study by Shiell\(^{250}\). Four treatment endpoints are identified in that study (treatment costs in parentheses): simple excision with primary closure ($216); excision with simple skin graft for small lesions performed in the surgeon’s own rooms ($520); excision with extensive skin graft for large lesions ($773); and treatment with interferon alfa-2b ($1,388).

PREVENTION

Carter, Marks and Hill\(^{2}\) report the potential cost-effectiveness of a national primary prevention program for skin cancer in Australia, based on the SunSmart campaign in Victoria. Their analysis is based on a 20-year national health promotion campaign with time lags of 5 and 15 years before any reductions in deaths from melanoma and NMSC respectively occur. While the cost per life-year saved is quite low when only the costs of the campaign to government are included in the cost of the program ($1,360 per life-year with no cost offsets for treatment cost savings), it is considerably higher when private costs for sunscreen and hats are included ($25,134 per life-year). Avoidance of deaths from melanoma constitutes the major source of health benefits in this analysis.

Smith and McGhan\(^{352}\) also discuss the costs of treatment of potentially malignant skin lesions and the benefits of prevention in the US context. However, no formal economic evaluation is undertaken.
Non-melanoma skin cancers are so common in this country that all of us, health carers included, are at least potential consumers. It may be useful, therefore, to give some consideration to the perspective of consumers. By doing this practitioners may be stimulated to think about all the queries and concerns they, and their lay friends, would have as consumers, and become better prepared to deal with such matters if they should arise, or if they ought to be raised, during a consultation or when speaking to an audience on the subject of skin cancers. This, in turn, should help towards achieving the objectives of these Guidelines, namely, to promote optimal care of these conditions and to meet the requirements of consumers.

The concerns of consumers, or potential consumers, are about the causes of skin cancer; the likelihood of getting it and how to prevent it; how to detect it and what to do about it; the effects, side-effects, effectiveness and cost of treatment; and after-effects, subsequent care and prognosis. In fact all the same topics as practitioners and care-providers are concerned about—and which these Guidelines deal with—but slanted away from the ultra-technical, specialised and statistical aspects of the subject towards what is personal, practical and understandable by the laity, and not only for curious or affected subjects themselves, but also for their children and other family members and friends in the community.

Consumers would like their doctors and other service providers to be aware of all their possible concerns and to be prepared to address them, respectfully and sincerely, even if they seem trivial or even silly or inappropriate. Furthermore, bearing in mind that they might not think of all the relevant questions at the time of the consultation, or be a bit too nervous or scared to ask them, or hesitant and embarrassed because they speak English poorly, they would like the practitioners, in their best ‘client oriented’ mode, to raise ones which might be relevant.

What follows could be regarded as a checklist, far from complete, of concerns which people have. They are loosely categorised and abbreviated: key words, thought-provokers, pointers towards topics of concern. Which concerns will, or should, be addressed in any consultation, and in what order, will, of course, be uniquely trimmed to each situation.
SPECIFIC TOPICS

Susceptibility

I realise there are different types of skin cancers. Tell me about them. Looking at me now, and at my inheritance and upbringing, what are the chances that I, or members of my family might develop skin cancers? Is the likelihood greater than average? Or less? For what reasons?

I have heard that being of Celtic or Anglo-Saxon origin and having fair sensitive skin as well as increasing age increases the risk of skin cancer. So, I wonder about me and my own particular type of skin, its colour and hairiness and whether my dark spots, freckles or other noticeable marks are suspect. What about hair colour? Is it true that people with red hair and freckles are especially at risk?

What about such factors as the geographical areas in which I have lived, my exposure to sunlight, and the times I got sun burnt, especially way back when I was a youngster? Am I put at risk by my present occupation, or by my smoking, or by my habit of not wearing long sleeves and a hat? What about old scars or grazes? Also, I have plastered many things on my skin over the years, and still do—such as oils, soap, lotions, perfumes, sprays and so on; could any of these do harm?

Prevention

Looking towards the future. I have gained some information, but tell me more about the known causes of skin cancer and what I can do to prevent or at least reduce the chance of getting it?

Tell me about sunshine, ultra-violet rays and any other important factors. How can I best protect myself from the sun? What are the bad seasons of the year, times of day, and geographical places? Is it true that even cloudy days, reflected sun and wind can be harmful? Am I safe in deep shade or under shadecloth, or behind glass in a car or in the house? Do my jobs or my recreational activities put me unduly at risk?

