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SIGN 140 • Management of primary cutaneous squamous cell carcinoma

A national clinical guideline

June 2014

Evidence

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS

LEVELS OF EVIDENCE

1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

RECOMMENDATIONS

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher quality evidence is more likely to be associated with strong recommendations than lower quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.

R	For **'strong'** recommendations on interventions that 'should' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm.
R	For **'conditional'** recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

GOOD PRACTICE POINTS

✓	Recommended best practice based on the clinical experience of the guideline development group

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Scottish Intercollegiate Guidelines Network
Gyle Square, 1 South Gyle Crescent
Edinburgh EH12 9EB

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Contents

1 Introduction

1.1 THE NEED FOR A GUIDELINE

1.1.1 BACKGROUND

Primary cutaneous squamous cell carcinoma (SCC) is a malignant tumour of keratinocytes arising within the epidermis or its appendages. It has a variable spectrum of clinical presentation and risk, ranging from the common, usually low-risk, keratotic plaque through to the less common, larger, rapidly growing and usually high-risk, exophytic skin lesion nodule.[1, 2]

Squamous cell carcinoma is the second most common skin cancer, after basal cell carcinoma (BCC) and its incidence is increasing throughout the world.[3-5] In the 10-year period from 2001 to 2011, Scotland saw a greater than 50% increase in incidence with now around 2,900 new cases presenting annually.[6]

The Scottish National Cancer Registry collects information on all new cases of SCC, but relies on accurate reporting to the cancer registry from the multiple different treatment pathways. Historically, skin cancers arising from keratinocytes, that is both basal cell and squamous cell cancers of the skin (non-melanoma skin cancers), have been grossly under-registered.[7, 8]

Skin cancers account for 30% of all referrals to dermatology and the estimated mean cost to the NHS in 2002 for treatment of each SCC was £1,149, approximating to an annual cost of around £23 million for the UK.[9]

1.1.2 RISK FACTORS

Most SCCs develop on the sun-exposed areas of the head and neck and sunlight is the most important environmental carcinogen with cumulative lifetime exposure to ultraviolet radiation (UVR) strongly correlated to development of SCC.[10] Males are more at risk than females and incidence increases with age.[11, 12]

Susceptible patients, for example patients with compromised immunity from immunosuppressive therapy such as solid organ transplant recipients[13] or those with haematological malignancies, commonly develop multiple primary tumours with the potential for significant surgical morbidity and associated health costs.[14]

1.1.3 STAGING

The tumour, node, metastases (TNM) classification is recognised to be inadequate for staging of cutaneous SCC.[15] Several staging systems try to address this, but accurately predicting tumour metastasis risk remains a challenge (*see sections 3.1 and 3.4*).

1.1.4 PROGNOSIS

The overall rate of cutaneous SCC metastasis is low (<5%), but where distant metastases are present, the five-year survival rate is poor at around 25–40%.[16] Treatment options are limited once distant metastasis or unresectable locoregional recurrence develops. The major clinical challenge is to identify those (few) patients with the highest risk SCC who require urgent and often aggressive management and to distinguish this group from the majority with low-grade tumours and an excellent prognosis,

Treatments for SCC are variable; from simple options for the smaller and low-risk tumours to complex procedures for the larger and high-risk tumours. Patients with high-risk SCC should be discussed at skin cancer multidisciplinary team (MDT) meetings (*see section 4*). Treatments are currently undertaken by a wide variety of doctors: general practitioners, dermatologists, radiotherapists and surgeons (general, plastic, oculoplastic, oral and maxillofacial or ear, nose and throat). There are regional variations, both in treatments and referral rates to the MDT, within and between specialties managing SCC across Scotland.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This evidence based guideline for management of primary cutaneous SCC will:

- help practitioners to more reliably identify the high-risk tumours which are most likely to metastasise
- help to direct available resources to the management of patients with high-risk SCC, thus reducing the incidence of metastatic SCC.

The guideline recommendations will also help address the following concerns:

- treatment variability amongst practitioners currently managing SCC
- that patients with high-risk SCC are not always referred to MDT meetings
- the limitations of the current TNM classification in identifying those SCC most likely to metastasise.

This guideline provides recommendations for referral, management and follow up of patients aged 18 years and over with primary invasive SCC including SCC arising:

- on both sun-exposed (SE) and non-SE sites
- in immunocompetent or immunosuppressed patients
- on historically accepted high-risk sites including the ear, lip (including the external mucosal lip) and scars
- in Bowen's disease
- in chronic wounds or areas of chronic inflammation.

The guideline excludes:

- actinic keratoses
- keratoacanthoma (the Royal College of Pathologists have re-classified keratoacanthoma as well-differentiated SCC)
- squamous intra-epidermal carcinoma/carcinoma-in-situ (Bowen's disease)
- metastatic SCC, including in-transit metastasis, locoregional and distant metastasis
- mucosal sites including internal mucosal lip
- anogenital sites
- SCC of the nail matrix bed
- recurrent SCC
- SCC arising in patients with cancer-predisposing genodermatoses such as xeroderma pigmentosum, recessive dystrophic epidermolysis bullosa, multiple self-healing squamous epithelioma of Ferguson Smith disease or albinism.

The key questions on which the guideline is based are outlined in Annex 1.

The following areas are also outwith the scope of this evidence based guideline but are important aspects of skin cancer management:

- primary and secondary prevention measures
- awareness-raising of risk factors and the signs of skin cancer to patients and the general public and the need to seek urgent medical attention
- the key role of primary care in differentiating SCC and other skin cancers from pre-cancerous conditions and referring patients to secondary care with appropriate urgency
- having systems in place in secondary care to allow efficient screening and prioritisation of referrals to the appropriate secondary care speciality. Screening should be done by an experienced skin cancer specialist, preferably a consultant dermatologist.

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of interest to dermatologists, histopathologists, oculoplastic, ear, nose and throat, oral and maxillofacial and plastic surgeons, skin cancer clinical nurse specialists and oncologists as well as general practitioners and patients and their families.

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.3.1 PATIENT VERSION

A patient version of this guideline is available from the SIGN website, **www.sign.ac.uk**

1.3.2 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off label' use.

Medicines may be prescribed off label in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally 'off label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.[17]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".[1]

The General Medical Council recommends that when prescribing a medicine 'off label', doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the the summary of product characteristics.[18] The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[19]

1.3.3 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

Healthcare Improvement Scotland processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Care Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

No SMC advice relevant to this guideline was identified.

2 Key recommendations

The following recommendations and good practice points were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

2.1 IDENTIFYING HIGH-RISK TUMOURS

✓ All clinicians should endeavour to identify high-risk tumours at the earliest opportunity and, when referring patients with suspected SCC, should include details of the high-risk clinical features: immunosuppression, tumour diameter and site.

2.2 REFERRAL TO THE MULTIDISCIPLINARY TEAM

R **Where any of the following high-risk features are present, patients with primary SCC should be discussed at a skin cancer multidisciplinary team meeting:**

- **SCC arising on the ear**
- **tumour diameter >20 mm**
- **tumour depth >4 mm**
- **tumour extension beyond dermis into or through subcutaneous fat**
- **perineural invasion**
- **poorly differentiated**
- **desmoplastic subtype**
- **immunosuppression.**

✓
- recurrent SCC
- established or suspected metastatic SCC
- nose, external lip, eyelid and scalp tumour site
- association with special clinical situations
- adenosquamous histological subtype
- spindle cell histological subtype
- pseudoangiosarcomatous histological subtype
- acantholytic histological subtype
- lymphovascular invasion
- tumour excision margin is involved at deep or peripheral margins.

MDT discussion is desirable where:

- a tumour is at a surgically challenging site
- the referring clinician requests discussion due to specific clinical management issues, such as cognitive impairment or significant medical comorbidities.

3 Identifying high-risk tumours

3.1 INTRODUCTION

Primary cutaneous SCC has a low rate of metastasis of around 5%,[16] but once it has metastasised to distant locations the prognosis is generally poor. The risk of metastasis increases significantly in patients with high-risk SCC.[20] The major clinical challenge is to identify those few patients with the highest risk SCC who require urgent and often aggressive management and to distinguish this group from the great majority with low-grade tumours and an excellent prognosis. The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) have adapted TNM classifications to improve their prognostic utility,[21,22] but they remain unable to accurately predict tumour metastasis risk for SCC.[20, 23, 24] A recent study has tried to address this, attempting to stratify risk using just four high-risk factors in a simplified prognostic indicator.[23] A number of studies provide evidence on those features that are associated with the greatest risk of local or regional recurrence, metastasis and disease-specific mortality, but all have limitations. Retrospective series can deliver the large datasets required to identify significant associations but are subject to recording bias and loss to follow up. The small number of cases included with relevant outcomes of interest generally limits prospective series. There is a need for large prospective studies.

✓ All clinicians should endeavour to identify high-risk tumours at the earliest opportunity, and when referring patients with suspected SCC, should include details of the high-risk clinical features: immunosuppression, tumour diameter and site.

If a surgery or biopsy specimen is taken, clinicians should use the national Histopathology Request Form (*see Annex 2*) that details high-risk clinical features.

The following sections detail the clinical and pathological features of SCC. They are also summarised in the management algorithm in Annex 3.

3.2 CLINICAL FEATURES

3.2.1 PATIENT SEX

In a large Dutch registry, 69,407 patients were diagnosed with primary cutaneous invasive SCC between 1989 and 2008 (males n=41,556, females n=27,851). The incidence of SCC in 2008 was greater in males than in females (42.5/100,000 *v* 32.5/100,000). The five-year overall survival rate in females was 94.9% (95% confidence interval (CI) 94.0 to 95.7) compared with 92.0% (95% CI 91.3 to 92.8) in males. Females presenting with advanced disease had poorer outcomes than males. Female five-year relative survival for advanced disease was 46% (95% CI 38 to 53) versus 62% for males (95% CI 56 to 68, p<0.001).[25]

No evidence was identified to support any recommendation for differential treatment according to sex.

3.2.2 PATIENT AGE

Although the incidence of SCC increases with age,[11] no studies were identified which examined age as a prognostic factor for the development of high-risk SCC tumours.

3.2.3 IMMUNE STATUS

Long term immunosuppression following solid organ transplantation is associated with more than a 100-fold increased risk of SCC. Squamous cell carcinoma risk in organ transplant recipients is influenced by age at transplantation, duration of transplant, intensity of immunosuppression and previous sun damage. Patients with haematological malignancies, human immunodeficiency virus (HIV) or other medical conditions requiring long term monotherapy, with for example azathioprine or cyclosporine, such as Crohn's disease and rheumatoid arthritis, also have an increased risk of developing skin cancers, especially SCC. Immunosuppressed patients will typically develop large numbers of primary tumours over time creating a significant burden of disease with both surgical morbidity and increased risk of SCC-associated death.[13]

In a multivariate analysis of risk factors examined in a prospective cohort of unselected patients (n=615, immunocompetent n=584, immunosuppressed n=31), immunosuppression was a significant risk factor for metastasis (hazard ratio (HR) 4.32, 95% CI 1.62 to 11.52, p=0.0035) at median follow up of 43 months. Immunosuppression was due to either chemotherapy or malignancy.[26] In a study combining these data with a retrospective dataset from a similar population (n=634) to compare two cutaneous carcinoma staging systems, immunosuppressed patients had a four-fold higher risk of metastasis (16%) compared with only 4% in immunocompetent patients.[20] **2++** **2+**

In a retrospective cohort analysis of high-risk primary SCC (n=256), 35 patients (15%) were immunosuppressed (15 organ transplant patients, seven with chronic lymphocytic leukaemia, 12 undergoing non-transplant steroid therapy, and one patient with HIV). Immunosuppression was a risk factor for local recurrence, (cause-specific HR 3.5, (95% CI 1.2 to 10.7). There was no significant association with nodal metastases or disease-specific death.[23] **2=** **2+**

The potential therapeutic effect of reduction in immunosuppression is discussed in section 5.6.

