



Clinical Practice Guide

Basal cell carcinoma, squamous cell carcinoma
(and related lesions) – a guide to clinical
management in Australia

November 2008

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Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgment and the patient's preference in each individual case.

The guide is designed to provide information to assist in decision-making. It is based on the best evidence available at time of compilation. The guide is not meant to be prescriptive.

Conflict of interest

The development of this clinical practice guide has been undertaken by a working party of the Australian Cancer Network, with support from the Department of Health and Ageing.

Some members have received sponsorship to attend scientific meetings, been supported in the conducting of clinical trials, or have been involved in an advisory capacity by pharmaceutical and biochemical companies. Others have special interests indicated in specific chapters.

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Corrigendum

Page 47

Key Point

Reference 4.4.3 should read 4.4.2

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FOREWORD

A multidisciplinary Working Party of volunteers has undertaken revision of NHMRC/ACN's *Clinical practice guidelines on non-melanoma skin cancer: guidelines for the treatment and management in Australia* (1992).

The Working Party has chosen a new title, *Basal cell carcinoma, squamous cell carcinoma (and related lesions)—a guide to clinical management in Australia*, to better represent the material covered.

The document aims to benefit general practitioners because they provide the majority of care for those suffering from non-melanoma skin cancer. It is hoped the document will prove useful for undergraduates, graduates preparing for examinations and a wide range of professional health personnel.

The revision is a consensus document developed by the Working Party under the Chairmanship of Professor Robin Marks AM. It provides information that can assist practitioners in making independent clinical decisions for individual patients. There is a significant degree of repetition throughout the document. This is purposeful, as many readers and users will refer to specific chapters only and so each one needs to be as complete as possible in itself.

The document was collated and formatted in the ACN Secretariat by Mrs Christine Vuletich, Executive Assistant and Ms Alice Winter-Irving, Office Assistant, whose unfailing courtesy and good humour have been matched by their flexibility and accuracy.

It is hoped that general practitioners will find the guide a valuable addition to their practice armamentarium.

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EXECUTIVE SUMMARY

Non-melanoma skin cancer continues to be a major public health problem in Australia, involving significant health costs and disfigurement from both the disease and its management.

Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) together involve the greatest cost of cancer in Australia, an estimated total of \$A345 million per year.

Basal cell carcinoma, squamous cell carcinoma (and related lesions)—a guide to clinical management in Australia observes consensus-based key points to assist in sound decision-making. The key points are not rules, nor are they prescriptive. They are aids to best-quality clinical practice.

The document aims to benefit general practitioners because they provide the majority of care for those suffering from non-melanoma skin cancer. It is hoped the document will also prove useful for undergraduates, graduates preparing for examinations and for a wide range of professional health personnel.

Solar radiation is the major environmental cause of non-melanoma skin cancer.

Education in sun-smart behaviour is a valuable component of the initial consultation.

Protection against solar radiation is recommended. Where possible, shade areas should be provided or sought when outdoors. Protective clothing should be worn because it provides the best 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 remains the prime treatment for non-melanoma skin cancers. Confirmation of complete removal of lesions is an essential part of management.

Cryotherapy, curettage and diathermy treatments have specific advantages and disadvantages which should be considered and discussed before implementation.

Other forms of therapy such as photodynamic therapy, 5% Imiquimod, 3% Diclofenac gel and 5% Fluorouracil cream have limited but definite applications in selected circumstances.

Radiotherapy should be reserved for the small minority of primary BCCs and SCCs that present peculiar problems for conventional surgery and for cases of persistent, recurrent or advanced BCCs and SCCs where surgery can be complemented by radiotherapy to improve control rates.

Transplantation and immunosuppression result in a higher risk of developing NMSC than the normal population and incidence is related to immunosuppressive dose.

Skin cancers in this group of patients are best managed by multidisciplinary specialist care.

A balance is required between avoiding an increased risk of skin cancer by excessive sun exposure and achieving enough sun exposure to maintain adequate vitamin D levels.

On completion of treatment specialists are expected to return patients to their referring general practitioner.

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.¹

Reference

1. *Clinical practice guidelines for non-melanoma skin cancer: guidelines for treatment and management in Australia, 2002.*

SUMMARY OF KEY POINTS

Key points	Refs
1. INTRODUCTION	
2. EPIDEMIOLOGY	
<ul style="list-style-type: none"> Solar radiation is the major cause of basal cell carcinoma and squamous cell carcinoma. Primary prevention of the majority of basal cell carcinoma and squamous cell carcinoma is possible through avoidance of excessive sun exposure starting from childhood. National education programs have achieved some improvements in sun protection behaviour and stabilisation of incidence of basal cell carcinoma and squamous cell carcinoma in young adults, but continued investment in sun-protection campaigns is required to maintain skin cancer prevention. 	7 32 2, 21, 22
Basal cell carcinoma <ul style="list-style-type: none"> The occurrence of BCC at earlier ages than SCC, its relatively common occurrence on the trunk as well as the face, and its probable origin in epidermal stem cells, suggests that BCC requires a lower threshold of total solar radiation before malignant transformation than is required for SCC. Retrospective case series show that nodular BCC occurs predominantly on the head and neck, while superficial BCC appears to have a predilection for the trunk. It is unclear whether differential underlying aetiology can explain these findings. 	9, 29, 30, 33-35 33, 34
Squamous cell carcinoma and related keratinocyte tumours <ul style="list-style-type: none"> The overall incidence rate of SCC in Australia was estimated to be 387 per 100,000 in people aged 14 years and over in 2002, more than double the estimated incidence in 1985, though most of this increase occurred in residents of southern Australian states. There is a significant latitude gradient such that the highest SCC incidence rates (around two times the national average) are seen in those living at low latitude locations such as Queensland. Infection with certain human papilloma virus types in the beta-genus may be associated with increased SCC risk (acting together with sun exposure). 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 3, 24, 25 78, 79 58, 59, 60

Key points	Refs
3. CLINICAL FEATURES	
<ul style="list-style-type: none"> The importance of asking about change and symptomatology in the course of assessing a lesion cannot be underestimated. Clinical history is important in diagnosis. 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. 	see chapter 4 1, chapter 2
Basal cell carcinoma <ul style="list-style-type: none"> Dermoscopy may be useful in enhancing diagnosis of basal cell carcinoma. In the implementation of dermoscopy it is imperative that appropriate training and skill maintenance be observed. Biopsy should precede treatment for a single localised erythematous scaling lesion. 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. Stretching the skin makes all of these variants of BCC more apparent. 	5,6,7 1,2
Squamous cell carcinoma <ul style="list-style-type: none"> 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. The majority of squamous cell carcinomas are thought to arise from solar keratosis. The clinical diagnosis of early squamous cell carcinoma can be difficult. Induration, thickening or tenderness in the erythematous base of a scaling lesion is very suggestive of early SCC. Immunosuppression for organ transplantation strongly predisposes to squamous cell carcinoma. 	1 11 section 3.4, chapter 10

Key points	Refs
<ul style="list-style-type: none"> 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. 	12
Keratoacanthoma <ul style="list-style-type: none"> Current management of keratoacanthoma is early excision. Current management is early excision rather than waiting for spontaneous resolution relying on correct clinical diagnosis. 	
4. PATHOLOGY (INCLUDING BIOPSY)	
Basal cell carcinoma <ul style="list-style-type: none"> The clinical location, the architectural pattern and excision margins are important determinants of the risk of recurrence. 	2–5
Solar keratosis, Bowenoid solar keratosis, squamous cell carcinoma-in-situ (Bowen's disease) and invasive squamous cell carcinoma <ul style="list-style-type: none"> These conditions may be regarded as a neoplastic continuum. However in many cases, solar keratosis regresses spontaneously and uncommonly, it evolves into invasive squamous cell carcinoma. Bowen's disease, even after many years, may also evolve into invasive squamous cell carcinoma. 	6, 7
Keratoacanthoma <ul style="list-style-type: none"> A history of rapid growth and a characteristic architecture help establish the diagnosis, but occasionally, a clear distinction from a squamous cell carcinoma is not possible. 	15
Good practice point The biopsy <ul style="list-style-type: none"> The clinician has an important role in contributing to a helpful report. At times, discussion between the clinician and the pathologist can often help further in diagnostic and management issues. 	17
5. PROGNOSIS	
Basal cell carcinoma <ul style="list-style-type: none"> Higher recurrence rates have been observed for all treatment modalities in the facial region—particularly in and around the nose, eyes and ears—compared with non-facial sites. 	1–12

Key points	Refs
<ul style="list-style-type: none"> 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 BCCs can have a very long history in recurrence pattern (10 to more than 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. 	
Squamous cell carcinoma	
<ul style="list-style-type: none"> The estimated prevalence of perineural spread from cutaneous SCC is in the order of 2.5%. 	62,63
<ul style="list-style-type: none"> Clinically diagnosed perineural invasion carries a poor prognosis. 	61, 62
<ul style="list-style-type: none"> Incompletely excised SCC has a recurrence rate of 50% or more and should be prophylactically re-excised or treated with radiotherapy. 	73
<ul style="list-style-type: none"> 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. 	68
<ul style="list-style-type: none"> SCCs of the scalp, ear and vermillion have a higher recurrence and subsequent nodal metastasis rate than SCCs elsewhere, in the order of 10 to 20% overall. 	71-73
6. SURGICAL TREATMENT	
Basal cell carcinoma	
<ul style="list-style-type: none"> The majority of basal cell carcinomas that are clinically favourable, that is, small, nodular or superficial types not located in the central face, can be satisfactorily excised under local anaesthetic with direct primary closure in an ambulatory care setting. 	1-3
<ul style="list-style-type: none"> In high-risk tumours or in high-risk skin areas, microscopic margins of less than 1mm require a discussion with the pathologist about further pathology sections to assess adequacy of the margin. High-risk skin cancers that are not re-excised to achieve histological complete excision should be followed long term. Recurrence following inadequate margin clearance may take years to become apparent. 	see 4.4.3
<ul style="list-style-type: none"> The majority of clinically favourable BCCs can be excised with a margin of 2-3mm with a very high chance of achieving complete excision and long-term control. Adequate microscopic margin is 0.5mm. 	1
<ul style="list-style-type: none"> If an aggressive form of BCC is suspected either clinically or on biopsy then a margin of 3-4mm is appropriate. 	11

Key points	Refs
<p>Important practice points</p> <p>The following lesions should fall within the scope of a general practitioner with experience and confidence in surgical procedures:</p> <ul style="list-style-type: none"> • well-defined primary lesions of the trunk and extremities up to 15mm, between 15 and 20 mm is a gray zone and they need referral depending on circumstances • well-defined primary lesions of the face, forehead or scalp up to 10mm. <p>Consider specialist referral for the following lesions:</p> <ul style="list-style-type: none"> • recurrent lesions • incompletely excised lesions • high-risk histological types, for example micronodular, infiltrating or morphoeic BCCs. • lesions involving the central face, ears, genitalia, digits, hand or leg. • poorly defined lesions. • lesions fixed to underlying structures • lesions involving or lying adjacent to significant nerves, for example facial nerve or accessory nerve. • trunk and extremities lesions greater than 20mm. • cheek, forehead and scalp lesions greater than 10mm. <p>Key points:</p> <p>Incompletely resected BCC</p> <ul style="list-style-type: none"> • Incompletely resected BCCs are defined as histologically incompletely or inadequately excised BCC. • 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. • 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. 	<p>13</p> <p>14</p> <p>15,16</p>
<p>Squamous cell carcinoma</p>	
<ul style="list-style-type: none"> • In SCC a histological margin of 1mm or less mandates consideration of further therapy. • The majority of SCCs are small and clinically favourable and can be excised expeditiously under local anaesthetic with direct primary closure as an outpatient. 	<p>28</p>

Key points	Refs
<ul style="list-style-type: none"> • The majority of clinically favourable SCCs of 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 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. • Consideration of specialist therapy should be considered for patients with an SCC showing perineural spread. 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 SCCs that behave aggressively. These patients should be referred for specialist management. 	<p>24,26-29</p> <p>36, 52 See chapter 5</p> <p>23,39</p> <p>chapter 10</p>
<p>Good practice points</p> <p>Low-risk patient checklist:</p> <ul style="list-style-type: none"> • Limited size and not located on the scalp, peri-ocular region, ears, lips, nose or genitalia • Not a recurrence or near a previously treated area • Not rapidly growing • Low grade • Less than 4mm in thickness • Not extending beyond the subcutaneous tissues • Favourable histology, i.e. well differentiated 	
<p>Metastatic disease</p> <ul style="list-style-type: none"> • Spread of SCC to regional lymph nodes is uncommon but is often associated with metastasis to distant sites and a poor outcome. 	43-46
<ul style="list-style-type: none"> • Clinically suspected lymph node metastases should be confirmed by fine needle aspiration cytology (under radiological or ultrasound guidance if required) if possible. Open surgical biopsy should be avoided. • The treatment of metastatic disease to lymph nodes is primarily surgical. 	<p>52</p> <p>48</p>

Key points	Refs
<p>Good practice point</p> <ul style="list-style-type: none"> Although cutaneous SCC is the obvious primary for 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 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. 	
<p>7. RADIOTHERAPY</p>	
<ul style="list-style-type: none"> Radiotherapy should be reserved for the small minority of primary BCCs and SCCs 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. Ideally, all BCCs and SCCs should be confirmed histologically by biopsy prior to radiotherapy treatment. If advice for patients regarding re-excision of an incompletely excised lesion is contentious, then the recommendation for radiotherapy is equally difficult. Immediate re-excision or radiotherapy for incompletely excised primary BCC reduces the recurrences rate to less than 9%. Radiotherapy for T1 and T2 primary BCC has comparable outcomes (marginally inferior) to specialist surgery. A radiation oncology opinion should be considered for T4 primary, persistent and recurrent BCC. Radiotherapy gives comparable control rates to 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. 	<p>1-12</p> <p>32</p> <p>1,3, 6-9, 12</p>
<ul style="list-style-type: none"> All salvage therapy for recurrent BCC has lower control rates than for primary BCC. Adjuvant radiotherapy following salvage surgery for recurrent BCC should be considered in patients with a poorer prognosis, namely: <ul style="list-style-type: none"> T4 tumours multifocal recurrence multiple recurrences poor prognosis histology subtypes inadequate normal tissue margins perineural invasion node-positive BCCs 	<p>38</p>

Key points	Refs
<p>Squamous cell carcinoma and related keratinocyte tumours</p> <ul style="list-style-type: none"> • Radiotherapy is an efficacious alternative treatment for primary untreated SCC in a minority of patients when surgery is disadvantageous: <ul style="list-style-type: none"> - when surgery is not feasible, for example patient unfit for surgery, patient refuses surgery, anticoagulation issues. - when surgery will cause cosmetic or functional morbidity unacceptable to the patient, for example nasectomy, loss of function of lips or eyelids, large tissue deficits, multiple lesions. • Radiotherapy is indicated as adjuvant treatment to surgery for incompletely excised (persistent) SCC. • Post-operative radiotherapy should be considered for tumours with high-risk disease following a complete excision. High-risk disease following complete excision include: <ul style="list-style-type: none"> - T4 tumours - rapidly growing tumour - recurrent disease - close margins (<5mm) - perineural invasion (major and minor nerves) - lymphovascular invasion - in-transit metastases - regional nodal involvement • Radiotherapy is important in the management of metastatic SCC. 	
<p>Squamous cell carcinoma—lymph node metastasis</p> <ul style="list-style-type: none"> • Spread of SCC to regional lymph nodes is uncommon but is often associated with metastasis to distant sites and a poorer outcome. • 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 with or without post-operative radiotherapy. 	<p>50,51</p> <p>52</p> <p>50-54</p>
<p>Solar keratosis and squamous cell carcinoma in situ</p> <ul style="list-style-type: none"> • Radiotherapy is rarely indicated for solar keratoses or SCC in situ, except for the uncommon long-standing large superficial SCC in situ disease refractory to dermatological care and unsuitable for excision. 	
<p>8. CRYOTHERAPY, CURETTAGE AND DIATHERMY/ELECTRODESSICATION</p>	

Key points	Refs
<ul style="list-style-type: none"> Cryotherapy is a simple and effective form of therapy for solar keratoses. If treatment protocols are optimal, cryotherapy achieves high cure rates for selected low-risk BCCs and SCCs in situ on the trunk and limbs. Acceptable cure rates, comparable to other standard treatment modalities, may be achieved for high-risk tumours in specialist clinics. 	1, 2, 5-12, 14-19, 21-29, 38
<ul style="list-style-type: none"> Cryotherapy achieves high cure rates for primary BCC in sites other than face and ears if tumour selection and treatment protocols are optimal. Cryotherapy achieves lower cure rates for larger BCCs. Cryotherapy achieves lower cure rates for BCCs at high-risk facial sites and is not recommended. Cryotherapy is contraindicated for ill defined or morphoeic (infiltrative) BCCs at any site. 	3-8, 16,-29, 36 8, 23, 25, 26, 29, 36 4-6, 8, 23, 26, 28, 29 2, 7, 17, 18, 22, 26-28
Key point <ul style="list-style-type: none"> Long-term follow-up is essential after treatment of BCC with cryotherapy, as late recurrences may occur. Level III 	3
Squamous cell carcinoma and related lesions <ul style="list-style-type: none"> Cryotherapy achieves consistently high cure rates for solar keratosis. Cryotherapy of Bowen's disease achieves high cure rates with optimal treatment protocols, but delayed healing may occur on lower limbs. 	1, 36, 75, 76 7, 9
<ul style="list-style-type: none"> Cryotherapy is not often used for keratoacanthomas, but may represent reasonable treatment for smaller lesions. If the diagnosis is in doubt then treatment should be as for SCC. (see 3.3.1—<i>Squamous cell carcinoma in chapter 3 – Clinical features</i>) Cryotherapy produces cure rates equivalent to other standard treatment modalities for low risk SCCs on the trunk and limbs. 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. Cryotherapy is contraindicated for recurrent SCC. Recurrence rates of less than 6% may be achievable if curettage and diathermy are used for appropriately selected BCC. 	2, 7, 15 7, 15, 16, 20 6, 7, 14, 16, 20 8 77, 78
Curettage and diathermy (C & D) <ul style="list-style-type: none"> Is not used on high-risk areas (nasal, paranasal, lips, eyelids, chin, jaw line and ears) or at least not for lesions larger than 5mm at these sites. 	77

Key points	Refs
<ul style="list-style-type: none"> Is not used on lesions larger than 10mm on middle-risk sites (face, forehead, temples and scalp). Is used for all sizes of lesion on low risk areas (neck, trunk and limbs). Is not used on clinically morphoeic lesions. Is not used for recurrent lesions. Is carried out by operators with appropriate supervised training in the procedures. Multiple SCCs may be treated in certain circumstances with curettage and electrodesiccation/diathermy and in specialised centres. 	<p>77</p> <p>77</p> <p>80</p> <p>77, 79</p> <p>77</p> <p>81</p>
<p>9. OTHER TREATMENTS (TOPICAL AGENTS—IMIQUMOD CREAM, DICLOFENAC GEL, FLUOROURACIL CREAM AND PHOTODYNAMIC THERAPY)</p>	
<ul style="list-style-type: none"> Imiquimod 5% cream, which is a topical cytokine and Interferon inducer, offers an alternative treatment option where surgery or other therapies are inappropriate or contraindicated. Approval has been given by the Therapeutic Goods Administration (TGA) in Australia for the treatment of primary superficial basal cell carcinomas and solar keratoses. 	<p>16</p>
<p>10. NON MELANOMA SKIN CANCER IN ORGAN TRANSPLANTATION AND OTHER CONDITIONS ASSOCIATED WITH PROLONGED IMMUNOSUPPRESSION</p>	
<ul style="list-style-type: none"> The management of skin cancers in organ transplant recipients is best undertaken by multidisciplinary specialist care. The risk of developing NMSC in organ transplant recipients is significantly higher than in the normal population and is increased with duration and dosage of immunosuppressive therapy. There is evidence that acitretin can be helpful in the reduction of NMSC in organ transplant recipients who have developed NMSC. Reduction of immunosuppression is considered a reasonable adjuvant management strategy for transplant recipients with numerous or life-threatening skin cancers. 	<p>6,7,30-34,36</p> <p>6,39-42</p> <p>49</p>
<p>11. PREVENTION (INCLUDING CHEMOPREVENTION)</p>	
<p>Key points</p> <ul style="list-style-type: none"> Use broad-spectrum sunscreens with an SPF of 15 or greater as an adjunct to sun avoidance and other sun protective measures. Level II 	<p>9, 13</p>
<ul style="list-style-type: none"> Use clothing, where possible, as the primary means of photo-protection. Level III 	<p>3</p>

Key points	Refs
<ul style="list-style-type: none"> • Stay in the shade wherever 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 any type of artificial UV radiation tanning device. 	
12. METASTASIS FROM NON-MELANOMA CANCER	
<ul style="list-style-type: none"> • Chemotherapy achieves responses in metastatic basal cell carcinoma and can be used to control symptoms. 	1-11
<ul style="list-style-type: none"> • Chemotherapy can be associated with high response rates in metastatic squamous cell carcinoma of the skin. • Appropriate radiotherapy can provide local symptom control. 	5-9 10-14
13. FOLLOW-UP	
<ul style="list-style-type: none"> • For patients with histological clearance, and low-risk tumours, for example basal cell carcinomas and well-differentiated squamous cell carcinomas, no specific follow-up scheme is recommended. • For patients following non-surgical treatments, where there is no histological evidence of clearance, follow-up should be initially at three months and then 6–12 monthly for up to three years. Examination includes a full skin check for new lesions as well as inspection of the site of the original lesion. • For moderately to poorly differentiated squamous cell carcinoma or SCC of the lip or ear, follow-up should be initially at three months and then every six months and always include examination of the draining lymph node basin. • All patients with a previous skin cancer are advised to undergo annual skin examination for life, as part of routine health checks by their health care provider, to look for the development of new lesions. • Following treatment of a primary tumour, all patients need to receive counselling about their risk for further primary tumours, local persistence of their previous primary tumour and for metastatic disease where appropriate. 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. In addition advice should be given regarding standard sun protection strategies. 	
Important practice point	
<ul style="list-style-type: none"> • It is appropriate for specialists to return patients to their referring GP for ongoing care when their treatment is complete. The time of return will depend on lesion and treatment and depend on agreement between the specialist and the referring GP. 	

Key points	Refs
14. WHO TREATS AND PROBLEMS TO REFER	
<ul style="list-style-type: none"> • GPs need to be aware of the limitations of their skills and should be prepared to refer to an appropriate specialist, especially where more complicated repairs than side to side closure are being contemplated. • Although complete excision of a skin cancer with a narrow margin may not affect outcome, it is better to avoid two procedures for the one lesion. • The first opportunity for treatment is the best opportunity to achieve cure. <p>Good practice points</p> <ul style="list-style-type: none"> • 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 3-4mm 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, plus or minus biopsy depending on circumstances. • Opportunistic screening with a total body cutaneous examination on all patients should be practised. • Young patients with sun-damaged skin need regular review. 	<p>1,3,5</p> <p>11</p>
15. ECONOMICS OF BASAL CELL AND SQUAMOUS CELL CARCINOMA AND RELATED CONDITIONS	
<ul style="list-style-type: none"> • Basal cell and squamous cell carcinomas are collectively the most expensive cancer type within the Australian health system, yet the true economic burden is likely to be substantially higher than previously estimated treatment costs. • Persons affected by multiple skin cancers are likely to incur substantial out-of-pocket expenses. • International economic evaluations on newer treatment modalities for SCC and BCC are emerging but have unclear relevance for Australian skin cancer medicine. • At this time, it is unclear whether newer treatment modalities are cost-effective within Australia until findings from well-designed studies emerge. • Primary prevention remains an important and cost-effective strategy for control of skin cancer in Australia. 	<p>1,2</p> <p>15</p> <p>20</p> <p>27</p> <p>28-30</p>
16. QUESTIONS AND CONCERNS THAT MAY ARISE DURING CONSULTATION	

1 INTRODUCTION

This guide is a revision of the NHMRC *Clinical practice guidelines on non-melanoma skin cancer: guidelines for treatment and management in Australia* endorsed by the NHMRC in October 2002 and first published in 2003. They were revised by a working party of the Australian Cancer Network comprising representatives of general practitioners, dermatologists, surgeons (including plastic surgeons), pathologists, epidemiologists, health economists and consumers (patients), who have reached consensus at each step.

An obvious change in this revision is the new title: *Basal cell carcinoma and squamous cell carcinoma (and related lesions)—a guide to clinical management in Australia*. Australian Medicare data show clearly that general practitioners treat the majority of these tumours in Australia. Hence this handbook is directed primarily at general practitioners, with many key points making it user-friendly in that setting.

Although it is fair to say that there have not been dramatic breakthroughs in either diagnosis or management since the original version was published, there have been changes in both areas sufficient to justify the update and sufficiently important to highlight. Hence there are a number of changes in all the areas covered in the previous version and the addition of a separate section on skin cancer in chronically immune-suppressed patients. These patients are assuming an important contribution to the burden of skin cancers treated in Australia and will do so increasingly for the foreseeable future.

The first change that is obvious is the change in title to define more precisely what we are referring to when we use the term *non-melanoma skin cancer*. It is clear that there is a substantial difference, both clinically and in management, between a basal cell carcinoma (BCC) and a squamous cell carcinoma (SCC) and its related epidermal keratinocyte dysplasias. Hence the new title. However, when this group of tumours is being considered as a whole in any of the sections, the term *non-melanoma skin cancer (NMSC)* is still used.

Chapter 2—Epidemiology highlights once again the huge burden of NMSC requiring treatment in Australians. The health economics estimate of the cost of providing treatment for people with these tumours, lesions that are potentially preventable in a substantial proportion of cases, is revealing. They highlight the need to continue the current public health campaigns on prevention of these sunlight-related tumours in our population. But in recent years there have been concerns about a potential for inducing vitamin D deficiency with overzealous sun protection in susceptible people. Hence *section 11.3 Vitamin D*, an addition to *chapter 11—Prevention*, covers this possibility and what seems a reasonable compromise between preventing NMSC and preventing Vitamin D deficiency in those at risk.

Chapter 3—Clinical features highlights once again the need for the basic skills of taking a good history and a thorough clinical examination in the diagnosis of any disease, and NMSC in particular. The vast numbers of these tumours in Australians mandate paying particular attention in medical training, particularly in general practitioner training, on developing these diagnostic skills. There is an evident shortage of dermatologists and plastic surgeons to undertake management of skin cancer in Australia, hence it is appropriate that general practitioners be trained to treat the majority of NMSC. Nevertheless, if a tumour recurs following apparently adequate primary treatment, it may be necessary to seek specialist help in subsequent management.