What benefit might be expected from various fabrics, colours and styles in clothing, swimwear and hats? What chemicals should, or should not, be put on skin—thinking of skin care products, cosmetics, soaps, tanning lotions, hair sprays and dyes?

What about food and drugs by mouth, and the cleaning agents and pesticides and paints and other things I use in the home and outside? What protects and what harms?
Diagnostic pointers

What should I be on the lookout for? How do I detect and assess anything which might be cancerous and warrant consultation? I’m thinking of my children as well as me.

Are there any sensations, such as itch, pain or numbness that I should take notice of and report? What might I see or feel? What are the important areas I should inspect and how often and what about the scalp, ears, nose, genitals and other tricky sites?

As for spots already on my skin, what should I watch out for? Changes in colour, size, shape, thickness, bleeding, discharge? Is there a place for photography which I have read about? I realise, of course, but need reminding, that it is unwise to feel or prod too much or pick at any spots or sores and wise to seek expert advice.

Consulting

When should I, or my family member, make an appointment to be seen? By whom? How often?

Are routine checkups at certain ages advisable? If I suspect a problem should I visit my general practitioner or go straight to a dermatologist? Would pharmacists, nurses or naturopaths be able to help me? What about general surgeons and plastic surgeons: how, when and for what purposes should they come into the picture?

How much are these consultations and investigations likely to cost me, taking Medicare into account and any private insurance and possible eligibility for Veterans Affairs assistance and Workers Compensation?

If I find a suspicious skin spot or lump how urgently should it be attended to?

Treatment

What can be done, should be done, or should not be done, by me or by whom?

If treatment is to be considered I would like to know the options and all about them.

Can I be convinced that my general practitioner will advise me well, treat my cancers well (if we both opt for him or her to carry out treatment at this stage), and refer me, if and when appropriate, to someone else who can competently deal with it?

Is there any way in which I can treat myself, or at least assist in the treatment? Or things I should not do, perhaps exercise, shaving or using certain soaps or creams?
Please tell me all about freezing, biopsy, excision and any other medical or surgical procedures that may be on the cards and what they may mean to me by way of preparation (including whether I should stop my medications), hospitalisation, complications, time off work, after-care and cost. Please take into account my frailties and my living arrangements.

**Progress/Watchfulness**

What next? What might I expect and what should I do in the future?

What do I need to watch and do immediately post-treatment? Might I need visits to be arranged from a community nurse or a home helper?

Can I then expect this to be the end of the problem, or is it likely to come back in the same place? Will there be any disfigurement? Is it likely to spread elsewhere? How would I know if this happens and what might the outcome of that be? Are there any tests that can be done to check for cure?

Do these cancers ever regress without treatment? Do they become more, or less, frequent with advancing age? What measures should I take to prevent or deter the problem developing in the future and in other areas?

When, how often and for how long should I attend my general practitioner or specialist for review?

**In General**

Consumers want expertise, information, answers to questions, advice, shared decision-making, actions to be taken on the basis of informed consent and coordination and continuity of care. They place high value on being treated with respect and patience, non-discrimination, privacy, confidentiality and, where needed, emotional support, involvement of family and friends and access to interpreters.

Attention to these concerns and desires of consumers can contribute to them becoming cooperative, compliant, satisfied people, rather than reluctant, critical, disgruntled patients—a happy outcome for the practitioner as well as the consumer. However, consumers may need to be made aware that health-care providers, too, have their own personal and professional concerns and desires, that knowledge of skin cancers and resources for the provision of services are limited and that probabilities and not certainties are generally the rule in matters of health, especially in regard to predictions, the actual outcome of treatment and prognosis.

It may also be helpful to consumers, and potential consumers, in this area of health to refer them to one or other of the agencies linked to The Cancer Council Australia, or even to provide them with appropriate pamphlets and other material available from those sources.
APPENDIX 1

INTERNATIONAL UNION AGAINST CANCER (UICC) TNM—CLASSIFICATION OF MALIGNANT TUMOURS

Fifth Edition
1997 ed.
Carcinoma of the Skin
(excluding eyelid, vulva, and penis)
(ICD-O C44.0, 2-9, C63.2)

Rules for classification

The classification applies only to carcinomas. There should be histological confirmation of the disease and division of cases by histological type.