R **Immunosuppression should be considered a high-risk clinical feature in patients with primary squamous cell carcinoma.**

✓ Patients who are immunosuppressed are more likely to develop multiple primary SCCs and there is increased risk for an individual SCC to behave aggressively. Healthcare professionals treating immunosuppressed patients need to be alert to the possibility of cutaneous malignancies and to exercise meticulous care at every stage of their SCC management.

A draft UK National Histopathology Request Form for skin biopsies (*see Annex 2*) suggests that the immune status of the patient should be recorded at referral for histopathology.[27]

✓ Immunosuppression, when present, should be indicated as part of the histopathology request form for skin biopsies from patients with suspected SCC.

3.2.4 TUMOUR SITE

In a multivariate analysis of risk factors examined in a prospective cohort of unselected patients (n=615), tumour site on the ear (n=81) was found to be an independent prognostic factor for metastasis (HR 3.61, 95% CI 1.51 to 8.67, p=0.004) at median follow up of 43 months. Localisation on the lip (n=159) was not an independent prognostic factor for metastasis on either univariate or multivariate analysis.[26] **2++** **2+**

In a large Dutch registry study of 69,407 patients, stratification by body site showed a reduction in relative five-year survival of males with an SCC on the scalp or neck (88.9%, 95% CI 86.7 to 91.0). No reduction in survival was observed for localization on either the lip or ear in either sex.[25] **3**

A retrospective study from the UK examined a highly selected group of patients (n=194, 143 males and 51 females) with head and neck SCC (n=218), excluding the lip. Localisation on the ear (n=44) was an independent prognostic factor for metastasis (odds ratio (OR) 16, 95% CI not stated). Localisation on both the nose and ear was associated with poorly differentiated SCC. Forty per cent (4/10) of tumours from the nose and 39% (17/44) from the ear were poorly differentiated compared to around 21% observed in the total number of lesions ($p<0.05$).[28] **2=**

In a registry study of 224 patients (131 males, and 93 females, mean age 72 years; range 12–91 years) 35 patients were immunosuppressed (22 with organ transplants, six with leukemia, four with non-Hodgkin's lymphoma, and three using immunosuppressive medication) a tumour located on the ear was a significant predictor for metastasis on univariate analysis (HR 21.3, 95% CI 2.5 to 182.2, p=0.005), but not on multivariate analysis, owing to the small number of events.[29] **3**

Although there is strong prospective evidence that the ear should be considered a high-risk site in primary SCC based on risk of metastasis, data for other tumour sites are conflicting and based on retrospective findings across a range of patient groups and outcome measures. A good quality clinical guideline summarised high-risk sites as: peri-orificial areas (nose, lips, outer ear and eyelids) and scalp, while noting that this is based largely on small case studies where analysis may not adjust for factors such as tumour thickness or depth of invasion.[30] **4**

Lip site is considered a joint high-risk factor in the AJCC7 staging system. This is based on a historical cohort and there is a lack of clarity around the definition of lip site;[31] different terminology is used in the literature, for example, dry versus wet lip, internal versus external lip, hair-bearing versus non-hair-bearing, which causes confusion. **4**

R **The ear should be considered the highest risk tumour site in patients with primary squamous cell carcinoma.**

✓ Nose, cutaneous lip, eyelid and scalp tumour sites should be considered as high-risk features in primary squamous cell carcinoma.

3.2.5 SPECIAL CLINICAL SITUATIONS

SCC may arise in specific clinical situations, such as scars and burns, chronic ulceration, radiation-induced lesions,[30] or in association with existing skin pathologies, such as Bowen's disease (intraepidermal carcinoma arising in non-sun-exposed skin, typically the lower leg),[30] hidradenitis suppurativa,[32,33] morphoea,[34] lymphoedema[35] and Hailey-Hailey disease.[36] The historical evidence for high-risk SCC arising within Bowen's disease was mostly in non-sun-exposed skin sites and there is no evidence for increased risk in association with bowenoid actinic keratosis on sun-exposed sites. Previous guidelines have differed in their recommendations.[30, 37] Although retrospective studies attempt to examine the prognostic implications of SCC arising in sites of chronic inflammation, the numbers of cases are small and the evidence is insufficient to support a recommendation for considering such tumours to be at high risk of metastasis.[38-40] Expert opinion suggests that it is good practice to classify them as high risk.[37] The very high mortality from cutaneous SCC in patients with recessive dystrophic epidermolysis bullosa suggests that special clinical situations can greatly influence risk of metastasis.[41] **3** **4**

✓ Squamous cell carcinoma arising within a site of skin trauma, eg burns, scar tissue, or a radiotherapy field, or within a site of pre-existing skin disease, eg venous leg ulceration or Bowen's disease, should be considered as high-risk SCC.

A prospective cohort of 653 patients with 753 SCCs treated with Mohs surgery showed an association between painful tumours and incidental perineural invasion (PNI) ($p<0.001$). It was not possible to show an independent association between PNI and clinical variables due to low numbers of PNI.[42] **2+**

Insufficient evidence was identified on which to base recommendations around psoralen plus ultraviolet A (PUVA) photochemotherapy, speed of tumour growth, field cancerisation, poorly defined clinical margins, or pain/dysaesthesia as features associated with high-risk cutaneous SCC.[43] The guideline development group considers that these features should prompt urgent referral for suspected SCC.

✓ The following features should prompt early referral:

- high levels of cumulative psoralen plus ultraviolet A photochemotherapy
- rapid tumour growth
- field cancerisation
- poorly defined clinical margins
- pain/dysaesthesia.

3.2.6 MAXIMUM CLINICAL DIAMETER

In a multivariate analysis of risk factors examined in a prospective cohort of unselected patients (n=615) increasing maximum diameter was associated with metastasis (HR 2.22, 95% CI 1.18 to 4.15, $p=0.0128$) at median follow up of 43 months. No tumour <20 mm metastasised in this series.[26] **2++**

A retrospective analysis of 200 patients treated with Mohs, examined factors associated with metastasis. Twenty five tumours metastasised (12.5%), 17 were >20 mm. Tumour size significantly correlated with metastasis ($p<0.04$) with an increasing risk for tumours larger than 20 mm. It was not clear whether size was determined clinically or histologically.[40] **2+**

A review of medical records of 48 patients with SCC with nerve involvement reported that, on multivariate analysis, the age-adjusted survival was significantly worse for patients with tumours >20 mm (p =0.004).[44] 3

R **Clinically determined horizontal tumour diameter of >20 mm should be considered a high-risk feature in patients with primary squamous cell carcinoma.**

✓ Healthcare professionals should be aware that metastases may occur in tumours ≤20 mm in diameter.

3.3 IMAGING FEATURES

The management of patients with high-risk SCC may be influenced by the extent of disease at the primary site and by detecting subclinical disease in the nodal basin.

Computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound scanning are the main imaging modalities used in evaluation of skin cancer. Various other anatomical imaging techniques have been used, mainly as research tools, including laser scanning confocal microscopy, optical coherence tomography, high-frequency ultrasound, terahertz pulsed imaging, and photoacoustic microscopy and high-resolution microcoil MRI.[45] Molecular imaging techniques, for example single photon emission computed tomography and positron emission tomography (PET), may have an increasing role in the future.[46]

An editorial review of the role of imaging in the management of high-risk SCC extrapolates evidence from the use of cross-sectional imaging in the management of patients with head and neck cancers. Since MRI has been shown to have a sensitivity of 95% for detecting PNI in head and neck cancers it is widely accepted as the imaging of choice in detecting PNI. Sensitivity decreases to 63% when it is used to detect the entire extent of PNI. MRI may be supplemented by CT when there is a concern around potential nerve involvement at the skull base, as CT scans are superior to MRI in outlining bony anatomy.[47] 4

A retrospective study analysed the presence and extent of PNI on MRI in 35 patients with cutaneous SCC or BCC with clinical symptoms of nerve involvement (pain, cutaneous dysesthesia and numbness). Those patients who had PNI on MRI had poorer local control, and poorer cause-specific and absolute survival rates than those with negative findings in MRI.[48] 3

A further retrospective analysis from the same institute reported that local control was inversely proportional to the radiographic evidence of nerve enlargement and involvement of the nerve between the skull base and brainstem.[49] 3

No evidence was identified to indicate when radiological imaging is warranted to search for nodal metastases. Conventional CT and MRI scans add little to the clinical examination of a node negative region. However, in patients where an SCC is deemed very high risk, particularly when drainage is to the parotid nodes, ultrasound is considered to be a sensitive and accessible method of evaluating the lymph nodes.[47] 4

✓ Imaging to determine the extent of a primary tumour may be appropriate in selected patients as determined by the MDT. This would include patients who have symptoms suggestive of perineural invasion or clinical evidence of bony erosion or at sites considered to be very high risk, for example arising on or around the ear. Where undertaken, regional lymph nodes may also be imaged.

3.4 PATHOLOGICAL FEATURES

There is evidence to support the influence of pathological tumour features over the risk of tumour recurrence and/or metastasis. These features are discussed individually in this section, but many are linked and in practice it is often difficult to assess the risk associated with one factor independent of other factors. Studies investigating the relative risk of outcomes associated with different tumour factors often give both an estimate without consideration of other potentially linked or associated factors (univariate analysis) as well as after correction for linked or associated factors (multivariate analysis). Where two factors are biologically linked or associated, as with desmoplasia and perineural invasion, it may be impossible to assign individual risk.

High-risk features may be additive and where multiple features are present together this may indicate a very high-risk SCC.[50] A recently proposed staging system separates T2 into many low-risk T2a tumours and fewer high risk T2b tumours on the basis of four pathological features significantly associated in multivariate analysis with at least two of three poor outcomes (local recurrence, nodal metastasis, disease-specific death; *see Annex 1*).[23, 51] This new staging system looks to be clinically useful in that T2b accounts for the majority of poor outcomes, but validation and audit are needed. **3** **2++**

A suggested histology reporting proforma for cutaneous SCC is be found in Annex 5. This is adapted from the Royal College of Pathologists minimum dataset.[27]

3.4.1 TUMOUR DEPTH/LEVEL OF INVASION

In a multivariate analysis of risk factors in a prospective cohort of unselected patients (n=653), tumour thickness was a key prognostic factor for metastasis (HR 4.79, 95% CI 2.22 to 10.36). No tumours less than 2 mm in thickness metastasised in this series. For tumours 2.1 to 6.0 mm thick the rate of metastasis was 4% and for thickness >6.0 mm the rate was 16%. Tumour depth was prognostic for local recurrence (HR 6.03, 95% CI 2.71 to 13.43).[20,26] **2++** **2+**

Retrospective studies and audits are consistent in showing that tumour depth is of critical importance in identifying high-risk tumours, and that the degree of anatomical invasion should be considered and reported.[15,23,29,52-54] Invasion beyond subcutaneous fat was identified as a prognostic factor for increased risk of metastasis.[23,52] **2+** **3**

NICE and the Royal College of Pathologists use >4 mm tumour depth or invasion into subcutaneous fat as indicators for referral to MDT.[27,55] AJCC7 uses >2 mm tumour depth as one of several indicators for high-risk factors where two factors are required to upstage pT1 to pT2.[31] **4**

✓ Tumour depth (in mm) and anatomical level should be reported as components of the core minimum dataset for primary squamous cell carcinoma.

