Cancer Council Australia

Clinical practice guidelines for keratinocyte cancer

The guideline recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on
7 November 2019 under section 14A of the *National Health and Medical Research Council Act 1992*.

Endorsed by Endorsement validity: 31 July 2020 – 30 June 2023

Download: Short-form keratinocyte cancer guidelines (recommendations only)

Please also see the following files:

- Administrative report
- Dissemination plan

This is a wiki-based guideline. A PDF version of the recommendations in the guideline (short-form guideline), has been made available for download using the link above.

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1 Foreword

These new keratinocyte cancer guidelines were put together by a multidisciplinary working party group of volunteers to revise the 2008 guidelines.

The term keratinocyte cancer encompasses skin cancers formerly known as non-melanoma skin cancers, comprising basal cell carcinoma and cutaneous squamous cell carcinoma.

These guidelines are of benefit to the general practitioners, the skin cancer clinic doctors, and also specialists who undertake therapy for patients with keratinocyte cancers in Australia.

The two areas where there has been a significant change are the treatment of advanced keratinocyte cancer with radiotherapy and immunotherapy, and also the role of immunosuppression in the development of keratinocyte cancers.

I would especially like to thank the members of the working party, the additional authors and co-authors of the chapters, and also Tamsin Curtis from Cancer Council Australia for overseeing and encouraging the authors in their revision of the guidelines.

I would also like to thank Jenni Harman the medical writer and editor for her invaluable help in putting these new guidelines together into a clear and readable format.

Stephen Shumack OAM FACD

Clinical Associate Professor, University of Sydney

Chair, Keratinocyte Cancer Guidelines Working Party

2 Introduction

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2.1 Introduction

Keratinocyte cancer (KC), formerly known as non-melanoma skin cancer,* comprises basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC).

Keratinocyte cancers cause approximately 560 deaths each year in Australia and are the reason for an estimated 939,000 treatments, based on 2015 data.[1] Keratinocyte cancers accounted for 8% of all health spending on cancer (excluding cancer screening) in Australia in 2008–2009, and Medical Benefits Schedule reimbursements for KC diagnosis, treatment and pathology cost an estimated $703 million in 2015. Thus, these mostly non-fatal cancers represent a large public health problem with disproportionately high costs.

2.2 Purpose and scope

The aim of these guidelines is to provide clear guidance on the diagnosis and management of KCs in the Australian population, based on current scientific evidence, in order to reduce morbidity (and, potentially, mortality) from these cancers.

These guidelines update the 2008 edition by reviewing literature published in the interim and incorporating new data. They provide up-to-date evidence-based recommendations, relevant to Australians and the Australian health care system, on skin cancer prevention and early detection, including the prevention and treatment of KCs in people at increased risk of the disease. The 2019 edition includes new information on advances in therapy, especially in the Metastatic disease and systemic therapies section. Sections on Organ transplantation and conditions associated with immunosuppression, Radiotherapy and Surgical treatment have been significantly revised. Guidance on managing KCs in patients who have undergone organ transplantation has been added throughout the guidelines, to aid clinicians who are increasingly involved in the care of these patients. A new section on Early detection has also been added.

2.3 Intended users

These guidelines are intended for use by health professionals, including those advising the general population about risk and prevention of KCs, those advising patients who are at increased risk of KCs (e.g. due to immunosuppression or a previous history of KC) about the need for and timing of future skin checks and follow-up, and all those involved in making the diagnosis or treating patients with KC.

They may also be of interest to policy makers and to educators providing training in medicine or other health sciences.

These guidelines are not intended as health information for the general public.

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2.4 Target populations

These guidelines cover the complete range of Australian adult populations and are an appropriate reference for health professionals treating adults of any age group.

It includes guidance on the asymptomatic general public, people at increased risk of KC, patients with KCs and related tumours of any stage, and patients who have received treatment for KC.

In implementing the recommendations, clinicians should consider the specific needs of patients with KC from culturally diverse groups, including younger people, Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities.

For each systematic review, the search strategies specifically included terms designed to identify data relevant to Aboriginal and Torres Strait Islander peoples. However, the literature searches did not identify any studies specifically relevant to Aboriginal and Torres Strait Islander populations that met the inclusion criteria.

Aboriginal and Torres Strait Islander peoples and people with darker skin are also at risk of developing KCs (albeit to a much lesser extent than those with lighter skin types), and it is important to deliver optimal care for all patients. The Optimal care pathway for Aboriginal and Torres Strait Islander people with canceris a useful reference resource for clinicians.

2.5 Healthcare settings in which the guideline will be applied

These guidelines apply to the range of public and private healthcare settings in which services are provided for the target populations. These include:

- general practice
- skin cancer clinics
- hospitals
- specialist clinics
- imaging services
- pathology services
- allied healthcare services.

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2.6 Funding

The Australian Government Department of Health commissioned and funded Cancer Council Australia to undertake the current revision and update of these guidelines.

2.7 NHMRC approved recommendation types and definitions

These guidelines include evidence-based recommendations, consensus-based recommendations and practice points as defined by National Health and Medical Research Council (NHMRC) level and grades for recommendations for guidelines developers[2] (see NHMRC approved recommendation types and definitions in the *Summary of recommendations* section).

2.8 Methodology

The methodology adopted for this guideline revision is described in the Guideline development process and the Technical Report, which lists the clinical questions and includes detailed technical documentation.

It should be noted that throughout this guideline, unless otherwise stated, tumour stage is according to the American Joint Committee on Cancer (AJCC) cancer staging manual 8th edition[3] and Union for International Cancer Control (UICC) TNM classification of malignant tumours 8th edition.[4]

See: Appendix A TNM Staging.

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2.9 Scheduled review of these guidelines

It is inevitable that parts of this guideline will become out of date as further literature is published. Newly published evidence relevant to each systematic review question will be monitored. If strong evidence supporting a change in the guideline is published, the working party will consider if an update is required for a specific section. We recommend that the guideline should be reviewed and updated every 5 years.

2.10 Acknowledgement

The update of the guidelines was overseen by a multidisciplinary working party with input by subcommittees. We thank the members of the working party, subcommittees, systematic reviewers and all others who contributed to the development of these guidelines.

Medical writing and editing services were provided by Jenni Harman, Meducation Australia.

*The term ‘non-melanoma skin cancer' (NMSC) still appears in national data sets and reports.

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2.11 References

1. ↑ Australian Institute of Health and Welfare (AIHW). *Reports and data: Health conditions, disability & deaths (Cancer).* [homepage on the internet] Australian Government; 2019 [cited 2019 Aug 16; updated 2019 Jan 9]. Available from: https://www.aihw.gov.au/reports-data/health-conditions-disability-deaths/cancer/overview.
2. ↑ National Health and Medical Research Council. *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines.* Canberra; 2009 Available from: www.mja.com.au/sites/default/files/NHMRC.levels.of.evidence.2008-09.pdf.

3. ↑ Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, et al. (Eds.). *AJCC Cancer Staging Manual (8th edition).* Springer International Publishing: American Joint Commission on Cancer; 2017 [cited 2016 Dec 28].
4. ↑ Brierley JD, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours, 8th Edition.* Wiley-Blackwell; 2017.

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3 Summary of recommendations

The guideline recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on
7 November 2019 under section 14A of the *National Health and Medical Research Council Act 1992*.

3.1 Summary of recommendations

This is a summary of all recommendations in these guidelines, please note that some chapters do not have associated recommendations.

Recommendations and practice points were developed by working party members and subcommittee members. See NHMRC approved recommendation types and definitions table at the end of this page.

Each EBR was assigned a grade by the expert working group, taking into account the volume, consistency, generalisability, applicability and clinical impact of the body of evidence according to NHMRC *Level and Grades for Recommendations for Guidelines Developers*.[1]

Jump to:

- 7. Surgical treatment*
- 8. Radiotherapy*
- 12. Metastatic disease and systemic therapies*
- 2. Prevention
- 3. Early detection
- 4. Clinical features
- 5. Pathology
- 6. Prognosis

- 9. Cryotherapy and electrodessication and curettage
- 10. Topical treatments and photodynamic therapy
- 11. Organ transplantation and conditions associated with immunosuppression
- 13. Follow-up
- 14. The role of primary care
- NHMRC approved recommendation types and definitions
- Evidence-based recommendation grades

*__Note:__ this section is not in sequential order, those sections that were systematically reviewed (see the Technical report) and have EBRs are at the top, all other sections follow the order of the table of contents.

3.2 7. Surgical treatment

3.2.1 7.1 Considerations before selecting a surgical treatment modality

Evidence-based recommendation	Grade
EBR 7.1.1. Both surgical and nonsurgical treatment modalities can be considered for superficial and nodular basal cell carcinomas in favourable sites.	**C**

3.2.2 7.3 Optimal surgical technique for the treatment of basal cell carcinoma

Evidence-based recommendation	Grade
EBR 7.3.1. Patients with high-risk recurrent facial basal cell carcinomas should be offered wide surgical excision or Mohs micrographic surgery. Regular follow-up should be provided.	**C**

Evidence-based recommendation	Grade
EBR 7.3.2. Non-surgical treatment modalities can be considered for patients with basal cell carcinomas assessed to have a low risk of recurrence based on favourable histological type (e.g. superficial or nodular types) and favourable anatomic locations (away from unique structures).	**C**

3.2.3 7.4 Considerations when planning surgical treatment for cutaneous squamous cell carcinoma

Practice point
PP 7.4.1. Referral to a multidisciplinary team or to a specialist for assessment and treatment should be considered for patients with cutaneous squamous cell carcinomas with poor prognostic features (e.g. poorly differentiated, fibrosing or ≥20mm).

3.2.4 7.5 Post-surgical care and interpretation of the pathology report

Practice point
PP 7.5.1. When perineural invasion is reported by the pathologist, the clinician should discuss this finding with the pathologist to ascertain its likely clinical significance.

Practice point
PP 7.5.2. Preoperative magnetic resonance imaging should be considered for patients with clinical evidence of perineural involvement.

3.2.5 7.6 Protocol to manage incompletely resected basal cell carcinoma

Evidence-based recommendation	Grade
EBR 7.6.1. Incompletely excised basal cell carcinomas should be assessed and treatment selected on a case-by-case basis.	**C**

Evidence-based recommendation	Grade
EBR 7.6.2. Incompletely excised basal cell carcinomas that have high-risk features, or occur in high-risk anatomical sites, should be re-excised, where possible.	**C**

3.2.6 7.7 Protocol to manage rapidly growing tumours

Evidence-based recommendation	Grade
EBR 7.7.1. For patients with cutaneous squamous cell carcinomas with features associated with poor prognosis, wider surgical margin should be planned, adjuvant radiotherapy should be considered, and regular follow-up for locoregional or distant recurrence should be provided.	**C**

Evidence-based recommendation	Grade
EBR 7.7.2. For tumours with perineural invasion, the combination of surgery and radiotherapy is recommended when a nerve with diameter >0.1mm is involved.	**C**

Evidence-based recommendation	Grade
EBR 7.7.3. Cutaneous squamous cell carcinomas with high-risk features should be managed with wider surgical margins, adjuvant radiotherapy, and regular follow-up for locoregional or distant recurrence.	**C**

Practice point

PP 7.7.1. For patients with cutaneous squamous cell carcinoma, consider referral to a specialist or multidisciplinary team if there are any risk factors for poor prognosis, such as:

- size >2 cm in diameter
- tumour depth > 4 mm
- recurrent lesion
- high-risk anatomic location
- perineural invasion or lymphovascular invasion
- poorly differentiated subtype
- immunosuppression.

Practice point

PP 7.7.2. Patients with rapidly growing squamous cell carcinomas should be referred timely for assessment for specialised therapies or combination therapies.

3.2.7 7.8 Criteria for choosing Mohs micrographic surgery in preference to other surgical techniques

Practice point

PP 7.8.1. Mohs micrographic surgery may also be considered as an alternative to wide surgical excision in the following types of basal cell carcinoma:

- poorly defined clinical border
- infiltrating, micronodular, sclerosing, and other aggressive histological subtypes
- residual following previous treatment
- located in the H-zone of the face
- large >10mm in diameter on the face
- if utilising MMS compared to wide excision the defect size reduction would be of clinical value.

3.2.8 7.9 Surgical management of advanced cutaneous squamous cell carcinoma

Practice point

PP 7.9.1. Dermal lymphatic spread (in-transit metastasis) should be managed by wide surgical excision followed by adjuvant radiotherapy.

Practice point

PP 7.9.2. For patients with cutaneous squamous cell carcinoma, consider referral to a specialist or multidisciplinary team if there are any risk factors for poor prognosis, such as:

- size >2 cm in diameter
- tumour depth > 4 mm
- recurrent lesion
- high-risk anatomic location
- perineural invasion or lymphovascular invasion
- poorly differentiated subtype
- immunosuppression.

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3.3 8. Radiotherapy

3.3.1 8.1 Radiotherapy with or without surgical treatment for keratinocyte cancer

Evidence-based recommendation	Grade
EBR 8.1.1. Radiotherapy can be used alone in the treatment of keratinocyte cancers when surgery is not possible or the patient declines surgery.	**D**

Evidence-based recommendation	Grade
EBR 8.1.2. Radiotherapy may be used in combination with surgical excision with the aim of improving locoregional control.	**D**

Practice point
PP 8.1.1. Radiotherapy should begin within 6 weeks following surgery, as macroscopic recurrence at the start of radiotherapy will necessitate a higher dose, which is associated with a higher risk of poor cosmetic and functional outcomes.

3.3.2 8.2 Radiotherapy for basal cell carcinoma

Evidence-based recommendation	Grade
EBR 8.2.1. Radiotherapy using curative doses can be considered as an alternative to surgical excision in the definitive treatment of basal cell carcinoma if surgery is either declined by the patient or surgery is inappropriate.	**D**

Consensus-based recommendation
CBR 8.2.1. For patients with T3/T4 primary persistent or recurrent basal cell carcinoma, consideration should be given to obtaining an opinion from a radiation oncologist as part of multidisciplinary care.

Practice point
PP 8.2.1. Clinical persistence or progression of a basal cell carcinoma after a standard curative dose of radiotherapy should be confirmed in consultation with the treating radiation oncologist. The lesion should be biopsied and managed with salvage excisional surgery.

Practice point
PP 8.2.2. Patients who have undergone complete excision of basal cell carcinomas should be offered referral to a specialist skin cancer clinic (or head and neck clinic) for individual assessment and consideration of postoperative radiotherapy or additional treatment if any of the following are present: + bone invasion + rapidly growing tumour + tumour recurrence (including multifocal recurrence or multiple recurrences) + inadequate margins on excision when further surgery is problematic + perineural invasion (major and minor nerves) + lymphovascular invasion + in-transit metastases + regional nodal involvement + histological subtype associated with poor prognosis (micronodular, infiltrative or metatypical).

3.3.3 8.3 Radiotherapy for cutaneous squamous cell carcinoma

Evidence-based recommendation	Grade
EBR 8.3.1 Radiotherapy using curative doses can be considered as an alternative to surgery for cutaneous squamous cell carcinomas if surgery is either declined by the patient or surgery is inappropriate.	**B**

Practice point
PP 8.3.1 If surgical excision of a cutaneous squamous cell carcinoma is not possible, referral for a radiotherapy opinion should be considered.

Practice point

PP 8.3.2 For patients with T3/T4 primary, persistent and recurrent cutaneous squamous cell carcinomas, a consideration should be given to obtaining an opinion from a radiation oncologist as part of multidisciplinary care.

Practice point

PP 8.3.3 Postoperative radiotherapy should be considered after complete excision for high-risk cutaneous squamous cell carcinomas, including when any of the following are present:

- T3/T4 tumours
- extradermal invasion beyond subcutaneous fat, bone
- >6mm depth of invasion
- rapidly growing tumour
- recurrent disease
- inadequate margins on excision when further surgery is problematic
- poorly differentiated tumour
- perineural invasion (major and minor nerves)
- lymphovascular invasion
- in-transit metastases
- regional nodal involvement.

Practice point

PP 8.3.4 Following incomplete surgical excision of a cutaneous squamous cell carcinoma, radiotherapy can be considered as an alternative to re-excision if further treatment is deemed advisable and re-excision is disadvantageous or not feasible.

Practice point

PP 8.3.5 For recurrent and/or locally advanced cutaneous squamous cell carcinomas, the draining regional nodes must be examined (even after treatment of the primary site), because of the relatively higher propensity of cutaneous squamous cell carcinoma to metastasise, compared with basal cell carcinoma.

3.3.4 8.4 Radiotherapy for regional (nodal) metastatic disease (non-distant)

Practice point

PP 8.4.1. For patients with extensive disease, such as those with very large nodes, multiple nodes, bilateral nodes and involvement of overlying skin or fixation of nodes, perineural invasion, multimodal treatment is indicated. In these instances, or if any doubt exists on the extent or integration of treatment, preoperative assessment and opinion from a multidisciplinary team is recommended. Involvement of a head and neck surgeon, reconstructive surgeon, dental oncologist, surgical oncologist, radiation oncologist and medical oncologist may be necessary for complex cases.

Practice point

PP 8.4.2. Modern radiotherapy techniques should be considered as the modality of choice for treating the regional lymph node basin, to limit rates of significant adverse events.

3.3.5 8.8 Management of radiotherapy side effects

Practice point

PP 8.8.1. When treating a patient who has undergone previous radiotherapy, the clinician (e.g. general practitioner or skin cancer specialist) should consult the radiation oncologist on the patient's history to ascertain the dose and location of prior radiation.

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3.4 12. Metastatic disease and systemic therapies

3.4.1 12.1 Systemic therapies for advanced and metastatic basal cell carcinoma

Practice point

PP 12.1.1. Patients with locoregional metastases of basal cell carcinoma should be offered surgical excision or radiotherapy if possible. It is appropriate to check for the presence of distant metastatic disease.

Practice point
PP 12.1.2. Patients with distant metastatic basal cell carcinoma should be referred to a medical oncologist or multidisciplinary team for consideration of hedgehog signalling pathway inhibitor treatment.

3.4.2 12.2 Systemic therapies for metastatic cutaneous squamous cell carcinoma

Evidence-based recommendation	Grade
EBR 12.2.1. For patients with resected high-risk cutaneous squamous cell carcinoma, adjuvant radiotherapy to reduce the risk of locoregional recurrence should be considered.	**D**

Evidence-based recommendation	Grade
EBR 12.2.2. For patients with cutaneous squamous cell carcinoma metastatic to cervical lymph node(s) who have adverse factors such as multiple node involvement, extra-nodal extension or involved margin, neck dissection followed by adjuvant radiotherapy is recommended.	**D**

Evidence-based recommendation	Grade
EBR 12.2.3. For patients with cutaneous squamous cell carcinoma metastatic to the parotid, surgery or radiotherapy of the ipsilateral neck is recommended, even if clinically uninvolved.	**D**

Evidence-based recommendation	Grade
EBR 12.2.4. Patients with resected primary cutaneous squamous cell carcinoma should be assessed for high-risk features and referred for consideration of adjuvant treatment, if appropriate.	**D**

Evidence-based recommendation	Grade
EBR 12.2.5. Do not routinely offer carboplatin chemotherapy in addition to adjuvant radiotherapy for patients who have undergone excision of high-risk head and neck cutaneous squamous cell carcinoma.	**B**

Consensus-based recommendation

CBR 12.2.1. Patients with cutaneous squamous cell carcinoma involving the parotid or cervical lymph nodes should be offered adjuvant radiotherapy after surgery.

Practice point

PP 12.2.1. Recurrences of cutaneous squamous cell carcinoma in the axillary, epitrochlear or inguinal lymph nodes should be treated with surgery and adjuvant radiotherapy.

Practice point

PP 12.2.2. Patients with resected lymph node metastases of cutaneous squamous cell carcinoma should be followed 3-monthly for the first 2 years after surgery.

Practice point

PP 12.2.3. Patients with unresectable local cutaneous squamous cell carcinoma can be considered for radiotherapy and, if fit for chemotherapy, platinum-based chemoradiation

Practice point

PP 12.2.4. Cemiplimab treatment should be considered for patients with unresectable locoregionally advanced cutaneous squamous cell carcinoma not suitable for surgery or radiotherapy.

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3.5 3. Early detection

3.5.1 3. Early detection of keratinocyte cancers

Practice point

PP 3.1.1. Patients at very high risk of keratinocyte cancers (e.g. organ transplant recipients) should be monitored in specialist clinics at least annually.

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3.6 4. Clinical features

3.6.1 4.2 Clinical features of cutaneous squamous cell carcinoma and related keratinocyte tumours

Practice point

PP 4.2.1. If a skin lesion is initially considered to be an actinic keratosis, but it persists following cryotherapy, enlarges or becomes tender, it should be biopsied to investigate the possibility of cutaneous squamous cell carcinoma or other dysplastic lesions.

Practice point

PP 4.2.2. Keratoacanthomas should be managed by early excision rather than relying on correct clinical diagnosis and waiting for spontaneous resolution.

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3.7 5. Pathology of keratinocyte cancer

3.7.1 5.4 Pathology of rare tumours

Practice point

PP 5.4.1 When a diagnosis is made on histopathology in the following conditions referral to a specialist for assessment and treatment should be undertaken:

- Merkel cell carcinoma
- extramammary Paget's disease
- mammary Paget's disease (refer to a breast surgeon)
- atypical fibroxanthoma or pleomorphic dermal sarcoma not otherwise (consider referral).

3.7.2 5.5 Biopsy considerations and the biopsy report

Practice point

PP 5.5.1. Excision biopsy should be performed when appropriate. If complete excision is not possible, punch biopsies, shave biopsy or curettage can be considered, as appropriate to the size and depth of the lesion.

Practice point

PP 5.5.2. A suture should be placed in the specimen and a diagram should be provided to enable the pathologist to orient the specimen within the anatomical site and/or lesion.

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3.8 6. Prognosis

3.8.1 6.2 Prognosis of cutaneous squamous cell carcinoma

Practice point

PP 6.2.1. Incompletely excised cutaneous squamous cell carcinomas should be prophylactically re-excised or treated with radiotherapy.

Practice point

PP 6.2.2. If a cutaneous squamous cell carcinoma recurs in a nodal basin after standard lymphadenectomy, the patient should be offered referral to a specialist advanced skin cancer clinic that can provide access to a multidisciplinary team (including surgeons, radiation oncologists, medical oncologists and allied health professionals) and the opportunity to participate in clinical trials.

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3.9 9. Cryotherapy and electrodessication and curettage

3.9.1 9.1 Cryotherapy and electrodessication and curettage for basal cell carcinoma

Practice point

PP 9.1.1. Long-term follow-up is essential after treatment of basal cell carcinoma with cryotherapy, as late recurrences may occur.

3.9.2 9.2 Cryotherapy and electrodessication and curettage for cutaneous squamous cell carcinoma

Practice point
PP 9.2.1. Cryotherapy is contraindicated for recurrent cutaneous squamous cell carcinoma.

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3.10 10. Topical treatments and photodynamic therapy

3.10.1 10.1 The role of topical treatments in the treatment of keratinocyte cancer

Practice point
PP 10.1.1. Skin biopsy is highly recommended before treatment of superficial basal cell carcinoma with imiquimod 5% cream (and is required for PBS-reimbursed prescription).

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3.11 11. Organ transplantation and conditions associated with immunosuppression

3.11.1 11.3 Strategies to manage keratinocyte cancer in organ transplant recipients

Practice point
PP 11.3.1. Chemoprophylaxis with systemic acitretin should be considered for reducing tumour burden in patients who develop multiple keratinocyte cancers.

Practice point

PP 11.3.2. Reduction of immunosuppression should be considered in organ transplant recipients who develop multiple keratinocyte cancers.

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3.12 13. Follow-up

3.12.1 13. Follow-up after treatment for keratinocyte cancer

Practice point

PP 13.1.1. For patients who have undergone non-surgical treatments, where histological evidence of clearance is not available, planned regular follow-up (not just reassessment prompted by clinical need) should be provided for up to 3 years. Examination includes a full skin check for new lesions as well as inspection of the site of the original lesion.

Practice point

PP 13.1.2. For patients with cutaneous squamous cell carcinoma that is moderately to poorly differentiated or occurs on the lip or ear, initial follow-up should be conducted at 3 months and then every 6 months. It should always include examination of the draining lymph node basin.

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3.13 14. The role of primary care

3.13.1 14. The role of primary care in the prevention and management of keratinocyte cancer

Practice point
PP 14.1.1. Uncomplicated small tumours should be removed by an elliptical excision and direct closure.

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3.14 NHMRC approved recommendation types and definitions

Type of recommendation	Definition
Evidence-based recommendation*	A recommendation formulated after a systematic review of the evidence, indicating supporting references
Consensus-based recommendation*	A recommendation formulated in the absence of quality evidence, after a systematic review of the evidence was conducted and failed to identify admissible evidence on the clinical question
Practice point	A point of guidance on a subject that is outside the scope of the search strategy for the systematic review, or guidance on topic not subject to a systematic review, formulated by a consensus process and based on a general literature review, clinical experience and expert opinion

*NHMRC recommendation. Note: The definition for Practice Points has been adapted from the original NHMRC definition.

Source: National Health and Medical Research Council.[2]

3.15 Evidence-based recommendation grades

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Source: National Health and Medical Research Council.[3]

3.16 References

1. ↑ National Health and Medical Research Council. *NHMRC levels of evidence and grades for recommendations for guideline developers.* Canberra: National Health and Medical Research Council; 2009 Available from: https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf.
2. ↑ National Health and Medical Research Council. *2016 NHMRC Standards for Guidelines.* [homepage on the internet] Canberra: NHMRC Australian Government; [cited 2019 Aug 22]. Available from: https://www.nhmrc.gov.au/guidelinesforguidelines/standards.
3. ↑ National Health and Medical Research Council. *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines.* Canberra; 2009 Available from: www.mja.com.au/sites/default/files/NHMRC.levels.of.evidence.2008-09.pdf.

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4 Plain-language summary

Contents

4.1 Introduction

Keratinocyte cancer, previously called non-melanoma skin cancer, includes two types of skin cancers: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

These types of skin cancers are very common in Australia. They make up the majority of the estimated one million skin cancers diagnosed and treated each year, and cost our health system hundreds of millions of dollars every year.

Very few people in Australia die from BCCs or SCCs. Most of these cancers are discovered and treated before they can spread. Some grow very slowly or stay the same for years. Others can spread into the layers under the skin, or nearby parts of the body. Rarely, a BCC or SCC will spread throughout the body and invade other organs.

This guideline is for health professionals, including general practitioners (GPs), surgeons, pathologists, dermatologists and oncologists. It contains recommendations about how to prevent, diagnose and treat BCC and SCC.

4.2 What causes keratinocyte cancers?

The most common cause of BCCs and SCCs is being out in the sun without strong protection against ultraviolet (UV) rays. These cancers are most common in people who have been sunburned during childhood, outdoor workers, people with naturally pale skin, people in the northern parts of Australia and people who use tanning beds. Both BCCs and SCCs are common on parts of the body that are exposed to sunlight, such as the head and neck, arms and legs.

Other causes include genetic skin conditions, and having a weak immune system due to a medical condition (e.g. HIV-AIDS, or chronic lymphocytic leukaemia), or due to drug treatment that weakens the immune system (e.g. for organ transplants). People with these conditions have a very high risk of skin cancer.

4.3 How can keratinocyte cancers be prevented?

Advice for preventing BCCs and SCCs is the same as for preventing melanomas: cover up with clothing, sunscreen, a broad-brimmed hat, shade and sunglasses whenever the UV index is 3 or higher. People can still get enough vitamin D while protecting themselves against skin cancers.

Drug treatment to prevent skin cancer is sometimes prescribed for people who have a very high risk of skin cancer (e.g. people with rare skin conditions or people who have already had several skin cancers).

Skin cancers can be prevented by finding and treating them at a precancerous stage. GPs should estimate each patient’s risk. Skin checks are not routinely recommended for people with no unusual skin spots or a low risk of skin cancers, but people at high risk should have regular skin checks. GPs should consider performing skin checks during physical examinations for anyone aged over 40 years with one or more risk factors (or younger people with sun-damaged skin). People with very high risk need to have skin checks more often. For people at high risk, it may be best to have skin checks done by a dermatologist or other doctor with special training and experience in skin cancer.

Organ transplant clinics should give patients information and check-ups for skin cancer.

People should also look out for new skin spots. A spot should be checked by a doctor if it has grown or changed shape or colour over weeks or months, looks different or stands out from other spots, is painful, bleeds easily, or seems to be a sore that doesn't heal. When someone notices a new skin spot, their doctor should always check it carefully.

4.4 How are keratinocyte cancers diagnosed?

Most BCCs and SCCs can be recognised by doctors by their appearance, along with information about whether the spot has changed over time and any symptoms (e.g. itch or pain).

BCCs can be flat, knobbly or look like a scar, and may be skin-coloured or have different colours. They don't usually cause any symptoms, but are sometimes itchy. Their surface may become raw (ulcerated). Many stay small, but some types can grow as wide as 10cm if not removed.

SCCs usually have crusty layer over top of the cancer. Bowen's disease and actinic keratosis (previously called solar keratosis) are early, pre-cancerous growths that can develop into SCC. Many spots that could have become SCCs are discovered and treated at a precancerous stage. Anyone who has had an actinic keratosis should have regular skin checks, to identify SCCs as early as possible.

Doctors can use a hand-held magnifying device (dermatoscope) to examine skin spots more closely. Sometimes it is hard to recognise a skin spot from its appearance. If there is any doubt, the doctor should remove the whole growth, or take a sample (biopsy), to be examined by a pathologist.

When a BCC or SCC is diagnosed, the doctor assesses how likely it is to spread and cause health problems. Some rare types of BCC and SCCs are known to have a high risk for spreading and invading other organs, or recurring after being removed. Other types tend to grow slowly or stay the same over time.

4.5 How are keratinocyte cancers treated?

Cutting out the whole cancer in one operation (surgical excision) is the most common treatment for BCCs and SCCs. Other treatments include freezing (cryotherapy), killing the cancer with an electric current and then scraping out the dead tissue (electrodessication and curettage), chemical treatment (e.g. creams) and radiation treatment (radiotherapy).

Surgery generally gives the best chance of a cure. It is recommended for skin cancers that have a higher risk of growing back. Sometimes radiotherapy is used as well as surgery to improve the chance of cure. For skin cancers with a low risk of growing back, the person can be offered other treatment choices.

GPs can remove most BCCs and SCCs. GPs should refer patients to a specialist if the cancer is in a difficult area (e.g. face, ears, fingers or lower leg).

4.5.1 Surgical excision

Surgery for skin cancers involves cutting around the cancer to remove it, and removing a margin of healthy skin around the edges and under the cancer below the skin.

The main aim of surgery is to avoid leaving behind any cancer that could grow back. The next most important aim of surgery is to save as much healthy tissue as possible, so that the part of the body from which the cancer was removed still functions well and looks as normal as possible.

Surgery for skin cancers is usually done under local anaesthetic and the patient can go home afterwards. Surgery could leave a scar, depending on the type of cancer and where it is on the body.

After surgery, the pathologist examines the whole removed piece of skin. The pathologist checks whether a wide enough margin around the cancer has been cut out. How wide is safe depends on the type of cancer and how it looks under the microscope.

If the pathology report says the cancer was low risk and the margin was wide enough, no more treatment is needed. If the pathologist finds that the cancer was high risk or the margin was too narrow, the person may need more surgery, with or without radiotherapy.

4.5.2 Mohs surgery

Mohs surgery is like surgical excision, but the removed cancer and surrounding skin is checked under a microscope straight away, before stitching up the wound. If the microscope shows that some of the cancer was too close to the edge of the piece removed, the surgeon slices more away.

Mohs surgery is usually performed under local anaesthetic. Usually the open surgical wound is covered and person can sit in a waiting room between each stage of the operation.

The main advantage is that it allows the least possible amount of skin to be removed, while finding out straight away if any cancer was left – instead of waiting several days after the operation for the pathology report. The main disadvantages are that it takes time, specially trained staff and special equipment, and is only available at some specialised clinics in Australia.

Mohs surgery can be considered for BCCs that don’t have easy-to-see edges, BCCs on the face, BCCs that have come back after previous treatment, or large BCCs, and some other types of skin cancer.

4.5.3 Cryotherapy

Some small BCCs and pre-cancerous growths can easily be frozen off in the doctor’s office using liquid nitrogen (cryotherapy). Cryotherapy leaves a white patch on the skin, so is usually not used on the face or for people with dark skin. Long-term follow-up is needed after cryosurgery for BCCs, because there is a small chance they could grow back years later.

4.5.4 Electrodessication and curettage

Some small BCCs and pre-cancerous growths can be removed using an electrical current that kills the cancer (electrodessication and curettage). This treatment is quick and can be done in the doctor’s office.

4.5.5 Radiotherapy

Radiotherapy can sometimes be as effective as surgery for curing cancers that are diagnosed early enough and don't have a high risk of growing back. It might be the best choice treatment for some cancers where surgery would remove too much tissue (e.g. for cancers on eyelids, lips or nose) or could damage nerves, or for people who cannot have surgery.

Radiotherapy can also be added to surgery to improve the chance of a cure (e.g. when the pathology report says the cancer was high-risk or the margin of healthy skin cut out was too narrow). When radiotherapy is given after surgery, it should be within 6 weeks of the operation. It is also used to treat skin cancers that have spread to other body parts.

Radiotherapy involves repeated doses over several weeks (e.g. 4–12 visits over 1–2 weeks for a small cancer, or 15–30 visits over 3–6 weeks for a large cancer). Possible side effects include redness and peeling of the skin, rawness and hair loss. Some skin changes can occur months or years after treatment.

Recent advances in radiotherapy equipment and techniques allows radiation to be directed more precisely to the shape of the cancers, and allow more precise dose.

4.5.6 Chemical treatment (creams and gels)

Another way to remove skin cancers and pre-cancerous growths is by applying creams or gels to the surface. Imiquimod cream can be used to remove some types of BCCs when surgery is not an option. Before starting treatment, a biopsy should be taken to be sure that the growth is a BCC. Imiquimod cream is usually applied at home by the patient three - five times per week and left on all day. Possible side-effects include redness, scabbing, or open sores.

Actinic keratosis (a type of pre-cancerous growth) can be treated with imiquimod cream, 5-fluorouracil cream, diclofenac gel or ingenol mebutate gel. Bowen's disease (an early, pre-cancerous form of SCC) can be treated with 5-fluorouracil cream.

4.5.7 Other treatments

Actinic keratosis, Bowen's disease, and some types of BCCs can be treated with light treatment (photodynamic therapy). Photodynamic therapy involves applying a cream to the cancer to make it sensitive to light, then using a special lamp. This treatment is useful for people who have precancerous spots over a large area of skin. It is not recommended for SCC. Special training and equipment is needed to do photodynamic therapy, so it is only available in some clinics.

Oral medicines are also available for treating BCC. They are sometimes used in combination with radiotherapy and surgery. These medicines are mainly used for people who keep getting BCCs due to genetic conditions.

4.6 What happens after treatment?

When someone has a BCC or SCC removed, their doctor should carefully explain the risk of new cancers, or treated cancers growing back. Almost half of people who have had a BCC removed will have a new BCC within 3 years. Almost one in five people who have had a SCC removed will have a new SCC within 3 years.

When skin cancers have been treated by a specialist, the specialist will usually provide check-ups for the first few years. How often the person needs a check-up will depend on the type of cancer and the pathology report. Check-ups should include full skin checks and checking to make sure the cancer has not spread from the skin.

After the first few check-ups by a specialist, the person will usually go back to their GP for long-term care, which will include skin checks. Anyone who has had a skin cancer should have a yearly skin check for the rest of their life.

4.7 What happens if the cancer comes back or spreads?

Less than one in 50 people will have their BCC grow back after it has been completely removed surgically. BCCs very rarely spread to other body parts. It is uncommon for SCCs to come back or spread to other body parts. When a BCC or SCC comes back, it usually happens within 2–3 years.

If there are signs that a skin cancer has spread to the nearby lymph nodes (e.g. if they are swollen and tender), a sample is taken with a needle for testing under the microscope.

If a skin cancer may have spread by growing along the nerves in the skin, the person should be referred to a specialist. If the cancer has spread from the skin into other parts of the body, the person should be referred to a specialist. Sometimes the best treatment involves a team of doctors with different types of expertise (e.g. head and neck surgeon, reconstructive surgeon, dental oncologist, surgical oncologist, radiation oncologist and medical oncologist).

Surgery, radiotherapy, chemotherapy, or a combination of treatments may be needed. Drug treatment (e.g. cemiplimab) should be considered for people with SCC that has spread from the skin, but who cannot have surgery or radiotherapy.

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4.1 1. Epidemiology – Introduction

4.1.1 Introduction

Keratinocyte cancer (KC), formerly known as non-melanoma skin cancer, comprises basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC).

In Australia, KCs accounted for an estimated 939,000 treatments in 2015,[1] although they cause only about 560 deaths annually.[2] Keratinocyte cancers accounted for 8% of all health spending on cancer (excluding cancer screening) in Australia in 2008–2009,[2] and Medical Benefits Schedule reimbursements for KC diagnosis, treatment and pathology cost an estimated $703 million in 2015.[1] Thus, these mostly non-fatal cancers represent a large public health problem with disproportionately high costs.

Moreover, the predilection of KCs for the head and neck means that their treatment is often clinically complex, with cosmetic ramifications for affected patients. Keratinocyte cancers are traditionally treated by surgical excision (see: Surgical treatment). A 2002 national survey found that over 70% of BCCs and the majority of cSCCs, regardless of body site, were excised.[3] The main non-surgical treatments are cryotherapy for upper and lower limb lesions, electrodessication and curettage (see: Cryotherapy and electrodessication and curettage), and topical agents like imiquimod (see: Topical treatments and photodynamic therapy).

The environmental cause of most BCCs and cSCCs is exposure to solar radiation.[4] This inference is supported by evidence from numerous epidemiological studies showing that KCs rarely develop in dark-skinned populations, who are far less sun-sensitive than white populations, and that white populations living in regions with high levels of ambient solar ultraviolet (UV) radiation have especially high KC rates.[3][5][6] Compared with people born in Australia, immigrants from high-latitude UK show lower incidence rates,[3] and their age of arrival in Australia is inversely proportional to their KC risk.[5] Strong positive associations between childhood sun exposure and BCC suggest that UV radiation received early in life increases BCC risk in adulthood.[6]

Less than 1% of skin cancers in Australia are attributable to other factors.[7] These include immunosuppression, exposure to ionising radiation, exposure to arsenic, human papillomavirus (HPV) infection, and cigarette smoking.

Skin cancers can be prevented by sun protection.[8] While KC eradication among Australians is not feasible, there is emerging evidence for the success of skin cancer awareness and prevention campaigns that commenced in the early 1980s with the aim of reducing the rates of both KC and melanoma, particularly among vulnerable and high-risk groups like children and outdoor workers (see: Prevention of keratinocyte cancer (UV protection strategies, chemoprevention and vitamin D).[9] Since the introduction of these campaigns, sun protection behaviour has improved among Australians.[10] Stabilisation of incidence rates of KC in Australians younger than 60 years was first seen around 2002,[11] and decreasing incidence has recently been reported among young adults.[12]

Primary prevention is known to be cost effective in reducing the large health expenditure on skin cancer,[13] but ongoing substantial investment in sun protection campaigns[8] is needed to maintain the trend of decreasing incidence in KC into the future and across all age groups (see also: Economics of keratinocyte cancer).

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4.2 1.1 Epidemiology of BCC

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4.2.1 Incidence of basal cell carcinoma

The incidence of basal cell carcinoma (BCC) is higher than that of any other cancer, though precise rates are unknown because generally BCCs are not registered and estimates from other sources are not current. The last national non-melanoma skin cancer survey, conducted in 2002, found the age-standardised annual incidence rate for BCC was 884 per 100,000, and was higher in men (1041 per 100,000) than in women (745 per 100,000).[1] The survey also showed a strong inverse association with latitude, with the highest incidence in northern Australia, confirming collective observations from various local population-based surveys. For example, in Townsville, northern Queensland, age-standardised annual BCC incidence rates per 100,000 were 2058 for men and 1195 for women in 1997,[2] similar to corresponding rates of 2074 and 1579 per 100,000 in Nambour, south-eastern Queensland, in 1992,[3] but much higher than the estimated annual rate of 672 per 100,000 in Maryborough, Victoria, in the 1980s.[4]

More recent estimates of BCC incidence for Australia (2011–2014) were based on data from a 10% random sample of Medicare administrative claims, examining item codes for excision of keratinocyte cancers (KCs), together with age- and sex-specific ratios of cutaneous squamous cell carcinoma (cSCC) to BCC from a population-based cohort. Annual incidence of BCC was estimated to be 770 per 100,000 (656 per 100,000 in women and 899 per 100,000 in men).[5] Consistent with the 2002 survey, an inverse latitude gradient was observed, with the highest rates in Queensland (1355 per 100,000) and the lowest in Tasmania and Victoria (482 per 100,000).

These incidence rates are based on the number of persons affected per year; when the incidence of lesions is considered, the rates are considerably higher. For example, a 1992 survey conducted in Geraldton, Western Australia, reported annual BCC tumour incidence rates of 7000 and 3380 per 100,000 in men and women respectively, reflecting the high risk of multiple BCCs in those affected.[5][6][7][8]

Incidence of BCC rises with age, but not linearly. In Australia, incidence in men is higher than in women up to approximately age 50 years, but similar at older ages.[9]

In both sexes, over 50% of BCCs occur on the head or neck (mostly the face, especially eyelid, lip and nasolabial fold, followed by ears, nose and cheek),[2] approximately 25% on the trunk and approximately 10% each on the upper and lower limbs.[1]

The mortality rate of BCC is very low, at 1.9 deaths per 100,000 person–years at risk (total population).[10]

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4.2.1.1 Host factors

Phenotypic factors that have been consistently and independently associated with increased risks of BCC include light skin that burns and does not tan (approximately 2-fold increase), propensity to freckling (approximately 2-fold increase), red hair (approximately 2-fold increase) and blue eyes (approximately 1.5-fold increase).[11][12][13]

Prospective cohort studies have demonstrated that people who have photodamaged skin also have increased risks of BCC. Signs of photodamage associated with increased risk include the presence of actinic keratosis (greater than 3-fold increase), telangiectasia (greater than 3-fold increase), solar lentigines (approximately 3-fold increase), and elastosis of the skin of the neck (approximately 2-fold increase).[11][14][15]

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4.2.1.2 Environmental factors

4.2.1.2.1 Sunlight

The substantial epidemiological evidence that ultraviolet (UV) radiation is the principal environmental cause of BCC is complemented by evidence from sequencing studies of BCC genomes. These studies have demonstrated exceedingly high burdens of genomic damage in BCC tumour DNA,[16] mostly due to characteristic 'signature mutations', which are incurred specifically through UV-induced photolesions.

Despite the strong association with UV radiation, the dose–response relationship shows no direct correlation between total cumulative dose and risk of BCC. For example, a large, prospective study reported no association between occupational UV radiation exposure and risk of BCC.[17] This finding mirrors those of the prospective Nambour Skin Cancer Study, which also found that BCC rates in outdoor workers were not significantly higher than rates among indoor workers.[3] However, there was evidence of self-selection bias, whereby people with sun-sensitive phenotypes were grossly under-represented among outdoor occupations.[3]

A meta-analysis of 24 studies found increased risks of BCC with outdoor work (summary odds ratio [OR] 1.43, 95% confidence interval [CI] 1.23–1.66), but observed significant heterogeneity by latitude, where studies conducted in countries with high levels of ambient UV radiation had less marked associations with outdoor work than studies conducted in high-latitude countries.[18] However, early life sun exposure appears important,[17][19] consistent with the observation that BCC is relatively common in younger age groups as well as older age groups.[5]

Patterns of exposure may also be important. High-quality prospective studies have shown strong associations with numbers of sunburns,[3][11] especially with sunburns occurring in early or middle life.[20]

4.2.1.2.2 Artificial UV radiation

Artificial tanning devices emitting UV radiation across wavelengths in the mutagenic spectrum are used for cosmetic purposes, especially by young women. The International Agency for Research on Cancer Working Group has classified such devices as 'carcinogenic to humans' (Group 1 carcinogen).[21] Evidence that exposure to tanning devices increases the risk of BCC comes largely from case-control studies showing up to 2-fold higher risks of BCC among ever users compared with never users.[22][23] Although commercial tanning devices were banned in Australia by 1 January 2016, many Australians have previously been exposed to commercial solariums and individuals can still use tanning devices privately.

Medical sources of exposure to artificial UV radiation include psoralen and ultraviolet A (PUVA), which was used in the past to treat psoriasis, and narrowband UVB, which superseded PUVA. In a US long-term prospective follow-up study with mean age 44 years at enrolment, patients who first received PUVA therapy in the mid-1970s had higher BCC rates than the general US population.[24]

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4.2.1.2.3 Other sources of radiation

There is consistent evidence that exposure to ionising radiation increases the risk of BCC.[25][26][27]

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4.2.1.2.4 Arsenic

Inorganic arsenic is found naturally in soil or rock, where it can enter surface and groundwater. In previous eras, it was used for the treatment of many diseases, from anaemia to syphilis. Its association with skin cancer has long been known.[28] Follow-up studies showed high rates of BCC among people in Queensland exposed to trivalent inorganic arsenic early in life through ingestion of an asthma medicine manufactured during the 1950s.[29]

High levels of arsenic have been found in contaminated drinking water supplies in many countries, and these have been associated with high rates of BCC.[30] The Australian drinking water guidelines recommend that arsenic concentrations in drinking water should not exceed 10µg/L.[31] Values observed in Australia typically range from less than 5µg/L to 15µg/L. While data are sparse, US studies have found no evidence that low-level arsenic in drinking water is associated with BCC risk.[32]

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4.2.1.2.5 Smoking

Two large meta-analyses conducted in 2012 reported inverse associations between smoking and BCC.[33][34] Subsequently, three large prospective cohort studies have also reported inverse associations between smoking and BCC.[35][36][37] On investigation, however, the observed decrease in BCC risk among smokers appeared to be a secondary (non-causal) association reflecting low BCC detection rates among current smokers, compared with non-smokers, due to the fact that smokers are less likely to undergo physician-led skin examinations and have asymptomatic BCCs diagnosed.[36]

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4.2.1.2.6 Alcohol

Numerous studies have examined the association between alcohol consumption and risk of BCC, with mixed results.

A meta-analysis combining various prospective and case-control studies found a significant dose–response relationship between alcohol and BCC (summary RR 1.07, 95% CI 1.04–1.09).[38] However, a well-characterised Australian skin cancer cohort study observed no association between total alcohol intake and BCC risk, or any associations with specific classes of alcoholic beverages.[39]

In summary, it is unlikely that a strong causal association exists, although modest contributory effects of alcohol to BCC risk cannot be discounted.

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4.2.1.2.7 Diet

Two comprehensive reviews published in in 2005 and 2010[40][41] found no consistent evidence that BCC risk is influenced by dietary intakes or serum levels of retinol (vitamin A), carotenoids, vitamin C, vitamin D, tocopherol (vitamin E), selenium, or trace elements (copper, iron, zinc).

Tea and coffee are two commonly consumed beverages that contain numerous bioactive compounds with anti-carcinogenic potential such as polyphenols and phytochemicals. Evidence from studies measuring the association between tea and coffee consumption and KC in humans is weak and inconsistent, showing either reduced risks of BCC associated with high levels of caffeinated coffee intake[42][43] or no evidence that overall caffeine consumption was associated with BCC.[44][45]

These limited findings must be interpreted cautiously, as very few dietary components have been investigated in randomised trials. Most data derive from observational studies, in which dietary measurement is extremely challenging.

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4.2.1.2.8 Viruses

Most research interest has focused on human papillomavirus (HPV) and the hypothesis that skin cells infected with beta-HPV types may be transformed by the expression of viral E6 and E7 proteins involved in cell stability. To date, there is relatively little evidence from studies comparing HPV status in people with BCC and in healthy controls without BCC, and available evidence is inconsistent.[46][47][48]

Overall, there is no strong evidence that HPV is causally associated with BCC.

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4.2.2 Genetic epidemiology

4.2.2.1 Rare, high-risk susceptibility genes

The first insights into the genetic causes of BCC were provided by studies of patients with naevoid BCC syndrome (Gorlin's syndrome),[49] a rare autosomal dominant disorder characterised by the development of multiple early-onset BCCs, other cancers, and other phenotypic abnormalities. The primary cause of naevoid BCC syndrome is mutations in the *patched 1 gene* (*PTCH1*), a tumour suppressor gene[50] that is a key regulatory component of the hedgehog signalling pathway. Activation of this pathway appears to occur early in BCC development.[51]

Other hereditary syndromes that cause early-onset BCC are Bazex-Dupre-Christol syndrome[52] and Rombo syndrome.[53]

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4.2.2.2 Common, low- to moderate-risk susceptibility genes

Genome-wide association studies have identified other susceptibility loci, including a variant at 9q21 (containing both the *CDKN2A* and *CDKN2B* genes), genes associated with pigmentation traits such as *ASIP, TYR, SLC45A2I* and *MC1R, 1p36, 1q42*,[54][55] variants in the *TERT-CLPTM1L* locus,[56] and two novel susceptibility loci at *TGM3* and *RGS22*.[57][58]

TGM3 is thought to influence susceptibility via disturbance of corneocyte differentiation (causing barrier defects), while the function of *RGS22* is unclear.[59]

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4.2.2.3 Somatic mutations

Sequencing studies show that BCCs have the highest mutation burden of all cancers. Most mutations have a UV radiation signature,[16] especially those of BCCs on chronically exposed anatomic sites. They commonly carry mutations in *PTCH1* and *TP53* and, to a lesser extent, SMO.[16][51]

A recent study of 293 BCC tumours identified recurrent mutations in other cancer-related genes including *MYCN, PPP6C, STK19, and LATS1*, as well *ERBB2, PKI3CA* and the *RAS* family.[60]

Frequent mutations within promoter regions of *TERT* and *DPH3-OXNAD1* have also been reported,[61][62] suggesting that BCCs likely arise through multiple molecular pathways.

Key point(s)
Sun protection throughout life (including appropriate use of clothing and Therapeutic Good Administration-approved sunscreen labelled SFP30 or higher) should be promoted and encouraged to reduce the risk of basal cell carcinoma.

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4.3 1.2 Epidemiology of cSCC

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4.3.1 Incidence of cutaneous squamous cell carcinoma

Cutaneous squamous cell carcinoma (cSCC) is generally not systematically registered and incidence estimates are derived from secondary sources, as for basal cell carcinoma (BCC). In the 2002 national non-melanoma skin cancer survey, the age-standardised incidence rate of cSCC (not including cSCC in situ) was 387 per 100,000 in people aged 14 years and over (499 in men and 291 in women per 100,000), with a significant latitude gradient as for BCC[1] (see: Incidence of basal cell carcinoma). Incidence was highest in males for all age groups. The incidence of cSCC increases steeply with increasing age from mid-adulthood.[1][2] Rates of cSCC among predominantly light-skinned European migrants to Australia are lower than rates of cSCC among those of similar ancestry who were born in Australia.[3]

More recently, cSCC incidence in the Australian population was estimated in an analysis of a 10% random sample of Medicare administrative data based on the frequency of item codes for excisions of keratinocyte cancers (KCs) with histology. By extrapolating data from a population-based cohort for which the age- and sex-specific ratios of cSCC to BCC were known, the incidence of excised cSCCs was estimated at 271 per 100,000 person years (209 per 100,000 in women and 341 per 100,000 in men).[4] Again, an inverse latitude gradient was observed, with the highest rates in Queensland (471 per 100,000) and the lowest rates in Tasmania and Victoria (221 per 100,000).

The head and neck are the most common sites of occurrence for cSCC in men, while in women the upper limbs are the most common site, followed by head and neck. When the body surface area is taken into account, the highest cSCC 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.[2]

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4.3.2 Host factors

Having a sun-sensitive pigmentary phenotype is also a strong and well-established risk factor for cSCC, as for BCC (see: Epidemiology of basal cell carcinoma).[5][6] Light skin, eye and hair colour are significant risk factors, as is the presence of freckling.

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4.3.3 Environmental factors

4.3.3.1 Sunlight

The principal environmental cause of cSCC is exposure to solar ultraviolet (UV) radiation, and there is a strong positive relationship between level of cumulative sun exposure and cSCC risk.[7][8] Evidence for a causal association derives from ecological, migration and analytical epidemiological studies. Laboratory studies have reported UVB-specific mutations in the TP53 tumour-suppressor gene of cSCC tumours[9] and in actinic keratoses (AK).[10] Signs of photoaging[11] and a history of AKs,[12] which in some cases can act as premalignant lesions for cSCC,[13] are strongly related to cSCC risk.

4.3.3.2 Artificial UV radiation

Exposure to artificial UV radiation from indoor tanning facilities is significantly associated with cSCC, with the highest risk observed in those first exposed before age 25 years.[14]

4.3.3.3 Other sources of radiation

A history of radiation treatment has been shown to increase risk of cSCC.[15][16]

4.3.3.4 Immunosuppression

Immunosuppression is a major risk factor for cSCC. Groups with an elevated risk of cSCC include solid organ transplant recipients[17] and those diagnosed with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS),[18] non-Hodgkin lymphoma[19] or chronic lymphocytic leukaemia.[20]

The incidence of cSCC among organ transplant recipients is 65–250 times higher than that of the general population.[21] The use of glucocorticoids, a class of medicines with immunosuppressive properties, is associated with an approximate 2-fold increased risk of cSCC.[22][23][24]

4.3.3.5 Smoking

The two previous meta-analyses of the association between smoking and skin cancer showed current smokers to have an increased risk of cSCC compared with never-smokers.[25][26] The results of two recent cohort studies have further shown that smokers have up to twice the risk of cSCC of non-smokers, and this risk is likely to be independent of the effect of sun exposure.[27][28]

4.3.3.6 Alcohol

Total alcohol consumption is associated with an increased risk of cSCC. A meta-analysis of case-control and cohort studies reported a significant dose–response relationship between alcohol and cSCC; for every 10g increase in ethanol consumption per day (equivalent to one standard drink) the summary relative risk was 1.11 (95% confidence interval 1.06–1.16).[29]

4.3.3.7 Viruses

Many studies have investigated the potential association between cutaneous cSCC and certain cutaneous human papillomavirus (HPV) types, mostly in the betapapillomavirus genus (beta-HPV),[30] though infection is common in the general population.[31] Suggestive associations have been seen between markers of beta-HPV infection (beta-HPV antibodies and beta-HPV DNA), and both AKs and cSCC, but not between beta-HPV markers and BCC.[32][33][34]

Betapapillomavirus has also been investigated as a possible infectious oncogenic agent that may explain the greatly increased cSCC risk in immunosuppressed organ transplant recipients.[35] A recent multi-centre prospective study in organ transplant recipients found that those with five or more different beta-HPV types in eyebrow hair follicles had nearly twice the risk of cSCC than those with between zero and four different types, and a similar risk was seen with high beta-HPV loads in eyebrow hair.[36] Serum beta-HPV antibodies were not associated with cSCC risk.

The current hypothesis is that, if beta-HPV is causally involved in development of cSCC, it acts to potentiate the effect of UV radiation possibly via viral inhibition of DNA repair and apoptosis following UV radiation exposure.[37][38]

4.3.3.8 Other risk factors

Other less common but well-established risk factors for cSCC include chemical exposures such as arsenic,[39] polycyclic aromatic hydrocarbons (found in industrial oils and lubricants),[40] pesticides and herbicides.[41]

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4.3.4 Genetic epidemiology

4.3.4.1 Rare, high-risk susceptibility genes

Several genes associated with cSCC have been identified in patients with hereditary disorders such as xeroderma pigmentosum (*XPA-XPG* and *XPV*), Ferguson-Smith syndrome (*TGFBR1*), oculocutaneous albinism (*TYR, OCA2, MATP/OCA4, TYRP1*) and epidermodysplasia verruciformis (*EVER1, EVER2*).[42] These mutations are associated with distinct phenotypes and are related to defects in either DNA repair, pigmentation or key signalling pathways. Affected individuals often develop multiple early-onset cSCCs, and are at increased risk of other malignancies.[43]

4.3.4.2 Common, low- to moderate-risk susceptibility genes

Genome- wide association studies have confirmed earlier findings from candidate gene approaches identifying common, low- to moderate-risk susceptibility genes that are related to pigmentation, including *MC1R, ASIP, TYR, SLC45A2, OCA2, IRF4* and *BNC2*, as well as identifying new loci associated with pigmentation traits (*DEF8, RALY*).[44][45][46] Other recently identified loci include *FOXP1, HLA-DQA1* and *CADM1* involved in immune response, *AHR* involved in anti-apoptotic pathways, *SEC16A*, an oncogene, and several other loci whose functions are yet to be elucidated (*TPRG1/GP63, BNC2/CNTLN*).[45][44]

4.3.4.3 Somatic mutations

Sequencing studies have identified extremely high mutation burdens in cSCC, consistent with UV-induced damage, and most of the genes identified are tumour suppressor genes. The long list of driver genes identified, including TP53, CDKN2A, NOTCH1, NOTCH2, AJUBA, HRAS, CPSP8, FAT1 and KMT2C (MLL3),[47] suggests that cSCC tumours arise through multiple pathways.

Key point(s)
Ongoing protection from incremental sun exposure throughout life, including appropriate use of clothing and sunscreen, should be promoted and encouraged, especially in those with sun-sensitive skin, to reduce the risk of cutaneous squamous cell carcinoma.

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4.3.5 References

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4.4 2. Prevention – Introduction

4.4.1 Introduction

Excessive exposure to sunlight (i.e., greater exposure than is appropriate for the person's skin type) is strongly associated with the development of keratinocyte cancer (KC), which includes cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC). Within Australia[1] and other large countries such as the USA,[2] the incidence of KC 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, cSCC rarely occurs on parts of the body that are not habitually exposed.[3]

Cutaneous squamous cell carcinoma and BCC appear to differ in their relationship to sun exposure. Cutaneous squamous cell carcinoma 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][5][6] Outdoor workers appear to have the highest risk. For BCC, in contrast, recreational and intermittent exposure may be more closely related to risk than the total amount of exposure, with indoor workers possibly having higher risk than outdoor workers.[5][6][7][8]

A randomised trial of daily sunscreen use in adults in Queensland showed a reduction in risk of cSCC,[9] and a reduction in BCC risk with longer follow up.[10] Randomised trials of regular sunscreen use showed a reduction in numbers of actinic (solar) keratoses, which are known precursors of cSCC.[11][12][13]

Studies of immigrants to Australia from countries with predominately light-skinned populations indicate that excessive sun exposure during childhood and adolescence is very important in causing both BCC[14] and cSCC.[15] For cSCC there is also more direct evidence of the impact of exposure to ultraviolet (UV) radiation early in life.[15] These findings indicate that particular emphasis should be placed on protection from 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 a cSCC) 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.

Cancer Council Australia does not distinguish between melanoma and keratinocyte cancers in its recommendations on sun protection in the prevention of skin cancer. It recommends that when the solar UV index is 3 or above, people should wear a wide-brimmed hat and clothing to cover exposed skin, wear wrap-around sunglasses, seek shade and use a sunscreen with sun protection factor (SPF) 30 or higher on skin left exposed.

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Topics covered in this section include:

- Strategies for ultraviolet radiation protection
- Chemoprevention
- Vitamin D

4.4.2 References

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4.5 2.1 UV protection

Contents

4.5.1 Background

While not always possible, minimising exposure to ultraviolet (UV) radiation from the sun is the most effective strategy to prevent skin cancer. This includes planning outdoor activities to occur outside of the peak UV period (2 hours either side of solar noon), when an estimated 60% of the day's UV radiation occurs. Around midday, skin will burn more quickly, and be exposed to more UVA as well as UVB, than earlier or later in the day. Outside of these times, the UV can still be intense, so sun protection is necessary for all times when the UV index is 3 or above. For the best protection during the daily sun protection times, people should use all five SunSmart steps – clothing, sunscreen, a broad-brimmed hat, shade and sunglasses. The Bureau of Meteorology and the SunSmart App provide up-to-date sun protection times for regions across Australia.

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4.5.2 Overview of evidence (non-systematic literature review)

Keratinocyte cancer occurs more frequently on parts of the body that are habitually exposed to sunlight.[1] Health professionals should advise and encourage everyone to practise the following strategies for protection against excessive exposure to UV radiation.

4.5.2.1 Hats, clothing and sunglasses

Wear broad-brimmed or legionnaire hats (those which cover face, neck and ears reduce the UV radiation exposure to the face and eyes) and comfortable clothing that protects the arms, legs, body and neck from the sun.

Choose a close-fitting, wrap-around style of sunglasses. Check the swing tag to make sure they meet the Australian Standard for eye protection.[2][3] The Standard has five categories of sun protection – choose category 2 or higher. These lenses absorb more than 95% of UV radiation.

Choose closely woven fabrics that can't be seen through when held up to the light and that covers as much of the body as practicable. Some clothing is specifically tested for its ability to provide protection from UV radiation. This clothing uses an Ultraviolet Protection Factor (UPF) rating scheme developed by Standards Australia to guide consumers.[4]

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4.5.2.2 Shade

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

4.5.2.3 Sunscreen

Sunscreen reduces the risk of cSCC and numbers of actinic (solar) keratoses, which are known precursors of cSCC.[5][6]

Apply a sunscreen liberally with a sun protection factor (SPF) of 30 or greater to all exposed areas of skin and reapply regularly.[7] A full-body application for the average adult would be 35mls (equivalent to 7 teaspoons) of sunscreen. The Therapeutic Goods Administration (TGA) permits labelling of a sunscreen up to SPF50+.[8]

All sunscreens approved to be sold in Australia offer broad-spectrum protection (protection from both UVA and UVB wavebands within sunlight).

Given that consumers generally do not apply sunscreen thickly enough, sunscreen should not be relied on as the only form of protection. Apply sunscreen 20 minutes before going outside and reapply it at least every 2 hours. For specific circumstances such as swimming, a water-resistant sunscreen should be selected.

Sunscreens should not be used to extend the duration of sun exposure as this will likely to lead to increased risk of excessive UV radiation exposure. It is advisable to apply sunscreen every day to exposed parts of the skin when the UV index is predicted to reach 3 or above.[9]

Some sunscreens may contain nanoparticles to improve cosmetic appeal and the efficacy of the product. Nanoparticles have not been found to cause harm when used as ingredients in sunscreens and when sunscreens are used as directed.[10]

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4.5.2.4 Window glass

Each type of glass has different UV transmission properties. For example, typical household window glass is equivalent to a SPF14 sunscreen in filtering UVB rays. Glass windows typically block out most UVB radiation, but the amount of UVA radiation that penetrates through different types of glass can vary greatly.[11]

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4.5.2.5 Home solariums

Exposure to artificial sources of UV radiation in a solarium (sun bed or tanning bed) increases the risk of developing cutaneous melanoma, cutaneous squamous cell carcinoma (cSCC), basal cell carcinoma (BCC), ocular melanoma, eye damage and premature aging of the skin. There is no such thing as a ‘safe tan’ and there are no substantiated health benefits, including boosting vitamin D levels, attributable to exposure to artificial UV radiation in a solarium.[12]

Commercial solariums are banned in all Australian states and territories except the Northern Territory, where there are no commercial UV tanning businesses. Private ownership and personal use of solariums remain legal (and unregulated) in all states and territories.

Cancer Council Australia, the Cancer Society of New Zealand and the Australasian College of Dermatologists do not recommend the use of artificial UV tanning devices for cosmetic purposes in any circumstances (see: Cancer Council Australia Position statement on private solariums).

Key point(s)

- Clinicians should strongly encourage patients to protect themselves from exposure to sunlight when the UV index is 3 or above, and talk to their patients about the use of hats, clothing, shade and the timing of outdoor activities for the purpose of UV protection. Patients should also be encouraged to apply SPF30+ sunscreen (approved by the Therapeutic Goods Administration) regularly and in conjunction with other forms of sun protection.
- Clinicians should strongly counsel patients against personal home use of sunbeds or sunlamps for cosmetic tanning purposes if these behaviours are suspected or revealed during consultations.

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Go to:

- Prevention of keratinocyte cancer (strategies for UV protection, chemoprevention and vitamin D) – Introduction
- Chemoprevention
- Vitamin D

4.5.3 References

1. ↑ English DR, Kricker A, Heenan PJ, Randell PL, Winter MG, Armstrong BK. *Incidence of non-melanocytic skin cancer in Geraldton, Western Australia.* Int J Cancer 1997 Nov 27;73(5):629-33 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9398037.
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4.6 2.2 Chemoprevention

Contents

4.6.1 Background

The main classes of agents used in the chemoprevention of keratinocyte cancer (KC) for individuals at extreme skin cancer risk are synthetic retinoids and nicotinamide.

Whilst large numbers of skin cancers can occur in immune competent individuals, chronically immunosuppressed organ transplant recipients (including heart/lung, hepatic and renal transplant recipients) have a greatly increased risk of developing skin cancer and are a major target population for chemoprevention (see: Organ transplantation and immunosuppression). For example, 25% of Australian renal transplant recipients will develop a KC by 5 years post transplantation and 44% by 9 years.[1] The most dramatic increase in incidence is seen in cutaneous squamous cell carcinoma (cSCC), though there is also an increase in the incidences of basal cell carcinoma (BCC) and melanoma.[2] A greater proportion of the cSCCs and BCCs occurring in this context show aggressive growth patterns and poor prognostic features.[3][4][5][6] Aggressive cSCCs contribute to substantial numbers of deaths in the Australian organ transplant population.[7]

Other causes of chronic immune suppression, such as chronic leukaemias and lymphomas, are associated with increased risk and aggressiveness of skin cancer,[8][9] and chemoprevention may sometimes be needed in this context.

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4.6.2 Overview of evidence (non-systematic literature review)

4.6.2.1 Synthetic retinoids

Four studies of retinoid chemoprophylaxis of skin cancer have been undertaken in renal transplant recipients. All have shown a significant reduction in rates of cSCCs during treatment.[10][11][12][13] In one study,[10] suppression of the incidence of KC was not maintained following cessation of retinoid chemoprophylaxis, suggesting that these agents act at a late stage in tumour development.

Due to the need for long-term therapy, it is recommended that retinoid treatment be instituted for transplant recipients and also for severely affected immune competent patients only when patients begin to suffer from numbers of cSCCs that are causing significant morbidity or are life-threatening. The long-term benefits must be weighed against the short- and long-term adverse effects of retinoids. The major long-term adverse effects are calcification of tendons and ligaments and spinal hyperostoses.[14]

4.6.2.2 Xeroderma pigmentosum

A trial using high dose isotretinoin in seven patients showed a 63% reduction in KCs, compared with the 2-year period before treatment.[15]

4.6.2.3 Naevoid basal cell carcinoma syndrome

Small trials of retinoids have demonstrated effective chemoprophylaxis of BCC in patients with naevoid BCC syndrome (Gorlin's syndrome).[16][17][18]

4.6.2.4 Betacarotene supplementation

Trials of betacarotene in the chemoprevention of KC have failed to demonstrate a beneficial effect.[16][19][20][21]

4.6.2.5 Nicotinamide

Nicotinamide is an amide form of vitamin B3 which enhances DNA repair after ultraviolet (UV) irradiation, and reduces the immune suppressive effects of sunlight on the skin.[22]

Oral nicotinamide reduced numbers of actinic (solar) keratoses (AKs) in phase II studies[23] and has been shown in one phase III randomised trial to reduce the incidence of KC in high-risk immune-competent individuals with multiple previous skin cancers.[24] Nicotinamide 500mg twice daily over 12 months reduced numbers of new KCs by 23% compared with placebo, with similar magnitudes of reduction observed for BCC and cSCC.[24] The rate of AKs was also reduced by approximately 15%. The chemopreventive effect was lost during a 6-month post-intervention follow-up period, suggesting that nicotinamide's mechanisms of action relate to the promotion rather than initiation stages of carcinogenesis.

Nicotinamide lacks the vasodilatory effects of nicotinic acid and was well tolerated. At very high doses (approximately 8g daily), nicotinamide has been associated with reversible liver function abnormalities. These side effects are not seen at lower doses. There is a potential drug interaction with carbamazepine.[24][25]

Small phase II studies suggest that nicotinamide may be useful for the chemoprevention of KC in organ transplant recipients,[26][27] but as yet there have been no large trials of its safety and efficacy in this population. Its effects on chemoprevention of melanoma are currently unknown.

Key point(s)
Nicotinamide may be a useful chemopreventive adjunct to sun protection and sunscreen use in high risk, immune-competent individuals with a history of multiple keratinocyte cancers. It should not be recommended for lower-risk individuals without a history of skin cancer.

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- Prevention of keratinocyte cancer (strategies for UV protection, chemoprevention and vitamin D) – Introduction
- Strategies for protection from excessive exposure to ultraviolet radiation
- Vitamin D

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4.7 2.3 Vitamin D

4.7.1 Background

Cancer Council Australia's position statement on the risks and benefits of sun exposure was developed to balance the risks of keratinocyte cancer (KC) and melanoma with vitamin D requirements.

This position statement is approved by the Australian and New Zealand Bone and Mineral Society, the Australasian College of Dermatologists, Cancer Council Australia, Endocrine Society of Australia and Osteoporosis Australia (see: Cancer Council Australia Position statement Sun exposure and vitamin D - risks and benefits).

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4.7.2 Summary of Cancer Council Australia's position statement

Cancer Council Australia's position statement on the risks and benefits of sun exposure includes the following key messages for health professionals and the general public.

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 strong evidence that vitamin D is beneficial for bone development and maintaining musculoskeletal health. Severe vitamin D deficiency leads to osteomalacia (softening of bones) in adults,[1] and rickets in children,[2] along with muscle weakness. Children and adults with low 25-hydroxyvitamin D in children and adults may have no obvious symptoms.

Vitamin D forms in the skin as a result of exposure to the ultraviolet (UV) B wavelengths in sunlight. Current evidence shows that sun exposure for short periods of most days of the week (well below a sunburning dose) is sufficient to maintain adequate vitamin D levels. On the other hand, there is considerable evidence showing that excessive sun exposure causes skin cancer. Research suggests that prolonged sun exposure does not cause vitamin D levels to continue to increase further[3] but does increase the risk of skin cancer.[4] Short periods (a few minutes) of sun exposure to a larger skin surface may be more efficient at producing vitamin D than long periods to a small skin surface[5] and daily exercise also assists the body to produce vitamin D.[6]

People who wear concealing clothing for religious or cultural reasons are at increased risk of vitamin D deficiency because they have very small areas of skin exposed to sunlight, and therefore may require vitamin D supplementation.[7] Women (especially those with naturally very dark skin, who are pregnant or planning pregnancy), people in institutional care, the elderly and those who are housebound should ask their medical practitioner for advice about their vitamin D requirements.

Extended sun exposure without any form of sun protection is not recommended, even for those diagnosed with vitamin D deficiency.

Production of vitamin D from exposure of the skin to sunlight is influenced by a number of factors including age, skin colour, latitude, season and time of day, making it difficult to provide advice to the population as a whole. Therefore, the recommendation for the general adult population is as follows:

When the UV index is 3 or above, a combination of sun protection measures (broad-brimmed hat, covering clothing, sunscreen, sunglasses and shade) is recommended when outdoors for more than a few minutes. Most Australian adults will maintain adequate vitamin D levels from sun exposure during typical day-to-day outdoor activities.

Key point(s)

- Most Australian adults will maintain adequate vitamin D levels from incidental sun exposure during typical day-to-day outdoor activities and therefore vitamin D testing of healthy individuals is generally not required.
- People who wear concealing clothing for religious or cultural reasons (especially those with naturally very dark skin) and women who are pregnant or planning pregnancy should be assessed to determine whether their vitamin D levels are adequate.

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- Prevention of keratinocyte cancers (strategies for UV protection, chemoprevention and vitamin D) – Introduction
- Strategies for protection from excessive exposure to ultraviolet radiation
- Chemoprevention

4.7.3 References

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5 3. Early detection

Contents

5.1 Definitions

‘Early detection’ is a broad term that covers a number of discrete activities including:

- screening – the systematic, population-wide evaluation of asymptomatic patients to identify those with (or likely to have) skin cancer

- surveillance – the ongoing follow-up of people after a previous diagnosis of keratinocyte cancer (KC) or those at pre-determined high risk of skin cancer (e.g. based on history or clinical phenotype)
- case-finding – opportunistic examination of patients who have presented for clinical care
- skin self-examination.

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5.2 Background

Keratinocyte cancer (KC) comprising basal cell cancer (BCC) and cutaneous squamous cell carcinoma (cSCC), causes enormous morbidity and small but important mortality in Australia.[1] Early detection is one arm of the overall skin cancer control strategy (along with primary prevention and optimal treatment) intended to reduce the burden of these cancers. Unresolved questions remain about the balance of harms and benefits arising from early detection, and hence the cost-effectiveness of this strategy when considered for the whole population.

While much has been written about this subject, there are few data from high-quality studies that have formally assessed the benefits and risks of various early detection strategies.[2][3][4][5][6]

Early detection of KCs through clinical inspection of the skin offers the potential to reduce morbidity. However, it is unlikely that a mortality benefit would ever be observed at the population level, because the age of onset is typically late and international data suggest that relative survival rates for patients with BCC (approximately 100%) and cSCC (approximately 95%) are very high under existing models of care[2] No Australian data are available to estimate relative survival for BCC or cSCC.

In the absence of data for assessing survival benefit, evidence of benefit must be assessed using other endpoints, including morbidity, quality of life, cosmesis and cost.

Given the uniquely high incidence and burden of KCs in Australia, the high levels of public awareness, and the fact that most such cancers are treated in primary care settings, these guidelines have sought evidence primarily from studies conducted in Australia, supplemented with findings from other populations where relevant.

A particular challenge when reviewing the literature is that all studies exploring the benefits and hazards of early detection of skin cancer have been designed with melanoma as the primary endpoint. Data on the incidence and burden of KCs following early detection activities has been captured as a secondary endpoint, if at all. In Australia, it is impossible to formally evaluate early detection programs for KCs independently of early detection for melanomas for several reasons:

- The principal mode of detection is the same (i.e. visual inspection of the skin surface, with or without dermoscopy or other technological aids).
- The populations of patients at risk of melanoma overlap with those at risk of KCs.
- All suspicious lesions arising from a clinical examination of the skin require a clinical decision to excise or not.

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5.3 Overview of evidence (non-systematic literature review)

5.3.1 What are the benefits versus hazards of early detection?

The principal intended benefit of early detection of KCs is to diagnose and excise the primary tumour when it is small in size, and before extension into the deeper dermis and subcutis or metastasis occur. Early excision restores skin health and should reduce the extent of surgical intervention or obviate it, thereby reducing patient discomfort and adverse events, achieving better cosmetic results, and lowering costs. While lower mortality is a theoretical benefit of early detection, in practice mortality rates from keratinocyte cancer are so low that improvements through early detection are not considered feasible (with the possible exception of patients undergoing solid organ transplants).

The principal hazard of early detection is overtreatment (i.e. medical or surgical intervention for lesions that are not malignant, or would never have led to morbidity or mortality had they been left untreated). The sequelae of overtreatment include unnecessary interventions, increased likelihood of adverse events and increased costs to patients and society.[7]

A recent systematic review by the US Preventive Services Taskforce examined the evidence for the effect of visual skin cancer screening in the general population on morbidity and mortality (specific and all-cause).[8] That review found no trials that reported on mortality but did report one ecologic study judged to be of ‘fair quality’ (the German SCREEN Study).[9] This skin cancer screening study reported that 4.4% of screened patients (n=360,288) underwent at least one excision following a visual inspection of the skin, of whom 18.2% had a confirmed malignant diagnosis and 74.3% had confirmed benign diagnoses. Thus, the majority of skin excisions in that screened population were for benign lesions. However, these findings cannot be generalised to the Australian population given the far lower incidence of KCs in Germany than Australia and the differences in training and service provision of clinicians.

5.3.2 Is early detection of keratinocyte cancer accurate?

A key determinant of the performance of early detection is the diagnostic accuracy of the examining clinician. Accuracy is a function of sensitivity (the proportion of histopathologically confirmed skin cancers among those diagnosed clinically as ‘skin cancer’) and specificity (the proportion of truly benign lesions among all those lesions diagnosed clinically as ‘benign’). Globally, data informing these parameters from well-designed studies are scarce.

(Note: the definitions of sensitivity and specificity given above are pragmatic, and based on the necessity to establish the true diagnosis using the gold-standard test of histopathological examination of excised lesions. This restriction means that one can never know the ‘true’ sensitivity or specificity, since the size of the pools of ‘population true negative lesions’ and ‘population false negative lesions' are unknown).

A large Queensland study compared the diagnostic performance of mainstream general practitioners (GPs) with those working in primary care skin cancer clinics.[10] Of the lesions excised, about 55% were KCs; the remainder were actinic keratoses (10%), benign naevi (11%), melanomas (1.5%) and other diagnoses. Sensitivity for diagnosing KCs in both groups was very high (skin cancer clinic doctors 0.94 versus GPs 0.92), but specificity was lower (skin cancer doctors 0.71 versus GPs 0.62). Thus when taken together, the proportion of lesions that were diagnosed clinically as KCs and which were histopathologically confirmed as such (the positive predictive value) was 0.72 for skin cancer doctors and 0.71 for GPs. On average, the primary care doctors in both settings excised about two lesions for each confirmed malignancy.

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5.3.3 Is early detection of keratinocyte cancer effective?

In its recent comprehensive review of the evidence, the US Preventive Services Task Force acknowledged the importance of the potential benefits of early detection of skin cancer, but could not determine whether there is an incremental benefit to detecting KC early through a program of regular clinical examination as compared with patient self-identification followed by clinical evaluation.[11] The task force concluded that the evidence is insufficient to assess the balance of the benefits and harms of visual skin examination by a clinician to screen for skin cancer.

Only one randomised controlled trial (RCT) with KC as the primary endpoint has tested the effectiveness of patient-led early detection activities in Australia,[12][13][14] although other studies have explored this issue using a variety of study designs. No studies have assessed mortality as an endpoint, and nor are they ever likely to owing to the very low case-fatality rate for KCs in the general population.

The RCT by Janda et al[13][14] tested the effectiveness of a video intervention, compared with control (printed materials), to encourage skin self-examination in 930 Queensland men aged over 50 years. Both the video and printed materials were effective in increasing skin self-examination behaviours in the target group, with around 50% of men in both groups reporting having performed skin self-examination in the 6-month interval between recruitment and follow-up, compared with 10% at baseline.[14] Rates of nonsurgical management of suspicious skin lesions during follow-up were similar in both groups, but the intervention group underwent significantly more excisions or biopsies than the control group (41% versus 27%) and had significantly more skin cancers detected (60% versus 40%, p=0.03).[12] The corollary is that both groups had large numbers of non-malignant lesions excised.

5.3.4 Is early detection cost-effective?

No studies have examined cost-effectiveness of early detection solely for BCC and SCC endpoints. A health economic analysis using data arising from the Australian early detection intervention trial in men over 50 years found that early detection was more expensive than usual care (AUD$5,298 versus $4,684), and was also inferior in terms of health utility measured in quality-adjusted life years (QALY) where 1 QALY equals 1 year lived in perfect health (mean QALY 7.53 versus 7.77).[15] In further analyses, it was found that the main driver of costs was the cost of treating benign lesions, cSCCs and BCCs detected during clinical follow-up, with essentially no impact on mortality and an adverse effect on QALYs.

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5.3.5 Are there high-risk groups who benefit from surveillance?

Organ transplant recipients (OTRs) have rates of cSCC up to 100 times higher than the general population and malignancy is the leading cause of death for this patient group.[16] There is no high-quality evidence that early detection programs for skin cancer lead to measurable benefits for OTRs, although there is broad international consensus across agencies and professional societies to recommend this practice. A recent systematic review identified 13 clinical practice guidelines for patients following transplantation of one or more solid organs.[17] Of these, 10 produced guidelines on screening for skin or lip cancer, and nine recommended annual examinations either by GPs (four guidelines) or by specialist (five guidelines). The single Australian guideline identified in the review was for the care of patients following kidney transplantation.[18] The Australian guideline, which was based on the international kidney diseases working group, suggests that 'a health care specialist with expertise in skin cancer diagnosis examine the skin and lips of kidney transplant recipients annually, especially those with previous history of skin cancers'. The guidelines assigned a D grading (very low quality of evidence) to this recommendation.

Recent Australian research shows that skin cancer follow-up for OTRs in Queensland was highly variable and that the incidence of SCC was extremely high.[19] Several recent articles also indicate the complexity of managing skin cancers and monitoring skin cancer risk in OTRs.[20]

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5.3.6 Can the risk of keratinocyte cancer be predicted reliably?

Prediction algorithms have been developed which estimate a person’s future risk of KC with high discriminatory accuracy.[21] Using such tools, people at high risk can be identified with high discrimination (area under the ROC curve 0.80, 95% confidence interval 0.79–0.81). The strongest factors contributing to future risk include past history of excision of KC, past history of ablation or destruction of an actinic skin lesion, and age. As yet, there are no data to determine whether using such tools improves outcomes for patients. However, there is widespread clinical support for regular skin examinations for people with a prior history of treatment for actinic lesions (i.e. surveillance).

A prediction algorithm tool[21] can be accessed here: QSkin keratinocyte cancer risk predictor

5.4 Practice Point

Practice point
PP 3.1.1. Patients at very high risk of keratinocyte cancers (e.g. organ transplant recipients) should be monitored in specialist clinics at least annually.

Key point(s)

- People in the general population who are at high risk for developing keratinocyte cancers should be identified using risk prediction tools, and should be offered regular skin examinations to minimise future morbidity.
- To encourage patients to seek medical attention for any suspicious skin lesions without delay, clinicians should consider whether patients' out-of-pocket healthcare costs are a barrier to assessment and treatment and consider strategies for minimising these, especially for those returning for multiple skin cancer treatments.

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5.5 Health system implications

5.5.1 Clinical practice

There is insufficient evidence to recommend systematic activities for early detection of KCs, such as screening of the general population.

Implementation of the practice points concerning high-risk groups would not change current practice, which does not involve screening for KCs in the asymptomatic population.

5.5.2 Resourcing

Surveillance activities for patients at high to very high risk of KC (e.g. organ transplant recipients and people with prior history of skin cancer) will require skilled clinicians with training and experience in the diagnosis and management of benign and malignant skin lesions.

Surveillance of patients at high risk of KC will occur predominantly in primary care settings. Patients at very-high risk of KC, particularly organ transplant recipients, will mostly be managed by specialists.

5.5.3 Barriers to implementation

For patients at high or very high risk of KC, access to services staffed by appropriately skilled clinicians is a barrier to recommended surveillance in some regions.

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5.6 Discussion

5.6.1 Unresolved issues

Overall mortality from KCs is very low, and it is not known whether mortality can be reduced further by early detection.[1] Similarly, at the population level, it is an open question whether early detection delivers morbidity benefits that outweigh the potential harms of over-diagnosis and over-treatment.

The advent of new technologies (e.g. reflectance confocal microscopy and optical coherence tomography for suspicious individual lesions; three-dimensional total body imaging, total body dermoscopy, and integrated genetic scores) which might deliver near-perfect positive predictive values for KCs and hence lessen the harms of over-treatment, could change the risk–benefit equation markedly.[22]

5.6.2 Studies currently underway

A large prospective study in Queensland, the QSkin Study,[23] has enrolled more than 45,000 participants and is following them through record-linkage to health registers and administrative databases, specifically monitoring skin cancer outcomes. That study is incorporating genetic risk prediction algorithms and health economics analyses as part of the research plan and aims to address some of the unresolved questions above.

The Skin Tumours in Allograft Recipients (STAR) study[24] (also based in Queensland) is tracking skin cancer incidence among different groups of organ transplant recipients. STAR is also monitoring health service utilisation of study participants.

5.6.3 Future research priorities

A high priority for research is to determine whether targeted detection activities among people at high risk of KC is effective or efficient. Stratification tools, incorporating phenotypic, genetic and clinical data, should be tested as a method for triaging those at highest risk. In particular, the stratification of patients into ‘high’ and ‘very-high’ risk remains to be defined.

New diagnostic technologies are in the process of being developed and validated in clinical trials to determine their effectiveness and cost-effectiveness for early detection.[25][26]

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5.1 4. Clinical features – Introduction

5.1.1 Introduction

The high prevalence of keratinocyte cancer (KC), previously known as non-melanoma skin cancer, in Australia makes it imperative that all clinicians are familiar with its various presentations. Early detection of these lesions is important in minimising their associated morbidity, costs of treatment and mortality.

Clinical examination that is conducted for other purposes, particularly in the general practice setting provides opportunities for opportunistic skin checks and early detection of KC.

In addition to the clinical features evident at the time of consultation, clinical history also provides important evidence on which to base a diagnosis. Keratinocyte cancers change over time, and this is generally evident over a period of months. Many are also symptomatic. These features vary between basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC), and related tumours.

Some lesions will be confidently diagnosed on clinical examination and history while others, particularly early lesions with subtle clinical features, will require biopsy. Biopsy techniques such as punch, shave, incisional and excisional biopsy can be appropriate in the assessment of selected KCs (see: Pathology).

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 treatment-related morbidity.

General practitioners (GPs) should consider skin checks for all patients over the age of 40, particularly for the elderly. Patients with special risk factors (see: Epidemiology) should be considered for entry to a regular surveillance program with their GP or dermatologist.

A substantial proportion of KCs 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 KCs.[1]

Key point(s)

- When assessing a skin lesion, always ask whether it has changed over time and whether there are any symptoms (e.g. irritation, discomfort). Lesions that are growing rapidly or associated with irritation or pain should be examined closely.
- Non-healing and/or local pain and induration should trigger suspicion of keratinocyte cancer.
- Examination for skin cancer should be considered during physical examination for all patients over the age of 40, particularly for the elderly.

Topics covered in this section include:

- Clinical features of basal cell carcinoma

- Clinical features of cutaneous squamous cell carcinoma and related keratinocyte tumours

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5.1.2 References

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5.2 4.1 Clinical features of BCC

Contents

5.2.1 Background

There are three common growth patterns of basal cell carcinoma (BCC) that have a distinctive clinical presentation:[1]

- superficial multifocal
- nodular

- sclerosing (morphoeic).

Numerous histological subtypes of BCC have been described, but most are uncommon and do not have distinctive clinical presentations. Some may be multiple and difficult to diagnose.

Superimposed on any of these growth patterns may be ulceration or pigmentation. Although ulceration and pigmentation lead to a distinctive clinical appearance, these features do not correspond to a specific histological growth pattern and are therefore no longer considered to represent separate subtypes of BCC.

Immunosuppression for organ transplantation predisposes to BCC (see: Organ transplantation and other conditions associated with prolonged immunosuppression).[2][3] Left untreated, over years, BCCs can cause significant morbidity for the patient.

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5.2.2 Overview of evidence (non-systematic literature review)

5.2.2.1 Dermoscopy

Dermoscopy (surface microscopy, epiluminescence microscopy, dermatoscopy) is a technique that is established as a significant aid in the diagnosis of pigmented lesions, particularly melanoma. More recently, it has been shown to have benefit in the diagnosis of BCC and other non-pigmented lesions, such as cutaneous squamous cell carcinoma (cSCC) in situ (also known as Bowen's disease or intra-epidermal squamous cell carcinoma). Dermoscopy is also useful in distinguishing between melanoma and pigmented BCC.[4]

The dermatoscope is a handheld magnifying device which requires formal training and continuous practice with the technology if the operator is to become proficient with its use in diagnosis.[5][6]

Dermoscopy is useful in enhancing diagnosis of basal cell carcinoma. For effective implementation of dermoscopy it is imperative that operators receive appropriate training and maintain their skills.[4][5][6][7][8][9][10][11]

5.2.2.2 Accuracy of clinical diagnosis of basal cell carcinoma

The diagnostic accuracy of clinical examination by experienced dermatologists for the diagnosis of BCC among randomly selected samples from the general community is around 59%[12] to 65%.[13] 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 USA 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.

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5.2.3 Superficial basal cell carcinoma

Superficial BCC is a subtype of BCC that commonly occurs in Australians. Superficial BCCs generally occur on the trunk or limbs. In younger people they occur more often than other growth patterns.

5.2.3.1 Clinical features

Superficial BCC usually presents as a reasonably well-defined, erythematous, scaling or slightly shiny macular lesion.[14][1] 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, to the naked eye, a peripheral thread-like pearly rim or islands of pearliness distributed through the lesion.

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

5.2.3.2 Causation

Exposure to sunlight is the most common cause of superficial BCC. Multiple superficial BCCs may also occur in the context of arsenic intoxication. Other stigmata of arsenic intoxication include punctate palmoplantar keratoderma, scattered macular hypopigmentation and longitudinal pigmented bands or horizontal hyperpigmented stripes in fingernails and toenails.

5.2.3.3 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.

5.2.3.4 Differential diagnosis

Superficial BCC should be distinguished from:

- actinic (solar) keratosis
- Bowenoid keratosis
- Bowen's disease
- amelanotic melanoma.

As the management of superficial BCC may differ from that of these other tumours, a biopsy to obtain definitive pathology should be undertaken prior to definitive treatment. The appearance may suggest an inflammatory dermatosis such as eczema or psoriasis. However, the clinical history of superficial BCC is one of inexorable enlargement over months or years while inflammatory lesions are generally more transient. Dermoscopy may be a helpful tool in diagnosis of these lesions.[15]

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5.2.4 Nodular basal cell carcinoma

Nodular BCCs are more often found on the head and neck in people who are somewhat older on average than those with superficial BCC.[1][16]

5.2.4.1 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 may lead to central umbilication of the lesion with a more raised rolled border. Islands of pigmentation may become clinically visible and the lesion may become darkly pigmented, suggesting melanoma. Like superficial BCC, these may be associated with sensory symptoms (only in a minority of cases) but, unlike superficial BCC, nodular lesions often ulcerate and bleed.

5.2.4.2 Differential diagnosis

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

The differential diagnosis also includes various benign lesions.

5.2.4.3 Clinical course

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

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5.2.5 Sclerosing basal cell carcinoma

Sclerosing (morphoeic) BCC has a similar body-site distribution to that of nodular BCC. Sclerosing BCCs are usually of long standing and tend to be deeply invasive.

5.2.5.1 Clinical features

These lesions have a sclerosing growth pattern with fibrosis surrounding areas of BCC. Basal cell carcinomas that are predominantly sclerosing have the appearance of a pale scar.

Palpation usually reveals firm induration, which may extend more widely and deeply than is evident on inspection. Sclerosing changes will frequently supervene in longstanding nodular BCCs and these lesions may retain some clinical features of nodular BCC.

Sclerosing BCCs are frequently asymptomatic. Those with nodular elements may show all the same symptoms as nodular BCCs.

5.2.5.2 Clinical course

Sclerosing BCCs may remain undetected by doctor and patient for many years and may slowly enlarge and deepen to reach a large size before being treated.

The major differential diagnosis of sclerosing BCC is scar tissue. Biopsy is necessary to establish the diagnosis.

Recurrence in sclerosing BCCs can be common, and therefore requires regular monitoring. Some recurrence may be due to local incomplete excision, with satellite islands of BCC either having not been visible at the time of surgery, or being distant from the primary lesion, particularly in those with certain genetic syndromes such as Gorlin's syndrome (naevoid BCC syndrome) or those with immunosuppression.

Sclerosing lesions should be reviewed more frequently and may benefit from specialist review.

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5.2.6 Influence of subtype on prognosis of basal cell carcinoma

Certain BCC subtypes (Table 1) are associated with a poor prognosis.

Table 1. Tumour-specific factors associated with recurrence of basal cell carcinoma

Key point(s)
■ Consider dermoscopy in the examination of all skin lesions in order to better identify changes in blood vessels and pigmentation. ■ Biopsy should precede treatment for a single localised erythematous scaling lesion. ■ Superficial basal cell carcinoma should be considered in the differential diagnosis when reviewing a bright pink, shiny erythematous macular lesion, particularly if well defined. ■ Nodular basal cell carcinoma should be considered when assessing any lesion that is shiny, translucent (pearly), telangiectatic and has papules or nodules. ■ Consider the possibility of sclerosing (morphoeic) basal cell carcinoma when assessing scar-like lesions. ■ Stretching the skin accentuates features in basal cell carcinoma subtypes (eg. nodular subtypes and sclerosing subtype).

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■ Clinical features of keratinocyte cancer – Introduction
■ Clinical features of cutaneous squamous cell carcinoma and related keratinocyte tumours

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5.3 4.2 Clinical features of cSCC and related tumours

Contents

5.3.1 Background

The majority of cutaneous squamous cell carcinomas (cSCCs) are thought to arise from actinic (solar) keratoses (AKs).[1] The age and body-site distribution is therefore similar to that of AK. A few develop from chronic ulcers or scars, sites of chronic radiation dermatitis or from infrared irradiation.

The risk of cSCC is higher among immunodeficient individuals. Immunosuppression for organ transplantation strongly predisposes to cSCC (see: Organ transplantation and other conditions associated with prolonged immunosuppression).

There is probably a histological continuum of keratinocyte dysplasia from AK to invasive cSCC (see: Pathology). The continuum includes Bowenoid keratosis and Bowen's disease (cSCC in situ, also known as intra-epidermal squamous cell carcinoma). Distinguishing between each of these may be difficult for the clinician.

All of these tumours produce keratin, manifested 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 cSCC). Poorly differentiated cSCCs may not produce large amounts of keratin.

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5.3.2 Overview of evidence (non-systematic literature review)

5.3.2.1 Cutaneous squamous cell carcinoma

5.3.2.1.1 Clinical features (cutaneous squamous cell carcinoma)

Cutaneous squamous cell carcinoma 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.

5.3.2.1.2 Accuracy of diagnosis of cutaneous squamous cell carcinoma

Experienced dermatologists working in a Queensland prevalence study achieved a diagnostic accuracy of 39%, considerably lower than the 59% found for basal cell carcinoma (BCC).[2]

The clinical diagnosis of early cSCC is difficult, particularly distinguishing it from a hypertrophic AK. It is likely that many early cSCCs are treated with cryotherapy based on a clinical diagnosis of AK.

The course of a cSCC 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, generally to regional lymph nodes.

5.3.2.1.3 Differential diagnosis

Squamous cell carcinoma 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. Dermoscopy is a useful adjunct in this diagnostic process and is recommended, particularly when pigment is present.

5.3.2.1.4 Clinical course

The majority of squamous cell carcinomas are thought to arise from AKs, although the vast majority of AKs do not become cSCCs.[3]

Certain cSCC subtypes, sites and other features are associated with a poor prognosis (Table 2).

Table 2. Tumour-specific factors associated with recurrence of squamous cell carcinoma

5.3.2.1.5 Practice Point (cutaneous squamous cell carcinoma)

Practice point
PP 4.2.1. If a skin lesion is initially considered to be an actinic keratosis, but it persists following cryotherapy, enlarges or becomes tender, it should be biopsied to investigate the possibility of cutaneous squamous cell carcinoma or other dysplastic lesions.

Key point(s)
■ All patients with actinic keratoses should be offered regular follow-up, with the aim of early detection of cutaneous squamous cell carcinoma, should it occur. ■ When induration, thickening or tenderness in the erythematous base of a scaling lesion is identified, the possibility of early cutaneous squamous cell carcinoma should be considered. ■ Dermoscopy is useful in diagnosing and differentiating cutaneous squamous cell carcinoma.

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5.3.2.2 Actinic keratoses (including Bowenoid keratosis)

Actinic (solar) keratoses 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. A Bowenoid keratosis may have a slightly thicker erythematous base than an AK (see: Pathology)

5.3.2.2.1 Clinical features

Actinic keratoses present as erythematous macules 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. Actinic keratoses may be symptomatic. A variety of sensory symptoms including pricking, burning and stinging may be felt with sun exposure or perspiration.

5.3.2.2.2 Differential diagnosis

Pigmented AK may need to be differentiated from solar lentigines and lentigo maligna. The erythema associated with hyperkeratosis is the most helpful distinguishing feature of AK. Actinic keratoses are less well defined at the periphery than cSCC in situ and are also less well defined than seborrhoeic keratoses, which are not normally erythematous.

Thickening and tenderness on lateral palpation are signs that a AK may have developed into invasive cSCC.

5.3.2.2.3 Clinical course

Only a small percentage of AK evolve into invasive cSCC. According to one estimate, the rate of malignant transformation is less than one in 1000 per year. Many cSCCs, however, evolve from AK.[4]

Key point(s)

- Consider actinic keratoses when assessing lesions that present as erythematous macules with superimposed hyperkeratosis.
- Only a small percentage of actinic keratoses evolve into invasive squamous cell carcinoma.
- Induration (thickening), erythema and tenderness on lateral and vertical palpation are signs that an actinic keratosis may have developed into invasive cutaneous squamous cell carcinoma.

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5.3.2.3 Bowen’s disease (squamous cell carcinoma in situ)

Classical Bowen’s disease was originally described by John Bowen[5][6] as scaling erythematous lesions in non-light exposed areas of skin. With the increasing use by pathologists of the term to classify any lesion with histology displaying full-thickness keratinocyte dysplasia (atypia) in the epidermis (cSCC in situ), ‘Bowen’s disease’ is now also applied to tumours with this histological characteristic in light-exposed areas.

5.3.2.3.1 Clinical features

Classical cSCC in situ 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 lesions with this histology also occur in frequently exposed areas, such as the head and neck. Squamous cell carcinoma in situ is generally asymptomatic. The clinical history is usually of a longstanding, slowly enlarging lesion.

Bowen's disease-like lesions on non-sun exposed areas (e.g. the areola/breast or genitals), could be Paget's disease.

5.3.2.3.2 Differential diagnosis

Classical cSCC in situ may be distinguishable from psoriasis by its long history, though the clinical appearances may be very similar. Superficial BCC may be distinguished from cSCC in situ by less hyperkeratosis, a shiny surface and the pearliness that becomes apparent on stretching a BCC. Hypertrophic cSCC in situ may mimic cSCC and a biopsy is frequently necessary to distinguish this from invasive cSCC. Pigmented Bowen's disease may mimic superficial BCC or superficial spreading melanoma.

5.3.2.3.3 Clinical course

Classical cSCC in situ will generally enlarge very slowly and will appear to the patient as a stable lesion. The rate of transformation to invasive cSCC has not been established, but would appear to be low. If a lesion changes, it should be biopsied to excluded transformation to invasive disease.

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5.3.2.4 Keratoacanthoma

Whether keratoacanthoma is a form of cSCC or a separate lesion is still under debate (see: Pathology of keratoacanthoma).

Many keratoacanthomas arise in association with AK, and the age and site distribution is similar to that of AK and cSCC. 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.

5.3.2.4.1 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 4–8 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 occasion, a keratoacanthoma may develop soon after trauma or surgery.

They may be multiple.[7]

Keratoacanthomas often undergo spontaneous resolution. Resolution generally occurs within 6–12 weeks, but they may persist, indicating likelihood of cSCC.

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

5.3.2.4.2 Aids to diagnosis

Partial biopsy will generally be unhelpful in differentiating keratoacanthoma from cSCC. 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.

5.3.2.4.3 Practice Point (keratoacanthoma)

Practice point
PP 4.2.2. Keratoacanthomas should be managed by early excision rather than relying on correct clinical diagnosis and waiting for spontaneous resolution.

Key point(s)

- In circumstances where excision of a lesion is not appropriate, clinical correlation is required to distinguish between keratoacanthoma and invasive cutaneous squamous cell carcinoma, particularly in cases where partial biopsy does not enable a definitive diagnosis.
- Always consider Paget's disease in the differential diagnosis of a skin lesion with the appearance of Bowen's disease that occurs in an areas of low sun exposure (e.g areola, breast and genitals).

5.3.3 Notes on the recommendations

Follow-up of patients after treatment is individually tailored according to patient factors, tumour factors, anatomic site and the perceived adequacy of treatment.

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Go to:

- Clinical features of keratinocyte cancer – Introduction
- Clinical features of basal cell carcinoma

5.3.4 References

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5.4 5. Pathology – Introduction

Introduction

Keratinocytic tumours form a wide continuum from benign tumours to malignant tumours. This spectrum includes:

- benign adnexal tumours, often showing follicular differentiation
- tumours of intermediate malignant potential, such as keratoacanthoma (which usually resolve)
- pre-invasive lesions, such as Bowen’s disease (cutaneous squamous cell carcinoma in situ) and actinic keratosis

- frankly malignant tumours, such as basal cell carcinoma and cutaneous squamous cell carcinoma
- rare tumours, such as Merkel cell carcinoma, Paget's disease and atypical fibroxanthoma.

Topics covered in this section include:

- Pathology of basal cell carcinoma
- Pathology of cutaneous squamous cell carcinoma and related tumours
- Pathology of keratoacanthoma
- Pathology of rare tumours
- Biopsy considerations and the biopsy report

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5.5 5.1 Pathology of BCC

Contents

5.5.1 Background

Basal cell carcinomas (BCCs) 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 tumour has a blue cell appearance.

5.5.2 Overview of evidence (non-systematic literature review)

5.5.2.1 Recurrence of basal cell carcinomas

Basal cell carcinomas may be locally destructive, but very rarely metastasise.[1] Local recurrence is not uncommon. There is an increased risk of local recurrence for large, deep or ulcerated tumours, especially if incompletely or narrowly excised, and for tumours of micronodular, infiltrating, sclerosing (morphoeic) or superficial multifocal subtype.[2][3][4] The risk of recurrence is greater if combinations of such features are present.

Other presentations and features associated with a higher risk of recurrence include (Table 1):[5][6]

- tumours on the nose or nasolabial fold
- tumours recurring after previous radiotherapy
- tumours associated with perineural spread, particularly on the head and neck
- naevoid BCC syndrome (Gorlin's syndrome), which is rare
- immunosuppression (see: Organ transplantation and other conditions associated with prolonged immunosuppression).

Table 1. Tumour-specific factors associated with recurrence of basal cell carcinoma

5.5.3 Histological diagnosis of basal cell carcinomas

Histological diagnosis of BCCs is usually straightforward. Most tumours are of nodular or nodulocystic subtype. Frequently, the tumour shows a mixed pattern.

Superficial BCC is a common subtype and frequently occurs on the trunk. It is characterised by small basaloid groupings 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 BCCs.

Differential diagnoses that should be considered include cutaneous squamous cell carcinoma (with basaloid cell features), Merkel cell carcinoma (an aggressive tumour; see Pathology of rare tumours) and various skin appendage tumours (commonly benign), particularly those of follicular origin.

Special staining by immunochemistry can be helpful. Basal cell carcinoma is typically positive for cytokeratin and Ber-ep4, and negative for epithelial membrane antigen (EMA). Merkel cell carcinoma is diffusely positive for cytokeratin 20 (CK20). Cytokeratin 20 is also useful in follicular neoplasms, which may contain a few CK20-positive Merkel cells.

Key point(s)
The clinical location, the architectural pattern and excision margins should be considered when determining the risk of recurrence.

Go to:

- Pathology – Introduction
- Pathology of cutaneous squamous cell carcinomas and related tumours
- Pathology of keratoacanthoma
- Pathology of rare tumours
- Biopsy considerations and the biopsy report

5.5.4 References

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5.6 5.2 Pathology of cSCC and related tumours

Contents

5.6.1 Background

In recent years there has been a growing appreciation that actinic keratosis (AK), bowenoid AK and cutaneous squamous cell carcinoma (cSCC) in situ (Bowen’s disease), and invasive cSCC appear to represent a neoplastic continuum. These conditions are all characterised by keratinocyte nuclear atypia, commonly with large, irregular, crowded and hyperchromatic nuclei with cellular disorganisation.

In many cases, AK regresses spontaneously, while uncommonly, it evolves into invasive cSCC.[1][2] Bowen's disease, even after many years, may also evolve into invasive cSCC.[3]

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5.6.2 Overview of evidence (non-systematic literature review)

5.6.2.1 Actinic keratosis

Actinic keratoses are lesions that have epidermal basal layer nuclear atypia with variable hyperkeratosis and parakeratosis, and background dermal solar elastosis.

Actinic keratoses may have several intraepidermal layers of atypical keratinocytes, even approaching full-thickness atypia. The term 'bowenoid' has been applied to such keratoses.

5.6.2.2 Cutaneous squamous cell carcinoma in situ (Bowen's disease)

Cutaneous squamous cell carcinoma in situ (Bowen's disease) refers to a 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.

Bowen's disease, particularly in non-sun-exposed sites, has increasingly been linked with human papillomavirus.

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5.6.2.3 Stages of the neoplastic continuum

The variations of patterns of in situ keratinocyte atypia may uncommonly evolve into invasive cSCC and can be viewed as cSCC in situ. In practice, the term 'in-situ keratinocyte atypia' is most commonly used with Bowen's disease.

Actinic keratosis uncommonly progresses to cSCC in-situ or invasive cSCC.[1][2] In many cases, AKs appear to regress spontaneously.[1]

Squamous cell carcinoma in situ (whether or not arising de novo), which commonly involves follicular structures, may develop into an invasive cSCC, often after many years. The frequency with which this occurs is unknown. When it becomes invasive, the cSCC is usually not well differentiated. Most invasive cSCCs arise in association with AK.[4]

In clinical practice, it is not always easy to distinguish between a thick (acanthotic) AK and a thin invasive cSCC.[5] Tenderness to palpation may be a clue.

A tumour is designated as an invasive cSCC when the cell masses, showing varying degrees of differentiation, are seen lying clearly in the dermis. Adjacent changes of AK 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 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 a distinction can be seen using immunostaining. Cutaneous squamous cell carcinomas stain positive for pan cytokeratin and CK5/6, and negative for S100 and Sox-10.

Factors associated with a greater risk of metastasis of invasive cSCC include (Table 2):

- greater tumour size and greater depth of the tumour (>6mm)
- a poor degree of differentiation
- an infiltrative growth pattern
- plentiful mitoses, a spindle cell pattern and single cell infiltrative patterns
- arising in site of burns and scars
- scalp, ear, vermilion of the lip or genital sites[6][7][8][9]
- perineural or endolymphatic spread.

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

Table 2.Tumour-specific factors associated with recurrence of squamous cell carcinoma

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- Pathology of rare tumours
- Biopsy considerations and the biopsy report

5.6.3 References

1. ↑ 1.0 1.1 1.2 Marks R, Foley P, Goodman G, Hage BH, Selwood TS. *Spontaneous remission of solar keratoses: the case for conservative management.* Br J Dermatol 1986 Dec;115(6):649-55 Available from: http://www.ncbi.nlm.nih.gov/pubmed/3801305.
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5.7 5.3 Pathology of keratoacanthoma

Contents

5.7.1 Background

Whether keratoacanthoma is a variant of cutaneous squamous cell carcinoma cSCC or is a separate entity has been the subject of debate for many years.

Keratoacanthoma primarily differs from cSCC in its natural history of rapid growth, which is often followed by regression. Histopathologists differ widely in their approach to the diagnostic classification of keratoacanthoma; one study found that the ratio of SCC diagnoses to keratoacanthoma diagnoses ranged from 2.5:1 to 139:1.[1]

Pathological diagnosis of keratoacanthoma depends on a combination of clinical history and microscopic appearance. There can be significant overlap between the histological features of keratoacanthomas and cSCCs, which at least partly accounts for the variation in pathological diagnosis. It is well documented that there are keratoacanthomas with cSCC components, keratoacanthoma-like cSCCs, and keratoacanthomas with malignant transformation.[2]

From a genetic perspective, recent studies have shown that the *MAP3K8* (*TPL2*) oncogene may be a driver of the development of both keratoacanthoma and cSCC.[3]

Taking all current evidence together, the editors of the 2018 edition of the World Health Organization (WHO) classification of skin tumours consider keratoacanthoma to be a variant of cSCC, rather than a separate entity.[4]

5.7.2 Overview of evidence (non-systematic literature review)

5.7.2.1 Histological diagnosis of keratoacanthoma

Keratoacanthoma 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. These lesions also occur in immunocompromised individuals (see 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.

A keratoacanthoma has a symmetrical crateriform architecture with overhanging shoulders, relatively limited nuclear atypia and a predominance of cells with abundant pale glassy cytoplasm within the lesion. Occasionally perineural invasion may be apparent, most often in facial lesions.[5] Such a finding warrants close follow-up to help rule out cSCC.

On partial biopsies it can be difficult to distinguish between keratoacanthoma and invasive cSCC. A history of rapid growth and a characteristic architecture help establish the diagnosis of keratoacanthoma, but occasionally, a clear distinction from a cSCC is not possible.

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. Frequently, overlap features occur with those of cSCC 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 avoid the need for more extensive therapy.

Key point(s)
Clinical correlation is required to distinguish between keratoacanthoma and invasive cutaneous squamous cell carcinoma in cases where partial biopsy does not enable a definitive diagnosis.

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- Pathology of basal cell carcinoma
- Pathology of cutaneous squamous cell carcinoma and related tumours
- Pathology of rare tumours
- Biopsy considerations and the biopsy report

5.7.3 References

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5.8 5.4 Pathology of rare tumours

Contents

6 References

5.8.1 Background

Rare keratinocytic tumours include Merkel cell carcinoma (MCC), cutaneous Paget's disease and atypical fibroxanthoma.

5.8.2 Pathology of Merkel cell carcinoma

Merkel cell carcinoma is a high-grade primary neuroendocrine carcinoma of the skin. It primarily effects the elderly and the immunosuppressed. Both chronic ultraviolet (UV) light exposure and integration of the Merkel cell polyomavirus are associated with MCC.[1]

Histologically MCC is composed of small blue round cells with stippled chromatin and an inconspicuous nucleolus. It stains positively for Cytokeratin 20 (CK20) and for the neuroendocrine markers chromogranin A and synaptophysin.

Merkel cell carcinoma is locally aggressive and also shows a tendency to metastasise to local lymph nodes. It can also be more widely metastatic.[1]

Sentinel lymph node biopsy is often indicated and specialist referral is recommended when this diagnosis is made.

Merkel cell carcinoma is staged according to the American Joint Committee on Cancer (AJCC) staging manual.[2]

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5.8.3 Pathology of mammary and extramammary Paget's disease

Mammary Paget's disease (also called Paget's disease of the nipple) is a condition that involves the nipple and areolar complex. It has an eczematous appearance. Paget's disease is often associated with underlying carcinoma of the breast.[1]

Histologically there is intraepidermal spread of carcinoma cells in a single cell scattering pattern (so called Pagetoid spread).

Extramammary Paget's disease is most common in the anogenital region. It may be primary to the skin or may present as complicated colorectal carcinoma, urethral carcinoma or carcinoma of the female genital tract.[1]

Specialist referral is recommended when this diagnosis is made.

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5.8.4 Pathology of atypical fibroxanthoma

Atypical fibroxanthoma is a dermally based tumour of uncertain histogenesis which is characterised by its pleomorphic appearance but generally low-grade clinical behaviour.[1] It occurs in the older age group, usually in the setting of marked solar elastosis on the head and neck. Atypical fibroxanthoma presents as a solitary nodule, which is often ulcerated and has a short clinical time course.

Histologically, the tumour is often pleomorphic and shows frequent and abnormal mitotic figures. There is a spindle cell variant.[1]

Immunoperoxidase stains are very important in the diagnosis of atypical fibroxanthoma, which is essentially a diagnosis of exclusion. The differential diagnosis includes squamous cell carcinoma, melanoma, leiomyosarcoma and angiosarcoma. Atypical fibroxanthoma usually stains for CD10 and is negative for the markers of cutaneous squamous cell carcinoma, melanoma, angiosarcoma and leiomyosarcoma. Frequently only CD10 is positive. Most atypical fibroxanthomas are benign, provided that strict criteria are used for diagnosis. A low percentage of cases recur and metastasis are rarely reported. If the tumour involves the subcutis it is better classified as a 'pleomorphic dermal sarcoma not otherwise specified' (PDS-NOS). Pleomorphic dermal sarcoma is a deeper form of AFX. It infiltrates into the subcutis and shows greater risk of recurrence and metastasis (although metastasis is rare).

5.8.5 Practice Point

Practice point

PP 5.4.1 When a diagnosis is made on histopathology in the following conditions referral to a specialist for assessment and treatment should be undertaken:

- Merkel cell carcinoma
- extramammary Paget’s disease
- mammary Paget’s disease (refer to a breast surgeon)
- atypical fibroxanthoma or pleomorphic dermal sarcoma not otherwise (consider referral).

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- Pathology of basal cell carcinoma
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- Pathology of keratoacanthoma
- Biopsy considerations and the biopsy report

5.8.6 References

1. ↑ 1.0 1.1 1.2 1.3 1.4 1.5 Elder DE, Massi D, Scolyer RA, Willemze R. *WHO Classification of Skin Tumours. 4th edn.* Lyon, France: International Agency for Research on Cancer; 2018.
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5.9 5.5 Biopsy considerations and the biopsy report

Contents

5.9.1 Background

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

5.9.2 Clinician's responsibilities

The best approach to biopsy is complete excision of the lesion (if appropriate) as this facilitates study of the architecture and cytological appearances of the tumour, assessment of its extent, and an assessment of adequacy of excision.

If complete excision is not considered appropriate, small representatives samples can be useful, such as those obtained by one or more punch biopsies, shave biopsy or curettage, 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. It is also helpful to indicate the site of any extension of the tumour to the specimen edges. By convention, the suture will be denoted as 12 o'clock when not otherwise indicated.

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 following clinical information should be provided on request form:

- patient identification (full name, age and sex)
- site of biopsy
- description and duration of the lesion and of any associated symptoms
- clinical diagnosis or differential diagnoses
- history of previous treatment of lesion
- history of previous biopsies
- history of other skin tumours
- presence of scars, burns or ulceration
- diagram of excision specimen with markers for orientation.

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5.9.3 Pathologist's responsibilities

5.9.3.1 Specimen sampling

The pathologist should ensure that there is optimal sampling of the specimen. Particularly for smaller specimens, the entire tissue should be sliced with multiple sections embedded for sectioning.

For skin specimens, significant (≥20%) shrinkage may occur with formalin fixation,[1] 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.

5.9.3.2 Components of the pathology report

The pathologist's report should contain:

- the clinical notes
- the macroscopic description
- the microscopic findings
- margins of excision
- prognostic factors.

5.9.3.3 Reporting of excision margins

Excision margins should be measured if necessary. This is particularly important with narrowly excised lesions.

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. Mohs micrographic surgery using frozen sections examines excision margins more comprehensively, leading to a lower recurrence rate (see: Surgical treatment), but the technique is not practical for use in all skin specimens submitted for histopathology[2]

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.

5.9.3.4 Prognostic information in the pathology report

The pathology report should include a synoptic checklist of information useful for prognosis. These include:

- tumour type
- degree of differentiation or subtype of the tumour
- tumour thickness in the dermis
- perineural, vascular or lymphatic spread.

Prognostically significant terms in pathology reports should be consistent and unambiguous (Table 3).

Table 3. Terms in the pathology report that have prognostic significance

Term	Explanation and notes
Poorly differentiated	Refers to tumours in which the products of differentiation, such as keratin or desmostromal attachments, are poorly expressed. Immunohistochemistry techniques for keratin subsets are often used to identify such tumours.
Basosquamous carcinoma, metatypical carcinoma	Uncommonly, tumours may show histological features intermediate between BCC and cSCC. These generally behave more like cSCC and, in practice, they should be considered to be forms of cSCC. Pathologists should generally avoid using these terms because they are potentially confusing.

Desmoplasia	Prominent fibrous or sclerotic stromal changes associated with tumours, especially BCC, and less commonly cSCC. Clinically, such tumours may be mistaken for scars. They are ill defined and prone to recurrence. Pathologists should generally avoid this term and instead use a term like 'fibrosing', to avoid confusion with the desmoplastic melanoma sub-type.
Large tumour	Tumour size greater than 2cm in diameter is associated with increased risk of tumour recurrence, particularly for cSCCs. For cSCCs of diameter more than 2cm, the risk of recurrence is two times higher (15.2% versus 7.4%) and the risk of metastasis is three times higher (30.3% versus 9.1%) than for small cSCCs.[3]
Perineural involvement	Neural involvement by tumours takes the form of perineural spread, which may extend into the deep tissue. This 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	Dermal lymphatic spread in satellite nodules may be seen as separate from the primary lesion and represents a poor prognostic sign.

BCC: basal cell carcinoma; cSCC: cutaneous squamous cell carcinomaBack to top

5.9.3.5 Other information in the pathology report

The pathology report may refer to previous biopsies.

On occasions, appended comments and references can be useful to assist the clinician with interpretation. The following are examples of appropriate comments to include in the pathology report:

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

5.9.4 Communication between the clinician and the pathologist

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.

If there is uncertainty in the pathology report, the clinician, in consultation with the pathologist, should seek further evaluations of the slides and/or specimen.

5.9.5 Practice Points

Practice point

PP 5.5.1. Excision biopsy should be performed when appropriate. If complete excision is not possible, punch biopsies, shave biopsy or curettage can be considered, as appropriate to the size and depth of the lesion.

Practice point

PP 5.5.2. A suture should be placed in the specimen and a diagram should be provided to enable the pathologist to orient the specimen within the anatomical site and/or lesion.

Key point(s)

Samples from different anatomical sites should be carefully labelled and placed in separate specimen containers.

The pathology request should include:

- the patient's full name, age and sex
- site of biopsy
- a description and duration of the lesion and any associated symptoms
- relevant clinical history (e.g. other skin tumours, the presence of scars, burns or ulceration)
- previous biopsies and treatment
- diagnoses under consideration.

The pathologist's report should contain:

- the clinical notes
- the macroscopic description
- the microscopic findings
- margins of excision
- a summary of prognostic factors including tumour type, tumour subtype or degree of differentiation, thickness in the dermis, perineural invasion, and vascular or lymphatic spread.

If there is uncertainty in the pathology report, the clinician, in consultation with the pathologist, should seek further evaluations of the slides and/or specimen.

Go to:

- Pathology – Introduction
- Pathology of basal cell carcinoma
- Pathology of cutaneous squamous cell carcinoma and related tumours
- Pathology of keratoacanthoma
- Pathology of rare tumours

5.9.6 References

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5.10 6. Prognosis – Introduction

5.10.1 Introduction

With prompt detection and effective treatment, basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) generally carry a good prognosis. These tumours are rarely fatal, causing only approximately 560 deaths each year in Australia.[1]

Outcomes generally reported in clinical trials BCC and cSCC management include recurrence, 5-year survival and treatment-related morbidity. These outcomes are influenced by tumour stage, site, morphological and histological subtype, treatment modality and excision margins.

Topics covered in this section include:

- Prognosis of basal cell carcinoma
- Prognosis of cutaneous squamous cell carcinoma

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5.10.2 References

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5.11 6.1 Prognosis of BCC

Contents

5.11.1 Background

Unless stated otherwise, tumour stage is according to the American Joint Committee on Cancer (AJCC) cancer staging manual 8th edition [1] and Union for International Cancer Control (UICC) TNM classification of malignant tumours 8th edition.[2]

The prognosis for patients with basal cell carcinoma (BCC), including recurrence, 5-year survival and treatment-related morbidity, is influenced by tumour characteristics, the site, and the treatment modality (Table 4.1).

Table 4.1. Factors associated with recurrence of basal cell carcinoma

Tumour-specific factors
Size (higher risk for >2cm)
Stage (higher risk for T4; deep invasion beyond subcutaneous tissue)

Subtype (higher risk for sclerosing [morphoeic], or micronodular subtypes)
Presence of perineural invasion
Anatomical site (higher risk for nose, eyelids, temple, pre- and post-auricular/ear, lower legs, lip)
Recurrence status (higher risk for recurrent tumours)
Patient-related factors
History of skin cancers (higher risk if history of multiple tumours)
Treatment-related factors
Treatment modality (lower risk for surgical excision)
Completeness of excision (lower risk for complete excision)

5.11.2 Overview of evidence (non-systematic literature review)

5.11.2.1 Recurrent tumours

Rates of control are lower after treatment for recurrent BCC than after treatment for primary BCC.[3][4][5][6]

For early-stage tumours, reported recurrence rates after standard surgical treatment of previously treated (recurrent) BCC are in the range of 15–30%, compared with previously untreated (primary) BCC of 1–10%.[7][8] Mohs micrographic surgery (MMS) can be an effective treatment for these tumours (see: Criteria for selecting Mohs micrographic surgery). However, most series also report excellent salvage results with radical surgery[8][9] (or, less commonly, using radiotherapy).[10][11]

These recurrence figures increase with increasing tumour stage,[12] and salvage becomes harder to achieve. Furthermore, control rates are likely to progressively diminish with each successive episode of recurrence and salvage treatment.[9][13]

5.11.2.2 Stage

Control rates diminish with increasing size and depth of invasion (T stage; Table 4.2). See Appendix A TNM staging.

Table 4.2. Overall estimated control rates of treated primary BCC by T stage[14][15][16][17][18][19][20][21][22][23]

T stage	Size (maximum diameter)	5-year control rates

T1	≤2cm	95%
T2	>2cm but ≤5cm	88%
T3	>5cm	80–85%
T4	Tumour deeply invaded beyond subcutaneous tissues	40–50%

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Cartilage and bone invasion are surrogate markers of more advanced stage, deeper invasion and/or recurrent BCC.[24] It is very difficult to control BCC that has infiltrated cartilage or bone because it is not possible to define the extent of spread, the tumour burden may be large, and radical treatment may not be possible or may involve significant morbidity that may not be acceptable to or tolerated by the patient.[17][18]

Rarely, patients present with very large primary BCCs (>10–20cm) due to patient neglect or denial. These 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.[25]

5.11.2.3 Site

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.[6][26]

The spectrum of morphological subtypes of BCCs occurring on the trunk and limbs tends to differ from that of BCCs occurring on the head and neck.[27] The subcutaneous anatomy of the face and scalp 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.

5.11.2.4 Morphological and histological subtype

Superficial and nodular BCCs are usually clinically and histologically well circumscribed and curable with all established treatment modalities.[5][19]

Sclerosing (morphoeic), micronodular and infiltrative (deeper induration) BCCs are harder to define macroscopically, and microscopically are associated with lower clearance rates following excision. They are associated with higher recurrence rates.[28][29][19][30]

Tumours that show histological features intermediate between BCC and cutaneous squamous cell carcinoma (cSCC), formerly called basosquamous or metatypical BCCs, are also more likely to recur.[31][19] These represent less than 5% of all BCCs.[19]

However, the quality of data supporting all the observed associations between morphological and histological subtype and prognosis is poor.

5.11.2.5 Treatment modality

Surgical excision remains the treatment of first choice. Complete excision (particularly MMS) delivers the highest and most prognostically reliable control rates (see: Surgical treatment).[7][8][4][9][28][32][33][34][23][35]

Radiotherapy, electrodessication and curettage, and cryotherapy each deliver lower control rates than surgical excision, in descending order (see: Radiotherapy, cryotherapy and electrodessication and curettage).[7][10][9][6][20][36][23][37]

5.11.2.6 Incomplete excision

Incomplete excision is associated with an overall recurrence rate of 30%. This finding emphasises the importance of achieving complete excision at the primary procedure.[13][38][36][39][40][41][42][43][44]

The risk of recurrence is highest in lesions where both lateral and deep margins are involved.[45][46][30]

Approximately one-third of incompletely excised BCCs are found to recur, with the proportion depending on the length of follow-up.[41][46][43][44]
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5.11.2.7 Perineural invasion

Perineural invasion (PNI) is uncommon among patients with BCC and even rarer than among patients with cSCC (see also Perineural invasion in Prognosis of cutaneous squamous cell carcinoma). It most often occurs in patients with BCC of the head and neck.[47][48][49][50]

Clinicians managing BCC with PNI should seek a specialist opinion on its clinical significance and optimal treatment (e.g. discuss with radiation oncologist).

5.11.2.8 Naevoid basal cell carcinoma syndrome

Naevoid BCC syndrome (Gorlin's syndrome) is a rare inherited disorder with early onset and a relentless, lifelong, high frequency of BCC.[51][52][53]

Diminishing reserves of normal skin with increasing age can eventually compromise control in these patients (see: Epidemiology).[52]

5.11.2.9 Measuring success of basal cell carcinoma treatment

The endpoint for measuring the success of BCC treatment (excluding cosmetic, functional and patient convenience factors) is not universally defined.

Survival (overall survival or disease-specific survival) is a poor measure of treatment success because BCC is rarely fatal and BCCs can have a very long history in recurrence pattern; commonly 10 to more than 20 years.[3][4][13]

The best available endpoint is a chronologically defined local control rate (e.g. 5-year and 10-year control or recurrence).

Completeness of excision is a useful surrogate measure because incomplete excision is associated with an overall recurrence rate of 30%.[13][38][36][39][41][42][43][44]

Key point(s)

- Patients with basal cell carcinoma without high-risk features can be reassured that the prognosis is generally excellent.
- When a patient has a basal cell carcinoma that is larger than 2cm, is on the face, or has recurred after a previous treatment, the clinician should explain that there is a risk of recurrence or spread. The clinician should offer follow-up or further treatment as appropriate, and carefully explain the risks and benefits of each management option.
- When incomplete excision of a basal cell carcinoma is reported, the surgeon or treating clinician should explain to the patient that there is a significant risk of the cancer recurring, and should offer further treatment as appropriate, carefully explaining the risks and benefits of each management option.

Note: Follow-up of patients after treatment is individually tailored according to patient factors, tumour factors, anatomic site and the perceived adequacy of treatment.

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Go to:

- Prognosis of keratinocyte cancer – Introduction
- Prognosis of cutaneous squamous cell carcinoma

5.11.3 References

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5.12 6.2 Prognosis of cSCC

Contents

5.12.1 Background

Unless stated otherwise, tumour stage is according to the American Joint Committee on Cancer (AJCC)cancer staging manual 8th edition[1] and Union for International Cancer Control (UICC) TNM classification of malignant tumours 8th edition.[2]

The biological potential of early cutaneous squamous cell carcinoma (cSCC) and the risk of metastasis can be predicted based on tumour-specific factors, site and tumour disposition.

Current evidence has identified nine broad categories of prognostic indicators (Table 4.3). Accurate weighting of individual prognostic factors has been complicated by the fact that individual participants in reported case series typically had multiple factors.

Table 4.3. Factors associated with recurrence poorer prognosis of cutaneous squamous cell carcinoma

Stage (see: Appendix A. TNM staging)
T stage
M stage
N stage
Regional spread (lymph nodes)*
Perineural invasion*
Histological grade
Higher risk for poorly differentiated subtype
Clinical signs
Higher risk with findings suggesting rapid growth or greater spread (e.g. palpable thickness, diffuse infiltration and induration with poor demarcation of tumour edges, tenderness and inflammation)
Anatomical site
Higher risk for ear, lip
Number of skin cancers (higher risk for multiple lesions)
Recurrence
Higher risk for recurrent/persistent lesions
Treatment
Higher risk for inadequately treated lesions
Aetiology[#]
Higher risk for non-UV-induced lesions e.g. infection with oncogenic HPV subtypes, exposure to arsenic
Comorbidity
Higher risk in presence of immunosuppression, skin-related comorbidities (e.g scleroderma, xeroderma pigmentosa)

*The current TMN system does not take into account risk associated with local metastatic spread (lymphatic or perineural).

#Cutaneous SCCs arising from aetiological factors other than ordinary sun exposure in otherwise healthy people (e.g. infection with oncogenic HPV subtypes, arsenic ingestion).

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5.12.2 Overview of evidence (non-systematic literature review)

5.12.2.1 Stage

Staging is a fundamental tool in cancer clinical research conducted with the aim of improving outcomes for patients. The application of the generic TNM staging system is a poor fit for cSCC, as a large proportion are classified as T1N0M0.[3] However, until a more sophisticated universal staging system for cSCC is developed, it remains an interim instrument.

See Appendix A. TNM staging.

5.12.2.1.1 T stage (size and depth of invasion of the primary tumour)

The size of a primary cSCC 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 cSCC in situ (Bowen's disease), which can grow to a large area and even become exophytic, yet remain in situ. A size greater than 2cm in greatest dimension remains a significant cut-off point for poorer prognosis.[4][5][6]

The T4 staging category identifies advanced (beyond subcutis) clinical invasion and has the poorest prognosis (Table 4.4). However, lesser intermediate depths of invasion are still not directly accounted for in the T1–3 staging system.[1]

For T1 and T2 tumours, limited evidence suggests that increasing depth of invasion of the dermis or tumour thickness measured histologically is associated with increasing incidence of nodal metastases.[3][7]

Other clinical parameters useful for assessing depth of invasion include:

- palpable thickness
- diffuse infiltration and induration with poor demarcation of tumour edges
- tenderness and inflammation.

All these clinical parameters are validated (though crude) signs of a more aggressive tumour.

Table 4.4. 5-year disease-free survival for primary cutaneous squamous cell carcinoma according to T stage

T-stage	5-year disease-free survival
T1	95–99%

T2	85–60%
T3	60–75%
T4	<40%

Source: AJCC[1]

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Estimated overall outcomes for cSCC (all comers) are as follows:[8][9]

- local recurrence 3%
- nodal metastasis 4%
- mortality 1.5–3%.

5.12.2.1.2 N stage (nodal status)

The presence of nodal metastasis of cSCC confers an overall 5-year survival of 40%.[10][9]

Recurrence in a nodal basin after standard lymphadenectomy (radical node dissection) almost invariably leads to the development of distant disease. Treatment is difficult and the patient should be referred to a specialist unit for management and offered participation in a clinical trial, if possible.[9]

The risk of regional recurrence after radical lymphadenectomy is related to two important factors (Table 4.5):[10][8][9]

- the number of nodes containing metastases on histopathology
- the presence of extranodal spread, manifested clinically by gross fixation of node(s).

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 on preoperative attempts at predicting this on clinical assessment and imaging using computed tomography (CT).

Table 4.5. 5-year survival for cutaneous squamous cell carcinoma according to presence of nodal metastasis[11]

Nodal involvement	**5-year survival**
Number of involved nodes	
1	49%
2	30%
>3	13%
Extracapsular extension	
Absent	47%

Present	23%

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5.12.2.1.3 M stage (metastasis)

Once haematogenous metastases have occurred, the cSCC is no longer curable. The most common site of metastases is the lung. Recent and ongoing clinical trials evaluating therapies directed against the programmed cell death 1 receptor (PDCD1) in patients with metastatic cSSC have reported very promising findings (see: Cutaneous squamous cell carcinoma: metastatic disease and systemic therapies).[12]

5.12.2.2 Perineural invasion

The estimated prevalence of perineural invasion (PNI) from cSCC is approximately 2.5%.[13][14]

The vast majority of cases involve the trigeminal (V) and facial (VII) cranial nerves, with primary sites on the face, lips, ears or perimeter zone of the face.[15][13]

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

- on histopathological examination of a primary cSCC (usually involving a minor dermal nerve)
- symptomatic presentation with either neuralgic-type pain, progressive paraesthesia or anaesthesia.

5.12.2.2.1 Perineural invasion identified on histopathological examination

The incidental finding of PNI (usually a minor dermal nerve) reported on histopathological examination of a primary cSCC is the earliest indication in an asymptomatic patient.

While this occurrence is relatively uncommon (2–14%), its frequency is unknown in the absence of controlled pathology studies.[11]

The incidental finding of PNI appears to confer a poorer prognosis.[13] Based on current data, it may require a more aggressive management approach such as wider excision, Mohs micrographic surgery, post-operative radiotherapy or, at the least, an opinion from an appropriate specialist.[14]

5.12.2.2.2 Perineural invasion identified following symptomatic presentation

The second, later, indication of PNI is symptomatic presentation as either of the following:

- neuralgic-type pain, or progressive paraesthesia/anaesthesia. These symptoms may arise due to involvement of various divisions of the sensory trigeminal nerve.
- a palpable lump along the course of a nerve (e.g. near the supraorbital or infraorbital notch or mental foramen)
- paresis of facial muscles due to involvement of the facial nerve.

These symptoms and signs most often occur after initial, seemingly successful, treatment of the primary cSCC.

Not uncommonly, the primary cSCC is no longer traceable by any means.

Magnetic resonance imaging (MRI) is the imaging modality of choice in diagnosing or assessing PNI in a symptomatic patient. However, a normal MRI does not preclude PNI. Clinically diagnosed PNI carries a poor prognosis.[15][13]

5.12.2.2.3 Locally recurrent, persistent or inadequately treated primary cutaneous squamous cell carcinoma

Locally recurrent cSCC and persistent cSCC are considered to be clinical expressions of the same category of 'uncontrolled cSCC at its primary site', as their pathogenesis, prognosis and treatment are similar.

Locally recurrent cSCC is clinically manifest by regrowth of a lump or ulcer at the primary site after clinical treatment that initially seemed adequate (e.g. complete excision) or clearance of the primary tumour (e.g. after radiotherapy).

The term 'persistent cSCC' signifies either of the following:

- high histopathological risk of residual cSCC reported by a pathologist following incomplete excision
- clinical observation of macroscopic tumour that has not completely resolved after treatment.

Incompletely excised cSCC has a recurrence rate of up to 50%.[6]

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5.12.2.3 Histology and growth rate

Cutaneous SCCs are graded histologically as well-differentiated, moderately differentiated or poorly differentiated. Growth patterns that are poorly 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.[6]

5.12.2.4 Anatomical site of primary

Cutaneous SCCs of the scalp, ear or vermilion border of the lower lip, genitalia, perineum and more recently, temple have been shown to be associated with poorer prognosis and to have a higher recurrence and subsequent nodal metastasis rate than cSCCs elsewhere.[9][12]

5.12.2.5 Cutaneous squamous cell carcinomas unrelated to UV irradiation

Cutaneous SCCs arising in a chronic scar include:

- chronic osteomyelitis sinus
- burns scars ('Marjolins ulcer)
- skin damaged by medical radiotherapy or other radioactive sources

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

5.12.2.6 General and skin-specific comorbidities

Skin comorbidity can be site-specific and 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.[16] The optimal treatment is surgical excision and skin grafting or other flap repair, which can demand several days of strict bed rest in hospital. Patients with asymptomatic lesions can be reluctant to undertake the required bed rest, and bed rest may compound comorbidities such as arthritis, thrombosis and diabetes in the elderly.

Younger adults (especially women) with facial skin cancers may seek unrealistic guarantees of good cosmetic results from treatment, potentially compromising appropriate and timely cancer treatment. In all these instances it is essential to provide careful patient counselling and education on the prognosis and results of treatment.

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5.12.2.7 Host factors

Immunosuppression both increases the risk of developing cSCCs and results in a poorer prognosis (see: Organ transplantation and other conditions associated with immunosuppression).

5.12.3 Practice Points

Practice point
PP 6.2.1. Incompletely excised cutaneous squamous cell carcinomas should be prophylactically re-excised or treated with radiotherapy.

Practice point
PP 6.2.2. If a cutaneous squamous cell carcinoma recurs in a nodal basin after standard lymphadenectomy, the patient should be offered referral to a specialist advanced skin cancer clinic that can provide access to a multidisciplinary team (including surgeons, radiation oncologists, medical oncologists and allied health professionals) and the opportunity to participate in clinical trials.

Key point(s)

- Recurrent, persistent or inadequately treated cutaneous squamous cell carcinomas require more aggressive clinical treatment.
- When discussing salvage management options for a patient with advanced cutaneous squamous cell carcinoma, the clinician should fully explain the cancer's lethal potential.
- For a patient with cutaneous squamous cell carcinoma in a site likely to heal poorly (e.g. below the knee, pretibial, sites affected by peripheral vascular disease or other comorbid conditions), the clinician should provide information about the prognosis and counselling about treatment options, making sure the person (and carers) have understood well.
- For a patient with facial cutaneous squamous cell carcinoma who is anxious about the cosmetic results of treatment, the clinician should carefully explain the potential consequences of delaying treatment or failing to achieve tumour clearance, as well as the potential adverse outcomes each treatment option, so that the person can make a treatment decision based on realistic expectations.
- When incomplete excision of a cutaneous squamous cell carcinoma is reported, the surgeon or treating clinician should explain to the patient that there is a significant risk of the cancer recurring, and should offer further treatment as appropriate, carefully explaining the risks and benefits of each management option.

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5.12.4 References

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5.13 7. Surgical treatment – Introduction

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5.13.1 Introduction

Most basal cell carcinomas (BCCs) and cutaneous squamous cell carcinomas (cSCCs) are managed by surgical treatment options, most commonly by simple surgical procedures. However, nonsurgical modalities are an alternative for selected, clinically favourable lesions.

Compared with non-surgical modalities, well-performed surgery has the advantage of providing a complete specimen for both histologic confirmation of the diagnosis and the adequacy of excision, and is associated with a high rate of local control. Complete excision can be expected to cure the majority of tumours.

However, surgery can cause unnecessary morbidity because of technique, or when alternative treatments may have achieved a better aesthetic outcome. Likewise, nonsurgical modalities can cause unnecessary morbidity when surgery should have been the preferred option. Treating practitioners should work within their capabilities or refer.

Some cSCCs behave aggressively, resulting in extensive tissue destruction, regional spread, or both. High-risk cSCC is biologically distinct and needs special management.[1] Longstanding BCCs can also be highly destructive. Surgery, encompassing a range of techniques, remains the primary treatment modality for many of these lesions. Some may necessitate extensive resections. Radiotherapy and biologic treatments also play a role.

The challenge is to adequately manage all tumours and select the most effective modality, while giving the patient the most aesthetic and functional outcome appropriate to their expected longevity. Clinicians treating patients with KC must be familiar with all modalities available, even though they may not be able to offer all of these themselves.

The advantages, disadvantages and the material risk of each treatment must be explained to the patient. ‘Material risk’ is defined as a risk that a reasonable person in the patient’s circumstances would be likely to attach significance to if warned of it, or that the medical practitioner is aware (or should reasonably be aware) that the particular patient would be likely to attach significance to if warned.[2] The most appropriate treatment should be offered that balances optimal long-term tumour control with aesthetic and functional outcome, and is acceptable to both patient and clinician.[3][4]

See also: Cryotherapy and electrodessication and curettage; Topical treatments and photodynamic therapy; Radiotherapy; Pathology.

5.13.2 Tumour recognition and biopsy

Tumour recognition and appropriate management are skills developed through experience as well as training. Before any treatment is undertaken that may cause morbidity, the lesion should be definitively recognised either clinically or histologically.

5.13.3 Clinical recognition

Experienced clinicians are likely to recognise KCs and be correct most of the time (see: Clinical features of keratinocyte cancer). The use of dermatoscopy may improve the clinical recognition of KCs.[5] However, clinical recognition is not always reliable,[6] and cannot always predict the behaviour or aggressiveness of all tumours.[6]

If the diagnosis is in doubt, appropriate biopsy is prudent (see: Pathology). Biopsy is highly recommended if surgical treatment is likely to result in significant tissue removal or resection of unique structures such as nose, eyelid, lip or ear.

5.13.4 Histologic confirmation with biopsy

If there is any doubt concerning the clinical diagnosis or the lesion is in a cosmetically sensitive location, an appropriate biopsy should be performed (see: Pathology).

A tumour's management should be based on the worst part of its histopathology. Some tumour types coexist. The biopsy should contain sufficient tissue to permit accurate histologic diagnosis. An insufficient biopsy may not represent all tumour types in a lesion with a mixed pattern of pathology.

Biopsy itself can cause morbidity.

Complete excision biopsy is the preferred technique because it permits the pathologist to examine the architecture and cytological appearances of the tumour, assessment of its extent, and an assessment of adequacy of excision.

If complete excision biopsy is not possible or appropriate, incision biopsy can be considered, taking into account the size and depth of the lesion under consideration (Biopsy considerations and the biopsy report). Incision biopsies include shave biopsy, curettage and punch biopsy.

Shave biopsy is appropriate for many lesions, especially if there is a possibility that the lesion is benign, in which case a minimal mark should be left.

Curettage usually obtains a representative amount of tumour to minimise the chance of missing mixed patterns. However, it may disrupt the architecture and so compromise the histological examination, and it may miss other (such as infiltrative) parts of the tumour.

Punch biopsy is the most commonly used method, but the biopsy specimen may be unrepresentative, especially in larger tumours. It is useful for small lesions and lesions with a subcutaneous component, and to sample the deeper infiltrative or fibrosing parts of a tumour.[7]

The biopsy should be repeated if the pathologist or proceduralist suspects that it is inadequate or unrepresentative.

If multiple biopsies are performed, it is essential to label all specimens and to ensure that the site can be identified unambiguously at a later date. Photographs, diagrams, and detailed descriptions are all useful and should be employed as appropriate.

Before the patient leaves the procedure room, the pathology specimens should be checked to confirm that a specimen is in each container and that they are labelled correctly with the patient's name and address as well as the surgical site.

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5.14 7.1 Considerations before selecting surgical treatment modality

Contents

5.14.1 Background

Most keratinocyte cancers (KCs) are amenable to surgical treatment, but non-surgical treatments are also available.

While an experienced clinician may be able to make a rapid decision as to the appropriate treatment modality for any given tumour, that decision-making process is based on a list of criteria that need consideration.

Factors that must be considered before opting for surgical excision include:

- the tumour biology
- the tumour site
- the general condition of the patient
- the timing of treatment.

In some cases, it may be helpful to discuss a case in a multidisciplinary team meeting, or with a pathologist or another clinician.

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5.14.2 Systematic review evidence

What factors need to be considered when determining if surgical treatment modalities are optimal over non-surgical modalities for the management and/or treatment of basal cell carcinoma or cutaneous squamous cell carcinoma?

A systematic review was undertaken to answer this clinical question. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

A total of eight studies reported relevant outcomes in patients with BCC or cSCC undergoing surgical or non-surgical treatment modalities. These included four randomised controlled trials (RCTs)[1][2][3][4][5] two case control studies[6][7] and two cohort studies.[8][9]

Surgical modalities include conventional excision (most studies) and Mohs micrographic surgery (MMS; one study).[9] Nonsurgical treatment modalities included aminolevulinic acid (ALA)-photodynamic therapy (PDT),[1][2][6][7] topical imiquimod[5][4][8] carbon dioxide laser ablation,[3] cryotherapy[3] and electronic brachytherapy.[9]

Reported outcomes included completeness of excision, recurrence rates and adverse events. Of the RCTs, one had a high risk of bias,[5][4] two had an unclear risk of bias[2][1] and one had a low risk of bias.[9] Both of the case control studies had a high risk of bias.[6][7] One cohort study had a low risk of bias,[9] while the other one had a moderate risk of bias.[8]

5.14.2.1 Imiquimod versus surgical excision

A UK RCT comparing imiquimod 5% cream and surgical excision in 501 nodular or superficial BCCs located on the face, neck, trunk, arm, leg and other locations[5][4] reported that 84% of the imiquimod group and 98% of the surgical group were recurrence-free at 3 years, with similar rates at 5-year follow-up. At 5-year follow-up there was a significantly lower risk of treatment failure among the surgical group: relative risk 0.84 (95% confidence interval 0.772–0.91); $p<0.001$). Most of the failures in the imiquimod group occurred within the first 12 months.

5.14.2.2 Aminolevulinic acid-photodynamic therapy versus surgical excision

A RCT comparing surgical excision with ALA-PTD in 196 patients with superficial BCC reported that, while surgery achieved a better clearance rate after 1 year (100% versus 91%), cosmetic outcome was superior for ALA-PDT.[2]

Another RCT in patients with nodular BCCs on the face (52%) or body (48%) also reported higher recurrence rates with ALA-PDT than surgical excision at 60 months' follow-up (30.7% versus 21.5%, p=0.0001).[1]

A case-control study comparing surgical excision with ALA-PTD in 94 patients with nodular or superficial BCCs reported similar 2-year recurrence rates of approximately 4%, with better cosmetic outcomes in the ALA-PDT group.[7]

Another case-control study reported similar cure rates among patients with BCCs (any type) who received ALA-PDT or surgical treatment.[6]

5.14.2.3 Electronic brachytherapy (superficial external beam radiotherapy) versus Mohs micrographic surgery

In a cohort of 369 patients with BCCs (54.3%) or cSCCs (45.7%), one tumour recurrence was seen in a patient who underwent electronic brachytherapy, and no recurrences were seen in those who underwent MMS, at approximately 3.4 years' follow-up (non-significant difference).[9] Cosmetic outcomes were similar in both groups.

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5.14.3 Overview of additional evidence (non-systematic literature review)

In general, compared with more malignant histopathological types, less aggressive surgery is required for low-grade tumour types including nodular BCCs, superficial multifocal BCCs, keratoacanthomas and well-differentiated cSCCs. Some may be suitable for non-surgical treatments.

5.14.3.1 Tumour biology

5.14.3.1.1 Basal cell carcinomas

Superficial multifocal BCCs are amenable to both surgical and non-surgical treatments. Potential non-surgical options include topical imiquimod, PDT (see: Topical treatments and photodynamic therapy), electrodessication and curettage, or cryotherapy (see: Cryotherapy and electrodessication and curettage). Surgery is suitable for lesions that are small, recalcitrant to or recurring after non-surgical treatments, or in anatomically sensitive areas.

Nodular or nodulocystic BCCs can often be successfully treated with excision and direct closure, or other options such as electrodessication and curettage in anatomically favourable areas (see: Tumour site below). Their margins are better defined than any other subgroup of BCC. They are less likely to recur, even in cases of close margins or incomplete excision.

Micronodular, infiltrating and fibrosing (morphoeic) BCCs are less well defined and need surgical excision with wider margins. Hence their rate of recurrence is higher if histologic margins are close or incompletely excised. Treatment for these tumours needs expert attention, including consideration of MMS, postsurgical adjuvant treatments in certain cases, and close follow-up. Poorer prognostic tumours include tumours >2cm on the trunk or extremities or >1cm on the head and neck, hands, feet, genitalia or lower leg, tumours with ill-defined borders, recurrent tumours, or tumours in sites of prior irradiation.[10]

5.14.3.1.2 Cutaneous squamous cell carcinomas and related tumours

Bowen's Disease (cSCC in situ) may be treated surgically or non-surgically. Non-surgical methods can be highly effective in treating such lesions.

Well-differentiated cSCCs and keratoacanthomas are often easily treated with excision and direct closure, but nonsurgical methods can be highly effective. The diagnosis of keratoacanthoma is often clinical, based on the observation of rapid growth (see: Keratoacanthoma in Clinical features). Histological diagnosis can be difficult if the entire tumour is not submitted for histopathologic evaluation (see: Pathology of keratoacanthoma).

Moderately differentiated cSCCs can usually be treated successfully with excision and direct closure, although non-surgical treatments may have a role.

Poorly differentiated cSCCs are often less well defined and need wider excision margins. Hence their rate of recurrence is higher if histologic margins are close or incompletely excised.

Tumours with a poorer prognosis include acantholytic, adenosquamous, carcinosarcomatous, desmoplastic or spindle cell subtypes, large tumours (>2cm), rapidly growing tumours, thick tumours (>6mm) or tumours with other high-risk features such as invasion into fat or surrounding structures, perineural invasion or lymphovascular invasion (Table 5).[11] Treatment for these tumours needs expert attention with consideration of adjuvant treatment in certain cases and close follow up. Discussion in a multidisciplinary clinic or with another clinician is often helpful.[10]

Table 5. Tumour-specific factors associated with recurrence of keratinocyte cancers

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5.14.3.2 Tumour site

The consequences of recurrence need to be borne in mind when discussing surgery. Favourable anatomical sites are those where local recurrence (histopathology aside) is unlikely to cause problems if monitored closely and further treatment would not cause much morbidity, either aesthetically or functionally.

However, local recurrence in sites close to apertures, or adjacent to unique structures can be devastating. Sites such as the so-called H zone (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular skin and sulci, temple, and ear) have a higher risk of recurrence and recurrence can be much more difficult to treat than the primary lesion.[12][13][14] Mohs micrographic surgery may be considered as a treatment option for these difficult-to-treat sites.

Patients have widely differing expectations of cosmetic outcome after skin cancer surgery.

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 relatively superficial and may be damaged during excision of lesions that overlie the course of the nerve over the zygoma, lateral periorbital and temple regions. The mandibular branch is at risk and it may pass below the line of the mandible. The accessory nerve after it emerges from behind the posterior border of the sternomastoid is subcutaneous and at risk when excisions are performed in the posterior triangle. The great auricular nerve is similarly at risk under the ear and over the sternomastoid.

Tumour resection that is likely to result in cosmetic or functional defects requires specialised reconstructive techniques. Patients who require this type of surgery should be referred for specialist care. 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.

Occasionally sacrifice of major structures, for example eyelid, tear duct or facial nerve, is necessary to achieve complete resection. Non-surgical treatment such as radiotherapy may be appropriate in some cases. It is therefore essential preoperatively to attempt to assess the level of tumour invasion (if any) into surrounding structures.

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5.14.3.3 General condition of the patient

Life expectancy can be an important factor in determining the appropriate aggressiveness of treatment for slow-growing tumours. Some patients may have tumours that will never cause them any trouble in the short term, but leaving such tumours can lead to later, more complex and difficult problems if patient selection is incorrect. Some BCCs and Bowen's disease, in particular, can take years to become troublesome. In some cases observation and regular review observation may be acceptable.

On the other hand, KCs in younger patients, particularly cSCC of the head and neck, can behave aggressively and need urgent and adequate treatment. Keratinocyte tumours in immunocompromised should be managed more aggressively (see: Organ transplantation and other conditions associated with immunosuppression).

One must also consider the rest of the patient’s skin. Patients who have multiple KCs need an overall treatment plan. It is clearly poor management to excise a biopsy-proven skin cancer and ignore several other obvious tumours or premalignant lesions.

See also: Prognosis.

5.14.3.3.1 Anticoagulant agents and surgery

Minor dermatologic surgery can be carried out safely without ceasing treatment with aspirin, warfarin or the newer oral anticoagulants.

Recent meta-analysis involving 30,000 patients showed little increase in intervention for bleeding in patients on antiplatelet therapy.[15] A systematic review of the effects of antiplatelet therapy on surgical outcomes[16] found an increase in bleeding risk in those on anticoagulants or antiplatelet agents, but the consequences were not significant enough to recommend cessation of such treatments in those that require them. Similarly, a US retrospective study[17] found that the novel oral anticoagulants (oral anticoagulants dabigatran, apixaban, and rivaroxaban) did not alter the morbidity of MMS and did not recommend their cessation. Other authors have recommended continuation of warfarin or low-dose aspirin treatment for patients undergoing skin surgery, because the risk of severe haemorrhagic complications is low.[18]

A prospective study of 2,326 consecutive patients undergoing minor dermatological excisional surgery[19] included those taking warfarin (n=28), aspirin (228) and 2073 patients taking no medication. Patients were reviewed postoperatively for bleeding and wound complications. There was no increase in complications among patients being regularly treated with either aspirin or warfarin, despite the older mean age and greater number of comorbidities in this subgroup.[19] The authors concluded that both aspirin and warfarin (provided that a clotting test is performed and international normalised ratio recorded prior to surgery) can be continued during minor dermatological excisional surgery, provided that strict surgical haemostasis is achieved.

Evidence from RCTs of perioperative aspirin for non-cardiac surgery, including a recent systematic review and meta-analysis of,[20] and a very large RCT of preoperative aspirin,[21] suggests that aspirin does not affect rates of death or nonfatal myocardial infarction, but increases the risk of major bleeding. However, these studies did not separately report outcomes in patients undergoing surgery for KCs.

While available evidence suggests that stopping aspirin is helpful in patients undergoing non-cardiac surgery, most cutaneous surgery may be an exception because bleeding is unusual and the areas are small.

5.14.3.3.2 Role of antibiotics in cutaneous surgery

No prospective RCTs have investigated the use of prophylactic antibiotics to prevent haematogenous prosthesis infection in patients who have undergone a dermatological procedure.[22] The Australian *Therapeutic Guidelines* recommend prophylactic perioperative antibiotics only for patients at the highest risk of endocarditis or prosthetic joint infections.[23]

Antibiotics are not usually indicated for minor procedures, but can be considered for larger excisions, excisions from sebaceous type of skin, or skin grafts or where the lesions are ulcerated or contaminated. A prospective observational study of patients undergoing MMS without prophylactic antibiotics[24] reported a very low rate of infection.

When used, antibiotics should be given at least 20 minutes before surgery (an hour if oral). There is rarely any indication for postoperative antibiotics. There is no role for topical antibiotics.[25]

5.14.3.3.3 Metastatic disease

Although KCs infrequently metastasise, lymph node examination should be carried out, particularly in the case of high-risk tumours, cSCCs on the head and neck, and immunocompromised patients (see: Metastatic disease and Prognosis). In larger tumours computed tomography (CT) or CT-positron-emission tomography (PET) may be appropriate.

5.14.3.3.4 Timing

When to operate on a tumour is a common dilemma in practice. When the diagnosis is made it is best to excise the tumour promptly to minimise morbidity associated with further growth of the KC. In practice, due to the constraints of surgical schedules many tumours are not excised until days or weeks after diagnosis, often with no clinically important consequences.

It is important to triage tumours according to risk factors to ensure that tumours capable of causing greater morbidity are excised as soon as practicable. Low-grade tumours, such as nodular BCCs in favourable sites, can often safely wait until time is available.

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5.14.4 Evidence summary and recommendations

Evidence summary	Level	References
Nonsurgical treatment generally resulted in higher rates of recurrence (0.53% to 30.7%) than surgical treatment (0% to 4.34%) for mainly low-risk BCCs located on various parts of the body after 12 to 60 months' follow-up.	II, III-2	[4], [2], [1], [9], [7], [8]
A higher percentage of adverse events occurred after non-surgical treatment than surgical treatment for mainly low-risk BCCs.	II, III-2	[5], [2], [7], [3], [9]
Overall clearance was lower after non-surgical treatment (mean 87.05%) than surgical treatment (mean 98.35%) for mainly low-risk BCCs on the trunk, neck, face, scalp, leg, arm and extremities after 3 months.	II, III-3, IV	[3], [2], [6], [7]

Evidence-based recommendation	Grade
EBR 7.1.1. Both surgical and nonsurgical treatment modalities can be considered for superficial and nodular basal cell carcinomas in favourable sites.	**C**

Key point(s)
Both surgical and nonsurgical treatment modalities can be considered for low-risk keratinocyte cancers in favourable sites. The decision must balance the probability of achieving clearance, recurrence risk, cosmetic and functional outcome, and patient preference.

Go to:

- Surgical treatment – Introduction
- Optimal primary excision techniques:
  - Optimal surgical technique for the treatment of basal cell carcinoma
  - Considerations when planning surgical treatment for cutaneous squamous cell carcinoma
- Post-surgical care and interpretation of the pathology report
- Protocol to manage incompletely resected basal cell carcinoma
- Protocol to manage rapidly growing tumours
- Criteria for choosing Mohs micrographic surgery in preference to other surgical techniques
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5.15 7.2 Optimal primary excision techniques

Contents

5.15.1 Background

Surgical excision is the removal of a tumour with a surrounding cuff of normal uninvolved tissue. The defect is then allowed to heal by second intention, or closed primarily (i.e. at the time of surgery) using methods such as direct closure, flap repair or graft repair, or secondarily (i.e. at a later time) by similar methods when histopathologic confirmation of clearance is complete.

A scalpel is not the only tool that can be used for excisions. Smaller excisions can be achieved with biopsy tools such as curettes or punch biopsies. Larger, more complex excisions, may require removal of composite tissues such as cartilage, bone, and other structures such as nerves if they are affected. The aim of treatment is to minimise the skin cancer's impact on a patient's quality of life.[1] Therefore treatment regimens should be tailored to allow this.

The majority of keratinocyte cancers (KCs) can be excised under local anaesthetic on an outpatient basis. Excision of small, clinically favourable lesions in straightforward sites should be within the skills of general practitioners who are capable and confident in the performance of minor surgical procedures. The most widely used technique is excision with an adequate margin and direct closure. The definition of adequate margin differs depending on tumour biology and anatomical site.

Other techniques for high- risk tumours include Mohs micrographic surgery and complete circumferential peripheral and deep-margin assessment using intraoperative frozen section assessment (see: Criteria for choosing Mohs micrographic surgery in preference to other surgical techniques).

5.15.2 Preparation and excision

The outline of the tumour should be outlined, then an appropriate margin of excision marked. The method of excision (and if necessary repair) is then is also marked. The area is then adequately infiltrated with local anaesthetic and then sufficient time allowed to elapse for dense anaesthesia to occur. Incision should be made around the marked area with a scalpel until full thickness release of the dermis has been achieved circumferentially. Removal of the specimen from one end to the other can then usually be achieved with a single (not multiple) grasp of the specimen taking an adequate and even layer of subcutaneous fat under the dermis.

Lateral and deep margins are important. Lateral margins need to be adequate to ensure complete excision. While lateral margins are easier to define, deep margins require experience. Deep margins are often clear on histopathology if a thin layer of subcutaneous fat is taken, as most tumours do not extend beyond the dermis. Nonetheless, adequate deep margins are very important, and the practitioner must tailor their excision to give an adequate deep margin. Fear of damaging underlying anatomy and inexperience may cause incomplete deep margins in otherwise easily resectable tumours. The orientation of excisions is important. Other factors being equal, tumours should be excised along relaxed skin tension lines, but in a line that avoids distortion. Therefore, tumours should be excised radial to apertures and unique structures. Judging optimal orientation requires training and experience. An example of incorrect decision-making is to excise lesions parallel to the eyelid or eyebrow instead of radial to such structures.
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5.15.3 Specimen handling

Excision specimens should be handled with care to avoid damaging margins. Multiple grasps of the specimen with forceps during excision should be avoided, as this can destroy margin evaluation. All specimens should be marked with a suture (or in such a way that the practitioner and the pathologist understand completely) and that location described absolutely (discrete anatomical location e.g. 'root of helix') or relatively (e.g. superior, inferior, lateral, medial, anterior, posterior, proximal, distal) so the histopathologist can accurately map margins.

Note that describing suture position as 12 o'clock or similar may be unhelpful unless it is known where 12 o' clock is located. The pathologist will usually designate the suture at 12 o'clock. This is particularly important when trying to assess the location of an incomplete margin, or when another practitioner has to do a wider excision.

When multiple excisions are performed, as with multiple biopsies, it is essential that specimens are labelled and the site can be identified unambiguously at a later date. Photographs, diagrams, and detailed descriptions are all useful and should be employed as appropriate.

Before the patient leaves the procedure room, the pathology specimens should be checked to confirm that a specimen is in each container and that they are labelled correctly with the patient's name and address and the surgical site.

5.15.4 Defect management

If the excision has been correctly planned, the defect can be closed directly in most cases. Virtually all KCs below the neck and above the knees, irrespective of size, can be closed directly. Many others on the lower leg and on the face can be treated likewise.

Other primary closure methods are flaps and grafts. While the majority of excisions do not need flaps or grafts, these may be required in certain defined circumstances. Flaps and grafts are used for defects:

- where closure of the defect would distort surrounding structures
- where the defect is too large to close directly
- where the defect is too complex, requiring the reconstruction of composite tissues or different cosmetic units.

Some areas can be allowed to heal by second intention.

Flaps should only be performed when clinically appropriate and by those with adequate surgical training. This technique needs careful planning and execution, and should not be offered by inexperienced operators. Poorly executed flaps can be a cause of morbidity in patients who would have had minimal morbidity if adequate planning had been undertaken and correct surgery had been performed.

A defect should not be closed with a flap if there is doubt as to the adequacy of excision. It is best to directly close, graft or leave open for secondary closure until such confirmation of histologic clearance has been achieved.

Key point(s)

- When submitting a biopsy specimen to pathology, the specimen orientation must be described unambiguously and stated clearly on the pathology request form.
- For complex specimens or sites, photographs and/or diagrams should be provided with the pathology request.

5.15.5 Evidence

See Optimal surgical techniques for the treatment of basal cell carcinoma

See Considerations when planning surgical treatment for cutaneous squamous cell carcinoma

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5.16 7.3 Optimal surgical technique – basal cell carcinoma

Contents

5.16.1 Systematic review evidence

What factors need to be considered when determining the optimal surgical technique for those with basal cell carcinoma?

A systematic review was undertaken to answer this clinical question. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

A total of 24 studies were identified that reported on outcomes of surgical treatment for basal cell carcinoma (BCC) according to various risk factors. These included one randomised controlled trial (RCT),[1][2] two case control studies,[3][4] one prospective cohort study,[5][6][7] five retrospective cohort studies[8][9][10][11][12] and 15 case series.[13][14][15][16][17][18][19][20][21][22][23][24][25][26][27]

One prospective cohort study[7] and two retrospective cohort studies[12][17] had a moderate risk of bias. Both RCTs[1][2] and all remaining studies had a high risk of bias.

Surgical techniques included surgical excision, Mohs micrographic surgery (MMS), and electrodessication and curettage.

Reported outcomes included completeness of excision, recurrence rates, and cure rates.

5.16.1.1 Recurrence rates

Studies reported recurrence rates for BCC according to the following treatment-related factors:

- surgical margin (two studies)[15][18]
- treatment type (six studies)[1][2][3][5][6][7][10][11][12]
- reconstruction technique (two studies).[15][25]

Studies also reported recurrence rates for BCC according to a range of tumour-related factors:

- tumour histology (five studies)[2][8][3][7][12][14][23][25][27]
- tumour location (12 studies)[1][2][3][5][6][7][8][11][12][14][15][20][25][27]
- tumour size (two studies)[8][5]
- tumour infiltration depth (one study).[25]

No RCT investigated the relationship between excision margins and recurrence rates. However, some studies found associations between recurrence rate and histologic subtype or tumour location, which suggest that wider surgical margins and more judicious follow-up may be necessary when excising BCCs with higher-risk features such as aggressive histological subtype, the presence of pigment, unfavourable anatomical sites (e.g. H-zone of the face).

Surgical margins of 3mm were used in the RCT comparing surgical excision with Mohs micrographic surgery (MMS) for BCCs of the face.[1][2] For primary BCCs, this study reported 10-year recurrence rates of 4.4% after MMS and 12.2% after surgical excision (statistically nonsignificant difference).[van Loo et al 2014] All recurrences appeared on the H-zone, and a high proportion (56%) of recurrences occurred after more than 5 years.

Overall aggressive histologic subtypes were found to be more likely to recur than non-aggressive types.[8][2][3][7][12][14][21][23][25][27] Tumours on the nose eyes lips and ears were more likely to recur than elsewhere on the face or body.[8][5][1][7][14][19][20][6]

Based on weak evidence (small non-randomised studies with inconsistent results), completeness of excision appears to be related to tumour histology[9][10][13][18][21][22] and to location.[9][10][16][17][21][22][26]

Evidence from studies examining the relationship between excision margins and recurrence rate was inconsistent and of poor quality,[4][17][18][24] as was evidence from studies examining the relationship between closure technique and recurrence rate.[9]

5.16.2 Evidence summary and recommendations

Evidence summary	Level	References
Basal cell carcinoma subtypes significantly associated with recurrence were aggressive, sclerodermiform and non-pigmented subtypes as well as those with infiltrative, metatypic-basaloid squamous cell-pleomorphic patterns, compared with less aggressive, nodular, adenoid, superficial and pigmented subtypes and subtypes with pilar differentiation.	II, III-2, III-3, IV	[2], [3], [7], [8], [12], [14], [21], [23], [25], [27]
Basal cell carcinomas on the face and H-zone of the face were generally more likely to recur after surgical excision than those on the rest of the body, forehead, cheek and temple. However, only tumours located on the nose, lips, eyes and superior eyelid were found to have significantly higher rates of recurrence than those on the forehead, check, temple, medial and lateral canthus and lower eyelid.	II, III-2, III-3, IV	[1], [5], [6], [7], [11], [8], [14], [19], [20]
There were no difference in recurrence rates between surgical margins 3,4 and ≥5mm on the nose. However, excision sizes >1.75cm^2 were associated with significantly higher recurrence than excision sizes <1.75cm^2 on the eyelid.	IV	[15], [18]
No significant difference was found in the mean size of tumours which did and did	II, III-	[8], [5]

Evidence summary	Level	References
not recur.	3	
BCCs that had invaded deep structures were more likely to recur than BCCs that had invaded into the reticular dermis, hypodermis and papillary dermis.	IV	[25]
Incomplete excision was generally found to be greater on the face and head than the rest of the body (trunk, legs and arms), and on the nose, eyelid and ears than the rest of the face and head.	III-2, III-3, IV	[9], [10], [16], [17], [21], [22], [26]
Rates of incomplete excisions were found to be higher with undefined and mixed histology, fibrosing, adenoid, and non-pigmented BCCs than pigmented and superficial BCCs. Rates of incomplete excision for nodular and infiltrative BCCs were mixed. No significant difference in rates of incomplete excision was found between groups with some aggressive types of BCC (morpheaform [sclerosing], infiltrative, nodulo-infiltrative) and non-aggressive (nodular, superficial, pagetoid) BCCs.	III-2, III-3, IV	[9], [10], [13], [18], [21], [22]
There was no significant association between completeness of excision for BCCs when comparing margin widths of ≤2mm, 3mm, 4mm, and ≥5mm. There was no significant association between completeness of excision comparing BCCs excised with 2mm and 4mm margins versus inspected healthy margins. Numerically higher rates of complete excision were reported for BCCs with 4-mm margins versus 3-mm and 5-mm margins, but these results were not statistically analysed.	III-2, IV	[4], [17], [18], [24]
BCCs that stopped before the reticular dermis had significantly higher rates of complete excision than those that had spread to the hypodermis, muscle, cartilage, bone and nerve.	III-3	[9]
There was no significant associated between mean diameter of tumours which were completely excised versus incompletely excised. However tumour size >3cm was associated with more complete excisions than <0.5cm.	III-2, III-3	[9], [10]
The 5-year cure rate was over 97% for BCCs surgically excised on the face in areas such as the nose, eyelid, temple, forehead, and cheek.	IV	[19], [27]

Evidence-based recommendation	Grade
EBR 7.3.1. Patients with high-risk recurrent facial basal cell carcinomas should be offered	**C**

Evidence-based recommendation	Grade
wide surgical excision or Mohs micrographic surgery. Regular follow-up should be provided.	

Evidence-based recommendation	Grade
EBR 7.3.2. Non-surgical treatment modalities can be considered for patients with basal cell carcinomas assessed to have a low risk of recurrence based on favourable histological type (e.g. superficial or nodular types) and favourable anatomic locations (away from unique structures).	**C**

5.16.2.1 Notes on the recommendations

Follow-up of patients after treatment is individually tailored according to patient factors, tumour factors, anatomic site and the perceived adequacy of treatment.

Current literature supports the use of wide surgical excision or Mohs surgery for primary high-risk facial BCCs.[1][2] The RCT[1][2] reported no significant difference between 10-year recurrence rates for primary BCCs treated by MMS or surgical excision. For recurrent BCCs, however, MMS achieved higher 10-year cure rates than surgical excision.[2]

Recent US guidelines for the management of BCC[Bichakjian et al 2018] recommend surgical excision for low-risk primary BCCs and selected high-risk BCCs, but make a stronger recommendation for MMS in high-risk tumours (defined according to National Comprehensive Cancer Network stratification[ref] to include all H-zone facial tumours as well as tumours that are large, poorly defined, recurrent, showing aggressive growth pattern or perineural invasion, at radiation therapy sites, or in immunosuppressed patients). The US working group based its recommendation for MMS in both primary and recurrent BCC mainly on the only available RCT,[1][2] but noted that 'these findings cannot necessarily be extrapolated beyond the scope of the study population with facial BCC.' The US working group further noted that the lack of availability of tissue blocks for molecular testing or further histological examination is a limitation of MMS, and suggested that this limitation should be minimised by careful selection of MMS candidates based on initial biopsy results.

Our recommendation was made after considering these same limitations, as well as the availability of MMS in Australia. MMS has a statistically significant advantage for high risk recurrent facial BCC, but not for primary at this stage.[2]

See also: Criteria for choosing Mohs micrographic surgery in preference to other surgical techniques.

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5.17 7.4 Considerations when planning surgical treatment for cSCC

Contents

5.17.1 Systematic review evidence

In patients undergoing surgical treatment for cutaneous squamous cell carcinoma, which surgery-related factors (margin width, depth of excision) or tumour-related factors (size, histological features, anatomical site) influence clinical outcomes (cure rate, local recurrence, regional lymph node involvement, metastasis)?

A systematic review was undertaken to answer this clinical question. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Fourteen studies were identified that reported outcomes of surgical treatment for cSCCs based on various risk factors. These included three case control studies[1][2][3] and 11 case series.[4][5][6][7][8][9][10][11][12][13][14] There were no randomised controlled trials (RCTs).

Two case series had a moderate risk of bias[4][6] and the remainder of studies all had a high risk of bias.

Surgical techniques included excision, Mohs micrographic surgery (MMS), biopsy and lymph node dissection.

Reported outcomes included local recurrence, regional recurrence, metastasis and death.

No studies were identified that examined the influence of surgical technique of other surgery-related factors on clinical cancer outcomes.

Studies reported recurrence rates according to a range of tumour-related factors:

- anatomical site (six studies)[4][8][9][12][14]
- histopathological features (six studies)[1][4][5][8][11][14]
- tumour size (three studies).[4][9][11]

Only one study reported recurrence rate according to surgical margin.[10]

Studies reported rates of metastasis according to a range of tumour-related factors:

- anatomical site (eight studies)[4][6][8][9][11][12][13]
- histopathological features (10 studies).[1][3][4][5][6][7][8][9][11]
- tumour size (five studies)[2][4][6][9][11]

Overall, aggressive histologic subtypes (spindle cell, poorly differentiated, fibrosing) and large tumours were found to be more likely to recur or metastasise than non-aggressive types or smaller tumours.[1][2][3][4][5][6][7][8][9][11]

Evidence for an association between anatomical site and risk of recurrence or metastasis was less certain, with no significant differences reported.[3][4][6][8][9][11][12][13] Variation in surgical technique and competence may be a confounding factor influencing the relationship between anatomical site and risk.

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5.17.2 Evidence summary and recommendations

Evidence summary	Level	References
RECURRENCE		
Anatomical site Two studies found there was no statistically significant correlation between recurrence and the site of the excised cSCC, while the other studies did not test for significance.	IV	[4], [8], [9], [12], [14]
Histology: fibrosing ('desmoplastic') One study found that desmoplasia (desmoplastic cSCCs compared with non-desmoplastic cSCCs) was a significant risk factor for recurrence.	IV	[4]
Histology: poorly differentiated/spindle cell carcinoma Two out of three studies found a significant association between poorly differentiated cSCCs and recurrence, while one found no correlation.	IV	[4], [5]
Tumour size (diameter) Two studies observed that tumours <20mm recurred less than tumours ≥20 mm (although one study observed no recurrence among tumours >40 mm). Neither study performed statistical analysis. Another study reported that tumour diameter >20 mm (compared with ≤20 mm) was associated with a significantly higher risk of recurrence after excision on univariate analysis, but not on multivariate analysis when other factors (e.g. tumour thickness, number of SCCs, anatomical site and immune status) were considered.	IV	[4], [9], [11]
Surgical margin Only one study reported on recurrence based on surgical excision margins but did not test their results for significance.	IV	[10]
METASTASIS		

Evidence summary	Level	References
Anatomical site There was inconsistent evidence on the relationship between risk of metastasis and the anatomical site of the excised SCC.	IV, III-3	[3], [4], [6], [8], [9], [11], [12], [13]
Histology: fibrosing ('desmoplastic') One study found desmoplastic cSCCs were significantly more likely to metastasise than non-desmoplastic cSCCs.	IV	[4]
Histology: poorly differentiated/spindle cell carcinoma The evidence for the relationship between risk of metastasis and histological finding of tumour differentiation/spindle cell carcinomas was mostly consistent; poorly differentiated SCCs metastasised more (7% to 82%) than well differentiated SCCs (0% to 56%), although only one study reported outcomes based on spindle cell carcinoma.	IV, III-3	[1], [3], [4], [5], [6], [7], [8], [9], [11]
Tumour size (diameter) The studies almost consistently found that larger (≥20mm in diameter) tumours had higher rates of metastasis (12% to 57%) than small (<20mm in diameter) tumours (0% to 19%).	IV, III-3	[2], [4], [6], [9], [11]

Practice point

PP 7.4.1. Referral to a multidisciplinary team or to a specialist for assessment and treatment should be considered for patients with cutaneous squamous cell carcinomas with poor prognostic features (e.g. poorly differentiated, fibrosing or ≥20mm).

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5.17.2.1 Notes on these recommendations

There is insufficient evidence on which to base evidence-based recommendations.

Reported associations between recurrence rate, metastases and histologic subtype suggest that wider surgical margins and more judicious follow-up may be necessary in the surgical treatment of SCCs with high-risk features.

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5.18 7.5 Post-surgical care and interpretation of the pathology report

Contents

5.18.1 Background

Ascertaining if surgical treatment for keratinocyte cancer (KC) has been adequate is crucial, because this will determine the follow-up regimen, and whether to offer further surgery, adjuvant treatment or other additional treatment (see Follow-up after treatment for keratinocyte cancer).

5.18.2 Overview of evidence (non-systematic literature review)

5.18.2.1 Histopathology

Usually the histopathology will be consistent with expectations based either on clinical diagnosis or biopsy prior to surgery. Certain histologic features, anatomical sites or other factors indicate a high likelihood of recurrence, despite appropriate surgical treatment (Table 5).

Occasionally the histopathology may be different from pre-surgical expectations, usually worse. The finding of features associated with higher risk than expected after excision may alter a clinician's determination of optimal treatment for the individual, leading to further surgery or adjuvant therapy.

Table 5. Tumour-specific factors associated with recurrence of keratinocyte cancers

5.18.2.1.1 Perineural invasion

Perineural invasion (PNI) occurs in both cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC).[1] Note that previously traumatised specimens from either biopsy or previous excision can show 're-excision PNI', a benign reparative process.[2][3][4] The finding of PNI should be discussed with the pathologist.

See: Biopsy considerations and the biopsy report.

5.18.2.1.2 Perineural invasion of cutaneous squamous cell carcinoma

Perineural invasion complicates the course of up to 5% of all patients with SCC.[5] Perineural invasion appears to be more common in lesions located in the head and neck. Perineural invasion may be incidental or clinical.

Symptoms that suggest clinical PNI include tingling, pain, paraesthesia, formication (a sensation like ants crawling under the skin), reduced sensation or reduced motor function. Preoperative magnetic resonance imaging (MRI) should be undertaken for patients with clinical evidence of PNI.[6] Clinicians should ask specifically for MRI neurography for large-nerve PNI. However, MRI does not always detect nerve involvement. Intraoperative margin control with frozen section can be used to attempt complete excision. Appropriate management usually involves review at a multidisciplinary head and neck clinic, appropriate investigations, and surgical resection of the involved nerve, which is usually followed by adjuvant radiotherapy (RT). Radiotherapy can be palliative or curative in intent, and generally covers the entire course of the nerve back to its origin from the central nervous system. Alternatively, RT alone to the course of the nerve may be appropriate for patients who are unable to undergo, or refuse, further surgery. Treatment invariably causes major morbidity.

Incidental PNI 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 perineural spread is limited to small dermal nerve fibres < 0.1mm,[7] and the tumour has been completely excised with a wide resection margin.[8]

Features associated with poorer prognosis are involvement of nerves lying deeper than the dermis or outside the tumour (any size), involvement of dermal nerves measuring ≥0.1mm in diameter, multiple nerves, clinical /radiological involvement of nerves or symptomatic nerve involvement.[9]

It may be appropriate to discuss the patient's pathology with a radiation oncologist.

The presence of PNI is reported to pose a very high risk of both local recurrence (which may be as high as 50%) and distant spread (35% risk).[10] 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.[11] It should be managed by wide surgical excision, where possible, and consultation with the radiation oncologist to arrange or consider postoperative RT. Where appropriate, the patient should be referred to a multidisciplinary head and neck clinic.

Re-excision PNI may not be clinically significant.[12] Perineural invasion is often seen in keratoacanthomas, but may not be clinically significant.[12]

5.18.2.1.3 Perineural invasion of basal cell carcinoma

The significance of PNI in BCC is unknown. It may make the tumour more likely to recur, but does not appear to carry the same poor prognosis as true PNI in cSCC. Features that are considered poor prognostic factors in PNI of cSCC might also be indicators of increased risk of recurrence in BCC.

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5.18.2.2 Margins

5.18.2.2.1 Low-risk tumours in favourable sites

The findings of case series conducted before 2000 to establish surgical excision margins for BCC[13] and for cSCC[14] report that a 4mm margin is required for most nodular BCCs and well-differentiated cSCCs to ensure complete histologic clearance.

However, excision of a BCC or cSCC with a positive margin does not imply the persistence of tumour or inevitable recurrence. This is a conundrum. The original papers analysed the margins after excision rather than the recurrence rate. While a margin of 4mm may excise most tumours, it may be excessive in some and insufficient in others. Electrodessication and curettage, and some non-surgical treatments, have a high cure rate in favourable histologic subtypes despite most likely resulting in a positive margin.

Incomplete deep margins need a more considered approach. The consequences of recurrence must be considered. If recurrence will impact significantly on quality of life then further management is required.

5.18.2.2.2 Tumours with high-risk features or at unfavourable sites

Tumours that are incompletely excised or have close margins probably need wider excision or Mohs micrographic surgery (MMS) when they are at unfavourable anatomical sites (e.g. eyelids, nose, lips, ears, and genitalia) or when high-risk features are present (e.g. more aggressive subtypes of BCC and SCC).

For most patients with high-risk tumours or KCs in unfavourable sites, achieving appropriate tumour clearance (according to the appropriate definition for the tumour subtype) is mandatory. The recurrence rate is not necessarily trivial and can be disastrous.[15] Surgery should be performed by someone who has the expertise to adequately excise and reconstruct the area.

If, on balance, wider excision would benefit the patient's quality of life, including psychological wellbeing, it may be prudent to re-treat such tumours. Proper clearance should be obtained in high-risk tumours and in unfavourable anatomic sites (see *Site* below). Other treatment modalities, such as RT, should only be considered after management by surgeons well trained in excision and reconstruction of these difficult tumours.

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5.18.2.3 Site

Location can also be extremely important in determining how aggressive a treatment needs to be. Certain sites seem to have a high propensity for recurrence, possible because the contours lead to inadequate excision in the first place. However, when considering treatment, one must consider the consequences of recurrence in those locations as unique structures can be at high risk. Such areas are the ears, eyebrows, eyelids, nose, nasolabial areas, lips, genitalia and, on occasion, hands and feet. Hair-bearing areas must also be carefully considered due to the propensity of some of these tumours to recur due to spread down pilosebaceous units.

When excision margins are either close or involve structures that are difficult to reconstruct (e.g. eyelids, facial nerve) the surgeon must consider whether that structure should be sacrificed and reconstructed. Mohs micrographic surgery can be considered or another nonsurgical treatment modality should be added. Well performed surgery by an expert in that particular field achieving good surgical margins and having an expertly performed surgical repair is far preferable to poor surgery, inadequate margins and postoperative RT. In particular, the addition of RT may help prevent the sacrifice of difficult-to-replace structures such as the facial nerve. Radiotherapy of an eyelid is not appropriate after inadequate surgery.

5.18.2.4 Patient

Tumours in fields of previous radiotherapy may also need wider margins, as do those in immunocompromised individuals.

Cutaneous SCCs in younger patients, particularly on the face (especially lips), can have a short and aggressive course, and are more at risk of developing subsequent cancers.[16]

5.18.2.5 Follow-up

Follow-up of patients after surgical treatment of KC is individually tailored according to patient factors, tumour factors, anatomic site and the perceived adequacy of treatment.

In all cases patients, should be educated on the possibility of recurrence, its possible manifestation, and the likelihood of additional tumours elsewhere.

See: Follow-up after treatment for keratinocyte cancer.

5.18.3 Practice Points

Practice point
PP 7.5.1. When perineural invasion is reported by the pathologist, the clinician should discuss this finding with the pathologist to ascertain its likely clinical significance.

Practice point
PP 7.5.2. Preoperative magnetic resonance imaging should be considered for patients with clinical evidence of perineural involvement.

Key point(s)
When an incomplete margin is reported on an excision specimen, the clinician should discuss the implications of potential recurrence with the patient. If recurrence would significantly compromise the person's quality of life, further treatment should be offered.

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- Optimal primary excision techniques:
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- Protocol to manage rapidly growing tumours
- Criteria for choosing Mohs micrographic surgery in preference to other surgical techniques
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5.19 7.6 Managing incompletely resected BCC

Contents

5.19.1 Background

Case series conducted before 2000 suggested that a 4mm margin is required for most nodular basal cell carcinomas (BCC) to ensure complete histologic clearance.[1] However, a 4mm margin may be excessive for some BCCs and insufficient in others.

The report of a positive margin does not indicate that tumour persists or the recurrence is inevitable. Incomplete deep margins may carry a worse prognosis than incomplete lateral margins.

Following a report of incomplete or close margins, re-excision to achieve clearance is generally considered necessary for BCCs with high-risk features (unfavourable anatomical site, type or histologic features associated with poorer prognosis).

5.19.2 Systematic review evidence

What should be the protocol to manage incompletely resected basal cell carcinoma?
A systematic review was undertaken to answer this clinical question. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Three studies reported relevant outcomes for incompletely resected BCCs after comparing two or more treatment interventions.[2][3][4] These included prospective cohort study[2] and two retrospective cohort studies,[3][4] all with a high risk of bias.

Treatment modalities included secondary surgical excision (re-excision), aminolevulinic acid-photodynamic therapy (ALA-PDT), electrodessication and curettage (EDC), topical imiquimod, topical 5-flourouracil and topical liquid nitrogen.

All three studies reported recurrence rates. A US retrospective cohort study in which patients received various treatments (including EDC, topical imiquimod, 5-flourouracil, liquid nitrogen) or observation only found that among incompletely excised low-risk tumours, recurrence was more likely in tumours of the head and neck, larger tumours and superficial subtype of BCC after a mean follow-up interval of 40 months.[4] The findings of this study supported a non-surgical approach to some recurrences, but the effect of this was not analysed.

The findings of a Chinese prospective cohort study suggest that ALA-PDT can possibly cure residual tumour, based on observed outcomes for patients with low grade lesions misdiagnosed as naevi, where the intention of initial excision was not curative.[2] However, there was no control group.[2]

A Brazilian retrospective cohort study comparing re-excision with observation found that recurrence was not inevitable with incomplete margins, and over 50% did not recur.[3]

Available evidence shows that Incomplete excision does not always lead to recurrence.

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5.19.3 Evidence summary and recommendations

Evidence summary	Level	References
ALA-PDT versus re-excision No significant difference in recurrence rates was found between ALA-PDT or re-excision.	III-3	[2]
Observation versus re-excision More tumours recurred after re-excision than observation. In the one study that reported this comparison, more tumours recurred after re-excision (50%) than observation (15%), in a small cohort of patients.	III-2	[3]
Observation versus EDC, topical imiquimod, topical 5-flourouracil, liquid nitrogen, dual treatment Incompletely resected BCCs treated with topical imiquimod were significantly more likely to recur than incompletely resected BCCs monitored with observation only.	III-2	[4]

Evidence-based recommendation	Grade
EBR 7.6.1. Incompletely excised basal cell carcinomas should be assessed and treatment selected on a case-by-case basis.	**C**

Evidence-based recommendation	Grade
EBR 7.6.2. Incompletely excised basal cell carcinomas that have high-risk features, or occur in high-risk anatomical sites, should be re-excised, where possible.	**C**

5.19.3.1 Notes on these recommendations

The available evidence supports an individualised approach in the management of incompletely resected BCCs at low-risk sites with low-risk histopathology.[3][4] High-risk tumours in high risk sites warrant further surgery, possibly including a wider excision or excision with a margin control technique.

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- Protocol to manage rapidly growing tumours
- Criteria for choosing Mohs micrographic surgery in preference to other surgical techniques
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5.19.4 Appendices

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5.20 7.7 Managing rapidly growing tumours

Contents

5.20.1 Background

Rapidly growing tumours are more likely to quickly enlarge to a size of more than 2cm diameter.[1]

Basal cell carcinoma (BCC) is generally regarded as a slow-growing tumour. Features of BCCs reported to be associated with rapid growth include those at the periocular site (particularly when recurrent, large, or in men).[2]

Cutaneous squamous cell carcinomas (cSCCs) in younger patients, particularly cSCCs of the face (especially lips), can have a short and aggressive course, and are more at risk of developing subsequent cancers.[3]

5.20.2 Systematic review evidence

What should be the protocol to manage rapidly growing tumours?

A systematic review was undertaken to answer this clinical question.The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

A total of nine studies reported relevant outcomes for cSCCs or BCCs with perineural invasion (PNI), or for poorly differentiated cSCCs, after different treatments.

These included one retrospective cohort intervention study[4] and eight retrospective case series.[5][6][7][8][9][10][11][12]

One case series[5] had a moderate risk of bias. All other studies had a high risk of bias.

Treatment modalities included radiotherapy, chemotherapy, excision and Mohs micrographic surgery (MMS).

Reported outcomes included recurrence, local control, local treatment failure, distant metastasis, recurrence-free survival and disease-free survival.

No study specifically investigated the management of rapidly growing tumours. The studies provided only indirect evidence to answer this clinical question.

A small Australian retrospective case series reported higher recurrence-free survival numbers for high-risk tumours treated with MMS plus radiotherapy or MMS, compared with excision alone or excision plus radiotherapy.[9]

Two other Australian case series[5][6] reported high cure rates with surgery and radiotherapy, although lower if PNI was symptomatic.

Another Australian case series[10] and a US retrospective cohort study[11] reported a possible survival benefit with extensive subcranial and cranial resection including nerve for patients with symptomatic PNI.

An Australian retrospective case series[12] found that most failures occurred in patients with gross PNI. Those with microscopic extensive PNI also received a benefit with radiotherapy, but those with microscopic focal PNI did well with or without irradiation.

A US cohort study[4] found a possible benefit with MMS and radiotherapy in head and neck cSCC, compared with surgery and RT.

A US retrospective case series in 131 patients with 155 cSCCs[7] found a benefit with RT in both incidental and symptomatic PNI. A Dutch retrospective case series[8] found that metastasis-free survival at 5 years was significantly higher in well-differentiated cSCCs (70%) compared with moderately differentiated (51%) and poorly differentiated cSCCs (26%; p=0.012).

5.20.3 Evidence summary and recommendations

Evidence summary	Level	References
Recurrence BCCs and cSCCs with PNI had higher recurrence rates with excision or excision with RT than MMS or MMS plus RT. **Recurrence-free survival** For tumours with PNI, recurrence-free survival rates were 58.6% after surgical excision in one study, and 62- 71% after surgery plus adjuvant RT in two studies. For tumours with microscopic focal PNI, recurrence-free survival was significantly higher after RT (94%) than observation (25%). However, there was no significant difference between radiotherapy and observation for tumours with microscopic extensive PNI.	III-3, IV	[9], [5], [6], [10], [12]
Cancer-specific mortality Among various observational studies, reported disease-free survival was highest after postoperative RT plus chemotherapy, followed by surgery plus RT (87%), MMS plus RT (84%) postoperative RT (76%), RT (58–74%), not MMS plus RT (68%), observation (40–62%), skull base/subcranial surgery (50–53.6%) and RT and palliative therapies (0%), and was only found to be significantly higher for MMS plus RT, RT and subcranial and skull base therapies than not MMS and RT, observation and palliative therapies. Cancer-specific mortality ranged from 10% to 53% after surgical excision.	III-3, IV	[5], [7], [8], [10], [6], [4], [12], [11]

Evidence summary	Level	References
Locoregional control Locoregional control was highest after postoperative RT plus chemotherapy (100%), then treatment other than MMS plus RT (92%), RT alone (84%), postoperative RT (77%), RT plus chemotherapy (62%) and postoperative RT (50%) for poorly differentiated cSCCs and cSCCs with PNI.	III-3, IV	[4], [5], [7]
Distal metastasis Most metastasis for mostly cSCCs with PNI or poor differentiation occurred after surgical excision (26%) or excision plus RT (12.5%), whereas distant metastasis-free survival at 2–5 years of follow-up was 100% for tumours treated with observation or RT.	III-3, IV	[8], [9], [12]

Evidence-based recommendation	Grade
EBR 7.7.1. For patients with cutaneous squamous cell carcinomas with features associated with poor prognosis, wider surgical margin should be planned, adjuvant radiotherapy should be considered, and regular follow-up for locoregional or distant recurrence should be provided.	**C**

Evidence-based recommendation	Grade
EBR 7.7.2. For tumours with perineural invasion, the combination of surgery and radiotherapy is recommended when a nerve with diameter >0.1mm is involved.	**C**

Evidence-based recommendation	Grade
EBR 7.7.3. Cutaneous squamous cell carcinomas with high-risk features should be managed with wider surgical margins, adjuvant radiotherapy, and regular follow-up for locoregional or distant recurrence.	**C**

Practice point

PP 7.7.1. For patients with cutaneous squamous cell carcinoma, consider referral to a specialist or multidisciplinary team if there are any risk factors for poor prognosis, such as:

- size >2 cm in diameter
- tumour depth > 4 mm
- recurrent lesion
- high-risk anatomic location
- perineural invasion or lymphovascular invasion
- poorly differentiated subtype
- immunosuppression.

Practice point

PP 7.7.2. Patients with rapidly growing squamous cell carcinomas should be referred timely for assessment for specialised therapies or combination therapies.

5.20.3.1 Notes on the recommendations

Follow-up of patients after treatment is individually tailored according to patient factors, tumour factors, anatomic site and the perceived adequacy of treatment.

The available evidence supports an individualised approach in the management of incompletely resected cSCCs at low-risk sites with low-risk histopathology. High-risk tumours in high risk sites warrant further surgery, possibly including a wider excision or excision with a margin control technique.

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5.20.4 Appendices

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5.21 7.8 Mohs micrographic surgery

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5.22 7.9 Surgical management of advanced cSCC

Contents

5.22.1 Background

The presence of nodal metastasis of cutaneous squamous cell carcinoma (cSCC) in associated with an overall 5-year survival rate of 40%.[1][2]

Recurrence in a nodal basin after standard lymphadenectomy radical node dissection almost invariably leads to the development of distant disease. The risk of regional recurrence after radical lymphadenectomy depends on the number of nodes containing metastases on histopathology, and the presence of extranodal spread manifested clinically by gross fixation of nodes.[1][3][2]

See also: Prognosis

5.22.2 Overview of evidence (non-systematic literature review)

5.22.2.1 Nodal involvement

Lymphadenectomy for disease in the axilla or groin is straightforward. Occasionally lymph node metastases of cSCC occur at unusual sites including the epitrochlear region and popliteal fossa.

For cervical lymph nodes, most authors recommend a selective neck dissection.[4] 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 postoperative radiotherapy should be considered in patients with a significant risk of recurrence (see: Radiotherapy). Risk factors for recurrence including involvement of multiple nodes, large size, extracapsular extension or tumour spill at the time of operation (including an open biopsy).

5.22.2.1.1 Recurrent nodal disease

Salvage surgery is sometimes possible if complete or durable control is not achieved with radiotherapy alone.

5.22.2.1.2 Dermal lymphatic spread (in-transit metastasis)

Dermal lymphatic spread (in-transit metastasis) 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.[5]

5.22.3 Practice Points

Practice point
PP 7.9.1. Dermal lymphatic spread (in-transit metastasis) should be managed by wide surgical excision followed by adjuvant radiotherapy.

Practice point

PP 7.9.2. For patients with cutaneous squamous cell carcinoma, consider referral to a specialist or multidisciplinary team if there are any risk factors for poor prognosis, such as:

- size >2 cm in diameter
- tumour depth > 4 mm
- recurrent lesion
- high-risk anatomic location
- perineural invasion or lymphovascular invasion
- poorly differentiated subtype
- immunosuppression.

Key point(s)

For patients with lymph node involvement who have a significant risk of recurrence, adjuvant postoperative radiotherapy should be considered after lymphadenectomy.

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5.23 7.10 Health system implications and discussion

Contents

5.23.1 Health system implications

5.23.1.1 Clinical practice

Implementation of recommendations for surgical management of keratinocyte cancers (KCs) would not change the way that care is currently organised. However, adherence to these guidelines may prevent unnecessary surgery on occasion.

5.23.1.2 Resourcing

Resourcing needs to be allocated for continuous training of GPs in management of KCs as well as appropriate Medicare reimbursement and funding for such management.

5.23.1.3 Barriers to implementation

No barriers to the implementation of these recommendations is envisaged.

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5.23.2 Discussion

5.23.2.1 Unresolved issues

Based on currently available evidence, the risks and benefits of surgical treatment for KCs, compared with non-surgical treatments, cannot be defined because outcome measures are not consistent between studies. Different perspectives for surgical and non-surgical interventions result in different endpoints being considered relevant. If clearance or non-recurrence is the end point, it may theoretically be possible to achieve 100% with surgery by taking very wide margins, but that may be cosmetically and functionally unacceptable. Accordingly, a certain rate of recurrence is acceptable with surgical interventions if we are to minimise morbidity. There is a need for further studies comparing surgical and non-surgical treatments using the same well-defined endpoints and outcome measures.

5.23.2.2 Studies currently underway

No relevant clinical trials are known to be underway.

5.23.2.3 Future research priorities

Further research, including appropriately designed randomised controlled trials, where feasible, is needed to:

- define adequate excision margins for cutaneous squamous cell carcinomas (cSCCs) and basal cell carcinomas (BCCs) according to other features identified before surgery
- identify features of cSCCs that predict superior outcomes with Mohs micrographic surgery, compared with conventional excision
- identify optimal management of high-risk primary facial BCCs
- determine whether antibiotic prophylaxis prevents endocarditis or prosthetic joint infections in patients undergoing excision of BCCs or cSCCs
- determine whether the use of dermoscopy, confocal microscopy, or other techniques to identify tumour margins is associated with reductions in recurrence rates.

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5.24 8. Radiotherapy – Introduction

Contents

5.24.1 Introduction

Radiotherapy (RT) is an effective treatment modality for keratinocyte cancers (KCs), including all stages of basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC). It is used in definitive (curative) treatment, postoperative treatment, in the management of recurrent or metastatic disease, and in palliative treatment.

For early-stage disease, results are comparable to surgery.[1]

5.24.2 Mechanism of action and modalities

Radiotherapy involves exposure of the target tissue to ionising radiation (x and γ rays, photons, β rays, electrons, particles) delivered by external-beam RT (EBRT) or brachytherapy.[2][3][4][5][6][7][8][9]

Radiotherapy works mainly through its effect on deoxyribose nucleic acid (DNA), which is very sensitive to radiation. Cancer cells have poor DNA repair capacity and die following damage from RT, while normal cells have a better DNA repair capacity,[10] repairing most RT damage to their DNA within 6 hours after a single treatment with an appropriate dose. In a mixed population of cancer cells and normal cells, RT can spare normal cells while eradicating cancer cells. [10]

External-beam RT modalities include superficial x-ray therapy,[11][12] orthovoltage radiotherapy, and megavoltage therapy from linear accelerators. Electronic brachytherapy is actually a type of EBRT.[13][14]

Brachytherapy is the use of isotopes applied directly to the tumour as a surface treatment or implanted into the tumour.[15] It can be applied using a sealed or unsealed source. Sealed sources are isotopes sealed within non-radioactive containers, such as a temporary high-dose rate source (e.g. iridium-192 source in a titanium casing) or a permanent low-dose rate source (e.g. iodine-125). The casing allows for accurate dosimetry and safety for patient and staff. Unsealed sources include topical rhenium-188. Brachytherapy deposits a high dose at the interface between the source and the tumour, with a rapid fall-off, thereby minimising the dose to deeper normal tissues. There is some evidence for better cosmesis with brachytherapy compared with EBRT.[16]

The selection of RT modality depends on the depth of penetration required to treat the lesion adequately. Superficial x-ray therapy is suitable for lesions with a depth of up to 5mm. Lesions with greater depth can be treated with modalities that achieve greater penetration, such as orthovoltage radiotherapy, megavoltage electrons, or photons produced by a linear accelerator.

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 cSCCs, but 1–1.5cm for larger ill-defined BCCs and more aggressive cSCCs. The margin depends on the quality of patient immobilisation and the modality (e.g. electrons have a wider penumbra than the photons delivered in superficial x-ray therapy.)

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5.24.3 Recent advances

Radiotherapy has significantly improved in the last few decades in two main areas: greater conformality of dose to tumour volume and more precise fractionation. These improvements have led to higher cure rates and reduced toxicity to normal tissue.[17]

Significant recent improvements in RT technology have enabled greater conformality of dose to tumour volumes and reduced conformality to normal tissue volumes. Improved understanding of radiobiology has led to understanding the importance of total dose and dose per fraction. Proper fractionation results in tumour control but minimal late effects in surrounding normal tissue. However, hypofractionation is effective in the treatment of KCs.[18][19][20] Hypofractionation is ideal for patient for whom function and cosmesis are not high priorities, and for whom attendance at a fully fractionated course of RT would be difficult due to comorbidities.[21][20][22][23]

Newer modalities such as volumetric modulated arc therapy enable definitive RT for large areas of skin field-cancerisation,[24][20] increasing the indications for RT in skin cancer.

5.24.4 Advantages of radiotherapy

Because RT can conserve tissue, it may achieve superior functional and cosmetic outcomes for cancer treatment in cases where surgical treatment is likely to result in bulk volume tissue loss, numbness or paralysis (e.g. due to facial nerve sacrifice). Cases where tissue conservation may be an advantage include treatment of cancers of the lip or eyelid commissures,[25] nasectomy or resection of nasal ala.

Radiotherapy does not require anaesthetic or excision. It also avoids issues that can complicate surgery, such as tissue tension causing poor healing, skin graft survival, and anticoagulant therapy. As no tissue is lost, RT margins can be greater than surgical margins.[26]

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5.24.5 Disadvantages of radiotherapy

Disadvantages of RT include the need for repeated treatments (fractionation). If too much RT is given in a single treatment (fraction), the repair capacity of normal cells is exceeded, and dead cells are eventually replaced by fibrous tissue. Late effects after RT can include hypopigmentation and sometimes induration in the RT field, causing tissue retraction, poor function and poor cosmesis. To minimise the risk of these late side effects, RT needs to be given in small doses (fractions).

In general, small doses (e.g.1.8–2.0 Gy daily) of RT result in greater survival of normal cells, and therefore superior function and cosmesis, compared with larger daily doses (>2.0 Gy daily). However, not all studies support a difference in cosmesis with fraction size.[27]

Delivering small daily doses of RT requires a greater number of treatments and therefore more visits to a RT facility to achieve an effective curative dose, compared with large daily doses. This may be problematic for some patients.

Standard curative dose schedules for treatment of small lesions (<2cm) usually require fewer treatments (4–12 attendances over 1–2 weeks) compared with larger lesions, which require 15–30 treatments over 3–6 weeks.

Following RT there is no histopathology report that verifies the cancer type or confirms that it has been completely treated.

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5.24.6 Limitations of the evidence

Relatively few studies have investigated RT in the treatment of skin cancer, and there is limited high-level evidence to guide treatment decisions. Cochrane reviews of interventions for BCC, cSCC and actinic keratosis (AK) have included very few or no RCTs evaluating RT.[28][29][30]

The evidence to support RT is based on data from retrospective studies, usually conducted in a single institution. Very few data are available from Australian studies, despite the high burden of KC in Australia.

In the absence of a large body of high-quality evidence to guide the selection of RT, it is currently prescribed according to accepted relative indications and contraindications derived from common sense (Table 6).[31]

Table 6. Relative indications and contraindications of radiotherapy for keratinocyte cancers

	Relative indications	Relative contraindications

Tumour factors	Sites or lesions where tissue conservation is crucial and surgery would result in major loss of function (e.g. tip of nose, lateral eyelid commissure, lip commissure, site proximal to facial nerve, large superficial lesions, PNI) Multiple lesions (especially superficial lesions) when impractical to excise	Invasion into bone or joints[(a)] Sites with poor vascularity, lower leg skin overlying anterior tibia or malleoli
Treatment factors	Circumstances where repeated surgery would be burdensome	Previous RT at site Sites where RT would result in unacceptable hair loss
Patient factors	Unfit for surgery Unacceptable anaesthesia risk Anticoagulant therapy Unable to tolerate multiple surgical procedures (e.g. due to ageing) Tendency to keloid development Patient preference Immunosuppression (e.g. OTR, patient with CLL, patient on long-term corticosteroid therapy)	Young age (increased risk of RT-induced malignancy, prioritisation of cosmesis) Naevoid BCC (Gorlin's syndrome) [(b)] (increased risk of in-field BCCs) Limited access to RT facility Active connective tissue disorders (e.g. scleroderma; increased risk of acute and late RT-related effects) Collagen vascular disease

BCC: basal cell carcinoma; CLL: chronic lymphocytic leukaemia; OTR: organ transplant recipient; PNI: perineural invasion; RT: radiotherapy.

(a) Cartilage involvement is not an absolute contraindication. Radiotherapy must be given cautiously in larger pinna lesions with extensive, inflamed or painful cartilage invasion. (b) excepting specific lesions for which RT is indicated. Sources[25][32][33]

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5.24.7 Misunderstandings of RT

The lack of high-quality evidence from well-designed prospective clinical trials has allowed misconceptions about RT in skin cancer to persist. These include the belief that RT should not be used for skin lesions below the knees, that radiation-induced cancer is common, and that only patients over 70 years old should have definitive radiotherapy for skin lesions. There are no prospective data to support any of these claims, yet they are perpetuated in some guidelines.[34]

A recent literature review reported the rate of RT-induced in-field cancer to be 1 in 1000 every 10 years[32]

The belief that the use of RT should be restricted to older patients is based on historical observations of poor long-term cosmetic outcomes (e.g. hypopigmentation, telangiectasia, cicatrisation and in-field fibrosis) associated with poor-quality RT, including hypofractionated treatment. These effects occurred during an era when RT was prescribed by clinicians other than trained radiation oncologists and large doses were used. Current knowledge of the radiobiological association between fraction size and chronic inflammation with fibrosis, and highly developed specialist training practices, have significantly improved cosmetic outcomes.

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Topics in this section include:

- Radiotherapy with or without surgical treatment for keratinocyte cancer
- Radiotherapy for basal cell carcinoma
- Radiotherapy for primary cutaneous squamous cell carcinoma
- Radiotherapy for regional (nodal) metastatic disease (non-distant)
- Radiotherapy for actinic keratosis and cutaneous squamous cell carcinoma in situ
- Radiotherapy for keratoacanthoma
- Recent advances in the radiotherapy of skin cancer
- Management of side effects of radiotherapy
- Radiotherapy – health system implications and discussion

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5.25 8.1 Radiotherapy with or without surgical treatment

Contents

Unless stated otherwise, tumour stage is according to the American Joint Committee on Cancer (AJCC) cancer staging manual 8th edition [1] and Union for International Cancer Control (UICC) TNM classification of malignant tumours 8th edition.[2]

5.25.1 Background

Radiotherapy (RT) is used extensively in Australia to treat skin cancer. Definitive RT is an alternative to surgery. Radiotherapy is particularly helpful when tissue conservation for functional and cosmetic reasons are a priority, or when surgery is problematic, such as when it would result in unacceptable tissue loss or when comorbidity or medication would compromise safety (e.g. in patients taking anticoagulant therapy).

As the majority of basal cell carcinomas (BCCs) and cutaneous squamous cell carcinomas (cSCCs) present early, surgery is the more common treatment because it usually requires a single treatment episode, is highly efficacious and delivers a complete specimen for pathology examination. Radiotherapy is reserved for lesions that present problems for conventional surgery and for cases of incompletely excised (persistent), recurrent or advanced BCC and cSCC[3][4][5][6][7][8][9][10][11][12][13][14] where multimodality treatment may be indicated.

The treatment of complex skin cancers should be managed by the multidisciplinary team. Ideally, all BCCs and cSCCs should be confirmed histologically by biopsy prior to RT.

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5.25.2 Systematic review evidence

When should radiotherapy be used alone, or in combination with surgical excision to treat those with keratinocyte cancers?

A systematic review was undertaken to evaluate the effects of radiotherapy when used alone or in combination with surgical excision to treat those with keratinocyte carcinomas.

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Eight studies meeting search criteria were identified that assessed outcomes of RT as monotherapy or in combination with surgical excision for patients with a keratinocyte cancer (KC).[15][16][17][18][15][16][19][20][21][19][22] These included one systematic review,[15] one prospective longitudinal observational cohort study,[21] and six retrospective cohort studies.[16][22][19][17][20][18] All were level 2 evidence. Two studies were assessed to be at low risk of bias[16][18] and the remainder were at high risk of bias.

All studies used external-beam RT.

A systematic review of surgical monotherapy versus surgery plus adjuvant RT in for patients with high-risk cSCC identified no randomised controlled trials.[15] Of 2,449 cases documented in observational studies, 91 received surgery plus adjuvant RT.[15] Tumour stage and surgical margin status before adjuvant RT were generally not reported in the included studies.[15] In 74 cases of perineural invasion, outcomes were statistically similar between patients who received surgical monotherapy and those who received surgery and adjuvant RT.[15] The investigators concluded that it was not possible to identify high-risk features in which adjuvant RT may be beneficial, based on the available data.[15]

A Greek prospective observational cohort study of 315 consecutive patients (145 males and 170 females) presenting with primary cSCC of the head and neck was designed to identify any clinical-pathologic factors associated with reduced overall and recurrence-free survival.[21] At a mean follow-up time of 46.7 months (range 12–124 months) for 222 surviving patients, adjuvant irradiation was associated with a 92% reduced risk for recurrence[21] The investigators concluded that, after excision with negative margins, patients with head and neck cSCCs should be referred to specialised multidisciplinary oncology clinics for counselling on adjuvant RT and follow-up.

Of the retrospective cohort studies, one compared two electron beam fractionation schedules in patients with KC (BCC or cSCC),[18] one reported outcomes in patients with aggressive cSCC at any site,[22] two reported outcomes in patients with cSCC of the lip,[16][20] and two reported outcomes in patients with KC (cSCC or BCC) of the eyelid. [19][17]

In the study comparing RT fractionation schedules (Netherlands),[18] one reported outcomes in patients with aggressive cSCC at any site,[22] two reported outcomes in patients with cSCC of the lip,[16][20] and two reported outcomes in patients with KC (cSCC or BCC) of the eyelid.[19][17]

In the study comparing RT fractionation schedules (Netherlands),[18] 333 patients with 434 epithelial skin cancers (332 BCCs and 102 cSCCs) received either 54 Gy in 18 fractions (159 tumours) or 44 Gy in 10 fractions (275 tumours).[18] Three-year local recurrence-free survival rates were high for all groups (97–98% for BCC and 94–97% for cSCC) and were not significantly different between fractionation schedules.[18]

In the study of aggressive cSCC at any site (USA), 27 patients with high-risk (n=5) or very high-risk (n=22) cSCC were identified among 1591 cases treated at a single institution between 2000 and 2011.[22] Among those with high-risk cSCC, one patient received surgery and RT while four received surgery only. At median follow-up of 5 years, all remained disease-free.[22] Among those with very-high-risk cSCC, four received surgery alone, 11 received surgery and RT, six received surgery plus cetuximab, and one received the combination of surgery, cetuximab, and RT. At follow-up, 12 patients showed disease progression, including three treated with surgery alone, seven treated with surgery and RT (median time to recurrence 6 months), and two treated with surgery and cetuximab.[22] No clear conclusions about the comparable effects of regimens with and without RT can be drawn from these data due to the lack of randomisation or control, and the absence of a standardised treatment protocol.[22]

An Australian retrospective cohort study compared surgery alone with surgery and adjuvant RT as a definitive treatment in patients with T1 or T2 (staging according to AJCC/UICC 7th edition) cSCC of the lip.[16] The addition of local adjuvant RT in patients with a close or positive margin was associated with a significant improvement in relapse-free survival.[16] Compared with patients having any RT, those undergoing surgery experienced a higher rate of locoregional recurrence.[16] The investigators concluded that the addition of adjuvant RT in patients with inadequate excision significantly decreased the risk of recurrence.[16]

In a Brazilian retrospective study designed to evaluate three histologic grading methods using data from 53 patients with cSCC of lip, surgical treatment combined with RT was associated with lower recurrence-free survival when applying a model based on tumour budding and depth of invasion. However, this observation may be due to selection bias if only those judged to be at higher risk received RT.[20]

A small US retrospective cohort study compared definitive primary RT (n=32) versus wide local excision plus postoperative RT (n=10) in patients with cSCC of the eyelid.[19] At median follow-up of 76 months, there were no significant differences between the treatment groups in 5-year local, regional, and distant control rates, and there were no grade 3 or 4 complications. The investigators concluded that primary RT for cSCC of the eyelid provided excellent locoregional control with reasonable complication rates and should be considered an alternative to surgery in selected patients.

A Turkish retrospective cohort study analysed data from 311 patients treated for BCC of the eyelid, of which most common histologic subtypes were infiltrative, nodular, and basosquamous BCC.[17] Approximately 30% of the patients had previous tumour recurrence. The investigators noted outcomes were worse than previously reported due to delay in treatment and previous inadequate treatments.[17]

5.25.2.1 Local recurrence

Four studies reported recurrence related outcomes in those treated with surgery alone, compared with surgery and RT, or RT alone.[15][16][17][18]

A systematic review of 49 cohort studies reported lower recurrence rates for patients with cSCC treated by surgery alone (7%, n=1874) compared with those treated with adjuvant RT (12%, n=68), with a follow-up period ranging from 1 month to 26 years. This difference was nonsignificant (p=0.10).

In the Australian cohort with T1 or T2 (staging according to AJCC/UICC 7th edition) cSCC of the lip,[16] recurrence rates were highest among those treated by surgery (43%, n=89), lower in those who had RT only (15%, n=89), and lower still in those treated by adjuvant RT (6%, n=26) with a follow-up of 5 years. In this same cohort, 5-year relapse-free survival was approximately 90% for RT alone and adjuvant RT groups, and 51% in the surgery only group. None of these patients underwent Mohs micrographic surgery.

The retrospective cohort of patients treated for BCC of the eyelid[17] reported the lowest recurrence in those who had surgery alone (5.3%, n=244), higher recurrence in the adjuvant RT group (10%, n=20), and higher again (21%, n=19) in the RT-only group, with a median follow-up of 33 months.

The study comparing RT fractionation schedules in patients with KCs[18] reported local recurrence rates of 3.1% (n=386) in those treated by RT alone, and 6.4% (n=48) in those treated with RT postoperatively, after a median follow-up of 42.8 months (p=0.919).

5.25.2.2 Survival

Five studies reported survival outcomes in patients with cSCC and BCC treated by surgery or adjuvant RT.[15][16][19][20][21]

The systematic review[15] reported a higher rate of KC-specific deaths in those treated with adjuvant RT (10%, n=91), compared with those treated with surgery alone (4%, n=1772), for a follow-up period ranging from 1 month to 26 years.

The Australian cohort study of patients with cSCC of the lip[16] reported 5-year overall survival rates of approximately 80% in patients treated with either surgery alone (79%, n=89) or RT alone (83%, n=89), and 68% in those treated by adjuvant RT (n=26). In a subgroup of patients who had close or positive margins at surgical treatment (n=45), relapse-free survival was 40% in the surgery-only group (n=23), and 90% in the adjuvant RT group (n=22).

The US retrospective cohort of patients with cSCC of the eyelid[19] reported 5-year disease free survival of 90% in the RT-only group and 69% in the adjuvant RT group, after a median follow-up of 76 months.

The Brazilian retrospective study of patients with cSCC of the lip reported 5-year recurrence free survival of 81.2% in surgery only patients, compared to 44.4% in adjuvant RT patients. This difference was significant (p=0.03).

The Greek prospective observational cohort study of patients with cSCC of the head and neck[21] reported 5-year overall survival of 83% in those treated by surgery only (n=160), 66% in those treated by adjuvant RT (n=112), and 40% for those treated by RT alone (n=20).

5.25.2.3 Control rate

The US retrospective cohort of patients with cSCC of the eyelid[19] reported 5-year local and regional control rates.

Reported 5-year local control rates were similar between tumours treated with RT alone and treated with adjuvant RT (89% versus 86%; p=0.91).[19]

Reported 5-year regional control rates were 100% for patients treated with adjuvant RT and 93% for those treated by RT alone (p=0.45).[19]

5.25.2.4 Response rate

Complete response (disease free at >9 months after treatment) was reported in a single small study of patients with aggressive cSCC.[22] Response rates of 63% (n=8) were reported for those treated by surgery and 42% for those treated with adjuvant RT (n=12).[22]

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5.25.3 Evidence summary and recommendations

Evidence summary	Level	References
Local recurrence rates at 5-year follow-up were similar between groups who received surgery alone, surgery with adjuvant RT, and RT alone.	III-2	[15], [16], [17], [18]
In general, overall survival and recurrence-free survival rates were higher after surgery, with follow-up intervals of 5 years or longer. Survival rates were generally lower among patients who received RT alone, and lower still among those who received surgery and adjuvant RT (although the adjuvant RT group included patients who received postoperative RT only if residual disease was detected/suspected after surgery as well as patients who received planned postoperative RT).	III-2	[15], [16], [19], [20], [21]
There is insufficient evidence to compare the control rate or response rate across treatment modalities (surgery alone, RT alone, or surgery plus adjuvant RT) for BCC or cSCC.	III-2	[19], [22]

Evidence-based recommendation	Grade
EBR 8.1.1. Radiotherapy can be used alone in the treatment of keratinocyte cancers when surgery is not possible or the patient declines surgery.	**D**

Evidence-based recommendation	Grade
EBR 8.1.2. Radiotherapy may be used in combination with surgical excision with the aim of improving locoregional control.	**D**

Practice point

PP 8.1.1. Radiotherapy should begin within 6 weeks following surgery, as macroscopic recurrence at the start of radiotherapy will necessitate a higher dose, which is associated with a higher risk of poor cosmetic and functional outcomes.

Key point(s)

Histological assessment of margins and other associated pathological features by the histopathologist are essential for predicting the need for further therapy.

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- Management of side effects of radiotherapy
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5.25.4 Appendices

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5.25.5 References

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5.26 8.2 Radiotherapy for BCC

Contents

Unless stated otherwise, tumour stage is according to the American Joint Committee on Cancer (AJCC) cancer staging manual 8th edition [1] and Union for International Cancer Control (UICC) TNM classification of malignant tumours 8th edition.[2]

5.26.1 Background

Radiotherapy (RT) has been used for treating basal cell carcinoma (BCC) for over a century. It is an efficacious alternative treatment for primary untreated BCC in a minority of patients when surgery is disadvantageous:

- when surgery is not feasible (e.g. in patients unfit for surgery, including those with significant coagulation risk)
- when the patient declines surgery
- when surgery will cause cosmetic or functional morbidity unacceptable to the patient (e.g. nasectomy, loss of function of lips or eyelids, large tissue deficits, multiple lesions).

Radiotherapy is also used in the management of metastatic BCC.

Unlike topical therapies, RT is not limited to certain BCC histological subtypes.[3]

The availability of new office-based portable systems is increasing the availability of RT for BCC.[4][5]

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5.26.2 Evidence

5.26.2.1 Systematic review evidence

In which patients with basal cell carcinoma does a radiotherapy modality achieve equal or better outcomes than conventional surgery?

A systematic review was undertaken to evaluate in which patients with basal cell carcinoma a radiotherapy modality achieves equal or better outcomes than conventional surgery.

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Twenty studies were identified that assessed outcomes in patients treated with RT for BCC and met the inclusion criteria,[6][7][8][9][10][11][12][13][14][15][3][16][17][18][19][20][21][22][23][24] including five representing level III-2 evidence [11][21][22][23][24] and 15 level IV.[14][3][17][19][20][8][9][7][12][13][15][16][18][6][10]

There were no randomised controlled trials. Three prospective studies were identified,[10][20][13] and the remainder were retrospective studies. All studies were at high risk of bias.

Participants were mainly patients for whom surgery was unsuitable. Many different RT techniques were used, including different types of external-beam radiotherapy (EBRT) and brachytherapy.

5.26.2.1.1 Survival

Seven studies reported survival outcomes in patients treated with EBRT or brachytherapy.[14][8][11][12][19][6]

Four studies[14][9][11][6] reported overall survival rates, which ranged from 61% after 1 year follow-up, to 97% after 5 years follow-up.

Six studies[14][9][11][12][19] reported disease-free survival, which ranged from 57% after 13 months follow-up to 90% after 5 years follow-up.

5.26.2.1.2 Response rates

Four studies reported response rates for patients with BCC treated with RT or brachytherapy. Three reported complete response rates greater than 95% following treatment by EBRT or brachytherapy, in a combined total of 231 patients, with follow-up ranging from 3 months to 4 years.[14][20][13] Another small study[18] reported a complete response rate of 97.9% for those treated with 40 Gy radiotherapy, and 88.9% response rate for those treated with 50 Gy (n=9).

5.26.2.1.3 Recurrence rates

Nine studies reported recurrence or relapse rates for patients treated by EBRT or brachytherapy.[14][17][11][21][7][23][25][10][24]

Recurrence rates ranged from 2% to 10% in a combined total of 2987 patients, with a follow-up of up to 5 years.

A single study[24] reported comparative recurrence rates in patients treated by surgery, adjuvant RT, or RT alone. After a median follow-up of 33 months, patients treated by surgery alone (n=244) had a recurrence rate of 5.3%. The recurrence rate rose to 10% in those treated by surgery and RT (n=20), and to 20% in those treated by RT alone (n=19).[24]

Recurrence can occur at any time after RT, but 88–90% of recurrences were reported to occur within the first 5 years.[26][27] Among patients treated with a curative dose, reported 5-year recurrence rates were approximately 5%.[14][3][17][11][21][7][23][25][10][24]

5.26.2.1.4 Control

Five studies reported control rates for patients treated with EBRT or brachytherapy only.[14][20][21][22][6]

Control rates at 5 years and 10 years post treatment were greater than 85% across all studies (reported for 974 patients).

5.26.2.1.5 Toxicity

Six studies[20][7][13][16][18][10] reported acute toxicity outcomes. Approximately 75% or more of patient reported grade 0 or 1 acute toxicities, in a cumulative total of 503 patients.

Only two studies.[12][18] reported late toxicity outcomes. Grade 0 or 1 late toxicity was reported in 78–91% of patients (n=127). There were no cases of necrosis.[12][18]

5.26.2.1.6 Cosmetic outcomes

Six studies[3][20][23][13][16][18] reported cosmetic outcomes for patients treated with EBRT or brachytherapy.

Good or excellent outcomes were reported in 62–100% of the 308 patients included.

Cosmetic outcomes for brachytherapy were generally inferior to those reported for EBRT[3][20][23][13][16][18]

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5.26.2.2 Overview of additional evidence (non-systematic literature review)

Outcomes of RT series and other relevant clinical findings were reported in additional studies that did not meet inclusion criteria.

5.26.2.2.1 Control rates

For BCC ≤2cm treated with RT, control rates of 95–99% at 5 years and 93–95% at 10 years have been reported (Table 7).[28][29][26][30][27][31][32][33]

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Table 7. Control rates for BCC treated with radiotherapy, according to AJCC/UICC stage (6th edition) [34][35][36][37][38][39][40][41]

Lesion size	T Stage	5 years	10 years
<2cm	T1	97%	95%
2–5cm	T2	92%	89%

>5cm	T3	60%	50%
T4 lesions	T4		

Note: Staging according to American Joint Committee on Cancer and International Union Against Cancer classification (AJCC/UICC) 6th edition,[42] which was the edition current at the time the cited studies were conducted.

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5.26.2.2.2 Basal cell carcinoma of medial canthus

Radiotherapy has comparable control rates to surgery[26] but results in superior tissue conservation.

A small case series reported good cancer outcomes and cosmetic outcomes for high-dose-rate brachytherapy in the treatment of tumours of the medial canthus of the eyelid, the majority of which were BCCs.[43] At median follow-up of 40 months investigators reported a local control rate of 94% and good or excellent cosmetic outcomes in 70% of patients.

Recurrent tumours of the medial canthus require surgical salvage.[44]

5.26.2.2.3 Recurrence of basal cell carcinoma following radiotherapy

Recurrent BCC should be treated with excisional surgery, including excision of the irradiated tissues, by a specialist surgeon.

Salvage re-irradiation can be considered In some circumstances (e.g. a long disease-free interval[45]) when surgery cannot be performed.[46][47] Surgery may be preferred to re-irradiation, as there is increased risk of more serious late RT-related sequelae (radionecrosis of skin and other underlying tissues).

5.26.2.2.4 Residual basal cell carcinoma following radiotherapy

Complete clinical resolution of a BCC following curative radiotherapy can occasionally take up to 4 months.[48] Most small BCC resolve by the time the acute radiation reaction has resolved (4–6 weeks after finishing radiotherapy).[48]

5.26.2.2.5 Postoperative radiotherapy for aggressive tumours

Postoperative RT has been reported to increase local control rates for extensive, locally advanced BCCs where complete surgical excision cannot be achieved,[49] and for head-and-neck BCCs with aggressive features on histopathology.[50]

A small case series reported a 5-year cure rate of 55.13% with definitive RT for extensive and recurrent BCC.[49]

5.26.2.2.6 Postoperative radiotherapy for residual tumours following incomplete excision

The observed recurrence rate of incompletely excised BCC is approximately 33% on average.[51][52][53][54][55][56][57][58][59][47][60]

Re-excision following incomplete excision of BCC is controversial (Protocol to manage incomplete resected basal cell carcinoma). Approximately two-thirds of incompletely excised BCCs do not recur. Some authors have reported similar rates for salvage of recurrent lesions. However, a Canadian case series of incompletely resected BCCs reported that 6% were eventually not controlled after salvage.[58] Numerically higher rates of recurrence have been reported when the deep margin is involved, compared with a lateral margin, and higher again when both are involved.[57][58]

Following incomplete excision, re-excision surgery is usually performed as complete excisional surgery is more accessible, expedient and convenient, and has optimal cancer outcomes and cosmetic outcomes. However, RT is an option following incomplete excision of primary BCCs when surgery is declined, likely to be associated with unacceptable function and cosmetic outcomes, or is not feasible (e.g. due to comorbidity). Margins added for RT fields depend on tumour size and histology.[61]

5.26.2.2.7 Salvage radiotherapy

Control rates after salvage therapy are lower than those for primary treatment and are associated with size of the recurrent tumour, number of recurrences and invasion of skeletal muscle, cartilage or bone.[32]

Radiotherapy has been reported to increase local control in advanced BCC.[62]

Radiotherapy has been reported to be successful as a salvage treatment for recurrence of BCC post Mohs micrographic surgery.[63]

Following recurrence of BCC after RT managed by salvage surgery, further recurrence rates of 14–18% have been reported.[27][51][64][65]

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5.26.3 Evidence summary and recommendations

Evidence summary	Level	References
Recurrence and control	III-2, IV	[14], [20], [13], [18], [3], [17], [11], [21], [7], [23], [25],

Evidence summary	Level	References
Recurrence rate were relatively low (≤10%) across all reported studies, and were comparable for surgery only and RT only. Short-term recurrence rates were variable across studies, and were dependent on patient-related factors. Control rates after approximately 10 years of follow-up were >90% in all studies.		[10], [24], [22], [6]
Survival Overall survival and disease-free survival were high, but variable across the included studies, ranging from 57% to 97%, depending on follow-up time. Survival outcomes were likely to have been influenced by patients' ages, disease characteristics, and comorbidities.	III-2, IV	[14], [8], [9], [11], [12], [19], [6]
Toxicity Substantial acute and late toxicities were reported in <25% of treated patients following RT or brachytherapy.	IV	[20], [7], [13], [66], [18], [10], [12]
Cosmetic outcomes and complications Treatment by RT or brachytherapy resulted in good or excellent cosmetic outcomes in most, if not all patients. Fewer than half of patients experienced treatment-related complications or side effects. Adverse effects were more pronounced in patients treated with higher RT doses and higher dose per fraction.	III-2, IV	[3], [20], [23], [13], [66], [18], [22], [25], [19]

Evidence-based recommendation	Grade
EBR 8.2.1. Radiotherapy using curative doses can be considered as an alternative to surgical excision in the definitive treatment of basal cell carcinoma if surgery is either declined by the patient or surgery is inappropriate.	**D**

Consensus-based recommendation
CBR 8.2.1. For patients with T3/T4 primary persistent or recurrent basal cell carcinoma, consideration should be given to obtaining an opinion from a radiation oncologist as part of multidisciplinary care.

Practice point

PP 8.2.1. Clinical persistence or progression of a basal cell carcinoma after a standard curative dose of radiotherapy should be confirmed in consultation with the treating radiation oncologist. The lesion should be biopsied and managed with salvage excisional surgery.

Practice point

PP 8.2.2. Patients who have undergone complete excision of basal cell carcinomas should be offered referral to a specialist skin cancer clinic (or head and neck clinic) for individual assessment and consideration of postoperative radiotherapy or additional treatment if any of the following are present:

- bone invasion
- rapidly growing tumour
- tumour recurrence (including multifocal recurrence or multiple recurrences)
- inadequate margins on excision when further surgery is problematic
- perineural invasion (major and minor nerves)
- lymphovascular invasion
- in-transit metastases
- regional nodal involvement
- histological subtype associated with poor prognosis (micronodular, infiltrative or metatypical).

Key point(s)

- Radiotherapy can be considered an alternative to re-excision in the management of incompletely excised basal cell carcinoma if further treatment is deemed advisable and re-excision is disadvantageous or not feasible.
- Radiotherapy can be considered as an alternative to excision surgery as a definitive treatment for T1 and T2 BCC when surgery is difficult due to patient-related factors (e.g. frailty), tumour-related factors (e.g. where tissue conservation or cosmesis is a high priority, such as in BCC of the eyelid), or treatment-related factors (e.g. concurrent anticoagulant therapy).

5.26.3.1 Notes on the recommendations

Radiotherapy may be considered in some cases when function and/or cosmesis are a high priority, as RT is tissue-conserving when compared with surgery.

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- Radiotherapy with or without surgical treatment for keratinocyte cancer
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- Radiotherapy for regional (nodal) metastatic disease (non-distant)
- Radiotherapy for actinic keratosis and cutaneous squamous cell carcinoma in situ
- Radiotherapy for keratoacanthoma
- Recent advances in the radiotherapy of skin cancer
- Management of side effects of radiotherapy
- Radiotherapy – health system implications and discussion

5.26.4 Appendices

	Evidence statement form	Systematic review report
PICO question RT2	RT2	RT2

5.26.5 References

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5.27 8.3 Radiotherapy for cSCC

Contents

Unless stated otherwise, tumour stage is according to the American Joint Committee on Cancer (AJCC) cancer staging manual 8th edition[1] and Union for International Cancer Control (UICC) TNM classification of malignant tumours 8th edition.[2]

5.27.1 Background

Radiotherapy (RT) has been used for treating cutaneous squamous cell carcinoma (cSCC) for over a century. It is an efficacious alternative treatment for primary untreated cSCC in patients when surgery is disadvantageous:

- when surgery is not feasible (e.g. in patients unfit for surgery, including those with significant coagulation risk)

- when the patient declines surgery
- when surgery will cause cosmetic or functional morbidity unacceptable to the patient (e.g. nasectomy, loss of function of lips or eyelids, large tissue deficits, multiple lesions).

Human papillomavirus infection, which is a risk factor for cSCC, may affect radiosensitivity.[3]

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5.27.2 Evidence

In which patients with cutaneous squamous cell carcinoma does a radiotherapy modality achieve equal or better outcomes than conventional surgery?

A systematic review was undertaken to identify groups of patients with cSCC in whom a radiotherapy modality achieves outcomes equal to or better than those achieved with conventional surgery.

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

5.27.2.1 Systematic review evidence

Twenty-nine studies were identified that assessed outcomes in patients treated with RT for cSCC and met search criteria.[4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32] These include one study representing level II evidence,[30] 12 level III-2 evidence,[9][10][15][17][20][21][23][24][26][27][28][32] and 16 level IV.[4][5][6][7] [8][11][12][13][14][16][19][19][22][25][29][31]

All studies were at high risk of bias.

Participants were mainly patients in whom surgery was unsuitable. Many different RT techniques were used, including different types of external-beam radiotherapy (EBRT) and brachytherapy.

The single prospective randomised controlled trial (RCT)[30] was a phase III Trans-Tasman Radiation Oncology Group (TROG) study comparing postoperative concurrent chemoradiotherapy with postoperative radiotherapy in patients with high-risk cSCC of the head and neck. The remainder were retrospective studies.

5.27.2.1.1 Survival

Twenty-one studies reported survival outcomes in patients with cSCC treated with EBRT or brachytherapy, alone or in comparison to other treatment modalities.[4][5][6][14][9][10][11][15][8][17][18][19][20][21][22][23][27][28][30][31][32] Thirteen studies reported overall survival[5][10][11][15][17][19][20][21][28][27][30][31][32]

Two studies reported overall survival for patients treated with RT or chemoradiotherapy:

- An Australian RCT[30] reported 5-year follow-up outcomes in patients treated with postoperative ERBT or chemoradiotherapy. There was no statistically significant difference between the EBRT and chemoradiotherapy groups for overall survival (76% versus 79%; p=0.86) or disease-free survival (67% versus 73%; p=0.44).
- A US study[32] reported no significant difference in median overall survival time between patients treated by adjuvant RT (41.3 months) or adjuvant chemoradiotherapy (40.3 months). However, median recurrence-free survival time was significantly longer for patients treated with adjuvant chemoradiotherapy than those treated with adjuvant RT (40.3 months versus 15.4 months; hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.13–0.78, p=0.01).[32]

Five studies reported overall survival for patients who underwent surgery, surgery and adjuvant RT, or RT alone:

- An Australian study[20] reported 5-year survival in a large (n=217) cohort of patients with cSCC of the lip treated by surgery alone (n=89), RT alone (n=89), or adjuvant RT (n=26). Overall survival was highest (83%) in those treated by EBRT alone, followed by surgery alone (79%) and adjuvant RT (68%).[20] Relapse-free survival was highest (92%) in those treated by adjuvant RT, followed by RT alone (87%), and then surgery alone (51%).[20]
- A Greek study[28] compared 5-year overall survival between patients treated by surgery, adjuvant RT, or RT alone. The highest survival (83%) was reported in those who had surgery only (n=160), followed by the adjuvant RT group (66%), and then the RT only group (40%).
- A small (n=36) US study[27] reported no statistically significant difference in 5-year overall survival or cause-specific survival rates between patients treated by RT with or without Mohs micrographic surgery.
- An Australian study[15] reported survival outcomes in a small cohort of patients treated with EBRT definitively or as adjuvant therapy. At 1-, 2-, and 5-year follow-up there were no statistically significant differences in overall survival or relapse-free survival rates. Overall survival rates were numerically higher for the adjuvant RT group.[15]
- A small (n=75) cohort study reported significantly higher 3- and 5-year disease-specific survival rates in patients treated by RT alone, compared with those treated with adjuvant RT (p=0.003).[4]
- Another small (n=42) cohort study reported no significant difference in 5-year disease-free survival in patients treated with RT or adjuvant RT (90% versus 69%).[23]

Two studies reported overall survival for patients treated with different RT doses:

- A large (n=385) Italian cohort study[21] reported significantly higher median overall survival time (months) among patients treated with 45 Gy RT than those treated with 36.75 Gy, at a median follow-up of 65.5 months. However, median disease-free survival time did not differ significantly between groups.[21]
- A Japanese study[17] reported 5-year overall survival in a small cohort of 38 patients treated with EBRT <56 Gy (75% survival) or ≥56 Gy RT (83.3% survival).

Four other studies reported survival outcomes for patients with cSCC treated with EBRT:

- An Australian study reported 2- and 5-year recurrence-free survival of 91% and 90%, respectively, in a cohort (n=93) of patients treated with RT only.[22]
- A US study[19] reported survival outcomes for a cohort of 70 patients treated by EBRT and followed for a median of 13.2 months. Overall survival was 61.4% and recurrence-free survival was 57.1%.
- Another study by the same investigators reported recurrence-free survival of 61.9% at median follow-up of 12 months in patients.[18]
- A large (n=180) cohort study reported 1-, 2-, 5-, and 10-year relapse free survival of 95.8%, 91.5%, 86.2%, and 80.4%, respectively.[14]

Five studies reported overall survival of patients with cSCC treated with brachytherapy:

- A French study[31] reported 5-year overall survival of 80% and disease-free survival of 82% in a cohort (n=86) of patients treated by brachytherapy.
- A Spanish cohort study of 121 patients treated with brachytherapy for cSCC of the lip[5] reported 89.5% overall survival, 97.5% cause-specific survival, and 86.6%,disease-specific survival, at follow-up of up to 15 years.
- A large (n=204) Spanish study[10] compared survival rates between 99 patients treated by low-dose-rate (LDR) brachytherapy and 104 patients treated by high-dose-rate (HDR) brachytherapy, followed for a median of 51–63 months. Overall survival rates were 76.7% and 64.4%, respectively, while cause-specific survival rates were 95.9% and 94.2%, respectively (nonsignificant differences).
- A US study[11] reported 2- and 3-years overall survival in a cohort of 40 patients treated by HDR brachytherapy. Overall survival rates were 89% and 79%, after 2- and 3-year follow-up, respectively.
- A very small (n=10) cohort study[6] reported disease-free survival of 90% following treatment by HDR brachytherapy, after a median of 39.5 months follow-up.

5.27.2.1.2 Recurrence rates

Seven studies reported recurrence rates.[6][7][12][16][20][21][26]

An cohort Australian study (n=204) reported 5-year follow-up recurrence rates of 43% for patients who underwent surgery only, 15% for those who received RT only, and 6% for those who received adjuvant RT.[20]

Two studies that compared RT doses[21][26] reported no significant difference in recurrence rates between groups after median follow-up of 65.5 months[21] and 42.8 months.[26]

In four other studies in which all patients received RT monotherapy, recurrence rates were:

- 1.8% at 2-year follow-up and 5.8% at 5-year recurrence rates of and respectively, in a large cohort of 861 patients treated with EBRT[16]
- 10% in a case series of 10 patients treated with HDR brachytherapy and followed for a median of 39.5 months[7]

- 4.8% in a large cohort of 273 patients treated with HDR brachytherapy and followed for a median of 25 months.[12]

5.27.2.1.3 Control rates

Six studies reported control rates.[5][10][11][13][23][24]

Reported control rates at 5 years were above 85% in all studies that reported this outcome.[5][10][11][13][23][24]

Local control rates for patients treated with RT were:

- 88% in a cohort of 25 patients treated with HDR brachytherapy, with 30 months median follow-up[11]
- 86% and 89%, respectively, in a cohort of 42 patients treated with RT only, or adjuvant RT, at follow-up of 5 years[23]
- 90% local control rate in a cohort of 121 patients treated with brachytherapy and followed for 15 years[5]
- 94.9% and 95.2% in a cohort of 203 patients treated with either LDR or HDR brachytherapy, respectively, and followed for a median of 51–63 months[10]
- 95% at 5- and 10-years following RT treatment in a large cohort of 720 patients[24]
- 100% in a small cohort of 15 patients treated with RT and followed for a median of 42 months.[13]

5.27.2.1.4 Toxicity

Five studies reported acute toxicity outcomes of RT:[5][12][29][7][25]

- A study comparing outcomes in patients receiving LDR brachytherapy or HDR brachytherapy reported no statistically significant differences in rates of grade 3 or grade 4 acute toxicities.[5]
- A large cohort (n=297) of patients treated with HDR brachytherapy reported rash in 86% and pruritus in 27% of patients.[7]
- In another large cohort of patients treated with HDR brachytherapy, less than 7% experienced grade 4 toxicities.[12]

Three studies reported late effects of RT:[4][25][7]

- In a cohort of 75 patients treated with EBRT, grade 4 late toxicities were reported in 1.3%.[4]
- In a large cohort of 297 patients treated with HDR brachytherapy, hyperpigmentation was reported in 6% of patients reported, and alopecia in 1%.[7] There were no cases of necrosis.
- In as small (n=21) cohort of patients treated with helical tomotherapy, 66.6% experienced late toxicity.[25] There were no cases of necrosis.

5.27.2.1.5 Cosmetic outcomes

In studies that reported cosmetic outcomes, these were reported to be excellent or good for most patients.[7][8][10][26]

5.27.2.2 Overview of additional evidence (non-systematic literature review)

Outcomes of RT series and other relevant clinical findings were reported in additional studies that did not meet inclusion criteria.

5.27.2.2.1 Definitive treatment of primary squamous cell carcinoma

Reported outcomes of RT for primary cSCC are comparable to those reported for surgery.[33][34][35]

Five-year control rates of primary cSCC treated with curative doses of radiotherapy are 93% for T1 lesions, 65–85% for T2 lesions and 50–60% for T3–4 lesions (staging according to AJCC/UICC 6th edition).[36][37][38][39][40][41][34][42][43][19][14]

Together with the findings of the Australian study that reported a 5-year control rate of 90% for early-stage cSCC of the lip,[22] these findings raise the clinical question of whether surgery can be reserved for salvage.

5.27.2.2.2 Postoperative radiotherapy for residual tumours following incomplete excision

Incompletely excised cSCC carries a local recurrence rate of over 50%.[44][45][46] Overall, tumour control of all stages of previously untreated primary cSCC with radiotherapy is 87%, but the tumour control rate for recurrent cSCC treated with radiotherapy is 65%.[47]

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5.27.3 Evidence summary and recommendations

Evidence summary	Level	References
Overall survival and disease-free survival Overall survival rates across reported studies were generally greater than 80%, with follow-up of 1–5 years for most studies. Disease-free survival was lower than overall survival in the same studies (although some of these studies included cSCCs of the lip) and did not significantly vary between treatment modalities.	II, III-2, IV	[4], [5], [6], [14], [9], [10], [11], [15], [8], [17], [18], [19], [20], [21], [22], [23], [27], [28], [30], [31], [32]

Evidence summary	Level	References
Acute and late toxicity and effects Toxicity (acute and late effects) were reported by a significant proportion of patients and varied depending on tumour site. Dermatitis was the most common side effect reported.	IV	[4], [5], [7], [25], [29], [12]
Control rate and recurrence Local control rates following treatment with brachytherapy or RT were >88%, with most patients reporting >94% local control. Recurrence rates were less than 10% at 5 years of follow-up.	III-2, IV	[13], [5], [6], [7], [16], [24], [10], [11], [20], [12], [21], [23], [26]
Cosmesis, complications, and functional outcomes Cosmetic outcomes were generally 'excellent' or 'good' for approximately >80% of patients following brachytherapy or RT. At least one-third of patients treated with RT experienced complications.	III-2, IV	[13], [7], [8], [10], [26]

Evidence-based recommendation	Grade
EBR 8.3.1 Radiotherapy using curative doses can be considered as an alternative to surgery for cutaneous squamous cell carcinomas if surgery is either declined by the patient or surgery is inappropriate.	**B**

Practice point

PP 8.3.1 If surgical excision of a cutaneous squamous cell carcinoma is not possible, referral for a radiotherapy opinion should be considered.

Practice point

PP 8.3.2 For patients with T3/T4 primary, persistent and recurrent cutaneous squamous cell carcinomas, a consideration should be given to obtaining an opinion from a radiation oncologist as part of multidisciplinary care.

Practice point

PP 8.3.3 Postoperative radiotherapy should be considered after complete excision for high-risk cutaneous squamous cell carcinomas, including when any of the following are present:

- T3/T4 tumours
- extradermal invasion beyond subcutaneous fat, bone
- >6mm depth of invasion
- rapidly growing tumour
- recurrent disease
- inadequate margins on excision when further surgery is problematic
- poorly differentiated tumour
- perineural invasion (major and minor nerves)
- lymphovascular invasion
- in-transit metastases
- regional nodal involvement.

Practice point

PP 8.3.4 Following incomplete surgical excision of a cutaneous squamous cell carcinoma, radiotherapy can be considered as an alternative to re-excision if further treatment is deemed advisable and re-excision is disadvantageous or not feasible.

Practice point

PP 8.3.5 For recurrent and/or locally advanced cutaneous squamous cell carcinomas, the draining regional nodes must be examined (even after treatment of the primary site), because of the relatively higher propensity of cutaneous squamous cell carcinoma to metastasise, compared with basal cell carcinoma.

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5.27.3.1 Notes on the recommendations

Keratinocyte cancers occur predominantly in sun- exposed areas (e.g. face) and these can be in cosmetically sensitive areas where the tissue loss that is inherent in surgery is not acceptable to the patient. Definitive RT can then be considered, with oncological outcomes approximately equivalent to surgery. This type of RT does require fractionation, which necessitates multiple visits to a radiation facility.

Go to:

- Radiotherapy – Introduction
- Radiotherapy with or without surgical treatment for keratinocyte cancer
- Radiotherapy for basal cell carcinoma
- Radiotherapy for regional (nodal) metastatic disease (non-distant)
- Radiotherapy for actinic keratosis and cutaneous squamous cell carcinoma in situ
- Radiotherapy for keratoacanthoma
- Recent advances in the radiotherapy of skin cancer
- Management of side effects of radiotherapy
- Radiotherapy – health system implications and discussion

5.27.4 Appendices

	Evidence statement form	Systematic review report
PICO question RT3	RT3	RT3

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5.28 8.4 Radiotherapy for regional (nodal) metastatic disease (non-distant)

Contents

Unless stated otherwise, tumour stage is according to edition American Joint Committee on Cancer (AJCC) cancer staging manual 8th edition [1] and Union for International Cancer Control (UICC) TNM classification of malignant tumours 8th edition.[2]

5.28.1 Background

Radiotherapy (RT) has been used in the treatment of metastasis to lymph nodes, lymph channels (in-transit disease in dermal lymphatics) or via perineural invasion (PNI).

5.28.1.1 Lymph node metastases

Nodal disease is associated with poor prognosis in patients with cutaneous squamous cell carcinoma (cSCC) or basal cell carcinoma (BCC). The prevalence of nodal disease is higher for cSCC than for BCC. Radiotherapy increases regional control rates in both cSCC and BCC.[3][4][5]

5.28.1.2 Basal cell carcinoma

Basal cell carcinomas rarely metastasise to lymph nodes. Most commonly, the patient has a long history of multiple recurrences, extending over many years, or an uncontrolled primary lesion. Other risk factors have been reported, including a history of prior radiotherapy, a large primary tumour, and head and neck site.[6][7]

5.28.1.3 Cutaneous squamous cell carcinoma

The incidence of lymph node metastases from cSCC occurring in UV-exposed skin is very low (less than 5%) but may be considerably higher in certain situations, including when cSCC occurs:[8][9][10]

- at sites of mucosal–squamous cell junction, including lip, anus and vulva
- at head and neck sites
- in a patient with immunosuppression[11]
- within chronically inflamed/irritated lesions.

Tumour-related factors associated with regional recurrence of cSCC include:[9][12]

- size – lesions greater than 2cm in diameter are twice as likely as smaller lesions to develop regional recurrence
- site – lesions located on the ear and lip have a higher rate of local recurrence than cSCC elsewhere
- grade – poorly differentiated cSCCs have double the metastasis rate of well-differentiated lesions
- thickness – cSCCs >6mm in thickness recur three times more commonly than thinner lesions
- recurrence – recurrent cSCC is twice as likely to metastasise than primary cSCC
- PNI – PNI is the strongest predictor of regional recurrence (up to 50% risk).

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

Spread of cSCC to regional lymph nodes is uncommon, but is associated with metastasis to distant sites and a poorer outcome.[8][9] Survival after lymph node metastasis is poor, with only one-third of patients surviving 5 years. Half of these patients die of uncontrolled regional disease without distant metastases.[13] For patients with regional spread from cSCC of the lip, survival rates may be twice as high.[8]

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 because 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.[14]

In Australia the most common malignancy of the parotid gland is metastatic cSCC to intraparotid nodes from a cutaneous malignancy.[15] 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 cSCC arising from a mucosal site needs to be excluded in the first instance.

An Australian retrospective series of patients with metastatic cSCC in the parotid gland observed a low rate (< 15%) of pathological involvement of cervical nodes among patients with clinically negative cervical nodes,[16] comparable to the low rate reported in a US study.[17]

For cervical lymph nodes, most authorities recommend a selective neck dissection.[18] 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.[18] Occasionally lymph node metastases occur at unusual sites, including the epitrochlear region and popliteal fossa.[19][20]

5.28.1.4 Perineural invasion

Perineural invasion is uncommon. In the past, it was thought to spread as skip lesions but new data suggest this observation was due to specimen processing and that PNI is actually contiguous.[21]

Perineural invasion may be incidental or, more rarely, symptomatic. The vast majority occur in head and neck cutaneous cSCC. Incidental PNI implies early spread, is asymptomatic and is recognised only after complete pathological examination of the specimen.

Perineural invasion is associated with a poor prognosis. Cohort studies reported that perineural invasion involving nerves with a diameter 0.1mm or greater 0.1mm was associated with increased risk of disease-specific mortality. [22][23]

Symptomatic perineural spread shows established spread of cSCC away from the primary cSCC site and carries a poorer prognosis.[24][25]

In patients with PNI of cSCC or BCC, magnetic resonance imaging (MRI) should be considered to map macroscopic extent for further therapy.[26] Intracranial macroscopic disease on MRI carries a poor prognosis and a palliative approach is suitable. Previously PNI was thought to predispose to increased nodal involvement but new data do not support this.[27]

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5.28.2 Overview of evidence (non-systematic literature review)

5.28.2.1 Radiotherapy for lymph node metastasis of basal cell carcinoma

5.28.2.1.1 Post-lymphadenectomy radiotherapy (BCC)

Regional control can usually be achieved with lymphadenectomy. Postoperative RT may be indicated for patients with a high risk of recurrence (i.e. extensive disease, multiple involved nodes, extracapsular extension, or close/involved surgical margins).[28][29]

5.28.2.1.2 Radiotherapy as an alternative to surgery

Radiotherapy alone is a reasonable alternative to surgery for patients who are poor candidates for surgery or the those requiring palliation.

5.28.2.2 Radiotherapy for lymph node metastasis of squamous cell carcinoma

5.28.2.2.1 Post-lymphadenectomy radiotherapy (SCC)

The treatment of metastatic disease to lymph nodes is primarily surgical with or without postoperative RT.[8][9][14][30][31]

Postoperative RT is generally recommended for patients with a high risk of recurrence, including those with any of the following:[30][31][32][33][34][35][36][37][38][39][40][41]

- parotid node metastases
- ≥ two nodes positive in the neck
- ≥ three nodes positive in the axilla or groin
- ≥3cm 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 (posterior triangle neck, supraclavicular fossa, occipital nodes from primary cutaneous cSCC of posterior scalp or upper trunk, epitrochlear nodes or popliteal nodes)

- nodal metastases accompanied by local relapse
- immunosuppression.

Some centres use one modality to manage parotid node metastases of cSCC:[42] either irradiation[18][43] or surgical lymphadenectomy [37] of the clinically negative ipsilateral neck, but not both. An Australian retrospective consecutive case series study reported that the addition of tissue equivalent bolus to adjuvant RT for intraparotid metastatic head and neck did not reduce local skin failure in the parotid region.[44]

Some,[39][40][41] but not all[19] studies observed worse outcomes for parotid node metastasis in immunosuppressed patients.

The role of postoperative chemoradiotherapy for high-risk cSCC of the head and neck has been resolved by a prospective randomised controlled trial (RCT) phase III conducted by the Trans-Tasman Radiation Oncology Group (TROG).[45] The investigators reported that postoperative RT achieved high rates of locoregional control, and that this was not significantly improved by the addition of postoperative concurrent chemoradiotherapy.[45]

In an observational cohort study in patients with parotid-area lymph node metastases, the combination of surgery and postoperative RT improved locoregional control, compared with RT alone.[46]

Whether postoperative RT increases survival is controversial, based on low-level evidence. A retrospective multicentre study reported adjuvant RT was associated with improved overall survival in patients with cSCC of the head and neck, and improved disease-free survival in a subset of patients with PNI and regional disease.[47] An Australian retrospective study of patients with neck node-positive cSCC of the head and neck reported adjuvant RT was associated with improved disease-free survival and overall survival, compared with surgery alone.[48]

Postoperative RT for cSCC of the groin and axilla increases locoregional control.[49][19] Modern RT techniques, such as volumetric modulated arc therapy, achieves better dosimetry than three-dimensional conformal RT for regionally metastatic cSCC of groin and axilla, and can be used to assist in reducing significant treatment-related adverse events.[50]

5.28.2.2.2 Curative radiotherapy as an alternative to lymphadenectomy for nodal metastases of squamous cell carcinoma

If lymphadenectomy is not possible in a patient with nodal metastases of cSCC because the patient is unfit for surgery or declines surgery, curative radiotherapy alone for is indicated.[51]

Salvage surgery is sometimes possible if complete or durable control is not achieved with radiotherapy alone.

5.28.2.2.3 Palliative radiotherapy

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.[52]

5.28.2.2.4 Radiotherapy for dermal lymphatic spread (in-transit metastases) of keratinocyte cancers

Dermal lymphatic spread (in-transit metastasis) of BCC or cSCC 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 RT. Further recurrence is not uncommon.[53]

5.28.2.2.5 Radiotherapy for perineural invasion of basal cell carcinoma or squamous cell carcinoma

A 2009 systematic review comparing surgical monotherapy with surgery plus adjuvant RT in patients with high-risk cutaneous squamous cell carcinoma[54] found no controlled trials. In 74 cases of PNI reported in included observational studies, there was no statistically significant difference in outcomes between groups.[54] Clear surgical margins were associated with better outcomes, while involvement of larger nerves was associated with worse outcomes. The benefit of adjuvant RT could not be determined on the data analysed[54] A 2011 narrative review reached the same conclusion.[55]

For symptomatic PNI, the involved nerve must be treated with RT back to the base of skull.[56]

The use of adjuvant RT following Mohs micrographic surgery in cases with incidental PNI is controversial.[57] Positive margins on PNI are associated with worse survival despite RT.[58] Surgical resection of the involved nerve, which is usually followed by adjuvant RT, can be associated with long term remission.[24][3][59][60][61] Alternatively, high-dose RT with palliative or curative intent covering the entire course of the nerve back to its origin from the central nervous system is acceptable. Relief of symptoms occurs in more than 50% of cases, with variable durability.[25]

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5.28.3 Practice Points

Practice point
PP 8.4.1. For patients with extensive disease, such as those with very large nodes, multiple nodes, bilateral nodes and involvement of overlying skin or fixation of nodes, perineural invasion, multimodal treatment is indicated. In these instances, or if any doubt exists on the extent or integration of treatment, preoperative assessment and opinion from a multidisciplinary team is recommended. Involvement of a head and neck surgeon, reconstructive surgeon, dental oncologist, surgical oncologist, radiation oncologist and medical oncologist may be necessary for complex cases.

Practice point

PP 8.4.2. Modern radiotherapy techniques should be considered as the modality of choice for treating the regional lymph node basin, to limit rates of significant adverse events.

Key point(s)

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

Key point(s)

Symptoms of perineural invasion should be elicited at the time of patient assessment of cutaneous squamous cell carcinoma, especially in cases of persistent, recurrent or locally advanced lesions. A positive response should prompt referral to a specialist clinic for further investigations, which may include magnetic resonance imaging.

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- Radiotherapy for keratoacanthoma
- Recent advances in the radiotherapy of skin cancer
- Management of side effects of radiotherapy
- Radiotherapy – health system implications and discussion

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5.29 8.5 Radiotherapy for actinic keratosis and cSCC in situ

Contents

Unless stated otherwise, tumour stage is according to the American Joint Committee on Cancer (AJCC) cancer staging manual 8th edition[1] and Union for International Cancer Control (UICC) TNM classification of malignant tumours 8th edition.[2]

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5.29.1 Background

Actinic keratoses (AKs) can be symptomatic and may be a precursor to invasive disease. A minority (less than 5%) become invasive, although genital lesions such as squamous cell carcinoma in situ of the penis (erythroplasia of Queyrat, Bowen's disease) may have higher rates of invasion (10–30%).[3]

Actinic keratoses can involve large areas (skin field cancerisation).[4]

Several authors recommend early treatment rather than waiting for invasive disease to arise[5][6][7] and recommend that the entire field should be treated.[8]

Actinic keratoses are routinely cleared with cryotherapy, 5-fluorouracil cream or surgery. Surgery has been considered the gold standard, but its superiority has not been definitively demonstrated in a properly conducted randomised controlled trial.[9]

Adequate surgical margins are important to achieve control,[10] but this involves more tissue loss.

All these modalities can cause significant side effects and may not achieve long-term control.[11]

Occasionally, longstanding cutaneous squamous cell carcinoma (cSCC) in situ can grow to a large diameter and become extended skin field cancerisation, which can be difficult to treat with the usual modalities. Field cancerisation can also occur in cosmetically sensitive areas such as the nose, where current treatments may not be possible or effective. Radiotherapy (RT) can be used to treat widespread and resistant AK.

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5.29.2 Overview of evidence (non-systematic literature review)

Historically, the role of RT in the treatment of AK has been considered to be limited to salvage treatment for smaller areas after a number of failed previous therapies in a minority of patients.[12]

A 2012 Cochrane review of interventions for AK[11] and a 2013 Cochrane review Cochrane review of interventions for cSCC in situ[13] did not include any studies assessing RT.

Squamous cell carcinoma in situ of the scalp has traditionally been treated with brachytherapy moulds.[14] Newer, improved external beam RT (EBRT) techniques provide better treatment options,[15][4][16] especially for convex areas of extensive skin field cancerisation, which comprise most ultraviolet (UV)-induced AK fields.

Techniques for RT in the treatment of AK have not been well defined. A review found that doses from 25–70 Gy were effective.[17] Fractions sizes over 4 Gy were associated with long-term poor cosmetic outcome.[17]

RT has been used in AK in the salvage setting and therefore most evidence is anecdotal and consists of small series and case studies. All have shown prolonged duration of control in heavily pre-treated patients. One case study using modern techniques (VMAT) shows enduring control.[18]

An Australian review[3] reported that a dose fractionation schedule of 40–50 Gy in 10–20 fractions using superficial (110–150 kVp) energy photons will achieve a local control rate of 95–100%.

Radiotherapy has been reported to be effective as a definitive treatment for periungual SCC in situ.[19][20]

Large convex surfaces of extensive skin field cancerisation are common and include the scalp, forehead, cheeks, forearms, legs, chest, upper back, and shoulders. Volumetric modulated arc therapy (VMAT) can now be used to treat these skin surfaces with definitive VMAT photon RT (see: Recent advances in the radiotherapy of skin cancer).[4]

Key point(s)
For patients with persistent or recurrent actinic keratosis, consider referral to a radiation oncologist for assessment.

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- Radiotherapy for keratoacanthoma
- Recent advances in the radiotherapy of skin cancer
- Management of side effects of radiotherapy
- Radiotherapy – health system implications and discussion

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5.30 8.6 Radiotherapy for keratoacanthoma

Contents

5.30.1 Background

Keratoacanthomas generally regress spontaneously and resolve within 6–12 weeks. However, they are difficult to distinguish from cutaneous squamous cell carcinoma (cSCC), both clinically and histologically on incisional biopsy (see: Pathology of keratoacanthoma and Clinical features of squamous cell carcinoma and related keratinocyte tumours).

5.30.2 Overview of evidence (non-systematic literature review)

There have been very few clinical trials of RT in the treatment of keratoacanthoma.

Radiotherapy hastens the natural history of resolution of keratoacanthomas, with advantages to the patient of shorter lesion duration and less scarring. A low dose of 25 Gy is sufficient.[1]

However, since keratoacanthomas can be difficult to distinguish from aggressive primary cSCCs they should be managed as an invasive cSCC if the diagnosis is in doubt.[2]

Key point(s)
Radiotherapy may be considered in the treatment of keratoacanthoma to hasten the natural history of resolution.

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- Recent advances in the radiotherapy of skin cancer
- Management of side effects of radiotherapy
- Radiotherapy – health system implications and discussion

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5.31 8.7 Recent advances in the radiotherapy of skin cancer

Contents

5.31.1 Background

Radiotherapy (RT) modalities and approaches currently under investigation for use in the treatment of keratinocyte cancer (KC) include volumetric modulated arc therapy (VMAT) and the combination of RT with adjuvant immunotherapies.

5.31.1.1 Volumetric modulated arc therapy (background)

Intensity-modulated RT occurs when multi-leaf collimators (MLCs) within the linear accelerator (linac) gantry move in real time across the RT beam, so modulating the intensity of the beam during treatment. This is an advancement on three-dimensional conformal RT in which the beam comes in 'blocks'. Intensity-modulated RT allows the dose volume to curve around structures such as volumes of tumour to be treated or organs to be avoided. This technology has enabled increased conformality of dose, which allows for dose escalation to tumour and dose de-escalation to normal tissue volumes, thereby increasing the therapeutic ratio.[1]

Volumetric modulated arc therapy represents a further stage of evolution towards complete dose conformality. This technology can be conceptualised as the application of computed tomography to the linac. The gantry moves in a continual arc, capable of changing the rotational velocity. Other aspects can change; the dose rate of RT coming out of the machine, and the velocity of the MLCs, leading to great precision. This type of external-beam RT is challenging brachytherapy as the ultimate conformal therapy.[2]

Results from clinical trials evaluating VMAT in the treatment of KCs are expected to become available from around mid-2019.[3]

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5.31.2 Overview of evidence (non-systematic literature review)

5.31.2.1 Volumetric modulated arc therapy

The rotating gantry now allows difficult-to-treat volumes to be adequately irradiated without damage to nearby dose sensitive structures[4] and can be combined with systemic therapies without significant dose limiting toxicities.[5] It also allows large convex areas to be treated,[6][2][7][3] and these include areas of actinic change in which RT is effective.

Results from clinical trials evaluating VMAT in the treatment of KCs are expected to become available from around mid-2019.[3]

5.31.2.2 Tumour mutation burden

Tumour mutation burden (TMB) is associated with better survival in some skin cancers, such as Merkel cell carcinoma[8] and melanoma.[9] Immunotherapy works better in cancers with high mutational load.[9][10] Adding RT to immune therapy in the treatment of melanoma has been associated with a greater response.[11]

The TMB of KCs is the highest of any cancer type.[12] Accordingly, the combination of RT with immunotherapy in high-risk KC may increase the response. This hypothesis is likely to generate a high volume of radiobiological research.

No data are currently available from clinical trials evaluating the effect of TMB on outcomes of RT for KCs.

5.31.2.3 Adjuvant therapies

5.31.2.3.1 EGFR inhibitors

Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor used for the treatment of head and neck cancer in combination with RT.[13][5] Inactivation of EGFR is associated with increased radiosensitivity.[14] In the palliative setting, cetuximab as monotherapy or in combination with RT can achieve durable control of advanced cutaneous squamous cell carcinoma (cSCC).[15][16][17][18][19]

Cetuximab was associated with statistically non-significant benefit for overall survival and disease-free survival, compared with platinum-based chemotherapy, in a retrospective observational series in which patients received RT with either concomitant platinum-based chemotherapy or cetuximab as definitive (48%) or adjuvant (52%) treatment for locally advanced cSCC of head and neck.[10]

Acne-like rash is one of the more serious side effects of cetuximab therapy.[20]

Erlotinib, another EGFR inhibitor, increases local control in cSCC with RT,[21] as does gefitinib.[22]

5.31.2.3.2 Vismodegib

Vismodegib is approved by the Australian Therapeutic Goods Administration for the treatment of basal cell carcinoma (BCC). It targets the hedgehog signalling pathway (which is upregulated in 90% of BCCs) and acts as a cyclopamine-competitive antagonist of the smoothened, frizzled class receptor (SMO).

Vismodegib shrinks BCCs.[23] Case reports have documented that, when combined with RT and surgery, vismodegib treatment can make BCC resectable[24] or amenable to being encompassed in an RT field,[25] or even achieve durable and acceptable stable disease.[26][27][28]

Vismodegib is particularly helpful for the treatment of patients with naevoid BCC (Gorlin's syndrome), in which RT is generally avoided because it can predispose to more in-field BCCs.

Vismodegib is also effective in RT-induced BCC[29] and those who have progressed through RT.[30]

Side effects can be significant, and include dysgeusia (distortion of the sense of taste) and new cSCCs.[31]

5.31.2.3.3 Other radiotherapy modalities

Proton and neutron therapies may also improve therapeutic ratio in locally advanced skin cancer by achieving greater conformality.[32]

A recent matched pair analysis reported that the outcomes of brachytherapy were equivalent to those of Mohs micrographic surgery in the treatment of early-stage KC.[33]

Unsealed-source brachytherapy is being trialled. Rhenium-188 as a topical therapy requires only one or two applications.[34][35]

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- Radiotherapy for actinic keratosis and cutaneous squamous cell carcinoma in situ
- Radiotherapy for keratoacanthoma
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- Radiotherapy – health system implications and discussion

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5.32 8.8 Management of radiotherapy side effects

Contents

5.32.1 Definition

Side effects of radiotherapy (RT) are unwanted effects in normal tissue within and adjacent to the RT treatment volume.

Side effects of RT are classified as acute (usually occurring within 30 days of treatment) or late (occurring months to years after treatment).

5.32.2 Background

Side effects of RT depend on the site treated, the radiotherapy modality, the overall total dose, the daily dose per fraction and the rate at which it is delivered.

Skin reactions to RT are usually treated by specialist radiation oncology nurses.[1][2]

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5.32.3 Overview of evidence (non-systematic literature review)

5.32.3.1 Acute radiation effects

Acute side effects arise 2–3 weeks after starting RT and last some weeks before completely resolving. The radiobiology of acute side effects is well understood.[2]

The most common side effect is skin inflammation. This increases as more radiation dose is given over days of the prescribed treatment course. The inflammation is first seen as erythema (skin redness), then dry desquamation (skin peeling) and finally, moist desquamation (patchy or confluent superficial ulceration). Temporary epilation[3] occurs at low doses around 6 Gy, while permanent alopecia occurs at 16 Gy.[4]

Treatment close to the eye may cause conjunctivitis, while treatment over the nose may cause increased nasal vestibule crusting and mucosal bleeding; these are treated as symptoms arise with topical therapies. Systemic pain relief is rarely needed.

Acute radiation reactions are transient and generally resolve within 6 weeks. A meta-analysis[5] and a systematic review[6] concluded that no treatment could be recommended to reduce acute effects. Both studies also found that the use of deodorants did not increase acute effects.

A randomised controlled trial (RCT) comparing a new non-woven dressing with silicon (*Mepitel film*) with standard care in the treatment of radiation dermatitis in patients with head-and-neck cancer has been registered.[7]

5.32.3.2 Late radiation effects

Late side effects occur months to years after treatment, 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).

The visible features of late radiation skin damage can change with time if RT is given in large fractions. An initial highly favourable cosmetic result can potentially deteriorate over subsequent years.

The late sequelae of radiotherapy can be minimised by reducing the daily dose per fraction (i.e. by delivering smaller daily doses over a greater number of treatments). The trade-off is that this increases the overall treatment time. When advanced basal cell carcinoma and squamous cell carcinoma invade cartilage (classically the pinna) or bone (e.g. mandible) there is a higher risk of chondroradionecrosis or osteoradionecrosis.[8]

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 the site due to the resulting late effects that may occur over time.

5.32.4 Practice Point

Practice point
PP 8.8.1. When treating a patient who has undergone previous radiotherapy, the clinician (e.g. general practitioner or skin cancer specialist) should consult the radiation oncologist on the patient's history to ascertain the dose and location of prior radiation.

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5.33 8.9 Health system implications and discussion

Contents

5.33.1 Health system implications

5.33.1.1 Clinical practice

The current recommendations do not change the way in which radiotherapy (RT) services are organised.

5.33.1.2 Resourcing

Modern RT techniques, particularly volumetric modulated arc therapy (VMAT), require significant resources for provisioning, commissioning and training.

For patients with KCs at sites where preservation of function, cosmesis, or both are high priority, fully fractionated RT requires multiple visits to a radiation facility.

5.33.1.3 Barriers to implementation

Lack of adequate training, provision and commissioning of modern RT techniques is a potential barrier to the implementation of these recommendations, particularly in non-metropolitan and remote regions.

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5.33.2 Discussion

5.33.2.1 Unresolved issues

The role of RT among, and in combination with, other treatment modalities for keratinocyte cancers (KCs) is not well defined. Well-designed Australian randomised clinical trials (RTCs) are needed.

The role of RT in the management of incompletely excised KC is even more contentious and ill-defined that that of surgical re-excision.

5.33.2.2 Studies currently underway

The use VMAT in the treatment of extended skin field cancerisation (ESFC) is currently being evaluated in a RCT comparing it with current therapy. Other RCTs in patients with ESFC are in progress.[1]

A randomised controlled trial (RCT) comparing a new non-woven silicon dressing (*Mepitel Film*) with standard care in the treatment of radiation dermatitis in patients with head and neck cancer has been registered.[2]

5.33.2.3 Future research priorities

There is an urgent need for high-quality RCTs in the treatment of KCs in the Australian setting, as we have a unique skin cancer population.

Prospective studies are needed to guide the care of patients with basal cell carcinomas as surgery and radiotherapy techniques improve.

More investigation is needed on the extent of therapy and the appropriate use of RT for the management of cutaneous squamous cell carcinoma with regional spread to the parotid.

Despite the frequency of RT side effects, there is still much research that needs to be done to inform their prevention and management.[3][4]

Basic laboratory work on the radiobiology of skin cancers would be a comparative advantage for Australia and may have implications for the radiation treatment of other cancers.

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5.34 9. Cryotherapy and electrodessication and curettage – Introduction

Contents

5.34.1 Introduction

The 'destructive therapies', cryotherapy (cryosurgery, cryoablation) and electrodessication and curettage (EDC), are commonly used in the day-to-day treatment of skin cancers and premalignant skin lesions.

Although these modalities have been widely used for decades to treat keratinocyte cancers (KCs) and related premalignant conditions, few randomised clinical trials have evaluated their efficacy. The evidence for efficacy is primarily based on non-controlled prospective or retrospective series.

5.34.1.1 Advantages and disadvantages of cryotherapy and electrodessication curettage

Cryotherapy and EDC are simple, inexpensive and quick procedures, compared with surgical excision, topical agents, photodynamic therapy or radiotherapy, and are easily carried out in a doctor's office.

Cryotherapy and EDC are useful treatment modalities when treating patients with large numbers of lesions and where other therapies may be impractical. They also provide an alternative when surgery may not be suitable (e.g. in patients with other medical conditions such as coagulopathies or those with pacemakers, or those with KCs at body sites where scar contractures may be a problem).

In addition to the limited availability of evidence to guide their use, the main disadvantage of destructive therapies is that their cosmetic results are unpredictable. Effects may include hyper- and hypo-pigmentation, and hypertrophic or atrophic scarring. Wounds at some sites, particularly lower limbs, may be slow to heal,[1] and patients may experience pain, during and after treatment.

The outcomes of cryotherapy and EDC are operator-dependent. Better outcomes have been reported for those who perform these procedures more often.[2][3]

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5.34.2 Cryotherapy

5.34.2.1 Definition and mechanism of effect (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 actinic (solar) keratoses (AKs).[4][5] In addition, cryotherapy has been employed for more than 50 years for the treatment of selected skin cancers.[1][6][7][8][9][10][11][3][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31]

The most common method of applying cryogenic agents is with the use of cryospray devices. These are considered to be more reliable than cotton-tipped applicators and the results more reproducible.

Cryotherapy causes tissue destruction through multiple mechanisms. Proposed mechanisms include 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.[32]

The aim of therapy is to produce a selective volume of tissue necrosis equivalent to that removed by simple excision.

5.34.2.2 Indications

In addition to its widespread use in the treatment of actinic keratoses, in general cryotherapy is most suited for low-risk primary tumours with well-defined margins on the trunk or limbs (Table 8), namely Bowen's disease (cutaneous squamous cell carcinoma in situ, also known as intra-epidermal squamous cell carcinoma),[10][12][13][14] primary superficial or small papular basal cell carcinomas (BCCs),[11][18][22][26] keratoacanthomas,[10][17] and small primary well-differentiated cutaneous squamous cell carcinomas (cSCCs).[8][10][17][18][22]

Cryotherapy may be combined with initial curettage to debulk the tumour and to provide a specimen for histological analysis.[19][24][27][33][34][35][36][37]

Cryotherapy for low-risk primary KCs (AK, Bowen's disease, BCC) may offer special advantages for elderly high-risk surgical patients, especially those with a pacemaker or coagulopathy,[34][38][39] for those who refuse surgery, and for sites where scar contracture is best avoided, such as digits.[40]

Occasionally, in geographical regions where access to surgical options is limited by cost and a lack of services, cryotherapy may be the preferred treatment option.[24]

Alternative forms of treatment, mainly surgical excision, are indicated for large nodular, sclerosing (morphoeic), or ill-defined BCCs,[10][24][26][29] moderately to poorly differentiated cSCCs,[8][18][19] recurrent/residual tumours, and certain high-risk facial sites.[5][8][10][19][28][29][30] Nevertheless, many studies attest to the efficacy and acceptable cosmetic results achieved by cryosurgery in specialist clinics, even for difficult cancers.[5][9][19][22][23][24][25][27][29][30][31][41]

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.[10][38][41]

Rarely, cryosurgery may be used for palliation of incurable cancers to lessen tumour bulk or pain and reduce malodorous discharge.[42]

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5.34.2.3 Relative contraindications

Cryotherapy at tumoricidal depth generally leaves hypopigmented atrophic scars, and is therefore not the treatment of choice when the cosmetic outcome is important. For the same reason, cryotherapy is relatively contraindicated in most dark-skinned individuals, in whom hypopigmentation can be obvious and disfiguring.

Table 8. Relative indications and contraindications for cryotherapy and electrodessication and curettage in keratinocyte cancers

	Relative indications	Relative contraindications
	Actinic keratoses (any site if discrete and non-suspicious)	

Tumour type	Bowen's disease (especially on trunk or limbs) Keratoacanthomas (if small and at low-risk sites) BCCs of low-risk type (especially on the trunk and limbs) cSCCs of low-risk type (especially on the trunk and limbs)	High-risk BCC (e.g. ill-defined or sclerosing) High-risk cSCC (e.g. poorly differentiated, thick tumours)
Tumour site	Sites with increased risk of keloid scars with other modalities (e.g. upper arms and upper trunk)	Site where cosmetic outcome is a priority (e.g. face and neck) Sites where difficult to ascertain depth of tumour penetration (e.g. face or neck) Sites where deep recurrence poses greater potential risks (e.g. face or neck)
Tumour stage	Palliation for inoperable tumours	Recurrent tumours where surgical excision with histological confirmation of clear margins is essential
Patient-related factors	Unfit for surgery due to comorbidity or age	Younger patients in whom cosmetic outcome is a priority
Health system-related factors	Geographic region with poor access to surgical facilities	

BCC: basal cell carcinoma; cSCC: cutaneous squamous cell carcinoma

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5.34.3 Electrodessication and curettage

5.34.3.1 Definition and mechanism of effect

Electrodessication and curettage is a specialised technique used in the management of BCC, cSCC, KA and Bowen's disease.

Electrodessication and curettage technique varies slightly between operators, but essentially involves one to three cycles of curettage, each followed by the application of electrodessication or diathermy (or CO2 laser ablation) to the base.

To achieve the cure rates described in published literature, both careful lesion selection and critical attention to technique are required.[2][43] Specialised training is considered to be a necessary prerequisite for the use of EDC.

Skin cancers appropriate for EDC have a stroma that is relatively gelatinous, compared with the surrounding normal dermis. In these lesions, the curette easily enucleates the gelatinous tissue, but makes no further progress when it reaches the surrounding healthy dermis. Thus, the operator can differentiate between normal and cancerous tissue.

5.34.3.2 Contraindications

Electrodessication and curettage is not appropriate for lesions that penetrate through the dermis, cicatricial lesions, or thin skin. If the lesion penetrates through into subcutaneous fat, the technique loses its selectivity because fat does not resist the curette in the same way as healthy dermis.

This technique is not effective in the treatment of cicatricial lesions such as sclerosing BCC, which do not have a gelatinous stroma.

On very thin skin, such as eyelids, lip or genitalia, tearing of tissue would allow the curette to break through to the subcutaneous layer.

5.34.3.3 Alternative curettage techniques

Some operators now use carbon dioxide laser in place of electrodessication.

For BCCs, other alternatives to electrodessication or diathermy are cryotherapy in combination with curettage and imiquimod 5% cream followed by curettage. Several single-centre, single arm, non-randomised, non-controlled studies have reported favourable results with these approaches in the treatment of BCC.[35][36][37][44][45]

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Topics covered in this section include:

- Cryotherapy and EDC for basal cell carcinoma
- Cryotherapy and EDC for cutaneous squamous cell carcinoma
- Cryotherapy and EDC – Health system implications and discussion

5.34.4 References

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5.35 9.1 Cryotherapy and EDC for BCC

Contents

5.35.1 Background

Certain basal cell carcinomas (BCCs) may be successfully treated by cryosurgery.

Electrodessication and curettage (EDC) is anecdotally reported to be 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 its use on the face to situations where the cosmetic result is not a high priority. It has the advantages of being rapid to perform, tissue conserving, and not being contraindicated in patients taking anticoagulant medication.

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5.35.2 Overview of evidence (non-systematic literature review)

5.35.2.1 Cryotherapy for basal cell carcinoma

Small (<2cm) superficial BCCs are ideally treated with cryotherapy if appropriate selection criteria are applied.

Patients with pale skin types are less likely to have pigmentation disturbances after treatment with cryotherapy than those with pigmented skin.

5.35.2.1.1 Evidence sources (cryotherapy)

No randomised controlled studies have compared cryotherapy with surgical excision or other treatment modalities in the treatment of BCC.

Many large series by specialist clinics have demonstrated cure rates with cryotherapy equivalent to those achieved with other treatment modalities.[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21]

5.35.2.1.2 Tumour selection (cryotherapy)

Investigators emphasise the importance of careful tumour selection to achieve acceptable results.[5][15][18][22] Histological confirmation of the BCC and analysis for high-risk features is strongly recommended.[5][23][24][25]

Cryosurgery is most effective for primary well-defined lesions of non-aggressive subtypes at sites other than the head and neck.[6][7][9][10][15] Patients in whom cryotherapy can achieve equivalent outcomes to surgical excision include those with appropriately selected small (<2cm) superficial BCC and less pigmented skin types where there is a low risk of post-treatment pigmentation disturbances.

In general, cryotherapy is contraindicated for sclerosing or ill-defined BCCs[5][8][9][13][18][19][26] and relatively contraindicated for high-risk facial sites such as lips, alar creases, inner canthi and periauricular regions.[15][24][27]

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5.35.2.1.3 Technique (cryotherapy)

Repeated freeze–thaw cycles with margins of 3–5mm are recommended.[5][15][24][28][29][30]

Thermocouple needles may be used to monitor the temperature at the base of lesions, and may be useful for thicker lesions. However, several clinical parameters correlate well with adequate-depth freeze and are more routinely employed.[24][25][27][28][29][31][32][33]

5.35.2.1.4 Cure rates (cryotherapy)

Cure rates for BCC by cryosurgery are technique-dependent. Cure rates consistently exceed 95% in specialty clinics where optimal selection and treatment protocols are used.[1][3][4][5][6][7][9][10][12][13][15][16][18][26] Suboptimal cryotherapy technique results in unacceptably low clearance rates.[2] One extensive review of multiple series reported a 5-year recurrence rate for cryosurgery of 7.5%, which is comparable to that of other standard treatment modalities.[1]

Most large series utilise liquid nitrogen in an open-spray technique with repeated freeze-thaw cycles.[3][5][7][8][10][12][13][15][16][17][18][20][26] However, superficial BCCs have been successfully treated with single freeze-thaw cycle cryotherapy, achieving cure rates of 96%.[6][9] Thermocouple needle monitoring of the temperature produced at the base of tumours (–40°C to –60°C) may be employed.[3][7][9][10][19][20][26]

5.35.2.1.5 Tumour features influencing outcome (cryotherapy)

Certain microscopic features are associated with a greater depth of invasion and a higher risk of recurrence (see: Pathology).[34] Clinical features are fundamental in choosing those BCCs suitable for cryosurgery. Primary BCCs constitute the great majority of tumours treated in reported series.[1][6][7][8][9][13][15][26] In general, such tumours are well-defined and non-sclerosing (morphoeic) in subtype. Most series exclude ill-defined or sclerosing BCCs in their selection criteria due to unacceptably high recurrence rates.[5][8][9][13][17][18][20][21][26]

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.[6][14][16][17][20][21] Recurrent BCCs respond less well to cryosurgery, with lower cure rates.[3][6] Mohs micrographic surgery is the preferred treatment for such lesions (see: Mohs micrographic surgery).[1][35]

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%.[7][10][15]

Less optimal results are achieved for sites on the head and neck,[2][3][4][6][14][17][19][20] although acceptable cure rates have been reported for selective cancers in specialist clinics with significant cryotherapy experience.[7][8][12][13][15][18][21][26]

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5.35.2.2 Role of curettage

Curettage is often combined with cryosurgery and may help improve the cure rate.[8][13][16][29][30][36][37][38][39]

A single-centre, randomised study that compared curettage followed by cryotherapy, with surgical excision, in the treatment of BCC reported no statistically significant difference in 5-year recurrence rates between groups.[37]

Curettage provides a sample for histology, facilitates cryotherapy of larger tumours by reducing the tissue volume to be ablated,[16] and may offer some advantages at sites such as nose and ears to define the full extent of tumour growth prior to cryosurgery.[8][9][11][12][13]

5.35.2.2.1 Follow-up (curettage)

Routine follow-up is essential for all patients treated by cryosurgery.

Most recurrences will become evident within 5 years[7][16] and many within 2 years.[5][18] However, some BCCs have recurred as late as 10–12 years after treatment.[1][24]

5.35.2.2.2 Training and supervision (curettage)

Cryosurgery should be performed only by operators with appropriate supervised training in the procedures.
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5.35.2.3 Electrodessication and curettage for basal cell carcinoma

Small (<2cm) nodular and superficial BCCs are suited to treatment with EDC.

Following EDC, healing with acceptable scarring is more likely for BCC in concave areas, compared with convex areas, and for older (>70 years) patients than younger patients.

5.35.2.3.1 Evidence sources (EDC)

No randomised controlled studies have compared EDC with surgical excision or other treatment modalities in the treatment of BCC.

Observational studies such as case series have reported outcomes of EDC in the treatment of BCC.[40][41]

5.35.2.3.2 Cure rates (EDC)

Cryotherapy achieves high cure rates for primary basal cell carcinoma in sites other than face and ears if tumour selection and treatment protocols are optimal. Cure rates of approximately 95% or higher have been reported for tumours smaller than 1cm in some sites (Table 9).

5.35.2.3.3 Tumour selection (EDC)

Lesion selection by site and size is critical (Table 9).

Electrodessication and curettage is used for all sizes of lesion on low-risk areas (neck, trunk and limbs).[42] Higher recurrence rates have been reported with previously treated lesions.[42][40][41]

Sclerosing (morphoeic) BCCs are not treated with EDC, 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; sclerosing and other infiltrating types of BCC characterised histologically by small cell clumps show higher recurrence rates.[41]
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5.35.2.3.4 Scarring (EDC)

Basal cell carcinomas in concave areas heal with reduced scarring post EDC compared with those in convex areas.

Older (>70 years) patients often have better scar outcomes post EDC, compared with younger patients.

Table 9 Control rates for basal cell carcinomas treated by serial curettage by diameter[42][40][41]

Lesion: size/location	Cure rate at 5 years
<1cm all sites	98.77%
<1cm nose	93.55%
>2cm all sites	84%
>2cm ears	67%
All sizes excluding head	> 96%
<1cm cheek, forehead and temple	94.7%
>1cm as above [5][43]	77.3%
<0.5cm nasal, paranasal, periorbital, lips, chin, jawline and ears[5][43]	94.7%
>0.5cm as above	77.3%

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5.35.2.3.5 Contraindications (EDC)

Electrodessication and curettage is not appropriate for:

- lesions in high-risk areas (nasal, paranasal, lips, eyelids, chin, jawline and ears), or at least not for lesions larger than 5mm at these sites[42]
- lesions larger than 10mm on middle-risk sites (face, forehead, temples and scalp)[42]
- clinically sclerosing lesions[41]
- recurrent lesions.[42][40]

5.35.2.3.6 Training and supervision (EDC)

Electrodessication and curettage should be performed only by operators with appropriate supervised training in the procedures.[42]

5.35.2.3.7 Follow-up (EDC)

Long-term follow-up is essential after treatment of BCC with EDC, as late recurrences may occur.

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5.35.3 Practice Point

Practice point

PP 9.1.1. Long-term follow-up is essential after treatment of basal cell carcinoma with cryotherapy, as late recurrences may occur.

Key point(s)

- For patients with primary basal cell carcinomas in sites other than face and ears, with optimal tumour selection and treatment protocols, cryotherapy may be considered as a treatment option.
- Cryotherapy is not recommended for basal cell carcinomas at high-risk facial sites, where it achieves lower cure rates.
- Cryotherapy is not recommended for the treatment of basal cell carcinomas larger than 2cm in diameter.
- Cryotherapy is contraindicated for ill-defined or sclerosing (morphoeic or infiltrative) basal cell carcinomas at any site.

5.35.3.1 Notes on the recommendations

Follow-up of patients after treatment is individually tailored according to patient factors, tumour factors, anatomic site and the perceived adequacy of treatment.
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- Cryotherapy and EDC – Introduction
- Cryotherapy and EDC for cutaneous squamous cell carcinoma
- Cryotherapy and EDC – Health system implications and discussion

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5.36 9.2 Cryotherapy and EDC for cSCC

Contents

5.36.1 Background

Cutaneous squamous cell carcinomas (cSCCs) are very common in Australia and are the second most common skin cancer. Small superficial and well-differentiated cSCCs in low risk sites can be adequately treated with cryotherapy or electrodessication and curettage (EDC).

Relative **indications** of cryotherapy and EDC for cSCC and related lesions include:

- Bowen's disease, especially on trunk or limbs
- cSCCs of low-risk type, especially on the trunk and limbs
- the treatment of lesions in elderly patients, especially those with medical disorders less tolerant of surgical procedures (e.g. those with pacemakers or coagulopathies)
- in geographic areas with poor access to surgical facilities
- palliation of inoperable tumours.

Cryotherapy may be appropriate for lesions at body sites with increased risk of keloid scars from other treatment modalities (e.g. curettage or surgical excision on the upper arms and upper trunk).

Relative **contraindications** of cryotherapy and EDC for cSCC and related lesions include:

- cosmetically sensitive sites, especially face and neck in younger patients
- high-risk body sites, especially on face and neck (i.e. sites where it is difficult to ascertain depth of tumour penetration or where deep recurrence poses greater potential risks)
- high-risk tumour categories (i.e. ill-defined or sclerosing BCC and moderately to poorly differentiated cSCC)
- recurrent cancers for which surgical excision with histological confirmation of clear margins is essential.

With the increasing number of organ transplant patients developing very large numbers of cSCCs, the use of EDC in selected tumours can be of value where surgical excision may be impractical.
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5.36.2 Overview of evidence (non-systematic literature review)

5.36.2.1 Cryotherapy for cutaneous squamous cell carcinoma and related tumours

Cryotherapy produces cure rates equivalent to other standard treatment modalities for low-risk cSCCs on the trunk and limbs.

Small (<1cm) well-differentiated cSCC in low-risk areas can often be adequately treated with cryotherapy.

Bowen's disease (cSCC in situ) can be often adequately treated with cryotherapy.

No randomised controlled studies have compared cryotherapy with surgery or other treatment approaches in the treatment of cSCC. Observational studies such as case series have reported outcomes of EDC in the treatment of cSCC.[1][2][references]]

5.36.2.1.1 Cryotherapy for cutaneous squamous cell carcinoma

Low-risk cSCCs can be treated by cryosurgery. It may be indicated for small primary well-defined and non-ulcerated tumours on the trunk and limbs, for which acceptable cure rates have been reported.[3][4][5][6][7][8] In general, less-well differentiated cSCCs, recurrent cSCCs and those on the head and neck are better treated by surgical excision or radiotherapy.[3][6][9][10][11]

Histological confirmation and analysis for high-risk features is essential prior to cryosurgery.[12]

Relative to their prevalence, fewer cSCCs are treated by cryotherapy than BCCs, implying that most published studies employ strict selection guidelines.[3][4][6][7]

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

- primary tumour[6][13]
- small size[3][6]
- well defined[3][6]
- clinically and histologically well differentiated[3][6][9][13]
- on trunk or limbs.[4][13][14]

Repeated freeze–thaw cycles with a minimum of 5mm margins are recommended.[6][15][16] Curettage may be used initially to debulk the lesion, followed by cryosurgery.[9][16]

Cure rates of greater than 95% are consistently achieved if selection criteria are strict and optimal treatment protocols are employed.[3][4][5][6][7][9][13][14][17][18][19][20]

Even with strict selection criteria in experienced clinics, there are some recurrences following cryosurgery for head and neck lesions,[4][6][20][21] in contrast to the very rare recurrences for those on the trunk and limbs.[4][14] Cryosurgical management of SCC on the head and neck should generally be limited to specialist clinics with the full range of treatment options available.

Residual or recurrent SCCs are better removed surgically, or treated with radiotherapy, as cryosurgery leads to unacceptably low cure rates.[5]

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5.36.2.1.2 Cryotherapy for actinic keratoses

Actinic (solar) keratoses (AKs) are common skin lesions displaying different clinical and histological features. They represent both markers of actinic damage and potential precursors of cSCCs.[22]

A continuum of clinical and histological dysplasia occurs from AK to Bowen's disease (cSCC in situ) and invasive cSCC. However, not all AKs progress to SCC and some can regress spontaneously[23] or following routine use of sunscreen application.[24][25] No clinical feature of AKs predicts which will become malignant. However, increased erythema, thickening, alteration or changes in size may indicate early progression to cSCC.[26] The risk of cSCC may be greater for immunosuppressed patients.[27]

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

Actinic keratoses may be treated for cosmetic reasons, due to irritation, or because of the potential for developing cSCC.

Topical 5 Fluorouracil cream may be used initially to highlight subclinical keratoses prior to cryotherapy treatment.[28]

Successful clearance of AKs using cryotherapy with good cosmetic results requires accurate diagnosis and adequately timed treatment protocols.[10][29][3][30] A single freeze–thaw cycle is usually recommended. Cure rates ranging from 69%[31][32] to greater than 98.8% have been reported.[33][21] Response rates tend to parallel the duration of the freeze time.[34]

Hyperkeratotic or suspicious AKs may be better treated by curettage alone, or curettage followed by cryotherapy, EDC or ablative laser to the base.[26] These techniques provide a specimen for histological confirmation.

A range of topical therapies can be used to reduce signs of photodamage and to treat established and preclinical actinic keratoses. These include chemical peeling, dermabrasion, laser resurfacing, alpha-hydroxy acids and retinoid formulations, diclofenac 3% in hyaluronic acid 2.5% gel,[35] imiquimod 5% cream,[36] ingenol mebutate, and photodynamic therapy.[37]

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5.36.2.1.3 Cryotherapy for Bowen's disease (cSCC in situ)

Bowen's disease (cSCC in situ) is not invasive and does not need to be treated in the same manner as cSCC. Bowen's disease has been treated successfully with cryosurgery, with many studies reporting greater than 95% cure rates and reasonable follow-up periods.[3][4][17][20][2][38] Suboptimal treatment protocols produce less satisfactory results.[28][39][40][41] A pre-treatment biopsy is usually recommended.[4][2][42][43]

A single freeze-thaw treatment cycle of 30 seconds with a 3mm margin is advised.[4][2] Slow healing was reported for lesions greater than 20mm in diameter and for those on the lower legs.[44][45][46] Cure rates greater than 99% are achieved with optimal cryotherapy[4][2] consisting of 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.[3][5][2][42][44][43][47]

Anatomical site does not appear to affect response to cryotherapy.[44]

The size of the lesion does not affect response and large lesions can be managed with overlapping treatment fields.[38][44]
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5.36.2.1.4 Cryotherapy for keratoacanthoma

Keratoacanthomas can be treated with cryotherapy, achieving cure rates equivalent to EDC, simple excision or radiotherapy.[4][6][7][21][48][49][14][8]

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.

Few studies have investigated outcomes of cryotherapy for keratoacanthomas.[4][14][21] 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.[4] Double freeze–thaw cycles of 30 seconds or more with 3–5 mm treatment margins were used.[4][14][21] Site differences in response to cryotherapy have not been noted in the small series reported.[4] Size appears to have been a factor in the choice of cryotherapy, with almost all treated lesions less than 20mms in diameter. One large keratoacanthoma responded to cryotherapy after initial shave excision.[14](See: Clinical features of cutaneous squamous cell carcinoma).

5.36.2.2 Electrodessication and curettage for cSCC

There is little evidence to determine the role of EDC in the management of cSCC and there is no international clinical consensus on its use.

No randomised controlled studies have compared EDC with surgery or other treatment approaches in the treatment of cSCC and related lesions. Observational studies such as case series have reported outcomes of EDC in the treatment of cSCC.[1][2]\

Electrodessication and curettage should only be performed by operators with appropriate supervised training in the procedures.[1]

5.36.2.2.1 EDC for cutaneous squamous cell carcinoma

One study demonstrated a cure rate of 96% in a group of 48 patients followed for 5 years and 98% in a group of 101 patients observed over 4 years.[50] 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.[50]
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5.36.2.2.2 EDC for Bowen's disease (cSCC in situ)

Electrodessication and curettage 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 does allow the curette to break through to the deeper tissues. This limitation precludes the use of the technique on eyelids, the genital area or lip.

As many cases occur on the legs of elderly patients, 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%.[42][51][52]

5.36.2.2.3 EDC for keratoacanthoma

Keratoacanthoma may be considered a relatively benign tumour and is commonly treated by dermatologists using the EDC technique.

Good cosmetic results have been reported anecdotally.[52][53] Published studies show acceptable cure rates but are compromised by follow-up times of less than 5 years.[52][53]

Electrodessication and curettage of keratoacanthoma involving the nail bed is controversial.[54][55]

Electrodessication and 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.

Electrodessication and curettage is not appropriate for:

- lesions in high-risk areas (nasal, paranasal, lips, eyelids, chin, jawline and ears), or at least not for lesions larger than 5mm at these sites[1]
- lesions larger than 10mm on moderate-risk sites (face, forehead, temples and scalp)[1]
- lesion of any size on low-risk areas (neck, trunk and limbs).[1]
- clinically sclerosing lesions.[56]
- recurrent lesions.[1][57]

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5.36.3 Practice Point

Practice point

PP 9.2.1. Cryotherapy is contraindicated for recurrent cutaneous squamous cell carcinoma.

Key point(s)

- Cryotherapy may be considered as a treatment option for patients with actinic keratosis.
- Cryotherapy may be considered as treatment option for patients with Bowen's disease. Patients should be informed about the potential delayed healing that may occur on lower limbs.
- Cryotherapy may be a reasonable treatment option for smaller keratoacanthomas. If the diagnosis is in doubt then treatment should be as for cutaneous squamous cell carcinoma.
- For patients with low-risk cutaneous squamous cell carcinomas on the trunk and limbs, cryotherapy may be considered as a treatment option.

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- Cryotherapy and EDC – Introduction
- Cryotherapy and EDC for basal cell carcinoma
- Cryotherapy and EDC – Health system implications and discussion

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5.37 9.3 Health system implications and discussion

Contents

5.37.1 Health system implications

5.37.1.1 Clinical practice

Implementation of the recommendations will not change the way that care is currently organised.

5.37.1.2 Resourcing

Equipment to undertake cryotherapy is usually readily available in most doctors' surgeries. Most general practices with have the equipment to undertake electrodessication and curettage (EDC).

5.37.1.3 Barriers to implementation

Adequate training is required to fully utilise the techniques of cryotherapy and EDC in the treatment of keratinocyte cancers.

5.37.2 Discussion

5.37.2.1 Unresolved issues

There are no unresolved issues about this topic.

5.37.2.2 Studies currently underway

There are no studies currently underway which, when published, may provide more information on this topic.

5.37.2.3 Future research priorities

There are no unresolved questions in regard to this topic nor suggestions of research priorities for the future.

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5.38 10. Topical treatments and photodynamic therapy – Introduction

Introduction

In addition to excisional surgery and the ‘destructive therapy’ approaches (cryotherapy and electrodessication and curettage), a number of treatment options are available for the management of superficial basal cell carcinoma (BCC), Bowen’s disease (cutaneous squamous cell carcinoma in situ) and actinic (solar) keratosis (AK). These treatments include topical agents and photodynamic therapy.

The topical therapies covered in this guideline are imiquimod 5% cream, diclofenac 3% gel, 5-fluorouracil 5% cream and ingenol mebutate gel. Their effective use requires expertise and experience. Most are best used as 'field treatment' for areas with multiple AKs and have less utility for the treatment of specific keratinocyte cancers. However, imiquimod 5% cream is approved by the Therapeutic Goods Administration for the treatment of superficial BCC.

Photodynamic therapy involves the use of light to activate a photosensitiser localised in diseased tissues, resulting in the formation of cytotoxic reactive oxygen species. Photodynamic therapy is used in the treatment of AK, Bowen's disease, and BCC.

Topics covered in this section include:

- Topical treatments (imiquimod, diclofenac, 5-fluorouracil, ingenol mebutate)
- Photodynamic therapy
- Topical treatments and photodynamic therapy – Health system implications and discussion

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5.39 10.1 Topical treatments

Contents

5.39.1 Background

Topical treatments for keratinocyte cancer (KC) used in Australia include:

- imiquimod 5% cream
- diclofenac 3% gel
- 5-fluorouracil 5% cream
- ingenol mebutate gel.

5.39.1.1 Imiquimod 5% cream

The mechanism of action of topical imiquimod 5% cream involves 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 nuclear factor kappa B subunit 1 (NFKB1), which induces the expression of various cytokines: interferon alpha 1 (IFNA1), tumour necrosis factor (TNF), interleukins (IL2, IL6, IL8 and IL12), chemokines and other inflammatory mediators. These factors promote apoptosis and also inhibit angiogenesis.

Imiquimod 5% cream is approved by the Australian Therapeutic Goods Administration (TGA) for the primary treatment of confirmed superficial basal cell carcinoma (BCC) where surgery is considered inappropriate, and for the treatment of actinic (solar) keratosis (AK) on the face and scalp.[1]

Imiquimod is available in sachets or a pump pack delivery system.

For the treatment of AK, application can be cyclical (3 nonconsecutive days per week in 4-week cycles until clearance is achieved), or continuous (3 nonconsecutive days per week for up to 16 weeks). For BCC, recommended application is 5 consecutive days per week for 6 weeks.[1]

Local reactions are common among patients treated for AK. These include severe erythema (24%), severe scabbing and crusting (20%), itching (14%) and burning (5%).[1] Skin infections have also been observed.[1] Among patients treated for BCC, common local reactions include severe erythema (31%), severe erosions (13%), and severe scabbing and crusting (19%).[1]

5.39.1.2 Diclofenac 3% gel

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.[2][3]

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).

Topical 3% diclofenac gel is approved by the Australian TGA for the treatment of AK.[4]

Twice-daily application for 90 days is recommended. The product is administered by the patient and is generally well tolerated. This field treatment can be combined with liquid nitrogen cryotherapy for more hypertrophic or resistant AK.

Local reactions are relatively common and include: irritation, inflammation, blistering, contact dermatitis, erythema, exfoliation, and skin ulcer.[4]

5.39.1.3 5-fluorouracil 5% cream

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

5-fluorouracil 5% cream is approved by the Australian TGA for the treatment of AK and Bowen’s disease.

Treatment of AK involves application (once or) twice daily for 2–4 weeks on the head and neck. Erythema, irritation, inflammation, pain, burning, vesiculation, crusting, dyspigmentation, photosensitivity, ulceration and other local adverse effects are common.

Bowen’s disease is treated with 5-fluorouracil 5% cream twice a day for between 4–8 weeks.

Local reactions are relatively common and include: local pain/pruritus, hyperpigmentation, burning, crusting, contact dermatitis, erosions, erythema, irritation, photosensitivity, ulceration, and infections including herpes simplex.[5]

5.39.1.4 Ingenol mebutate gel

The mechanism of action of ingenol mebutate is not fully understood.[6] Its effects are thought to be due to local cell death and a local inflammatory response characterised by production of proinflammatory cytokines, chemokines and infiltration of immunocompetent cells, which induce epidermal necrosis.[6]

Topical ingenol mebutate gel is approved by the Australian TGA for the treatment of AK.[6] Two formulations are available:

- 0.015% for AK on the face and scalp (applied daily for 3 consecutive days)
- 0.05% for AK on the trunk and extremities (applied daily for 2 consecutive days)

Each tube contains enough gel to cover an area of approximately 25cm^2.

Ingenol mebutate is not TGA-approved for the treatment of Bowen's disease, BCC or cutaneous squamous cell carcinoma (cSCC).

Local reactions are relatively common and include: application site pain, pruritus, irritation, infection, erythema, flaking, scaling, crusting, swelling, vesiculation, pustulation, erosion, ulceration, headache, and application site pigmentation change.[6]

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5.39.2 Systematic review evidence

What role does ingenol mebutate gel have in the treatment and management of basal cell carcinoma and/or cutaneous squamous cell carcinoma?

A systematic review was undertaken to evaluate the effectiveness of ingenol mebutate gel in the treatment of KCs.

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Two randomised clinical trials (RCTs) that met inclusion criteria reported outcomes in patients treated with BCC or cSCC in situ treated with ingenol mebutate.[7][8]

An Australian multicentre Phase IIa RCT[7] with a low risk of bias compared ingenol mebutate 0.0025%, 0.01% and 0.05% gel and matching vehicle gel, administered as two applications (on 2 consecutive days or 1 week apart) in 60 patients each with a single histologically confirmed BCC on the arm, shoulder, chest, face, neck, abdomen, back, leg or scalp considered suitable for surgical excision (maximum diameter of 4–15mm and maximum thickness of 4mm). Among those who received treatment on 2 consecutive days, 0.05% ingenol

mebutate gel was associated with histological clearance at 85 days post treatment in 5 of 8 participants (65%), compared with 0 of 6 participants in the control (vehicle gel) group. Adverse events included mild-to-moderate erythema extending beyond the treatment site (n=2), mild application-site pain (n=2), and mild-to-moderate headache (n=2).[7] Most local effects resolved completely within 1 week, and the remainder resolved within the study period.[7] Severe treatment-related events included vesicles (n=4), flaking/scaling/dryness (n=2), oedema (n=1), erosion/ulceration (n=1), and erythema and scabbing/crusting (n=1).

Another Australian RCT[8] with an unclear risk of bias compared ingenol mebutate 0.05% gel with no treatment (lesions randomised to full occlusion, partial occlusion or no occlusion) in 75 patients with histologically confirmed superficial BCC (4–15mm in diameter and <1mm thick) on the trunk or extremities. Complete clinical clearance rates and complete histological clearance rates were 70.4% and 74.1%, respectively, for full occlusion, 37.5% and 75.0% for semi-occlusion, and 54.2% and 75.0% for no occlusion (statistical analysis not reported).[8] A total of 15 treatment-related adverse events were reported, of which 11 were in the full occlusion group. All were resolved or resolving by the end of the trial period. Adverse effects included application-site pain, hypopigmentation and scarring.[8]

5.39.2.1 Evidence summary and recommendations

Evidence summary	Level	References
Ingenol mebutate is well tolerated in the treatment and management of BCC, with only mild to moderate adverse events reported.	II	[7], [8]
Response rates (histological and clinical clearance rates) to ingenol mebutate in the treatment of superficial BCC were highest after treatment with 0.05% gel (versus 0.0025% and 0.01%) and after treatment on two consecutive days (versus treatment one week apart). Complete clinical clearance rates after treatment of superficial BCC with 0.5% ingenol mebutate were similar with full occlusion, semi-occlusion and no occlusion, but the complete histological clearance rate was higher with full occlusion.	II	[7], [8]
There is a lack of evidence on recurrence rates following the treatment and management of BCC with ingenol mebutate gel.	II	[7], [8]

Key point(s)
All prescribers should discuss the relative harms and benefits of ingenol mebutate gel with patients offered this treatment option.

5.39.2.2 Notes on the evidence

At present there is inadequate evidence to inform patient selection for treatment of BCC and cSCC with ingenol mebutate gel as an alternative to established treatment options. Were more clinical trial data to become available supporting its use, its role is likely to be restricted to the treatment of BCC or cSCC in patients who are unable to undergo surgical excision or destructive therapies, and in whom other topical therapies are less suitable.

Although adverse effects of ingenol mebutate gel may not evolve until after the completion of a course of 2 or 3 consecutive days of treatment, prescribers should clearly advise patients to discontinue use if they experience severe adverse effects during treatment. Further use (completion of the interrupted course or a future course of treatment) should be discouraged unless adverse effects were only mild or moderately severe.

5.39.3 Overview of evidence (non-systematic literature review)

Note: no systematic reviews were undertaken for evidence on topical treatments other than ingenol mebutate (see: Systematic review evidence).

5.39.3.1 Imiquimod 5% cream

5.39.3.1.1 Actinic keratoses

The short-term efficacy of topical Imiquimod 5% cream in patients with AK has been assessed in five large, double-blind placebo-controlled RCTs.[9][10][11][12][13]

Complete clearance rates varied between 45% and 57%.[9][10][11][12][13] Clearance rates of more than 75% of lesions were achieved in up to 72% of patients.[13]

No data on recurrence and progression rates for follow-up beyond 1 year are available.

Imiquimod is applied once daily, three times per week, for up to 16 weeks, or alternatively applied up to three times per week for two 4-week cycles.

Care should be used if applications are used to areas greater than $25cm^2$.

The cycle may be repeated after a month (off therapy) if necessary to increase efficacy. Rest periods (i.e., missed applications) are advised if the inflammatory reaction becomes excessive.

5.39.3.1.2 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.[14] The cream was applied daily for 16 weeks and allowances were made for rest periods.

Complete clearance was observed in 73% of 15 patients who received imiquimod 5%, compared with 0% of those who received placebo. No recurrence was seen at 6-months follow-up. In clinical practice, most practitioners treat areas of Bowen's disease for 4–6 weeks with applications three to 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.

5.39.3.1.3 Superficial basal cell carcinoma

Phase III studies[15] demonstrate that the recommended imiquimod regimen for primary superficial BCC (application five times per week for 6 weeks) results in a histological clearance rate of 82%.

Skin biopsy to confirm the diagnosis is highly recommended. Histological confirmation of the diagnosis before treatment is a requirement for Pharmaceutical Benefits Scheme (PBS) reimbursement.

Imiquimod cream is applied to the tumour and a 5mm margin of surrounding normal skin. The area of application should not be increased even if inflammation extends beyond the initial area.

Efficacy assessments are made clinically at three months post therapy. Regular clinical follow up is recommended for 3 years post treatment.

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

5.39.3.2 Diclofenac 3% gel

A double-blind placebo-controlled RCT in 96 patients, with five or more AK each, reported that twice-daily application for 90 days (the standard recommended protocol) resulted in complete clearance of baseline AK in 50% of patients, compared with 20% of the placebo group ($p<0.001$).[16]

5.39.3.3 5-fluorouracil 5% cream

Twice daily application for 2–4 weeks on the head and neck results in significant inflammation that settles within 1–2 weeks of ceasing therapy. Published evidence for 5-fluorouracil efficacy is scant.[17] A recent study reported that the probability of tumour-free survival, 5 years after treatment, was 70.0% for 5-fluorouracil (95% CI = 62.9-76.0).[18]

5.39.3.3.1 Actinic keratoses

A RCT comparing topical 5-fluorouracil 5% cream (applied twice daily for 4 weeks), topical imiquimod and cryosurgery in the treatment of AK, reported sustained complete field clearance at 12-month follow-up in 33% of the 5-fluorouracil 5% group, compared with 73% of the imiquimod group ($p<0.01$).[19]

Another recent RCT comparing common field-directed treatments for AKs on the hand reported that the cumulative probability of remaining free from treatment failure 12 months after treatment was significantly higher among patients who received 5-fluorouracil (74.7%; 95% confidence interval [CI] 66.8–81.0) than among those who received imiquimod (53.9%; 95% CI 45.4 to 61.6), ingenol mebutate (28.9%; 95% CI 21.8–36.3) or methyl aminolevulinate-photodynamic therapy (MAL-PDT) (37.7%; 95% CI 30.0–45.3.[20]

5.39.3.3.2 Bowen's disease

Studies evaluating 5-fluorouracil cream twice a day for between 4–8 weeks in the treatment of Bowen's disease have demonstrated cure rates ranging between 87% and 92%.[21] A European multicentre RCT in 225 patients with histologically confirmed cSCC in situ (6–40mm) reported a 12-month sustained complete response of 69% and a good or excellent cosmetic response in 76% of patients following treatment with 5-fluorouracil 5% cream, (compared with 80% and 94%, respectively, in patients treated with MAL-PDT; difference statistically nonsignificant).[22][23]

5.39.3.4 Ingenol mebutate

In a pooled analysis of two multicentre RCTs investigating ingenol mebutate 0.015% in the treatment of AK on the face and scalp,[12] the rate of complete clearance of AK was higher with ingenol mebutate than with placebo (42.2% versus 3.7%, $p<0.001$).

In a pooled analysis of two multicentre RCTs investigating ingenol mebutate 0.05% in the treatment of AK on the trunk and extremities, the rate of complete clearance was also higher with ingenol mebutate than with placebo (34.1% versus 4.7%, $p<0.001$).[12] Adverse events were generally mild to moderate in intensity and resolved without sequelae.[12]

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5.39.4 Practice Point

Practice point
PP 10.1.1. Skin biopsy is highly recommended before treatment of superficial basal cell carcinoma with imiquimod 5% cream (and is required for PBS-reimbursed prescription).

Key point(s)
■ Imiquimod 5% cream, a topical cytokine- and interferon-inducer, can be considered for the treatment of actinic keratoses and primary basal cell carcinomas where surgery or other therapies are inappropriate or contraindicated. ■ Skin biopsy is not required when treating actinic keratoses with imiquimod 5% cream.

Key point(s)

- Imiquimod 5% cream is contraindicated for sclerosing, infiltrative and micronodular basal cell carcinoma subtypes.
- Long-term follow-up is essential after treatment of basal cell carcinoma with imiquimod 5% cream.
- The use of 5-fluorouracil 5% cream can be considered for the treatment of actinic keratoses and Bowen's disease.
- Supervision of 5-fluorouracil 5% cream therapy in first-time users is essential.
- Whilst they are effective as spot treatments, the principal role of topical therapies is field therapy for multiple actinic keratoses or for superficial keratinocyte carcinomas (Bowen's disease and superficial basal cell carcinoma).

Note: Follow-up of patients after treatment is individually tailored according to patient factors, tumour factors, anatomic site and the perceived adequacy of treatment.
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5.39.5 Appendices

	Evidence statement form	Systematic review report
PICO question OT1	OT1	OT1

5.39.6 References

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5.40 10.2 Photodynamic therapy

Contents

3 References

5.40.1 Background

Photodynamic therapy (PDT) involves the use of light to activate a photosensitiser that is localised in diseased tissues, resulting in the formation of cytotoxic reactive oxygen species. Light sources include high-intensity lamps, lasers and, more recently, daylight.

Topical PDT is a non-invasive treatment option for some patients with actinic keratoses (AKs), Bowen's disease, and superficial and thin basal cell carcinomas (BCCs).[1]

Each treatment session involves gentle debridement or removal of scales for AK, Bowen's disease and superficial BCC, or debulking of nodular BCC, typically without the requirement for local anaesthesia.

In conventional PDT, the photosensitising cream is then applied 1mm thick to the treatment field for AK 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 is applied for 7–9 minutes.

More recently 'daylight PDT' with the photosensitiser methyl aminolevulinate (MAL; *Lumexia*) was approved by the Australian Therapeutic Goods Administration (TGA) for the treatment of AK. It is used as per the current product information with daylight exposure beginning within 30 minutes of the application of the photosensitiser MAL and continuing for 2 hours.[2]

The alternative photosensitiser, 5-aminolevulinic acid (ALA), has also been investigated in PDT (ALA-PDT).

Good cosmetic results have been reported for PDT, with minimal scarring seen after most PDT treatments.[3]

For AK, the recommended regimen is a single session of PDT, with the effects assessed at 3 months.[4] Any residual lesions can, if required, then receive a second session of treatment.

For Bowen's disease and BCC, the recommended regimen is two sessions of treatment, 1 week apart, although in practice the interval between the two sessions may be up to a month.

Photodynamic therapy can be delivered in a single treatment session over large surface areas, and is therefore suitable for the treatment of patients with multiple AK.

Specialised equipment and training is required for PDT (except for daylight MAL-PDT). It is therefore primarily restricted to specialist use or use within centres specialising in skin cancer management.
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5.40.2 Overview of evidence (non-systematic literature review)

5.40.2.1 Actinic keratosis

There is now a large body of evidence to support the use of PDT for the treatment of AK, including four phase III randomised controlled trials (RCTs) evaluating MAL-PDT and two evaluating ALA-PDT.[3][5][6][4][7]

The complete response rate for AK at 3 months and 6 months after two treatments sessions is approximately 90%.[5][6][4][8]

Photodynamic therapy is generally well tolerated by patients.[4][7] 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.[3][5][6]

The introduction of daylight MAL-PDT has enabled longer, lower intensity light delivery. This advance has largely addressed the pain issue without compromising efficacy permitting the successful field treatment for large areas of AKs, provided that supervised preparation and application protocol is followed.[3][5][6][9][10][11]

In phase III studies investigating the use of MAL-PDT in AK, the cosmetic outcome was rated as excellent or good by over 90% of investigators and patients.[3][5][6]
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5.40.2.2 Bowen’s disease

The efficacy of PDT in Bowen’s disease has been shown to be at least equal to that of cryotherapy and 5-fluorouracil, with fewer complications and superior cosmetic outcomes.[12][13][14]

A 64-month recurrence rate of 17% has been reported in Bowen’s disease.[15]

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.[13]

5.40.2.3 Cutaneous squamous cell carcinoma

While some studies have demonstrated efficacy for the use of PDT in superficial cSCC, there have been relatively high recurrence rates.

Thus, PDT cannot be recommended for the treatment of cSCC.[16][17]

5.40.2.4 Basal cell carcinoma

Longer-term (5-year) follow-up data demonstrate efficacy and good cosmetic results for PDT in the treatment of superficial BCC or nodular BCC.[18][19]

5.40.2.5 Superficial basal cell carcinoma

Prospective studies,[20][21] including RCTs, have reported 3-month clearance rates ranging from 80% to 97% for MAL-PDT in the treatment of primary superficial BCC.[20][21]

An RCT comparing PDT with cryotherapy in the treatment of superficial BCC outcomes reported no difference in 5-year recurrence rates between the two treatments (20% with cryotherapy versus 22% for MAL-PDT p=0.86). The investigators noted that the cosmetic result was excellent with MAL-PDT (60% versus 16% with cryotherapy p=0.00078).[18] A recent meta-analysis concluded PDT is an effective treatment for low-risk BCC, with excellent cosmesis and safety.[22]

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5.40.2.6 Nodular cell basal cell carcinoma

With topical PDT for nodular BCC, delivery of sufficient photosensitiser and light to the full depth of the lesion is critical to achieve cure.[21] 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.[21] Re-treatments may well be necessary in these circumstances.[20][23][24][25][21]

An RCT comparing PDT with surgical excision in the treatment of nodular BCC reported 5-year clearance rates of 76% (95% confidence interval [CI] 59–87%) and 96% (95% CI 84–99%), respectively.[19] The investigators noted that PDT was associated with a more favourable cosmetic outcome than surgery.[19] A single-centre study reported that there were significantly higher estimated recurrence rates for nodular BCCs compared with superficial BCCs.[26]

Photodynamic therapy does not complicate future surgery if it is required.

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Key point(s)

- Specialised equipment and training are required with photodynamic therapy.
- Methyl aminolevulinate photodynamic therapy and 5-aminolevulinic acid photodynamic therapy can be considered for the treatment of actinic keratoses, Bowen’s disease and superficial basal cell carcinoma.
- Thin nodular basal cell carcinoma can be treated with photodynamic therapy.
- Photodynamic therapy is not recommended for invasive squamous cell carcinoma.

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- Topical treatments (imiquimod, diclofenac, 5-fluorouracil, ingenol mebutate)
- Topical treatments and photodynamic therapy – Health system implications and discussion

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5.41 10.3 Health system implications and discussion

Contents

5.41.1 Health system implications

5.41.1.1 Clinical practice

The updated recommendations do not represent any significant change from current clinical practice.

5.41.1.2 Resourcing

Experience and education of practitioners in the use of topical treatments is required. Specialised equipment and training are required for the use of photodynamic therapy (PDT). However, implementation of the updated recommendations is not likely to increase resource requirements for organisations or the Australian health system.

5.41.1.3 Barriers to implementation

No barriers to the implementation of these recommendations are envisaged.

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5.41.2 Discussion

5.41.2.1 Unresolved issues

Based on current evidence, it cannot be ascertained whether or not the treatment of actinic keratoses with spot therapy or field therapy reduces subsequent risk of developing cutaneous squamous cell carcinoma (cSCC).

There are insufficient long-term data from well-designed studies investigating the use of ingenol mebutate gel in the treatment of keratinocyte cancers to guide patient selection.

5.41.2.2 Studies currently underway

Studies are underway comparing various formulations of photosensitisers, penetration enhancers and light sources to improve the efficacy and tolerability of PDT.

Clinical trials are underway evaluating CLL442, a new topical treatment for cSCC in situ.[1]

5.41.2.3 Future research priorities

Evidence for the use of ingenol mebutate gel for basal cell carcinoma (BCC) and cSCC is limited to small early-phase clinical trials with low response rates. Since the development program was halted for the use of ingenol mebutate gel for the treatment of either BCC or cSCC, further research in this area would be warranted.

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5.42 11. Organ transplantation and conditions associated with immunosuppression – Introduction

Introduction

Susceptibility to keratinocyte cancers (KCs) is increased by conditions or drugs that dysregulate or suppress the immune system. Affected patients include people with human immunodeficiency virus and acquired immunodeficiency syndrome (HIV-AIDS), people with chronic lymphocytic leukaemia (CLL) and organ transplant recipients treated with immunosuppressant drugs.

The management of KCs can be difficult in patients who have been immunosuppressed for many years and are at especially high risk of KCs due to high tumour load. The care of these people is best provided in multidisciplinary specialist care settings, where a combination of specific strategies can be used to reduce the KC burden.

Topics covered in this section include:

- Epidemiology of keratinocyte cancers in immunosuppressed patients
- Management of keratinocyte cancer risk in organ transplant recipients
- Strategies to manage keratinocyte cancer in organ transplant recipients
- Organ transplantation and other conditions associated with immunosuppression – Health system implications and discussion

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5.43 11.1 Epidemiology – immunosuppressed patients

Contents

5.43.1 Background

Intact immunosurveillance is essential for defence against development of skin cancer. Hence, people with conditions affecting the immune system are at increased risk of keratinocyte cancer (KC), whether due to immune-related disease, immune-modulating treatments, or both.[1]

5.43.2 Overview of evidence (non-systematic literature review)

5.43.2.1 Keratinocyte cancer prevalence, incidence and mortality in organ transplant recipients

Immunosuppressant drugs prevent organ rejection in organ transplant recipients (OTRs) but greatly increase the risk of cutaneous squamous cell carcinoma (cSCC) in particular, and of basal cell carcinoma (BCC), compared with the general population.

In Australia, available data on KC rates among OTRs are mainly from studies conducted in Queensland. A Queensland cross-sectional study investigated KC risk among kidney and liver transplant recipients (mean age 54 years) immunosuppressed for approximately 9 years, most of whom had a history of KC or actinic keratoses (AKs). It reported that 135 (27%) participants had BCC, cSCC or Bowen's disease present on dermatological examination (and confirmed histologically within 3 months), while AKs were present in over 80%.[2]

Among Queensland kidney transplant recipients aged over 40 years or immunosuppressed for 10 years or more, and with a history of KC or AK, the estimated annual incidence rates of KC are approximately 120 per 1000 person–years for cSCC and 88 per 1000 person–years for BCC.[3] Estimated annual incidence rates are approximately one-third lower among liver recipients of the same average age and duration of immunosuppression.

Keratinocyte cancer incidence rates are highest among heart transplant and lung transplant recipients, due to their very high immunosuppressant medication levels.[4] The current incidence of cSCC and BCC among lung transplant recipients in Queensland is 201 and 171 persons affected respectively per 1000 person–years.[5] The burden of cSCC and BCC is even higher when incidence calculations account for multiple tumours, which are the norm for affected OTRs.

In OTRs, unlike in the general population, cSCC has a measurable mortality rate[6] because these patients are more likely to have aggressive disease with high rates of invasion. For example, among 17,628 kidney transplant recipients in Australia and New Zealand with 175,084 years of observation followed between 1980 and 2013 inclusive, there were 154 deaths from KC. This is around 50 times the rate of death from KC seen in people in the general population of the same age and sex during the same period: standardised mortality ratio 51; 95% confidence interval (CI) 44–60.[7] Among 619 cardiothoracic transplant patients in an early study in New South Wales, 19 were diagnosed with aggressive cSCCs, and 8 died from uncontrolled local disease or metastasis.[8]

5.43.2.2 Risk factors for keratinocyte cancer in organ transplant recipients

Risk of skin cancer in OTRs is correlated with similar sun exposure-related factors as for immunocompetent patients, including older age, light skin colour and high exposure to ultraviolet (UV) radiation.[9][10]

The risk of KC in OTRs also depends directly on duration of immunosuppression.[9] In addition, cSCC is associated with independent carcinogenic effects of azathioprine[11] and with voriconazole, a photosensitising fungicide often used in lung transplant recipients.[12]

5.43.2.3 Patients receiving stem cell transplantation

A systematic review of studies to December 2013 showed that bone marrow transplant recipients are at risk of both BCC and cSCC.[13] The 20-year cumulative incidence was 6.5% for BCC and 3.4% for cSCC and risk varied according to the type of primary disease, graft-versus-host disease, duration of immunosuppression, radiation exposure, and T-cell depletion, in addition to skin colour and sex.[13]

These findings are supported by the results of a large case-control study in white US Medicare patients aged over 65 years who had at least one visit to a dermatologist in 2010–2011. Those who had received bone marrow transplantation, especially those with graft-versus-host disease, were at significantly raised risk of both cSCC and BCC compared with those without immune-related disorders.[1]

5.43.2.4 Patients with rheumatoid arthritis

In elderly US Medicare patients who had seen a dermatologist at least once in a 2-year period, those with rheumatoid arthritis (RA) showed a very small overall increase in the risk of cSCC but not BCC, compared with a control group of patients treated for a variety of non-immune-related diseases.[1]

A UK study found that patients with RA treated with either disease-modifying anti-rheumatic drugs (DMARDs) or anti-tumour necrosis factor (anti-TNF) therapy had significantly higher KC risks (up to two-fold higher) than the general population, but there was no evidence that anti-TNF therapy increased risk compared with DMARD.[14] However, the findings of studies in Denmark[15] and Taiwan[16] have suggested that biological therapy for RA is associated with increased KC risk, although the increase was not statistically significant in the Taiwanese study.

Studies assessing the risk of cSCC in patients exposed to biological therapies for RA, compared with biological-naïve patients, have reported inconsistent findings, with significantly increased cSCC risk in one study[17] but not in others.[14][18]

Similarly, evidence of increased risk of BCC with anti-TNF therapy is also inconsistent, with different studies showing modest[17] or no association.[14]

5.43.2.5 Patients with psoriasis

Biological therapies, including anti-TNF therapies, are increasingly used to treat psoriasis, an autoimmune inflammatory skin disease.

The risk of KC in patients with psoriasis, compared with a control population, was examined in a systematic review of randomised controlled trials, prospective cohort studies and previous systematic reviews to August 2016.[19] Most studies assessing the specific risk of cSCC and BCC in psoriasis patients treated with biologicals, compared with either the general population[20][21] or biological-naïve patients,[22] reported significant increases in risk of cSCC, but not BCC. However, one study of US patients treated with adalimumab observed increased BCC risk, compared with the general population.[23]

5.43.2.6 Patients with inflammatory bowel disease

The two main forms of inflammatory bowel disease (IBD), Crohn’s disease and ulcerative colitis, affect people from a young age with potentially severe complications, warranting the use of strong and sustained immunosuppression. Immunosuppressive agents used in IBD include potent steroids, thiopurine or its derivatives, and more recently, anti-TNF and anti-interleukin 23 (IL23) biological therapies.

Increased KC incidence has been reported in patients with IBD across a variety of populations, ranging from an approximately 1.5-fold increase in higher-incidence populations like the USA[24] or the Netherlands,[25] to a 9-fold increase in Crohn's disease and a 14-fold increase in ulcerative colitis in a cohort of 2621 patients in the low-incidence Hong Kong population.[26]

5.43.2.6.1 Thiopurines

In a French prospective national cohort of more than 19,000 patients with IBD, the incidence of KC was raised (by around 10-fold for BCC, 4-fold for cSCC) only in those treated with thiopurine,[27] consistent with findings from a case-control study in the USA.[24] Neither age, sex nor type of IBD appeared to influence the association.[27] Past users of thiopurine continued to be at raised KC risk, pointing to DNA damage as the likely mode of carcinogenesis.[27]

5.43.2.6.2 Biological therapies

It remains controversial whether the main anti-TNF treatments for IBD (adalimumab and infliximab) increase KC risk, since many biologic-treated patients have also been treated with thiopurines. Newer inhibitors of the IL23-IL17 pathway have yet to be evaluated.

When adalimumab was assessed as a monotherapy versus in combination therapy in a cohort of 1500 patients with Crohn's disease, it did not result in any increased incidence of KC, compared with a 3-fold KC increase with combination therapy with thiopurines.[28] This finding is consistent with a recent meta-analysis of existing clinical trials of anti-TNF therapies in patients with IBD.[29]

5.43.2.7 Patients with chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is a low-grade lymphoproliferative disorder of B cells and is the most common adult leukaemia.

Skin cancers are the most common secondary non-haematological malignancy in patients with CLL, and the risk of KC is increased 5- to 8-fold.[30][31] Whilst cSCCs comprise the vast majority (at least 90%) of skin cancers in patients with CLL, the rates of BCC are also increased.[31][32]

Keratinocyte cancers in patients with CLL demonstrate more aggressive behaviour than in other patients, with increased rates of local recurrence, regional and distant metastases and death.[32][33][34] An Australian population-based study in people with CLL found that the standardised mortality ratio for skin cancers (KC and melanoma) was the highest for all causes of death.[35] Similarly, a 20-year retrospective study at two academic centres in the USA showed that the risk of death from skin cancer among patients with CLL was as high as that from CLL itself (13% versus 14%).[30]

In terms of surgical management of KC in CLL patients, leukaemic lymphocytic infiltrates around tumours may complicate interpretation of histological margins, especially where tissue is processed by frozen section (e.g. in Mohs micrographic surgery) instead of paraffin sections.[33][36]

5.43.2.8 Patients with HIV

There is evidence from several cohort studies that human immunodeficiency virus (HIV)-positive patients are at increased risk for KC.[37][38] The larger cohort study of 6560 HIV-positive patients and 36821 HIV-negative patients found that KC incidence rate was increased two-fold in the HIV-positive group, with the risk of cSCC slightly higher than that of BCC.[38] In this cohort, cSCCs, but not BCCs, were associated with immunodeficiency defined as low CD4 count (<200 cells/μL).

Key point(s)
Regular and close skin cancer surveillance should be provided routinely for patients with conditions characterised by immune-system dysregulation, such as HIV and chronic lymphocytic leukaemia.

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- Organ transplantation and other conditions associated with immunosuppression – Introduction
- Management of keratinocyte cancer risk in organ transplant recipients
- Strategies to manage keratinocyte cancer in organ transplant recipients
- Organ transplantation and other conditions associated with immunosuppression – Health system implications and discussion

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5.44 11.2 Management of organ transplant recipients

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5.44.1 Background

Australian organ transplant recipients (OTRs) are at increased risk of developing keratinocyte cancers (KCs) due to iatrogenic immunosuppression, with a high burden of disease.[1]

Strategies for managing KC risk in patients who have undergone organ transplant include a combination of primary prevention and, treatment of established disease. Australian guidelines since 2008 have recommended that this care be provided in transplant-dedicated specialist clinics, where possible.

Specific treatment strategies include:

- systemic acitretin chemoprophylaxis
- reduction in immunosuppression
- treatment with mechanistic target of rapamycin kinase (MTOR) inhibitors.

5.44.2 Overview of evidence (non-systematic literature review)

5.44.2.1 Primary prevention of keratinocyte cancer

Skin cancer prevention in OTRs should begin before transplantation, with education about how immunosuppressive medication will raise their risk of cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC). This should emphasise the need constantly to protect themselves from high sun exposure after transplantation and include education about sun avoidance, especially in the middle of the day, sunscreen use[2] and protective clothing.

A study conducted among OTRs in Queensland found that their use of sun protection measures was suboptimal.[3] The findings of international and Australian studies show that ongoing advice and encouragement about sun protection, given in a clinical setting, appear to be especially effective in achieving behaviour change among people undergoing organ transplantation.[4][5]

Chemopreventive medicines, including acitretin, capecitabine and vitamin B3 (nicotinamide), have been used to reduce KC risk in people undergoing organ transplantation.[6][7][8] However, none of these are established as part of routine preventive care for OTRs.

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5.44.2.2 Role of transplant-dedicated dermatology clinic

The importance of integrated specialist care in the management of skin cancer in organ transplant recipients has been widely recognised.

The various models of care described include:

- transplant-dedicated dermatology subspecialty clinics[9][10]
- multidisciplinary transplant clinics[9]
- existing dermatology clinics where transplant care is integrated[9]
- high-throughput skin cancer surgery and surveillance clinics for high-risk OTRs[11]
- nurse-led surveillance clinics with consultant dermatologist support[12][13][14]

The type of clinic adopted is influenced by available resources.

The UK National Institute for Health and Care Excellence (NICE) recommends that all OTRs be followed up in transplant-dedicated specialist dermatology clinics.[15] The transplant-dedicated dermatology clinic typically comprises dermatologists and dermatologic surgeons with consultation from plastic surgeons, head and neck surgeons, medical oncologists and radiation oncologists as needed.[10] Transplant physicians may consult simultaneously in some clinical settings,[9] and close collaboration with transplant physicians is essential in all clinic models, to co-ordinate care and negotiate adjustments to immunosuppression and commencement of systemic chemoprophylaxis, such as with oral acitretin.

Efficient scheduling of transplant-dedicated specialist clinics increases accessibility, accommodating timely excision of multiple lesions and access to emergency visits.[9][11] Adequate time and staffing can be allocated to provide surgical management on the day of assessment when appropriate, streamlining care for patients who already commit a significant amount of time to medical appointments, and so facilitating adherence and follow-up (see: Importance of adherence to keratinocyte cancer screening, below).[11][16]

Dermatology assessment prior to transplantation aims both to treat identified disease and to assess risk, guiding physicians in the timing of transplantation and determining when transplantation may be relatively contraindicated.[9][17]

The regular surveillance and proactive approach adopted by these clinics promote early detection and treatment, with the aim of improving prognosis and minimising cost. A prospective cohort study of high-risk OTRs followed over 22 years determined that surveillance every 4 months was required to ensure <15% of cancers developed before the subsequent review.[18] Recommendations from this study included 3-monthly reviews for patients who had developed two or more skin cancers and more frequent reviews for those with high-risk tumours or new cancers arising before 3 months, in agreement with other studies. [2][16][17] Patients who were cancer-free for 12 months could be reviewed annually.[18]

Dedicated transplant dermatology clinics provide an opportunity for reinforcing tailored education regarding photoprotection[5] and skin-self surveillance. Education early in the post-transplantation period using multiple methods has been shown to improve long-term retention and behavioural change.[19][20][21]

Multidisciplinary care by a team of specialists who understand the unique care needs of OTRs allows for shared decision-making and continuity of care. These clinics also facilitate research[9] and provide opportunities for teaching dermatology trainees who may provide care to OTRs in peripheral settings. [17]

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5.44.2.3 Importance of adherence to keratinocyte cancer screening

Adherence to screening recommendations has an important effect on clinical outcomes among OTRs. A population-based cohort study of 10,183 OTRs in Canada reported that high adherence to annual dermatology assessments was associated with a 34% reduction in KC-related morbidity or death, compared with low adherence.[22]

Key point(s)

- Organ transplant recipients should be educated about sun-protection measures and regularly encouraged to practise them.
- Where resources permit, patients undergoing organ transplant should be offered preventive and ongoing care for keratinocyte cancers within dedicated specialist clinics. Where access to dedicated clinics is not available, organ transplant recipients need to be closely and regularly monitored for skin cancer, especially those with previous skin cancer.

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5.44.3 References

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5.45 11.3 Strategies to manage keratinocyte cancer in organ transplant recipients

Contents

5.45.1 Background

Targeted strategies for the management of keratinocyte cancer (KC) in organ transplant recipients (OTRs) include chemoprophylaxis with systemic acitretin and revision of immunosuppression. This revision may involve reduction of immunosuppression or treatment with mechanistic target of rapamycin kinase (MTOR) inhibitors.

These strategies are generally reserved for OTRs who develop multiple or high-risk KCs. Potential adverse effects of such strategies need to be considered and these decisions should be made in a multidisciplinary setting.

5.45.2 Overview of evidence (non-systematic literature review)

5.45.2.1 Chemoprophylaxis with acitretin

Acitretin is a synthetic retinoid which is thought to aid in chemoprevention through its effects on cell cycle control, induction of apoptosis, promotion of cellular differentiation, and immunomodulation as well as inhibition of ornithine decarboxylase, cellular proliferation and keratinisation.[1]

5.45.2.1.1 Clinical trials in organ transplant recipients (chemoprophylaxis)

A single randomised double-blind placebo-controlled trial was identified that evaluated acitretin in OTRs.[2] It included 38 kidney transplant recipients, of whom 19 received treatment with 30 mg of acitretin daily.[2] Over the 6-month trial period there was a significant reduction in new cSCCs in the treatment group, compared with the placebo group. The effect was most marked in patients with a history of KC.

An Australian prospective open randomised crossover trial of 23 kidney transplant recipients with a history of KC allocated to either 25 mg of acitretin daily or placebo and crossed over at one year also showed fewer cSCCs while on acitretin than in the medication-free period.[3]

Both these studies observed a rebound in the number of cSCCs after cessation of treatment in the treatment group,[2][3] which was also seen in other studies.[4][5]The effect appears to be most marked in those taking acitretin for longer than 12 months.[4]

5.45.2.1.2 Current clinical practice (chemoprophylaxis)

Acitretin is usually reserved for high-risk patients as an adjunct therapy to standard skin cancer management, given the limited evidence supporting its use in primary prevention, its adverse effect profile, and the need for long-term treatment.

The following indications have been suggested for commencement of oral acitretin in OTRs:[6][7][8]

- development of multiple (5–10) KC lesions per year
- development of countless actinic keratoses with multiple KC lesions
- acceleration in the frequency of occurrence of KC lesions
- development of multiple KC lesions in high-risk areas
- high-risk KC (risk for metastasis >20%)
- eruptive keratoacanthomas
- metastasis
- solid organ transplantation with a history of leukemia or lymphoma and KC.

The effective dose of acitretin varies across studies and low doses may be sufficient.[9] Clinical response should be assessed and the risk-benefit ratio should be considered in determining maintenance dosing. Ongoing treatment with acitretin is required to establish long-term effectiveness.

5.45.2.1.3 Safety profile and adverse effects (chemoprophylaxis)

Acitretin appears not to adversely affect renal grafts in kidney transplant recipients, with several clinical trial observing no deterioration in renal function.[2][3][10]

Drug tolerability is a limiting factor, although most side effects are reversible.[11][12] The most common adverse effects necessitating dose reduction or treatment cessation are mucocutaneous xerosis (70–100%), alopecia (44–47%), headache (40%) and myalgia (20–35%).[11][12] In the three trials, 8– 39% of patients withdrew due to adverse effects, while additional patients interrupted treatment for several weeks.[2][3][10]

High-dose treatment may cause osteoporosis, hyperostotic axial skeletal changes and liver function abnormalities as well as tendon and ligament calcification.[9][13][6] However long-term data in the organ transplant population are lacking. These adverse effects may be mitigated by gradual dose titration and monitoring of symptoms and laboratory tests, including full blood count, renal function tests, liver function tests and fasting lipid profile.

Retinoids are highly teratogenic, so strict contraceptive measures should be employed in women of childbearing age.

Key point(s)
Current data suggest acitretin is relatively safe and effective in reducing KC in select OTRs.

5.45.2.2 MTOR inhibition

The MTOR inhibitors, particularly sirolimus and everolimus, were initially used in the immunosuppression regimen for kidney transplant recipients to mitigate calcineurin inhibitor (CNI)-induced renal dysfunction and thus enhance graft survival. Further investigation confirmed the dual immunosuppression and antineoplastic properties of MTOR inhibitors, leading to the speculation that they may confer additional survival benefit by protecting against the development or progression of malignancies.[14]

5.45.2.2.1 Clinical trials in organ transplant recipients (MTOR inhibition)

There is more evidence for sirolimus use than for everolimus, because sirolimus has been in use at least a decade longer than everolimus.

Similarly, there is more evidence for the use of MTOR inhibitors in kidney transplant recipients, due to the early uptake of sirolimus in that group, compared with other OTRs. Of note, both sirolimus and everolimus are now used in kidney transplant recipients, whereas everolimus is primarily used in liver transplant recipients and heart transplant recipients.

A double-blind randomised controlled trial (RCT) investigating the elimination of calcineurin inhibition and substitution with MTOR inhibition demonstrated that sirolimus use was associated with reduced risk in the development of KC in kidney transplant recipients.[15] Multiple clinical trials have shown reduced numbers of KC in OTRs after a therapeutic switch to, or addition of, MTOR inhibitors.[16][17][18][19][20] This benefit was magnified if there was a prior history of KC, and there was a greater effect on the development of cSCC and Bowen's disease, compared with BCC. The greater impact on cSCC formation may relate to differential phospho-MTOR expression.[21]

A systematic review of 29 trials has shown decreased KC incidence, better preservation of renal function, increased risk of acute organ rejection and no difference in mortality among OTRs treated with MTOR inhibitors, compared with those treated with CNIs.[22] A meta-analysis of data from 21 RCTs in 5876 kidney transplant recipients confirmed a 56% reduction in the risk of KC development among sirolimus-treated patients, compared with the control group (treatment regimens not containing sirolimus).[23] However, there was a significantly increased risk of death from all causes in patients on sirolimus.[23]

There is a small amount of evidence challenging the findings of these studies. In a retrospective study of a sizeable Californian cohort of 3539 OTRs (kidney, liver, heart and lung), which investigated the relationship between sirolimus exposure (488 patients) and KC incidence, sirolimus use was not associated with a lower risk of developing KC; in fact, there was a non-significant increase in KC in this group. [24] The investigators

postulated that prior studies reporting the benefits of MTOR inhibitors on KC development might have been examining the positive effect of co-interventions, namely CNI dose reduction or elimination. These findings have been challenged in turn, citing lack of information regarding doses of MTOR inhibitors (only low-dose MTOR inhibitors are antineoplastic), previous or concomitant exposure to CNI, immunosuppression regimens, and skin cancer clinical risk factors, such as skin type and sun exposure. Furthermore, histological subtype of cSCC (invasive cSCC versus Bowen's disease) was not reported. The real number of KCs may have been underestimated if Bowen's disease was treated by techniques not requiring pathological examination.[25]

5.45.2.2.2 Current clinical practice (MTOR inhibition)

An expert consensus panel recommended a moderate reduction of immunosuppression once 25 or more KCs develop per year.[6]

However, the optimal time to reduce immunosuppression appears to be after the development of the first KC. Recent data suggest that, once multiple KCs have developed, the benefit of introducing MTOR inhibitors (and switching from CNIs or reducing their dose) may be lost. Prophylactic use of MTOR inhibitors does not seem warranted, particularly given their adverse effect profile.

5.45.2.2.3 Safety profile and adverse effects (MTOR inhibition)

Adverse effects of MTOR inhibitors include oedema, impaired wound healing, acneiform eruptions, aphthous ulcers, proteinuria, hyperlipidaemia, lymphocele, pneumonitis and myelosuppression. Intolerance of these adverse effects has limited the widespread uptake and long-term use of MTOR inhibitors by OTRs.

Moreover, the high rate of dose reduction or discontinuation (up to 39%) due to treatment-related adverse effects in many MTOR inhibitor studies makes it difficult to interpret the data and judge whether reported outcomes are clinically meaningful.[19][20]

Successful side-effect management is the key to taking advantage of the potential benefits of MTOR inhibition.

Although complete discontinuation of CNIs and antimetabolites appears beneficial with respect to malignancy risk, it must be weighed against the risk of transplant rejection. While antimetabolite use has been phased out in newer immunosuppression regimens for OTRs, it has not been feasible to eliminate CNI in all types of organ transplants, due to the issues with tolerability of MTOR inhibitors. Therefore, some regimens involve a combination of both agents (i.e. low-dose CNI with low-dose MTOR inhibitors), keeping their trough levels to the minimum required for immunosuppression.[26]

5.45.2.2.4 Summary (MTOR inhibition)

In summary, there is a role for MTOR inhibitors in the prevention and management of KC, the most common cancer faced by OTRs in the long term.

Multiple clinical trials, especially in the kidney transplant population, have explored the role of sirolimus, and to a lesser extent, everolimus, in the immunosuppression regimen.[15] Multiple clinical trials have shown reduced numbers of KC in OTRs after a therapeutic switch to, or addition of, MTOR inhibitors.[16][17][18][19][20] The overall trend is toward benefit without increased risk of acute graft rejection, particularly in those with a history of, or high risk for, cancer. Only a few studies have not shown a clear advantage over current immunosuppression regimens.[24]

Despite these positive findings, the use of MTOR inhibitors in the transplant setting remains low, due to poor tolerability and physician concerns regarding adverse effects. Thus, complete CNI elimination has proven to be unachievable in many circumstances.

To improve the morbidity and mortality related to KC, a combination of low-dose CNI and low-dose MTOR inhibitors should be considered on a case-by-case basis.

5.45.2.3 Reduction in immunosuppression

The correlation between intensity of immunosuppression and the risk of KC is well established and provides a rationale that reduction of immunosuppression can reduce the burden and behaviour of KC in OTRs.[27]

Coincident with the increasing trend towards the use of combination MTOR inhibitor and CNI therapy in OTRs with increased KC load,[26] little new evidence is available from studies investigating the reduction of MTOR inhibitors and CNI immunosuppression (either in combination or alone) as a means of adjunctive management of high-risk/multiple KCs.[6][28]

5.45.2.3.1 Clinical trials in organ transplant recipients (reduction in immunosuppression)

The largest randomised control trial, conducted over 20 years ago, studied cyclosporin dose reduction versus non-reduction in 231 kidney allograft recipients 12 months after transplant.[29] Halving cyclosporin trough blood levels reduced malignant complications but had no effect on long-term graft function or survival. However, increased acute graft rejection episodes were noted with lower cyclosporin doses, though these episodes were medically manageable and had no effect on overall graft survival.

Subsequently, reductions of KC load have been reported in small series of OTRs where immunosuppression was ceased due to allograft failure or high load of KC.[30][31]

5.45.2.3.2 Current clinical practice (reduction in immunosuppression)

Expert consensus guidelines have advised mild reduction of immunosuppression once the number of skin cancers exceeds 25 per year, or for skin cancers with a 3-year risk of mortality estimated at 10%.[28][32][33]

5.45.3 Practice Points

Practice point
PP 11.3.1. Chemoprophylaxis with systemic acitretin should be considered for reducing tumour burden in patients who develop multiple keratinocyte cancers.

Practice point
PP 11.3.2. Reduction of immunosuppression should be considered in organ transplant recipients who develop multiple keratinocyte cancers.

Key point(s)

- The use of MTOR inhibitors can be considered as a strategy in organ transplant recipients who develop multiple keratinocyte cancers.
- Reduction of immunosuppression due to cutaneous carcinogenesis needs to be balanced against the risk of graft rejection in OTRs, but severe reduction in immunosuppression is recommended for life-threatening KCs.

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- Epidemiology of keratinocyte cancers in immunosuppressed patients
- Management of keratinocyte cancer risk in organ transplant recipients
- Health system implications and discussion

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5.46 11.4 Health system implications and discussion

Contents

5.46.1 Health system implications

5.46.1.1 Clinical practice

The care and surveillance of immunosuppressed patients who develop multiple keratinocyte cancers should ideally be performed by in a multidisciplinary setting.

5.46.1.2 Resourcing

Multidisciplinary team care and routine dermatological surveillance require investment by the health system and coordinated delivery of health services. Currently resourcing for such care is available only in a few metropolitan centres and tertiary hospitals.

5.46.1.3 Barriers to implementation

Lack of routine skin care integrated into existing services for immunosuppressed patients, necessitating out-of-pocket payments by patients, is a major barrier to implementation of early detection for many immunosuppressed patients.

Lack of routine, ongoing patient education about the need for sun protection measures is also a barrier to implementation of primary prevention.

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5.46.2 Discussion

5.46.2.1 Unresolved issues

It remains uncertain whether biologic therapies, such as anti-tumour necrosis factor (TNF) therapies, raise the risk of keratinocyte cancer (KC) above the risk of KC in patients with immune-related disease receiving standard (non-biologic) treatment.

5.46.2.2 Studies currently underway

The Oral Nicotinamide after Transplant (ONTRANs) study is a multicentre, Australian randomised controlled trial, in which high-risk organ transplant recipients with multiple KCs are randomised to receive either nicotinamide 500 mg or placebo twice daily over a 12-month period, with the primary objective of investigating whether this treatment can reduce KCs.[1]

5.46.2.3 Future research priorities

The role of human papillomavirus (HPV) in the development of KC and the potential for HPV vaccination in the prevention of KC, particularly in the organ transplant population.

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5.47 12. Metastatic disease and systemic therapies – Introduction

Contents

5.47.1 Introduction

Metastatic keratinocyte cancers are uncommon but potentially lethal malignancies.

5.47.1.1 Basal cell carcinoma

Metastatic basal cell carcinoma (BCC) is rare.[1]

Targeted therapy directed against the hedgehog signalling pathway has been shown to achieve responses among patients with metastatic BCC.[2][3]

The role of immunotherapy in treating patients with BCC is also being investigated, following case reports of checkpoint immunotherapy and the observation of a high mutation burden in patients BCC. In some cases, systemic therapy may be appropriate for patients with locally advanced disease that is not amenable to further local treatment such as surgery or radiotherapy, or where these therapies may lead to significant morbidity. Review of such patients by an experienced multidisciplinary team is recommended.

5.47.1.2 Cutaneous squamous cell carcinoma

Conventional chemotherapy is used in the treatment of metastatic cutaneous squamous cell carcinoma (cSCC), based on limited evidence.[4][5][6][7][8]

More recently, evidence has emerged for the efficacy and durability of checkpoint inhibitor immunotherapy in the treatment of metastatic cSCC.[9]

Topics in this section include:

- Systemic therapies for advanced and metastatic basal cell carcinoma
- Systemic therapies for metastatic cutaneous squamous cell carcinoma
- Metastatic disease and systemic therapies – Health system implications and discussion

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5.48 12.1 Systemic therapies for advanced and metastatic BCC

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5.48.1 Background

Metastatic basal cell carcinoma (BCC) is a rare event, with estimated incidences ranging from 0.0028 to 0.1%.[1] Lung and bone are the most common sites. If distant metastasis of BCC is suspected, confirmation should be obtained by biopsy.

The management of metastatic BCC is largely based on clinical evidence and experience in the management of locally advanced BCCs. Definitions of locally advanced BCC vary between clinical trial investigators and between disciplines, but it is generally acknowledged to include BCCs that have recurred after prior treatment, lesions in locations that preclude surgical excision, and large lesions.

In clinical practice, locally advanced BCC describes a range of clinical presentations in which a primary or locally recurrent BCC is not easily treated by local surgery or radiotherapy. Locally advanced BCC can arise due to tumour-related factors, patient-related factors or treatment-related factors.

To overcome the lack of an agreed definition of locally advanced BCC (and, in particular, to avoid over-reliance on lesion size as an independent criterion) the term 'difficult-to-treat' has been proposed to identify BCCs that require a treatment approach similar to that of advanced disease. A European study reported that 6.6% of all BCC were difficult to treat and 0.6% were very difficult to treat,[2] while a tertiary referral centre in the UK reported that up to 20% of BCCs are difficult to treat although not necessarily advanced.[3]

See: Prognosis of basal cell carcinoma and Table 1.

Table 1. Tumour-specific factors associated with recurrence of basal cell carcinoma

Tumour characteristics can include a large neglected primary lesion, infiltrative growth pattern, or proximity to a critical structure in the face. Patient factors can include comorbidities or the decision to decline certain treatment modalities. Treatment factors may include tumour recurrence after prior surgery and radiotherapy, or unsuitability of surgical excision where this would leave a large functional or cosmetic defect (e.g. orbital exenteration).

Tumour size alone does not necessarily determine whether the patient has locally advanced disease, as complexity may be more relevant. For example, a large, neglected BCC overlying the back in an otherwise reasonably healthy patient may be amenable to relatively straightforward curative-intent surgery with skin grafting, whereas it may be much more difficult to manage a small lesion located near the eye that has recurred after prior surgery, with an infiltrative growth pattern and poorly defined margins.

Patients with complex, locally advanced disease are best treated by a multidisciplinary team including surgeons, dermatologists, radiation oncologists and medical oncologists. Curative-intent surgery or radiotherapy (or both) is the optimal approach but, if these are not possible, systemic therapy with hedgehog pathway inhibitors (HPIs) can be considered.

Basal cell carcinoma may sometimes show metastatic spread to regional lymph nodes and, occasionally, in-transit metastases. In such cases direct treatment such as surgery or radiotherapy, if possible, would be appropriate after first evaluating if more widespread metastatic disease is present.

Radiotherapy may be useful in palliation of distant metastases.

Selecting patients appropriate for systemic therapy for advanced BCC requires consideration of the individual's functional status, comorbidities, social support and likely compliance with treatment and follow-up. The clinician must discuss potential side effects of proposed treatment with the patient and ensure appropriate clinical support.

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5.48.2 Overview of evidence (non-systematic literature review)

5.48.2.1 Hedgehog pathway inhibitors

Potential candidates for HPI therapy include patients with inoperable BCC, those in whom surgery is not appropriate, and those with metastatic BCC who have an adequate performance status. Hedgehog pathway inhibitors are administered orally once daily in an outpatient setting.

Targeted therapy using HPIs has been demonstrated to be effective in patients with proven metastatic BCC. Data are available from well-conducted trials in patients with confirmed histological diagnoses of metastatic BCC and response assessment according to modern radiological criteria.

Research is currently underway assessing the use of systemic HPIs to achieve tumour reduction prior to definitive surgery in patients with locally advanced BCC.[4][5]

5.48.2.1.1 Efficacy

Vismodegib, the first HPI, was reported to show a significant degree of activity in sporadic inoperable BCC.[6] At long-term follow-up (39 months after accrual), objective response rates were 60.3% among patients with locally advanced BCC and 48.5% among those with metastatic BCC, with comparable findings across patient subgroups including those with aggressive histologic subtypes (e.g. infiltrative BCC).[7] Median duration of response was 26.2 months among patients with locally advanced BCC and 14.8 months among those with metastatic BCC.[7] Median overall survival was 33.4 months in the metastatic BCC cohort and could not be estimated in the locally advanced BCC cohort.[7] Vismodegib has also been shown to reduce new lesion formation in patients with naevoid BCC syndrome (Gorlin's syndrome).[8]

A phase 2 randomised controlled trial (RCT) comparing sonidegib 200mg or 800mg daily in patients with metastatic BCC or locally advanced BCC not amenable to curative surgery or radiation reported that efficacy was similar for both doses, while the lower dose showed a better toxicity profile.[9] At 30 months' follow-up, objective response rates for patients treated with sonidegib 200mg were 56.1% as assessed by central review and 71.2% as assessed by investigator review among patients with locally advanced BCC, and 7.7% (central)/23.1% (investigator) among those with metastatic BCC.[10] Median duration of response was 26.1 months (central) /15.7 months (investigator) in among patients with locally advanced BCC and 24.0 months (central)/18.1 months (investigator) among those with metastatic BCC.[10] Overall survival rates at 2 years were 93.2% for patients with locally advanced BCC and 69.3% for those with metastatic BCC. Median overall survival could not be calculated.[10] Among patients with locally advanced BCC, efficacy did not differ between subgroups according to aggressive or non-aggressive histology.[10]

The sonidegib registration trial[11] used a more stringent response assessment method than was used in the vismodegib registration trial,[6] resulting in lower rates of complete and partial responses. However, overall disease control rates were similar.

Allowing for differences in trial assessment, sonidegib and vismodegib appear to have similar efficacy.

5.48.2.1.2 Adverse effects

Allowing for differences in trial assessment, sonidegib and vismodegib appear to have a similar spectrum of side effects. Elevated blood creatine kinase was noted in the registration sonidegib study,[11] but creatine kinase levels were not routinely tested in the vismodegib studies. Symptomatic muscle cramps have been reported with both agents.[12][13]

For a patient experiencing intolerable class side effects from HPI (such as hair loss, taste loss, cramps), switching between HPI agents may result in similar side effects. For other side effects that are likely to be agent-specific, switching to the alternative HPI is a reasonable strategy. Disease progression is unlikely to be sensitive to a change in HPI unless drug-specific side effects have prevented full dosing.

Intermittent dosing has been proposed as a strategy for reducing side effects of HPI therapy while maintaining efficacy. A RCT evaluating two intermittent regimens in patients with multiple BCCs reported effective anti-cancer activity and acceptable adverse effects[14]

5.48.2.1.3 Managing side effects

Patient and carer education and expectations about side effects are important and should be adequately discussed prior to commencing treatment and supported with written information (such as the EviQ patient information document).[15][16] Attention to nutrition, monitoring of weight, and dietitian review if necessary help with taste loss with the goal of preventing weight loss and nutritional deficiencies.

Nausea, diarrhoea, constipation and abdominal cramps may be alleviated with specific supportive medications (such as anti-emetics, laxatives and spasmolytic agents such as hyoscine). For symptomatic cramps, magnesium supplements and calcium channel antagonists have been proposed as well as analgesia, which can include as-required opioids such as oxycodone for severe cramps. Minoxidil 5% twice daily has been suggested to treat alopecia.[17]

Routine monitoring includes blood tests for full blood count, liver function tests, creatinine and creatine kinase.

See: EviQ recommendations for monitoring vismodegib and EviQ recommendations for monitoring sonidegib.

For patients with metastatic/locally advanced BCC who develop resistance or intolerance to a first-line HPI, other systemic therapies can be considered.

5.48.2.1.4 Resistance

Proposed resistance mechanisms by BCC to HPI include acquired mutations in smoothened (*SMO*) gene or glioma associated oncogene homolog (*GLI*) genes. Other pathways of resistance include over-expression of epidermal growth factor receptor (EGFR), Mitogen Activated Protein Kinase (MAPK) and Akt. Treatment with EGFR inhibitors has been proposed as a strategy for patients with treatment-resistant BCC with demonstrated expression of EGFR.[18]

Ongoing research into escape mutations in hedgehog pathway signalling aims to develop newer drugs to help overcome resistance to sonidegib and vismodegib.

5.48.2.1.5 Combination with other therapies

Combination treatment with vismodegib, itraconazole, and imiquimod has been proposed in order to target different parts of the hedgehog signalling pathway.[19] This strategy may help reduce the development of resistance and increase efficacy.

5.48.2.2 Conventional chemotherapy

Systemic chemotherapy is rarely used in metastatic BCC or for locally advanced disease.

Single-case reports document responses to the combination of cisplatin or carboplatin with paclitaxel in patients with metastatic BCC.[20][21] A 1996 review evaluating platinum containing chemotherapy in 46 patients with progressive BCC reported an overall response rate of 83%,with a median time to progression of 24 months.[22] A 2004 Australian case study reported rapid symptomatic response to cisplatin in combination with paclitaxel in a patient with metastatic BCC, but noted late neurotoxicity.[21]

The role of systemic chemotherapy in the era of HPI targeted therapy and immunotherapy remains to be defined.

5.48.3 Practice Points

Practice point
PP 12.1.1. Patients with locoregional metastases of basal cell carcinoma should be offered surgical excision or radiotherapy if possible. It is appropriate to check for the presence of distant metastatic disease.

Practice point
PP 12.1.2. Patients with distant metastatic basal cell carcinoma should be referred to a medical oncologist or multidisciplinary team for consideration of hedgehog signalling pathway inhibitor treatment.

Key point(s)

- Patients with advanced basal cell carcinoma (e.g. patients who would require complex surgery and those whose BCCs have recurred after prior surgery and radiotherapy or systemic therapy) should be assessed by a multidisciplinary team.
- Hedgehog pathway inhibitors should be considered for patients with advanced basal cell carcinoma where curative-intent treatment (surgery, radiotherapy or both) is not appropriate. Some patients who have a marked response may become candidates for surgery.
- Patients treated with hedgehog pathway inhibitors should be monitored carefully for side effects.
- Health professionals treating patients who are receiving Hedgehog pathway inhibitors should be aware of the potential side effects of these agents and practise management strategies to optimise compliance.

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- Squamous cell carcinoma: metastatic disease and systemic therapies
- Metastatic disease and systemic therapies – Health system implications and discussion

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5.49 12.2 Systemic therapies for metastatic cSCC

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5.49.1 Background

Certain features of primary cutaneous squamous cell carcinoma (cSCC) are associated with a higher risk of recurrence and lymph node involvement. Different systems, including TNM (American Joint Committee on Cancer [AJCC] Cancer Staging Manual 8th edition)[1] and the Brigham and Women's Hospital tumour staging system, are used to estimate risk and guide further management.[2]

When the primary lesion is on the head and neck there may be anatomical constraints to performing surgery with curative intent.

Perineural involvement (PNI) of the large nerves is associated with a higher risk of relapse. Patients may present sometime after excision of the index cSCC with facial nerve weakness or pain/numbness in part of the trigeminal nerve distribution. There is often a significant delay to diagnosis.

Special populations include patients with solid organ transplants and patients with concurrent haematological malignancy. Both these clinical circumstances present challenges in managing localised, high-risk and recurrent /metastatic cSCC.

Locoregional advanced cSCC represents a spectrum that comprises:

- unresectable locally advanced disease presenting de novo
- unresectable locally advanced disease recurring after prior surgery and radiotherapy (RT)
- regional lymph node metastasis, usually presenting subsequent to treatment of a primary lesion.

Locoregionally advanced cSCC should be managed with the goals of clearing the local disease, preventing local recurrence and preventing regional or distant metastases, which may otherwise compromise patient survival.

However, treatment options may be limited by the location of the primary tumour and by comorbidities.

Adjuvant RT following surgery is widely practised for patients deemed to be at high risk of local or regional relapse. However, this approach has not been evaluated in randomised controlled trials (RCTs).

5.49.2 Systematic review evidence

What should be the protocol to manage or treat locoregionally advanced cutaneous squamous cell carcinoma?

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Twenty-three studies were identified that reported treatment outcomes in patients with locally advanced or metastatic SCC treated by various modalities, including chemotherapy.[3][4][5][6][7][8][9][10][11][12][13][14][15][16] [17][18][19][20] [21][22][23][24][25]

They include one RCT,[20] 16 cohort studies[3][4][5][6][7][8][9][11][12][13][14] [15][18][21][22][23] and six case studies [10][16][17][19][24][25]

Ten studies were at moderate risk of bias[7][8][11][13][14][22][23][24][25] 12 at high risk of bias[3][4][5][6][9][12][15][21][10][16][24][25] and one at unclear risk of bias.[20]

An Australian RCT[20] compared postoperative concurrent chemoradiotherapy with postoperative RT in patients with high-risk cSCC of the head and neck.

The observational studies included cohorts of patients with metastases of cSCC to the parotid,[3][10][13][14] metastases to the axilla or groin[7] cSCC of the head and neck,[5][8] as well as cohorts with a broader range of cSCC presentations.

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5.49.2.1 Recurrence

5.49.2.1.1 Locoregional control

One RCT[20], six retrospective cohort studies[5][6][8][11][13][14] and one case series[24] reported locoregional control outcomes.

The RCT[20] reported no significant difference in locoregional control rates between patients with high-risk cSCC of the head and neck who received postoperative RT and those who received postoperative concurrent chemoradiotherapy (83% versus 87%).

One retrospective cohort study with a moderate risk of bias[13] reported a superior locoregional control rate among patients with parotid cSCC metastasis who received postoperative RT compared with those who received either radiotherapy only or preoperative neoadjuvant RT (83% versus 53%, p=0.008).

Of the three retrospective cohort studies that reported local control rates,[6][8][12] none reported significant effects.

5.49.2.1.2 Progression-free survival

Six retrospective cohort studies[3][5][7][11][18][21] and one case series[16] reported progression-free survival/local recurrence-free survival/relapse-free survival.

One retrospective cohort study (high risk of bias) in patients with cSCC of the head and neck[21][10] reported a significantly higher proportion of patients without recurrence at 5-year follow-up among those treated with surgery plus adjuvant RT group than those treated with surgery alone (78% versus 30%; p=0.02).

A non-comparative study evaluating cetuximab in elderly patients with advanced cSCC reported median progression-free survival of 9 months.[19] Another non-comparative study evaluating gefitinib in patients with incurable cSCC amenable to curative therapy including surgery or RT reported median progression-free survival of 3.8 months.[25]

5.49.2.1.3 Overall survival

One RCT,[20] 10 retrospective cohort studies[4][5][6][7][8][11][14][15][18][21] and three case series[10][16][17] reported overall survival rates.

The RCT[20] reported no significant difference in 5-year overall survival rates between patients with high-risk cSCC of the head and neck who received postoperative RT and those who received postoperative concurrent chemoradiotherapy (76% versus 79%).

Three retrospective cohort studies reported significant differences in survival between treatment groups: a retrospective cohort study with a moderate risk of bias[8] reported a survival benefit with RT 240–250 cGy /fraction over other doses in patients with keratinocyte cancers of the head and neck, of which the majority were cSCCs.

Another study with a moderate risk of bias[11] reported a survival advantage for RT plus concurrent systemic chemotherapy, compared with RT alone, in patients with locally advanced cSCC of head and neck (median overall survival 20.9 months versus 34.4 months; p = 0.03).

A study with a high risk of bias[21] reported higher 5-year survival among patients with cSCC of head and neck treated with surgery plus adjuvant RT compared with surgery alone (79% versus 46%, p<0.05).

A non-comparative study evaluating cetuximab in elderly patients with advanced cSCC reported median overall survival of 13 months.[19]

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5.49.2.1.4 Survival time

Four retrospective cohort studies[8][9][11][22] and two case series[19][25] reported survival times.

One retrospective cohort study with a high risk of bias[9] reported significantly longer median survival among patients with regionally metastatic cSCC of head and neck treated with adjuvant RT than those treated with surgery alone (23 months versus 10 months, p=0.002).

5.49.3 Overview of additional evidence (non-systematic literature review)

5.49.3.1 Locoregional metastasis

Overall, the evidence for management of locoregional SCC is of low quality. It is estimated that less than 5% of primary cSCC give rise to local recurrence or regional lymph node metastasis (see: Prognosis).

Several risk factors for recurrence have been identified (Table 2).

Table 2. Tumour-specific factors associated with recurrence of keratinocyte cancers

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Currently used staging systems to identify patients at higher risk of relapse include the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (8th edition) [1] and the Brigham and Women's Hospital staging system for cSCC.[26]

The head and neck region are the most common sites of primary cSCC and, therefore, the commonest lymph node metastasis sites are the parotid and cervical lymph nodes. Prognosis appears worse for patients with more extensive involvement of cervical lymph nodes.[27] Metastases to groin, axilla or epitrochlear lymph nodes should be managed surgically and adjuvant RT should be considered.[28]

Available evidence, albeit from non-randomised trials, consistently supports the use of adjuvant RT after surgery for patients with metastatic SCC involving the parotid or cervical lymph nodes. Adjuvant RT is associated with reduced local recurrence and improved disease-free and overall survival.[29][30]

5.49.3.2 Distant metastases

Distant metastases from cSCC are uncommon.[31] They rarely precede the development of regional metastases or occur in isolation from regional metastasis.

The time to occurrence after presentation with the original primary lesion is short, usually within 2 years. The lung and liver are the most common sites of spread, 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.[32] Survival is poor despite treatment, with few patients surviving more than 2 years.[32]

More recently, the efficacy of checkpoint inhibitor immunotherapy has been demonstrated in metastatic and locally advanced cSCC. Response rates of 47% and a high overall disease control rate have been reported, with prolonged responses seen in a proportion of patients.[33] First-line immunotherapy may become the standard of care for metastatic/inoperable locally advanced cSCC. However, this therapy is not currently funded by the Pharmaceutical Benefits Scheme in Australia.

5.49.3.3 Other systemic therapies

Epidermal growth factor receptor (EGFR) inhibitors have some activity in patients with cSCC.[17] In patients with other malignancies, EGFR inhibitors are typically used with other agents. Their role in combination with chemotherapy or checkpoint inhibitor immunotherapy in the treatment of cSCC remains to be clarified. EGFR inhibitors are not registered for use in cSCC in Australia currently and use would be off label.

Cetuximab is approved by the Australian Therapeutic Goods Administration for the treatment of SCC of the head and neck, either in combination with RT for locally advanced disease, or in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.[34] However, cetuximab is not subsidised by the PBS for the treatment of cSCC.

5.49.3.4 Patient selection

Patient performance status, comorbidities, social support and likely compliance with treatment, follow up and supportive interventions are important.

5.49.3.5 Managing side effects

Common adverse effects of checkpoint inhibitor immunotherapy include rash, itch, fatigue and thyroid disturbance. Less common effects include pneumonitis, colitis and other endocrinopathies. Rare adverse effects include renal and neurological autoimmune effects.[35]

Typical adverse effects of cisplatin include nausea, vomiting, fatigue, low blood cell counts, infection, renal toxicity, neurotoxicity and ototoxicity.[36] Carboplatin generally has fewer side effects than cisplatin and does not require intravenous hydration, unlike cisplatin. Typical carboplatin side effects include fatigue, nausea and thrombocytopenia.[37]

Common adverse effects of 5-fluorouracil include nausea, diarrhoea, fatigue, and rash. Rare effects include severe diarrhoea and coronary artery spasm. Continuous-infusion 5-fluorouracil requires placement of a venous access device and is given over a number of days via an infusion device.[36]

5.49.3.6 Chemotherapy

Systemic chemotherapy has been used for metastatic cSCC. It can be used alone or as part of multimodality therapy. Most phase II studies used cisplatin, often combined with doxorubicin.[38][39][40][41][42] Other drugs include methotrexate, 5-fluorouracil, bleomycin and vindesine.[43][44][31][45][46] Objective response rates of >80% have been reported, with complete response rates of around 30%.[44]

In some patients, locally advanced disease can be rendered operable with the combination of cisplatin-based chemotherapy and radiotherapy.[47]

Oral 5-fluoropyrimidine analogues are well tolerated and can achieve effective palliation in patients who are elderly and have significant comorbidities.[48]

5.49.3.7 Follow-up

The majority of relapses after lymph node metastasis resection and adjuvant radiotherapy occur within 2 years, so 3-monthly follow-up for the first 2 years has been suggested.[49]

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5.49.4 Evidence summary and recommendations

Evidence summary	Level	References
Local recurrence free survival/freedom from locoregional relapse /progression-free survival Eight studies reported data for one or more of these outcomes. Studies assessing surgery plus adjuvant radiotherapy as a treatment modality consistently reported survival rates of 70–90% range at follow-up of 3–5 years. No treatment modality could be identified that consistently improved local recurrence-free survival, relapse-free survival or progression-free survival across all studies that reported these outcomes.	III-2, IV	[3], [5], [7], [11], [16], [50], [23]
Overall survival/mean survival time Eighteen studies reported data for overall and mean survival times. The addition of radiotherapy to surgery improved overall survival in three studies comparing these modalities. Adding chemotherapy to radiotherapy only showed inconsistent improvements to overall survival. Whether or not chemotherapy, in addition to adjuvant radiotherapy, improved overall survival cannot be ascertained from current evidence due to insufficient data and inconsistent findings. Generally, overall survival was higher in patients who received adjuvant radiotherapy compared with those who received definitive radiotherapy only. There were insufficient studies comparing modalities to ascertain the best treatment modality or combination with respect to mean survival time.	II, III-2, IV	[4], [5], [6], [7], [8], [9], [10], [11], [14], [15], [16], [17], [18], [19], [20], [21], [22], [25]
Local control/locoregional control Nine studies reported data for one or both outcomes. The addition of chemotherapy to radiotherapy improved locoregional control rates, compared with radiotherapy only in four studies that reported this outcome. Some studies reported that the addition of radiotherapy to surgery improved locoregional control rates, but data were inconsistent. Adjuvant radiotherapy improved locoregional control, compared with radiotherapy alone.	II, III-2, IV	[5], [6], [8], [11], [12], [13], [14], [20], [24]

Evidence summary	Level	References
There were too few studies and the data were too inconsistent data to enable conclusions about the best treatment modality for local control rates. The use of radiotherapy alone, or in combination with other modalities reported high (>80%) local rates, even up to 10 years post treatment.		
Distant-metastasis free survival/distant control Only single studies reported these outcomes, all of which reported similar rates between modalities reported.	III-2	[11], [12]

Evidence-based recommendation	Grade
EBR 12.2.1. For patients with resected high-risk cutaneous squamous cell carcinoma, adjuvant radiotherapy to reduce the risk of locoregional recurrence should be considered.	**D**

Evidence-based recommendation	Grade
EBR 12.2.2. For patients with cutaneous squamous cell carcinoma metastatic to cervical lymph node(s) who have adverse factors such as multiple node involvement, extra-nodal extension or involved margin, neck dissection followed by adjuvant radiotherapy is recommended.	**D**

Evidence-based recommendation	Grade
EBR 12.2.3. For patients with cutaneous squamous cell carcinoma metastatic to the parotid, surgery or radiotherapy of the ipsilateral neck is recommended, even if clinically uninvolved.	**D**

Evidence-based recommendation	Grade
EBR 12.2.4. Patients with resected primary cutaneous squamous cell carcinoma should be assessed for high-risk features and referred for consideration of adjuvant treatment, if appropriate.	**D**

Evidence-based recommendation	Grade
EBR 12.2.5. Do not routinely offer carboplatin chemotherapy in addition to adjuvant radiotherapy for patients who have undergone excision of high-risk head and neck cutaneous	**B**

Evidence-based recommendation	Grade
squamous cell carcinoma.	

Consensus-based recommendation

CBR 12.2.1. Patients with cutaneous squamous cell carcinoma involving the parotid or cervical lymph nodes should be offered adjuvant radiotherapy after surgery.

Practice point

PP 12.2.1. Recurrences of cutaneous squamous cell carcinoma in the axillary, epitrochlear or inguinal lymph nodes should be treated with surgery and adjuvant radiotherapy.

Practice point

PP 12.2.2. Patients with resected lymph node metastases of cutaneous squamous cell carcinoma should be followed 3-monthly for the first 2 years after surgery.

Practice point

PP 12.2.3. Patients with unresectable local cutaneous squamous cell carcinoma can be considered for radiotherapy and, if fit for chemotherapy, platinum-based chemoradiation

Practice point

PP 12.2.4. Cemiplimab treatment should be considered for patients with unresectable locoregionally advanced cutaneous squamous cell carcinoma not suitable for surgery or radiotherapy.

Key point(s)

Patients with high-risk resected cutaneous squamous cell carcinoma should be encouraged to participate in clinical trials of adjuvant therapy including radiotherapy, chemotherapy and immunotherapy.

5.49.4.1 Notes on the recommendations

Overall the evidence for management of local-regional cSCC is of low quality.

Neck dissection followed by adjuvant radiotherapy has been advocated for patients with adverse features such as multiple involved nodes, extranodal extension or close/involved margins.[14][49] One series showed equivalent outcomes for elective neck node radiotherapy to 50–60Gy, and elective neck dissection followed by radiotherapy.[12]

Patients with resected cSCC who are most likely to benefit from adjuvant radiotherapy cannot be clearly identified based on current evidence. However, features may include:

- lesion size over 2cm
- tumour spread to local lymph nodes
- PNI affecting large nerves.

Lymph node recurrences in the axilla, epitrochlear or groin should be managed with surgery and adjuvant radiotherapy, although the risk of lymphoedema following axillary and groin dissection needs to be considered.[28]

Although low dose carboplatin given concurrently with adjuvant radiotherapy for resected nodal metastases did not improve outcome over radiotherapy alone in patients with high-risk cSCC of the head and neck in a RCT,[20] a non-randomised series in which patients with high-risk cSCC received platinum-based chemotherapy reported an apparent improvement in risk of local relapse, compared with radiotherapy alone.[22] In this study, most patients received cisplatin (n=24) rather than carboplatin (n=10), and mostly at a relatively high dose.[22]

Patients with unresectable local disease can be considered for radiotherapy (platinum-based chemoradiation, if the patient is fit for chemotherapy).[47]

The EGFR agents cetuximab[17][19] and gefitinib[25] have been reported effective in palliative treatment for patients with unresectable or metastatic cSCC. Cetuximab is registered for use in metastatic or locally recurrent SCC of the head and neck but use at other anatomical sites, or use of oral EGFR inhibitors would be off label.

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- Systemic therapies for advanced and metastatic basal cell carcinoma
- Metastatic disease and systemic therapies – Health system implications and discussion

5.49.5 Appendices

	Evidence statement form	Systematic review report
PICO question MS1	MS1	MS1

5.49.6 References

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5.50 12.3 Health system implications and discussion

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5.50.1 Health system implications

5.50.1.1 Clinical practice

The optimal use of targeted therapy and combination therapies may require greater collaboration and coordination between surgeons, radiation oncologists, dermatologists and medical oncologists and GPs, including more shared decision making.

Implementation of the recommendations will not otherwise result in changes to the way that care is currently organised.

5.50.1.2 Resourcing

Implementation of the recommendations for review and assessment by multidisciplinary teams with experience in managing advanced keratinocyte cancers (KCs) would require adequate funding to ensure equitable access for patients in rural and remote regions.

Increased use of hedgehog signalling pathway inhibitors (HPIs) would result in high per-patient costs to the Pharmaceutical Benefits Scheme (PBS) for a very small proportion of patients with KCs.

5.50.1.3 Barriers to implementation

Checkpoint inhibitor therapy is not currently funded in Australia by the PBS, although the agents are available for use if patients are able to self-fund or if alternative funding mechanisms can be provided.

Better access to multidisciplinary clinics and clinical trials is likely to improve patient outcomes.

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5.50.2 Discussion

5.50.2.1 Unresolved issues

The roles of chemotherapy in the management of advanced KC have not been defined. More evidence is needed to determine its efficacy in combination with surgery or radiotherapy (RT), as definitive treatment, as adjuvant treatment in combination with RT, or alone after surgery in patients with cutaneous squamous cell carcinoma (cSCC) who are not eligible for further RT.

Research into novel therapies and strategies for managing immune suppressed patients should be a priority. Sentinel node biopsy is a new technique already used in the management of melanoma and breast cancer, which may be applicable also in high-risk cutaneous cSCC.

A proportion of patients experience potentially fatal relapse of cSCC after surgical resection and adjuvant RT for locoregional recurrence following initial treatment. Better strategies and protocols for identifying these patients are needed.

Current studies are exploring the addition of immunotherapy to adjuvant RT to improve outcomes for patients with high-risk cSCC or BCC.

Clinical experience of new therapies in patients with chronic lymphocytic leukaemia and other haematologic malignancies, outside the context of clinical trials, may inform the management of advanced cSCC.

5.50.2.2 Studies currently underway

The following relevant clinical trials are underway:

- Radiotherapy with avelumab in unresectable cSCC – a phase II study of immune stimulation with pembrolizumab and radiotherapy in patients with unresectable cutaneous squamous cell carcinoma.[1]
- PD-1 in Patients With Advanced Basal Cell Carcinoma Who Experienced Progression of Disease on patients with advanced basal cell carcinoma who experienced progression of disease on hedgehog pathway inhibitor therapy, or were intolerant of prior hedgehog pathway inhibitor therapy – a study of cemiplimab after tumour progression on, or intolerance to, hedgehog signalling pathway inhibitor therapy in patients with locally advanced or metastatic basal cell carcinoma.[2]
- Direct local injection of talimogene laherparepvec into refractory KCs combined with nivolumab immunotherapy.[3]

The following clinical trial has been proposed:

- checkpoint inhibitors in addition to radiotherapy, compared with RT alone, as adjuvant treatment for high-risk resected SCC (including in patients with lymph node involvement) – Trans Tasman Radiation Oncology Group (TROG).

5.50.2.3 Future research priorities

Research priorities for the management of BCC include:

- developing topical formulations of HPIs for the treatment of locally advanced KC, with the goal of minimising systemic exposure and therefore minimising systemic side effects
- evaluating the combination of HPIs with RT evaluating the cost effectiveness and patient experience of pre-operative HPI therapy
- evaluating the combination of HPIs with immunotherapy in patients with metastatic disease.

Research priorities for the management of cSCC include:

- the role of checkpoint inhibitor immunotherapy as an adjuvant treatment following surgery, either alone or in combination with RT
- combining other types of immunotherapy (such as interleukin-2) or chemotherapy with checkpoint inhibitors

- improving the ability to identify patients with resected cSCC who are at high or low risk of recurrence or local metastases.

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- Systemic therapies for advanced and metastatic basal cell carcinoma
- Systemic therapies for metastatic cutaneous squamous cell carcinoma

5.50.3 References

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6 13. Follow-up

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6.1 Background

There are three reasons to undertake follow-up for patients who have been treated for keratinocyte cancer (KC):

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

Several studies have reported the higher incidence of subsequent KC following an index case.[1][2]

The frequency and duration of review for patients who have undergone treatment for a KC will be determined by the location of the original lesion, the original histopathology findings, the histological margin of the original lesion, the method of treatment of the original lesion and the number of previous KCs.

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. Visual examination (both with and without magnification) should be followed by appropriate physical examination, where needed, for signs such as induration and tenderness.

There is a lack of evidence to guide recommendations on follow-up after treatment for KC. No study has assessed the possible benefit from regular medical review for patients who have been treated for KCs, compared with observation by the patients themselves.

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6.2 Overview of evidence (non-systematic literature review)

Lesion-related factors associated with higher risk of recurrence include certain subtypes and sites (Table 5).[3]

Table 5. Tumour-specific factors associated with recurrence of keratinocyte cancers

Tumour type	Normal risk	High risk
Basal cell carcinoma	Nodular subtype Nodulocystic subtype Superficial subtype Fibroepithelioma subtype	Infiltrative subtype Sclerosing (morphoeic) subtype Micronodular subtype Basosquamous carcinoma Recurrence
	In situ subtype	Poorly differentiated subtype Adenosquamous subtype

Cutaneous squamous cell carcinoma	Well-differentiated subtype Moderately well-differentiated subtype Location on area other than head and neck	Spindle cell subtype Increasing thickness of the primary tumour Location on the head and neck especially the lip, ear and genitalia Origin in a burn scar Recurrence

6.2.1 Recurrence of basal cell carcinoma

Approximately 44% of people will develop a second basal cell carcinoma (BCC) within 3 years of a BCC excision.[1] This represents a 10-fold increase, compared with the general population.

Local recurrence is rare (<2%)[2] after histological clearance, with most local recurrences occurring within 2 to 3 years, but up to 20% may occur within 5–10 years.

Regional recurrence is extremely rare. Clinical assessment for regional recurrence is unnecessary, except in those with significant immunosuppression or genetic syndromes associated with increased risk of metastases.

6.2.2 Recurrence of cutaneous squamous cell carcinoma

Overall, the 3-year cumulative risk of a subsequent cutaneous squamous cell carcinoma (cSCC) after an index cSCC is 18%; at least a 10-fold increase in incidence, compared with the incidence of first tumours in a comparable general population.[1]

Local recurrence is uncommon after wide excision, but the risk of recurrence increased in the presence of risk factors including certain anatomical sites, certain subtypes, and perineural invasion (PNI), for a tumour in a previously treated site, and for a recurrent lesion (versus primary lesion) (see: Surgical treatment).[1] Most local recurrences occur within 2–3 years.

Regional recurrence is uncommon and usually occurs in patients with risk factors for local recurrence (including tumour sites of lip, ear or genitalia) and in certain groups. Recurrence is usually within 2 years.

A systematic review and meta-analysis of 36 studies (17,248 patients with 23,421 cSCCs) of low-to-moderate quality identified the following risk factors for recurrence of cSCC, in descending order of risk ratio (RR):[3]

- Breslow thickness >2mm (RR 9.64; 95% confidence interval [CI] 1.30–71.52)
- invasion beyond subcutaneous fat (RR 7.61; 95% CI, 4.17–13.88)
- Breslow thickness >6mm (RR 7.13; 95% CI 3.04–16.72)
- PNI (RR 4.30; 95% CI 2.80–6.60)
- diameter >20mm (RR 3.22; 95% CI 1.91–5.45)
- location on the temple (RR 3.20; 95% CI 1.12–9.15)
- poor differentiation (RR 2.66; 95% CI, 1.72–4.14).

Risk factors for metastasis were:[3]

- invasion beyond subcutaneous fat (RR 11.21; 95% CI 3.59–34.97)
- Breslow thickness >2mm (RR 10.76; 95% CI, 2.55–45.31)
- Breslow thickness >6mm (RR 6.93; 95% CI, 4.02–11.94)
- diameter >20mm (RR 6.15; 95% CI, 3.56–10.65)
- poor differentiation (RR 4.98; 95% CI 3.30–7.49)
- PNI (RR 2.95; 95% CI 2.31–3.75)
- immunosuppression (RR 1.59; 95% CI 1.07–2.37)
- location on the temple (RR 2.82; 95% CI 1.72–4.63)
- location on the ear (RR 2.33; 95% CI 1.67–3.23)
- location on the lip (RR, 2.28; 95% CI 1.54–3.37).

Risk factors for cancer-specific death were:[3]

- diameter >20mm (RR 19.10; 95% CI 5.80–62.95)
- poor differentiation (RR 5.65; 95% CI 1.76–18.20)
- location on the ear (RR 4.67; 95% CI, 1.28–17.12)
- location on the lip (RR, 4.55; 95% CI 1.41–14.69)
- invasion beyond subcutaneous fat (RR 4.49; 95% CI 2.05–9.82)
- PNI (RR 4.06; 95% CI 3.10–5.32).

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6.3 Follow-up

Following treatment of a primary KC or related 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, any signs or symptoms they should look for, and when medical assessment is needed.

In addition, patients should be advised about prevention strategies (e.g. ultraviolet radiation protection strategies and chemoprevention, including nicotinamide for patients with multiple previous KCs), and Vitamin D intake (see: Prevention of keratinocyte cancer [UV protection strategies, chemoprevention and vitamin D]).

It is appropriate for specialists to return patients to their referring general practitioner (GP) for ongoing care when their treatment is complete. The time of return will depend on the individual's lesion, type of treatment, and on agreement between the specialist and the referring GP.

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6.4 Future research

As more information about testing for specific genetic markers in KC becomes available, affected patients with genetic markers may require specific, yet unknown, follow-up regimes.

6.5 Practice Points

Practice point

PP 13.1.1. For patients who have undergone non-surgical treatments, where histological evidence of clearance is not available, planned regular follow-up (not just reassessment prompted by clinical need) should be provided for up to 3 years. Examination includes a full skin check for new lesions as well as inspection of the site of the original lesion.

Practice point

PP 13.1.2. For patients with cutaneous squamous cell carcinoma that is moderately to poorly differentiated or occurs on the lip or ear, initial follow-up should be conducted at 3 months and then every 6 months. It should always include examination of the draining lymph node basin.

Key point(s)

- For patients with histological clearance of primary keratinocyte cancers and low-risk tumours, such as basal cell carcinomas and well-differentiated cutaneous squamous cell carcinomas, no specific evidence-based follow-up scheme is recommended.
- All patients with a previous skin cancer should be 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.
- Patients should be offered counselling about their risk for further primary tumours, local persistence of their previous primary tumour and for metastatic disease.

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6.6 Health system implications

6.6.1 Clinical practice

Implementation of the guidance on follow-up of KC would not alter current clinical practice.

6.6.2 Resourcing

Performing effective skin examinations, including dermatoscopy, requires adequate training and experience (see: The role of primary care in the prevention and management of keratinocyte cancer). In primary care, primary care nurses can undertake patient education about protection from UV radiation.

6.6.3 Barriers to implementation

No barriers to the implementation of this guidance are envisaged.

6.7 Discussion

6.7.1 Unresolved issues

Unlike for some other cancer types, there are no standardised protocols for surveillance (including monitoring strategies and intervals) after treatment of KC.

6.7.2 Studies currently underway

None.

6.7.3 Future research priorities

As more information about testing for specific genetic markers in KC becomes available, affected patients with genetic markers may require specific, yet unknown, follow-up regimens. Combining evidence for all known predictors might enable clinicians to choose a tailored follow-up strategy taking that better matches an individual's absolute risk of recurrence or other adverse outcomes,

6.8 References

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7 14. The role of primary care

Contents

7.1 Introduction

Medicare payment statistics reveal that in 2018 almost 1,000,000 skin cancers were diagnosed and treated in Australia. The vast majority of these were for keratinocytic cancers (KCs).[1] With the large and increasing skin cancer burden that affects so many Australians,[2] it is imperative that all clinicians acquire the necessary knowledge and skills to diagnose skin cancer. The training in dermatology and skin cancer for medical students is variable, and some graduates will have received no training in skin examination and skin cancer diagnosis.[3] Accordingly, many doctors undertake postgraduate training in skin cancer and there are specific programs available to upskill in this area.[4][5]

Accessibility and affordability of medical services are important considerations for patients who have the need for skin cancer assessment, which may impact on early diagnosis. Primary care practitioners such as general practitioners (GPs) necessarily play a central role in the diagnosis and management of skin conditions.

Malignant skin neoplasms occur at an estimated rate of 1.1 per 100 encounters in a GP's caseload.[6] The central position of GPs within the Australian Health System accounts for the fact that they diagnose and manage most suspicious skin lesions in Australia.[7][8] GPs have been shown to achieve a relatively high accuracy in the clinical diagnosis of KCs,[9] and the use of dermatoscopy has been shown to improve the diagnostic accuracy for melanoma as well as KCs within a primary care skin cancer practice.[10]

Difficulty in managing KCs is 'due to atypical or unusual presentations as well as a poor understanding of their histological variants'.[11] In addition, there is evidence that among people with basal cell carcinoma (BCC) – at least in northern Australia – infiltrative and micronodular types, which are associated with a high risk of recurrence, occur more frequently on the face and neck, where the likelihood of incomplete excision is increased.[12] This finding highlights the importance of appropriate training and acquisition of skills for GPs.

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7.2 Whether to treat or refer

Treatment decisions are influenced by many factors, including the experience and skills of the doctor of first contact, geographical location, and local facilities, including the availability of radiotherapy services and other specialists such as surgeons and dermatologists.

The most appropriate practitioner to manage uncomplicated primary KCs is the adequately trained GP, who can readily remove most of them by an elliptical excision with an adequate margin and primary closure.[13]

Early presentation and diagnosis facilitate implementation of the recommendations in the guideline . The more experience that the GP acquires, largely from hands-on treatment, the better the management process. There is a wide variation in skills, training and confidence among GPs, with some (particularly rural GPs or those with surgical training) possessing skills to manage more complex skin tumours.

GPs should also be aware of the variety of treatment modalities for KCs, including surgical excision, cryotherapy, curettage, topical therapies, photodynamic therapy and radiotherapy. Each management decision should be tailored to the particular lesion in that particular patient. Generally, however, simple surgical excision with direct closure is the treatment of choice for most skin cancers.

The treating GP should have an adequately equipped treatment room with good lighting and sterile instruments. GPs should be prepared to excise many tumours at first contact, which is both beneficial for the patient and cost-effective for the health system. They should also be skilled to perform basic skin biopsy techniques (punch and shave) to establish a diagnosis where appropriate when KC is suspected.

A review of Medicare data on services provided for excision of skin tumours reveals that, along with dermatologists and plastic surgeons, Australian GPs excise a substantial proportion of these lesions on the face and body; not just tumours less than 10mm diameter, but also including those 10–20mm. A 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.[14]

The actual decision to refer for specialist management can be difficult.[15] 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 are being contemplated.

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7.3 Tumours requiring experience and care

GPs managing KCs need to be aware of:

- the required excision margins for each tumour presentation (see: Surgical treatment)
- tumour-specific factors associated with recurrence of keratinocyte cancers (Table 5)
- the pitfalls of surgical excision at certain anatomical sites
- other risk factors for poor outcomes (see: Prognosis).

Anatomical sites associated with increased risk for poor outcomes include:[11][15]

- the face – risk of poor cosmetic result and potential nerve damage (e.g. temporal branch of facial nerve)
- the lips – high risk of metastasis of cutaneous squamous cell carcinomas (cSCCs)
- helix of the ear – high risk of metastasis of cSCCs
- the eyelids
- the inner canthus of the eye with close proximity to the nasolacrimal duct
- mid-sternomastoid muscle area (Erb's Point) where the accessory nerve is superficial
- fingers – risk of functional impairment
- lower leg – potential for poor healing.

Table 5. Tumour-specific factors associated with recurrence of keratinocyte cancers

Tumour type	Normal risk	High risk
Basal cell carcinoma	Nodular subtype Nodulocystic subtype Superficial subtype Fibroepithelioma subtype	Infiltrative subtype Sclerosing (morphoeic) subtype Micronodular subtype Basosquamous carcinoma Recurrence
Cutaneous squamous cell carcinoma	In situ subtype Well-differentiated subtype Moderately well-differentiated subtype Location on area other than head and neck	Poorly differentiated subtype Adenosquamous subtype Spindle cell subtype Increasing thickness of the primary tumour Location on the head and neck (especially the lip and ear) or genitalia Origin in a burn scar Recurrence

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7.4 Indications for referral

For specific lesions, it is appropriate to refer to a dermatologist or surgeon, even when the GP is experienced in managing KCs. In many instances it is reassuring for both the patient and their GP to refer a technically difficult problem to an experienced specialist colleague.

GPs should consider referral when any of the following are present or apply:

- uncertainty of diagnosis
- any doubts about appropriate treatment
- larger tumours (BCCs or cSCCs >2cm diameter or cSCC >6mm deep)
- multiple tumours
- tumours in technically difficult sites (e.g. ear, tip of nose or eyelid)
- tumour recurrence despite appropriate treatment
- incomplete excision, (especially when complete excision may be difficult)
- tumours for which the recommended treatment is beyond the skills of the practitioner
- anticipation of difficulty with technique or anatomy (an appropriate colleague should be consulted)
- cSCCs on the lips and ears
- infiltrating or sclerosing (morphoeic) BCCs (particularly those on the nose or around the nasolabial fold, where it may be difficult to determine tumour extent and depth)
- cosmetic concerns (e.g. lesions of the upper chest and upper arms, where keloid scarring is a potential problem)
- cSCC accompanied by palpable regional lymph nodes in head and neck, axilla or groin, suggestive of metastatic spread
- large lesions which may require complicated methods of closure such as grafts and flaps, when the GP is inexperienced in these techniques
- GP unavailable for regular follow-up, especially for a SCC.

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7.5 Follow-up

All patients treated for KCs, 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.

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7.6 Opportunistic surveillance and case-finding

Examination for skin cancer 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 occur on the trunk and limbs. Accordingly, a total-body skin examination is appropriate for many patients, not only in those identified as being at greater risk due to family history, individual medical history (e.g. immunosuppression or past KCs) and skin type (see: Early detection). Such an examination may be a feature of the annual check-up[16] but is recommended in those with previous KCs and immunosuppression.

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7.7 Education of GPs

The curriculum of all university medical schools should encompass the foundations of knowledge and diagnostic skills in dermatology and skin cancer, including the use of dermoscopy.

General practitioners are at the forefront of screening and diagnosis of skin cancer in Australia. Formal postgraduate education and training in this area of their practice, including the proficient use of dermoscopy, is essential. Clinicians should seek a formal qualification and training through universities and, medical colleges or other accredited educational organisations that offer postgraduate courses in dermoscopy. These skills should be assessable within postgraduate training programs.

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7.8 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. One strategy is to place wall charts and patient education material in the waiting room, as well as providing opportunistic education of patients through preventive advice.

A clear explanation of the tumour, the management plan and the reason for any referral is simple, good and sensible medical care.

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7.9 Practice Point

Practice point
PP 14.1.1. Uncomplicated small tumours should be removed by an elliptical excision and direct closure.

Key point(s)
■ GPs should use caution when managing keratinocyte cancers on the head and neck. ■ GPs should be aware of indications for referral of patients for management of keratinocyte cancers. ■ Total body skin examination could be considered opportunistically in many patients, particularly those with Fitzpatrick skin types 1–3 skin and those with significant sun exposure. ■ GPs should offer all patients regular skin examinations according to their level of risk for keratinocyte cancers, assessed based on the individual's skin type, signs and history of ultraviolet exposure, and other risk factors such as history of keratinocyte cancers or immunosuppression.

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8 15. Economics of keratinocyte cancer

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8.1 Background

Keratinocyte cancers (KCs) are the most common malignant neoplasms in Australia and consequently they exert a large burden on the Australian health system. Although keratinocyte cancer is not notifiable to cancer registries and the precise incidence is unknown, incidence is estimated at 1531 per 100,000 person-years, based on data from recent national Medicare claims.[1]

Since 7% of Australian adults can be expected to have at least one skin cancer excised during a 3-year period,[1] the burden on health services is substantial. Keratinocyte cancers are likely to have the highest costs of all cancers in Australia due to their high incidence rather than high cost per case.[2] As most KCs are treated in general practice and have low mortality potential, they are sometimes viewed as inconsequential. However, overall morbidity of KCs is considerable. Many individuals have multiple KCs and there were 115,237 hospital separations for keratinocyte cancers recorded in 2016–2017.[3]

Although virtually all KCs are amenable to cure, 642 deaths due to KC were recorded in 2015.[4] Keratinocyte cancers accounted for 2.8% of non-fatal cancer burden as measured by years lived with disability.[5] In addition to the burden on the health system, KCs are also associated with costs for patients, including out-of-pocket medical expenses and the costs of prevention.

Through Medicare, the Australian Government pays for a large majority of services and medicines listed on the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Schedule (PBS). Skin cancer treatments undertaken in public hospital as inpatient or outpatient care are paid by state governments at no cost to public patients. For skin cancer diagnosis and treatment in Australia, most services and medications are provided through Medicare (Table 10.1) either by general practitioners (GPs) in primary care or by specialists (i.e., dermatologists, plastic surgeons) in private practices.

Except where otherwise indicated, MBS item numbers and fees, and PBS codes and listings, are cited as at November 2017.[6][7]

Just as the incidence data for KCs are not routinely collected, their associated costs are not routinely recorded and are difficult to estimate.

Table 10.1. Medicare reimbursement for keratinocyte cancer services

Medical service	MBS item number or PBS code#	Medicare item fee (AUD)	Approximate % lesions by treatment modality
First visit GP (up to 20 minutes)	23	$37.60	-
First visit specialist	104	$86.85	-
Biopsy	30071	$52.20	-
Pathology – level 3 complexity	72816-72817	$86.35–96.80	
Excision – BCCc/SCC	31356-31369	$221.35–330.15	78–83%[1][6][7]
Cryotherapy	30202	$48.35	8–11%[1]
Curettage or diathermy	30196	$126.30	9–10%[1]
Cream - Imiquimod 5% (sachets or pump)[a]	PBS 2546B, 2637T, 4134N, 4559Y	$86.86 to $91.41	1.2%[6]
- 5-Fluorouracil (20g) Efudix[b]	PBS 4222F	$65.52	1.2%[6]
Radiotherapy – 1 field	15000	$42.55	0.25–0.63%[1]
- 2 or more fields up to 5	15003 (fee for each additional field)	$17.10	
Flap repairs	45200-45203, 45206	$284.35–413.95	0.01–1.63%[8]
Wedge excision	45665	$326.05	0.06%[8]
Graft	45445,45448	$376.00–555.60	0.16%[8]
Mohs micrographic surgery	31000-31002	$580.90–871.30	0.8%[6]
Follow-up visits GP	23	$37.60	-
Follow-up visits specialist	105	$43.65	-

BCC: basal cell carcinoma; cSCC: cutaneous squamous cell carcinoma; MBS: Medicare Benefits Schedule; PBS: Pharmaceutical Benefits Schedule

The list of Medicare codes is not exhaustive. MBS and PBS item numbers and costs as at November 2017.[6][7] [a]Available through the PBS and Repatriation PBS and for patients with biopsy-confirmed primary superficial BCC, previously untreated. Patients not meeting these criteria will face a private payment of up to $180.00. [b]Available through the Repatriation PBS (limited to Department of Veterans' Affairs beneficiaries holding a Repatriation Health Card or a Repatriation PBS card).

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8.2 Overview of evidence (non-systematic literature review)

8.2.1 Costs to the healthcare system

Fransen et al. (2012) estimated the total cost of KC to the Australian health system in 2015 would be $703.0 million (95% confidence interval [CI], $674.6 to 731.4 million).[8] These cost estimates include diagnosis, treatment and pathology services.

A recent Australian study on the Medicare costs associated with the treatment of skin cancer was published by Gordon et al. (2017)[9] using data from a large, prospective cohort study in Queensland. This is the first cost analysis for skin cancer that specifically examines the cost burden of multiply affected persons. In a 3-year period, over 50% of participants with KC had multiple KCs.[9]

Costs were heavily right-skewed and, as might be expected, increased linearly with greater numbers of skin cancers. The study aggregated the costs for all the skin cancer-related MBS and PBS items for 5134 participants with at least one primary excision for KC.[9] Participants were followed for an average of 3 years (range 1.7–3.7 years).

In total 47% had 1 cancer, 24% had 2, 10% had 3, 9% had 4 or 5 and 10% had more than 5 KCs (Table 10.2). The median government subsidy for keratinocyte cancers over three years was $369 for one cancer rising to $2126 for individuals with six or more cancers, with a maximum cost of $54,618.[9] In addition, costs for other benign skin lesion excisions added $70 to $202 median costs for those individuals in the high-frequency skin cancer groups over 3 years (Table 10.2).

Table 10.2. Medicare costs among individuals by frequency of incident skin cancers (2016 AU$)

	Number of keratinocyte skin cancers per person				
	1	**2**	**3**	**4–5**	**≥6**
Number of persons (%)	2424 (47%)	1231 (24%)	510 (10%)	481 (9%)	488 (10%)
Skin cancer 3-year costs* mean (SD)	$ 521 (487)	$ 784 (644)	$ 1157 (1022)	$ 1369 (949)	$ 2721 (3,083)

median (min, max)	369 (0, 5735)	624 (0, 9321)	946 (0, 13519)	1169 (161, 12978)	2126 (372, 54618)
Benign skin lesion 3-year costs* mean (SD) median (min, max)	$ 152 (240) 0 (0, 2014)	$ 191 (291) 70 (0, 2150)	$ 237 (320) 145 (0, 2982)	$ 245 (367) 134 (0, 8982)	$ 354 (558) 202 0, 6089)

SD: standard deviation

*Skin cancers refer to those histopathologically diagnosed and skin lesions refer to any benign lesion treated under the dedicated MBS codes for benign skin lesions. Source: Gordon et al. (2018)[9]

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Besides multiplicity, costs were higher for people with private health insurance, university education and retirement.[9] Consideration of the cost burden of KCs should also include the additional burden of benign lesions that are treated concurrently during skin examinations of persons with suspicious skin lesions.[9] In addition to costs incurred in primary care and specialist private practice estimated by MBS and PBS claims, economic burden of skin cancers borne by hospitals were substantial. In a study by Shih et al. (2017),[10] the costs of treating KCs during inpatient admissions to Victorian public hospitals were estimated at $29 million per annum. If combined with outpatient clinic attendances at the Victorian public hospitals for management of melanoma of the skin and KCs, the estimated costs increased to between $48 million and $56 million in 2012–2013 (Table 10.3).

Moving beyond the public hospital system, an additional $72 million were attributed to the private hospital admissions in Victoria. The estimated total costs between $121 million and $127 million per annum, based on available information, only partially presents the total burden of skin cancers on the hospital systems in the State of Victoria.[10]

Table 10.3: Estimated inpatient admission costs and outpatient clinic costs for the Victorian public hospital system 2012–2013

Inpatient admissions costs				
AR-DRG Code	**DRC description**	**Average cost per separation**	**Melanoma ($ million)**	**Keratinocyte cancers ($ million)**
J69A	Skin Malignancy with complications	$ 16,183	$ 4.25	
J69B	Skin Malignancy no complications	$ 10,137	$ 7.43	$ 29.05
	Skin Malignancy, same			

J69C	day	$ 805	$ 1.68	
Total			$ 13.36	$ 29.05
Outpatient clinic costs				
	Estimation for hospital	**Estimation for ICS**	**Estimation for Victorian public hospital system ($ million)**	
Hospital A	$ 533,000	$ 1,761,000	$ 10.12	
Hospital B	$ 557,000	$ 557,000	$ 6.90	
Hospital C	$ 2,386,000	$ 3,874,000	$ 13.32	

AR-DRG: Australian Refined Diagnosis Related Group classification system; ICS: integrated cancer service. Source: Shih et al. (2017)[10]

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8.2.2 Costs to patients

Out-of-pocket expenses are likely to be substantial in patients with multiple skin cancers over time (Table 10.4). 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 quickly[11] and may be particularly distressing for patients with several concurrent health conditions. In private practices, patients should be given written information about the expected out-of-pocket expenses for their treatment. This written information should be provided at the initial consultation with the clinician (GP or specialist), before starting treatment.

The overall bulk-billing rate for skin cancer reported by Gordon et al. (2017) for over 5000 patients was between 34% and 60%, depending on skin cancer frequency.[9] These rates were substantially lower than the GP bulk-billing rate reported for Australia overall (79–82%) during 2011–2014[12] and were also lower than the national KC bulk-billing rate (81%).[13] Participants with many skin cancers in this study were less likely to be bulk-billed compared with participants with only one or two skin cancers. Older persons and people with a university education have higher than average levels of private health insurance, and private health insurance is the strongest factor contributing to reportable Medicare out-of-pocket costs.[9]

However, the scope of the analyses did not capture all potential costs that may occur subsequent to the excision (e.g. dressings, antibiotics for infections) and were not recognised in Medicare data as relating to skin cancer treatment.[9] Also omitted were out-of-pocket expenses related to receiving care such as travel and parking expenses and income lost through interruptions to employment. These additional expenses may be high for patients treated on multiple occasions and those living long distances from treatment centres. Consequently, there are wider societal burdens to employers, partners and carers and the longer-term economic burden is likely to be substantial. Doran et al (2015) estimated total lifetime costs of skin cancer diagnosed in 2010 in

New South Wales at $536 million, of which 72% of total costs were direct costs and 28% were indirect costs.[14] KC accounted for 68% of the total skin cancer economic costs, $365 million.[14] Indirect costs, including productivity cost associated with morbidity and premature mortality using the human capital approach, were $131 million for melanoma and $18 million for KC.[14] Average lifetime cost based on this incidence-based estimate was $44,796 per melanoma and $2459 per KC.[14]

Table 10.4. Patient out-of-pocket costs among individuals by frequency of incident skin cancers (2016 AU$)

	Number of keratinocyte skin cancers per person				
	1	**2**	**3**	**4-5**	**≥6**
Number of persons, n (%)	2424 (47%)	1231 (24%)	510 (10%)	481 (9%)	488 (10%)
Skin cancer 3-year costs	$	$	$	$	$
Number (%) persons bulk billed*	1445 (60%)	675 (55%)	271 (53%)	272 (57%)	206 (42%)
mean (SD	407 (598)	545 (699)	598 (554)	739 (787)	1520 (1,698)
median (min, max)	197 (2, 7177)	336 (3, 8704)	475 (2, 2803)	502 (2, 5753)	1008 (5, 13673)
Benign lesion 3-year costs	$	$	$	$	$
Number % persons bulk billed*	1916 (79%)	943 (77%)	375 (74%)	348 (72%)	318 (65%)
mean (SD)	156 (203)	180 (219)	152 (175)	164 (178)	193 (251)
median (min, max)	86 (3, 2257)	88 (3, 1116)	92 (6, 1439)	105 (2, 1043)	104 5, 1966)

SD: standard deviation

*Bulk billed refers to patients having zero out-of-pocket costs and services are fully covered by Medicare Australia. Source: Gordon et al. (2018)[9]

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8.2.3 New treatments for keratinocyte cancers

Vismodegib (Erivedge) is listed on the PBS for the treatment of metastatic or locally advanced basal cell carcinoma, for which neither surgery nor curative radiotherapy is appropriate.[7] It is administered in 150mg capsules, 28 per pack for a course of treatment. An estimated 113 Australians per year now have access to vismodegib at $39.50 per month, which would otherwise cost $7450 for a course of treatment.[15]

Sonidegib (Odomzo) is also listed on the PBS for metastatic or locally advanced basal cell carcinoma for which neither surgery nor curative radiotherapy is appropriate.[7] It is administered in 200mg capsules, 30 per pack for a course of treatment at $39.50 per month for patients, and a cost of $7971 for a course of treatment to government.

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8.2.4 Investment in skin cancer prevention

Skin cancer prevention programs have great potential to reduce healthcare expenditure but there has been no national spending on prevention of skin cancer for over a decade since the first national skin cancer campaigns between 2006 and 2008. In 2017, Shih et al[16] reported that for an additional $AUD 0.16 ($USD 0.12) per capita investment in future skin cancer prevention across Australia, 140,000 skin cancer cases would be prevented over a 20 year period between 2011 and 2030. Return on investment of skin cancer prevention, from the government perspective, is remarkable. Strong economic credentials of skin cancer prevention have been reported.[16][17][18][19] In Australia, for every dollar spent in the skin cancer prevention programs/campaigns, there was $3.20[16] and $3.85[18] in return by averting cancers and savings in future healthcare and societal costs.

Solarium legislation began in Victoria in 2007, which limited the use of people aged under 18 or with very fair skin (skin type 1). The following years saw the other states also introduce age limits; however, compliance with the regulations were poor. From 2012, laws have now passed in all states banning commercial solarium businesses. This was underpinned by campaigning of health organisations including Cancer Council Victoria, Australian Medical Association, Skin & Cancer Foundation Inc., and the Australasian College of Dermatologists. Australia is one of two countries in the world (the other being Brazil) with an outright ban. The prevalence of sunbed use in the previous year among adults was less than 1% in 2016–2017.[20] However, recent media reports have uncovered a black market of illegal solariums, and tanning beds may still legally be purchased and used for private use in peoples' own homes.

In 2015, a systematic review synthesised evidence from 11 studies reporting on the cost-effectiveness of skin cancer prevention programs.[21] These included four secondary prevention (or screening) studies and seven primary prevention studies. Primary prevention programs or policies were consistently cost-effective or cost-saving for governments, while screening was favourable in certain targeted scenarios only.[21] The primary prevention programs were heterogeneous ranging from sun protection promotion to solarium regulation and school-based education initiatives. However, the quality of the economic analyses were good, the analytical approaches sound, transparent, comprehensive and the model inputs based on best available epidemiological data.[21]

Seven additional economic studies involving KCs and melanomas have been published since the 2015 review,[10][16][18][11][22][23][24] three studies on primary prevention[10][16][23] and three on screening/surveillance[11][22][24] with five being Australian.[10][16][18][11][22]

The primary prevention studies showed strong economic benefits expected with SunSmart (or equivalent program) investments and sunbed regulation.[10][16][23]

Shih et al. (2017) predicted net social benefits of $1.43 billion over a 20-year period[16] for Australia including direct health system and indirect productivity gains while Pil et al. (2016) estimated returns on investment of €3.6 for €1 invested in primary prevention initiatives in Belgium.[23]

For secondary prevention, a Queensland-based skin awareness intervention for men over 50 years would be more expensive, and potentially worsen quality of life as more in situ melanomas and KCs would not outweigh the benefits of the awareness program.[11] However, in high-risk individuals with a past history of melanoma, an intensive skin surveillance program was cost-effective as melanomas were diagnosed earlier, less extensive treatment was needed and importantly, there was a lower excision rate for suspicious lesions.[22] Finally, including KCs in their analyses, a Belgian study concluded that melanoma diagnosis by dermatologists adequately trained in dermoscopy resulted in both a gain of quality-adjusted life years (less morbidity and/or mortality) and a reduction in costs.[24]

Key point(s)

To encourage patients to seek medical attention for any suspicious skin lesions without delay, clinicians should consider whether patients' out-of-pocket healthcare costs are a barrier to assessment and treatment and consider strategies for minimising these, especially for patients returning for multiple skin cancer treatments.

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8.3 Discussion

8.3.1 Future research priorities

Sun protection strategies reduce skin cancers, but most benefits accrue in the future. Conversely, while early detection strategies detect thinner melanomas, it can lead to over-treatment and attendant high costs. On economic grounds there is good evidence that favours primary prevention efforts[25][26][27][28][29][30][31] and some also favour melanoma screening[25][27][29] but the two strategies have never been compared against each other for their relative cost-effectiveness.

Further research is necessary to provide information on the priority for government investment in skin cancer prevention. In addition, further studies will be beneficial on the value of interventions that assist in identifying and/or screening targeted populations for their high burden of multiple KCs.

Consistent and sustained prevention measures over an extended period are the key elements of skin cancer prevention to lessen the huge economic burden in Australia. It has been well-documented that sun protection behaviours can be influenced by mass media campaigns and education programs. Evidence also shows that sun protection behaviours change and sunburn incidence decreases during skin cancer prevention campaigns.[32] A sustained and intensive sun protection program is warranted to maintain the prevention benefits.

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9 16. Common concerns raised by patients

9.1 Background

Patients want considered answers to their questions, involvement in the process of making decisions about their health care, appropriate referral (particularly where the practitioner lacks expertise) and continuity of care. They expect to be treated with respect, kindness and patience.

When deciding on treatment for a keratinocyte cancer (KC) or related lesion, clinicians should discuss with patients the intent of treatment, suitable treatment options, and the risks and benefits of each option, including the likely outcomes and side effects.

This section addresses questions and objections that may arise during the skin cancer consultation and provides guidance for practitioners as to how these might be handled.

Common questions include:

- I am worried about this spot, Doctor – could it be skin cancer?
- What should I look for when I check myself for possible skin cancer?
- Does my tattoo protect me from skin cancer?
- How often should I have a full skin check?
- At what age should my child have a skin check?
- Am I at less risk of developing skin cancer because I tan easily/have a tan?
- I never even go out in the sun, so why have I developed skin cancer?
- Why should I have a biopsy? Why not just cut it out?
- What does the subtyping of my basal cell carcinoma mean?
- My pathology report says there is perineural invasion (PNI) associated with my skin cancer. What does this mean?
- Have we got it all or could the skin cancer to come back?

Patients' beliefs and preferences about skin cancer prevention and treatment also commonly include the following:

- I don't use sunscreen because it feels unpleasant/causes low vitamin D/contains dangerous nanoparticles.
- It's too late for sunscreen: the damage is already done!
- I'm planning to use black salve (e.g. Cansema) for my skin cancer.

Each patient is different, of course. How you answer their queries may depend on multiple factors including likely adherence to treatment or management advice and the person's underlying fears and concerns, as well as individual risk factors.

Great care should always be taken to protect privacy and confidentiality. Where appropriate, involvement of family and friends may be prudent. For some patients, the involvement of a medical interpreter should be considered.

It may also be helpful to refer patients to available support services in the community, which can be accessed via Cancer Council Australia.

The Cancer Australia-endorsed Optimal care pathway for people with basal cell carcinoma or squamous cell carcinoma may also be a useful reference for patients with KCs.

Written information addressing a concern or treatment protocol should be given, where available.

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9.2 I am worried about this spot, Doctor – could it be skin cancer?

If your patient raises concern about a skin lesion, it should be given special attention. Anecdotally, many patients can relate stories of friends or family having been reassured, sometimes with fatal consequences, when showing their doctor a skin cancer. It is important to have a high index of suspicion for malignancy to avoid missing a skin cancer that the patient has flagged.

It is prudent to take a careful history documenting why the patient is worried about the lesion, how long it has been there and how it has changed since first noticed. A lesion that has only been present for a week or so is more likely to be inflammatory. As such, simply covering it to avoid trauma and irritation for a few days may be all that is needed.

Histology is warranted in the following scenarios:

- The lesion has changed over a period of weeks or months.
- The lesion has bled repeatedly with minor trauma such as towelling off.
- The lesion is painful when knocked or touched.
- A sore has failed to heal fully within 6 weeks.

With sufficient training, examination of the lesion with a dermatoscope may greatly assist in reaching a clinical diagnosis.

Regardless of how it looks macroscopically or dermoscopically, however, a new or evolving firm, raised lesion must always be excised, rather than monitored, because of the possibility of nodular melanoma (see: Clinical practice guidelines for the diagnosis and management of melanoma).[1]

You may choose to do a biopsy rather than excision. However, if there is a possibility of melanoma, complete excision or incisional biopsy (including lesion/normal skin interphase) is paramount to help ensure accurate diagnosis.[1] Almost 1 in 4 melanomas are missed on partial punch biopsy.[2]

The differential diagnosis for a pink macule includes superficial multifocal basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC) in situ, dermatitis and amelanotic melanoma. Always read the punch biopsy histology report very carefully, even where a benign diagnosis is given; if there are melanocytes within the biopsied pink lesion you should precede to full excision because of the possibility of a misdiagnosed melanoma.

If you decide to ask the patient to return for follow-up of the lesion, rather than perform biopsy or excision, it is important to document this clearly and to add your patient to the practice recall system so they can be contacted if they fail to attend for review. It may be prudent to leave sequential digital imaging to colleagues who are experienced in skin cancer diagnosis and dermoscopy, since the focal changes seen in early melanoma at dermoscopy follow-up can be quite subtle.

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9.3 What should I look for when I check myself for possible skin cancer?

Many patients want to be aware of how skin cancers present macroscopically so they can attend early for treatment if necessary. Self-monitoring should not replace a full skin check, particularly in higher risk patients.

Medical review of a lesion is warranted if a lesion:

- has changed in size, colour or shape over a period of weeks or months
- is new and stands out from the others ('ugly duckling')
- is painful to touch or pressure
- has bled easily (e.g. on drying off with a towel)
- is a sore that has failed to heal completely over a few weeks

9.4 Does my tattoo protect me from skin cancer?

Some patients believe that tattoo ink can protect the underlying skin from sunburn. It is worth exploring this misconception with your patient explaining that tattooed skin needs the same protection with sunscreen and clothing as skin elsewhere; the pigment injected into a patient's skin does not protect it from damage caused by exposure to ultraviolet (UV) radiation. Additionally it can be helpful to point out that tattoos may mask new and established skin lesions, making it harder to diagnose a skin cancer early.

9.5 How often should I have a full skin check?

The individual's skin cancer risk must be carefully weighed up before answering this question.

Factors to take into account include:

- the number and seriousness of previous skin cancers
- age
- Fitzpatrick skin type
- recreational sun habits
- work-related sun exposure
- frequency of sunscreen use
- visible active sun damage
- immune status.

For those at low risk of skin cancer, annual skin checks may be a waste of valuable resources. Conversely, for those at the highest risk of skin cancer, regular skin checks will assist with early diagnosis, thereby reducing associated morbidity and the need for complex intervention.

For example, you might advise a skin check at 5-year intervals for a 22-year old indoor worker who has never had a previous skin cancer and is aware of and uses sun protection. On the other hand, a 6-monthly skin check may be prudent for a 60-year old outdoor worker who has already had 20 or more invasive skin cancers.

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9.6 At what age should my child have a skin check?

In children, a skin check is extremely unlikely to reveal skin cancer. However, diligent parents may nonetheless wish to have concrete reassurance and this medical visit can be used to reinforce the message to both parents and children of the importance of sun avoidance and protection during the child's most vulnerable sun-exposure years.

Adults who have been habitually exposed to Australia's high UV index in childhood are much more likely to develop skin cancer than those who spent their early years at latitudes with lower UV indices likely to develop skin cancer than those who spent their early years at latitudes with lower UV indices (see: Epidemiology).

See also: Strategies for protection from excessive exposure to ultraviolet radiation

9.7 Am I at less risk of developing skin cancer because I tan easily/have a tan?

There is no such thing as a healthy suntan. Developing a suntan should be avoided regardless of Fitzpatrick skin type.

It is certainly true that someone with Fitzpatrick type 1 skin is at greater risk of developing KC than someone with Fitzpatrick 3 skin after the same amount of sun exposure. Having a tan, however, is no protection from developing skin cancer, regardless of Fitzpatrick skin type.

9.8 I never even go out in the sun, so why have I developed skin cancer?

It is a common myth that skin cancers will only develop after erythematous or blistering sun burn. As the UV index is so high for much of the day throughout the year in Australia and New Zealand, intermittent cumulative, chronic low-grade sun exposure can also cause skin cancer.[3][4]

The Bureau of Meteorology and the SunSmart app provide up-to-date information on the UV index and sun protection times across Australia.

It may be worthwhile inviting your patient to closely observe sun damage on others. Actinic keratosis (AK) and skin cancer are seen much more frequently on the right forearm, dorsum of the hand, temple and cheek than the left on account of low grade sun exposure through glass with everyday driving.

Skin cancers may also occur on relatively covered areas of the body because of inadequate sun protection factor (SPF) afforded by clothing, especially when people habitually wear lighter-coloured or thinner materials.

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9.9 Why should I have a biopsy? Why not just cut it out?

It is understandable that many patients might prefer to go straight to excision rather than agreeing to the expense and time commitment of an intervening biopsy.

You should carefully explain (and document) why you wish to do a biopsy so your patient is able to give informed consent or dissent.

Biopsy is usually done for a suspected KC for one of the following reasons:

- You are uncertain that surgery is actually warranted and a biopsy is much less invasive, faster and cheaper than an unnecessary complete excision.
- You know it is a skin cancer but want more information about the aggressiveness or depth of the tumour to help guide you with ideal excision margins.
- Establishing the diagnosis before referring the patient for surgery will inform triage, so the patient will be seen faster if it is warranted.

9.10 What does the subtyping of my basal cell carcinoma mean?

Subtyping of BCC is important for ongoing management of the patient and deciding on optimal clinical excision margins.

It may be helpful to refer patients to available patient information, which can be accessed via Cancer Council Australia.

9.11 My pathology report says there is perineural invasion (PNI) associated with my skin cancer. What does this mean?

Perineural invasion means that the tumour has invaded into a nerve. This finding is of particular concern on the head and neck, especially if the tumour is closer to a cranial nerve foramen. Keratinocyte cancers are able to spread further from the tumour body following PNI as the nerve affords much less resistance to tumour growth than dermis.

When PNI is reported, further discussion with the histopathologist may be helpful to ascertain whether this was seen within or beyond the tumour body and, if the latter, how close to the free margin it was. In most cases of PNI, a wider and deeper excision will be required. If you are not comfortable to do the wider excision, explain to the patient that referral to a surgeon will be required.

If PNI is associated with a KC on the head and neck an expert opinion regarding the need for radiation therapy following the wider excision should be sought. This is particularly important if it involves a nerve greater than 0.1 mm in diameter or multiple smaller nerves. Additionally, if your patient is immunocompromised, early referral is imperative.

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9.12 Have we got it all or could the skin cancer to come back?

Even with reported ‘clear’ histological margins it is important for patients to realise that tumour recurrence is possible, so they can be vigilant of any change within or close to their excision scar.

It is helpful to ask your pathologist to routinely provide you with actual histological clearance margins in millimetres for KC, so you can judge yourself whether a wider excision may in fact be warranted.

Whether the KC margins are adequate is often an educated guess on the part of the treating doctor that will be made in light of the following information (see: Prognosis):

- tumour margin in millimetres provided by the histopathologist
- histological subtype in the case of a BCC
- the degree of differentiation in the case of a cSCC
- presence of associated perineural invasion
- size, depth and anatomical site of the tumour
- whether the patient is immunocompromised.
- whether the tumour is recurrent.

See: Table 4.1 in Prognosis of BCC and Table 4.3 Prognosis of cSCC.

If you judge that a wider excision or a second opinion is warranted, explanation (with the use of a descriptive diagram) of how their specimen has been assessed in the laboratory is often helpful for your patient. Explain that the specimen is cut into three or four larger pieces that are then embedded in wax so that a few very thin slices (4µm; four thousandths of a millimetre thick) can be shaved off with a microtome and then reviewed under the microscope after staining. This is referred to as ‘breadloafing’ of the specimen and means that only a few ultra-thin slices (and perhaps less than 0.1% of the perimeter) of the tumour are in fact examined on histology.

Armed with this information, your patient will understand that the clearance margin reported is not representative of the entire tumour and that it is quite possible for a histology report to claim that ‘the tumour appears completely excised’ even though there is residual tumour left behind. This will be important for higher risk tumours.

9.13 I don’t use sunscreen because it feels unpleasant/causes low vitamin D/contains dangerous nanoparticles

Research confirms that daily, rather than discretionary, sunscreen use reduces the risk of AK and prevents skin cancer. Patients are often keen to start daily sunscreen when you present the evidence, though some raise concern about the thick sticky feel of sun screen, the fear that it will lower their vitamin D levels, or concern that the nanoparticles most sunscreens contain may be dangerous.

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9.14 Responding to concerns about the consistency or feel of sunscreen

If your patient is not going to be sweating or swimming, an option is to use a lighter-weight non-waterproof sunscreen. This may be an ideal option for the indoor worker wishing to protect themselves while driving to and from work and for brief outdoor lunchtime or after-school activities.

9.15 Responding to concerns about vitamin D deficiency

Studies show that people who spend time outdoors with sunscreen on are more likely to have normal and high vitamin D levels than people who avoid going outside.

If sunscreen were applied thickly enough, it would completely block UVB and hence vitamin D production. However, studies show that people habitually apply sunscreen at much lower than recommended volumes. This amount of sunscreen while sufficient to help prevent erythema and sun damage does not block vitamin D production.[5]

See also: Vitamin D

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9.16 Responding to concerns about exposure to nanoparticles

Most sunscreens do contain nanoparticles and as a result are transparent rather than white once applied. However, no study to date or evidence of any kind has shown that sunscreen may be harmful to the human body.

9.17 It’s too late for sunscreen: the damage is already done!

There is irrefutable evidence that daily use of sunscreen reduces established AK and prevents future skin cancer. Studies comparing daily sunscreen use with discretionary sunscreen use show that daily use is the key to prevention,[6][7] because chronic intermittent low-grade sun exposure as well as sunburn is implicated in the development of sun damage and skin cancer (see: Strategies for protection from excessive exposure to ultraviolet radiation).[3][4]

Additionally, if your patient has already had multiple skin cancers it is worth also considering oral nicotinamide (vitamin B3 500 mg twice daily) as this has been shown to reduce visible AK as well as prevent KCs.[8] At this time, nicotinamide is not recommended as prophylaxis for someone who has not previously had skin cancer or has had only a few (see: Chemoprevention).

It is also likely that treating visible sun damage with an approved topical AK field treatment (applied to both visibly damaged and normal looking skin in the treatment area) will reduce future skin cancer (see: Topical treatments).

Studies have shown that photodynamic therapy used as an AK field treatment may additionally be helpful in treating established sun damage and preventing future skin cancer.

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9.18 I’m planning to use black salve (e.g. *Cansema*) for my skin cancer

Black salve is a common name given to a number of escharotic agents. These are caustic agents that may destroy some skin cancer cells but also indiscriminately destroy healthy cells, usually leaving an ulcer that often heals with a suboptimal cosmetic outcome.[9][10] When a skin lesion has healed with scarring or has not resolved fully after the use of black salve, it is often challenging for the pathologist to make a histological diagnosis with confidence.[11] Despite evidence to the contrary, it is often falsely claimed that black salve does not affect healthy cells, promotes healing, and leaves no scar.

Although not approved for human use in Australia, black salve remains a controversial alternative skin cancer treatment that has gained recent popularity.[12]

Patients may have read unsubstantiated testimonials and believe that the main reason it is not an approved mainstream treatment is that pharmaceutical companies cannot benefit from it.

It is understandable that patients might wish to avoid surgery. It may be helpful to empathise with this sentiment, going on to explain your reasons for advising against the use of this topical preparation.

To protect patients, it may be helpful to explain that some cancer lines are in fact relatively resistant to black salve and that valuable time may be lost waiting for a surface ulcer to heal while the cancer continues to expand in the underlying tissues. The consequences could be significant in the case of a more aggressive skin cancer. Case studies have reported death from metastatic nasal BCC and development of metastatic melanoma following self-treatment with black slave. [13]

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9.19 References

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9.1 TNM classification of primary cutaneous carcinomas

Appendix A provides updated information on staging using UICC TNM 8,[1] which should be used for all tumours diagnosed after 1 January 2018.

This combines the UICC TNM 8 guidance for skin carcinoma of the head and neck and carcinoma of the skin (essentially limbs and trunk but excluding eyelid, vulva, penis, non-hair bearing lip and non-hair bearing perianal skin within 5cm of the perianal margin).

This includes basal cell carcinoma, squamous cell carcinoma and adnexal carcinomas, but excludes Merkel cell carcinoma.

Contents

9.1.1 Primary tumour (pT)

UICC TNM 8 states pT is identical to T.

pTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour
pTis	Carcinoma in situ
pT1	Tumour ≤20mm or less in maximum dimension (this is the clinical dimension but the pathological dimension, usually macroscopic, can be used if the clinical is not available)
pT2	Tumour >20mm to ≤40mm in maximum dimension (this is the clinical dimension but the pathological dimension, usually macroscopic, can be used if the clinical is not available)
pT3	Tumour >40mm in maximum dimension (this is the clinical dimension but the pathological dimension, usually macroscopic, can be used if the clinical is not available) pT1 or pT2 can be upstaged to pT3 by one or more high-risk clinical/pathological features including deep invasion*, specifically defined perineural invasion** or minor bone erosion
pT4a	Tumour with gross cortical/marrow invasion
pT4b	Tumour with axial skeleton/skull base/foraminal invasion

High-risk features in relation to pT1 and pT2 upstaging to pT3:
*Deep invasion: this is defined as depth of invasion (DOI) to a level beyond the subcutaneous fat and/or tumour depth/thickness >6mm. Depth is measured in millimetres from the granular layer of the nearest adjacent normal epidermis to the deepest point of the tumour.
**Specifically defined perineural invasion using clinical or pathological criteria: this relates to a named nerve or a nerve ≥0.1mm diameter or a nerve deeper than the dermis or tumour cells within the nerve.

9.1.2 Regional lymph nodes (pN)

The division between non-head and neck and head and neck (trunk and limbs) regions anteriorly represents the level of the acromioclavicular joint and posterior the level of the upper margin of the shoulder blade.

9.1.2.1 Table A.1 Carcinoma of the skin (essentially limbs and trunk but excluding the eyelid, vulva, penis or perianal area)

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in a single ipsilateral lymph node ≤30mm in greatest dimension
pN2	Metastasis in a single ipsilateral lymph node >30mm, but not more than 60mm in greatest dimension, or in multiple ipsilateral lymph nodes, but not more than 60mm in greatest dimension
pN3	Metastasis in a lymph node >60mm in greatest dimension

A contralateral nodal metastasis (unlike with skin carcinoma of head and neck below) represents a distant metastasis.

There is an expectation that at least six lymph nodes will be identified in a lymphadenectomy specimen.

9.1.2.2 Table A.2 Skin carcinoma of head and neck (excluding vermillion lip)

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in a single ipsilateral lymph node ≤30mm in greatest dimension, without extranodal extension
pN2a	Metastasis in a single ipsilateral lymph node, more than 30mm but not more than 60mm in greatest dimension, without extranodal extension
pN2b	Metastasis in multiple ipsilateral lymph nodes, none more than 60mm in greatest dimension, without extranodal extension
pN2c	Metastasis in bilateral or contralateral lymph nodes, none more than 60mm in greatest dimension, without extranodal extension
pN3a	Metastasis in a lymph node, more than 60mm in greatest dimension, without extranodal extension
pN3b	Metastasis in a lymph node with extranodal extension

Extranodal extension can be defined by clinical or pathological criteria.

There is an expectation that at least 10 lymph nodes will be identified by selective lymphadenectomy and at least 15 in radical or modified radical lymphadenectomy.

9.1.2.3 Table A.3 Distant metastasis (M)

M0	No distant metastasis
M1 /pM1	Distant metastatic disease

Note: MX and pM0 do not exist.

9.1.2.4 Table A.4 Staging group

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IVA	T1, T2, T3	N2, N3	M0
	T4	Any N	M0
Stage IVB	Any T	Any N	M1

9.1.3 References

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9.2 Guideline development process

Contents

9.2.1 Introduction

These clinical practice guidelines are a revision and update of the 2008 edition *Basal cell carcinoma, squamous cell carcinoma (and related lesions) – a guide to clinical management in Australia*. The first edition (*Clinical practice guidelines on non-melanoma skin cancer: guidelines for the treatment and management in Australia*) was published in 1992.

This current revision and update was commissioned and fully funded by the Australian Government Department of Health.

These guidelines cover all aspects of keratinocyte cancer (KC). The broad areas covered include prevention of KC, epidemiology of the disease, clinical features and pathology, and treatment modalities including surgery, radiotherapy, cryotherapy, topical and photodynamic therapies and systemic therapies. These guidelines also deal with the clinical management of populations at increased risk of KCs, including organ transplant recipients and immunosuppressed patients. Aspects of the cost of treatment are also covered.

The guideline project commenced in July 2017 and in February 2019 the National Health and Medical Research Council (NHMRC) agreed to consider approving the guideline, provided it was developed according to NHMRC procedures and requirements. The guideline was submitted to NHMRC for consideration and approval of the recommendations in August 2019.

9.2.2 Guideline development group

The Management Committee was responsible for the overall management and strategic leadership of the guideline development process. This group acted as a steering committee to establish the scope of the guideline revision and ensure that all deliverables agreed in the project plan were delivered to acceptable

standards in accordance with NHMRC requirements, within agreed timeframes and within the approved budget. A wider multidisciplinary Working Party of relevant experts, including the management committee members, section lead authors and GP representatives, was then convened to develop the revised guideline and author specific sections. This approach was taken to ensure that representatives from all specialities and disciplines involved in the care of people with or at risk of KCs were included. Two consumer representatives were invited to be part of the Working Party (see: Working party members and contributors for full details).

Declarations of interests were collated from all nominated individuals and evaluated before the first working party meeting. All working party members were required to forward any further updates to their declarations of interest, in line with Cancer Council Australia's *Code of practice for dealing with conflict of interests*.[1] Any updates were forwarded for evaluation and the register updated accordingly.

See: Disclosure of interest register and the Administrative Report for information on disclosures of interest.

The guideline sections were allocated to specific guideline Working Party members to act as lead authors according to their areas of expertise. Each lead author team was able to co-opt additional experts as co-authors for their allocated questions. The Management Committee assessed the suggestion of any additional co-authors including their declaration of interest.

A project team based at Cancer Council Australia conducted the systematic reviews, which comprised of systematic literature searches, literature screening against pre-determined inclusion and exclusion criteria and critical evaluation and data extraction of the included literature. The project team was responsible for liaising with the Working Party members to draft evidence statements and supporting text, review the content and compile the required documentation.

9.2.3 Guideline scope

At the start of the project, members of the Management Committee with expertise in KCs were asked to review the clinical questions and sections of the 2008 guidelines and advise on the currency and relevance of clinical questions, suggested a review approach for updating the topic (systematic literature review or general literature update) and suggest any new clinical questions or topics to be considered. The Clinical question list summarises the included clinical questions updated by systematic review as well as the topic areas that were updated by a general literature review.

When reviewing each question, the Management Committee were asked to consider the following factors:

- whether new, up-to-date guidance is needed due to new evidence requiring a change of practice, and whether there is contested evidence, uncertainty, or unwarranted variation in practice
- the extent to which answering the question would reduce poor outcomes or high disease burden
- whether there is no other current, valid or relevant guidelines available that address this question and are applicable to the Australian context.

The Management Committee decided that new evidence published between 1 January 2008 and 30 November 2018 would be integrated into the existing guideline structure.

The project plan determined that there were enough resources to answer 10 clinical questions systematically (Table A1), and the remainder of content was addressed non-systematically.

Table A1 Clinical questions selected for systematic review	
Surgery	What factors need to be considered when determining if surgical treatment modalities are optimal over non-surgical modalities for the management and/or treatment of basal cell carcinoma or cutaneous squamous cell carcinoma?
	What factors need to be considered when determining the optimal surgical technique for those with basal cell carcinoma?
	In patients undergoing surgical treatment for cutaneous squamous cell carcinoma, which surgery-related factors (margin width, depth of excision) or tumour-related factors (size, histological features, anatomical site) influence clinical outcomes (cure rate, local recurrence, regional lymph node involvement, metastasis)?
	What should be the protocol to manage incompletely resected basal cell carcinoma?
	What should be the protocol to manage rapidly growing tumours?
Radiotherapy	When should radiotherapy be used alone, or in combination with surgical excision, to treat those with KCs?
	In which patients with basal cell carcinoma does a radiotherapy modality achieve equal or better outcomes than conventional surgery?
	In which patients with cutaneous squamous cell carcinoma does a radiotherapy modality achieve equal or better outcomes than conventional surgery?
Metastatic disease and systemic therapies	What should be the protocol to manage or treat locoregionally advanced cutaneous squamous cell carcinoma?
Topical treatments and photodynamic therapy	What role does ingenol mebutate gel have in the treatment and management of basal cell carcinoma and/or cutaneous squamous cell carcinoma?

9.2.4 Steps in preparing clinical practice guidelines to NHMRC criteria

This clinical practice guideline has been developed according to the procedures and requirements for meeting the 2016 NHMRC standard for clinical practice guidelines.[2] The development program has been designed to meet the scientific rigour required by the standard for developing high quality, evidence-based clinical practice

guidelines. A series of NHMRC resources and handbooks[3][4][5][6][7][8][9][10][11] outlining the major steps and expectations involved in developing guidelines were utilised to guide the process. These documents provided the definitions and protocols for developing research questions and search strategies, conducting systematic literature reviews, summarising and assessing the relevant literature and finally, formulating and grading the recommendations. They also included checklists and templates created to satisfy designated standards of quality and process. For every systematic review question the below steps were followed:

For every question the below steps were followed:

<table>
<tr><td colspan="2">1. Develop a structured clinical question using the PICO (population, intervention [or exposure], comparison and outcomes) framework</td></tr>
<tr><td colspan="2">2. Search for existing relevant guidelines and systematic reviews</td></tr>
<tr><td colspan="2">3. Process if relevant clinical practice guideline was identified (3a) or not (3b)</td></tr>
<tr><td>3a If a relevant clinical practice guideline was found and assessed as suitable for adaption

Conduct systematic literature review update for the question of the existing clinical practice guideline

Screening of literature update results against pre-defined inclusion and exclusion criteria

Critical appraisal and data extraction of each new included article

Update evidence table of evidence review of existing guideline with new literature update results</td><td>3b If no relevant clinical practice guideline was found

Check if an existing systematic review of high quality exists and can be used to inform the systematic review process

Developing the systematic review protocol and systematic literature search strategy for each clinical question

Conducting the systematic literature search according to protocol

Screening of literature results against pre-defined inclusion and exclusion criteria

Critical appraisal and data extraction of each included article</td></tr>
<tr><td colspan="2">4. Summarise the relevant data</td></tr>
<tr><td colspan="2">5. Assess the body of evidence and formulate recommendations</td></tr>
<tr><td colspan="2">6. Write the content narrative</td></tr>
</table>

9.2.4.1 Developing a structured clinical question

During the scoping process the clinical questions included in the 2008 guideline were assessed for clinical importance to the target audience and currency (see Clinical question list).

The included clinical questions were used to develop a PICO framework table for each question to be systematically reviewed. When a clinical question involved risk factors, a population, risk factors and outcomes (PRO) table was used. The lead author and subcommittee members provided the systematic review team with feedback to refine the PICO framework or PRO table.

9.2.4.2 Search for existing relevant guidelines and systematic reviews

For each clinical question, the National Guideline Clearinghouse (previously accessible via http://guideline.gov) the Guidelines Resource Centre (http://www.cancerview.ca/) as well as the scoping search for the clinical question were scanned for relevant clinical practice guidelines that could potentially be suitable for adaption. No existing guidelines were identified to be suitable for adaption. However, relevant guidelines that did not meet the criteria for adaption were checked for systematic reviews that could be used as a source of relevant references to inform the systematic review process for the clinical question. Full systematic reviews were then performed as outlined in the following sections.

9.2.4.3 Developing a systematic search strategy

For each clinical question, systematic literature search strategies were developed by the technical team. Search strategies were refined as necessary according to the PICO or PRO framework using keywords or MESH and subject terms. Systematic search strategies were derived from these terms for each included electronic database. The included standard databases searched were PubMed, EMBASE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment, CINAHL and PsycINFO databases for all questions.

9.2.4.4 Conducting the systematic literature search according to NHMRC protocol

Clinical practice guidelines should be based on systematic identification and synthesis of the best available scientific evidence.[3] For each clinical question that required a systematic literature review, literature searches were conducted systematically with the literature cut-off date of 30 November 2018. The following electronic databases were part of the systematic literature search strategy:

- PubMed (US National Library of Medicine): bibliographic references and abstracts to articles in a range of languages on topics such as clinical medical information and biomedicine, and including the allied health fields, biological and physical sciences
- EMBASE: major pharmacological and biomedical database indexing drug information from over 3500 journals
- Database of Abstracts of Reviews of Effects and Health Technology Assessment: contains details of systematic reviews that evaluate the effects of healthcare interventions and the delivery and organisation of health services
- The Cochrane Database of Systematic Reviews: contains systematic reviews of primary research in human health care and health policy, and are internationally recognised as the highest standard in evidence-based health care
- CINAHL: bibliographic references and abstracts to journal articles, book chapters, pamphlets, audiovisual materials, software, dissertations, critical paths, and research instruments on topics including nursing and allied health, biomedicine, consumer health, health sciences librarianship, behavioural sciences, management, and education
- PsycINFO: Bibliographic references and abstracts to journal articles, book chapters, dissertations and technical reports on psychology; social, clinical, cognitive and neuropsychology; psychiatry, sociology, anthropology and education, with source material from a wide range of languages.

A search filter to retrieve relevant literature considering Aboriginal and Torres Strait Islander peoples was added to each question.

Additional relevant papers from reference lists and, where appropriate, clinical trial registries, were also identified for retrieval as part of the snowballing process.

The full detailed systematic literature search strategy for every clinical question is fully documented in the Technical report.

9.2.4.4.1 Limitations of searches

A small number of identified articles that met search criteria could not be accessed, and therefore could not be assessed against search criteria. These were excluded.

9.2.4.5 Screening of literature results against pre-defined inclusion and exclusion criteria

Part of the systematic review process is to screen all retrieved literature results against the pre-defined inclusion and exclusion criteria in two stages:

1. First screen – during the first screening round, the titles and abstracts of all retrieved literature were screened by one or two reviewers. All irrelevant, incorrectly identified and duplicate articles were removed.
1. Second screen – a second screen was undertaken based on the full article. A reviewer assessed each article for inclusion against the pre-defined inclusion and exclusion criteria for each question. In the case of a disagreement between the reviewers, a third independent reviewer assessed the article against the inclusion and exclusion criteria. Articles that met the inclusion criteria were forwarded for quality assessment and data extraction.

9.2.4.6 Critical appraisal and data extraction of each included article

Two assessors independently assessed the risk of bias of each of the included studies using a study design specific assessment tool and where necessary pre-specified criteria. The quality assessment tools are listed in the Technical report. Any disagreements were adjudicated by a third reviewer. For all included articles, the relevant data were extracted and summarised in study characteristics and evidence table. Included and excluded articles are documented within each question's systematic review report within the Technical report.

9.2.4.7 Summary of the relevant data

For each outcome examined, the results, level of the evidence, the risk of bias due to study design, and the relevance of the evidence for each included study were documented a body of evidence table. Each question was addressed by a systematic review resulting in a systematic review report. All systematic review reports are published in the Technical report of the guideline. Levels of evidence are in Table A2.

9.2.4.7.1 Table A2. Designations of levels of evidence according to type of research question

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
		A study of test accuracy with: an independent, blinded comparison with a			A randomised

II	A randomised controlled trial	valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study

	Interrupted time series without a parallel control group				Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council[11]

9.2.4.8 Assessment of the body of evidence and formulation of recommendations

The systematic review report and evidence statement for each question was forwarded to each lead author. The authors, in collaboration with their subcommittee members and systematic review team (who conducted the systematic reviews and provided the reports), assessed the body of evidence and completed the NHMRC Evidence Statement form to record the volume of the evidence, its consistency, clinical impact, generalisability and applicability and developed evidence statements (see: Technical report). The process is described in NHMRC additional levels of evidence and grades for recommendations for developers of guidelines (2009).[11]

Following grading of the body of evidence and development of evidence statements, expert authors were asked to formulate evidence-based recommendations that is based on the summarised body of evidence. The method of grading recommendations is shown in Table A3 and the classification of recommendation grades are shown in Table A4.

9.2.4.8.1 Table A3. Grading of recommendations

Component of Recommendation	**Recommendation Grade**			
	A **Excellent**	**B** **Good**	**C** **Satisfactory**	**D** **Poor**
Volume of	one or more level I studies with	one or two level II studies with a low risk of bias or a systematic review/several	one or two level III studies with a low risk	level IV studies, or level I to III studies

evidence [1**]	a low risk of bias or several level II studies with a low risk of bias	level III studies with a low risk of bias	of bias, or level I or II studies with a moderate risk of bias	/systematic reviews with a high risk of bias
Consistency [2**]	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

[1] Level of evidence determined from level of evidence criteria

[2] If there is only one study, rank this component as 'not applicable'

[3] For example results in adults that are clinically sensible to apply children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer.

**For a recommendation to be graded A or B, the volume and consistency of evidence must also be graded either A or B.

Source: National Health and Medical Research Council[11]

9.2.4.8.2 Table A4. Overall recommendation grades

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Source: National Health and Medical Research Council[11]

In addition to developing evidence-based recommendations as a result of the systematic review for a question, expert authors could also draft consensus-based recommendations in the absence of evidence after having performed a systematic review, or practice points, when a matter was outside the scope of the search strategy for the systematic review. The NHMRC approved recommendation types and definitions are shown in Table A5.

9.2.4.8.3 Table A5. NHMRC approved recommendation types and definitions

Type of recommendation	Definition
Evidence-based recommendation*	A recommendation formulated after a systematic review of the evidence, indicating supporting references
Consensus-based recommendation*	A recommendation formulated in the absence of quality evidence, after a systematic review of the evidence was conducted and failed to identify admissible evidence on the clinical question
Practice point	A point of guidance on a subject that is outside the scope of the search strategy for the systematic review, or guidance on topic not subject to a systematic review, formulated by a consensus process and based on a general literature review, clinical experience and expert opinion

*NHMRC recommendation. Note: The definition for Practice Points has been adapted from the original NHMRC definition.

Source: National Health and Medical Research Council.[2]

9.2.4.9 Writing the content

For each clinical question, the assigned lead authors were asked to draft their guideline chapter using the following format:

- general introduction to the clinical question
- background to the clinical question, including its clinical importance and historical evidence, where relevant

- review of the evidence, including the number, quality and findings of studies identified by the systematic review
- evidence summary in tabular form including evidence statements, levels of evidence of included studies and reference citations
- evidence-based recommendation(s) and corresponding grade(s), consensus-based recommendations and practice points
- implications for implementation of the recommendations, including possible effects on usual care, organisation of care and any resource implications
- discussion, including unresolved issues, relevant studies currently underway and future research priorities
- references.

For sections not based on systematic review, the lead author was directed to follow a similar process and to draw on high-level evidence, particularly international guidelines, consensus statements and key literature considered to be relevant to Australian practice, to develop information and practice points.

The content draft was then reviewed by subcommittee members who were available. The draft documents often underwent several iterations.

Where contentious issues and areas for debate arose during the development of these guidelines, these are stated in *Notes on these recommendations* and *Unresolved issues* sections within each topic.

9.2.4.10 Review of the draft chapters

A face-to-face meeting with all available Working Party members was held 5 November 2018 to review and finalise the first set of sections ready as a draft guideline for public consultation. Prior to this meeting, the first batch of draft guideline sections were circulated to the Working Party members and posted on Cancer Council Australia's Clinical Guidelines Network digital platform. The group was asked to review the content and submit feedback. All members were asked to review the content, individual recommendations and practice points in detail, and to identify and note any controversies and points to be discussed at the group meeting.

During the meeting, each section was tabled as an agenda point and key updates, recommendations and practice points were discussed in detail. All clinical guidance was reviewed and approved by consensus. In some cases, the authors agreed on specific actions for the content or discussed further sections or amendments to be added. These were actioned by the authors.

A second face-to-face meeting with all available Working Party members was held 8 April 2019 to finalise the second set of sections ready as a draft guideline for public consultation; any revisions to recommendations from the first set prepared for November 2018 were reviewed again to ensure consensus.

9.2.5 Public consultation and independent expert reviewers

A complete draft of the guideline was sent out for public consultation between 7 June and 8 July 2019 and submitted to NHMRC for an independent review.

Public consultation comments and suggestions received from NHMRC from the independent expert reviewers were considered and integrated in the final draft and submitted to NHMRC for approval.

Submissions were invited from the general public, professional societies and groups and other relevant stakeholders. The consultation was publicised by email to key stakeholders, including contacting professional societies and groups, consumer groups and other relevant parties.

Feedback on the draft received during the consultation and review period was compiled and sent to the relevant author and subcommittee to review their draft content, assessing and considering the submitted comments.

9.2.5.1 Feedback received during the consultation and review period

The two review stages, public consultation and the NHMRC methodological and expert review, are an integral part of the guideline development process. The feedback was reviewed and incorporated in order to improve the guideline's quality, legitimacy and acceptability to end users and the public.

All comments received during the consultation and review period were collated in a register and were considered by the relevant section authors.

Additional papers submitted during public consultation were assessed by the methodology team against the systematic review protocol to determine if they could be included.

The Working Party reviewed all feedback received from the public consultation process at a face-to-face meeting on 5 August 2019.

The final face-to-face Working Party meeting was held after the NHMRC review and public consultation period to consider the feedback received and the amended guideline content. Subsequent changes to the draft were agreed by consensus, based on consideration of the evidence. This process followed the same consensus process that was followed prior to public consultation. All changes resulting from the public consultation submission reviews were documented.

The guideline draft was revised in response to review comments and all agreed amendments were documented in the Register of public consultation submissions.

9.2.5.2 Post-public consultation draft revisions

In response to feedback received during public consultation the definition of a Practice Point (PP) was revised from 'A *recommendation* on a subject that is outside the scope of the search strategy for the systematic review, based on expert opinion and formulated by a consensus process' to 'A *point of guidance* …' in order to make a clearer distinction between PPs and recommendations. The amended definition better conveys the status of PPs as guidance notes that can be utilised by the clinician using their own clinical expertise and judgement.

One significant revision across the whole guideline, in response to feedback, was the reassessment of the PPs and the development of new 'Key Points' in each section. Key Points were derived from draft PPs that did not express clinical guidance in the form of actions, but represented important information for clinicians. This process, and a revision to one of the systematic review reports noted below (MS1), reduced the number of PPs compared with the pre-public consultation draft (from 132 to 40) and resulted in a more concise Summary of recommendations in the final draft submitted for Council consideration.

The new Key Points feature appear either below or in place of the original PPs and so can be read within the same sections of the guideline.

9.2.5.3 Revisions to technical documentation prior to submission of final draft

Post-public consultation revisions included close checking of the systematic review reports and evidence statements to identify and remove any reported clinical trial outcomes that were not specified in the PICO research question and incorrectly included in the draft evidence reports. This process resulted in changes to material based on systematic reviews for four of the clinical questions.

The supporting technical documentation for the following clinical questions was accordingly revised (see the Technical report):

- Clinical question MS1 – all recurrence rate data (local recurrence, time to recurrence, distant recurrence) was removed and within the survival data sections, cause-specific and disease-specific survival data were removed, as these were not an outcome of the PICO for this clinical question. Six studies were excluded from the systematic review based on this correction. Relevant portions of the evidence statement and summary table were updated based on the removal of these outcomes. Two recommendations were affected by this revision: wording of EBR 12.1.1. was changed from “local recurrence” to “locoregional recurrence” for clarity and what was originally the fifth EBR was revised to a Practice Point (now PP 12.1.1.) due to the removal of some supporting evidence.
- Clinical question RT2 – sections reporting response rate were removed as response was not an outcome reported in the PICO table for this systematic review. One study was excluded from the systematic review based on this correction. Relevant portions of the evidence statement were updated based on the removal of these outcomes. This revision resulted in minimal corrections to the evidence summary table. No recommendations were affected by this revision.
- Clinical question RT3 – sections reporting response rates were removed as response was not an outcome reported in the PICO table for this systematic review. Two studies were excluded from the systematic review based on this correction. Relevant portions of the evidence statement were updated based on the removal of these outcome. This revision resulted in minimal corrections to the evidence summary table. No recommendations were affected by this revision.
- Clinical question SX2 – experience of the operator and intervention studies were removed as this PICO was designed to focus on patient risk factors. No evidence was excluded from the systematic review based on this correction. Four evidence statements were removed. No recommendations were affected by this revision; recommendations may have been revised due to public consultation feedback as noted in the register above.

9.2.6 Organisations formally endorsing the guidelines

The following medical colleges and professional bodies may be approached to endorse the guideline after it is finalised:

- Skin Cancer College Australasia (SCCA)
- The Australasian College of Dermatologists (ACOD)
- Australian College of Rural and Remote Medicine (ACRRM)
- Clinical Oncology Society of Australia (COSA)
- Medical Oncology Group of Australia Incorporated (MOGA)
- Royal College of Pathologists of Australia (RCPA)

- Royal Australian College of Physicians (RACP)
- Royal Australian College of Surgeons (RACS)
- Royal Australian College of General Practitioners (RACGP)
- Royal Australian and New Zealand College of Radiologists (RANZCR).

9.2.7 Dissemination and implementation

Cancer Council Australia has created a plan for the dissemination of the guideline in Australia (see: Dissemination plan).

The guideline will be available online via the Cancer Council Australia Clinical Guidelines Network digital platform. The online guideline version increases availability as well as accessibility, and usage will be tracked and analysed with a web analytics solution. Interlinking and listing the guidelines on national and international guideline portal is an important part of the digital dissemination strategy. Important Australian health websites, such as EviQ and healthdirect Australia will be approached to link to the online guideline.

The guideline will also to be listed on national and international guideline portals such as Australia's Clinical Practice Guidelines Portal.

The Clinical Guidelines Network digital platform is a responsive website that is optimised for mobile and desktop access. When accessing the guidelines with a mobile and tablet device, an icon can be easily added to the home screen of mobile devices, offering easy mobile access.

In addition, the final guideline document will be launched via email alert to professional organisations, interested groups and clinical experts in the field, directing them via URL link to the online guideline and all associated resources.

The Clinical Guidelines Network digital platform is based on semantic web technology, so the guidelines are available in a machine-readable format, which offers the possibility to easily integrate the guideline content with systems and web applications used in the Australian healthcare context.

It is recognised that a planned approach is necessary to overcome specific barriers to implementation clinical settings and to identify appropriate incentives to encourage uptake of guideline recommendations. Implementation of the guidelines will require a combination of effective strategies and may include further continuing medical education/professional development initiatives and interactive learning, the development and promotion of computer-assisted decision aids and electronic decision-support systems, and the creation of audit and other clinical tools.

Lead authors are encouraged to develop journal articles for publication and submit abstracts and posters to conferences out of the guideline as part of the dissemination plan.

9.2.8 Future updates

The incoming literature updates will continue to be monitored for each systematic review question. If there is strong evidence emerging in a specific area of keratinocyte cancer management, the Management Committee will be reconvened to assess if this warrants a guideline update (full or partial). It is recommended that the guideline be updated after 5 years.

9.2.9 References

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9.3 List of clinical questions

Contents

This page lists the questions answered by *systematic review and modelling*. For full details about the reviews, including the inclusion and exclusion criteria, please see the Technical report.

9.3.1 Epidemiology (section lead: Adele Green & David Whiteman)

Background chapter based on general literature summary. The 2008 content was reviewed and updated where required. Practice points were included as guidance.

9.3.2 Prevention (section lead: Craig Sinclair)

Background chapter based on general literature summary. The 2008 content was reviewed and updated where required. Practice points were included as guidance.

9.3.3 Early detection (section lead: David Whiteman)

Background chapter based on general literature summary. This is a new section of the guideline. Practice points were included as guidance.

9.3.4 Clinical features (section lead: Morton Rawlin)

Background chapter based on general literature summary. The 2008 content was reviewed and updated where required. Practice points were included as guidance.

9.3.5 Pathology (section lead: Vicki Howard)

Background chapter based on general literature summary. The 2008 content was reviewed and updated where required. Practice points were included as guidance.

9.3.6 Prognosis (section lead: David Speakman)

Background chapter based on general literature summary. The 2008 content was reviewed and updated where required. Practice points were included as guidance.

9.3.7 Surgical treatment (section lead: Peter Callan)

Clinical question SX1: What factors need to be considered when determining if surgical treatment modalities are optimal over non-surgical modalities for the management and/or treatment of basal cell carcinoma or cutaneous squamous cell carcinoma?

Population	Risk factors	Outcomes
Patients with basal or squamous cell carcinoma	Tumour location Tumour histology Depth of invasion Risk of surgery Diffuse disease Patient factors (family history, immunocompromised, comorbidities)	Local recurrence rates Disease-free survival Adverse events Cure rate Completeness of excision Preservation of function

Clinical question SX2: What factors need to be considered when determining the optimal surgical technique for those with basal cell carcinoma?

Population	Risk factors	Outcomes
	Patient with primary basal cell carcinoma Experience of the operator	

Patient with primary basal cell carcinoma	Type of basal cell carcinoma Histological features: ■ morphoeic ■ micronodular ■ infiltrating Tumour size (surface area) Tumour location Lesion depth of invasion Perineural invasion Excision margin	Cure rate Local recurrence rate Completeness of excision Preservation of function

Clinical question SX3: In patients undergoing surgical treatment for cutaneous squamous cell carcinoma, which surgery-related factors (margin width, depth of excision) or tumour-related factors (size, histological features, anatomical site) influence clinical outcomes (cure rate, local recurrence, regional lymph node involvement, metastasis)?

Population	**Risk factors**	**Outcomes**
Patients with primary squamous cell carcinoma	Surgical margin (2-10 mm) Surgical margin (1 mm) Tumour size (surface area) Histological features: ■ well-differentiated ■ poorly differentiated ■ desmoplasia ■ spindle cell carcinoma ■ acantholytics squamous cell carcinoma ■ adenosquamous tumours Depth of excision Anatomical site	Cure rate Local recurrence rate Positive regional lymph nodes Distal metastasis

Clinical question SX4: What should be the protocol to manage incomplete resected basal cell carcinoma?

Population	Intervention	Comparator	Outcomes
Patients with incomplete resected basal cell carcinoma	Re-excision Radiotherapy Observation	An alternative management or treatment modality	Recurrence

Clinical question SX5: What should be the protocol to manage rapidly growing tumours?

Population	Intervention	Comparator	Outcomes
Basal or squamous cell carcinoma patients with perineural invasion	Surgery + definitive radiotherapy Surgery + adjuvant radiotherapy High dose radiotherapy Surgery (Mohs Micrographic surgery)	An alternative treatment modality or no comparator	Recurrence rate Cancer-specific mortality Local regional spread Distal metastases

9.3.8 Radiotherapy (section lead: Gerald Fogarty)

Clinical question RT1: When should radiotherapy be used alone, or in combination with surgical excision to treat those with keratinocyte cancers?

Population	Intervention	Comparator	Outcomes
Patients diagnosed with basal cell carcinoma or squamous cell carcinoma	Radiotherapy alone	Radiotherapy and surgical excision	Recurrence rates Local control Regional control Distant control Overall survival Relapse-free survival Disease-specific survival Cosmetic outcomes Functionality outcomes

Clinical question RT2: In which patients with basal cell carcinoma does a radiotherapy modality achieve equal or better outcomes than conventional surgery?

Population	Intervention	Comparator	Outcomes
Patient with basal cell carcinoma	Definitive radiotherapy	Alterative treatment no comparator alternative radiotherapy dose	5-year local control recurrence rates cosmetic and/or functional aspects survival outcomes

Clinical question RT3: In which patients with cutaneous squamous cell carcinoma does a radiotherapy modality achieve equal or better outcomes than conventional surgery?

Population	Intervention	Comparator	Outcomes
Patients with squamous cell carcinoma	Definitive radiotherapy	Alterative treatment no comparator alternative radiotherapy dose	5-year local control recurrence rates cosmetic and/or functional aspects survival outcomes

9.3.9 Cryotherapy and electrodessication and diathermy (section lead: Peter Foley & Stephen Shumack)

Background chapter based on general literature summary. The 2008 content was reviewed and updated where required. Practice points were included as guidance.

9.3.10 Topical treatments and photodynamic therapy (section lead: Peter Foley & Stephen Shumack)

Clinical question OT1: What role does ingenol mebutate gel have in the treatment and management of basal cell carcinoma and/or cutaneous squamous cell carcinoma?

Population	Intervention	Comparator	Outcomes
Patients with primary basal cell carcinomas (BCC) or			Adverse events (AEs)

squamous cell carcinomas (SCC), including: - Superficial BCC (sBCC) - SCC in situ (SCCIS)	Ingenol mebutate (IM) gel topical treatment	Alternative concentration of IM gel, or alternative treatment regime	Recurrence rates Response rates

9.3.11 Organ transplantation and conditions associated with immunosuppression (section lead: Alvin Chong & Adele Green)

Background chapter based on general literature summary. The 2008 content was reviewed and updated where required. Practice points were included as guidance.

9.3.12 Metastatic disease and systematic therapies (section lead: Alex Guminski)

Clinical question MS1: What should be the protocol to manage or treat locoregionally advanced cutaneous squamous cell carcinoma?

Population	Intervention	Comparator	Outcomes
Patients with locally advanced squamous cell carcinoma, including recurrent disease, nodal involvement, a bulky or invasive primary, perineural invasion, or gross/microscopic positive margins.	One of the following: ■ Cetuximab alone ■ Cetuximab + chemotherapy ■ Cetuximab + radiotherapy ■ Cisplatin (or Pt) + radiotherapy ■ Surgery + chemotherapy + radiotherapy ■ Surgery + radiotherapy ■ Surgery + adjuvant radiotherapy ■ Systemic therapy + adjuvant radiotherapy	An alternative treatment, or no comparator.	Local regional control Distant control Progression-free survival Overall survival Mortality

9.3.13 Follow-up (section lead: Morton Rawlin)

Background chapter based on general literature summary. The 2008 content was reviewed and updated where required. Practice points were included as guidance.

9.3.14 The role of primary care in the prevention and management of keratinocyte cancer (section lead: Paul Fishburn)

Background chapter based on general literature summary. The 2008 content was reviewed and updated where required. Practice points were included as guidance.

9.3.15 Economics of keratinocyte cancer (section lead: Louisa Gordon)

Background chapter based on general literature summary. The 2008 content was reviewed and updated where required. Practice points were included as guidance.

9.3.16 Common concerns raised by patients (section lead: Helena Rosengren)

Background chapter based on general literature summary. The 2008 content was reviewed and updated where required. Practice points were included as guidance.

9.4 Technical report

This Technical Report accompanies the *Clinical practice guidelines for keratinocyte cancer*, developed by Cancer Council Australia.

It outlines the guideline development process and methodology, lists the clinical questions, provides all accompanying NHMRC Statement Forms, the detailed technical documentation for each question and the risk of bias assessment tools used to assess the included literature as a result of a systematic review.

9.4.1 Guideline development process

9.4.2 Clinical question list

9.4.3 Evidence statement forms, systematic review reports and modelling reports

The following reports are for questions that were answered by a new systematic literature review or modelling. The associated technical documentation appears at the bottom of the relevant content pages.

The questions were given alphanumeric codes when they were developed, please refer to the codes below and see the Clinical question list for more detail.

SX1: *What factors need to be considered when determining if surgical treatment modalities are optimal over non-surgical modalities for the management and/or treatment of basal cell carcinoma or cutaneous squamous cell carcinoma?*
Evidence statement form SX1
Systematic review report SX1

SX2: *What factors need to be considered when determining the optimal surgical technique for those with basal cell carcinoma?*
Evidence statement form SX2
Systematic review report SX2

SX3: *In patients undergoing surgical treatment for cutaneous squamous cell carcinoma, which surgery-related factors (margin width, depth of excision) or tumour-related factors (size, histological features, anatomical site) influence clinical outcomes (cure rate, local recurrence, regional lymph node involvement, metastasis)?*
Evidence statement form SX3
Systematic review report SX3

SX4: *What should be the protocol to manage incompletely resected basal cell carcinoma?*
Evidence statement form SX4
Systematic review report SX4

SX5: *What should be the protocol to manage rapidly growing tumours?*
Evidence statement form SX5
Systematic review report SX5

RT1: *When should radiotherapy be used alone, or in combination with surgical excision to treat those with keratinocyte cancers?*
Evidence statement form RT1
Systematic review report RT1

RT2: *In which patients with basal cell carcinoma does a radiotherapy modality achieve equal or better outcomes than conventional surgery?*
Evidence statement form RT2
Systematic review report RT2

RT3: *In which patients with cutaneous squamous cell carcinoma does a radiotherapy modality achieve equal or better outcomes than conventional surgery?*
Evidence statement form RT3
Systematic review report RT3

MS1: *What should be the protocol to manage or treat locoregionally advanced cutaneous squamous cell carcinoma?*
Evidence statement form MS1
Systematic review report MS1

OT1: *What role does ingenol mebutate gel have in the treatment and management of basal cell carcinoma and /or cutaneous squamous cell carcinoma?*
Evidence statement form OT1
Systematic review report OT1

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9.5 Working party members and contributors

Contents

9.5.1 Guideline Working Party members and contributors

The Management Committee established a multidisciplinary working party to develop these guidelines.

The multidisciplinary Working Party consists of the Management Committee members, the lead authors for guideline sections, consumer representatives as well as the Cancer Council Australia Project team members.

Management committee members	
Name	**Affiliation**
Associate Professor Stephen Shumack (Chair)	Dermatologist, Royal North Shore Hospital and The University of Sydney
Professor Sanchia Aranda	CEO, Cancer Council Australia
Dr Peter Callan	Specialist Plastic surgeon, Geelong, Victoria
Dr Alvin Chong	Adjunct Associate Professor, Department of Medicine (Dermatology), St Vincent's Hospital Melbourne
Associate Professor Gerald Fogarty	Director of Radiation Oncology, St Vincent's, Sydney
Dr Peter Foley	Head of Dermatology, Department of Dermatology, St Vincent's Hospital, Fitzroy, Victoria
Professor Adele Green	Head, Cancer and Population Studies Group, QIMR Berghofer Medical Research Institute
Associate Professor Alexander Guminski	Associate Professor Medicine, The University of Sydney
Dr Vicki Howard	Pathologist, Douglass Hanly Moir Pathology
Dr Morton Rawlin	General practitioner; Medical Director, Royal Flying Doctor Service (VIC)
Dr David Speakman	Chief Medical Officer, Peter MacCallum Cancer Centre
Professor David Whiteman	Deputy Director of QIMR Berghofer; NHMRC Senior Principal Research Fellow; Head, Cancer Control Group
Tamsin Curtis	Project Manager, Clinical Guidelines, Cancer Council Australia

Guideline section leaders		
Name	**Specialty**	**Section**
Dr Peter Callan	Surgery	Surgical treatment
Dr Alvin Chong	Dermatology	Organ transplantation and conditions associated with immunosuppression (co-lead)
Associate Professor Gerald Fogarty	Radiotherapy	Radiotherapy
Dr Peter Foley	Dermatology	Cryotherapy and electrodessication and curettage (co-lead) and Topical treatments and photodynamic therapy (co-lead)
Prof Adele Green	Epidemiology	Epidemiology (co-lead) and Organ transplantation and conditions associated with immunosuppression (co-lead)

Management committee members		
Name	**Affiliation**	
Associate Professor Alexander Guminski	Medical oncology	Metastatic disease and systemic therapies
Associate Professor Louisa Gordon	Health economics	Economics of keratinocyte cancer
Dr Vicki Howard	Pathology	Pathology and Common concerns raised by patients (co-lead)
Dr Morton Rawlin	General practice	Clinical features (co-lead), Follow-up, The role of primary care in the prevention and management of keratinocyte cancer (co-lead) and Common concerns raised by patients (co-lead)
Associate Professor Stephen Shumack	Dermatology	Cryotherapy and electrodessication and curettage (co-lead) and Topical treatments and photodynamic therapy (co-lead)
Adj. Associate Professor Craig Sinclair	Prevention	Prevention (co-lead)
Dr David Speakman	Surgery	Prognosis
Prof David Whiteman	Epidemiology	Early detection and Epidemiology (co-lead)
Dr Helena Rosengren	General practitioner	Common concerns raised by patients (co-lead)
Representative working party members (GP and Consumer)		
Name	**Specialty**	
Dr Helena Rosengren	General practice representative	
Dr Paul Fishburn	General practice representative	
Danny Brennan	Consumer representative	
Ann Strokon	Consumer representative	

9.5.2 Cancer Council Australia Project Team

Member name	Specialty/position
Tamsin Curtis	Project Manager, Clinical Guidelines Network
Dr Albert Chetcuti	Senior Systematic Reviewer, Clinical Guidelines Network
	Project Officer, Systematic Literature Reviews, Keratinocyte Cancer Guidelines (May 2018 –

Member name	Specialty/position
Annika Stollery	May 2019)
Annie Bygrave	Systematic Reviewer (May – June 2018)
Dr Adelaide Morgan	Project Officer, Systematic Literature Reviews (May – June 2018)

9.5.3 Guideline section details

*Denotes lead author

9.5.3.1 Epidemiology

Name	Affiliation
Professor David Whiteman*	Deputy Director of QIMR Berghofer; NHMRC Senior Principal Research Fellow; Head, Cancer Control Group
Professor Adele Green*	Head, Cancer and Population Studies Group, QIMR Berghofer Medical Research Institute
Associate Professor Catherine Olsen	Senior Research Officer, Division of Population and Clinical Sciences, Queensland Institute of Medical Research

9.5.3.2 Prevention

Name	Affiliation
Adjunct Associate Professor Craig Sinclair*	Head, Prevention Division, Cancer Council Victoria
Professor Diona Damian	Dermatologist, The University of Sydney
Professor Gary Halliday	Professor of Dermatology, University of Sydney
Professor Robyn Lucas	Professor and Head, National Centre for Epidemiology and Population Health, Australian National University

9.5.3.3 Early detection

Name	Affiliation
Professor David Whiteman*	Deputy Director of QIMR Berghofer; NHMRC Senior Principal Research Fellow; Head, Cancer Control Group
Professor John Kelly	Dermatologist, Victorian Melanoma Service, Alfred Health, Melbourne
Professor Peter Soyer	Director, School of Medicine, University of Queensland; Director, Dermatology Department, Princess Alexandra Hospital

9.5.3.4 Clinical features

Name	Affiliation
Dr Morton Rawlin	General practitioner; Medical Director, Royal Flying Doctor Service (VIC)

9.5.3.5 Pathology

Name	Affiliation
Dr Vicki Howard	Pathologist, Douglass Hanly Moir Pathology

9.5.3.6 Prognosis

Name	Affiliation
Dr David Speakman*	Chief Medical Officer, Peter MacCallum Cancer Centre
Dr Helena Rosengren	General practitioner

9.5.3.7 Surgical treatment

Name	Affiliation
Dr Peter Callan*	Specialist Plastic surgeon, Geelong, Victoria
Dr James Emmett	Plastic surgeon
Dr Brian De'Ambrosis	Director, South East Dermatology Brisbane; Chair, Non-melanoma Skin Cancer Sub-committee, Queensland Cancer Control Safety and Quality Partnership

9.5.3.8 Radiotherapy

Name	Affiliation
Associate Professor Gerald Fogarty*	Director of Radiation Oncology, St Vincent's, Sydney
Dr Howard Liu	Radiation Oncologist

9.5.3.9 Cryotherapy and electrodessication and curettage

Name	Affiliation
Dr Peter Foley*	Head of Dermatology, Department of Dermatology, St Vincent's Hospital, Fitzroy, Victoria
Professor Stephen Shumack* (Chair)	Dermatologist, Royal North Shore Hospital and The University of Sydney
Dr Michelle Goh	Consultant dermatologist, Peter MacCallum Cancer Centre, Skin Health Institute, St Vincent's Hospital Melbourne, Alfred Health, Austin Health
Dr Gilberto Moreno	Dermatologist

9.5.3.10 Topical treatments and photodynamic therapy

Name	Affiliation
Dr Peter Foley*	Head of Dermatology, Department of Dermatology, St Vincent's Hospital, Fitzroy, Victoria
Professor Stephen Shumack* (Chair)	Dermatologist, Royal North Shore Hospital and The University of Sydney
Dr Michelle Goh	Consultant dermatologist, Peter MacCallum Cancer Centre, Skin Health Institute, St Vincent's Hospital Melbourne, Alfred Health, Austin Health
Dr Gilberto Moreno	Dermatologist

9.5.3.11 Organ transplantation and conditions associated with immunosuppression

Name	Affiliation
Dr Alvin Chong*	Adjunct Associate Professor, Department of Medicine (Dermatology), St Vincent's Hospital, Melbourne
Professor Adele Green*	Head, Cancer and Population Studies Group, QIMR Berghofer Medical Research Institute
Dr Hsien Chan	Dermatologist
Clinical Associate Professor Patricia Lowe	Dermatologist, Senior Staff Specialist, Royal Prince Alfred Hospital; Clinical Associate Professor, Sydney Medical School (Central), The University of Sydney
Dr Sarah Brennand	Dermatologist
Dr Michelle	Consultant dermatologist, Peter MacCallum Cancer Centre, Skin Health Institute, St Vincent's

Name	Affiliation
Goh	Hospital Melbourne, Alfred Health, Austin Health
Dr Katherine Allnutt	Education and Research Fellow, Skin and Cancer Foundation
Professor Kiarash Khosrotehrani	Experimental Dermatology Group Leader, The University of Queensland Diamantina Institute; Senior Medical Officer, Department of Dermatology, Princess Alexandra Hospital; Senior Medical Officer, Heart and Lung Transplant Services, Prince Charles Hospital; Board member and Visiting Medical Officer, Queensland Institute of Dermatology, Queensland Skin and Cancer Foundation

9.5.3.12 Metastatic disease and systemic therapies

Name	Affiliation
Associate Professor Alexander Guminski*	Associate Professor Medicine, The University of Sydney
Professor Sydney Ch'ng	Associate Professor of Surgery (Plastic Surgery, Head & Neck, Melanoma), University of Sydney, Royal Prince Alfred Hospital and Chris O'Brien Lifehouse Cancer Centre

9.5.3.13 Follow-up after treatment for keratinocyte cancer

Name	Affiliation
Dr Morton Rawlin*	General practitioner; Medical Director, Royal Flying Doctor Service (VIC)
Dr Helena Rosengren	General practitioner

9.5.3.14 The role of primary care in the prevention and management of keratinocyte cancer

Name	Affiliation
Dr Paul Fishburn*	General practitioner
Dr Morton Rawlin*	General practitioner; Medical Director, Royal Flying Doctor Service (VIC)

9.5.3.15 Economics of keratinocyte cancer

Name	Affiliation
Associate Professor Louisa	Senior Research Fellow/Lab Head, QIMR Berghofer Medical Research

Name	Affiliation
Gordon*	Institute, Brisbane
Dr Sophy Shih	Senior Research Fellow and Health Economist, Deakin University

9.5.3.16 Common concerns raised by patients

Name	Affiliation
Dr Helena Rosengren	General practitioner
Dr Vicki Howard	Pathologist, Douglass Hanly Moir Pathology
Dr Morton Rawlin	General practitioner; Medical Director, Royal Flying Doctor Service (VIC)

*Denotes lead author

9.5.4 Acknowledgements

With thanks to Jenni Harman, medical writer and editor, Meducation Australia.

9.6 Declarations of interest register

Declarations of interest register

Last updated: 28 Aug 2019

See also: A Code of Practice for Declaring and Dealing with Competing Interests

9.7 Glossary of technical terms and abbreviations

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9.7.1 Abbreviations

Abbreviation	Term
AIDS	acquired immune deficiency syndrome
AK	actinic keratosis
AJCC	American Joint Committee on Cancer
BCC	basal cell carcinoma
CNI	calcineurin inhibitor
CLL	chronic lymphocytic leukaemia
CD4	cluster of differentiation 4
CT	computed tomography
CI	confidence interval
cSCC	cutaneous squamous cell carcinoma
C20	cytokeratin 20
DNA	deoxyribonucleic acid
DMARD	disease modifying anti-rheumatic drug
EDC	electrodessication and curettage
EGFR	epidermal growth factor receptor
EMA	epithelial membrane antigen
GP	general practitioner
HPI	hedgehog pathway inhibitor
HIV	human immunodeficiency virus
HPV	human papillomavirus
IBD	inflammatory bowel disease
IFNA1	interferon alpha 1
IL	interleukin
INR	international normalised ratio
ITSCC	International Transplant Skin Cancer Collaborative
KC	keratinocyte cancer (previously known as non-melanoma skin cancer)
Linac	linear (particle) accelerator
MRI	magnetic resonance imaging

MTOR	mechanistic target of rapamycin kinase
MCC	Merkel cell carcinoma
MMS	Mohs micrographic surgery
MLC	multi-leaf collimator
NICE	National Institute for Health and Care Excellence (UK)
NFKB1	nuclear factor kappa B subunit 1
OR	odds ratio
OTR	organ transplant recipient
OA	osteoarthritis
PTCH1	patched 1 gene
PNI	perineural invasion
PDT	photodynamic therapy
PUVA	psoralen and ultraviolet A
RT	radiotherapy
RCT	randomised controlled trial
ROC	receiver operating characteristic
RA	rheumatoid arthritis
SCOPE	Skin Care in Organ Transplant Patients, Europe
STAR	Skin Tumours in Allograft Recipients
SMO	smoothened, frizzled class receptor
SMR	standard mortality ratio
SIR	standardised incidence ratio
SPF	sun protection factor
TMB	tumour mutation burden
TNF	tumour necrosis factor
TNM	Tumour, lymph nodes, metastases (classification system)
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
UICC	Union for International Cancer Control
VMAT	Volumetric modulated arc therapy

9.7.2 Glossary

Term	Definition
Actinic keratosis	An intraepithelial dysplastic lesion that sometimes leads to invasion, occurring on chronically sun-exposed skin and characterised by inflamed, reddened scaly patches on the skin (previously called solar keratosis)
Basal cell carcinoma	An intraepithelial dysplastic lesion that sometimes leads to invasion
Basosquamous	A term used to describe basaloid tumours that show evidence of squamatisation (synonymous with metatypical). Basosquamous/metatypical tumours should be viewed as equivalent to squamous cell carcinoma and are classified as aggressive subtypes of basal cell carcinoma by the World Health Organization.[1]
Bazex-Dupre-Christol syndrome	An inherited medical condition that causes early-onset basal cell carcinoma
Bowen's disease	Cutaneous squamous cell carcinoma in situ (also known as intra-epidermal squamous cell carcinoma) – a pre-cancerous growth
Bowenoid solar keratosis	An actinic keratosis that shows full-thickness atypia, without dermal invasion (equivalent to cutaneous squamous cell carcinoma in situ)
Brachytherapy	A method of delivering radiotherapy to a localised area by placing the source of the radiation on or very close to the lesion being treated.
Calcineurin inhibitor	A class of immunosuppressant agents that includes everolimus and sirolimus
Chemoprophylaxis	The use of pharmacological products to prevent disease (in this case, skin cancer)
Cluster of differentiation 4	A type of glycoprotein found on the surface of immune cells (antigen)
Cockayne syndrome	A 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. The most commonly used agent is liquid nitrogen (boiling point –196°C).
Curettage	The use of a sharp debriding instrument (curette) to remove skin cancer or related dysplasias from the skin under local anaesthetic
Cutaneous squamous cell carcinoma	A malignant tumour derived from epidermal keratinocytes. It may arise in actinic keratosis or Bowen's disease and may show a range of differentiation. It is more likely to spread than basal cell carcinoma.
Desmoplasia	Tumour-induced sclerotic and extensive fibrous stroma, which may be mistaken for a scar. Desmoplastic tumours often present as infiltrative cords of cells, may have ill-defined boundaries, and are prone to recurrence. Squamous cell carcinoma, basal cell

	carcinoma and other tumours may produce this pattern.
Diathermy	The use of a direct electrical current to produce heat so as destroy and remove tissue (e.g. skin cancer) and achieve haemostasis
Electrodessication	The use of an electric current to destroy and remove tissue (e.g. skin cancer) and achieve haemostasis
Ferguson-Smith syndrome	An autosomal dominant syndrome characterised by multiple keratoacanthomas that appear during adolescence, spontaneously involute and recur many times
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
Gorlin's syndrome	An autosomal dominant syndrome characterised by multiple basal cell carcinomas occurring from an early age (also called naevoid basal cell carcinoma syndrome)
H-zone	The area of the face that includes the central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular skin and sulci, temple, and ear
Imiquimod	A keratinocyte cancer treatment that induces expression of cytokines related to cell-mediated immune responses, including interferon alpha 1, tumour necrosis factor and various interleukins
Interferon	A naturally occurring cytokine with antiviral, antimicrobial, anti-tumour and immunomodulatory actions
Intraepidermal squamous cell carcinoma	See Bowen's disease.
Keratinocyte cancer (previously known as non-melanoma skin cancer)	A group of skin cancers that includes basal cell carcinoma and squamous cell carcinoma (previously known as non-melanoma skin cancer)
Keratoacanthoma	A skin tumour commonly found on sun-exposed skin and characterised by rapid growth and spontaneous regression, with a close histological resemblance to well-differentiated conventional cutaneous squamous cell carcinoma. Keratoacanthoma is classified by World Health Organization as a variant of cutaneous squamous cell carcinoma.[1]
Laser therapy	The use of laser technology to ablate skin cancer and related dysplasias
Mechanistic target of rapamycin kinase (MTOR) inhibitor	A group of drugs with immunosuppressive and antineoplastic effects, which includes sirolimus and everolimus
Megavoltage radiotherapy	The use of very high voltage electric current to create high-energy radiotherapy that can deeply penetrate tissues and is usually skin sparing.

Merkel cell carcinoma	A primary neuroendocrine tumour of the skin
Metatypical	See basosquamous.
Micronodular	A histopathological description of a growth pattern of basal cell carcinoma (a high-risk subtype)
Mohs micrographic 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 maximising normal tissue conservation and function. Once the tumour clearance has been confirmed, the wound is closed.
Morphoeic	See Sclerosing.
Multi-leaf collimator	A feature of modern linear accelerators that helps define a radiotherapy beam
Naevoid basal cell carcinoma syndrome	See Gorlin's syndrome.
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 keratinocyte cancer
Patched 1 gene	A tumour suppressor gene, mutations of which are associated with nevoid basal cell carcinoma syndrome
Perineural invasion (also known as perineural spread)	Invasion of a tumour in the perineural compartment of a peripheral nerve fibre, exhibited by some of the more aggressive keratinocyte cancers (also known as perineural spread)
Photodynamic therapy	The use of light to activate a photosensitiser that is localised in diseased tissues, resulting in the formation of cytotoxic reactive oxygen species
Poorly differentiated tumours	Tumours in which products of differentiation (e.g. keratin or desmosomal attachments) or adnexal differentiation are poorly expressed. Immunohistochemistry techniques for keratin subsets are often used to identify such tumours.
Radiotherapy	The use of ionising radiation to treat cancer and related disease
Rombo syndrome	A hereditary syndrome that causes early-onset basal cell carcinoma
Sclerosing	Scar-like (morphoeic) – a term used to describe one of the clinical variants of basal cell carcinoma
Skin flap (surgical	A surgical technique in which an area of healthy skin is partly detached and moved to cover a nearby wound (e.g. after removal of a large skin cancer). The skin flap may fat or

technique)	muscle as well as skin. The flap usually stays attached to its original site at one end so that it remains connected to a blood vessel.
Skin graft	A surgical technique in which an area of healthy skin is removed and transplanted onto a new place on the body (e.g. to replace skin lost when surgically removing a large skin cancer).
Smoothened, frizzled class receptor	A protein encoded by the SMO gene, which is a component of the hedgehog signalling pathway
Solar keratosis	See actinic keratosis.
Specialist	Medical practitioners who through training, experience and peer opinion specialise in the management of keratinocyte cancers.
Squamous cell carcinoma in situ	See Bowen's disease.
Sun protection factor	Laboratory-derived rating system for sunscreens active in the ultraviolet B (UVB) range. The SPF number indicates 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.
Superficial radiotherapy	Radiotherapy that is absorbed within the first few millimetres of skin and does not penetrate to the deeper tissues. Usually means external beam radiotherapy in which a certain machine is used that is not a linear accelerator and shielding requirements are not as complex or time consuming.
TNM classification	A classification system for cancers based on assessment of the tumour, lymph nodes, and metastases. Unless stated otherwise, tumour stage is according to the American Joint Committee on Cancer (AJCC) cancer staging manual 8th edition[2] and Union for International Cancer Control (UICC) TNM classification of malignant tumours 8th edition.[3]
Tumour necrosis factor	A cell signalling protein (cytokine) involved in the regulation of immune cells
Ultraviolet (UV) radiation	The solar spectrum reaching the Earth's surface in the wavelength range of 290–400nm. It includes UVA (ultraviolet radiation of wavelength 320–400nm) and UVB (ultraviolet radiation of wavelength 290–320nm.
Volumetric modulated arc therapy	External beam radiotherapy from a linear accelerator with multi-leaf collimators and capable of rotational treatment that can give a very conformal homogeneous dose of radiotherapy to a volume with minimal exposure to surrounding normal tissue in a short time frame. Volumetric modulated arc therapy is for extended skin field cancerisation of convex surfaces.
Xeroderma pigmentosum	A rare hereditary disorder associated with multiple early-onset squamous cell carcinomas and increased risk of other cancers

9.7.3 References

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