The following are the procedures for assessing T, N, and M categories:

- **T categories**
  - **Physical examination**

- **N categories**
  - **Physical examination and imaging**

- **M categories**
  - **Physical examination and imaging**

Regional Lymph Nodes

The regional lymph nodes are those appropriate to the site of the primary tumour.

**TNM Clinical Classification**

- **T** Primary tumour
- **TX** Primary tumour cannot be assessed
- **T0** No evidence of primary tumour
- **Tis** Carcinoma in situ
- **T1** Tumour 2cm or less in greatest dimension
- **T2** Tumour more than 2cm but not more than 5cm in greatest dimension
- **T3** Tumour more than 5cm in greatest dimension
- **T4** Tumour invades deep extradermal structures, ie cartilage, skeletal muscle or bone

**Notes:** In the case of multiple simultaneous tumours, the tumour with the highest T category is classified and the number of separate tumours is indicated in parentheses, e.g. T2(5).
**N—Regional lymph nodes**

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

**M—Distant metastasis**

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

**pTNM Pathological classification**

The pT, pN, and pM categories correspond to the T, N, and M categories.

**pN0** Histological examination of a regional lymphadenectomy specimen will ordinarily include 6 or more lymph nodes.

**G Histopathological Grading**

- GX: Grade of differentiation cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- G4: Undifferentiated

**Stage grouping**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
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**Summary**

**Skin Carcinoma**

- T1: <2cm
- T2: >2 to 5cm
- T3: >5cm
- T4: Deep extradermal structures (cartilage, skeletal muscle, bone)
- N1: Regional
APPENDIX 2

SOURCES FOR CANCER INFORMATION

For information relating to cancer, contact the Cancer Information Service (Cancer Helpline) 13 11 20

The Cancer Council ACT
159 Maribyrnong Avenue
KALEEN ACT 2617
Tel: (02) 6262 2222
Fax: (02) 6262 2223
Email: actcancer@actcancer.org
Website: www.cancer.org.au/act
Executive Officer: Joan Bartlett

The Cancer Council New South Wales
153 Dowling Street
WOOLLOOMOOLOO NSW 2011
Tel: (02) 9334 1900
Fax: (02) 9358 1452
Email: feedback@nswcc.org.au
Website: www.cancercouncil.com.au
CEO: Dr Andrew Penman

The Cancer Council Northern Territory
Shop 3 Casi House
Vanderlin Drive
CASUARINA, NT 0810
Tel: (08) 8927 4888
Fax: (08) 8927 4990
Email: uvstop@cancernt.org.au
Website: www.cancercouncilnt.citysearch.com.au
Executive Director: Brian McCarthy

The Cancer Council Tasmania
140 Bathurst Street
HOBART TAS 7000
Tel: (03) 6233 2030
Fax: (03) 6233 2123
Email: infotas@cancer.org.au
Website: www.cancer.org.au/ tas Executive
Director: Lawson Ride

The Cancer Council Victoria
1 Rathdowne Street
CARLTON VIC 3053
Tel: (03) 9635 5000
Fax: (03) 9635 5270
Email: enquiries@cancervic.org.au
Website: www.cancervic.org.au
Director: Professor David Hill

The Cancer Council South Australia
202 Greenhill Road
EASTWOOD SA 5063
Tel: (08) 8291 4111
Fax: (08) 8291 4122
Email: cancersa@cancersa.org.au
Website: www.cancersa.org.au
Executive Director: Assoc. Prof. Kerry Kirke AM

Cancer Foundation of WA
46 Ventnor Avenue
West Perth WA 6005
Tel: (08) 9212 4333
Fax: (08) 9212 4334
Email: info@cancerwa.asn.au
Website: www.cancerwa.asn.au
Acting CEO: Phillip Schmaal

Queensland Cancer Fund
553 Gregory Terrace
FORTITUDE VALLEY QLD 4006
Tel: (07) 3258 2200
Fax: (07) 3257 1306
Email: qldcf@qldcancer.com.au
Website: www.qldcancer.com.au
Exec. Director: Graeme Brien AM
APPENDIX 3