The recent increase in Australia of the number of practising overseas-trained medical graduates from countries where NMSC is not common suggests a need to highlight NMSC in their training and in the examination administered by the Australian Medical Council for those who wish to practise here. An irony of the regulations that specify where recently-arrived overseas medical graduates can practise in Australia is the requirement that they practise for a substantial time in rural areas, where the frequency of NMSC is likely to be highest.

Chapter 4—Pathology covers in a more precise way the dilemma that has been occurring with the confusing pathological terminology used for labelling the intra-epidermal keratinocytes dysplasias (atypias). Although John Bowen described in the early twentieth century ‘pre-cancerous’ clinical lesions in non-light-exposed areas that showed pathologically full thickness intra-epidermal dysplasia, the term *Bowen’s disease* has subsequently been used by pathologists for any full thickness intra-epidermal dysplasia, particularly those in light-exposed areas, which are not the lesions described by Bowen. In recent years pathologists have described three different forms of these dysplasias depending on the layers of the epidermal keratinocytes involved. The full-thickness dysplasia is now frequently labelled *SCC in situ*. Previously the terms Bowen’s disease and *SCC in situ* have been used as synonymous terms.

As there has been no accompanying education program for general practitioners to explain that these lesions are not invasive cancers, there has been substantial concern expressed by patients and general practitioners when this term has been used in a pathological report and, on occasion, unnecessary institution of treatment of the nature required for invasive SCC.

Under the existing Medicare fee schedule, treatment of *SCC in situ* attracts a fee for the treatment of an SCC, whereas treatment of a solar keratosis does not. The only difference is in the level of dysplasia in the epidermis. There are no data to show that there is any difference in their clinical behaviour, particularly in risk of transformation to an invasive SCC. In this edition we have preferred the term *SCC in situ* rather than *Bowen’s disease* in the hope that eventually practitioners will come to realise that in the majority of cases *SCC in situ* is not a special lesion requiring substantially more treatment than a solar keratosis.

Chapter 4 also highlights the need to establish a good working relationship between the treating practitioner and the anatomical pathologist. A narrow margin of excision in the histopathological examination, particularly with an SCC, is an example of when the clinician should speak to the pathologist to ensure that they are confident of complete excision before accepting that no further treatment is necessary. If there is any doubt the clinician should consult with the anatomical pathologist and request advice on how to further evaluate the specimen and slides.

Chapter 6—Surgical treatment makes the point very strongly that the vast majority of BCCs and SCCs in Australia can be excised with a simple ellipse and primary closure at the time of the operation without the need for anything more sophisticated, in particular a flap repair or a skin graft. There has been recent concern about the frequency of use of these procedures, and particularly as to whether they are always necessary. Flap repair of various types and skin grafting are specialised techniques that require considerable training, not only on how to do them but also in selecting which repair might be appropriate for a particular patient and tumour. Thus the indications in *chapter 14—Who treats and when to refer* on when to seek specialist advice, whether from a dermatologist, a plastic surgeon or a radiation oncologist, are pertinent to this problem.

It is also clear in chapter 6 that for the primary procedure, surgery remains the gold standard with the highest rate of cure. Hence all other treatments, including those covered on non-surgical treatments such as cryotherapy and curettage (chapter 8) and photodynamic therapy and topical imiquimod therapy (chapter 9), should be compared with surgery when discussing with the patient the likelihood of cure in selection of a particular treatment. These non-surgical treatments are being used with increasing frequency. They require adequate knowledge and training to ensure correct selection and use, especially treatments such as photodynamic therapy and topical imiquimod.

A specialist surgical technique, Mohs micrographically controlled surgery, is presented briefly in section 6.8 as it is a procedure used with increasing frequency in Australia, although by a relatively small number of trained operators (approximately 30 Mohs proceduralists at the time of this update). It is obviously not freely available, nor necessary, for the vast majority of NMSC treated in Australia. But the margin control it offers for particularly difficult tumours is a useful addition to the therapeutic regimes available at the moment. Hence there is a need to give it some coverage in this guide.

A disappointing feature of this review is the lack of well designed prospective randomised studies trying to answer critical questions about surgery in the treatment of these tumours, including careful studies comparing surgery with and without Mohs technique of margin control. There have been virtually no new major publications since this Guide was last published looking at areas such as excision margins for both BCC and SCC, critical areas that require further work. It is hoped that the lack of definitive answers to such questions will prompt those working in this area to undertake such studies in the future.

Chapter 13—Follow-up also highlights the lack of evidence to suggest any particular routine examination interval. But it highlights the data showing that a person who has had one NMSC is at risk of another in subsequent years. Thus patients should be encouraged to examine their own skin regularly and to seek early attention from a general practitioner if they notice something new or changing that is different to surrounding spots. The frequency of these tumours also mandates that a complete skin examination be performed as part of the general examination and health check that general practitioners perform on their adult patients each year.

In summary, this revised version aims to update knowledge and skill in the treatment of these extremely common cancers and related abnormalities in Australia. Directed primarily at general practitioners, it seeks to ensure that the very large number of people who develop NMSC each year will receive treatment that is adequate, timely and provided at a fair and reasonable cost to both the patient and the community.

Professor Robin Marks AM
Skin and Cancer Foundation Victoria
Chair, ACN Working Party to revise Management of Non-melanoma Skin Cancer Guidelines (2002)

2 EPIDEMIOLOGY

2.1 Overview

Non melanoma skin cancer, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) continue to represent a large public health problem among the Australian population. The costs of screening and treating these usually non-fatal cancers cause a disproportionately high burden on the Australian health system, while cosmetic ill-effects such as facial disfigurement negatively affect quality of life. The incidence of treated BCC and SCC is more than five times the incidence of all other cancers combined,¹ making these cancers by far the most expensive cancers to treat. Skin cancers are avoidable however and these costs could potentially be substantially reduced through primary prevention.²

Because cancer registries do not routinely report skin cancers apart from melanoma, exact incidence rates are not known. The best available Australia-wide data have come from four national surveys in 1985, 1990, 1995 and 2002. These surveys across random households show that the incidence rates of skin cancer in Australia are the highest in the world. In 2002, it was estimated that 256 000 people were treated for BCC and 118 000 for SCC, and age-standardised incidence rates were estimated to be 884 per 100 000 for BCC and 387 per 100 000 for SCC.³ Incidence rates showed a threefold gradient between northern and southern Australia.¹ Moreover, compared to 1985, age-standardised incidence rates of BCC and SCC (not including SCC in situ) in 2002 had increased by 35% and 133% respectively.¹ These increases were greatest for persons aged 60 years and older, however rates in younger age groups had stabilised. Below the age of 55 years, women were more likely to be affected by BCC than men, but above this age rates were higher for men. Men were more commonly affected by SCC than women after the age of 40.¹

Surgical excision remains the most common treatment modality, with over 70% of the BCC lesions recorded in the 2002 national survey surgically excised. For BCC not surgically excised, cryotherapy was more commonly used for upper and lower limb lesions than facial lesions, and 10% of BCCs were treated with curettage and diathermy. The majority of SCC lesions, regardless of body site, were treated by surgical excision.³

Patients affected by BCC and SCC are at high risk of subsequent lesions. Of a representative sample of BCC patients in a Queensland population, 47% had a second episode of BCC diagnosis within 4.5 years, with an average time interval between diagnoses of 28.5 months,⁴ while the general risk of a subsequent SCC after a first diagnosis has been estimated from published studies to be about 18% after three years.⁵ In Australia about 400 people die each year from skin cancers (other than melanoma),⁶ predominantly SCC but also including some deaths due to BCC or Kaposi's sarcoma.

Solar radiation is the major environmental cause of basal cell carcinoma and squamous cell carcinoma.⁷ Numerous epidemiological studies have consistently shown that in populations who receive low ambient sun exposure or in those whose dark skins are protective, BCC and SCC rarely develop.^{7,8} In Australia it follows 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 and have 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 sites and the site most densely affected by basal cell carcinoma and squamous cell carcinoma in any population^{3,9}—hence their major cosmetic impact. In contrast, sites that are virtually never sun-exposed, such as the buttocks, are not affected. Migrants to Australia from the UK, which has lower levels of ambient UV than Australia, have lower skin cancer incidence than that of native-born Australians.³ The age at which migrants arrive in Australia is inversely related with their risk of BCC and SCC.¹⁰ Strong positive dose–response relationships with

childhood sun exposure suggest that the UV radiation dose received early in life is an important predictor of BCC risk.¹¹

A very small proportion of skin cancers in Australia (<1%) is attributable to causative factors apart from solar UV, including arsenic,¹² ionising radiation therapy¹³, scars¹⁴ and immunosuppression.^{15,16} In addition, for a proportion of SCC, human papilloma virus (HPV)¹⁷ may act in concert with UV.^{18,19}

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. However, results of the extensive skin cancer prevention campaigns that have been in place since the 1980s are beginning to appear in the stabilisation of incidence rates of non melanoma skin cancer in Australians younger than 60 years of age in 2002 compared to 1985.¹ General improvements in sun-protective behaviour peaked in the late 1990s²⁰ but may have waned in adolescents in recent years,²¹ indicating a need for continued investment in sun protection campaigns² which can be cost-effective in reducing the large expenditure on skin cancer.²²

Key points

- Solar radiation is the major cause of basal cell carcinoma and squamous cell carcinoma.⁷
- Primary prevention of the majority of basal cell carcinoma and squamous cell carcinoma is possible through avoidance of excessive sun exposure starting from childhood.³²
- National education programs have achieved some improvements in sun protection behaviour and stabilisation of incidence of basal cell carcinoma and squamous cell carcinoma in young adults, but continued investment in sun-protection campaigns is required to maintain skin cancer prevention.^{2,21,22}

2.2 Basal cell carcinoma

2.2.1 Incidence in the general population

Basal cell carcinoma is the most common cancer affecting Australians. In the most recent national survey (2002), the incidence rate of BCC was estimated to be 1041 per 100 000 in men and 745 per 100 000 in women. There is a strong inverse association with latitude,^{1,3} with the highest rates of BCC in northern, lower-latitude areas of Australia. In Nambour, Queensland, age-adjusted annual incidence rates of BCC in men and women aged 25–75 years were estimated to be 2074 and 1579 per 100 000 respectively in 1992.²³ In the northern city of Townsville, yearly age-standardised incidence rates between 1997 and 1999 were 1445 and 943 per 100 000 for men and women respectively, with incidence rates of BCC tumours up to twice as high in men due to multiple occurrences in individuals.²⁴

In both sexes, a high proportion of BCC lesions occur on the head or neck (52%), followed by the trunk (27%), upper limbs (13%) and lower limbs (8%).³ When the body 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.²⁵ Relatively high rates are also seen on the neck, back and shoulders in men and neck, shoulders and outer arms in women²⁵ in sun-exposed Australian populations.

2.2.2 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, despite an overall lack of association between BCC and self-reported chronic sun exposure.^{23,26} Current evidence increasingly points to the hair follicle stem cell or inter-follicular stem cell as the likely cell of origin of BCC.^{27,28} Because the epithelial cells from which BCCs arise are believed to be stem cells, the threshold of total solar radiation for malignant transformation may be low. In comparison, a higher dose appears to be needed to transform the more differentiated epithelial keratinocytes of the epidermis from which SCC arise.

The ‘intermittent UV’ exposure theory proposes that the pattern of sun exposure rather than the total amount of exposure determines the risk of BCC. In particular, it is suggested that a certain dose of solar UV delivered in infrequent, intense increments will increase the risk of BCC more than the same total dose delivered continuously over the same period.^{26,29} The intermittent pattern theory does not explain all the epidemiologic evidence of BCCs UV dose dependence however,^{23,30} and the same empirical evidence could perhaps be interpreted otherwise.

UV dose-dependence may also vary among the commonest BCC subtypes as suggested by their clinical and histological differences. Patients with superficial BCC tend to be younger than those with other BCC subtypes,^{9,31,32} suggesting that superficial BCC has a lower threshold for UV carcinogenesis than the nodular subtype. Also, the increase in incidence with age is slow but steady for superficial BCC in contrast to a progressive and dramatic age-related increase in incidence of nodular BCC.⁹

In terms of the distribution of different BCC sub-types on body sites, the evidence is inconsistent. Studies from The Netherlands,³¹ France³³ and Melbourne³² showed that superficial BCC has a clear predilection to occur on the trunk (49% on the trunk versus 23% on head and neck in the Victorian study) and that nodular BCC predominantly occurred on the head and neck. However, data from Italy³⁴ and lower-latitude locations in Northern Queensland⁹ showed more equal distributions of superficial BCC between trunk and head/neck. Interpretation of these site distributions is further complicated by the fact that, for example, despite the possible predilection of superficial BCC for the trunk, nodular BCCs predominated over superficial BCCs on the trunk in the Victorian series³² and they occurred in similar proportions on the trunk in the Dutch series.³¹ In a recent cohort study, BCCs of the trunk had a relatively strong association with sunburns and truncal lentigenes but were not associated with sun sensitivity, compared with BCCs of the head and neck.³⁵ These findings were thought to suggest that superficial (truncal) BCCs result from acute, intense sun exposure sufficient to cause sunburn among people whose ability to tan makes the skin of their face less susceptible to UV carcinogenesis.

Most studies of the site distribution of BCC sub-types are based on retrospective review of hospital records, which may be biased by dependency of referral patterns on histological sub-types and body site of occurrence. Also, bias may be caused by differential management and subsequent opportunities for histological identification between lesion types. Thus further evidence from close monitoring and molecular investigations is needed to elucidate the unique biology of the different BCC subtypes.

As above, other factors associated with *increased* BCC occurrence are:

- exposure to ionising radiation therapy¹³
- exposure to arsenic³⁶—this would play a relatively small part in the overall burden of BCC in Australia
- scars¹⁴ (especially vaccination scars)
- immunosuppression, especially after organ transplantation¹⁵ and use of glucocorticoids.¹⁶

Factors associated with *decreased* BCC occurrence are:

- sunscreen use (in particular repeated BCC occurrence⁴)
- dietary factors.³⁷⁻³⁹

Dietary factors

There is early evidence that dietary factors may be associated with skin cancer risk in the population, which is supported by a large body of evidence from animal models. The mechanisms underlying such associations may relate to the role of antioxidant nutrients in the skin's defence against UV-induced genetic and cellular damage, and the effect of dietary fats on the UV-induced inflammatory response through modification of prostaglandin production.

In relation to BCC and fat intake, a low fat intake (~20% of energy from fat) compared to normal fat intake (~40% of energy from fat) was shown to reduce the incidence of skin cancers.³⁷ However, since BCC and SCC were combined in the analyses of this study, it is unclear whether these associations would equally apply to each cancer type. Furthermore, interpretation of these findings is complicated by the observation that intake of beta-carotene, vitamin C, and fibre was increased in the group of patients who adopted a low-fat diet.⁴⁰

A large American cohort study showed a small (13%) but significant increase in risk of BCC for men with a high intake of long chain n-3 fatty acids and an inverse association with intake of total and monounsaturated fat.³⁹ Other studies have not found clear evidence for an association between dietary fat and BCC risk.⁴¹ Studies of BCC risk and intake of antioxidant nutrients have shown weak and inconsistent results for retinol, beta-carotene, vitamin E, vitamin C, and selenium, while evidence regarding other carotenoids is lacking.^{38,41}

As these studies are early, it must be emphasised there is insufficient evidence at this stage to make any recommendations about dietary modification specific to the prevention of BCC.

2.2.3 Genetic epidemiology

Patched mutations and the Sonic Hedgehog pathway

Much insight into the pathogenesis of BCC has been obtained from the study of patients with Gorlin's syndrome (nevroid basal cell carcinoma syndrome), an autosomal dominant disorder characterised by the development of multiple BCCs at an early age.⁴² Affected patients carry mutations in the *patched* gene, a tumour suppressor gene: one defective copy of this gene is inherited but tumours arise after inactivation of the remaining allele.²⁸ They develop BCCs as early as two years of age, with a clear increase in tumour numbers between puberty and 35 years of age.⁴² Ninety per cent of white-skinned Gorlin's syndrome patients develop BCC but only 40% of affected black patients develop these cancers,⁴³ indicating the aetiological role of UV exposure in addition to the genetic component.

The *patched* gene product is part of the Sonic Hedgehog Shh protein receptor, which is involved in embryonic development. When Sonic Hedgehog binds to *patched* it releases *smoothed*, a trans-membrane signalling protein. Mutations of the *patched* and *smoothed* genes result in upregulation of the Hedgehog signalling pathway and activation of downstream target genes that are associated with cell growth and differentiation,⁴⁴ including the Gli family of transcription factors.⁴⁵ Evidence for the importance of Shh pathway activation in BCC carcinogenesis comes from transgenic human-skin models in which Shh-expressing human keratinocytes formed BCC-like lesions when grafted onto the skin of immune-deficient mice.⁴⁶ Also, *patched* heterozygous knockout mice develop BCC-like lesions when exposed to UV or ionising radiation.⁴⁷ Only around 0.5% of all BCC cases arise in individuals with Gorlin's syndrome but up to 90% of sporadic BCC show *patched* mutations⁴⁸ and 20% *smoothed* mutations.⁴⁹

DNA repair defects

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder which is part of a family of nucleotide excision repair (NER) diseases.⁵⁰ Study of this disorder has contributed significantly to the understanding of the role of genetic predispositions to BCC, which is common in these patients. XP manifests as an extreme photosensitivity to UV radiation as the result of a deficiency in the enzyme that permits excisional repair of UV-damaged DNA. It occurs in approximately 1 in 250 000 people in the United States and Europe and 1 in 40 000 in Japan.⁵¹

Cancer is a characteristic of XP but not of some other NER diseases such as Cockayne syndrome, despite the sun sensitivity in both disorders. It has therefore been suggested that the increased mutation rates in both XP and Cockayne syndrome patients may be necessary but not sufficient for carcinogenesis. Additional chromosome instability as seen in XP may therefore be required for cancer development in these patients.⁵⁰

Skin tumours in XP patients show high levels of ras oncogene activation, Ink4a-Arf and p53 tumour suppressor gene modifications, and aberrations of the Sonic Hedgehog pathway.⁵² UV-specific mutations of the *smoothened* gene are three times higher in XP patients as in normal sporadic BCCs, confirming the high rate of UV-induced mutations in these DNA-repair deficient persons.⁵³ Mutations in the Sonic Hedgehog gene are very rarely found in sporadic BCC but at significant levels in BCC (but not in SCC) of XP patients.⁵⁴

Detoxifying proteins

The enzyme family glutathione-S-peroxidase is part of the skin's defence mechanism against UV-induced oxidative stress. Polymorphisms in GSTM1, GSTM3, GSTT1, and GSTP1 in particular appear to be associated with increased occurrence of BCC.^{55,56}

The p53 tumour suppressor gene

Mutations in the *p53* tumour suppressor gene are detected in around half of all BCC tumours. However, people suffering from the Li-Fraumeni syndrome, characterised by germline mutations in the *p53* gene, do not show increased incidence of BCC and thus *p53* mutations are presumed to be secondary events in BCC pathogenesis.²⁸

Melanocortin-1 receptor

See section 2.5—Squamous cell carcinoma.

Key points

- The occurrence of BCC at earlier ages than SCC, its relatively common occurrence on the trunk as well as the face, and its probable origin in epidermal stem cells, suggests that BCC requires a lower threshold of total solar radiation before malignant transformation than is required for SCC.^{9,29,30,33–35}
- Retrospective case series show that nodular BCC occurs predominantly on the head and neck, while superficial BCC appears to have a predilection for the trunk. It is unclear whether differential underlying aetiology can explain these findings.^{33,34}

2.3 Squamous cell carcinoma and related keratinocyte tumours

2.3.1 Incidence in the general population

In the most recent national survey of treated skin cancer (2002) the age-standardised incidence rate of SCC (not including in situ SCC) was estimated to be 387 per 100 000 in people aged 14 years and over (499 in men and 291 in women per 100 000),³ with a significant latitude gradient: the highest rates are seen in those living at latitudes less than 29°S (as for BCC). Incidence was highest in males for all age groups. Overall SCC incidence in 2002 rose by 133% compared to 1985, but this was mostly due to increases in residents of the southern Australia (latitude higher than 37°S). Migrants to Australia have lower risks of SCC than people born in Australia.¹⁰ As for BCC, the incidence of SCC increases with increasing age.^{3,25}

Data from skin cancer studies other than the national surveys have confirmed the high incidence of SCC at tropical and subtropical latitudes in Australia. In the township of Nambour (26°S), annual age-adjusted incidence rates of SCC in men and women aged 25 to 75 years were estimated to be 1035 and 472 per 100 000 respectively in 1992.²³ Further north in Townsville (19°S), similar incidence rates of 805 per 100 000 men and 424 per 100 000 women have been reported.²⁴

The head and neck are the most common sites of occurrence for SCC in men, while the upper limbs followed by head and neck are the most common sites in females. As for BCC, few SCC (8%) arise on the trunk in both males and females.³ When the body surface area is taken into account, the highest SCC incidence in both men and women is found on the face, especially the lip region, ears, nose, cheek and eyelid, with neck, dorsa of hands and forearms next most affected.²⁵

Solar keratoses are one of the most frequent conditions treated by dermatologists in Australia and constitute a significant burden to the health system. However, some solar keratoses have also been found to develop into an SCC. Over time, solar keratoses can clear spontaneously, persist, or progress into invasive skin cancer (usually SCC). Definitive evidence on progression rates from long-term, closely monitored studies is lacking. The general rate of progression has been estimated at 0.025–1.6% per year.⁵⁷ In a medium-term (5-year) study based in Maryborough, Victoria,⁵⁸ 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).⁵⁹ Not one of more than 1000 SKs in 200 Queensland residents, who were followed up every 2–6 months for 18 months, underwent malignant transformation.⁶⁰ Higher rates of progression to invasive cancers have been reported for Bowen's disease and SCC in situ, with an estimated 3–5% of patients developing invasive carcinomas from such lesions.⁶¹ Such estimates may be biased however due to differential follow-up patterns.⁶²

The probability that an individual SCC has arisen from solar keratosis is high. However, 60% of incidental SCCs in the Victorian study arose from a lesion diagnosed previously as a solar keratosis⁵⁸ while another Australian study reported that 72% of SCCs were contiguous with solar keratoses.⁶³

There are no published population-based incidence rates of people who develop solar keratoses 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.⁶⁴ In a population-based prevalence study in Nambour, Queensland (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,⁶⁵ the most common sites of occurrence. Prevalence of SKs is strongly age dependent,⁵⁹ reflecting incidence and recurrence rates that exceed rates of regression as people age.⁶⁰ A spontaneous remission rate of 26% has been reported based on follow-up after 12 months,⁶⁴ though with more intense lesion surveillance, substantially higher rates of remission are seen.⁶⁰

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 non-melanoma skin cancers in Australia. Keratoacanthoma, an epidermal tumour characterised by rapid growth and spontaneous resolution, typically occurs between the ages of 50 and 69 years, although it has been reported in all age groups.⁶⁶ The incidence of keratoacanthoma was estimated as 36 per 100 000 person-years in a national survey of treated skin cancers in 1990.⁶⁷ Five percent of all lesions reported in the 2002 national survey were identified as keratoacanthoma.³ The incidence rate of seborrhoeic keratoses is not known but the prevalence was 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.⁶⁸ A retrospective analysis of Australian skin cancer patients showed that seborrhoeic keratoses are rarely associated with other cutaneous malignancies (associated skin cancers were found in 9% of patients). BCC was the most common skin cancer associated with seborrhoeic keratoses (32% of all seborrhoeic keratoses with associated skin cancers).⁶⁹

2.3.2 Environmental risk factors

The strongest environmental risk factor for SCCs and related squamous keratinocyte tumours is chronic sun exposure: their anatomic site distribution reflects sites of maximal sun exposure. The UV radiation spectral regions of sunlight—the wavelengths 280–320nm (UVB) and 320–400nm (UVA)—are those specifically implicated in carcinogenesis. In studies of SCC in Queensland and Western Australia there were strong associations with clinical signs of chronic skin damage, especially SKs^{23,70} and in Western Australia total site-specific sun exposure based on recall was strongly related to risk of SCC.⁷⁰ In the Nambour (Queensland) study population, high levels of occupational exposure and sunburns were strongly and significantly associated with SK prevalence, especially in those people with multiple SKs.⁷¹ While SKs share many of the same determinants as SCC, they are a more sensitive indicator of intense sunlight exposure.⁷²

Dietary factors

There is early evidence that a diet high in antioxidant-rich foods may help prevent SCC in those at high risk. An Australian prospective study of food intake and SCC tumour risk showed a 55% reduced SCC risk for high intake of green leafy vegetables in adults with a history of skin cancer.⁷³ Results from this observational study were fully adjusted for and thus independent of possible confounding factors such as age, sex, past UV-exposure, and skin type. The protective association of green-leafy vegetables in this study was most likely due to intake of lutein and zeaxanthin, two carotenoids commonly found in green-leafy vegetables.³⁸ The same Australian study showed a doubling of SCC tumour risk associated with high intake of unmodified dairy products (e.g. full cream dairy milk and cheese) in adults with a history of skin cancer.⁷³ Further study of this population extended this finding to show that a “meat and fat” dietary pattern, characterized by other components such as processed meat, discretionary fat, and white bread, had an additional association over and above the association with the high-fat dairy food group alone in the development of subsequent SCC tumours.⁷⁴

Because intervention studies that tested specific antioxidants in the form of a dietary supplement have generally not shown an effect on skin cancer risk,⁷⁵ it may be the unique compositions of whole foods that are able to modify skin cancer risk rather than individual nutrients, but more evidence for this is needed.

As these studies are early, it must be emphasized that there is insufficient evidence at this stage to make any recommendation about dietary modification specific to the prevention of SCC.