- The tumour depth should be measured in the same way as Breslow depth is measured for melanomas, ie from epidermal granular layer or ulcer base to deepest contiguous tumour cell. For tumours with a papillomatous surface architecture, measurements should be taken from the bottom of epidermal troughs, rather than the tip of peaks, to avoid an overestimation of tumour depth. The measurement should be recorded to the nearest 0.1 mm. The use of the term 'Breslow depth' should be avoided in pathology reports for SCC and reserved for melanoma.
- Pathology reports should state clearly whether the tumour is limited to the dermis or invades subcutaneous fat. If additional structures such as bone, skeletal muscle or cartilage are involved, this should be stated in the pathology report. The use of the term 'Clark level' should be avoided in pathology reports for SCC.

R **Tumour depth >4 mm should be considered a high-risk feature in patients with primary squamous cell carcinoma with depth >6 mm indicating a very high-risk tumour.**

Tumour extension beyond the dermis into or through subcutaneous fat should be considered a high-risk feature in patients with primary squamous cell carcinoma.

3.4.2 MAXIMUM TUMOUR DIAMETER

Horizontal tumour diameter is pivotal in current staging systems for cutaneous SCC,[21] with consistent evidence that tumour diameter >20 mm is an independent risk factor for tumour recurrence and metastasis (*see section 3.2.6*). It is often unclear from studies whether tumour diameter is being determined clinically or pathologically and whether macroscopic or microscopic measurements were taken in the laboratory.

R **Tumour horizontal diameter of >20 mm should be considered a high-risk feature in patients with primary squamous cell carcinoma.**

✓ The maximum diameter (to the nearest mm) of the macroscopic specimen should be reported as an essential component of the core minimum dataset for primary squamous cell carcinoma.

3.4.3 PERINEURAL INVASION

Most studies which examine PNI as a risk factor report that it is prognostic for local recurrence[15,23,54] and reduced five-year recurrence-free survival.[56] When risk of metastasis is considered there is inconsistency in the findings.[29] **2+ 3**

A prospective multicentre study showed incidental PNI to be associated with high-risk factors such as larger tumour diameter (p<0.001), location on the head and neck (p=0.039), the presence of palpable lymph nodes (p=0.012) and recurrent lesions (p<0.001). Due to a low number of patients with PNI in the cohort (4.6%) it was not possible to show an independent association.[42] **2+**

A retrospective cohort study examining the association between risk of metastasis and the size of the involved nerve in patients with PNI reported that nerve calibre >0.1 mm was associated with increased risk of metastasis (HR 5.6, 95% CI 1.1 to 27.9) although this was due in part to the association with other high-risk factors such as tumour diameter and depth of invasion.[52] **3**

Many skin cancer staging systems use PNI as a high-risk feature.[21, 27]

R **Perineural invasion should be considered a high-risk feature in patients with primary squamous cell carcinoma.**

✓ Presence or absence of perineural invasion should be reported as a component of the core minimum dataset for primary squamous cell carcinoma. Reporting on the extent of perineural invasion and the size of the largest nerve branch involved is desirable.

3.4.4 LYMPHOVASCULAR INVASION

Two studies in high-risk patient groups identified PNI and/or lymphovascular invasion (LVI) (composite feature) as an independent risk factor for nodal metastasis and disease-specific death.[15, 23] A small underpowered series found no evidence for LVI as an independent risk factor.[28] **2+ 3**

In multivariate analyses LVI is associated with PNI and desmoplasia.[26,52] **2++ 3**

There is limited evidence for LVI as a feature of high-risk SCC. The association with PNI and desmoplasia support consideration of LVI as an indicator of high risk.

✓ Lymphovascular invasion should be considered a high-risk feature in patients with primary squamous cell carcinoma.

Presence or absence of lymphovascular invasion should be reported as a component of the core minimum dataset for primary squamous cell carcinoma.

3.4.5 TUMOUR SUBTYPE

In a multivariate analysis of risk factors examined in a prospective cohort of unselected patients (n=653), the local recurrence rate at median follow up of 43 months was 24% for those who had desmoplastic SCC (n= 51), compared with only 1% for those without desmoplastic growth.[26] In a study combining these data with a retrospective dataset to compare two staging systems it was concluded that desmoplastic subtype is a risk factor for local recurrence and metastasis.[20] **2+ 2+**

R **Desmoplastic subtype should be considered a high-risk feature in patients with primary squamous cell carcinoma.**

✓ To categorise an SCC as being of desmoplastic subtype, at least one third of the tumour should show the desmoplastic phenotype, ie strands and nests of tumour cells surrounded by a prominent fibrous stromal response.

Tumour subtype should be reported as part of the core minimum dataset for primary squamous cell carcinoma.

Most SCCs are of no special type (classic subtype). Other than for the desmoplastic subtype no good quality evidence was identified examining the association between subtype and risk of recurrence or metastasis. Clinical expert opinion based on mostly very small case series suggests an association between poor outcomes and adenosquamous, spindle cell variety, pseudoangiosarcomatous and acantholytic subtypes.[30,37] The World Health Organisation Classification of Tumours and Royal College of Pathologists Dataset regard adenosquamous, pseudovascular, acantholytic and spindle cell SCC arising after radiotherapy as high-risk subtypes.[27,57] **4**

✓ Consideration should be given to treating the following tumour subtypes as high-risk variants of primary squamous cell carcinoma:

- adenosquamous
- spindle cell carcinoma
- pseudoangiosarcomatous
- acantholytic.

3.4.6 DIFFERENTIATION

Analysis of the impact of tumour differentiation status on outcomes is hampered by the lack of standardisation in assessing and reporting the degree of tumour differentiation. Tumour differentiation reporting is complicated by the heterogeneous nature of many SCCs with considerable 'within tumour' variation in the degree of differentiation. Predominantly well-differentiated SCC will often have focal areas that are moderately or poorly differentiated. This tumour heterogeneity is a possible explanation for metastasis from a well-differentiated SCC and complicates standardisation of reporting. There is no doubt, however, that metastasis can and does occur from well-differentiated SCC, particularly when there are additional patient-related risk factors such as immunosuppression, chronic skin wounding or secondary skin pathologies as seen in patients with recessive dystrophic epidermolysis bullosa where 80% will die from metastatic SCC by age 55 years.[41]

✓ Differentiation status should be reported as part of the core minimum dataset for primary squamous cell carcinoma.

In line with the Royal College of Pathologists dataset, a three-item system should be used when reporting tumour differentiation in primary squamous cell carcinoma:

- well differentiated
- moderately differentiated
- poorly differentiated.

A combination of the following morphological features should be used in the assessment of differentiation:

- degree of keratinisation
- presence/absence of intercellular bridges
- degree of nuclear pleomorphism
- number and nature of mitoses.

By convention, tumour grade is assessed on the most poorly differentiated area in the tumour.

Poorly-differentiated tumours are associated with high risk of local recurrence and metastasis. The majority of studies identify degree of differentiation as a risk factor for recurrence and metastasis on univariate analysis but not multivariate analysis. On multivariate analysis degree/grade of differentiation is positively associated with metastasis in correlation with tumour diameter and depth.[23,54] **2+ 3**

A retrospective case control study in male patients compared outcomes for 30 patients with non-well-differentiated SCCs with 30 matched patients who had well-differentiated tumours. The non-well-differentiated tumours were more locally aggressive with increased proliferation rate (Ki-67 index 77% *v* 61%, p= 0.001).[53] **3**

R **Poorly-differentiated tumour status should be considered a high-risk feature in patients with primary squamous cell carcinoma.**

3.4.7 INCOMPLETE EXCISION (POSITIVE MARGINS)

There are no guidelines for optimum histological clearance margins. In conventional histopathological processing a limited assessment of the specimen margin is made; the apparent clearance will vary according to the site sampled giving rise to possible sampling error.[58] The main area of debate is what to do when histological margins are close. The definition of close is also debatable (<0.5 mm, <1 mm, <2 mm, <3 mm). If high-risk features are present then it is better to re-excise if the benefits outweigh the risks. A survey of Mohs surgeons demonstrated a range of management preferences in high-risk cases and so management may differ between institutions.[59] **3**

A retrospective study from the UK examined a highly selected group of patients with head and neck cutaneous SCC, excluding the lip (n=194). Incomplete excision was independently associated with regional metastasis (OR 2.0, 95% CI not stated).[28] **3**

One study was identified which examined the recurrence rate at 28 month follow up of a population (n=84) who had undergone wider re-excision following the identification of positive excision margins. Recurrence occurred in 29% of those with positive re-excisions compared with 5% of those with negative re-excisions and this was independent of association with tumour diameter or depth.[60] **2+**

There is insufficient evidence about incomplete excision on which to base a recommendation.

✓ Where the tumour is present at the margin (the margin is involved) the case should be referred for discussion at the skin cancer MDT.

Where the tumour margin is close (<1 mm) to deep or peripheral excision margins and there are other high-risk features present, cases should be discussed at the skin cancer MDT for consideration of re-excision or radiotherapy.

The recommendation from the MDT will vary according to the site, size and number of high-risk features present. For many high-risk SCCs, an apparent pathological clearance margin of 1 mm would be considered insufficient. For some very high-risk SCCs, the recommendation will be for a clinical margin of 6-10 mm.

Where the apparent clearance margin is close (<1 mm) to deep or peripheral excision margins in low-risk tumours further excision may not be required.

The nearest peripheral and deep excisional margin should be measured to the nearest 0.1 mm and should be reported as a component of the core minimum dataset for primary squamous cell carcinoma. For orientated excisions, it is desirable to comment on which peripheral margin(s) is/are involved, or are closest to the tumour edge.

3.5 SENTINEL LYMPH NODE BIOPSY

Three reviews and a small retrospective study examined the utility of sentinel lymph node biopsy (SLNB) in patients with primary SCC.[61-64] No controlled studies were identified that investigated whether a positive sentinel node is predictive of patient outcomes or whether finding a positive sentinel node results in improved patient outcomes due to the additional treatments that ensue. There is evidence supporting the use of SLNB in intra-oral SCC, but no evidence was identified for cutaneous SCC.[65]

2++
2+
4

✓ For patients with SCC, sentinel lymph node biopsy should be conducted as part of a clinical trial.

3.6 BIOMARKERS

A number of biomarkers are being investigated as potential indicators of prognosis in patients with SCC. Preliminary retrospective studies focus on high-risk tumours.[66-68] No prospective studies were identified and there is insufficient evidence to make a recommendation on the use of biomarkers for identification of high-risk tumours.

3

4 Referral to the multidisciplinary team

A suggested management algorithm is outlined in Annex 3.

Multidisciplinary care is recognised as the preferred model of care for patients with skin cancer, and NICE recommends that all SCC be referred to the local MDT.[55] The MDT structures are different in Scotland but as a minimum the MDT should comprise, alongside the coordinator; a dermatologist, pathologist and surgeon. Ideally a clinical nurse specialist and oncologist should be involved as well as the referring clinician or their deputy. Where this guideline refers to the MDT, this would be equivalent to the Specialist Skin Cancer MDT (SSMDT) in England and Wales.

The guideline development group considers that referral is appropriate where any of the high-risk features identified in section 3 are present.

R **Where any of the following high-risk features are present, patients with primary SCC should be discussed at a skin cancer multidisciplinary team meeting:**

- **SCC arising on the ear**
- **tumour diameter >20 mm**
- **tumour thickness >4 mm**
- **tumour extension beyond dermis into or through subcutaneous fat**
- **perineural invasion**
- **poorly differentiated**
- **desmoplastic subtype**
- **immunosuppression.**

✓
- recurrent SCC
- established or suspected metastatic SCC
- nose, external lip, eyelid and scalp tumour site
- association with special clinical situations
- adenosquamous histological subtype
- spindle cell histological subtype
- pseudoangiosarcomatous histological subtype
- acantholytic histological subtype
- lymphovascular invasion
- tumour excision margins involved at deep or peripheral margins.

MDT discussion is desirable where:

- a tumour is at a surgically challenging site
- the referring clinician requests discussion due to specific clinical management issues, such as cognitive impairment or significant medical comorbidities.

All SCC including low risk SCC should be reported on a minimum dataset (*see Annex 5*) which allows all high-risk SCCs to be fast tracked to the MDT.

Data on all SCC should be subject to clinical audit and sent to the Cancer Registry.

5 Therapeutic interventions

5.1 SURGICAL TECHNIQUES

5.1.1 INTRODUCTION

Treatment for primary SCC involves complete removal or destruction of the tumour whilst preserving functional and aesthetic outcomes as much as possible.[69] Standard excisional surgery allows histological assessment of a proportion of peripheral and deep margins which is important for management of high-risk SCC. Removal by curettage and cautery or other destructive modalities does not allow any assessment of margin control. There is limited published evidence on the majority of treatment modalities and individual patient factors may influence the appropriate choice.[69]

✓ Treatment choices should be discussed with patients taking account of the risks and benefits in functional and aesthetic outcomes balanced against clinical outcomes.

5.1.2 STANDARD SURGICAL EXCISION

Conventional histological assessment of excision specimens with vertical bread-loaf sectioning examines 0.2–2% of the margins. Mohs micrographic surgery (MMS) uses en-face sections of the entire peripheral and deep margins of the excised tissue to allow examination of 100% of the margin. In one prospective study MMS was used to investigate the minimum peripheral margin required for clearance of SCC in 111 patients with 141 tumours. An initial margin of 2 mm was increased by 2 mm increments to compare 2 mm with 4 mm and 6 mm margins. Outcomes included the proportion of SCCs cleared at defined margins and the rate of tumour clearance as a function of tumour grade, location, and subcutaneous invasion. The overall clearance rate was 78% with a 2 mm margin, 96% with a 4 mm margin and 99% with a 6 mm margin. For tumours with high-risk features a 2 mm margin was associated with a poor rate of clearance; tumour diameter ≥20 mm, clearance rate of 55%, poorly differentiated tumours, clearance rate of 20%, tumour on ear, lip, scalp, eyelids or nose, clearance rate of 53%. A 4 mm margin resulted in clearance of 98% of those tumours with no subcutaneous invasion but only 90% of those with subcutaneous invasion. The study is limited by the small number of tumours with high-risk features and the lack of clinical follow up.[70] What constitutes an appropriate surgical margin is an area of great uncertainty with limited available evidence (*see section 9.2*). **3**

No evidence was identified on which to base a recommendation for the optimum deep margin. The surgical deep margin dimension depends on the anatomical site. When the skin is thin with minimal subcutis, for example on the ear, underlying cartilage may require excision to confidently achieve a deep clearance. Similarly, due to anatomical restriction, for all suspected scalp SCCs excision beneath the galea down to the periosteum should be carried out routinely to maximise the deep clearance in those cases where the tumour is clinically thought not to be invading periosteum or skull on clinical examination.[71] A retrospective observational study of 101 patients analysing histological deep clearance margins after attempted excision of scalp SCC showed local recurrence in three out of 37 patients with deep clearance <2 mm. No local recurrence was seen in 39 patients with deep clearance of 2–6 mm or in 20 patients with deep clearance >6 mm. Five patients had involvement of the periosteum with or without involvement of the outer table of skull and proceeded to excision of outer table of the skull; three out of five of these patients had local recurrence. Regional recurrence was seen in seven patients (2 in the <2 mm deep clearance group and 5 in the 2–6 mm deep clearance group). These findings suggest that a narrower deep histological margin may be associated with an increased risk of local recurrence, however the cause of local recurrence may be due to other possible confounding tumour and patient factors not taken into account in the study.[71] When periosteum bone is involved clinically, either deeper excision of the periosteum with or without outer table of skull may be performed in combination with adjuvant radiotherapy, or the patient should have adjuvant radiotherapy alone.[71] If choosing a surgical option pre-operative imaging may be helpful in surgical planning. **3**

✓ The aim of surgery for squamous cell carcinoma should be complete histological clearance at peripheral and deep margins. To achieve adequate deep clearance, the surgeon should excise at the anatomical plane deep to the clinically apparent level of tumour invasion. This anatomical plane will vary according to tumour site.

R **For high-risk tumours a clinical peripheral margin of 6 mm or greater is indicated, where surgically achievable and clinically appropriate.**

For low-risk tumours a clinical peripheral margin of 4 mm or greater is indicated where surgically achievable and clinically appropriate.

✓ An adequate diagnostic biopsy (incisional ellipse or wedge) can be helpful for planning the most appropriate treatment.

When clinical clearance is uncertain, a delayed reconstruction pending the results of paraffin wax histology may be prudent.

5.1.3 MOHS MICROGRAPHIC SURGERY

During Mohs micrographic surgery frozen sections of excised skin and subcutis can be oriented and studied to determine whether tumour clearance has been obtained. Horizontal sectioning of excised tissue allows 100% of the peripheral and deep margins to be checked giving reassurance about clearance and when necessary, to excise more tissue in as precise a way as possible. There is the added benefit of avoiding excessive excision of normal tissue. MMS also provides a means of identifying perineural invasion and following involvement until clearance is achieved or is deemed not possible due to the presence of a cranial foramen.[72] Although accepted as treatment for patients with high-risk BCCs, MMS is used less often for high-risk SCCs due to concerns about the presence of in transit metastases and the possibility of skip lesions, and the more challenging interpretation of slides (permanent sections may be preferred to frozen sections).[73,74,75] Experience of using Mohs in some institutions shows low five-year recurrence rates for both primary and recurrent SCC. The largest prospective multicentre case series of 1,263 patients reported in 2005 and used the Australian Mohs surgery database of patients with SCC treated with MMS between 1993 and 2002. Recurrent tumours were larger, had larger end-surgical defects, required more stages to excise and had more subclinical extension than primary tumours. Of 381 patients (30%) followed up at five years local recurrence had occurred in 2.6% with primary SCC and 5.9% with previously recurrent SCC.[76] **4 3**

A meta-analysis identified 18 case series reporting outcomes from MMS in patients with SCC. Local recurrence was reported in 10 studies (n=1,572) and ranged from 0% to 5.7% with a pooled average of 3.0% (95% CI 2.2% to 3.9%). Mean follow-up periods in the studies varied from 18.6 months to 77.3 months.[69] **3**

No evidence was identified comparing outcomes after MMS with surgical excision.

MMS requires specialist training, skills and equipment and is a limited resource within NHSScotland.

Where a high-risk SCC arises in a critical anatomical site requiring both complete clearance and preservation of normal tissue, surgical excision with margin control may be recommended by the skin cancer MDT. In such cases, MMS would be the treatment of choice.[75,76] Use of conventional vertical frozen sections is less precise with sampling error potentially giving false positive or false negative results (from 13 samples two were false positive (15.4%) and two were false negative).[77,78] **4 3**

R **Mohs micrographic surgery should be considered at the multidisciplinary team meeting, for selected patients with high-risk tumours where tissue preservation or margin control is challenging, and on an individual case basis for patients with any tumour at a critical anatomical site.**

✓ Use of conventional frozen section histology in high-risk SCC is not advised.

5.2 DESTRUCTIVE TECHNIQUES

5.2.1 CURETTAGE AND CAUTERY

Where curettage and cautery is used for treatment of patients with low-risk SCC, a blunt curette allows delineation of friable tumour tissue from surrounding normal tissues facilitating adequate removal at deep and peripheral margins.

A meta-analysis identified eight retrospective case series examining outcomes following curettage (with a blunt curette) plus cautery (also referred to as electrodessication). Pooled average recurrence (the nature of which was unspecified) from seven of the studies (n=1,131) was 1.7% (95% CI 0.6% to 3.4%). In this pooled analysis 91% of the tumours had a horizontal diameter <20 mm. One series reported using two treatment cycles and one using three but most series did not indicate the number of treatment cycles.[69] **3**

No studies were identified on curettage performed with a single-use sharp ring curette.

R **Curettage and cautery can be considered for patients with low-risk SCCs, if healthcare professionals have had appropriate training with a blunt curette.**

✓ Curettage and cautery is not suitable for high-risk SCC and should not be used where there are any high-risk clinical features.

If the dermis is breached during curettage then the procedure should be converted to formal excision.

If the pathology report indicates any high-risk feature the patient should be referred to a skin cancer MDT for consideration of further treatment, since histological margins cannot be assessed.

5.2.2 SAUCERISATION/DEEP SHAVE EXCISION

In a systematic review no evidence was identified on the effectiveness of saucerisation in the treatment of primary squamous cell carcinoma.[69]

In practice, this technique is used as an alternative to curettage and cautery as a treatment for possible low-risk SCC, for example when a differential diagnosis of bowenoid actinic keratoses or intra-epidermal carcinoma is being considered. It has the advantage of achieving a single intact specimen, which can be orientated with a marking suture and so comment can also be made on tumour depth and histological clearance. Cautery of the surgical defect can be performed as a destructive technique in the same way as after curettage.

5.2.3 PHOTODYNAMIC THERAPY

A meta-analysis identified 14 small prospective studies of photodynamic therapy using topical or systemic photosensitisers. Eight of the studies examined outcomes following apparent complete response and the pooled odds of recurrence at six to 38 months were 26.4% (95% CI 12.3% to 43.7%) based on 119 tumours.[69] **2+**

R **Photodynamic therapy should not be used for treatment of primary squamous cell carcinoma.**

5.2.4 CRYOTHERAPY

A meta-analysis identified eight case series (n=273) examining outcomes following cryotherapy. One series of seven patients used nitrogen peroxide as a freezing agent. Three series (n=206) used a technique of curettage followed by cryotherapy. Two series used a thermocouple at the base of the lesion to monitor the temperature (n=139). These techniques are not used routinely in Scotland. Two series (n=45) used a liquid nitrogen spray method. The pooled recurrence rate was 2%. Follow-up duration was between six months and five years. Most lesions in the analysis were low-risk SCCs (<20 mm).[69] Intervention protocols were not standardised and are likely to be user dependent. **3**

There is insufficient evidence on which to base any recommendation.

5.2.5 LASER THERAPY

A meta-analysis identified one retrospective study reporting outcomes from patients with non-melanoma skin cancers (SCC n=86) treated with neodymium laser after a mean follow up period of 8.2 years. In patients with SCC >20 mm in diameter recurrence was 14.2% (95% CI 0.4% to 57.9%).[69] **2+**

There is insufficient evidence on which to base any recommendation.

5.3 TOPICAL THERAPIES

5.3.1 IMIQUIMOD

A systematic review identified nine studies reporting on the use of imiquimod for cutaneous SCC in small numbers of patients, commonly where surgery was not appropriate. Eight of the studies (n=12) reported complete response post-treatment. Follow up ranged from six months to four years and there were no reported recurrences. Skin irritation was frequently reported.[69] **2+**

There is insufficient evidence on which to base any recommendation.

5.4 CHEMOTHERAPY

5.4.1 SYSTEMIC CHEMOTHERAPY

Evidence on the use of systemic chemotherapy, either alone or in combination with radiotherapy in the management of cutaneous SCC is mainly from small case series. A review highlights how chemotherapy has been used neoadjuvantly, either prior to surgery or radiotherapy for advanced high-risk tumours. This strategy has been applied to squamous cell cancers at other sites such as the head and neck and anus but the evidence in cutaneous SCC is based on small case series. Agents that have been used include cisplatin, vindesine, mitomycin C, 5-fluorouracil, methotrexate, bleomycin, interferon and doxorubicin. The review included one small randomised study (n=36) of adjuvant 13-cis-retinoic acid and interferon in patients with high-risk features following surgery, which failed to demonstrate any benefit compared to a control group.[79] Chemotherapy has been added to postoperative radiotherapy in patients with high-risk tumours but the only randomised controlled studies pertain to head and neck tumours and there is insufficient evidence to recommend this for cutaneous SCC.[30] **4**

There is insufficient evidence on which to base any recommendation.

✓ Systemic chemotherapy for the management of patients with primary cutaneous SCC should not be used outside of a clinical trial.

Systemic chemotherapy may be appropriate for patients with metastatic SCC.

5.4.2 INTRALESIONAL/TOPICAL 5-FLUOROURACIL

A systematic review identified three studies of intralesional/topical 5-fluorouracil (5FU) in patients with SCC. A prospective study (n=23) reported histologically confirmed clearance in 96% of patients at 16 weeks post-treatment. Recurrence beyond this period was not assessed. A single case report recorded no recurrence at five-month follow up. One series reported a post-treatment tumour regression in 42 of 53 (79%) cutaneous SCCs with three courses of 5%, 10% or 20% topical 5FU. No recurrences were observed in those patients who were disease free at one year after treatment.[69] **2+**

There is insufficient evidence on which to base any recommendation.

5.4.3 INTRALESIONAL INTERFERON

A systematic review identified four small studies examining the use of a range of types of interferon (IFN). The largest prospective series in 27 patients used intralesional IFN-alfa-2b and reported histological clearance in 89% of the patients at 18 weeks. There was no further follow up reported. In this series 65% of patients had more than one adverse event. These included headache, fever and flu-like symptoms. Severe adverse events were reported in 10% of patients.[69] **2+**

There is insufficient evidence on which to base any recommendation.

5.5 RADIOTHERAPY

5.5.1 PRIMARY RADIOTHERAPY

A meta-analysis identified one prospective and 13 retrospective studies of primary radiotherapy in patients with SCC. Radiation sources included orthovoltage, megavoltage or electron therapy. Dose, fractionation and fields were not uniformly reported and were variable. Follow up ranged from less than six months to over ten years and the prognostic features (size, site and stage) of the tumours varied widely. Local recurrence was 6.4% (95% CI 3.0% to 11.0%) based on seven studies (n=761). Disease-specific death was 9.1% (95% CI 1.4% to 22.8%) based on five studies (n=191).[69] **2+**

A meta-analysis identified four prospective and two retrospective studies (n=88) examining a range of brachytherapy techniques. Local recurrence was 5.2% (95% CI 1.6% to 10.5%) with a range of follow-up periods with a median of 55 months.[69] **2+**

Previous guidelines recommend that radiotherapy should be used with caution on sites where the intervention is poorly tolerated such as the back of the hand, lower limb and where the tumour invades bone or cartilage. There are contraindications related to long term cosmesis in younger patients and the potential for radiation-induced second malignancy.[37] **4**

Radiotherapy is contraindicated in patients with previously irradiated sites and with genodermatoses predisposing to skin cancer.[37] **4**

Radiotherapy may be particularly indicated in older patients where comorbidities or significant risks associated with general anaesthetic prevent consideration of surgery. It may also be suitable where a patient has anxiety disorder or is intolerant to local anaesthetic.[30] **4**

R **Primary radiotherapy should be considered for individual patients where surgical excision would be extremely challenging or difficult to perform or would be likely to result in an unacceptable functional or aesthetic outcome.**

✓ Radiotherapy should be delivered by a clinical oncologist with a special interest in the management of skin cancer including SCC.

5.5.2 ADJUVANT RADIOTHERAPY

A systematic review of 49 reports involving 2,449 patients with cutaneous SCC documented 91 cases (4%) receiving adjuvant radiotherapy. The reasons for giving adjuvant radiotherapy were provided in eight studies, but tumour size and margin status were not defined (clear margins were specifically documented in only 39% of cases). As regional and distant recurrences were higher in patients who received adjuvant radiotherapy, it is probable that patients referred for radiotherapy had more advanced disease or positive surgical margins. A statistically equivalent local recurrence and disease-specific death rate for surgery alone and surgery plus radiotherapy, may represent evidence that adjuvant radiotherapy is effective in controlling local recurrence in advanced disease.[30,80] **3**

A retrospective study of 217 patients with T1/T2 squamous cell carcinoma of the lip demonstrated that the addition of local adjuvant radiotherapy in patients with a close or positive surgical margin (defined arbitrarily as <2 mm) was associated with significant improvement in relapse-free survival compared to patients with close margins who had surgery alone (p=0.008). A tumour thickness of greater than 4 mm was also associated with an increased risk of recurrence, especially within the regional nodes.[81] **2+**

Perineural invasion is one of the most commonly cited reasons for considering adjuvant radiotherapy (ART) in patients with SCC.[30,80]

A systematic review of uncontrolled studies of ART identified five studies (n=22) using ART because of the presence of perineural invasion. The pooled local recurrence rate after ART was 18.2% (95% CI 3.9 to 39.8%). Data were pooled from four studies (n=47) using ART in patients with no other high-risk tumours and the corresponding rate was 11.1% (95% CI 2.4% to 25.0%).[69] No comparative studies were identified.[80] **2+**

The extent of PNI appears to affect outcome (*see section 3.4.3*) but the selection of patients for postoperative adjuvant radiotherapy and the benefit of this management strategy remains unknown. This therapy is highlighted as an area for future research (*see section 9.2*).

R **Adjuvant radiotherapy should be considered for patients with a high risk of local recurrence or with close or involved margins where further surgery may be associated with increased risk of complications including functional or aesthetic morbidity.**

5.6 REDUCTION OF IMMUNOSUPPRESSION

Previous guidelines recommend that in organ transplant recipients with multiple, frequent or high-risk SCC, consideration should be given to reduction of immunosuppression.[37] This may be achieved by reducing doses of anti-metabolites or calcineurin inhibitors or by switching to mTOR (mammalian target of rapamycin) inhibitors. **4**

In a retrospective pilot study of organ transplant recipients (n=9) with high-risk SCC, reduction of immunosuppression was associated with prolongation of metastatic disease-free survival.[82] **3**

In a multicentre RCT of 120 transplant recipients with a history of SCC maintained on ciclosporin or converted to sirolimus-based immunosuppression, a significantly longer SCC-free survival was demonstrated in the sirolimus group (15 *v* 7 months p=0.02) with a relative risk of new SCCs in the sirolimus group of 0.56 (95% CI 0.32 to 0.98).[83] **2+**

A similar study of 155 renal transplant recipients with a history of prior cutaneous SCC demonstrated a significant risk reduction of new SCCs at one year (HR 0.50, 95% CI 0.28 to 0.90, p=0.021) but this was not significant at two years (HR 0.76, 95% CI 0.48 to 1.2; p=0.255).[84] **2+**

No evidence was identified demonstrating that switching to mTOR inhibitors results in increased survival in patients with high-risk SCC.

✓ In organ transplant recipients with high-risk SCC, particularly those with multiple tumours or recurrent disease, minimisation or substitution of immunosuppression should be considered at a skin cancer MDT and discussed with the patient's transplant physician where appropriate.

5.7 SYSTEMIC RETINOIDS

A systematic review of studies, published up until 2003, examining the use of oral retinoids for secondary prevention of skin cancers in solid organ transplant recipients identified three RCTs. All participants were renal transplant recipients. Two studies compared acitretin 25 mg and 35 mg respectively to placebo. Both studies reported a significant reduction in the number of new skin cancers developing in the acitretin groups. A third RCT comparing high- (0.4 mg/kg/day) and low-dose acitretin (0.2 mg/kg/day) reported no significant difference in the number of malignant lesions developing between high- and low-dose groups. Acitretin-related side effects, such as headaches, rash, musculoskeletal symptoms and hyperlipidaemia were common across all studies and caused withdrawal from treatment.[85] No evidence was identified to demonstrate whether systemic retinoids influence outcome of an established SCC although it is used as a treatment strategy for certain high-risk clinical situations such as immunosuppressed patients. **1+**

R **Selected patients who have developed multiple SCCs following renal transplantion should be considered for low-dose acitretin treatment** (10-30 mg/day) **for secondary prevention.**

Healthcare professionals should be aware that adverse effects are common, are dose related and may lead to dose reduction or discontinuation of treatment.

6 Follow up

Optimum follow-up interval and duration depends on identifying the small proportion of people with tumours most likely to recur or spread. The recurrence rates reported in prospective and retrospective series at various time points provide the evidence base for recommendations on follow up.

For lesions at low risk of recurrence where there is a small solitary tumour with clear margins and no high-risk features on the pathology report, follow up may be unnecessary.[20] **2+**

In a prospective series (n=615) 3% of patients developed local recurrence. Of these cases, 65% occurred within the first year of follow up. Local recurrence did not occur after the sixth year.[26] **2++**

A retrospective analysis of 200 patients treated with Mohs surgery compared characteristics of tumours that did and did not metastasise. Where metastasis occurred 80% of the cases were identified after three years of follow up.[40] This is in agreement with an audit study of clinical and histological prognostic factors in SCC.[86] Another study was also consistent in finding that most of the metastases (69%) occurred in the first year, with 84% in the second and 91% of cases identified by three years.[16] Local recurrence was 75% after two years and 83% after three years.[16] **2+ 3**

R **Patients with SCC with any high-risk features should be offered follow-up appointments every three to six months for 24 months following treatment. One further appointment at three years may be appropriate depending on the clinical risk.**

✓ Patients treated for low-risk SCC should be offered a review appointment to check histopathology (if not previously assessed), conduct skin surveillance and facilitate patient education in self examination and skin cancer prevention, if not previously undertaken.

Patients who are immunosuppressed and those who are developing multiple SCC should be offered long-term follow up. Advice on sensible photoprotection measures and self-skin examination should be offered to all patients at high risk of recurrence.

Ongoing follow up may be undertaken by an appropriately trained general practitioner with a specialist interest in dermatology or by a clinical nurse specialist. This is an opportunity to detect further primary skin cancers.

The psychological impact of skin cancer should be considered at follow up and patients referred for psychological support as appropriate.

7 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing squamous cell carcinoma with patients and carers and in guiding the production of locally produced information materials.

7.1 SOURCES OF FURTHER INFORMATION

7.1.1 ORGANISATIONS SPECIFIC TO SKIN CONDITIONS

British Association of Dermatologists
Willan House, 4 Fitzroy Square, London W1T 5HQ
Tel: 020 7383 0266
www.bad.org.uk • Email: admin@bad.org.uk

One of the aims of the British Association of Dermatologists is to raise awareness of all facets of skin disease. This charity provides a range of patient information leaflets.

British Skin Foundation
4 Fitzroy Square, London W1T 5HQ
Tel: 020 7391 6341
www.britishskinfoundation.org.uk

The British Skin foundation supports research into skin conditions. It provides information on the treatment of squamous cell cancer.

Changing Faces Scotland
Tel: 0845 4500 640 (Monday to Thursday, 8.30am to 3.00pm)
Email: scotland@changingfaces.org.uk

Changing Faces Scotland provides psychological support to people and families who are living with conditions, marks or scars that affect their appearance.

MASScot (Melanoma Action and Support Scotland)
17 Cairnhill Road, Bearsden, East Dunbartonshire G61 1AU
Tel: 0773 823 1260
www.masscot.org.uk • Email: leigh@masscot.org.uk /info@masscot.org.uk

MASScot is a skin cancer charity run by patients for patients. It aims to provide emotional support to patients and their carers. Referrals are made to qualified and insured therapists who provide a wide range of complementary therapies, paid for by the charity. MASScot raise awareness of skin cancers and patients needs with politicians, health boards, education departments, schools and sporting bodies.

7.1.2 ORGANISATIONS SPECIFIC TO CANCER

Cancer Support Scotland
The Calman Centre, 75 Shelly Road, Glasgow G12 0ZE
Freephone: 0800 652 4531 • Tel: 0141 337 8199
www.cancersupportscotland.org

Cancer Support Scotland provides emotional and practical support on a one-to-one basis and through community based groups. It provides complementary and talking therapies to anyone affected by cancer.

Cancer Research UK
Angel Building, 407 St John Street, London EC1V 4AD
Tel: 0300 123 1022
www.cancerresearchuk.org

Cancer Research UK funds research into cancer, campaigns on cancer issues and produces patient information leaflets.

CancerHelp UK
Tel: 0800 800 4040
www.cancerhelp.org.uk • www.cancerresearchuk.org/cancer-help

CancerHelp UK is a free information service about cancer and cancer care for people with cancer and their families. It is provided by Cancer Research UK. The site includes a comprehensive range of information including cancer prevention, diagnosis, treatment and follow up.

Macmillan Cancer Relief
89 Albert Embankment, London SE1 7UQ
Tel: 0808 808 0000
www.macmillan.org.uk

Macmillan Cancer Relief supports people with cancer and their families with specialist information, treatment and care.

Maggie's Cancer Caring Centres Scotland
The Gatehouse, 10 Dumbarton Road, Glasgow G11 6PA
Tel: 0300 123 1801
www.maggiescentres.org • Email: enquiries@maggiescentres.org

Maggie's provides practical, emotional and social support to people with cancer, their family and friends. Built alongside NHS cancer hospitals and staffed with professional experts, Maggie's Centres are warm and welcoming, full of light and open space, with a big kitchen table at their heart.

Marie Curie Cancer Care Scotland
14 Links Place, Edinburgh EH6 7EB
Tel: 0800 716 146
www.mariecurie.org.uk

Marie Curie Cancer Care provides practical nursing care at home and specialist care across its Marie Curie centres.

7.1.3 CANCER NETWORKS IN SCOTLAND

North of Scotland Cancer Network (NOSCAN)
www.noscan.scot.nhs.uk

South East Scotland Cancer Network (SCAN)
www.scan.scot.nhs.uk

West of Scotland Cancer Network (WOSCAN)
www.woscan.scot.nhs.uk

7.1.4 INFORMATION LEAFLETS FOR PATIENTS AND HEALTHCARE PROFESSIONALS

www.bad.org.uk/site/792/default.aspx

www.skincancer.org/squamous-cell-carcinoma.html

www.intelihealth.com/home

www.dermnetnz.org/lesions/squamous-cell-carcinoma.html

7.2 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers/relatives may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

In primary care
• Explain SCC fully including the clinical features and how (or why) they develop. • Advise patients that removal or biopsy of the tumour may occur at the initial visit. • Advise patients that it is appropriate to refer them to a specialist and how long they should expect to wait for an appointment.
At the specialist clinic
• Explain to patients how a diagnosis will be reached including: o clinical examination o types of biopsy and the need for local anaesthetic o how, when and by whom biopsy results will be given. • With any surgical procedure, whether small biopsy or large excision, explain about surgical complications which include: pain, swelling, bleeding, bruising, loss of function and unpredictable scarring including keloid scarring. • Advise patients about how long they should expect to spend at the hospital. • Be clear about the time between biopsy and treatment. • Describe what treatments will be offered.
At the specialist clinic once the diagnosis is known
• Explain the nature of the patient's particular SCC in precise terms. • Explain what further treatments are appropriate and what options there are. • Explain whether any other tests are appropriate, such as scans. • Give as much information as possible about the likely prognosis. • Explain how the majority of SCCs arise. • Where appropriate, explain that the patient's case will be referred to the MDT. • Explain whether other specialists will be involved in the treatment, such as Mohs surgeons, plastic surgeons, oral and maxillofacial surgeons, oncologists, clinical nurse specialists, etc. • Explain what might be involved in any one particular treatment eg flaps, grafts, complex reconstruction. • Try to give the patient some idea of the time to their definitive treatment, acknowledging that this might be difficult if other specialists are involved.

Follow up

- Discuss how well the treatment went and whether any further treatment is needed: surgery, radiotherapy or input from oncologists.
- Discuss the prognosis in light of the definitive treatment.
- Discuss the risk of recurrence and how the patient might detect this; and whether any tests are indicated to detect recurrence.
- Advise the patient about the likely length of follow up.
- Ensure patients are aware of the support role of a clinical nurse specialist and other health professionals eg Maggie's centre or camouflage clinic and refer if appropriate.
- Allow sufficient time to discuss the following with patients:
  - psychological adjustment after a diagnosis and treatment for skin cancer
  - anxiety and low mood
  - coping strategies
  - being visibly different/stigma
  - use of camouflage and cosmetics.
- Advise patients to bring a written list of questions or concerns. A proforma that addresses these aspects can focus the discussion time.
- Offer patient education about self-care for example:
  - explain self checking and getting to know their body
  - what to look for, eg features of abnormal skin lesions and what actions to take if they are concerned
  - discuss prevention including:
    - use of high-factor sunscreen
    - the damaging effects of sun beds
    - the need for precautions while working and taking holidays in the UK.
- Provide patients with written information leaflets and advise them how they can access self help groups (*section 7.1*).

8 Implementing the guideline

8.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

8.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

	Recommendation	Section
R	**Where any of the following high-risk features are present, patients with primary SCC should be discussed at a skin cancer multidisciplinary team meeting:** • **SCC arising on the ear** • **tumour diameter >20 mm** • **tumour thickness >4 mm** • **tumour extension beyond dermis into or through subcutaneous fat** • **perineural invasion** • **poorly differentiated** • **desmoplastic subtype** • **immunosuppression.**	**4**
✓	• recurrent SCC • established or suspected metastatic SCC • nose, external lip, eyelid and scalp tumour site • association with special clinical situations • adenosquamous histological subtype • spindle cell histological subtype • pseudoangiosarcomatous histological subtype • acantholytic histological subtype • lymphovascular invasion • tumour excision margins involved at deep or peripheral margins.	**4**
	MDT discussion is desirable where: • a tumour is at a surgically challenging site • the referring clinician requests discussion due to specific clinical management issues, such as cognitive impairment or significant medical comorbidities.	**4**
	All SCC including low risk SCC should be reported on a minimum dataset (*see Annex 5*) which allows all high-risk SCCs to be fast tracked to the MDT.	**4**
	Data on all SCC should be subject to clinical audit and sent to the Cancer Registry.	**4**
Implementation of these recommendations is a major change in practice which will require increased resource in terms of staff time for all involved specialties. Economic analysis of the potential impact is available in the supporting material section for this guideline at **www.sign.ac.uk**		

Recommendation		Section
R	**Mohs micrographic surgery should be considered at the multidisciplinary team meeting, for selected patients with high-risk tumours where tissue preservation or margin control is challenging, and on an individual case basis for patients with any tumour at a critical anatomical site.**	**5.1.3**

The recommendation may require specialist training for surgeons and new equipment for health boards where it is not currently used.

8.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- number/proportion of patients with features suggestive of high-risk SCC referred to a skin cancer multidisciplinary team meeting
- number/proportion of SCC pathology reports recording high-risk features
- use of a pathology core minimum dataset
- number/proportion of surgical specimens with sufficient clinical details on a histopathology request form
- diameter of lesion reported at referral
- documentation of clinical excision margins
- achievement of complete excision margins (histology margins equal or >1 mm)
- number of SCC with high-risk clinical features that are treated with curettage
- recurrence rates at five years after excision or curettage
- number/proportion of cases referred by MDT for Mohs micrographic surgery
- national audit of data capture for SCC.

9 The evidence base

9.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2007-2012. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

9.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to early management of patients with SCC. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Officer and presented to the guideline development group.

9.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (*see Annex 1*). The following areas for further research have been identified:

- Comparison of AJCC7 and Brigham and Women's Hospital (BWH) tumour staging.
- RCT comparing Mohs micrographic surgery with standard surgical excision of high-risk SCC. Outcomes to include recurrence, metastasis and disease-specific mortality.
- Study of the optimal clearance margin in high-risk tumours. Comparison of 2 mm versus 4 mm versus 6 mm versus MMS.
- RCT of the effect of adjuvant radiotherapy on local recurrence and mortality for high-risk tumours compared to surgery alone.
- Consistency of intra-observer variation in pathology reporting of features associated with high-risk tumours.
- RCT comparing curettage and electrodessication with standard surgical excision of low-risk SCC. Outcomes to include recurrence, metastasis and disease-specific mortality.
- RCT comparing blunt curettage with sharp curettage with 2 mm surgical excision.
- Large prospective audit studies in the UK to define the risk factors for SCC including the presence of pain/dysaesthesia and unusual clinical sites/subtypes.
- Effectiveness and cost effectiveness of SLNB in comparison with high-resolution ultrasound or microchip MRI or other high-resolution imaging modality (dependent on local availability).
- SLNB plus/minus completion lymph node dissection in high-risk SCC (eg T2a and T3 of BWH staging system).
- Evaluation of biomarkers for identification of high-risk tumours.
- Effect of patient education on the rate of patient self reporting of the development of new SCC.

9.3 REVIEW AND UPDATING

This guideline was published in 2014 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

10 Development of the guideline

10.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in "SIGN 50: A Guideline Developer's Handbook", available at **www.sign.ac.uk**

10.2 THE GUIDELINE DEVELOPMENT GROUP

Professor Charlotte Proby *(Chair)*	*Professor of Dermatology, Jacqui Wood Cancer Centre, Ninewells Hospital and Medical School, University of Dundee*
Dr Andrew Affleck	*Consultant Dermatologist and Dermatological Surgeon, Ninewells Hospital, Dundee*
Dr Peter Bowden	*Lay Representative, St Andrews*
Ms Juliet Brown	*Evidence and Information Scientist, SIGN*
Ms Moira Crumley	*Clinical Nurse Specialist in Skin Cancer, Glasgow Royal Infirmary*
Mr Roger Currie	*Consultant Oral and Maxillofacial Surgeon, Crosshouse Hospital, Kilmarnock*
Dr Alan Evans	*Consultant Dermatopathologist, Ninewells Hospital, Dundee*
Miss Katherine Farquhar	*Medical Student, Glasgow*
Ms Wilma Ford	*Macmillan Skin Cancer Nurse Specialist, Western Infirmary, Glasgow*
Dr Girish Gupta	*Consultant Dermatologist, Monklands Hospital, Airdrie*
Dr Khalid Hassan	*General Practitioner/Associate Specialist in Dermatology, Vale of Leven Hospital, Alexandria*
Dr Lorna Mackintosh	*Consultant Dermatologist, Western Infirmary, Glasgow*
Dr Marie Mathers	*Consultant Histopathologist, Western General Hospital, Edinburgh*
Dr Catriona McLean	*Consultant Clinical Oncologist, Western General Hospital, Edinburgh*
Dr Colin Moyes	*Consultant Dermatopathologist, Southern General Hospital, Glasgow*
Dr Lisa Naysmith	*Consultant Dermatological Surgeon and Dermatologist, Royal Infirmary of Edinburgh*
Dr Jonathan Norris	*Consultant Dermatologist, Dumfries and Galloway Royal Infirmary, Dumfries*
Ms Fiona Oakey	*Skin Cancer Clinical Nurse Specialist, Glasgow Royal Infirmary*
Mr Taimur Shoaib	*Consultant Plastic Surgeon, Glasgow Royal Infirmary*
Ms Leigh Smith	*Lay Representative, Chair of Melanoma Action and Support Scotland*
Ms Ailsa Stein	*Programme Manager, SIGN*
Dr Lorna Thompson	*Programme Manager, SIGN*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at **www.sign.ac.uk**

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on the contacts page of the SIGN website **www.sign.ac.uk**

Mr Euan Bremner	*Project Officer*
Mrs Lesley Forsyth	*Events Coordinator*
Mrs Karen Graham	*Patient Involvement Officer*
Ms Gemma Hardie	*Distribution and Office Coordinator*
Mr Stuart Neville	*Publications Designer*
Miss Rachel Wielinga	*Guideline Coordinator*

10.3 ACKNOWLEDGEMENTS

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

Dr Louise Lansbury	*Research Associate, Centre of Evidence Based Dermatology and School of Health Sciences, University of Nottingham*
Professor Jo Leonardi-Bee	*Associate Professor in Medical Statistics, University of Nottingham*
Mr Andy Malyon	*Consultant Plastic Surgeon, Glasgow Royal Infirmary*
Dr Alastair Milne	*Consultant Pathologist, Crosshouse Hospital, Kilmarnock*

10.4 CONSULTATION AND PEER REVIEW

10.4.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 6 December 2013 and was attended by 86 representatives of the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

10.4.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by external reviewers, and must justify any disagreement with the reviewers' comments. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Fiona Bath-Hextall	*Reader and Associate Professor in Evidence Based Healthcare, University of Nottingham*
Dr Thomas Brenn	*Consultant Dermatopathologist, Western General Hospital, Edinburgh*
Dr Patrick Cadigan	*Registrar, on behalf of the Royal College of Physicians, London*
Dr Graham Colver	*Consultant Dermatologist, Chesterfield Royal Hospital*
Dr Colin Fleming	*Consultant Dermatologist and Dermatological Surgeon Ninewells Hospital, Dundee*
Professor Nicole Kelleners-Smeets	*Associate Professor Dermatology, Maastricht University Medical Centre, The Netherlands*

Dr Charles Kelly	*Lead of Radiotherapy/Lead Oncologist on behalf of the Royal College of Radiologists, London*
Dr Daniel Kemmett	*Consultant Dermatologist, Royal Infirmary of Edinburgh/ President, Scottish Dermatology Society*
Dr Louise Lansbury	*Research Associate, Centre of Evidence Based Dermatology and School of Health Sciences, University of Nottingham*
Ms Lesley Lockhart	*Team Leader, Fellowship Support Unit, on behalf of the Royal College of Physicians of Edinburgh*
Dr Andrew Marsden	*Chair, Evidence Review Committee, Scottish Health Technology Group, Healthcare Improvement Scotland*
Mrs Kirsty MacFarlane	*Principal Pharmacist, on behalf of the Scottish Medicines Consortium*
Dr Richard Motley	*Consultant in Dermatology and Cutaneous Surgery, Welsh Institute of Dermatology, University Hospital of Wales, Cardiff*
Dr Frank Muller	*Consultant Dermatologist, Aberdeen Royal Infirmary*
Dr M Firouz Mohd Mustapa	*Clinical Standards Manager, on behalf of the British Association of Dermatologists*
Miss Carrie Newlands	*Consultant Oral and Maxillofacial Surgeon, Royal Surrey County Hospital, Guildford*
Professor Barry Powell	*Professor of Plastic and Reconstructive Surgery, Royal Surrey County Hospital, Guildford*
Dr Chrysalyne D Schmults	*Assistant Professor of Dermatology, Harvard Medical School, Boston, USA*
Dr David Slater	*Consultant Dermatopathologist, Royal Hallamshire Hospital, Sheffield*
Mr Martin Telfer	*Consultant Maxillofacial Surgeon, York Hospital*
Dr Ian Zealley	*Consultant Radiologist, Ninewells Hospital, Dundee*

10.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows.

Mr Ian Colquhoun	*Royal College of Physicians and Surgeons of Glasgow*
Mr Andrew de Beaux	*Royal College of Surgeons of Edinburgh*
Dr Richard Herriot	*Royal College of Pathologists*
Dr Roberta James	*SIGN Programme Lead; Co-Editor*
Professor John Kinsella	*Chair of SIGN; Co-Editor*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council Membership page of the SIGN website **www.sign.ac.uk**

Abbreviations

5FU	5-fluorouacil
AJCC	American Joint Committee on Cancer
ART	adjuvant radiotherapy
BCC	basal cell carcinoma
BWH	Brigham and Women's Hospital
CI	confidence interval
CT	computed tomography
FNA	fine needle aspiration
HIV	human immunodeficiency virus
HR	hazard ratio
IFN	interferon
LVI	lymphovascular invasion
MA	marketing authorisation
MDT	multidisciplinary team
MMS	Mohs micrographic surgery
MRI	magnetic resonance imaging
MTA	multiple technology appraisals
mTOR	mammalian target of rapamycin
NICE	National Institute for Health and Care Excellence
OR	odds ratio
PET	positron emission tomography
PNI	perineural invasion
PUVA	psoralen plus ultraviolet A
SCC	squamous cell carcinoma
SE	sun-exposed
SIGN	Scottish Intercollegiate Guidelines Network
SLNB	sentinel lymph node biopsy
SMC	Scottish Medicines Consortium
SSMDT	specialist skin cancer multidisciplinary team
TNM	tumour node metastasis
UICC	Union for International Cancer Control
UVR	ultraviolet radiation

Annex 1

Key questions used to develop the guideline

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Key question	***See guideline section***
1. Which features, or combination of features best identify high-risk tumours (or facilitate risk stratification) in patients with primary invasive cutaneous squamous cell carcinomas?	
• Clinical features	3.2
- age	
- sex	
- immunosuppression (via disease or medication)	
- comorbidities	
- site	
- number	
- clinical size	
- speed of growth	
- pain (neurological) dysaesthesia/numbness	
- previous radiotherapy	
- recurrence	
- poorly defined borders	
- chronic injury	
- PUVA therapy	
- field cancerisation	
- association with Bowens disease.	
• Imaging features	3.3
• Pathological features	3.4
- tumour subtype	
- mitotic rate	
- horizontal size	
- depth	
- differentiation	
- perineural invasion	
- lymphovascular invasion	
- incomplete excision	
• Sentinel lymph node biopsy	3.5
• Biomarkers	3.6
2. What are the most effective interventions for management of patients with primary invasive cutaneous squamous cell carcinomas?	
• Surgical techniques	5.1
- standard surgical excision	
- Mohs micrographic surgery	
• Destructive techniques	5.2
- curettage and cautery	

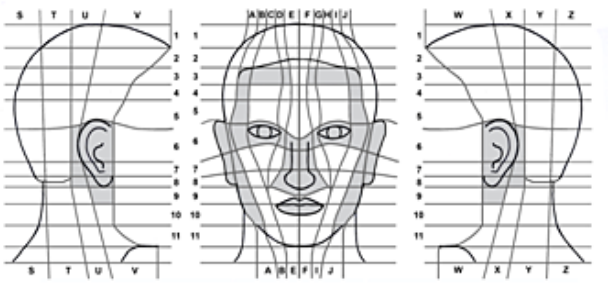
	- shave - cryotherapy - electrodessication • Topical therapies • Chemotherapy • Radiotherapy • Reduction of immunosuppression	 5.3 5.4 5.5 5.6
3.	Which patients should be referred into the local/regional skin cancer MDTs?	4
4.	What is the appropriate follow-up interval/duration following treatment for SCC in each risk grouping?	6

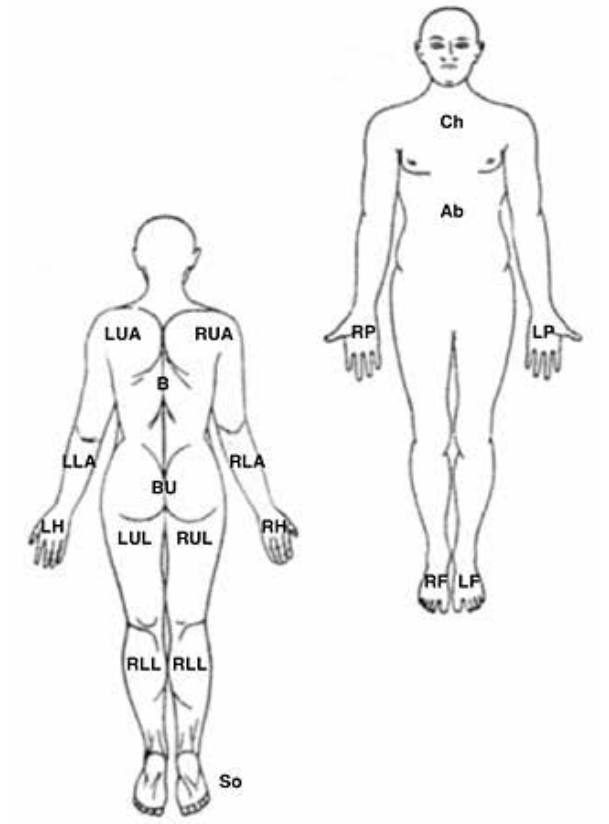
Annex 2

The UK national histopathology request form for skin biopsies

Date of surgical procedure	
Name of surgeon	
Clinical diagnosis: free text	
Please attach patient details	
Grade of surgeon: Nurse, Specialist trainee, Consultant, Hospital Practitioner, Other	

Mandatory for Clinicians to complete:	**First biopsy**	**Second**	**Third**	**Fourth**
Site Code as per image (insert LUL etc)				
Clinical diagnosis (select either BCC, SCC, melanoma, atypical mole, other tumour or other). For inflamatory lesions add clinical details as free text.				
Clinical size of lesion sampled (max diameter) (mm)				
Intention of the surgeon (select biopsy, excision or curative curettage)				
Procedure (select curettage, shave biopsy, punch, incisional biopsy or excision)				
For tumours give measured surgical clinical margin (mm)				
Is this a recurrent tumour?	Y/N	Y/N	Y/N	Y/N
Is the patient immunocompromised?	Y/N			
Is the tumour arising in areas of radiation or thermal injury, chronic draining sinuses, chronic ulcers, chronic inflamation or Bowen's Disease	Y/N	Y/N	Y/N	Y/N
Is the tumour arising in a genetically predisposed individual?	Y/N			



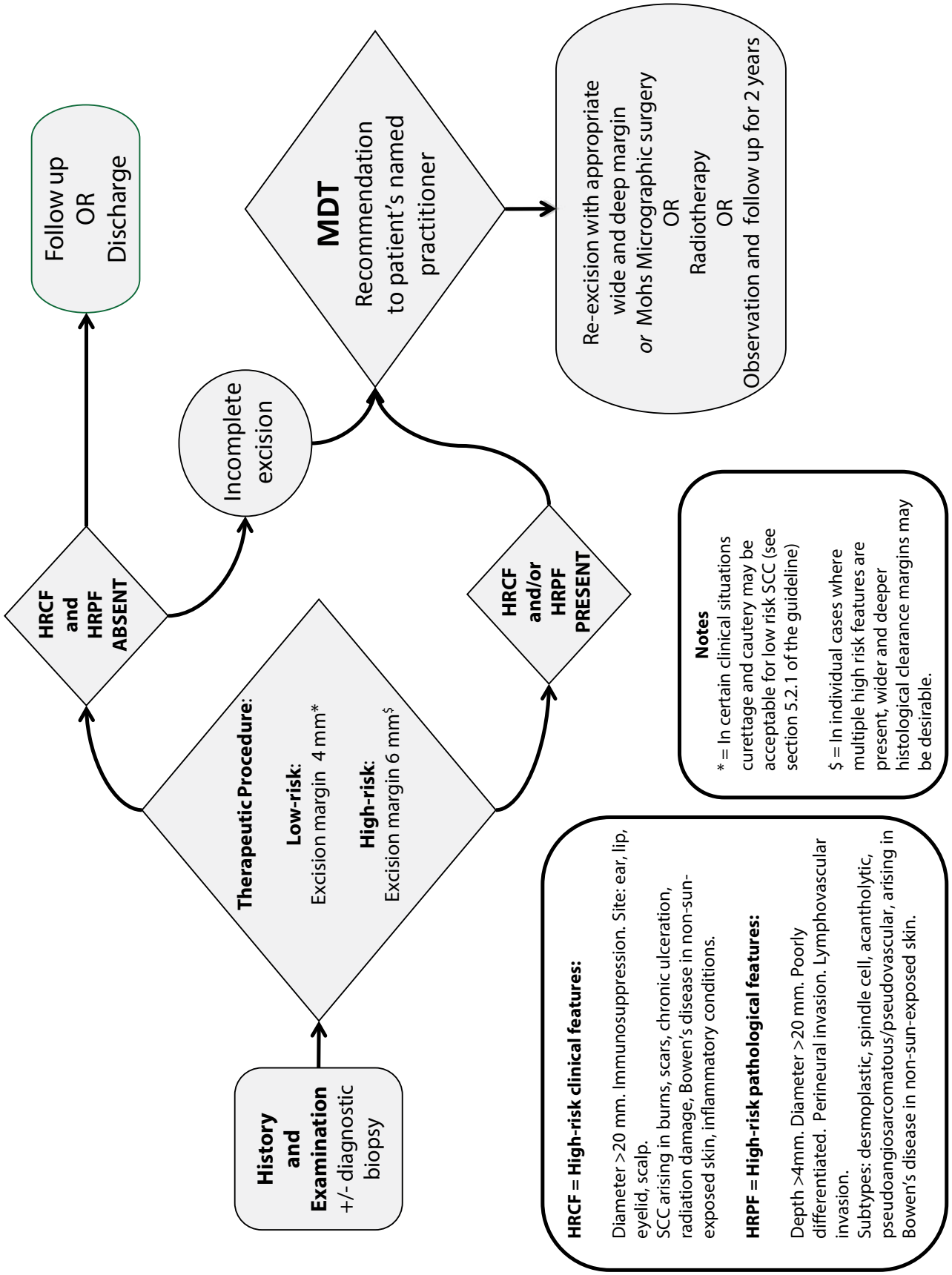


Please mark site of samples taken on the above images For head and neck skin cancers the site code will be made up of the number in the horizontal grid and the letter from the vertical grid (eg for a tumour in the middle of the nose that might be code 8E). Where a lesion lies across grid lines then that grid reference in which the greater part of the tumour lies should be used OR if the lesion impacts on a grey shaded area or on the lips then that code should be used. Where the tumour is on the marked lips then the code LIP should be used. For tumours outside the head and neck the letters are indicated on the body map eg a tumour on the left lower arm is LLA).

Reproduced with permission from the National Cancer Intelligence Network[27]

Annex 3

SCC Management algorithm



Annex 4

Staging systems

Table 1: Summary of the AJCC, UICC, and BWH Tumor (T) Staging Systems	
Tumor Staging System	Definition
AJCC	
T1	Tumor ≤2 cm in greatest dimension with fewer than two high-risk factors*
T2	Tumor >2 cm in greatest dimension or with two or more high-risk factors*
T3	Tumor with invasion of orbit, maxilla, mandible, or temporal bones
T4	Tumor with invasion of other bones or direct perineural invasion of skull base
UICC	
T1	Tumor ≤ 2 cm or less in greatest dimension
T2	Tumor >2 cm in greatest dimension
T3	Tumor with invasion of deep structures (eg, muscle, cartilage, bone [excluding axial skeleton], orbit)
T4	Tumor with invasion of axial skeleton or direct perineural invasion of skull base
BWH	
T1	0 high-risk factors†
T2a	1 high-risk factor
T2b	2–3 high-risk factors
T3	≥4 high-risk factors or bone invasion

Abbreviations: AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; T, tumor stage from TNM staging system; UICC, International Union Against Cancer.

*AJCC high-risk factors include '>2 mm thickness, Clark leve' ≥IV, perineural invasion, primary site ear, primary site non–hair-bearing lip, or poorly differentiated histology.

†BWH high-risk factors include tumor diameter '≥2 cm, poorly differentiated histology, perineural invasion' ≥0.1 mm, or tumor invasion beyond fat (excluding bone invasion which automatically upgrades tumor to BWH stage T3).

Reprinted with permission. © (2014) American Society of Clinical Oncology. All rights reserved. Karia PS, Jambusaria-Pahlajani A, Harrington DP, Murphy GF, Qureshi AA, Schmults CD. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital Tumor Staging for Cutaneous Squamous Cell Carcinoma. J Clin Oncol. 2014;32(4):327-34

Annex 5

Pathology reporting proforma

PATHOLOGY REPORTING PROFORMAFOR PRIMARY CUTANEOUS SQUAMOUS CELL CARCINOMA

Patient's Name _____ Report no._____

CHI No _____ Date of Birth _____Sex _____

Hospital _____

Date of receipt _____ Date of reporting _____

Pathologist _____ Surgeon _____

CLINICAL DETAILS

Clinical site _____ ☐High risk site (ear, nose, lip, eyelid, scalp)*

Immunosuppressed Not stated ☐ Yes* ☐

Specimen type

Excision biopsy ☐ Incisional (diagnostic) biopsy ☐ Punch biopsy ☐

Shave biopsy ☐ Curettings ☐ Not specified ☐

MACROSCOPIC EXAMINATION

Size of specimen length _____mm x breadth _____ mm x depth _____mm

Maximum size of lesion _____mm Greater than 20 mm ☐ No ☐ Yes*

MICROSCOPY

HISTOLOGICAL SUBTYPE

☐ 1. No special type ☐ 2. Verrucous

☐ 3. Desmoplastic* ☐ 4. Acantholytic/pseudoglandular/pseudovascular*

☐ 5. Adenosquamous* ☐ 6. Spindle/sarcomatoid/metaplastic*

☐ 7. Keratoacanthoma-like

☐ 8. Other (please specifiy) _____

TUMOUR THICKNESS **LEVEL INVOLVED**

☐≤4 mm ☐ Limited to dermis

☐>4 mm* ☐Into subcutaneous fat*

Depth in mm _____ ☐ Beyond fat* into - ☐muscle* ☐cartilage* ☐bone*

DIFFERENTIATION

☐ Well ☐ Moderate ☐ Poor *

PERINEURAL INVASION

☐ Not identified ☐ Present*

LYMPHATIC OR VASCULAR INVASION

☐ Not identified ☐ Present*

TUMOUR MARGINS

Peripheral clearance _____ mm ☐ Involved (0 mm)* ☐ Close (<1 mm)*

Deep clearance _____ mm ☐ Involved (0 mm)* ☐ Close (<1 mm)*

RISK ASSESSMENT FOR MDT (MULTIDISCIPLINARY TEAM) REFERRAL –
A PATIENT SHOULD BE CONSIDERED FOR MDT REFERRAL IF ONE OR MORE HIGH RISK FEATURES ARE PRESENT

Summary of high-risk features present (all high-risk are features marked with *)

Immunosuppressed	
High-risk site (ear, nose, lip, eyelid, scalp)	
Macro diameter > 20 mm	
Desmoplastic/adenosquamous/spindle	
Tumour thickness > 4 mm	
Invasion into subcutis or deeper	
Poorly differentiated	
Presence of perineural invasion	
Presence of lymphatic or vascular invasion	
Close or involved margin (<1 mm clearance)	
TOTAL NUMBER OF HIGH RISK FEATURES	

SUMMARY

RISK STATUS FOR *MDT REFERRAL* ☐**Low risk** ☐**High risk (≥1 high-risk feature)**

TNM (pT) STAGE (AJCC7) _____

COMMENTS _____

_____

_____

_____

PATHOLOGIST _____**DATE** _____

Adapted from Royal College of Pathologists[27]

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Edinburgh Office | Gyle Square |1 South Gyle Crescent | Edinburgh | EH12 9EB
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Glasgow Office | Delta House | 50 West Nile Street | Glasgow | G1 2NP
Telephone 0141 225 6999 Fax 0141 248 3776

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