MEMBERS OF THE ACN MANAGEMENT OF NON-MELANOMA SKIN CANCER WORKING PARTY

Professor Robin Marks AM  Dermatology (Chairman)
Dr Jill Ainslie  Radiotherapy
Dr Philip Bekhor  Dermatology
Professor Adele Green  Epidemiology
Mr Michael Henderson  Surgical Oncology
Dr Dudley Hill  Dermatology
A/Professor John Kelly  Dermatology
A/Professor Steven Kossard  Dermatopathology
Mr Allan MacLeod  Plastic Surgery
Professor John Murtagh AM  General Practice
A/Professor Ian Olver  Medical Oncology
Dr Robert Sinclair  Dermatology
Ms Margaret Staples  Epidemiology
Professor David Weedon AO  Pathology
Emeritus Professor Malcolm Whyte AO  Consumer
Emeritus Professor Tom Reeve AC CBE  Executive Officer, Australian Cancer Network (Convenor)

Special thanks to:

James R.G. Butler, PhD
Senior Fellow (Health Economics) & Deputy Director
National Centre for Epidemiology and Population Health (NCEPH)
The Australian National University, Canberra

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and

Mrs Christine Vuletich, who has shown infinite patience in responding to all requests in preparation, alteration and finalising the manuscript.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCC</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>C</td>
<td>Curettage</td>
</tr>
<tr>
<td>DFTC</td>
<td>Double freeze-thaw cycle</td>
</tr>
<tr>
<td>HPU</td>
<td>Human papilloma virus</td>
</tr>
<tr>
<td>HTT</td>
<td>Halo thaw time</td>
</tr>
<tr>
<td>IEC</td>
<td>Intra-epidermal squamous cell carcinoma (Bowen’s disease)</td>
</tr>
<tr>
<td>KA</td>
<td>Keratoacanthoma</td>
</tr>
<tr>
<td>M</td>
<td>Margin treated beyond clinically visible tumour</td>
</tr>
<tr>
<td>mm</td>
<td>Millimetres</td>
</tr>
<tr>
<td>NMSC</td>
<td>Non-melanoma skin cancer</td>
</tr>
<tr>
<td>OST</td>
<td>Open spray technique with liquid nitrogen</td>
</tr>
<tr>
<td>PDT</td>
<td>Photodynamic therapy</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>S</td>
<td>Shave excision</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>SFTC</td>
<td>Single freeze-thaw cycle</td>
</tr>
<tr>
<td>SK</td>
<td>Solar keratosis</td>
</tr>
<tr>
<td>SPF</td>
<td>Sun protection factor</td>
</tr>
<tr>
<td>TCN</td>
<td>Themocouple needle</td>
</tr>
<tr>
<td>TTT</td>
<td>Total thaw time</td>
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<tr>
<td>UVA</td>
<td>Ultraviolet radiation (320–400 nm)</td>
</tr>
<tr>
<td>UVB</td>
<td>Ultraviolet radiation (290–320 nm)</td>
</tr>
<tr>
<td>XP</td>
<td>Xeroferma pigmentosum</td>
</tr>
</tbody>
</table>
GLOSSARY

Basosquamous or Meta typical
Terms used for basaloid tumour which show evidence of squamatisation. These tumours should be viewed as equivalent to squamous cell carcinoma.

Bowen’s disease
A well-demarcated erythematous scaling plaque that histologically demonstrates full thickness intraepidermal keratinocyte dysplasia.

Bowenoid solar keratosis—see chapter 4
A pathological description of a solar keratosis which shows full thickness keratinocyte dysplasia, rather than just keratinocyte dysplasia at the basal layer of the epidermis.

Brachytherapy
A method of giving high dose radiotherapy to a localised area by placing the source of the radiation close to the lesion being treated.

Chemoprophylaxis
The use of pharmacological products to prevent disease, in this case, skin cancer.

Cryotherapy
The use of very low temperature to treat skin cancer and related dysplasias. Liquid nitrogen is used most commonly, having a temperature of −190° C.

Curettage
The use of a sharp curette to remove skin cancer or related dysplasias from the skin under local anaesthetic.

Deep radiotherapy
Radiotherapy that penetrates deeply through the skin and affects tissues below it.

Desmoplasia
Tumours which induce sclerotic and extensive fibrous stroma that may be mistaken for a scar. The tumours often present as infiltrative cords of cells that may have ill defined boundaries and are prone to recurrence. Both squamous cell carcinoma and basal cell carcinoma may produce this pattern.