2.3.3 Human papilloma virus

It has been suggested that infection with certain cutaneous HPV types is associated with increased cutaneous SCC risk. Originally identified in studies of patients with epidermodysplasia verruciformis,⁷⁶ these PV types have been classified mostly in the beta genus of papilloma viruses.⁷⁷ Infection with this virus is very common not only in immunosuppressed recipients of organ transplants but among the general population as well.⁷⁸ A number of studies that have measured beta-HPV antibodies, as well as those that have assessed the presence of beta-HPV DNA, have shown beta-HPVs to be associated with solar keratoses and SCC.^{17,79-81} It is likely that beta-HPV, if etiologically involved, acts to potentiate the effect of UV radiation possibly via viral inhibition of DNA repair and apoptosis following UV radiation.^{18,19}

2.3.4 Genetic epidemiology

SCC occurs commonly in xeroderma pigmentosum patients (*see section 2.2—Basal cell carcinoma*). In addition, the rare Ferguson-Smith syndrome may predispose to the development of lesions that are indistinguishable from SCC, although they tend to resolve spontaneously. Recent gene mapping has excluded *patched* as a causative gene but has shown loss of heterozygosity, suggesting that the gene for this syndrome is likely a tumour-suppressor gene.⁸²

Mutations of the *p53* tumour-suppressor gene are found in the majority of SCCs.⁸³ These mutations are often ‘UV-signature mutations’ which indicates that they are the result of damage caused by exposure to UV radiation or sunlight. Mutations in the *p53* gene can lead to uncontrolled cell proliferation and loss of apoptosis, thus promoting cancerous growth. Immunohistochemically detectable clusters of epidermal cells with accumulated nuclear *p53* protein (‘*p53* patches’) are found in normal skin before tumours arise. These patches are thought to be an early step in the development of actinic keratoses and subsequent SCC, though as above, the progression rate is probably very small.⁸⁴

Variants of the melanocortin-1 receptor (*MC1R*) gene are associated with phenotypic features such as red hair, light skin colour and tanning ability of the skin. A number of *MC1R* variants are also independently associated with risk of BCC and SCC,^{85,86} with carriers of certain variants carrying an up to threefold increased risk of SCC compared to other individuals with the same skin type.⁸⁷

Other factors associated with *increased* SCC risk are:

- immune suppression⁸⁸
- tobacco use (in particular SCC on the lip⁸⁹)
- exposure to arsenic (in association with arsenical keratoses)³⁶
- chronic ulcers, sinus tracts and scars.⁹⁰

Factors associated with *decreased* SCC risk are:

- sunscreen use^{91,92}
- nutritional factors.^{73,74}
- use of non-steroidal anti-inflammatory drugs (NSAIDs)⁹³

Key points

- The overall incidence rate of SCC in Australia was estimated to be 387 per 100 000 in people aged 14 years and over in 2002, more than double the estimated incidence in 1985, though most of this increase occurred in residents of southern Australian states.³
- There is a significant latitude gradient such that the highest SCC incidence rates (around two times the national average) are seen in those living at low latitude locations such as Queensland.^{3,24,25}
- Infection with certain human papilloma virus types in the beta-genus may be associated with increased SCC risk (acting together with sun exposure).^{78,79}
- 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.^{58,59,60}

2.3.5 Tobacco and skin cancer

Squamous cell carcinoma has been shown to be associated with smoking in several studies.^{94,95} In a cohort study of 107, 900 predominately “white young women smokers had a 50% greater chance of developing cutaneous SCC than non-smokers (RR 1.5; 95% CI 1.1 – 2.1)”.⁹⁶ In a hospital based case-control study tobacco smoking was observed as an independent risk factor for SCC (RR 2.3, 95% CI 1.5 – 3.6), current smokers were 3.3 times more likely (95% CI 1.9 – 5.5) to develop SCC while the risk for former smokers was 1.9 relative risk (95% CI 1.2 – 3.0).⁹⁷

On the other hand, the risk factor for development of BCC remains controversial.⁹⁸ Discouraging smoking is an effective preventive intervention in health promotion and prevention of adverse cutaneous effects of tobacco.^{99,100}

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3 CLINICAL FEATURES

3.1 Introduction

The high prevalence rates of non-melanoma skin cancer (NMSC) in Australia make it imperative that all clinicians are familiar with its various presentations. Early detection of these lesions is important in minimising the 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 opportunistic screening and early detection of NMSC.

In addition to the clinical features that are evident at any one 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. Biopsy techniques such as punch, shave, incisional and excisional 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—Epidemiology*) 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.¹

Key points

- Clinical history is important in diagnosis.
- Biopsy techniques such as punch, shave and incisional biopsy are appropriate. (*see chapter 4*)
- Examination for skin cancer should be considered during physical examination for all patients over the age of 40 and particularly for the elderly.¹ (*see chapter 2*)

3.2 Basal cell carcinoma

Numerous histological types of basal cell carcinoma (BCC) have been described but most are uncommon and do not have distinctive clinical presentations. Some may be multiple and difficult to diagnose. There are three common growth patterns of BCC (superficial multifocal, nodular and morphoeic) that have a distinctive clinical presentation.² 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.^{3,4}

Dermoscopy

Dermoscopy (surface microscopy, epiluminescence microscopy, dermatoscopy) is a technique that is becoming established as a significant aid for the diagnosis of pigmented lesions, particularly melanoma. More recently it has been shown to have a possible benefit in the diagnosis of basal cell carcinoma and other non-pigmented lesions, such as Bowen's disease. Dermoscopy may also be useful in distinguishing between melanoma and pigmented basal cell carcinoma.⁵

The dermatoscope is a hand-held magnifying device which requires formal training and continuous practice with the technology if the operator is to become proficient with its use in diagnosis.^{6,7}

Key point

- Dermoscopy may be useful in enhancing diagnosis of basal cell carcinoma. In the implementation of dermoscopy it is imperative that appropriate training and skill maintenance be observed.⁵⁻⁷

3.2.1 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%⁸ to 65%.⁹ 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 on occasion.

3.2.2 Superficial

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

Clinical features

Superficial BCC usually presents as a reasonably well-defined, erythematous, scaling or slightly shiny macular lesion. The degree of erythema present may vary 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 the most common symptom. Though these lesions are readily eroded by minor trauma, a history of ulceration or bleeding is uncommon.

Causation

Apart from sunlight, the most common cause, 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 5–10cm 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 should be distinguished from:

- solar keratosis
- Bowenoid keratosis
- Squamous cell carcinoma in situ (Bowen's disease)
- amelanotic melanoma.

As the management of superficial BCC may be different to these other tumours, a biopsy to obtain definitive pathology should be undertaken prior to definitive treatment.

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.

Key point

- Biopsy should precede treatment for a single localised erythematous scaling lesion.

3.2.3 Nodular

Nodular BCCs are more often found on the head and neck in people who are somewhat older on average than those with superficial BCC.^{2,10}

Clinical features

Nodular BCC typically presents as a shiny, translucent (pearly), telangiectatic papule or nodule. **The translucent or pearly appearance is more obvious if the clinician stretches the skin during examination.** As the lesion enlarges the dilated capillaries may be seen coursing across the surface of the lesion. These are often radially arranged. Ulceration may occur with time and 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 only in a minority of cases but unlike superficial BCC, nodular lesions may often ulcerate and bleed.

Differential diagnosis

Nodular BCCs need to be differentiated from SCC, amelanotic nodular melanoma and rarely Merkel cell carcinoma.

Clinical course

Nodular BCCs may progressively enlarge and ulcerate over a period of months to years.

3.2.4 Morphoeic

Morphoeic or sclerosing BCC has a similar body-site distribution to nodular BCC.

Morphoeic BCCs are usually of long standing and tend to be deeply invasive.

Clinical features

As the name ‘morphoeic’ suggests, these lesions have a sclerosing growth pattern with fibrosis surrounding areas of BCC. BCCs that are predominantly morphoeic have the appearance of a pale scar. Palpation usually reveals firm induration, which may extend more widely and deeply than is evident on inspection. Morphoeic changes will frequently supervene in long standing nodular BCCs and these lesions may retain some clinical features of nodular BCC. Morphoeic BCCs are frequently asymptomatic. Those with nodular elements may show all the same symptoms as nodular BCCs.

Clinical course

Morphoeic 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 morphoeic BCC is scar and biopsy is necessary to establish the diagnosis.

Key points

- Superficial basal cell carcinomas present as a bright pink, shiny, usually well-defined erythematous macular lesion.^{1,2}
- Nodular basal cell carcinomas typically present as a shiny, translucent (pearly), telangiectatic papule or nodule.
- Basal cell carcinomas that are predominantly morphoeic look like a scar.
- Stretching the skin makes all of these variants of BCC more apparent.

3.3 Squamous cell carcinoma and related keratinocyte tumours

3.3.1 Squamous cell carcinoma

The majority of squamous cell carcinomas (SCCs) are thought to arise from solar keratoses.¹ 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 (*see chapter 10—Immunosuppression*). As discussed in *chapter 4—Pathology*, it is likely that there is a histological continuum of keratinocyte dysplasia from SK to invasive SCC. The continuum includes Bowenoid keratosis and Bowen’s disease (SCC in situ). Distinguishing between each of these may be difficult for the clinician.

All of these tumours produce keratin, manifest as crusting. It is not the crusting or horn formation that represents the tumour, it is the erythematous base. Thickening, induration or tenderness on gentle lateral pressure of an erythematous base is suggestive of dermal invasion (invasive squamous carcinoma).

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 pre-existing 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.¹¹

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.

Key point

- 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.

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. Pearliness, telangiectasia and islands of pigment are 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 keratosis.¹
- The clinical diagnosis of early squamous cell carcinoma can be difficult.¹¹
- Induration, thickening or tenderness in the erythematous base of a scaling lesion is very suggestive of early SCC.
- Immunosuppression for organ transplantation strongly predisposes to squamous cell carcinoma.^{3,4} (see chapter 10)

3.3.2 Solar keratoses (including Bowenoid keratosis)

(see chapter 4—Pathology)

These lesions are usually found on the chronically sun-exposed sites of head and neck, dorsum of hands and forearms. They are generally multiple and may be very numerous or confluent. Bowenoid keratosis may have a slightly thicker erythematous base than a solar keratosis.

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. The erythema associated with hyperkeratosis is the most helpful distinguishing feature of solar keratosis. Solar keratoses are less well defined at the periphery than Bowen's disease and are also less well defined than seborrhoeic keratoses, which are not normally erythematous.

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. Many SCCs, however, evolve from solar keratoses.¹²

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.¹²
- Thickening and tenderness on lateral palpation are signs that a solar keratosis may have developed into invasive squamous cell carcinoma.

3.3.3 Squamous cell carcinoma in-situ (Bowen's disease)

Classical Bowen's disease was originally described by John Bowen^{13,14} as scaling erythematous lesions in non-light exposed areas of skin. With the increasing use by pathologists of the term *Bowen's disease* to classify any lesion with histology displaying full-thickness keratinocyte dysplasia (atypia) in the epidermis (SCC in situ), 'Bowen's disease' is now also applied to tumours with this histological characteristic in light-exposed areas.

Clinical features

Classical Bowen's disease presents as a sharply defined, erythematous, round-to-oval hyperkeratotic plaque. The degree of hyperkeratosis may vary, with some lesions producing a keratotic horn. It has a predilection for the lower limbs, particularly in females, but as explained above, lesions with this histology also occur in frequently exposed areas, such as the head and neck. Bowen's disease is generally asymptomatic. The clinical history is usually of a long-standing, slowly enlarging lesion.

Differential diagnosis

Classical Bowen's disease may be distinguishable from psoriasis by its long history, though the clinical appearances may be very similar. Superficial BCC may be distinguished from Bowen's disease by less hyperkeratosis, a shiny surface and the pearliness that becomes apparent on stretching a BCC. 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

Classical 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.

3.3.4 Keratoacanthoma

Keratoacanthoma (KA) is likely to be a 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. Occasionally it may occur in sites related to trauma, surgery or burns.

Key point

- Current management of keratoacanthoma is early excision.

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. On occasions a KA may develop soon after trauma or surgery. They may be multiple on occasions.¹⁵ Resolution generally takes 6–12 weeks, but persistence may occur, indicating likelihood of SCC.

Rare differential diagnoses include amelanotic melanoma, atypical fibroxanthoma and Merkel cell tumour.

Key point

- Current management is early excision rather than waiting for spontaneous resolution relying on correct clinical diagnosis.

Aids to diagnosis

Partial biopsy will generally be unhelpful in differentiating keratoacanthoma from SCC. Partial biopsy will almost always be reported as SCC because the pathologist requires the architecture of the entire lesion to suggest the possibility of keratoacanthoma.

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4 PATHOLOGY (INCLUDING BIOPSY)

4.1 Basal cell carcinoma

Basal cell carcinomas are a group of tumours comprising masses of basaloid cells with hyperchromatic nuclei and scanty cytoplasm, resembling cells of the basal layer of the epidermis and of follicular epithelium.

The tumours may be locally destructive, but very rarely metastasise.¹ Local recurrences are not uncommon. There is an increased risk of local recurrence for large, deep or ulcerated tumours, especially if incompletely or narrowly excised, tumours of micronodular, infiltrating, **fibrosing** (morphoeic) or superficial multifocal type,²⁻⁴ or tumours showing a spiky outline of cell groups.⁵ The risk of recurrence is greater if combinations of such features are present. Tumours on the nose and nasolabial fold, or tumours recurring after previous radiotherapy are also at greater risk of recurrence. Tumours associated with perineural spread, particularly on the head and neck, are likewise at higher risk of recurrence. The frequency of basal cell carcinoma and the frequency of recurrences are also much greater in immunosuppressed individuals, and in the rare naevoid basal cell carcinoma syndrome (*see chapter 10—Non-melanoma skin cancer in organ transplantation and other conditions associated with prolonged immunosuppression*).

Histological diagnosis is usually straightforward with most tumours being of **nodular** or **nodulocystic** type. Not uncommonly, the tumour shows a mixed pattern. Frequently this is of nodular type superficially and partly of fibrosing morphoeic type in its deep portion. **Superficial basal cell carcinoma** is a common subtype and frequently occurs on the trunk. It is characterised by small basaloid tumour masses attached to the deep aspect of the epidermis and is sometimes associated with a deeper nodular component. Peripheral nuclear palisading is a characteristic feature of most basal cell carcinomata. Occasionally, various differential diagnoses need to be considered. These include squamous cell carcinoma (with basaloid cell features), Merkel cell carcinoma (an aggressive tumour) and various skin appendage tumours (commonly benign), particularly of follicular origin. In doubtful cases, special staining by immunochemistry can be helpful.

4.2 Solar keratosis, Bowenoid solar keratosis, and squamous cell carcinoma in-situ (Bowen's disease) and invasive squamous cell carcinoma

In recent years there has been a growing appreciation that these conditions, despite their various names, appear to represent a neoplastic continuum. These conditions are all characterised by keratinocyte nuclear atypia, commonly with large, irregular, crowded and hyperchromatic nuclei-

Solar keratosis is a term used to denote lesions which have epidermal basal layer nuclear atypia with variable hyperkeratosis and parakeratosis and background dermal solar elastosis. Solar keratoses may have several intraepidermal layers of atypical keratinocytes, even approaching full thickness atypia. The term 'Bowenoid' has been applied to such keratoses.

Squamous cell carcinoma in situ (Bowen's disease) refers to a clinically distinctive erythematous patch or plaque (in sun-exposed or non sun-exposed skin) with full thickness epidermal nuclear atypia. that often extends down and replaces the follicular infundibular epithelium. Increasingly Bowen's disease particularly in non sun exposed sites has been linked with human papilloma virus.

All these variations of patterns of in situ keratinocyte atypia may uncommonly evolve into invasive squamous cell carcinoma⁶ and can be viewed as squamous cell carcinoma in situ but in practice this term is most commonly used with Bowen's disease.

There may not necessarily be a serial progression through all these stages. In fact, solar keratosis uncommonly progresses to SCC-in-situ or invasive squamous cell carcinoma.^{7,8} In many cases, solar keratosis appears to regress spontaneously.⁷ SCC-in-situ, whether or not arising de novo and commonly involving follicular structures, may develop into an invasive squamous cell carcinoma often after many years. The frequency with which this occurs is unknown. When it becomes invasive, the squamous cell carcinoma is usually not well differentiated. Most invasive squamous cell carcinomas arise in association with solar keratosis.⁹ In clinical practice, it is not always easy to distinguish between a thick (acanthotic) solar keratosis and a thin invasive squamous cell carcinoma.¹⁰ Tenderness to palpation may be a clue.

A tumour is designated as an invasive squamous cell carcinoma when squamous cell masses, showing varying degrees of differentiation, are seen lying clearly in the dermis. Commonly, adjacent changes of solar keratosis of varying severity may be seen. Especially when poorly differentiated, the squamous cell dermal masses show apparent loss of the epidermal basement membrane, loss of normal cell polarity, and cytological atypia including nuclear pleomorphism. There are often many mitoses, which may be frequently be abnormal. The tumour may extend deeply into the dermis as cell masses of varying sizes and shapes and sometimes as single atypical cells. Occasionally, perineural spread may be noted. Better differentiated tumours, often showing abundant keratin formation, may at times resemble keratoacanthomas. Poorly differentiated tumours may sometimes resemble invasive melanomas, but immunostaining can allow a ready distinction.

In general, the risk of metastasis of invasive squamous cell carcinoma is greater with greater size and depth of the tumour, a poor degree of differentiation, and an infiltrative growth pattern. Plentiful mitoses, a spindle cell pattern and single cell infiltrative patterns are also adverse risk factors. Acantholytic squamous cell carcinoma or squamous cell carcinoma arising in burns and scars are at greater risk of metastasis, as are lesions on the scalp, ear and vermillion of the lip.¹¹⁻¹⁴ Perineural or endolymphatic spread also increase the risk of metastasis.

The above considerations need to be kept in mind when assessing clinical risks and in planning treatment.

4.3 Keratoacanthoma

The precise status and nature of keratoacanthoma and its relationship to squamous cell carcinoma is uncertain. It represents a rapidly growing squamous epithelial growth within the dermis, possibly of follicular origin, which, after weeks or even many months, tends to regress spontaneously.¹⁵ Notwithstanding the tendency to regress, some regard keratoacanthoma as a variant of squamous cell carcinoma.¹⁶

Lesions may occur at sites of trauma of various types, such as following burns and previous radiotherapy, at skin-graft donor sites, and at the sites of previous skin cancer excision. They also occur in immunocompromised individuals (*see chapter 10 Non-melanoma skin cancer in organ transplantation and other conditions associated with prolonged immunosuppression*), and with the rare Muir-Torre syndrome (which may be associated with a variety of sebaceous tumours and various visceral neoplasms).

Characteristically, a keratoacanthoma has a symmetrical crateriform architecture with overhanging lip-like edges, relatively limited nuclear atypia, and a predominance of cells with abundant pale cytoplasm within the lesion. Occasionally, perineural spread may be apparent, often in facial lesions.¹⁵ Such a finding warrants close follow-up to help rule out squamous cell carcinoma. In a phase of regression, prominent scarring is characteristically noted beneath an irregular shallow epidermal depression and commonly, apoptosis (individual keratinocyte death) may be observed. Not

infrequently, overlap features occur with those of squamous cell carcinoma and a clear histological distinction may not always be possible.

These aspects need to be considered in planning clinical management, particularly as these lesions may be locally destructive and early diagnosis and treatment can help to avoid more extensive therapy.

4.4 Biopsy considerations and the biopsy report

Both the clinician and the anatomical pathologist have responsibilities in enhancing the value of the biopsy report.

For the *clinician*, complete excision of the lesion, if appropriate, is the best approach as this facilitates study of the architecture and cytological appearances of the tumour, its extent, and an assessment of adequacy of excision. If complete excision is not considered appropriate, small representative samples such as by one or more punch biopsies, shave biopsy or curettage can be useful, especially taking into account the size and depth of the lesion under consideration. With curettage, the risk of disruption of the architecture should be kept in mind. Samples from different anatomical sites should be carefully labelled and placed in separate specimen containers. Suture markers and appropriate accompanying diagrams are important guides for the pathologist, particularly in the assessment of completeness of excision, or indicating the site of any extension of the tumour to the specimen edges.

An accompanying description and duration of the lesion and of any associated symptoms should be provided. Also important are patient identifying information (full name, age and sex), site of biopsy, previous biopsies and treatment, a history of other skin tumours and relevant additional history such as the presence of scars, burns or ulceration. Diagnoses under consideration should be indicated as this information can prompt the anatomical pathologist to take special measures, such as examining extra sections or using special stains to assess these possibilities, particularly with lesions on the face.

The *pathologist* should ensure that there is optimum sampling of the specimen. Ideally, and particularly for smaller specimens, the entire tissue should be sliced with multiple sections and all embedded for sectioning. It is important to note that significant shrinkage of skin specimens, of 20% or more¹⁷, may occur with formalin fixation, leading to disparity between clinical measurements of the lesion and excision margins, and corresponding measurements made on prepared sections. Shrinkage is less with specimens from older individuals and with specimens from the head and neck. This is thought to reflect loss of elastic strength in photo-damaged skin.

The pathologist's report should contain the clinical notes, the macroscopic description and the microscopic findings. If there is uncertainty, the clinician, in consultation with the pathologist, should seek further evaluation of the slides and/or specimen.

Relevant prognostic factors (see below) and margins of excision (measured if necessary, particularly with narrowly excised lesions) are also important aspects of 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, infiltrating, morphoeic and micronodular subtypes of basal carcinoma may occasionally have undetected extensions to surgical margins. The Mohs technique using frozen sections examines excision margins more comprehensively, leading to a lower recurrence rate, but the technique is not practical for use in all skin specimens submitted for histopathology¹⁸ (see chapter 6—*Surgical treatment*).

On occasions, appended comments such as exemplified below and references can be useful components of a report.

Selected examples of appended comments:

- Solar keratosis may be regarded as the earliest stage of squamous cell carcinoma, but with a low risk of progression.
- Carcinoma in situ does not have the same prognostic significance as invasive squamous cell carcinoma, and may not have the same implications for level of treatment.
- The follicular involvement noted (in Bowen's disease) suggests that recurrence may not be prevented with some forms of superficial therapy.

Ideally, the report should cover a 'synoptic type' checklist of important issues that relate in particular to prognostic factors. These include reference to the type of tumour, degree of differentiation or subtype of the tumour, tumour thickness in the dermis, and perineural, vascular or lymphatic spread. Excision clearance margins (measured if narrow) are important observations. It is helpful to measure the thickness of deeply extending tumours in the dermis as this information may help the clinician in planning subsequent treatment. For complex specimens, an attached diagram indicating the method of sampling and the relationship of the tumour to lines of excision can be helpful to the clinician. Finally, reference to earlier biopsies may be made.

4.4.1 Communication between the clinician and the pathologist

In addition to the above matters, the clinical value of the biopsy report will often be enhanced by communication between *the clinician and the pathologist*. This may entail obtaining additional clinical information, discussing technical aspects of the biopsy, interpreting the report, and planning for future management.

4.4.2 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

Specimens from separate sites should be submitted in individual containers.

Key words with prognostic significance

Poorly differentiated refers to tumours in which the products of differentiation, such as keratin or desmo-stromal attachments, are poorly expressed. Immunohistochemistry techniques for keratin subsets are often used to identify such tumours.

'Basisquamous' and 'metatypical' carcinoma. Uncommonly, tumours may be encountered which show histological features intermediate between basal cell carcinoma and squamous cell carcinoma. These generally behave more like squamous cell carcinoma and in practice should be considered to be forms of squamous cell carcinoma. As these terms are potentially confusing, they are probably best avoided.

Desmoplasia refers to prominent fibrous or sclerotic stromal changes associated with tumours, especially basal cell carcinoma, and less commonly, squamous cell carcinoma. Clinically such tumours may be mistaken for scars and are ill-defined and prone to recurrence. As the term

desmoplasia has been used to categorise a type of melanoma, it is best to avoid this term in favour of a term such as 'fibrosing'.

Large tumour size, particularly in squamous cell carcinoma, there is an increased risk of tumour recurrence with twice the risk in tumours greater than 2cm in diameter (15.2% versus 7.4%) and three times the risk of metastasis (30.3% versus 9.1%) as compared with small squamous cell carcinomas.¹⁹

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.

Key points

Basal cell carcinoma

- The clinical location, the architectural pattern and excision margins are important determinants of the risk of recurrence.

Solar keratosis, Bowenoid solar keratosis, squamous cell carcinoma-in-situ (Bowen's disease) and invasive squamous cell carcinoma

- These conditions may be regarded as a neoplastic continuum. However in many cases, solar keratosis regresses spontaneously and uncommonly, it evolves into invasive squamous cell carcinoma. Bowen's disease, even after many years, may also evolve into invasive squamous cell carcinoma.

Keratoacanthoma

- A history of rapid growth and a characteristic architecture help establish the diagnosis, but occasionally, a clear distinction from a squamous cell carcinoma is not possible.

Good practice point

The biopsy

- The clinician has an important role in contributing to a helpful report. At times, discussion between the clinician and the pathologist can often help further in diagnostic and management issues.

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5 PROGNOSIS

5.1 Basal cell carcinoma

5.1.1 Introduction

The factors affecting the outcome of both the BCC itself plus the treatment necessary to manage it can be subdivided into:

- recurrent tumours
- multiple tumours
- size and depth of invasion (stage)
- morphoeic, infiltrating and micronodular
- morphological and histological subtype
- treatment modality
- incomplete excision
- perineural spread
- naevoid basal cell carcinoma syndrome
- Special sites
 - nose
 - eyelids
 - temple
 - pre and post auricular
 - lower legs

Recurrent tumours¹⁻¹²

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 15–30% compared with previously untreated (primary) BCC of 1–10%. However, most series also report 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.

Size and depth of invasion (stage)¹³⁻²¹

Control rates diminish with increasing size (*see TNM Staging Appendix 1*).

Overall estimated control rates of treated primary BCC by stage

Table 5.1 Overall estimated control rates of treated primary BCC by stage

T stage	Size (maximum diameter)	% Control rates at 5 years
T1	≤2cm	95
T2	>2cm but ≤5cm	88
T3	>5cm	
T4	tumour deeply invaded beyond subcutaneous tissues	50

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 >10–20cms 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 consequently may be very difficult to treat.

Site

Key point

- Higher recurrence rates have been observed for all treatment modalities in the facial region—particularly in and around the nose, eyes and ears—compared with non-facial sites.

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.¹⁹ The face and scalp subcutaneous anatomy is far more complex and critical than in non-facial sites, posing potentially graver consequences for deep invasion of BCC and greater risk of morbidity from injudicious treatment.

Morphological and histological subtype^{9,22-26}

Superficial and nodular BCC are usually clinically and histologically well circumscribed and curable with all treatment modalities. Morphoeic, micronodular and infiltrative (deeper induration) BCC are harder to macroscopically define and microscopically clear and associated with higher recurrence rates. Basosquamous (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.

Treatment modality^{2-5,7-9,12,23,27-49}

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

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

Incomplete excision^{8,10,38,50-58}

Incomplete excision is accompanied by a 30% recurrence rate. This emphasises the importance of complete excision at the primary procedure. The risk of recurrence is highest in lesions where both lateral and deep margins are involved.

Perineural spread^{38,59-63}

This feature is a rare event for BCC and even rarer than in SCC (*see below, p36*). It occurs in head and neck BCC and specialist opinion on management is advised.

Naevoid basal cell carcinoma syndrome⁶⁴⁻⁶⁶

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. (*See chapter 2—Epidemiology.*)

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 BCCs can have a very long history in recurrence pattern (10 to more than 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.

5.2 Squamous cell carcinoma

5.2.1 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 in nine broad categories. These prognostic findings are frequently multiple in single-case scenarios:

- multiple lesions
- staging T, N, M (Appendix 1)
- local metastatic spread via lymphatics or nerves not embraced by current staging systems and most often associated with recurrent or persistent tumours
- locally recurrent and/or persistent SCC and/or inadequately treated SCC
- histological grade (such as poorly differentiated SCC) and clinical expressions of growth rate
- anatomic site of primary
- SCCs arising from aetiological factors other than ordinary sun exposure in otherwise healthy people
- patient factors \equiv immunosuppression and other patient and skin-related co-morbidities

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 \equiv 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 in situ.

The T4 staging category identifies advanced (beyond subcutis) clinical invasion and has the poorest prognosis. However, lesser intermediate depths of invasion are not directly accounted for in the T 1–3 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.^{67,68} 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. All are valid crude signs of a more aggressive tumour.

Table 5.2 Application of generic TNM staging system for carcinoma to SCC of the skin

T stage	Five-year disease-free survival of treated primary SCC
T1	95–99%
T2	85–60%
T3	60–75%
T4	<40%

(See chapter 7—Radiotherapy, section 7.5—Primary cutaneous squamous cell carcinoma.)

*N stage—nodal status*⁶⁹⁻⁷¹

The presence of nodal metastasis confers an overall five-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 are based on the surgical pathology findings, and pre-operative attempts at predicting this on pre-operative clinical and radiological (CT) assessment.

Table 5.3 Presence of nodal metastasis on five-year survival

No of nodes involved	Five-year survival
1	49%
2	30%
≥3	13%
Extracapsular extension	
Absent	47%
Present	23%

M stage

Once haematogenous metastases have occurred, the patient is no longer curable. Lung is the most common site of metastases.

Perineural spread

Key point

- The estimated prevalence of perineural spread from cutaneous SCC is in the order of 2.5%.^{62,63}

The vast majority of cases involve the Trigeminal (IV) and Facial (VII) cranial nerves, with primary sites on the face, lips, ears or perimeter zone of the face.^{61,62}

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

- 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 there have not been any controlled pathology studies.

The presence of incidental perineural invasion, however, appears to confer a poorer prognosis⁶² and on current data may require a more aggressive management approach (eg wider excision, Mohs surgery, post-operative RT or at the least, an opinion from an appropriate specialist).⁶³

- 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.

Key point

- Clinically diagnosed perineural invasion carries a poor prognosis.^{61,62}

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 clinical treatment that initially seemed adequate (eg complete excision) or clearance of the primary tumour (eg after RT).

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

- Incompletely excised SCC has a recurrence rate of 50% or more and should be prophylactically re-excised or treated with radiotherapy.⁷²
- 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.⁶³

Histology and growth rate

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

Growth patterns that are less well differentiated and more infiltrative are associated with an increasing risk of recurrence and metastases.

Spindle cell variants are particularly aggressive. Identification of perineural and/or lymphatic infiltration carries a poorer prognosis.⁷²

Anatomical site of primary

Key point

- SCCs of the scalp, ear and vermillion have a higher recurrence and subsequent nodal metastasis rate than SCCs elsewhere, in the order of 10 to 20% overall.⁷¹⁻⁷³

Cutaneous SCCs unrelated to UV irradiation

SCCs arising in a chronic scar

- chronic osteomyelitis sinus
- burns scars—‘Marjolin’s’ ulcer
- X-irradiation damaged skin.

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

Host factors

Immunosuppression (*refer to chapter 10—Non-melanoma skin cancer in organ transplantation and other conditions associated with prolonged immunosuppression*).

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, which patients with asymptomatic lesions can be reluctant to undertake and which may compound their co-morbidities (such as arthritis, thrombosis, diabetes and fear in the elderly).

Another site-specific co-morbidity occurs in younger adults (especially women) with facial skin cancers who seek unattainable guarantees of good 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.

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6 SURGICAL TREATMENT

6.1 Introduction

Surgery is the most common method of management of basal cell carcinoma and squamous cell carcinoma (NMSC) - it remains the gold standard and provides excellent five year cure rates. Compared with non-surgical modalities, surgery has the advantage that it 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. (*See chapter 4—Pathology (including biopsy).*)

Although the overwhelming majority of NMSCs can be managed by simple surgical procedures, consideration may be given to non-surgical modalities for clinically favourable lesions.

On the other hand, some NMSCs behave aggressively, resulting in extensive tissue destruction. Surgery remains the primary treatment modality for these lesions, which may necessitate extensive surgical resections.

6.2 Objectives of treatment

The objectives of surgical treatment of BCCs and SCCs are:

- to cure, by achieving histologically-confirmed complete excision of the tumour with a clear 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 that 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.

6.3 Principles of surgical management

The general principles of performing surgical excision of BCC and SCC are:

1. Patients should be informed of the options (surgical and non-surgical) as well as the risks and benefits of surgery. The procedure should be explained, including what should be expected in the post-operative period, the eventual cosmetic and functional outcome, and the possible complications. The patient should also be informed that any tissue removed will undergo pathological evaluation and that further surgery may be necessary to obtain complete removal of the lesion.
2. An understanding of the biology of the NMSC in the context of the anatomic location is essential in the effective planning of the procedure. For example, a nodular BCC of the inner canthus should be treated more aggressively than a nodular BCC of the back, as should a morpheic BCC of the back compared with a nodular BCC of the back.
3. Specific features of the lesion need to be appreciated, such as fixation to deeper tissues or involvement of other structures such as nerves.
4. Biopsy: if there is any doubt concerning the clinical diagnosis or the lesion is in a cosmetically sensitive location, an appropriate biopsy, for example a punch or shave incision

biopsy, should be considered prior to definitive surgical excision. In some cases it may be more expeditious to completely remove a small lesion.

5. The majority of cutaneous NMSC can be excised under local anaesthetic on an outpatient basis.
6. Virtually all NMSC, irrespective of size, below the neck and above the knees can be closed directly. There may be occasions when a graft may be necessary on the back of the hand.
7. Excision of small, clinically favourable lesions in straight-forward sites should be within the skills of general practitioners who are capable and confident in the performance of minor surgical procedures.

The visible extent of the lesion should be marked on the skin with a surgical marker. An appropriate margin (see below for discussion) should then be marked around the lesion. Once drawn, this margin should then not be compromised or adjusted, especially to make it easier to close. Then an ellipse should be drawn incorporating the excision margin, with the long axis lying in the direction of the skin creases or perpendicular to the direction of least skin tension. This can usually be determined by gently pinching the skin in various directions. The suggested ratio of length to width for the ellipse is 3 or 4 to 1. The skin should then be injected with local anaesthetic, which includes adrenaline to minimise bleeding. A 30-gauge needle should be used on a Leur lock syringe to minimise discomfort to the patient. Longer (1 inch) needles reduce the number of needle stabs, particularly as fine needles rapidly become blunt. Slow injection technique also helps to minimise pain. The skin should be cut vertically with the blade at 90 degrees to the skin. The depth of excision should be through uninvolved subcutaneous fat. The skin can be closed with simple interrupted sutures using a monofilament suture such as nylon.

The following can be used as a guide as to the most appropriate gauge of suture:

- face—5/0 – 6/0
- limbs—4/0 – 5/0
- torso—3/0 – 4/0

Sutures on the face should be removed no later than seven days. Sutures on the upper limb could be removed by ten days and sutures on the back and lower limb should remain for two weeks. If in doubt remove alternate sutures and review in a week.

Consideration should be given to using buried absorbable sutures to avoid suture marks or to allow earlier removal of simple interrupted sutures.

8. All resected tissue must be sent for pathological evaluation. A careful description of the site of excision is essential as is orientation of the specimen with either a stitch or a nick to allow identification of any areas where excision is incomplete. A simple diagram or a phone call, particularly if multiple lesions are removed, can be of great assistance to the pathologist.
9. 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, for example eyelid, tear duct or facial nerve, is necessary to achieve complete resection.

Tumours on the face are best treated by trained and experienced practitioners to minimise alteration in function of the eyelids or mouth and to 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.

Patients have widely differing expectations of cosmetic outcome after skin cancer surgery. The risk of hypertrophic scarring must always be discussed with the patient prior to surgery along with some explanation of the timecourse of scar maturation.

10. 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 that overly the course of the nerve over the zygoma and lateral peri-orbital and temple regions and the mandibular branch which may pass below the line of the mandible. 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.
11. 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.
12. 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 (either by the technique known as Mohs micrographically controlled surgery [see 6.8—*Mohs micrographically controlled surgery*] or by standard frozen section intraoperative control techniques).

6.4 Advantages and disadvantages

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

- an excellent overall cure rate, superior to all other techniques
- pathological evaluation of complete tumour removal
- a generally acceptable cosmetic and functional result with rapid healing.

The disadvantages of surgical intervention include:

- haematoma, infection, wound dehiscence
- 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

6.5 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.

Key point

- The majority of basal cell carcinomas that are clinically favourable, that is, small, nodular or superficial types not located in the central face, can be satisfactorily excised under local anaesthetic with direct primary closure in an ambulatory care setting.¹⁻³

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.

In reviewing published studies that 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, that is, 2mm, to more extensive margins of 5mm or more.¹ 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.² This probably explains why as many as one-third of careful excisions may have close or involved margins.

A 2–3mm margin is probably adequate for the majority of simple BCCs. For more complex lesions either due to anatomical location or histological subtype, or for clinically poorly-defined lesions, a wider margin of up to 5mm may be required.¹ All non-melanoma skin cancers can grow in an asymmetrical manner with unexpected extensions growing many millimeters beyond the apparent clinical margin. A pathology report may have only one section through the tumour. This would represent less than 1% of the margin of a large lesion. Clinicians therefore need to carefully assess any pathology report indicating close margins. Further pathology sectioning may show involvement of margins further along the excised lesion.

Key point

- In high-risk tumours or in high-risk skin areas, microscopic margins of less than 1mm require a discussion with the pathologist about further pathology sections to assess adequacy of the margin. High-risk skin cancers that are not re-excised to achieve histological complete excision should be followed long term. Recurrence following inadequate margin clearance may take years to become apparent. (see section 4.4.3)

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 critical and must be considered during the planning of the proposed surgery.

Key point

- The majority of clinically favourable BCCs can be excised with a margin of 2–3mm with a very high chance of achieving complete excision and long-term control. Adequate microscopic margin is 0.5mm.¹

It is important to acknowledge that there is considerable variation in the behaviour of BCCs.³

Factors known to be associated with the development of recurrent disease include tumour size and site and tumour type.

6.5.1 Tumour size and site

Tumour size has been noted to be associated with an increased risk of local recurrence by some authors⁴ but not by all.⁵ 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. It is not known whether this is due to features specific to this site, or is related to difficulties in obtaining complete excision due to either reluctance or inability to perform a wide and complete excision, which may result in significant aesthetic or functional impairment. It has been suggested that the lack of a barrier to invasion at sites of embryological fusion (e.g. naso-labial fold, peri-orbital region) may explain higher rates of local recurrence in the face, although there is little evidence to support this concept.^{6,7}

6.5.2 Tumour type

Several studies have confirmed variation in behaviour of tumours associated with the histologic type of the lesion including morphoeic, micronodular and infiltrating. BCCs showing histological appearances of sclerosis, ulceration and infiltration and which are clinically recognisable as thick, scar-like 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.⁸⁻¹⁰ 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.¹⁰

Unfortunately, accurate clinical recognition of the more aggressive forms of BCCs can be difficult.¹¹

Key point

- If an aggressive form of BCC is suspected either clinically or on biopsy then a margin of 3–4mm is appropriate.

6.5.3 Perineural invasion

Occasionally, perineural invasion is seen histologically in BCC, although less commonly than in SCC. The lesions tend to be of a more aggressive histological subtype and located in the head and neck¹² (*see page 53*). Most instances of perineural invasion are clinically unsuspected, small, isolated foci that require no further treatment if completely resected with wide histological clearance of the BCC.

Important practice points

The following lesions should fall within the scope of a general practitioner with experience and confidence in surgical procedures:

- well-defined primary lesions of the trunk and extremities up to 15mm, between 15 and 20 mm is a gray zone and they need referral depending on circumstances
- well-defined primary lesions of the face, forehead or scalp up to 10mm

Consider specialist referral for the following lesions:

- recurrent lesions
- incompletely excised lesions
- high-risk histological types, for example micronodular, infiltrating or morphoeic BCCs
- lesions involving the central face, ears, genitalia, digits, hand or leg
- poorly defined lesions
- lesions fixed to underlying structures
- lesions involving or lying adjacent to significant nerves, for example facial nerve or accessory nerve
- trunk and extremities lesions greater than 20mm
- cheek, forehead and scalp lesions greater than 10mm

6.5.4 Incompletely resected BCC

Key point

- Incompletely resected BCCs are defined as histologically incompletely or inadequately excised BCC.¹³

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.

Tumour recurrence rate after excision with margin involvement averages 38%.¹³

Reviewing histological margins, one study¹⁴ reporting primary non-multifocal basal cell carcinomas and correlating the recurrence rate to the microscopic margin showed that basal cell carcinoma excised beyond 0.5 mm, or one microscopic high-power field ($\times 400$), of normal tissue had a recurrence rate of 1.2%. When the tumor was within 0.5 mm, or one microscopic high-power field of the surgical margin, 12% of the lesions recurred. When the tumor involved the margin itself, 33% recurred.

Salvage of recurrent BCCs appears to be highly effective although the series are selective and retrospective. Richmond et al reported a ten-year local control rate of 92% for patients who underwent immediate re-excision versus 90% for patients undergoing excision of clinically recurrent disease. At 20 years, 91% of the immediately excised group were disease free compared with 40% in those who waited for clinical recurrence before excision.¹⁵ Liu et al, who managed limited persistent disease with adjuvant radiotherapy, reported similar results.¹⁶ 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 that 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% versus 17%) of patients with inadequate lateral margins.¹⁶

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 undergo histologically complete re-excision.

Standard surgical procedures with intraoperative frozen section margin control or Mohs surgery has been used successfully in the management of persistent disease. (*Refer to section 6.8—Mohs micrographically controlled surgery.*)

The role of adjuvant radiotherapy for persistent disease is unresolved (*see chapter 7—Radiotherapy*) Limited studies suggest that it probably provides similar rates of control to complete surgical re-excision but may be more inconvenient in some instances.¹⁵ 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 for whom the morbidity of re-excision is not justifiable.

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

Key point

- 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.¹⁴

6.5.5 Recurrent basal cell carcinoma

Among recurrent BCCs, lesions located in the central face and peri-auricular region, large tumours (>2cm), aggressive subtypes (infiltrative, ulcerated and morphoeic and persistent BCCs are over-represented.¹⁶ The type of primary treatment—that is, surgery, radiotherapy, curettage, electro-desiccation—for appropriately selected lesions gives very high similar rates of local control, however, larger lesions treated by non-surgical techniques are more likely to develop a recurrence.¹⁷

The time course to recurrence is important when considering an observational policy. At least two-thirds of recurrences occur within three years of initial treatment, although up to 20% will recur between five and ten years.¹⁸

Recurrent BCCs are associated with a higher risk of further local recurrence, at least 50% higher than previously untreated lesions.¹⁹ 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.^{20,21} 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.²² 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 may be 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 (using either standard or Mohs techniques) may be of value in ensuring complete removal of BCCs. But these techniques 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.²³ They are both highly sensitive and specific in evaluating margins.

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.

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.^{15,16}

6.6 Squamous cell carcinoma

The aims of surgical management of SCC are similar to that for BCC in that the main objective is histologically confirmed complete removal of the tumour. In general, the 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 further local recurrence (23%) and subsequent metastasis predominantly to the regional lymph nodes (30%) if further local recurrence occurs.²³ 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%.^{24,25} The recommended surgical margin of excision for SCC varies from 2 to 10mm.^{26,27}

Histological margins of 1mm or less mandate discussion with a pathologist to determine their confidence that excision is complete. This may require that further sections be examined. If doubt remains further therapy may be necessary. Favourable lesions, for example well-differentiated lesions less than 2cm in diameter, will be adequately excised with a 4mm margin in 95% of cases.²⁸ Tumours larger than 2cm require larger margins up to 10mm to obtain similar rates of local control.²⁹ For very large lesions even wider margins may be necessary.³⁰ 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. Evaluation of frozen section margin control is generally available only in hospitals and although time-consuming and expensive, is

highly sensitive and specific.²³ Alternatively, Mohs technique with intra-operative evaluation of the margins is an option if available.

Key point

- In SCC a histological margin of 1mm or less mandates consideration of further therapy.²⁸
- 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 are listed below. Many of these factors are not independent of each other. Analysis of a prospectively accrued group of patients identified local recurrence of SCC, invasion beyond subcutaneous tissues, peri-neural invasion, and size and depth of invasion as predictive of disease specific survival, but not age or lymphatic and/or vascular invasion. On multivariate analysis, invasion beyond subcutaneous tissues, peri-neural invasion and tumor size greater than 4cm were independently predictive of disease-free survival. Patients with no risk factors had a 100% three-year disease-free survival compared to 70% for patients with one or more of these three independent risk factors.³¹

6.6.1 Tumour size

The diameter of SCC correlates with risk of recurrence. Tumours less than 2cm in diameter have a five-year recurrence rate of 7.4% compared with 15.2% for tumours greater than 2cm in diameter.³² In another study, for tumours greater than 4cm in size the three-year disease-specific survival was 67% compared to 93% for smaller tumours.³¹

6.6.2 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%.³²

6.6.3 Histological features

- Patients with poorly differentiated tumours had twice the risk of local recurrence compared to those with well-differentiated lesions.³² The local recurrence rate increased from 7% for well-differentiated tumours to 28% for high-grade lesions.³³ In addition, poorly differentiated tumours are more likely to metastasise to regional nodes and other sites.³⁴ Patients with evidence of desmoplasia have an increased risk of both local recurrence and metastasis.³⁵
- 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.^{34,36} The risk increases with further thickness. In one small series only tumours extending to and beyond the reticular dermis developed local recurrence.³³ Extension of tumour beyond the subcutaneous tissues rather than depth of invasion was a better predictor of disease-specific survival in a multivariate analysis of a prospectively followed cohort.³¹
- 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.³⁴

Key points

The majority of clinically favourable SCCs of 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 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.^{24,26-29}

6.6.4 Rapidly growing tumours

Although uncommon, rapid growth of SCC has been noted to be associated with an increased risk of recurrence and death.³⁷

Perineural invasion

Perineural invasion is far more common in SCC than BCC, complicating the course of up to 5% of all patients with SCC.³⁰ Perineural invasion appears to be more common in lesions located in the head and neck. Perineural spread may be incidental or symptomatic. Incidental implies early asymptomatic disease and is recognised on pathological examination of the specimen. No further intervention is indicated if complete pathological examination shows that the peri neural spread is limited and completely and widely resected.

Tingling, pain, paraesthesia, formication, reduced sensation or motor function suggest perineural invasion. Pre-operative MRI should be considered for patients with clinical evidence of large nerve involvement.³⁸ Intra-operative margin control with frozen section can be used to attempt complete excision. Surgical resection of the involved nerve, which is usually followed by adjuvant radiotherapy, with palliative or curative intent covering the entire course of the nerve back to its origin from the CNS is appropriate. Alternatively, radiotherapy alone to the course of the nerve may be appropriate for patients unable to undergo further surgery. Treatment invariably causes major morbidity.

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% in perineural invasion.³⁶ 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.³²

Key point

- Consideration of specialist therapy should be considered for patients with an SCC showing perineural spread. Wide excision is recommended and consideration should be given to post-operative radiotherapy.^{32,36}

6.6.5 Previously treated SCC

SCCs that recur following previous treatment have an increased incidence of further recurrence, with approximately one third developing regional metastasis.³⁹ The rate appears to be higher for SCC of the ear (45%) than the lip (32%) or other sites (25%).²³

Key point

- 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.^{23,39}

6.6.6 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. (*See chapter 10—Non-melanoma skin cancer in organ transplantation and other conditions associated with prolonged immunosuppression.*)

Key point

- Chronically immunosuppressed patients frequently develop multiple SCCs that behave aggressively. These patients should be referred for specialist management. (*see chapter 10*)

6.6.7 Aetiology

A number of pre-existing factors that 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 high frequency incidence of metastasis (10–30%) and local recurrence.^{40,41} 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 five years.⁴² SCC arising in other scars including osteomyelitis and chronic stasis ulcers are characterised by similar rates of local and regional recurrence and poor survival.

Good practice points

Low-risk patient checklist:

- Limited size and not located on the scalp, peri-ocular region, ears, lips, nose or genitalia
- Not a recurrence nor near a previously treated area
- Not rapidly growing
- Low grade
- Less than 4mm in thickness
- Not extending beyond the subcutaneous tissues
- Favourable histology, i.e. well differentiated, no peri-neural invasion.

6.7 Metastatic disease

6.7.1 Basal cell carcinoma

Lymph node metastases

Metastasis of BCCs to lymph nodes is extremely rare. 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, and large primary tumours and head and neck lesions have also been noted.^{43,44} Regional control can usually be achieved with lymphadenectomy. Post-operative radiotherapy may be indicated for patients with a high risk of recurrence, that is, extensive disease, multiple involved nodes, extra capsular extension, close/involved surgical margins.^{45,46} 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 recurrent disease.

Distant disease

Metastatic disease from BCC is an *extraordinarily* rare event and patients so affected should be referred to a specialist unit.

6.7.2 Squamous cell carcinoma

Lymph nodes 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:

- SCC occurring at sites of mucosal–squamous cell junction, including lip, anus and vulva
- immunosuppression
- previous radiotherapy
- SCC arising in chronically inflamed/irritated lesions.

Among patients developing regional recurrence, specific tumour factors related to the development of regional recurrence include²⁴:

- *Tumour size*: SCCs greater than 2cm are twice as likely as smaller lesions to develop regional recurrence.
- *Tumour site*: lesions located on the ear and lip have a higher rate of local recurrence than cutaneous SCC elsewhere.
- *Tumour grade*: poorly differentiated SCCs have double the recurrence rate of well-differentiated lesions.
- *Tumour thickness*: SCCs greater than 4mm in thickness recur three times more commonly than thinner lesions.
- *Recurrent SCC* is twice as likely to recur.⁴⁷
- *Peri-neural invasion* is 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

- Spread of SCC to regional lymph nodes is uncommon but is often associated with metastasis to distant sites and a poor outcome.^{43–46}

Any clinical suspicion of node metastases warrants investigation by CT scanning or ultrasound. The diagnosis of nodal metastases should be confirmed by fine needle aspiration cytology (FNAC),

preferably under ultrasound guidance. 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 anaesthetic.

Key point

- Clinically suspected lymph node metastases should be confirmed by fine needle aspiration cytology (under radiological or ultrasound guidance if required) if possible. Open surgical biopsy should be avoided.⁵²
- The treatment of metastatic disease to lymph nodes is primarily surgical.⁴⁸

Good practice point

- Although cutaneous SCC is the obvious primary for 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 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.

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.

Adjuvant post-operative radiotherapy should be considered in patients with a significant risk of recurrence, including multiple nodes involved, large size, extracapsular extension or tumor spill at the time of operation (including an open biopsy). Recurrence of nodal disease is associated with a very poor prognosis. While no randomised trials exist to support the role of post-operative radiotherapy in cutaneous SCC, evidence extrapolated from mucosal-related metastatic SCC is strongly supportive. Curative radiotherapy alone for nodal metastases is indicated if lymphadenectomy is not possible because the patient is unfit for surgery or refusing surgery. Salvage surgery is sometimes possible if complete or durable control is not achieved with radiotherapy alone. Palliative radiotherapy is appropriate for inoperable, advanced regional metastases to treat pain, prevent skin ulceration, and reduce bleeding. It is unlikely to prolong survival. Survival after lymph node metastasis is poor, with only one third surviving five 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.^{48,49}

Dermal lymphatic spread (in transit metastases)

Dermal lymphatic spread (in transit metastases) 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.⁵⁰

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 and widely excised. Radiotherapy treatment recommendations are found in *chapter 7—Radiotherapy*. 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 radiotherapy 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.^{24,48} 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 two 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-fluorouracil, bleomycin and vindesine.⁵¹⁻⁵³ Survival despite treatment is poor, with few patients surviving more than two years. Specialist referral is indicated.

6.8 Mohs micrographically controlled surgery

Mohs micrographically controlled surgery is named after Frederick Mohs, who pioneered this technique. His original chemosurgery procedure has been modified to a fresh frozen tissue technique. The key to this technique is in its careful marking of the specimen at surgical removal and then use of horizontal sections to perform topographic and microscopic analysis of the whole outer margin of tissue excised at the time of operation. It aims to ensure complete tumour clearance while maximising normal tissue conservation and function.^{4,24,54-62,62,63,63-68} It is undertaken in several specialised centres in Australia⁶⁹⁻⁷⁶ and is primarily used in a tertiary referral setting for difficult-to-treat tumours.

Mohs surgery is usually performed under local anaesthetic. Following excision of the tumour, almost the entire peripheral and deep margins of the excised tissue are examined by frozen section^{1,66,77-79} (much like a pie crust around a pie; specifically all the edges of the pie crust against the pie tin are inspected^{2,80}). In contrast, standard sectioning used by pathologists may examine only 0.1–1.0% of the surgical margin.

Mohs technique involves mapping and staining of the excised tissue and a specialised tissue sectioning procedure that enables precise localisation of any residual tumour. If any residual tumour is detected, the above process is repeated until the margin is tumour-free. The resulting defect is then ready for repair as appropriate for the particular site. A key component of Mohs surgery is that the proceduralist removing the tumour also examines the histological slides, thus eliminating the communication errors that can occur in a multi-disciplinary approach.⁸⁰

It is a time-consuming procedure, with each excision taking 5–30 minutes and the processing and reading of stained frozen sections taking from 15 minutes to several hours, depending on the size and complexity of the specimen. The procedure is capital intensive both in equipment and staff. The technique requires specific training and expertise, both for the Mohs proceduralist and also for the assisting technicians. In addition, disconnected foci of tumor can result in a recurrence, and for certain tumours frozen section interpretation may be difficult (e.g. poorly differentiated or spindle cell subtypes of squamous cell carcinoma).⁸¹

Despite high cure rates, Mohs surgery remains unnecessary for the vast majority of tumours. It has been estimated that Mohs surgery is appropriate for and is used in approximately about 1–2% of NMSC in Australia. (See chapter 5–Prognosis). To date there has only been one randomised clinical trial looking at surgical margins using recurrence of tumour as a study endpoint.⁸² The study by Smeets et al compared recurrence at 30 months following standard excision and Mohs' surgery. There was no significant difference in terms of recurrence between the two groups. There is a clear need for further controlled studies to determine the value of Mohs technique compared with surgical excision without margin control. Nevertheless, this technique is becoming increasingly available and therefore it is important that medical practitioners treating skin cancer know about it. As it is a highly specialised technique required for only a very small number of tumours, the decision to refer a patient for consideration for Mohs surgery should be by a medical practitioner experienced in skin cancer diagnosis and management who has a clear understanding of the technique and its value.

Mohs surgery may be considered in the following situations:

- tumours with poorly defined borders, in particular those with poor tumour biology and located in anatomically sensitive areas
- tumours that have been recurrent (or residual) following previous treatment
- extensive disease.

Patients who may also benefit from Mohs technique of margin control during surgery are included in the list on page 49.

6.9 Anticoagulants and surgery

Discussion continues as to whether cessation of Aspirin or Warfarin therapy should be considered before surgery, some surgeons espouse the view that such treatment can be continued with little risk of increased bleeding at and after surgery. At this time, there is a need for adequately powered prospective studies to clarify the risk of intra and post operative bleeding and other complications of the continued use of Aspirin and Warfarin during surgery.⁸³ Some herbal agents have an anticoagulant potential and may increase bleeding after cutaneous surgery.⁸³

In a prospective study of patients undergoing minor dermatological excisional surgery in 2,326 consecutive patients, Warfarin used by 28, Aspirin used by 228 and 2073 taking no medication. Patients were reviewed postoperatively for bleeding and wound complications. In this study⁸⁴ there was no increase in complications noted in patients being regularly treated with either Aspirin or Warfarin despite their being older and having a greater number of co-morbidities. It was concluded that both Aspirin and Warfarin (provided an INR is performed prior to surgery) can be continued in the presence of minor dermatological excisional surgery a proviso being strict surgical haemostasis.

The decision to continue or to discontinue either Aspirin and/or Warfarin before surgery will remain in controversy until appropriate trials are done,⁸³⁻⁸⁵ however, cutaneous excisional dermatological surgery suggests the risk of bleeding complication to be similar to that of patients not taking Aspirin or Warfarin. The caveat is that meticulous haemostasis be observed.⁸⁴ A meta-analysis reports that while bleeding is of low risk for those on the medications, the risk for these patients may be above the baseline.⁸³ The exercise of clinical judgement and the conducting of RCTs is encouraged.

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7 RADIOTHERAPY

7.1 Introduction

Radiotherapy is the use of ionising radiation to treat cancer and related diseases. It is a well established and effective treatment modality used to treat all stages of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), with results comparable to surgery for early stage disease. Radiotherapy (RT) has a role in the definitive (curative), post-operative, recurrent, metastatic and palliative treatment of non-melanomatous skin cancer.¹⁻¹²

The vast majority of cutaneous BCCs and SCCs present as small early lesions that are amenable to surgery, which is commonly simpler, more convenient and expedient for patients because it is a single episode, highly efficacious and delivers a complete specimen for pathology examination. Thus, radiotherapy is less commonly used to treat small lesions and is limited to a specialised role in the overall spectrum of the disease.

Treatment of complex non-melanomatous skin cancers should be managed by the multidisciplinary team.

Key point

- Radiotherapy should be reserved for the small minority of primary BCCs and SCCs 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.¹⁻¹²

Ionising radiation (x and γ rays photons, β rays electrons; particles) can be delivered by external beam therapy or brachytherapy. External beam therapy is produced by superficial x-ray therapy (SXRT), deep x-ray therapy (DXRT) and linear accelerators. The higher the energy the greater the depth of penetration of the effective beam. Brachytherapy is the use of sealed isotopes applied directly to the tumour as a surface treatment or implanted into the tumour. Brachytherapy deposits a high dose at the interface between the source and the tumour, with a rapid fall off, therefore minimising the dose to surrounding normal tissues.

The type of radiotherapy modality chosen depends on the depth of penetration that is required to adequately treat the lesion. SXRT is suitable for lesions with a depth of ≤ 5 mm, while lesions with a depth of 1–2cm are treated with either low energy electrons (6 MeV) or photons (4–6MV) (produced by a linear accelerator) or DXRT. For deeper tumours, high-energy electrons or photons are used.

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.

In general, small daily doses (1.8–2.0Gy daily) of radiotherapy result in superior cosmesis compared with larger daily doses (>2.0 Gy daily). However, delivering small daily doses of radiotherapy requires a greater number of treatments to achieve an effective curative dose compared with large daily doses. Standard curative dose schedules for treatment of small lesions (<2 cm) usually require fewer treatments (4–12 attendances over one to two weeks) compared with larger lesions which require 15–30 treatments over three to six weeks.

Key point

- Ideally, all BCCs and SCCs should be confirmed histologically by biopsy prior to radiotherapy treatment.

The effective radiation field encompasses the tumour plus a normal tissue margin (the perimeter of normal-appearing skin adjacent to the skin cancer). The normal tissue margin is usually 0.5cm width for small well-defined BCCs and well differentiated SCCs, but 1–1.5cm for larger ill-defined BCCs and more aggressive SCCs.

7.1.1 Tissue conservation

Radiotherapy may provide a superior functional and cosmetic outcome when anaesthesia (numbness), paralysis or bulk volume tissue loss are expected 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, tip of nose, resection of lip or eyelid commissures.

7.2 Side effects of radiotherapy

Side effects are divided into acute (usually occurring within 30 days of treatment) or late (occur months to years following treatment). Side effects depend on the site treated, the radiotherapy modality, the overall total dose, daily dose per fraction and the rate at which it is delivered.

7.2.1 Acute radiation effects

Acute side effects arise two to three weeks after starting radiotherapy and last some days to weeks before completely resolving. The most common side effect is skin reaction. This includes 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. Treatment close to the eye may cause conjunctivitis while treatment over the nose may cause increased nasal crusting and mucosal bleeding; these are treated symptomatically. Acute radiation reactions are transient and generally resolve by six weeks following treatment.

7.2.2 Late radiation effects

Late side effects occur months to years following treatment and are irreversible and can be progressive. The long-term features of radiation damage to the skin may include atrophy (thinning), loss of skin appendages (alopecia, loss of sweating), variable change in colour (pallor or pigmentation), development of variable telangiectasia (fine blood vessels), 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. The late sequelae of radiotherapy can be minimised by reducing the daily dose per fraction, that is, by delivering smaller daily doses using a greater number of treatments. The trade-off is that this increases the overall treatment time. When advanced BCC and SCC invades cartilage (classically the pinna) or bone (e.g. mandible) the risk of chondro- or osteoradio necrosis is higher. Radiotherapy rarely damages nerves or muscle and does not cause major tissue deficit.

A previous course of radiotherapy may influence future surgery and wound healing at that site due to the resulting late effects that may occur over time.

7.2.3 Relative indications for definitive radiotherapy

Based on the limitations and advantages of radiotherapy, the following checklist is useful when considering referral for a radiotherapy opinion for the definitive treatment of BCC or SCC.

Relative indications for definitive radiotherapy are:

- Tissue preservation
When surgery would result in major loss of function (e.g. nasectomy, tip of nose, resection of lateral eyelid commissure, resection of lip commissure, large superficial lesions with loss of tissue or facial nerve sacrifice)
- Older patients where long-term scarring deterioration is inconsequential
- Multiple, especially superficial lesions when impractical to excise
- Patients wishing or needing to avoid invasive procedures (e.g. refuse or unfit for surgery or anaesthesia, or have anticoagulation problems)
- Patients prone to keloid formation

7.2.4 Relative contraindications for definitive radiotherapy

Relative contraindications for definitive radiotherapy are:

- Younger patients (usually <70 years of age) if the lesion is readily excisable
- Lesions in hair-bearing areas or overlying the lacrimal gland
- Invasion into bone or joints*
- Sites of poor vascularity.
- Previous radiotherapy to the skin lesion in question
- Patients with Gorlin's Syndrome, unless there is a specific lesion for which radiotherapy is indicated

* Cartilage involvement is not an absolute contraindication, however radiotherapy is best avoided in larger pinna lesions with extensive, inflamed or painful cartilage invasion.

7.3 Basal cell carcinoma

7.3.1 Definitive radiotherapy for basal cell carcinoma

Control rates for BCC ≤ 2 cm (T1) with radiotherapy are 95–99% at five years to 93–95% at ten years.^{1,3,6-9,12}

Table 7.1 Control rates for BCC treated with radiotherapy, by stage¹³⁻²⁰

Lesion size	T Stage	5 years	10 years
<2cm	T1	97%	95%
2–5 cm	T2	92%	89%
>5cm	T3		
T4 lesions	T4	60%	50%

Radiotherapy has a limited role in treatment of small primary BCCs because complete excisional surgery is more accessible, expedient and convenient with optimal outcomes (control rates and cosmesis).

Radiotherapy should be reserved for the minority of T1, T2 and T3 primary BCCs when surgery is disadvantageous or not feasible.

7.3.2 Residual basal cell carcinoma following radiotherapy

Complete clinical resolution of a BCC following curative radiotherapy can occasionally take up to four months. Most small BCC have disappeared by the time the acute radiation reaction has resolved (four to six weeks after finishing radiotherapy).

Clinical persistence or progression of a BCC after a standard curative dose of radiotherapy should be confirmed in consultation with the treating radiation oncologist, biopsied and treated with excisional surgery.

7.3.3 Post-operative radiotherapy for residual BCC following surgery

The observed recurrence rate of incompletely excised BCC is, on average, 33%.²¹⁻³¹

As approximately two thirds of incompletely excised BCCs 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 et al 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, and higher again when both are involved.^{27,28}

Key points

- If advice for patients regarding re-excision of an incompletely excised lesion is contentious, then the recommendation for radiotherapy is equally difficult.
- Immediate re-excision or radiotherapy for incompletely excised primary BCC reduces the recurrences rate to less than 9%.³²

The presence of perineural spread, micronodular, infiltrative and metatypical (basisquamous) histology and invasion of skeletal muscle, cartilage and bone requires referral to a specialist skin cancer or head and neck clinic (>75% will be head and neck lesions) for individual assessment and advice regarding the merit of post-operative radiotherapy or additional treatment.

7.3.4 Recurrent basal cell carcinoma following radiotherapy

Recurrence can occur at any time after RT but 88–90% of recurrences are reported to occur within the first five years.^{6,8}

Recurrent BCC should be treated with excisional surgery, including the irradiated tissues, by a specialist surgeon. In certain circumstances (e.g. long disease-free interval³³) salvage with re-irradiation can be considered when surgery cannot be performed.^{6,30} Surgery is preferred to re-irradiation as the risk is higher of more serious late sequelae (radionecrosis of skin and other underlying tissues).

Control rates after salvage therapy³⁴ are lower than primary treatment and dependent on the same factors, namely size of the recurrent tumour, number of recurrences and T4 invasion (invasion of skeletal muscle, cartilage or bone). The recurrence rate after recurrence following radiotherapy and salvaged by surgery is between 14 and 18%.^{8,21,35-37}

Key points

- Radiotherapy for T1 and T2 primary BCC has comparable outcomes (marginally inferior) to specialist surgery.^{1,3,6-9,12}
- A radiation oncology opinion should be considered for T4 primary, persistent and recurrent BCC.
- Radiotherapy gives comparable control rates to 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.

Key points

- All salvage therapy for recurrent BCC has lower control rates than for primary BCC.³⁸
- Adjuvant radiotherapy following salvage surgery for recurrent BCC should be considered in patients with a poorer prognosis, namely:
 - T4 tumours
 - multifocal recurrence
 - multiple recurrences
 - poor prognosis histology subtypes
 - inadequate normal tissue margins
 - perineural invasion
 - node-positive BCCs

7.4 Primary cutaneous squamous cell carcinoma

Key points

- Radiotherapy is an efficacious alternative treatment for primary untreated SCC in a minority of patients when surgery is disadvantageous:
 - when surgery is not feasible, for example patient unfit for surgery, patient refuses surgery, anticoagulation issues
 - when surgery will cause cosmetic or functional morbidity unacceptable to the patient, for example nasectomy, loss of function of lips or eyelids, large tissue deficits, multiple lesions
- Radiotherapy is indicated as adjuvant treatment to surgery for incompletely excised (persistent) SCC
- Post-operative radiotherapy should be considered for tumours with high-risk disease following a complete excision. High-risk disease following complete excision include:
 - T4 tumours
 - rapidly growing tumour)
 - recurrent disease
 - close margins (<5mm)
 - perineural invasion (major and minor nerves)
 - lymphovascular invasion
 - in-transit metastases
 - regional nodal involvement
- Radiotherapy is important in the management of metastatic SCC

7.4.1 Definitive treatment of primary cutaneous SCC

Radiotherapy for primary SCC has comparable outcomes to surgery.^{6,11,39} 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%.^{1-5,9,11,40,41} (see Appendix 1 - *International Union Against Cancer (UICC) TNM—classification of malignant tumours.*)

7.4.2 Post-operative radiotherapy of primary cutaneous SCC

Incompletely excised SCC carries a local recurrence rate of over 50%.⁴²⁻⁴⁴ 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%.⁴⁵ Recurrent SCC has higher mortality rates than primary SCC. Any SCC residual or recurrence after a standard curative dose of radiotherapy should be excised, including the accompanying irradiated tissues. Patients with high-risk features (listed in 7.4—*Squamous cell carcinoma and related keratinocyte tumours*) should be referred to a radiation oncologist for consideration of post-operative radiotherapy.

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.

7.5 Regional (nodal) metastatic disease (non-distant)

7.5.1 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.^{46,47}

Regional control can usually be achieved with lymphadenectomy. Post-operative radiotherapy may be indicated for patients with a high risk of recurrence, that is, extensive disease, multiple involved nodes, extra capsular extension, close/involved surgical margins.^{48,49} Radiotherapy alone is a reasonable alternative to surgery for the poor operative candidate or the patient with inoperable disease requiring palliation.

7.5.2 Squamous cell carcinoma

Lymph node metastases

The incidence of lymph node metastases from SCC occurring in sun-affected skin is very low (less than 5%) but may be considerably higher in certain situations, including:^{50,51}

- SCC occurring at sites of mucosal-squamous cell junction, including lip, anus and vulva
- head and neck
- immunosuppression
- SCC 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 include⁵¹

- *Tumour size:* SCCs greater than 2cm are twice as likely as smaller lesions to develop regional recurrence
- *Tumour site:* lesions located on the ear and lip have a higher rate of local recurrence than cutaneous SCC elsewhere
- *Tumour grade:* poorly differentiated SCCs have double the metastasis rate of well-differentiated lesions
- *Tumour thickness:* SCCs greater than 4mm in thickness recur three times more commonly than thinner lesions
- *Recurrent SCC* is twice as likely to metastasise
- *Peri-neural invasion* is 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

- Spread of SCC to regional lymph nodes is uncommon but is often associated with metastasis to distant sites and a poorer outcome.^{50,51}

Any clinical suspicion of node metastases warrants referral to a multidisciplinary head and neck or skin clinic and further staging investigations. 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 anaesthetic.⁵²

Key point

- Clinically suspected lymph node metastases should be confirmed by fine needle aspiration cytology (under radiological guidance if required). Open surgical biopsy should be avoided.⁵²

The most common malignancy of the parotid gland in Australia is metastatic SCC to intra-parotid nodes from a cutaneous malignancy. In many cases these patients have had multiple skin cancers of the head and neck treated and the index lesion may not be known. In this situation, metastatic SCC arising from a mucosal site needs to be excluded in the first instance.

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, the involved node(s) and the extent of the disease. Generally the facial nerve, accessory nerve and sternomastoid muscle can be preserved, which reduces the morbidity of the procedure. Occasionally lymph node metastases occur at unusual sites, including the epitrochlear region and popliteal fossa.

Key point

- The treatment of metastatic disease to lymph nodes is primarily surgical with or without post-operative radiotherapy.⁵⁰⁻⁵⁴

Post-operative radiotherapy is generally recommended for patients with a high risk of recurrence including:⁵³⁻⁵⁵

- parotid node metastases
- \geq two nodes positive in the neck
- \geq three nodes positive in the axilla or groin
- ≥ 3 cm node
- significant extra nodal extension
- close or involved surgical margins
- skin infiltration
- major nerve involvement (e.g. facial nerve)
- recurrent nodal metastases, salvaged surgically

- node metastases in unusual sites, namely posterior triangle neck / SCF / occipital nodes (from primary cutaneous SCC of posterior scalp, upper trunk), epitrochlear and popliteal nodes
- nodal metastases accompanied by local relapse

The role of post-operative chemo-radiotherapy for high-risk cutaneous SCC remains unresolved and is being addressed by an Australian and New Zealand multi-centre randomised phase III trial (POST Study: Trans Tasman Radiation Oncology Group 05.01)

For patients with extensive disease, for example 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.

Curative radiotherapy alone for nodal metastases is indicated if lymphadenectomy is not possible because the patient is unfit for surgery or refusing surgery. Salvage surgery is sometimes possible if complete or durable control is not achieved with radiotherapy alone. Palliative radiotherapy 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 five 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.⁵⁰

Dermal lymphatic spread (in transit metastases)

Dermal lymphatic spread (in transit metastases) 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.⁵⁶

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. Symptomatic perineural spread is late or established spread of SCC away from the primary SCC site along a named 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.⁵⁷⁻⁵⁹ Alternatively, high-dose radiotherapy with palliative or curative intent covering the entire course of the nerve back to its origin from the CNS is acceptable. Relief of symptoms occurs in >50% of cases, with variable durability.⁶⁰

7.6 Solar keratosis and SCC in situ

Radiotherapy is rarely used, as solar keratoses do not require treatment and are routinely cleared with cryotherapy, 5-fluorouracil (5FU) cream or surgery. These modalities are more convenient and generally less morbid for patients than radiotherapy. Occasionally, long-standing SCC in situ 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 SCC in situ except for the uncommon long-standing large superficial SCC in situ disease refractory to dermatological care and unsuitable for excision.

7.7 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.⁶¹

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8 CRYOTHERAPY, CURETTAGE AND DIATHERMY/ELECTRODESICCATION

8.1 Introduction

The destructive therapies, cryotherapy, curettage, and diathermy/electrodesiccation play an important role in the day-to-day treatment of skin cancers and premalignant skin lesions.

8.1.1 Advantages

When these methods are compared with surgical excision, topical immunomodulatory agents, photodynamic therapy or radiotherapy, they are simple, cheap and quick procedures that are easily carried out in a doctor's office. These methods of treatment are useful when dealing with patients with large numbers of lesions and where other therapies may become impractical. They also provide an alternative when surgery may not be suitable, for example in patients with other medical conditions such as pacemakers or coagulopathies, or at body sites where scar contractures may be a problem, such as the digits.

8.1.2 Disadvantages

The major disadvantage of destructive therapies relate to the issue of efficacy. Cryotherapy, curettage and diathermy/electrodesiccation have been widely used for decades to treat non-melanoma skin cancers and related premalignant conditions. The evidence for efficacy is primarily based on non-controlled prospective or retrospective series. Randomised controlled trials are few in number. The other main disadvantage of a destructive therapy is the unpredictable cosmetic result, which may include hyper- and hypo-pigmentation, and hypertrophic or atrophic scarring. These therapies are operator-dependant, with better outcomes reported in those who perform these procedures more often.

8.2 Cryotherapy

Cryotherapy is the destruction of tissue by the direct application of a cryogenic agent such as liquid nitrogen or less commonly, carbon dioxide snow or nitrous oxide. It is a widely used, rapid, cost efficient and effective therapy for solar keratoses (SKs).^{1,2} In addition, cryotherapy (cryosurgery) has been employed for more than forty years for the treatment of selected skin cancers.^{3-6,6-29}

Cryotherapy causes tissue destruction through multiple proposed mechanisms, including physical damage of cellular components by ice crystals, osmotic damage during thawing, ischaemic damage due to cold injury to small vessels, and immunological stimulation with the release of antigenic components. The extent of injury is proportional to the rate of freezing and thawing. Repeated freeze-thaw cycles produce much greater tissue damage than a single freeze due to increased conductivity and impaired circulation of previously frozen tissue, allowing for a faster and greater degree of cold penetration.³⁰

In addition to its widespread use in the treatment of solar keratoses, in general cryotherapy is most suited for low-risk primary tumours with well-defined margins on the trunk or limbs, namely Bowen's disease (intraepidermal squamous cell carcinoma, squamous cell carcinoma in situ),^{7,10-12} primary superficial or small papular basal cell carcinomas (BCCs),^{8,16,20,24} keratoacanthomas (KAs),^{7,15} and small primary well-differentiated squamous cell carcinomas (SCCs).^{5,7,15,16,20}

It is often combined with initial curettage to provide a specimen for histological analysis.^{17,22,25,31,32}

Cryosurgery may offer special advantages for elderly high-risk surgical patients, especially those with a pacemaker, or coagulopathy³²⁻³⁴ for those who refuse surgery and for sites where scar contracture is best avoided, such as digits.³⁵

Occasionally, in certain areas, cost and accessibility to surgical care may make cryotherapy the preferred treatment option.²²

Alternative forms of treatment, especially surgical excision, are indicated for large nodular, morpheic, or ill-defined BCCs,^{7,22,24,27} moderately to poorly differentiated SCCs,^{5,16,17} recurrent tumours, and certain high-risk facial sites.^{2,5,7,17,26-28}

Nevertheless, many studies attest to the efficacy and acceptable cosmetic results achieved by cryosurgery in specialist clinics, even for difficult cancers.^{2,6,17,20-23,25,27-29,36}

A biopsy giving histological confirmation of the tumour is mandatory before treatment if used for invasive tumours, or if there is evidence of residual tumour following treatment.^{7,33,36}

Rarely, cryosurgery may be used for palliation of incurable cancers to lessen tumour bulk or pain and reduce malodorous discharge.³⁷

Cryotherapy at tumoricidal depth generally leaves hypopigmented atrophic scars such that it is not the treatment of choice when the cosmetic outcome is important. It is probably contraindicated in most dark-skinned individuals where hypopigmentation can be obvious and disfiguring:

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 selected low-risk BCCs and SCCs in situ on the trunk and limbs. Acceptable cure rates, comparable to other standard treatment modalities, may be achieved for high-risk tumours in specialist clinics.^{1,2,5-12,14-19,21-29,38}

8.2.1 Basal cell carcinoma

Basal cell carcinomas may be successfully treated by cryosurgery. There are many large series by specialist clinics demonstrating cure rates equivalent to other treatment modalities.^{3-8,16-29,36} The importance of careful tumour selection is emphasised to achieve acceptable results.^{7,24,27,39}

Histological confirmation of the BCC and analysis for high-risk features is strongly recommended.^{7,40-42}

Cryosurgery is most effective for primary well-defined lesions of non-aggressive type at sites away from the head and neck.^{8,16,18,20,24} In general, it would be contraindicated for morphoeic or ill-defined BCCs^{2,7,17,18,22,27,28} and relatively contraindicated for high-risk facial sites such as lips,^{24,33} alar creases,³³ inner canthi^{33,41} and periauricular regions.⁴¹ Repeated freeze–thaw cycles with 3–5mm margins are recommended.^{7,24,41,43-45} 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.^{33,41-44,46-48} Curettage is often combined with cryosurgery and may help improve the cure rate.^{17,22,25,31,44,45} 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.^{2,3,5-8,16,18,20-22,24,25,27,28} Suboptimal cryotherapy technique results in unacceptably low clearance rates.⁴ One extensive review of multiple series reported a five-year recurrence rate for cryosurgery of 7.5%, comparable to other standard treatment modalities.³

Most large series utilise liquid nitrogen in an open-spray technique with repeated freeze–thaw cycles.^{2,5,7,16,17,20-22,24-26,28,29} However, superficial BCCs have been successfully treated with single freeze–thaw cycle cryotherapy, achieving cure rates of 96%.^{8,18} Thermocouple needle monitoring of the temperature produced at the base of tumours (–40 to –60 degrees Centigrade) may be employed.^{2,5,16,18,20,21,28,29} Certain microscopic features are associated with a greater depth of invasion and a higher risk of recurrence.⁴⁹ Curettage provides a sample for histology, facilitates cryotherapy of larger tumours by reducing the tissue volume to be ablated,²⁵ and may offer some advantages at sites

such as nose and ears to define the full extent of tumour growth prior to cryosurgery.¹⁷⁻²² Clinical features are fundamental in choosing those BCCs suitable for cryosurgery. Primary BCCs constitute the great majority of tumours treated in reported series.^{2,3,8,16-18,22,24} In general, such tumours are well-defined and non-morphoeic in type. Most series exclude ill-defined or fibrosing BCCs in their selection criteria due to unacceptably high recurrence rates.^{2,7,17,18,22,26-28,36} 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.^{8,23,25,26,29,36} Recurrent BCCs respond less well to cryosurgery with lower cure rates^{5,8} and Mohs surgery (*see chapter 6—Surgical treatment*) is the preferred treatment for such lesions.³

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%.^{16,20,24} Less optimal results are achieved for sites on the head and neck^{4-6,8,23,26,28,29} although acceptable cure rates have been reported for selective cancers in experienced specialist clinics.^{2,16,17,21,22,24,27,36} Routine follow-up is essential for all patients treated by cryosurgery. Most recurrences will become evident within five years^{16,25} and many within two years.^{7,27} However, some BCCs have recurred as late as 10–12 years after treatment.^{3,41}

Key points

- Cryotherapy achieves high cure rates for primary BCC in sites other than face and ears if tumour selection and treatment protocols are optimal.^{3,8,16,29,36}
- Cryotherapy achieves lower cure rates for larger BCCs.^{8,23,25,26,29,36}
- Cryotherapy achieves lower cure rates for BCCs at high-risk facial sites and is not recommended.^{4-6,8,23,26,28,29}
- Cryotherapy is contraindicated for ill-defined or morphoeic (infiltrative) BCCs at any site.^{2,7,17,18,22,26-28}

Key point

- Long-term follow-up is essential after treatment of BCC with cryotherapy, as late recurrences may occur.³ **Level III**

8.2.2 Squamous cell carcinoma and related lesions

Squamous cell carcinomas

Squamous cell carcinomas (SCC) of low-risk type can be 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.^{5,7,8,16,18,19} In general, less-well differentiated SCCs, recurrent SCCs and those on the head and neck are treated by surgical excision.^{5,16,17,34,50} Repeated freeze–thaw cycles with a minimum of 5mm margins are recommended.^{16,31,51} Curettage may be used initially to debulk the lesion, followed by cryosurgery.^{17,51} Histological confirmation and analysis for high-risk features is essential prior to cryosurgery.⁴⁰

Relative to their prevalence, fewer SCCs are treated by cryotherapy than BCCs, implying that most published studies employ strict selection guidelines.^{5,7,16,18}

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

- primary tumour^{16,20}

- small size^{5,16}
- well defined^{5,16}
- clinically and histologically well-differentiated^{5,16,17,20}
- on trunk or limbs.^{7,15,20}

Cure rates of greater than 95% are consistently achieved if selection criteria are strict and optimal treatment protocols are employed.^{5-8,14-18,20,21,36} The risks of recurrence and metastasis are increased at certain facial sites, especially lips, ears, periocular regions and perhaps scalp.^{52,53} One retrospective Australian study on deaths from SCC of the skin found that 76.5% originated from the head and neck.⁵³ Even with strict selection criteria in experienced clinics, some recurrences occur following cryosurgery for head and neck lesions^{2,7,16,36} in contrast to the very rare recurrences for those on the trunk and limbs.^{7,15} Management of SCC on the head and neck with cryosurgery should generally be 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.⁸

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.⁵⁴

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 spontaneously⁵⁵ or following routine use of sunscreen application.^{56,57} 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 changes in size.⁵⁸

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.⁵⁹

Topical 5 Fluorouracil cream may be used initially to highlight subclinical keratoses prior to cryotherapy treatment.⁶⁰

Successful clearance of SKs using cryotherapy with good cosmetic results requires accurate diagnosis and adequately timed treatment protocols.^{34,43,46,48} A single freeze–thaw cycle is usually recommended. Cure rates ranging from 69%^{61,62} up to greater than 98.8% have been reported.^{1,2} Response rates tend to parallel the duration of the freeze time.⁶³

Hyperkeratotic or suspicious SKs may be better treated by curettage alone or curettage followed by cryotherapy, electrodesiccation or ablative laser to the base.⁵⁸ These techniques provide a specimen for histological confirmation.

Chemical peeling, dermabrasion, laser resurfacing, alpha hydroxy acids and retinoid formulations, 3% Diclofenac in 2.5% Hyaluronan gel,⁶⁴ Imiquimod 5% cream⁶⁵ and photodynamic therapy⁶⁶ may be used topically to reduce signs of photo damage and to treat established and pre-clinical solar keratoses.

Bowen's disease (SCC in situ)

Bowen's disease (SCC in situ) is not invasive and does not need to be treated in the same manner as SCC. Bowen's disease has been treated successfully with cryosurgery, with many studies reporting greater than 95% cure rates and reasonable follow-up periods.^{5-7,9,10,36} Non-optimal treatment

protocols produce less satisfactory results.^{60,67-69} A pre-treatment biopsy is usually recommended.^{7,9,11,70}

A single freeze–thaw treatment cycle of 30 seconds with a 3mm margin is advised.^{7,9} Slow healing was reported for lesions greater than 20mm in diameter and for those on the lower legs.^{12,71,72} Cure rates greater than 99% are achieved with optimal cryotherapy.^{7,9} 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.^{5,8,9,11,12,70,73} Body site appears to make no difference in response to cryotherapy, but delayed healing was reported for lesions on the lower limbs.¹² Size does not adversely affect response and large lesions can be managed with overlapping treatment fields.^{10,12}

Keratoacanthoma

Keratoacanthomas can also be treated with cryotherapy, achieving cure rates equivalent to curettage plus electrodesiccation, simple excision or radiotherapy.^{2,7,15,16,18,19,32,74} 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.^{2,7,15} A cure rate of 87.5% was achieved in one series of five lesions on the head and neck and three lesions on the trunk and limbs.⁷ Double freeze–thaw cycles of 30 seconds or more with 3–5mm treatment margins were used.^{2,7,15} Site differences in response to cryotherapy have not been noted in the small series reported.⁷ Size appears to have been a factor in the choice of cryotherapy, with almost all treated lesions less than 20mm in diameter. One large KA responded to cryotherapy after initial shave excision.¹⁵

Key points

- Cryotherapy achieves consistently high cure rates for solar keratosis.^{1,36,75,76}
- Cryotherapy of Bowen's disease achieves high cure rates with optimal treatment protocols, but delayed healing may occur on lower limbs.^{7,9}
- Cryotherapy is not often used for keratoacanthomas, but may represent reasonable treatment for smaller lesions. If the diagnosis is in doubt then treatment should be as for SCC^{2,7,15} (See 3.3.1—*Squamous cell carcinoma* in chapter 3—*Clinical features*.)
- Cryotherapy produces cure rates equivalent to other standard treatment modalities for low-risk SCCs on the trunk and limbs.^{7,15,16,20}
- 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.^{6,7,14,16,20}
- Cryotherapy is contraindicated for recurrent SCC.⁸

Relative indications

- Elderly patients, especially those with medical disorders less tolerant of surgical procedures, for example, with pacemakers, coagulopathies.
- In geographic areas with poor access to surgical facilities.
- At body sites with increased risk of keloid scars from other treatment modalities, for example, curettage or surgical excision on the upper arms and upper trunk.
- Solar keratoses at any site if discrete and non-suspicious.
- Bowen's disease, especially on trunk or limbs.

- Keratoacanthomas if small and at low-risk sites.
- BCCs and SCCs of low-risk type, especially on the trunk and limbs.
- Palliation of inoperable tumours.

Relative contraindications

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

8.3 Curettage and diathermy/electrodesiccation

Curette and diathermy/electrodesiccation (C & D) is a specialised technique used in the management of BCC, SCC, keratoacanthoma and Bowen's disease. To achieve the cure rates described requires both careful lesion selection and critical attention to technique.^{77,78} *It is considered that specialist training is a necessary prerequisite for the use of C & D.*

8.3.1 Mechanism

The stroma of those skin cancers appropriate for C & D is gelatinous by comparison to surrounding normal dermis and thus these lesions 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 in the same way as healthy dermis. It is therefore not appropriate for lesions penetrating to the depth of the dermis. Neither will it be effective in the treatment of cicatricial lesions, which do not have a gelatinous stroma, for example morphoeic BCC. The technique varies slightly between operators but essentially involves one to three 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.

8.3.2 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 is not contraindicated in anti-coagulated patients.

8.3.3 Control rates for BCC treated by serial curettage by diameter^{77,79,80}

Table 8.1 Control rates for BCC treated by serial curettage by diameter

Lesion: size/type/location	Cure rate at 5 years
<1cm all sites	98.77%
<1cm nose	93.55%
>2cm all sites	84%
>2cm ears	67%
All sizes not head	> 96%
<1cm cheek, forehead & temple	94.7%
>1cm as above ^{7,9}	77.3%
<0.5cm nasal, paranasal, periorbital, lips, chin, jawline and ears ^{7,9}	94.7%
>0.5cm as above	77.3%

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.^{77,79,80} 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 show higher recurrence rates.⁸⁰

Key point

- Recurrence rates of less than 6% may be achievable if curettage and diathermy are used for appropriately selected BCC.^{77,78}

Key points

Curettage and diathermy (C & D)

- Is not used on high-risk areas (nasal, paranasal, lips, eyelids, chin, jawline and ears) or at least not for lesions larger than 5mm at these sites.⁷⁷
- Is not used on lesions larger than 10mm on middle-risk sites (face, forehead, temples and scalp).⁷⁷
- Is used for all sizes of lesion on low-risk areas (neck, trunk and limbs).⁷⁷
- Is not used on clinically morphoeic lesions.⁸⁰
- Is not used for recurrent lesions.^{77,79}
- Is carried out by operators with appropriate supervised training in the procedures.⁷⁷
- Multiple SCCs may be treated in certain circumstances with curettage and electrodesiccation/diathermy and in specialised centres.

8.3.4 Squamous cell carcinoma and related lesions

Squamous cell carcinoma

The use of C & D 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 demonstrated a cure rate of 96% in a group of 48 patients followed for five years and 98% in a group of 101 patients observed over four years. In both groups selection was based on a lesion size of less than 2cm and ‘unusually invasive, destructive, or sclerosing lesions were treated by irradiation or surgery’⁸¹ 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 (SCC in situ)

Curettage and diathermy/electrodesiccation is one of a number of modalities used by dermatologists in the management of Bowen’s disease on exposed areas. The technique requires that the skin 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. As 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%.^{11,82,83}

Keratoacanthoma

Keratoacanthoma may be considered a benign tumour and is commonly treated by dermatologists using the technique of C & D. The cosmetic results are anecdotally regarded as good.^{84,85} Published studies show acceptable cure rates but are compromised by follow-up times of less than five years.^{84,85} Curettage of keratoacanthoma involving the nail bed is controversial.^{86,87}

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 1cm 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.

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9 OTHER TREATMENTS (TOPICAL AGENTS— IMIQUIMOD CREAM, DICLOFENAC GEL, FLUOROURACIL CREAM AND PHOTODYNAMIC THERAPY)

9.1 Interferon

9.1.1 Introduction

Interferons (IFN) are a family of proteins synthesised by cells of the immune system, classically leukocytes (IFN α), fibroblasts (IFN β), and lymphocytes (IFN γ), 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.¹

Systemic interferon α , β , γ have been successfully utilised in the management of Kaposi's sarcoma, cutaneous T-cell lymphoma, viral papilloma and malignant melanoma.² Subcutaneous interferon α -2a combined with oral retinoids may be useful for multiple lesions of Bowen disease.³

9.1.2 Basal cell carcinoma and squamous cell carcinoma

Intralesional injection of interferon α -2b as the treatment for nodular and superficial BCC has been reported as having response rates of 24–100%, reflecting variation in dose regimens, technique and duration of follow-up.^{1,4-9}

Intralesional interferon is no longer available commercially for the treatment of BCCs in Australia.

9.2 Imiquimod 5% cream*

Topical Imiquimod 5% cream provides its clinical efficacy secondary to a complex array of molecular events that result in the stimulation of both the innate and cell mediated immune responses to tumour antigens.

The main effects of Imiquimod are induced by the stimulation of toll-like receptors (TLR7 and TLR8) on immune cells, primarily monocytes/macrophages and dendritic cells, which help in the recognition of pathogen-associated molecular patterns. This results in the activation of NF Kappa B which induces the expression of various cytokines: IFN α , Tumour Necrosis Factor (TNF) α , Interleukins—IL2, IL6, IL8, IL12, and other chemokines and inflammatory mediators.¹⁰ The above factors inhibit angiogenesis and also promote apoptosis.

9.2.1 Solar keratoses

The short-term efficacy of topical Imiquimod 5% cream in patients with solar keratoses has been assessed in five large, randomised, double-blind trials versus placebo.¹¹⁻¹⁵

Complete clearance rates varied between 45% and 57%. Clearance rates of more than 75% of lesions were achieved in up to 72% of patients.

The approved indication in Australia is for applications to be applied once daily, three times per week, for up to sixteen weeks. However, in practice, most clinicians are instructing their patients to apply the cream two–three times a week for two–four week cycles. Two sachets per application are required to treat both cheeks, both temples and the forehead. The cycle may be repeated after a month if necessary to increase efficacy. Rest periods (i.e. missed applications) are advised if the inflammatory reaction becomes excessive. The lost time is not added at the end of treatment period.

9.2.2 Superficial basal cell carcinoma

The approved indication for the use of Imiquimod in Australia for biopsy-proven, primary superficial BCC is application five times a week for six weeks. Results of phase III studies¹⁶ indicate that this regimen of Imiquimod application results in a histological clearance rate of 82%.

Skin biopsy must confirm the diagnosis prior to treatment and is highly recommended. The cream is applied to the tumour and a 5mm margin of normal skin surrounding it. The area of application should not be increased even if inflammation occurs outside the area. Efficacy assessments are made clinically at two–three months post therapy

The inflammatory response to treatment may vary significantly between patients and between different lesions on the same patient. During treatment the inflammatory reaction may become excessive and the patient may require rest periods where the cream is not applied. The cream application regime is recommenced when the excessive inflammation has resolved.

9.2.3 Nodular basal cell carcinoma

A phase II study looking at the efficacy of Imiquimod as a treatment for nodular basal cell carcinomas¹⁷ indicated clearance rates of only 70–76% for Imiquimod applied five times a week to daily for between six and twelve weeks. The treatment of nodular BCCs is not an approved indication in Australia. However, it may be considered for use as for superficial BCCs if other treatment options are contraindicated.

The short-term use of topical Imiquimod 5% cream (once daily for four weeks) as an adjunct to curettage and electrodesiccation appeared to be effective in a randomised double-blind trial.¹⁸ The comparison between histologically confirmed clearance rates for adjuvant Imiquimod versus placebo (with curettage and electrodesiccation) were 90% and 60%, respectively. The use of Imiquimod in this way may improve the efficacy and cosmetic outcome of lesions treated with curettage and electrodesiccation. Imiquimod is not used for BCC showing histologic subtypes of morphoeic, infiltrating or micronodular.

9.2.4 Squamous cell carcinoma in situ (Bowen's disease)

A randomised double-blind vehicle-controlled trial has investigated the use of topical Imiquimod 5% cream in the treatment of patients with Bowen's disease.¹⁹ The cream was applied daily for sixteen weeks and allowances were made for rest periods.

Complete clearance was observed in 73% of these 15 patients compared with 0% in the placebo recipients. No recurrence was seen in the six months follow-up described in the study. In clinical practice, most practitioners treat areas of Bowen's disease for four–six weeks with applications three–five times per week. Clinical review during treatment may be required because of the development of excessive inflammation in some patients. Rest periods may be required in some patients during treatment.

Key point

- Imiquimod 5% cream, which is a topical cytokine and Interferon inducer, offers an alternative treatment option where surgery or other therapies are inappropriate or contraindicated. Approval has been given by the Therapeutic Goods Administration in Australia for the treatment of primary superficial basal cell carcinomas and solar keratoses.¹⁶

** Chapter contributors R Marks, P Foley and S Shumack have participated in clinical studies of Imiquimod 5% cream initiated by and supported with grants from 3M Pharmaceuticals, St. Paul, Minnesota.*

9.3 3% Diclofenac gel

3% Diclofenac in 2.5% hyaluronan gel is approved in Australia for the treatment of solar keratoses.

It is applied twice daily for 90 days. The product is administered at home by the patient and is well tolerated. This field treatment can be combined with liquid nitrogen cryotherapy for more hypertrophic or resistant solar keratoses.

The mechanism of action of 3% Diclofenac gel is not yet fully understood. Diclofenac inhibits the cyclo-oxygenase and lipo-oxygenase enzymes, resulting in a decrease in the downstream by-products of arachidonic acid metabolism. These metabolites have been shown to play a pivotal role in promoting epithelial tumour growth. Diclofenac induces apoptosis, inhibits cell proliferation, and suppresses angiogenesis.^{20,21} Hyaluronic acid is believed to enhance the partitioning of Diclofenac into human skin and its retention and localisation in the epidermis (forming a depot effect).

The recommended twice-daily application for 90 days results in 50% of patients with complete clearance of baseline solar keratoses.²²

** Chapter author/contributor P Foley has participated in Solaraze medical advisory board meetings for CSL.*

9.4 5% 5-fluorouracil cream

5% 5-fluorouracil cream has been used for many years to treat solar keratoses and Bowen's disease. Fluorouracil is an antimetabolite that blocks thymidine synthesis inducing cell-cycle arrest and apoptosis.

The common regime used for the treatment of solar keratoses is application twice daily for two–four weeks on the head and neck. This results in significant inflammation that settles within one–two weeks of ceasing therapy. Published evidence for its efficacy is scant.²³ Twelve-month sustained complete field clearance after four weeks of twice-daily application was seen in 33% of patients.²⁴ Bowen's disease is treated with 5% 5-fluorouracil cream twice a day for between four and eight weeks. Efficacy results demonstrate cure rates ranging between 87% and 92%.²⁵

9.5 Photodynamic therapy*

9.5.1 Introduction

Photodynamic therapy involves the use of light to activate a photo-sensitiser that is localised in diseased tissues, resulting in the formation of cytotoxic reactive oxygen species. It is recommended that solar keratoses are treated with a single session of PDT and assessed at 3 months. Any residual lesions can, if required, then receive a second session of treatment. Bowen's disease and BCC are recommended to receive 2 sessions of treatment one week apart, although in practice this may be up to a month apart. Each treatment session involves gentle debridement or removal of scales for solar keratoses, Bowen's disease and superficial BCC, or debulking of nodular BCC, typically without the requirement for local anaesthesia. The photosensitising cream is then applied 1mm thick to the treatment field for solar keratoses or the lesion (plus a 5mm margin), then covered with an occlusive dressing. This preparation takes approximately 15 minutes. The cream is left in place for 3 hours, the area is then wiped clean with saline and illumination for 7-9 minutes follows.

Topical photodynamic therapy is effective in the treatment of solar keratoses, Bowen's disease, and superficial and thin nodular BCCs. Cosmetic results are good, with minimal scarring seen after most

photodynamic therapy treatments. Specialised equipment and training is required for photodynamic therapy treatment. It is therefore primarily restricted to specialist use or use within centres specialising in skin cancer management.

Methyl aminolevulinate (MAL), marketed as Metvix, is available in Australia. Some studies have also investigated the alternative photo-sensitiser 5-aminolevulinic acid (ALA).

9.5.2 Solar keratoses

There is now a large body of evidence to support the use of PDT for the treatment of solar keratoses, including four phase III randomised controlled MAL PDT studies and two using ALA PDT.²⁶⁻³⁰

Three and six month solar keratoses complete response rate for MAL PDT is approximately 90% (for two treatments sessions).^{27-29,31}

PDT is generally well tolerated by patients although pain at the time of the illumination can be problematic and may require interventions such as the temporary suspension of illumination and/or the injection of local anaesthetic.

In phase III studies with the use of MAL-PDT in solar keratoses, the cosmetic outcome was rated as excellent or good by over 90% of investigators and patients.²⁶⁻²⁸

PDT can be used in a single treatment session over large surface areas and is therefore suitable for the treatment of patients with multiple solar keratoses.

9.5.3 Squamous cell carcinoma in situ (Bowen's disease)

There have been a number of reports of the use of PDT in Bowen's disease demonstrating high levels of efficacy.

With a 64-month recurrence rate of 17% in Bowen's disease, PDT can be viewed as having an acceptable long-term efficacy comparable with more established therapies.^{31,32} The efficacy of PDT in Bowen's disease has been found to be at least equal to that of cryotherapy and 5-Fluorouracil, with fewer complications and superior cosmetic outcomes.³³⁻³⁵

Topical PDT is well suited for treatment of Bowen's disease in slow healing sites such as the lower limb. Healing is quicker in these sites and there is less risk of the development of a non-healing ulcer or an infection compared with more destructive or surgical therapies.

9.5.4 Squamous cell carcinoma

While some studies have demonstrated efficacy for the use of PDT in superficial SCC there have been relatively high recurrence rates, thus PDT cannot be recommended for the treatment of SCC at present.^{36,37}

9.5.5 Superficial basal cell carcinoma

Photodynamic therapy is a non-invasive treatment option for superficial BCC that has been specifically evaluated for efficacy and cosmetic outcome.

Three-month clearance rates with MAL-PDT range from 80% to 97% in primary superficial BCC.^{38,39}

9.5.6 Nodular cell basal cell carcinoma

With topical PDT for nodular BCC, delivery of sufficient photo-sensitiser and light to the full depth of the lesion is critical. Therefore with the use of PDT for nodular BCCs greater than 2mm in depth, the

response may be optimised by debulking the tumour prior to treatment with a curette or shave excision. Re-treatments may well be necessary in these circumstances.³⁸⁻⁴²

9.5.7 Long term results for PDT

Long term results for PDT for BCC Five-year recurrence data for MAL-PDT in superficial and nodular BCCs have become available, demonstrating that MAL-PDT has reliable long-term efficacy. PDT treatment does not complicate future surgery if it is required.

At five years clearance rates of 76% (95% CI, 59-87%) resulted from PDT as compared to excisional surgery 96% (95% CI 84-99%) in a randomised study for nodular BCC. PDT was noted as having a more favourable cosmetic outcome than surgery.⁴³

In another randomised study topical PDT outcomes compared with cryotherapy for treating superficial BCC outcomes after a five year period. There was no difference in five year recurrence rates between the two treatments (20% with cryotherapy versus 22% for MALPDT $p=0.86$). Again it was noted that the cosmetic result was excellent with MALPDT (60% versus 16% with cryotherapy $p=0.00078$).⁴⁴ Both studies support the therapeutic value of MALPDT and support its more favourable cosmetic effect.

9.6 Follow up

Any non-melanoma skin cancer treated by non-surgical means, where histological clearance has not been confirmed, should be closely monitored at regular intervals for up to three years where possible to ensure that there is no residual disease.

The basis for this is that no recurrences were seen after 3 years in the 5-year follow up studies for PDT and nodular and superficial BCC.^{43,44}

** Author/contributor P Foley has participated in clinical studies of MAL-PDT initiated and supported with grants from Galderma.*

9.7 Laser therapy

Laser therapy is used infrequently in clinical practice nowadays, and has been replaced with Imiquimod and PDT therapy to achieve superior cosmetic outcomes.

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10 NON-MELANOMA SKIN CANCER IN ORGAN TRANSPLANTATION AND OTHER CONDITIONS ASSOCIATED WITH PROLONGED IMMUNOSUPPRESSION

10.1 Introduction

Solid organ transplant recipients are at a greatly increased risk of developing non-melanoma skin cancer (NMSC), in particular squamous cell carcinomas (SCCs). The management of such patients is difficult due to the tumour load and is best managed by multidisciplinary specialist care.

10.2 Transplant dermatology subspecialty/dedicated dermatology clinic

The archetypal dedicated transplant dermatology clinic model has been well described.^{1,2} Depending on staffing and resources, such clinics are able to manage the majority of the transplant patients at their institution. Ideally, such a clinic would have surgical facilities equipped to deal with patients with large tumour loads. Education and screening of transplant recipients and pre-transplant patients would also be essential.

The advantages of such a clinic are these:

- Concentration of expertise in a facility—a specialist dermatology clinic for transplant recipients gives patients access to dermatologists, surgeons and other staff who understand the unique care required in these patients. It is likely that these clinicians would be more familiar with the latest research in prevention and management of carcinogenesis and other skin disorders in transplant recipients and subsequently more proactive in their care.
- The clinic can be set up specially to deal with clinical problems occurring in this population, for example, the need for multiple procedures per visit, and easy access to emergency visits. The main advantage is that this reduces the time-burden of skin care for transplant recipients. Since these patients often spend vast amounts of their time looking after their other medical requirements, they are more likely to neglect their skin problems if they are time-consuming or difficult, leading to more difficult management.
- Specialised transplant dermatology clinics allow teaching of dermatology trainees in the discipline, which subsequently improves the management of all transplant recipients when they are attended to in the general dermatology arena.

10.3 Multidisciplinary clinics integrated with transplant clinics

These clinics run concurrently with transplant clinics and are true multidisciplinary clinics, attended by transplant physicians, dermatologists, surgeons, oncologists and radiation oncologists and others interested in the management of skin cancers. The advantages are essentially the same as dedicated transplant clinics, with the additional benefit of input from physicians on issues such as reduction / alteration of immunosuppression in certain patients. This kind of set-up also enables education and screening of patients before they develop skin malignancy or other problems. Transplant recipients are rarely referred to dermatology before they develop these problems, which is well after the optimal time for education on risk factors, prevention and early detection of skin malignancy.

10.4 Epidemiology

10.4.1 Organ transplant recipients

Currently, there are approximately 10 000 living organ transplant recipients in Australia, the majority of whom are renal transplant recipients (RTRs)³ (ANZDATA report). NMSC, mainly SCC, are the most common post-transplant malignancy. In a study including renal and heart transplant recipients, SCCs were observed to occur 65 times more frequently than in the general population.⁴ The overall incidence of BCC was reported to be ten times higher than in the general population.⁵ The cumulative incidence of NMSCs increases with time post-transplantation, with one Australian study reporting figures of 38% at ten years and 70% at 20 years after renal transplantation. This is the highest reported incidence in the world—the adjusted risk for the development of skin cancer in the Australian population compared with the Dutch population was RR: 3.6.⁶

Another Australian study on RTRs reported the mean NMSC accrual at 1.85 tumours per person per year, increasing to 3.35 tumours after 20 years of immunosuppression.⁷ The increased skin cancer burden contributes to significant morbidity and mortality in these patients. Whereas the metastasis rate in immunocompetent individuals for NMSC is 0.01% to 0.1%, a 7% recurrence and metastasis rate has been found in RTRs.⁸ An Australian study of cardiothoracic transplant patients found that aggressive cutaneous malignancy accounted for 13 of 27 deaths at four years post-transplantation.⁹ A Swedish study has compared the mortality rate of 5931 organ transplant recipients from cutaneous SCCs compared to the general population. In this cohort of patients there were 544 SCCs in 201 patients. Of these, seven renal transplant recipients died from cutaneous SCCs. The mortality from SCC was compared with the general Swedish population and there was a highly-increased risk, with the standardised mortality ratio calculated at 52.2 (95% CI 21.0–107.6).¹⁰

There is some evidence that for SCC there was a higher risk in heart transplant recipients than in renal transplant recipients.⁴ This is thought to be due to higher doses of immunosuppression used to prevent rejection compared to renal transplant patients.¹¹ While liver transplant patients are also at increased risk of developing skin cancer,^{12,13} it has been suggested that the incidence of NMSC is lower due to a lower dose of immunosuppression compared with other organ transplant recipients.¹⁴

Table 10.1 The relative risks of developing NMSC depending on the organ transplanted

	Cumulative incidence at 5 years	Cumulative incidence at 10 years	Cumulative incidence at 20 years
Cardiac transplants ¹¹	31%	43%	N/A
Renal transplants ⁶	25%	38%	70%
Liver transplants ¹³	8%	16.6% at 8 years	N/A

Studies have shown that older transplant recipients are more likely to develop skin cancer, probably due to pre-existing sun-damage.^{15,16} However, even in the paediatric transplant population, skin cancer is the second most common malignancy after lymphoproliferative disorders.¹⁷ In a study of Dutch paediatric organ transplant recipients, the increased risk for NMSC has been reported to be 222-fold higher than the control population.¹⁸

10.5 Chronic lymphocytic leukaemia patients

Patients with chronic lymphocytic leukaemia (CLL) are at an increased risk of developing NMSC. In a large prospective cohort study following up 17 400 patients with CLL over a mean of 3.1 years, the relative risk of SCC in these patients was found to be 8.6. Several retrospective studies have also

shown an increased risk in the development of SCCs.¹⁹⁻²² The risk for BCCs is also increased, but less than that of SCCs.²¹

Retrospective studies of CLL patients who have undergone Mohs micrographic surgery have shown a higher recurrence rate for both BCC and SCC. A recurrence rate of 22% after five years was reported for BCCs in 24 CLL patients who were treated with Mohs' surgery, which was 14 times higher than the recurrence rate observed in controls.²³ For SCCs, a recurrence rate of 19% after five years was observed in 28 CLL patients, seven times greater than for normal control patients.²⁰ A retrospective case-control study also found that 28 CLL patients with SCC had a higher mortality rate compared with controls, with a cumulative five-year metastasis rate of 18% and an increased mortality rate.²⁰ Another small retrospective study of twelve CLL patients found that more than 50% of the tumours were of a high grade, with three patients having recurrent SCCs and two patients dying from SCC.²⁴

10.6 HIV patients

There is evidence that the incidence of NMSC is increased in HIV patients. A large retrospective study on 15 207 HIV positive patients found that the SIR of NMSC compared with matched controls was 6.5.²⁵ However, the ratio of BCC to SCC was greater than for the normal population. A prospective cohort study following up 724 HIV positive patients over 36 months found that 1.8% of patients developed BCC and only 0.28% developed SCC.²⁶ A retrospective case control study of 48 HIV cases followed up over four years found that the recurrence rate of SCC after surgery was 20% and that for BCC was 5.4%.²⁷

10.7 Rheumatoid arthritis patients

Rheumatoid arthritis (RA) patients are often treated with long-term immunosuppressive therapy. They can therefore be considered an archetypal non-transplant immunosuppressed population. A large retrospective cohort study of 53 067 RA inpatients found that the incidence of NMSC was increased with a SIR of 1.66.²⁸ Another retrospective study with 15 789 RA patients found that RA patients had an increased risk of NMSC with a hazard ratio of 1.19.²⁹ No studies were found that related to the prognosis of NMSC in RA patients.

10.7.1 Evidence that immunosuppressive therapy increases the risk of NMSC in organ transplant recipients

There is evidence that in organ transplant patients, the risk of NMSC is increased with increased duration of immunosuppressive treatment,^{7,30-34} the cumulative dosage of immunosuppressive treatment,³⁵ the presence of graft rejection,³⁶ the presence of triple immunosuppressive therapy versus double immunosuppressive therapy,³⁷ and higher dosage of cyclosporine A versus lower dosage of cyclosporine A.³⁸

10.7.2 Interventions effective in reducing the risk of NMSC in organ transplant recipients

There is evidence that the use of acitretin in organ transplant recipients with a previous history of NMSC is effective in reducing the number of NMSC.^{6,39-42} In a randomised controlled trial (RCT) on RTRs, photodynamic therapy had no significant effect on the development of SCC compared to placebo.⁴³ In another RCT, topical Imiquimod was found to reduce the number of NMSC in the areas treated compared to placebo, but this reduction did not reach significance.⁴⁴

There is some evidence that reduction of immunosuppression may result in improved prognosis in renal transplant patients with aggressive SCC.⁴⁵ Another study has shown that high doses of immunosuppression was associated with decreased survival in organ transplant recipients who were diagnosed with head and neck SCCs.⁴⁶ An expert consensus survey convened by the International Transplant Skin Cancer Collaborative and Skin Care for Organ Transplant Patients Europe Reduction

of Immunosuppression Task Force has recommended that reduction of immunosuppression is considered a reasonable adjuvant management strategy for transplant patients with numerous or life-threatening skin cancers.¹⁴

There is evidence that the use of newer mTOR inhibitors, such as sirolimus, has been associated with a reduced risk of development of NMSC in renal transplant recipients.⁴⁷

10.8 Management of transplant patients

The management of cutaneous SCC and BCC in these patients is no different compared to immunocompetent patients, with surgical excision being the mainstay of therapy. Follow-up intervals depend on the tumour load and can range from annual visits to three-monthly. Some patients with severe problems with cutaneous carcinogenesis may need to be seen as frequently as monthly. Other facets of management are more particular to the OTR population, and will be discussed in more detail.

10.9 Specific treatments

The concept of a field area of precancerous change predisposing to malignant transformation within OTRs mandates that these lesions will need to be managed early. In addition to utilising destructive modalities such as cryotherapy, surgical excision and curettage and excision, medical modalities that manage ‘field-change’, such as photodynamic therapy, topical 5-Fluorouracil (5-FU), and topical Imiquimod should be considered.

10.9.1 Photodynamic therapy

In RTRs, photodynamic therapy has been shown to be effective against actinic keratoses and Bowen’s disease, although the recurrence rate of these lesions was 52% after 48 weeks post treatment.⁴⁸ Photodynamic therapy has not been shown to reduce the number of cutaneous SCC in a RCT.⁴³

10.9.2 5-Fluorouracil

Recommended usage of 5-Fluorouracil in RTRs is for patients with extensive sun damage where cyclical 5-Fluorouracil is used one–two times per day for three weeks with cycles repeated every six months.⁴⁹

10.9.3 Imiquimod

In renal transplant patients, a small-scale RCT suggest a reduction in numbers of actinic keratoses and warts in RTRs, however, this reduction did not reach statistical significance.⁴⁴ There is no evidence that use of topical imiquimod increases the risk of graft rejection.

10.9.4 Radiotherapy

Surgery with or without adjuvant radiotherapy remains the treatment of choice for cutaneous SCC in these patients. However there are certain clinical scenarios in which radiotherapy may be preferable, such as diffuse, multifocal disease, which can occur in the immunosuppressed, and where surgery is impractical and would require extensive skin grafting. Other indications for definitive radiotherapy in preference to surgery are similar to those discussed in chapter 7 - Radiotherapy.

10.10 Recurrent aggressive SCC

Immunosuppressed patients can develop aggressive recurrent SCC following surgery, especially in the head and neck. For this reason these patients should be referred to specialist head and neck clinics for consideration of adjuvant treatment.⁵⁰

10.11 Prevention

There is currently no formal education program in Australia for organ transplant recipients. There are no Australian data on the attitudes and behaviour of transplant recipients regarding sun-associated behaviour. Both are worth exploring. Currently organ transplant recipients should be advised to minimise UV exposure to prevent NMSC.

Key points

- The management of skin cancers in organ transplant recipients is best undertaken by multidisciplinary specialist care.
- The risk of developing NMSC in organ transplant recipients is significantly higher than in the normal population and is increased with duration and dosage of immunosuppressive therapy.^{6,7,30-34,36}
- There is evidence that acitretin can be helpful in the reduction of NMSC in organ transplant recipients who have developed NMSC.^{6,39-42}
- Reduction of immunosuppression is considered a reasonable adjuvant management strategy for transplant recipients with numerous or life-threatening skin cancers.⁴⁹

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11 PREVENTION (INCLUDING CHEMOPREVENTION)

11.1 Introduction

Exposure to sunlight is strongly associated with the development of non-melanocytic skin cancer. Within Australia¹ and other countries such as the USA,² 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.³ In particular, squamous cell carcinoma (SCC) rarely occurs on parts of the body that are not habitually exposed.³ 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).⁴⁻⁶ 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.^{4,5,7,8}

A randomised trial of adults in Queensland showed that sunscreen reduced the risk of SCC,⁹ even in the long term,¹⁰ and reduced repeated BCC occurrence.¹¹ Randomised trials of sunscreens showed that they reduced the prevalence of solar keratoses, which are known precursors of SCC.¹²⁻¹⁴

Studies of immigrants to Australia indicate that sun exposure during childhood and adolescence is very important in causing both BCC¹⁵ and SCC.¹⁶ There is also more direct evidence of the importance of exposure early in life for SCC.¹⁶ 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.

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.

Avoid exposure

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.

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.¹⁷)

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.¹⁸ (The Australian Standards Association permits labelling of the sun protection factor of a sunscreen up to 30+¹⁸.)

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.

Window glass

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

Solariums

Solariums emit UVA and UVB radiation both known causes of skin cancer.¹⁹ Although solariums predominantly emit UVA, a proportion of UVB is added by manufacturers, often at intense radiation levels, to speed up the tanning process. Measurements taken in solarium units operating Sydney and Melbourne (n=15) had levels of radiation intensity equivalent to a UV Index between 15-38 (or up to 3 times stronger than sunlight in Brisbane at midday in summer).²⁰ There is mounting evidence of an association between exposure to artificial UVR for cosmetic purposes and the elevated risk of melanoma and SCC, with the risk of SCC double for users of artificial tanning devices compared with non-users.^{21,22} A higher risk has also been found for BCC, however the findings are inconclusive.²²

In a position statement entitled 'Dangers of solariums' by the the Cancer Council Australia, its member organisations, the Cancer Society of New Zealand and endorsed by the Australasian College of Dermatologists (August 2007), the following recommendations were made:

1. The public avoid use of any type of artificial ultraviolet (UV) radiation tanning device (solarium) for cosmetic purposes.
2. The public be informed of the risks associated with solarium use.
3. State and territory governments implement comprehensive legislation governing the operation of solariums that prohibits access for those under 18 years of age, provides for informed client consent, bans unsupervised solarium operations and ensures adequate training of staff.

Key points

- Use broad spectrum sunscreens with an SPF of 15 or greater as an adjunct to sun avoidance and other sun protective measures.^{9,13} **Level II**
- Use clothing, where possible, as the primary means of photoprotection.³ **Level III**
- Stay in the shade wherever 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 any type of artificial UV radiation tanning device.

11.2 Chemoprevention

11.2.1 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 (see *chapter 10—Non-melanoma skin cancer in organ transplantation and other conditions associated with prolonged immunosuppression*). This has been shown to affect 25% of Australian renal transplant recipients by five years and 44% by nine years post transplantation.²³ The most dramatic increase in incidence occurs in SCC though there is also an increase for BCC.²⁴ A greater proportion of the SCCs occurring in this context show aggressive growth patterns and poor prognostic features.^{25,26}

Aggressive SCCs 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.²⁴ These may play an aetiological role in the development of SCCs. 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 SCCs during treatment.²⁷⁻³⁰ 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 SCCs 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.³¹

Xeroderma pigmentosum

A trial using isotretinoin in seven patients showed a 63% reduction in skin cancers compared with the two-year period before treatment.³²

Naevoid basal cell carcinoma syndrome

Several trials of retinoids have demonstrated effective chemoprophylaxis of BCC in this context.³³⁻³⁵

Betacarotene supplementation

Trials of betacarotene in the chemoprevention of skin cancer have failed to demonstrate a beneficial effect.^{9,33,36,37}

11.3 Vitamin D

A position statement on the risks and benefits of sun exposure was developed through a collaboration of The Cancer Council Australia, the Australian and New Zealand Bone and Mineral Society, Osteoporosis Australia and the Australasian College of Dermatologists.³⁸ The material below is summarised from that position statement.

A balance is required between avoiding an increase in the risk of skin cancer by excessive sun exposure and achieving enough sun exposure to maintain adequate vitamin D levels.

There is good evidence that vitamin D is beneficial for maintaining musculoskeletal health and reducing the risk of bone fractures.^{39,40} Vitamin D deficiency in infants and children can cause rickets, characterised by muscle and bone weakness and bone deformities.

Vitamin D forms in the skin as a result of UVB exposure, but few studies have investigated the amount of UVB that people require to make enough vitamin D.⁴¹ There is evidence to suggest that prolonged sun exposure does not cause Vitamin D levels to continue to increase.⁴² Therefore, people should continue to protect themselves from overexposure, especially during peak ultraviolet radiation periods. Further scientific investigation of the amount of UV radiation exposure required to ensure adequate vitamin D levels for people of different skin types in Australia is needed.

Certain people are at high risk of skin cancer. They include individuals who have had skin cancer, have received an organ transplant or are highly sun-sensitive. These people need to have more rigorous sun protection practices and therefore should discuss their vitamin D requirements with their medical practitioner to determine if dietary supplementation rather than sun exposure is appropriate.

The National Health and Medical Research Council recommends that older adults boost their vitamin D intake by taking a daily supplement at the recommended dose or as advised by a medical practitioner.⁴³

Essentially the advice about covering up applies when the UV index is 3 or greater. Although varying across Australia, the covering up probably does not apply in the winter in the Southern States where there may be a risk of vitamin D deficiency if the summertime precautions are carried through to the winter.⁴⁴

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12 METASTASIS FROM NON-MELANOMA SKIN CANCER

12.1 Basal cell carcinoma

12.1.1 Distant metastases

Metastatic disease from basal cell carcinoma (BCC) is a rare event ranging from 0.0028 to 0.1%.¹ Lung and bone are the commonest sites. Reported experience, often only case reports or small series, indicates that cisplatin-based regimens appear to be the most effective, most recently combining cisplatin or carboplatin with paclitaxel.^{2,3} Response rates of up to 83% have been reported with a median duration among responders of 24 months.⁴ Radiotherapy may be useful in palliation of distant metastases.

12.1.2 Chemotherapy

Systemic Treatment: Systemic chemotherapy is *rarely* used in metastatic BCC or for locally advanced disease. Most regimens include cisplatin or carboplatin. Complete response rates of up to 37% have been reported in small groups of patients and control of symptoms is achieved.¹⁻¹¹

Key point

- Chemotherapy achieves responses in metastatic basal cell carcinoma and can be used to control symptoms.¹⁻¹¹

12.2 Squamous cell carcinoma

12.2.1 Distant metastases

Distant metastases from squamous cell carcinoma (SCC) are uncommon.¹² 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 two 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. Survival despite treatment is poor, with few patients surviving more than two years.

12.2.2 Chemotherapy

Systemic Treatment: Systemic chemotherapy has been used for metastatic SCC of the skin. It can be used alone or as part of multimodality therapy. The most commonly reported phase II studies use cisplatin often combined with doxorubicin.⁵⁻⁹ Other drugs include methotrexate, 5-Fluorouracil, bleomycin and vindesine.¹⁰⁻¹⁴ Objective response rates of >80% have been reported, with complete response rates of around 30%.

Key point

- Chemotherapy can be associated with high response rates in metastatic squamous cell carcinoma of the skin.⁵⁻⁹
- Appropriate radiotherapy can provide local symptom control.¹⁰⁻¹⁴

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13 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 compared with observation by the patient themselves.

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

- identify new lesions
- identify recurrent lesions
- identify metastatic disease.

The frequency and duration of review will be determined by the location of the original lesion, nature of the original pathology, histological margin of the original cancer, method of treatment of the original lesion, and the number of previous NMSC.

A number of studies have indicated the higher incidence of subsequent NMSC following an index case.

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.

13.1 Basal cell carcinoma

Approximately 44% of people will develop a second basal cell carcinoma (BCC) within three years of a BCC excision.¹ This represents a tenfold increase compared with the general population.

Local recurrence is rare (<2%)² after histological clearance, with most local recurrences occurring within two to three years, but up to 20% may occur within five to ten years.

Regional recurrence is extremely rare and does not need to be assessed clinically.

13.2 Squamous cell carcinoma

Overall, the three-year cumulative risk of a subsequent squamous cell carcinoma (SCC) after an index SCC is 18%, at least a tenfold increase in incidence compared with the incidence of first tumours in a comparable general population.¹

Local recurrence is uncommon after wide excision, but in certain circumstances there is an increased risk of recurrence (site, subtype, perineural involvement, tumour in previously treated site and primary versus recurrent lesion. See chapter 6—*Surgical treatment*). Most local recurrences occur within two–three years.

Regional recurrence is uncommon and usually occurs in patients at increased risk for local recurrence and in certain groups, including lip, ear and genitalia. The time interval to development of recurrence is usually within two years.

Key points

- For patients with histological clearance and low-risk tumours, for example basal cell carcinomas and well-differentiated squamous cell carcinomas, no specific follow-up scheme is recommended.
- For patients following non-surgical treatments, that is no histological evidence of clearance, follow up should be initially at 3 months and then 6–12 monthly for up to three years. Examination includes a full skin check for new lesions as well as inspection of the site of the original lesion.
- For moderately to poorly differentiated squamous cell carcinoma or SCC of the lip or ear follow up should be initially at 3 months and then every six months and always include examination of the draining lymph node basin.
- All patients with a previous skin cancer are advised to undergo annual skin examination for life, as part of routine health checks by their health care provider, to look for the development of new lesions.
- Following treatment of a primary tumour, all patients need to receive counselling about their risk for further primary tumours, local persistence of their previous primary tumour and for metastatic disease where appropriate. 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. In addition, advice should be given regarding standard sun protection strategies.

Important practice point

- It is appropriate for specialists to return patients to their referring GP for ongoing care when their treatment is complete. The time of return will depend on lesion and treatment and depend on agreement between the specialist and the referring GP.

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14 WHO TREATS AND PROBLEMS TO REFER

14.1 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.^{1,2} Morbidity studies highlight the very high incidence of NMSC in Australia and thus general practitioners' high workload and significant decision making for skin cancer management.³ Raasch and others raise questions about the current practice of 'excising suspicious skin lesions as informal screening for skin cancer'.^{3,4}

A recent study in the Townsville area of Queensland³ and a recent study published in the Medical Journal of Australia (MJA)⁵ confirmed the general understanding that excision biopsy is the standard preferred management for clinically diagnosed NMSC and that the lesions that were diagnosed as clinically benign were not excised or biopsied.³ The study also found 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'.⁶ In addition, there is evidence that, at least in northern Australia, infiltrative and micronodular BCCs (high-risk types for recurrence) occur more frequently on the face and neck where the likelihood of incomplete excision is increased.⁷ This highlights the importance of appropriate training and acquisition of skills for GPs. As Marks points out, with this background GPs should be able to treat a large proportion of skin cancers (see chapter 1 – Introduction).

14.2 Whether to treat or 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.⁸ 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 them by an elliptical excision with a 3–4mm margin and primary closure. Early presentation and diagnosis facilitates implementation of the process described in the *Non-Melanoma Skin Cancer: Guidelines for treatment and management in Australia* and the more experience that the GP acquires, largely 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 particular 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 for appropriately trained GPs to treat low-risk superficial BCCs, but histological diagnosis is essential before such destructive forms of therapy.⁹ 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 10mm, but also including those 10–20mm in size. A recent study of skin cancer surgery in Australia from 2001 to 2005 revealed that GPs excise the majority of skin cancers and they are increasingly using skin flaps for repair.¹⁰

Key point

- GPs need to be aware of the limitations of their skills and should be prepared to refer to an appropriate specialist, especially where more complicated repairs than side to side closure are being contemplated.

14.3 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 is a summary of potential or real problem areas:^{6,8}

- the face—for cosmetic reasons
- the face—for potential nerve damage, for example 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.

14.4 Problems to refer

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 and certainly larger than 2cm
- multiple tumours
- tumours in technically difficult sites such as the ear, tip or nose or eyelid

- 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, namely head and 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.

Good practice points

- Although complete excision of a skin cancer with a narrow margin may not affect outcome, it is better to avoid two procedures for the one lesion.
- The first opportunity for treatment is the best opportunity to achieve cure.

14.5 Follow-up

All patients treated for NMSC, whether by 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 in regard to particular concerns.

14.6 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 in all patients, not only in those at greater risk (family history, past personal history and skin type). Such an examination should be a feature of the annual check-up.

14.7 Education of GPs

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

14.8 Education of the patient

An important health promotion and educational task for GPs is to educate 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.¹¹ Clear explanation of the tumour, the management plan and the reason for any referral is simple, good and sensible medical care.

14.9 Summary

The patient's GP is the first to be confronted with a suspicious skin lesion, hence the importance of providing optimal undergraduate to graduate training for GPs, with a heavy emphasis on recognition of skin cancer. Correct diagnosis and appropriate management are linked.³

For most clinically obvious or suspicious NMSCs, the best management is excision with a 3–4mm margin followed by primary closure and then histological confirmation.

It is imperative that GPs be aware of their limitations and refer where appropriate, thus the guidelines above on when to refer to a specialist with training in skin surgery and other treatment modalities.

Good practice 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 3–4mm 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, plus or minus biopsy depending on circumstances.
- Opportunistic screening with a total body cutaneous examination on all patients should be practised.
- Young patients with sun-damaged skin need regular review.

Table 14.1 Tumour features that indicate a high risk (after R Rosen)

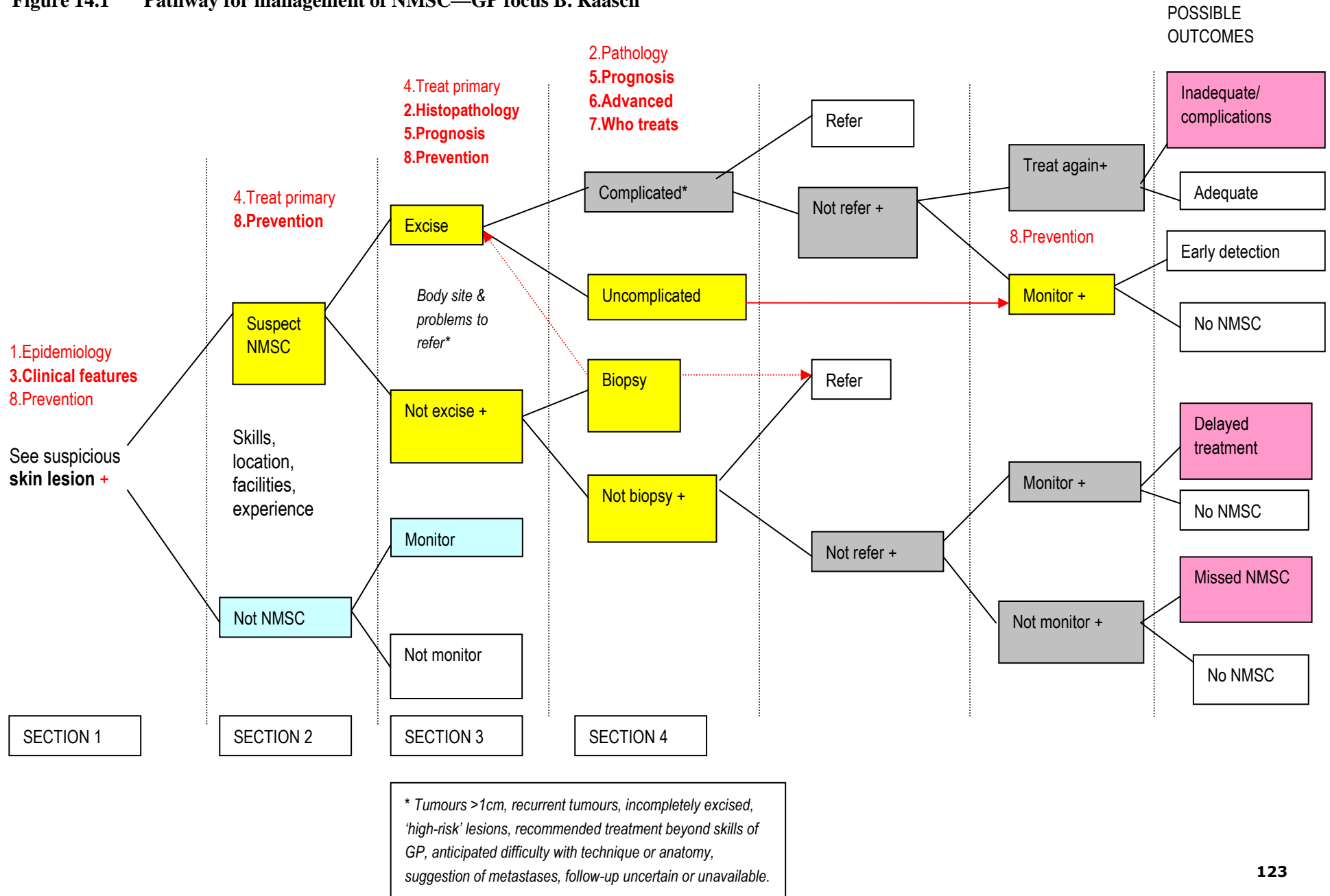
Basal cell carcinoma

- Recurrent
- Incompletely excised
- Larger than 2cm
- Poorly defined
- Morphoeic, infiltrating
- Micronodular, perineural
- Poor prognosis histology subtypes
- Inadequate normal tissue margins
- Node positive BCCs
- Special sites:
 - nose
 - eyelids
 - temple
 - pre- and post-auriculae
 - lower legs

Squamous cell carcinoma

- Recurrent disease
 - Incompletely excised lesions
 - Close histological margins (<2mm)
 - Larger than 2cm
 - Deeper than 6mm
 - Primary mucosal SCC
 - Poorly differentiated SCC
 - Perineural involvement (major and minor nerves)
 - Lymphovascular invasion
 - In-transit metastasis
 - Regional lymph node involvement
 - Rapidly growing tumour
-

Figure 14.1 Pathway for management of NMSC—GP focus B. Raasch



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15 ECONOMICS OF BASAL CELL AND SQUAMOUS CELL CARCINOMA AND RELATED CONDITIONS

15.1 The growing economic burden in Australia

Collectively, SCCs and BCCs are the most common malignant neoplasms in Australia, with an estimated incidence of 374,000 cases in 2002.¹ This represents a 32% increase from previous estimates in 1996.² Despite many of these cases being amenable to cure and hence not life-threatening, 390 deaths were reported in 2003.³ Due to their very high incidence, BCCs and SCCs are the most expensive cancers to the Australian health system where treatment costs were estimated at \$264 million in 2000-01⁴ (or approximately \$345 million in current dollars). This total cost figure comprised Medicare Australia reimbursements for GP and specialist visits (31%), pathology & imaging (23%), private and public hospital visits (primarily outpatient and day surgery)(45%) and prescribed pharmaceuticals (0.4%).⁴ It also encompassed private medical services within hospitals (e.g., dermatology outpatient clinics). These figures appear to over-estimate current hospital-based treatment for BCCs and SCCs however as the demand for dedicated dermatology services is outstripping supply.⁵ This is evident from the rapid growth of open-access skin cancer clinics, employing GPs who focus on skin cancer management.

The Australian Government invests increasing health resources in the diagnosis and treatment of skin cancers. From 1993/94 to 2001/02, treatment expenditure rose in real terms by 24% for BCCs and SCCs.⁴ More recent online Medicare Statistics data show that costs per 100,000 persons for surgical BCC and SCC excisions, by state, rose 15-34% between 2000-2006 with the highest increase seen in Queensland. The total expenditure for BCC/SCC excisions in 2006-07 was over \$58 million, while expenditure on topical creams was \$1.3 million⁶ and on Mohs surgery, \$2.4 million.⁷ The annual volume of Mohs surgery procedures during 2007 was 6,452 nationally.⁷ Beyond Medicare Australia, costs to health insurers and out-of-pocket expenses to consumers are unknown; hence the magnitude of the treatment of basal cell and squamous cell cancer to these additional co-payers of health care is also unknown.

It is important to note that the costs of malignant skin lesions are likely to represent only a small fraction of all the resources consumed in the health system for benign lesions mentioned in this document. This is partly due to newer treatment procedures used in private practice (e.g. photodynamic therapy) that are not captured by national administrative databases. It is also due to the reimbursement available through Medicare Australia to physicians for various treatments of skin lesions (benign and malignant) and of photo-damaged skin. Some treatments for skin cancers and for benign lesions such as solar keratoses are the same (i.e. cryotherapy, topical creams). Widespread treatment of these benign lesions has the potential for benign lesions to become an economic burden.

15.2 Medicare Australia costs per lesion and per individual

In 2001, the Australian Institute of Health and Welfare reported the estimated cost to remove a keratinocytic skin cancer was \$700.⁴ However, it is unclear if this included the overall management costs including not only surgical excision, but also costs of physician consultations, pathology and follow-up medical care. Table 15.1 provides the Medicare reimbursements (November 2007) for consultations, procedures and topical medications used in the management of skin cancer. The average number of GP visits per lesion was typically three.⁸

Table 15.1. Medicare reimbursement for SCC and BCC services (MBS November 2007)

Medical service	Medicare Item #.	Medicare Item cost \$	Approx. % lesions by treatment modality
First visit GP (up to 20 mins)	23	\$32.80	-
First visit Specialist	104	\$77.25	-
Biopsy	30071	\$47.15	-
Pathology – level 3 complexity	72816-72817	\$87.10-94.75	
Excision - BCC/SCC	31255-31290	\$140.75-285.10	78-83% ^{1,8,9}
Cryotherapy	30202	\$43.65	8-11% ¹
- 10 or more lesions	30203	\$153.75	
Curettage or diathermy	30196	\$114.05	9-10% ¹
- 10 or more lesions	30197	\$397.40	
Cream -Imiquimod 5% (12 sachets)			
Aldara ^{®a}	2546B, 4559Y	\$158.97	1.2% ⁸
Cream 5-Fluorouracil (20g) Efudix ^{®b}	4222F	\$49.40	1.2% ⁸
Radiotherapy	15000	\$38.45	0.25-0.63% ¹
- repeated fields up to 5	15003	\$15.45	
Flap repairs	45200-45206	\$256.80- 346.40	0.01-1.63% ¹⁰
Wedge excision	45665	\$294.45	0.06% ¹⁰
Graft	45445-45448	\$339.55-502.65	0.16% ¹⁰
Micrographically controlled serial excision (Mohs surgery)	31000-31002	\$524.55-\$786.90	0.8% ⁸
Follow-up visits GP	23	\$32.80	-
Follow-up visits Specialist	105	\$38.80	-

a. Available through the PBS and Repatriation PBS and for patients with biopsy-confirmed primary superficial BCC, previously untreated. Patients not meeting this criteria will face a private payment of up to \$180.00.

b. Available through the Repatriation PBS (to war veterans only).

As opposed to ‘cost per tumour’ estimates, there is little information available on the cost of keratinocytic skin cancers per *individual*. For the high proportion of skin cancer patients who have multiple occurrences of primary skin cancer a year, annual costs per patient will be substantial. Recent analyses of a Queensland community-based cohort study that monitored participants for over 12 years till 2004, have shown person-based costs of managing skin cancers (incurred by Medicare Australia) ranged from approximately \$236 to \$11,498 (median \$656).¹¹ The cohort consisted of 33 persons with ≥ 5 cancers and associated average costs of \$3,368.¹¹ Costed resources included those for diagnosis, treatment, pathology and GP visits. In contrast, the average medical cost per tumour was \$445 (range \$131-997).¹¹ In this context, medical costs for persons affected with multiple skin cancers over time are comparable with the lifetime health system costs of melanoma (\$3,341) and approaches that for other major cancers (e.g., breast \$11,897, kidney \$15,892⁴). When solar keratoses are treated, mainly by cryotherapy, the overall management cost is between \$55-250 per patient, depending on the complexity of the case,¹² and this will substantially increase costs per patient if the same individuals are affected by both SKs and skin cancers.¹³

15.3 Patient out-of-pocket expenses

Out-of-pocket expenses to consumers for skin cancer treatment are not documented. Individuals treated by their GP or in GP-operated skin cancer clinics are likely to be financially protected if the GP bulk-bills, as the majority currently do (77%)¹⁴ or if they are treated in public hospitals. Currently (2008), the Pharmaceutical Benefits Scheme (PBS) and the Veterans Affairs (VA) subsidise patients for imiquimod 5% (12 sachets by Aldara[®]) and 5-fluorouracil (Efudix[®]) at \$31.30 and \$5.00 in selected cases (see Table 15.1). However, for newer non-surgical or specialist treatments (methyl aminolaevulinate photodynamic therapy [MAL-PDT], Mohs micrographic surgery, flap repairs) that

are more likely to be performed by medical specialists in private clinics, out-of-pocket costs will be significantly higher. Consumers are not presently subsidised by Medicare Australia for MAL-PDT while Mohs surgery is subsidised at \$524.55-\$786.90, depending on the number of sections excised.⁷ Again, out-of-pocket expenses are likely to be substantial in patients with multiple lesions over time. Patient out-of-pocket expenses should not be ignored in the consideration of treatment options as trends in Australia suggest that health care co-payments by consumers, in general, are rising quickly¹⁵ and may be particularly distressing for patients with several concurrent health conditions.

15.4 Cost-effectiveness of treatment options for non-melanoma skin cancers (NMSC)

Cost-effectiveness studies evaluate the costs and health effects of different options for health care interventions and provide information on whether the option in question represents good value for money. Present understanding of the cost-effectiveness of treatments for NMSC is limited¹⁶ since there have been few formal economic evaluations of different treatment modalities for NMSC or related conditions. These assessments are further complicated by the fact that the generic outcome typically used in economic evaluations, 'quality-adjusted life-years', is largely irrelevant because NMSC are generally non life-threatening and quality of life concerns are unknown. A number of people who have multiple cancers every year or who suffer (e.g. facial) deformities where skin cancers are excised will certainly have their quality of life affected. Existing quality-of-life tools are likely to be insensitive to the aesthetic concerns many patients with NMSC excised are likely to face¹⁷ and this is an area of emerging research.

To date only three studies have comprehensively evaluated the cost-effectiveness of newer treatment modalities for NMSC, including MAL-PDT,¹⁸ imiquimod 5% cream¹⁹ and Mohs surgery²⁰ in comparison with surgical excision. Caekelbergh *et al*¹⁸ in Belgium examined the cost-effectiveness of MAL-PDT compared with surgical excision for nodular and superficial BCC and compared with cryotherapy for solar keratoses. Patients comprised those with nodular BCC suitable for surgical excision and superficial BCC suitable for cryotherapy situated in the H-zone if small or elsewhere if large, while patients with solar keratoses had lesions larger than 5mm in diameter on the face or scalp. MAL-PDT was found to have acceptable cost-effectiveness within the Belgium health system compared with surgical excision for nodular and superficial BCC.¹⁸

In Spain, the cost per patient cured (i.e. 100% tumour clearance) was analysed following treatment with imiquimod 5% cream, (applied 5 times per week for 6 weeks requiring 36 sachets), versus excision, in patients with single superficial BCC smaller than 2 cm (n=209). The efficacy of topical imiquimod used in the economic model was 82% at one year.²¹ Imiquimod was found to reduce the cost per patient cured compared with surgery in both dermatology and non-dermatology services and was deemed a cost-effective alternative within the Spanish health system.¹⁹ However, a limitation of the study was that the costs of treating the failures and follow-up of possible failures were not included.

Compared to surgical excision, Mohs micrographic surgery involves more extensive resource use for operative time and tissue processing events. The variability in costing estimates for this technique may arise due to different practice styles and surgeon's experience in addition to tumour characteristics of size, site and depth with costs rising with higher numbers of stages required (see Table 1).²² However, generally Mohs surgery is known to be significantly more expensive compared to surgical excision due to personnel costs arising from longer theatre time.^{20,23-25} Two cost-comparison studies in the US suggested that there were no significant differences in costs between Mohs surgery and surgical excision for BCCs, both undertaken by specialist surgeons,^{23,24} while in contrast a large prospective study in The Netherlands found significantly higher costs for Mohs surgery over 30 months.²⁵ However, without also assessing the health outcomes alongside costs, these studies are limited in informing decisions about which option represents value for money. A full economic evaluation by

Essers *et al.* (2006) in The Netherlands concluded that Mohs surgery was not cost-effective in comparison to surgical excision²⁰ for recurrent and primary BCC on the face due to the high cost of Mohs surgery but relatively small gains in health benefits. There have been published comments discussing the deficiencies of the above two articles (the authors themselves, Hruza G. (Journal Watch Dermatology March 28, 2006), Otley, C. (Cost Effectiveness of Mohs Micrographic Surgery Versus Surgical Excision for Basal Cell Carcinoma of the Face. *Arch Dermatol* 2006;142:1235-7) and the Guidelines for the Management of Basal Cell Carcinoma 2007 by the British Association of Dermatologists Therapy Guidelines and Audit Subcommittee). As an example the cost-effectiveness ratio was largely affected by the small difference in recurrence rates, that is recurrence rates were 1.9% for Mohs surgery and 2.8% for surgical excision for primary BCC at 30 months (difference 1%) and 0% for Mohs surgery and 3.2% surgical excision for recurrent BCC at 18 months. These follow-up times are too short to fully capture the longer-term recurrence rates of BCC.²⁰ The recurrence rates quoted for surgical excision in the Smeets and Essers' articles are significantly lower than larger published studies (Rowe, Carroll and Day. Long Term Recurrence Rates In Primary BCC: Implications For Patient Follow Up. *J Dermatol Surg Oncol* 1989 March; 15(3):315-28). However, despite the deficiencies of the Essers study it is the only comprehensive economic evaluation of Mohs surgery and therefore evidence for cost-effectiveness remains inconclusive. Unfortunately at this point in time there are very few comprehensive economic evaluations for any of the skin cancer treatments.

The interpretation of these emerging economic findings and their relevance in an Australian context remain unclear. The abovementioned studies report on resource utilisation and associated costs that reflect different healthcare systems and clinical practices. For example, in the US and Europe, significantly higher surgical excision costs are experienced compared with those in Australia because they are performed by private dermatologists.²⁶ Longer-term efficacy outcomes beyond one-year are likely to be important in Australia where persons typically experience multiple NMSC as above, and the associated treatment costs may be substantial.¹¹ In addition, no study has compared the cost-effectiveness of the newer treatment options when traditional surgical excision is not possible. In Australia, a submission to list MAL-PDT (Metvix[®]) on the Pharmaceutical Benefit Scheme, specifically for persons where surgical excision is inappropriate, was rejected in 2005. This was due to the lack of available rigorous research supporting its efficacy compared with current treatments and to a weak proposal of its economic worth.²⁷

15.5 Investment in skin cancer prevention

Carter, Marks and Hill²⁸ reported the potential cost-effectiveness of a national primary prevention program for skin cancer in Australia, based on the SunSmart campaign in Victoria. Their analysis was based on a 20-year national health promotion campaign with modelled time lags of 5 and 15 years before any reductions in deaths from melanoma and BCC respectively, occurred. On a per capita basis, the national investment in SunSmart was approximately 14c per person nationally.²⁸ While the cost per life-year saved was quite low when only the costs of the campaign to government were included in the cost of the program (\$1,360 per life-year saved with no cost offsets for treatment cost savings), it was considerably higher when private costs for sunscreen and hats were included (\$25,134 per life-year saved). Avoidance of deaths from melanoma constitute the major source of health benefits in this analysis however, cost savings for avoided treatment of NMSC and of solar keratoses were included in the cost-analyses.

A cost-effectiveness analysis of sunscreen use has been undertaken using primary data from a 1992-1996 randomized controlled trial, the Nambour Skin Cancer Prevention Trial,^{29,30} with 8-year follow-up data. The intervention involved sunscreen being distributed to half the participants who were randomised to daily application of sunscreen to their hands, arms and face for 4½ years. The remainder of the participants applied sunscreen at their usual discretion. The sunscreen intervention was estimated to cost society an extra ~\$84 per skin cancer prevented (i.e. BCC or SCC) over 12 years.¹¹ This intervention yielded considerable cost-savings to the Government. Consequently, the

promotion of regular sunscreen use in Australia is seen as a cost-effective and practical strategy in the prevention of skin cancers and solar keratoses.^{29,30} However, this study highlighted the effort and expense incurred by individuals beyond the trial period for their ongoing sunscreen use and purchases to maintain habitual sun-protective behaviours.

Key points:

- Basal cell and squamous cell carcinomas are collectively the most expensive cancer type within the Australian health system, yet the true economic burden is likely to be substantially higher than previously estimated treatment costs.^{1,2}
- Persons affected by multiple skin cancers are likely to incur substantial out-of-pocket expenses.¹⁵
- International economic evaluations on newer treatment modalities for SCC and BCC are emerging but have unclear relevance for Australian skin cancer medicine.²⁰
- At this time, it is unclear whether newer treatment modalities are cost-effective within Australia until findings from well-designed studies emerge.²⁷
- Primary prevention remains an important and cost-effective strategy for control of skin cancer in Australia.²⁸⁻³⁰

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16 QUESTIONS AND CONCERNS THAT MAY ARISE DURING CONSULTATION

Non-melanoma skin cancers are so common in this country that all of us, health carers included, are at least potential patients. It may be useful, therefore, to give some consideration to the perspective of patients. By doing this practitioners may be stimulated to think about all the queries and concerns they and their lay friends would have as patients, and thus become better prepared to deal with such matters should they arise or should they be raised during a consultation or when speaking to an audience about skin cancers. This in turn should help achieve the objectives of this guide, namely to promote optimal care of these conditions and to meet the requirements of patients.

The concerns of patients, or potential patients, 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 topics practitioners and care-providers are concerned about—and which this guide addresses—but slanted away from the ultra-technical, specialised and statistical aspects of the subject towards what is personal, practical and understandable by laypeople, not only the curious, or affected subjects themselves, but also their children, other family members and friends in the community.

Patients 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 patients 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 others that might be relevant.

What follows could be regarded as an incomplete checklist of peoples’ concerns. They are loosely categorised and abbreviated: key words, thought-provokers, and 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.

16.1 Specific topics

16.1.1 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? What are the 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, over the years I have plastered many things—such as oils, soap, lotions, perfumes, sprays—on my skin, and still do. Could any of these do harm?

16.1.2 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, ultraviolet 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 on cloudy days, reflected sun and wind can be harmful? Am I safe in deep shade or under shade cloth, 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, pesticides, paints and other products I use in the home and outside? What protects and what harms?

16.1.3 Diagnostic pointers

What should I be on the lookout for? How do I detect and assess anything that 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 keeping a photographic record of them, 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.

16.1.4 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 into account Medicare, 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?

16.1.5 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 my GP 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.

16.1.6 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 from 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?

16.2 In general

Patients 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 patients can help them become cooperative, compliant, satisfied people rather than reluctant, critical, disgruntled patients—a happy outcome for the practitioner as well as the patient. However, patients 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 is limited, and that probabilities, not certainties, are the general rule in matters of health, especially in regard to predicting the actual outcome of treatment and prognosis.

In this area of health it may also be helpful to refer patients and potential patients to one 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

Sixth Edition
2002 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:

<i>T categories</i>	Physical examination
<i>N categories</i>	Physical examination and imaging
<i>M categories</i>	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, i.e. cartilage, skeletal muscle or bone

Note: 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. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

G Histopathological grading

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

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

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

5 Richmond Avenue
FAIRBAIRN ACT 2609
Tel: (02) 6257 9999
Fax: (02) 6257 5055
Email: reception@actcancer.org
Website: <http://www.actcancer.org/>
CEO: Ms Joan Bartlett

The Cancer Council New South Wales

PO BOX 572
KINGS CROSS NSW 1340
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

PO BOX 42719
CASUARINA NT 0811
Tel: (08) 8927 4888
Fax: (08) 8927 4990
Email: admin@cancernt.org.au
Website: <http://www.cancercouncilnt.com.au/>
CEO: Mrs Helen Smith

The Cancer Council Queensland

PO BOX 201
SPRING HILL QLD 4006
Tel: (07) 07 3258 2200
Fax: (07) 07 3257 1306
Email: info@cancerqld.org.au
Website: <http://www.cancerqld.org.au/>
CEO: Dr Jeff Dunn

The Cancer Council South Australia

PO BOX 929
UNLEY SA 5061
Tel: (08) 8291 4111
Fax: (08) 8291 4122
Email: tcc@cancersa.org.au
Website: www.cancersa.org.au
CEO: Associate Professor Brenda Wilson

The Cancer Council Tasmania

GPO BOX 1624
HOBART TAS 7001
Tel: (03) 6233 2030
Fax: (03) 6233 2123
Email: infotas@cancertas.org.au
Website: <http://www.cancertas.org.au/>
CEO: Mr 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
CEO: Professor David Hill AM

The Cancer Council Western Australia

46 Ventnor Avenue
WEST PERTH WA 6005
Tel: (08) 9212 4333
Fax: (08) 9212 4334
Email: please see website for where to direct specific email enquiries
Website: www.cancerwa.asn.au
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APPENDIX 3 MEMBERSHIP OF THE AUSTRALIAN CANCER NETWORK MULTIDISCIPLINARY WORKING PARTY AND CONTRIBUTORS

Membership of the Australian Cancer Network Working Party to revise Management of Non-melanoma Skin Cancer Guidelines (2002)

Professor Robin Marks AM (Chair)	Dermatologist—Melbourne
Professor Bruce Barraclough AO	Medical Director, ACN—Sydney (<i>until 31 December 2007</i>)
Professor Richard Bloom	Plastic surgeon—Melbourne
Dr Alvin Chong	Dermatologist—Melbourne
Professor Christopher Commens	Dermatologist—Sydney
Dr Brian De' Ambrosis	Dermatologist—Brisbane
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Dr Gerald Fogarty	Radiation oncologist—Sydney
Dr Peter Foley	Dermatologist—Melbourne
Dr Louisa Gordon	Epidemiologist/ Economist—Brisbane
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A/Professor Michael Henderson	Oncology surgeon—Melbourne
Dr Peter Linton	General practitioner, consumer—Melbourne (<i>until March 2008</i>)
Professor John Murtagh AM	General practitioner—Melbourne
Professor Ian Olver	Medical oncologist—Sydney
A/Professor Sandro Porceddu	Radiation oncologist—Brisbane
Professor Richard Scolyer	Anatomical pathologist—Sydney
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Special thanks to:

- Members of the Goulburn Valley Division of General Practice Ltd. The following members of the Division met and advised the Working Party through a GP Focus Group – regarding salient features for mass distribution of GPs:

Dr Sue Furphy (Convenor), Dr Simon Sneyd, Dr Neville Leslie, Dr Solange Adad, Dr Nanette De Mestre, Dr Satpal Singh, Dr Peter Poon, Dr Pratap Acharya, Dr Tianming Wang, Dr Kyi Wann.

- Ms Laura Buccini—University of Wollongong, for organising literature searches and systematic review of the evidence.
- Ms Christine Vuletich and Alice Winter-Irving—ACN Secretariat, for their preparation of a series of drafts and for finalising the manuscript.

Draft “Basal cell carcinoma, squamous cell carcinoma (and related lesions) – a guide to clinical management in Australia” Public Consultation May – June 2008

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APPENDIX 4 GUIDE DEVELOPMENT PROCESS

Basal Cell Carcinoma, Squamous Cell Carcinoma (and related lesions)—A Guide to Clinical Management in Australia has been developed as a consensus document in a revisionary process from ‘Non-melanoma skin cancer: Guidelines for treatment and management in Australia’ endorsed by the NHMRC in 2002.

Purpose, scope and development process of the ‘Guide’

The funding to develop the revision required its completion within a one-year period, this was extended to December 2008. The standard process required by the NHMRC could not be met in this time frame. The reason to produce the ‘Guide’ was to update the information content and direct attention towards and assist in the improvement of the education and practice of general practitioners in this area of practice, which ‘represents a huge public health problem among Australians’, while the cost of managing patients who are affected with these diseases ‘causes a large burden on the Australian health care system’.

Working Party

A multidisciplinary Working Party was established with the assistance of specialist Colleges and specialist societies in dermatology, pathology, epidemiology, surgery, plastic surgery, health economics and general practice, and also involving consumers (*see Appendix 3 and Introduction*). The Working Party reached **consensus** on each chapter.

The initial meeting was held in July 2007 by telephone when Professors Marks, Reeve and Green developed a strategic plan for the development process. Following recruitment of members, **the Working Party met in September 2007**. A decision was taken to develop the ‘guide’ in consensus mode. The Working Party embraced the observations that an aide such as the ‘guide’ can promote ‘improved consistency of care and patient outcomes’.^{1,2} A further aide is to be developed in the form of a desktop card addressing the main features of the ‘Guide’ and summarising special advice on referral and specific points of management.

The Working Party decided that the work plan would embrace development of a ‘guide’:

- To assist practitioners in decision making in relation to non-melanoma skin cancer.
- To promote better clinical assessment on non-melanoma skin cancer and assure quality of clinical care.
- To address cost factors and effectiveness to heighten awareness of this element of care.
- To ‘provide better understanding through education of all involved’ in the care of non-melanoma skin cancer.

The Working Party focused on outcomes and assessed the best available scientific evidence. The Working Party then adjourned to address these components of non-melanoma skin cancer management.

At its **meeting in December 2007** the Working Party discussed authorship of the components of the Guide. It sought systematic review of chapters 6, 7, 12, 15 (1997–2007) and 10 (1982–2007) and these were done by Ms Laura Buccini and associates of the Graduate School of Public Health, School of Health Sciences, University of Wollongong. The remaining chapters were all to be carefully reviewed and revised by those designated to do so.

At its **meeting in February 2008** the Working Party reviewed manuscripts for all chapters and an extra chapter to address immunosuppressed patients. Several consultant specialists were asked to review special factors. The Chair and Convenor met three more times face to face and significant electronic and telephone contact was made until a penultimate draft was produced.

Public submissions were invited – an advertisement being placed in *The Weekend Australian* on 10 May 2008 with submissions due on 10 June 2008.

A meeting of the full Working Party was held on **25 June 2008** at Melbourne airport. This meeting reviewed the Guide, fine tuned the points raised by Public Consultation and suggested that General Practitioner views be sought. A decision was taken to ask the General Practice Division in the Goulburn Valley to offer advice. The document or individual chapters proceeded to consultants for review.

Most data was level IV evidence and where a higher level was determined it is acknowledged.

Designation of levels of evidence

- I Evidence obtained from a systematic review of all relevant randomised controlled trials.
- II Evidence obtained from at least one properly designed randomised controlled trial.
- III-1 Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
- III-2 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.
- III-3 Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
- IV Evidence obtained from case series, either post-test or pre-test and post-test. In effect we listed all level III—as III regardless of category.

These levels of evidence ratings have been adapted from US Preventative Service Task Force (1989), *Guide to clinical preventative services: an assessment of the effectiveness of 169 interventions* (ed M Fisher), Williams and Williams, Baltimore, Appendix A, p388.

The process of developing the Guide was informed by *A guide to the development, implementation and evaluation of clinical practice guidelines*, NHMRC Canberra 1999.

The substance of the document is presented as Key Points and more practical data as Good or Important Practice Points.

References

- 1 Haines A, Donald A. Making better use of research findings. *BMJ* 1998; 317(7150):72–75.
- 2 Thomas LH, McColl E, Cullum N, Rousseau N, Soutter J, Steen N. Effect of clinical guidelines in nursing, midwifery, and the therapies: a systematic review of evaluations. *Qual Health Care* 1998; 7(4):183–191.

ABBREVIATIONS

ACM	Aggressive cutaneous malignancies
BCC	Basal cell carcinoma
C	Curettage
CI	CINHAL
CLL	Chronic lymphocytic leukaemia
CO	Cochrane
CT	Computed tomography
CTTR	Cardiothoracic transplant recipient
DFTC	Double freeze-thaw cycle
HPU	Human papilloma virus
HTT	Halo thaw time
IC	Immunoincompetent
IEC	Intra-epidermal squamous cell carcinoma (Bowen's disease)
INR	International Normalised Ratio
IS	Immunosuppression/ immunosuppressed
KA	Keratoacanthoma
M	Margin treated beyond clinically visible tumour
M	Medline
mm	Millimetres
MRI	Magnetic resonance imaging
NMSC	Non-melanoma skin cancer
OA	Osteoarthritis
OR	Odds ratio
OST	Open spray technique with liquid nitrogen
OTR	Organ transplant recipients
PDT	Photodynamic therapy
PNI	Perineural invasion
PNS	Perineural spread

RA	Rheumatoid arthritis
RCT	Randomised control trial
RT	Radiotherapy
RTR	Renal transplant recipient
S	Shave excision
SCC	Squamous cell carcinoma
SD	Science Direct
SFTC	Single freeze-thaw cycle
SIR	Standardised incidence ratio
sig	Significance/ significant
SK	Solar keratosis
SMR	Standard mortality ratio
SPF	Sun protection factor
TCN	Thermocouple needle
TTT	Total thaw time
UVA	Ultraviolet radiation (320–400nm)
UVB	Ultraviolet radiation (290–320nm)
WLE	Wide local excision
XP	Xeroferma pigmentosum

GLOSSARY

Basosquamous or Metatypical	Terms used for basaloid tumour that 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.
Cockayne syndrome	Rare autosomal recessive congenital disorder, characterised by growth failure and sensitivity to sunlight.
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.
Electrodessication	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.
Ferguson-Smith syndrome	Autosomal dominant – keratoacanthomas appear during adolescence, spontaneously involute and recur many times.
Gorlin's syndrome	(Nevoid basal cell carcinoma syndrome) autosomal dominant – multiple BCC at an early age.
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	A highly specialised procedure where there is careful orientation and mapping of the specimen at surgical removal, followed by the horizontal frozen sectioning of the tissue. This results in topographic and microscopic analysis of the whole outer margin of the specimen. A key component of the technique is that the proceduralist removing the tumour also examines the histological slides. The Mohs procedure aims to ensure complete tumour clearance while maximizing normal tissue conservation and function. Once the tumour clearance has been confirmed, the wound is closed. (Corrigendum)
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.

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