Diathermy treatment
The use of a direct current electrical apparatus to ablate skin cancer and related dysplasias.
**Electrodesiccation**

Use of diathermy treatment to ablate skin cancer and related dysplasias.

**Fine needle aspiration cytology**

The use of a fine needle to biopsy a tumour or lymph node to obtain cells for cytological confirmation of diagnosis.

**Imiquimod**

An immune response modifier that induces cytokines related to cell mediated immune responses including interferon-α (IFN-α), IFN-γ, and interleukin.

**Interferon**

A naturally occurring cytokine having antiviral, antimicrobial, anti-tumour and immuno-modulatory actions.

**Laser therapy**

The use of laser technology to ablate skin cancer and related dysplasias.

**Megavoltage**

The use of very high voltage electric current to create high energy radiotherapy that can be deeply penetrating through tissues.

**Melanocyte stimulating hormone**

Melanocyte stimulating hormone is derived from the pituitary gland and keratinocytes amongst other cells and is capable of stimulating melanin production by melanocytes to increase pigmentation.

**Micronodular**

A histopathological term describing a growth pattern of basal cell carcinoma in the dermis.

**Mohs’ surgery**

Surgery where microscopic confirmation of complete tumour clearance is achieved at the time of the operation with a pathologist using a specialised sectioning technique to examine microscopically the tissue removed to confirm complete tumour clearance. Once this is confirmed, the wound is closed.

**Morphoeic**

Morphoeic means scar like and is a term used to describe one of the clinical variants of BCC.

**p53 gene**

A tumour suppressor gene. Abnormalities of this gene leading to dysfunctional P53 protein have been demonstrated in cancers of many different types, including non-melanoma skin cancer.
Perineural
Perineural applies to the invasion of a tumour along, but not in, a nerve.

Photodynamic therapy
The use of light, plus a photo-absorbent porphyrin related chemical, to destroy skin cancer and related dysplasias.

Poorly differentiated
Tumours in which products of differentiation such as keratin, desmosomal attachments or glandular differentiation are poorly expressed. Immunohistochemistry techniques for keratin subsets are often used to identify such tumours.

Radiotherapy
Radiotherapy (RT) is the use of ionising radiation to treat cancer and allied disease.

Solar keratosis
A solar keratosis is clinically an erythematous scaling lesion in the heavily light exposed areas of skin that histologically has keratinocyte dysplasia at the basal layer of the epidermis.

SPF 14
SPF stands for Sun Protection Factor, a laboratory derived rating system of sunscreens active in the UVB range. The SPF number is the multiple by which a dose of ultraviolet radiation which causes minimal erythema in human skin needs to be increased to cause minimal erythema in the same person when the tested sunscreen has been applied to their skin prior to exposure. For example, when an SPF 14 sunscreen is correctly applied in the laboratory, the dose of radiation necessary to cause minimal erythema through the sunscreen is 14 times the dose required to produce minimal erythema in the skin without any screen applied.

Superficial radiotherapy
Superficial applies to radiotherapy that is absorbed and has its major effect within the skin and not the tissues deeper to it.

UV
UV (ultraviolet) is the solar spectrum reaching the Earth’s surface in the wavelength range of 290–400nm.

UVA
Ultraviolet radiation in the wavelengths 320–400nm.

UVB
Ultraviolet radiation in the wavelengths 290–320nm.
REFERENCES


244. Green H. Cutaneous Tumours: condyloma, basal cell carcinoma, squamous cell carcinoma and melanoma. Galveston: University of Texas, 1 A.D.


301. Anonymous. Sunscreen products—evaluation and classification. 1998; Standards Australia. AS2604:


320. Merimsky O, Neudorfer M, Spitzer E, Chaitchik S. Salvage cisplatin and adriamycin for advanced or recurrent basal or squamous cell carcinoma of the face. Anticancer Drugs 1992; 3:481–484.


334. delCharco JO, Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Mendenhall NP. Carcinoma of the skin metastatic to the parotid area lymph nodes. Head Neck 1998; 20:369–373.


349. Mathers C, Vos T, Stevenson C. The burden of disease and injury in Australia. 1999; Canberra: Australian Institute of Health & Welfare. Cat No. PHE17:

