British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma 2020

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British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma 2020

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NICE has renewed accreditation of the process used by the British Association of Dermatologists to produce clinical guidelines. The renewed accreditation is valid until 31 May 2021 and applies to guidance produced using the processes described in Updated guidance for writing a British Association of Dermatologists clinical guideline – the adoption of the GRADE methodology 2016. The original accreditation term began on 12 May 2010. More information on accreditation can be viewed at www.nice.org.uk/accreditation. www.nice.org.uk/accreditation.

Footnote:

This is an updated guideline prepared for the British Association of Dermatologists (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines Sub-committee. Members of the Clinical Standards Unit that have contributed are: NJ Levell (Chair, Therapy & Guidelines subcommittee), B McDonald, A Salim, SL Chua, G. Petrof, A Bardhan, P Rakvit, M Hashme [BAD Information Scientist], LS Exton [BAD Guideline Research Fellow], MF Mohd Mustapa [BAD Clinical Standards Manager].

1.0 Purpose and scope

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the management of cutaneous squamous cell carcinoma (cSCC). The document aims to:

- offer an appraisal of all relevant literature up to 30th January 2020, focusing on any key developments
- address important, practical clinical questions relating to the primary guideline objective.
- provide guideline recommendations and if appropriate research recommendations

The guideline is presented as a detailed review with highlighted recommendations for practical use in primary, secondary and tertiary care, in the clinic and in the appropriate Skin cancer MDT meetings (see section 3.0. These may be either local Skin MDTs (LSMDTSs or specialist skin cancer MDTs (SSMDTs) depending on the clinicopathological features of the SCC. Clinicans treating people with cSCC should be Core members of the appropriate MDT or sanctioned by the MDT to treat the tumour. https://www.nice.org.uk/guidance/csg8/evidence/full-guideline-2006-pdf-2191950685. There is also an updated Patient Information Leaflet (PIL; available on the BAD website, http://www.bad.org.uk/public).

1.1 Exclusions

The guideline does not cover:

- non-cutaneous primary SCC or *SCC in situ* (Bowen's disease). There is a separate guideline for SCC *in situ*.[1]
- mucosal SCC, e.g. for the lip the remit of this guideline stops at the vermillion border
- secondary prevention[2,3]

2.0 Methodology

This set of guidelines has been developed using the BAD's recommended methodology,[4] further information can be found in Appendix J (see Supplementary Information) with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument [www.agreetrust.org][5] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (https://www.gradeworkinggroup.org). Recommendations were developed for implementation in the UK National Health Service (NHS).

The guideline development group (GDG) consisted of seven consultant dermatologists (representing England, Northern Ireland, Scotland and Wales), two consultant clinical oncologists (radiation oncologists), a consultant plastic surgeon, a consultant maxillo-facial surgeon, a dermatopathologist, a general practitioner, a Macmillan dermatology clinical nurse specialist, two patient representatives and a technical team (consisting of an information scientist, a guideline research fellow and project manager providing methodological and technical support).

The GDG established several clinical questions pertinent to the scope of the guideline and a set of outcome measures of importance to patients, ranked according to the GRADE methodology[6] (see section 2.1 & Appendix A; see Supporting Information).

The GDG agreed to adopt the Royal College of Pathologists (RCPath) Dataset for the histological reporting of cSCC, https://www.rcpath.org/uploads/assets/9c1d8f71-5d3b-4508-8e6200f11e1f4a39/dataset-for-histopathological-reporting-of-primary-invasive-cutaneous-squamous-cell-carcinoma-and-regional-lymph-nodes.pdf. Along with Public Health England, this endorses the Union for International Cancer Control 8th edition (UICC8)[7] (Tables 1 & 2), rather

than the American Joint Committee on Cancer 8th edition cancer staging manual (AJCC8) which only covers head and neck cSCC.[8] The GDG agreed that risk is part of a spectrum and not dichotomous and the evidence from the literature searches supported a division based on low, high and very-high risk status. As shown in Figure 1 in section 3 (summary of recommendations) this division was achieved by integrating clinical, pathological, TNM staging and margin criteria.

A systematic literature search of PubMed, MEDLINE, EMBASE and Cochrane databases was conducted by the technical team to identify key articles on cSCC from 1 January 2007 to 30 January 2020; search terms and strategies are detailed in Appendix K (see supplementary information). Additional references relevant to the topic were also isolated from citations in reviewed literature and the previous versions of the guidelines.[9,10] Data extraction and critical appraisal, data synthesis, evidence summaries, lists of excluded studies and the PRISMA diagram were prepared by the technical team. Evidence from included studies was rated according to the GRADE system (high, moderate, low or very low quality).

Recommendations are based on evidence drawn from systematic reviews of the literature pertaining to the clinical questions identified, following discussions with the entire GDG and factoring in all four factors that would affect its strength rating according to the GRADE approach (i.e. balance between desirable and desirable effects, quality of evidence, patient values and preferences and resource allocation). All GDG members contributed towards drafting and/or reviewing the narratives and information in the guideline and supporting information documents. When there is insufficient evidence from the literature, informal consensus is reached based on the experience of the GDG.

The summary of findings with forest plots (Appendix B; see Supporting Information), clinical evidence summary (Appendix C; see Supporting Information), tables Linking the Evidence To the Recommendations (LETR) (Appendix D; see Supporting Information), GRADE evidence profiles indicating the quality of evidence (Appendix E; see Supporting Information), summary of included studies (Appendix F), narrative findings for non-comparative studies (Appendix G; see Supporting Information), PRISMA flow diagram (Appendix H; see Supporting Information) and list of excluded studies (Appendix I; see Supporting Information) are detailed in the supplementary information. The strength of recommendation is expressed by the wording and symbols as shown in Table 3.

2.1 Clinical Questions and Outcomes

The GDG established a number of clinical questions pertinent to the scope of the guideline (see Appendix A for full review protocols see Supporting information). The GDG also established a set of outcome measures of importance to patients for each clinical question, that were ranked according to the GRADE methodology,[6] by the patient representatives. This uses a 9-point scale with outcomes ranked 9 those the patient representatives considered most important. Outcomes ranked 9, 8 or 7 are critical for decision-making; those ranked 6, 5 or 4 are important but not critical for decision making and those ranked 3, 2 or 1 are the least important for decision making. Data on these outcome measures were extracted from included studies (Appendices B, C, E, F & G; see Supporting Information).

Review Question 1: Treatment

In people with 'higher-risk' primary cSCC how clinically effective are surgical (standard and Mohs[1]) and non-surgical treatments (radiotherapy[2] and electrochemotherapy) compared with each other?

- Survivorship 9
- Recurrence rate 9
- Cosmetic outcome 7
- Convenience of treatment 7

Review Question 2: Treatment

In people with low risk primary cSCC how clinically effective are surgical (standard excision, Mohs[a], curettage & cautery, cryosurgery and carbon dioxide laser) and non-surgical treatments (topical therapies, photodynamic therapy or radiotherapy[b]) compared with each other or with no treatment (observation)?

- Convenience of treatment 9
- Cosmetic outcome 7
- Recurrence rate 7

Review Question 3: Surgical margin

[1] Mohs: The tumour is curetted or surgically debulked, and the defect usually excised with a small (1-2 mm) margin of surrounding skin. The patient waits with a dressed wound pending histological confirmation by the Mohs surgeon that the tumour has been completely removed. If residual tumour is identified, a further layer of tissue is removed, and the process repeated until the surgical wound is confirmed to be tumour-free. The wound is then repaired by conventional surgical techniques.

[2] radiotherapy including brachytherapy where appropriate

In people with cSCC who undergo standard surgical excision, what surgical margin and surgical plane should be used?

- Lack of clinical recurrence after 5 years 9
- Lack of clinical recurrence after 2 years 9

Review Question 4: Involved margins

In people with cSCC who undergo excision of the primary tumour and where histological analysis shows either one or more involved or clear but close margins (less than 1 mm), what is the appropriate subsequent management?

- Survivorship 9
- Recurrence 9

Review Question 5: Adjuvant radiotherapy

In people with primary cutaneous squamous cell carcinoma following surgical excision with clear histological margins, what is the role of adjuvant[3] radiotherapy in reducing the risk of local recurrence?

- Survivorship 9
- Recurrence rate 9
- Cosmetic outcome 7
- Convenience of treatment 6
- Patient reported outcomes 6

Review Question 6: Metastatic SCC

In people with any metastasis from cSCC how clinically effective are standard surgical and non-surgical treatments (chemotherapeutic therapy, radiotherapy[b], immunotherapy) compared with each other or with no treatment (observation)?

- Survivorship 9
- Recurrence rate 9
- Cosmetic outcome 7
- Convenience of treatment 7
- Patient reported outcomes 6

[3] "adjuvant" in the guidelines refers to any treatment (radiotherapy) after primary treatment (surgery)

Review Question 7: Follow-up

In people with a diagnosed higher-risk cSCC what is the appropriate follow-up period following treatment?

- Survivorship 9
- Recurrence 9
- Metastases 9
- Patient reported outcomes 6

3.0 Summary of recommendations

There are few randomized controlled trials (RCTs) to support the following guidelines for the management of cSCC.

The following recommendations and ratings were agreed upon unanimously by the core members of the GDG and patient representatives. The recommendations cover suspected and diagnosed cSCC. All recommendations would also generally relate to children, young people and adults, unless specified otherwise. Those under 24 years of age with cSCC should be managed by the SSMDT but must additionally be referred to the appropriate children's or teenagers and young adults service for their specific expertise. These guidelines do not include specific recommendations for subungal or periungal SCCs. For further information on the wording used for recommendations and strength of recommendation ratings see Section 2. The evidence for recommendations is based on the studies as listed (for details and discussion of the evidence see Appendices B-F in the Supporting Information). The GDG recommendations relating to referral pathways are based on discussion and clinical experience, as evidence-based details are not available at the time of writing. The GDG is aware of the lack of high-quality evidence for some of these recommendations, therefore strong recommendations with an asterisk (*) are based on available evidence, as well as consensus and specialist experience. Good practice point (GPP) recommendations are derived from informal consensus.

Pre-treatment

R1 (↑↑): Obtain histological confirmation of cSCC lesions in the event of diagnostic uncertainty, before planning definitive treatment. This must be a representative sample of the tumour; in most

instances, this will be a full thickness incisional biopsy ideally incorporating both the peripheral and the deep margins.

R2 (GPP): Offer discussion on the risks and benefits of all treatment options (outcomes, function, cosmesis) to people with cSCC and their family/carers and make the treatment decision together.

R3 (↑↑): Record the maximum clinical cSCC lesion dimension prior to any diagnostic or treatment procedure (usually diameter, in millimetres), the plane of the deep excision margin, whether recurrent tumour or in field of previous radiotherapy and immune status of the patient on the specimen request form for the pathologist

R4 (GPP): Take a good quality clinical photograph of the cSCC lesion for the patient record to aid future management and assessment of area post healing. In multi-site disease the lesions to be treated should ideally be marked on the photograph to limit the risk of wrong-site procedures.

Treatment options for primary cSCC

Standard surgical excision

R5 (↑↑): Offer* standard surgical excision as the first-line treatment option to people with resectable primary cSCC.

R6 (↑↑): Peripheral tumour margins should be determined under bright lighting and magnification or dermoscopy. Excise* with a clinical peripheral surgical margin of:

- at least 4 mm for a low risk† cSCC tumour
- at least 6 mm for a high risk† cSCC tumour
- at least 10 mm for a very-high risk† cSCC tumour.

†See Figure 1

R7 (↑↑): Ensure **at least** a 1 mm histological clearance of cSCC excisions at all margins by including sufficient peripheral and deep tissues (see R6 for appropriate standard surgical excision margins).

- For mobile lesions the deep margin should be within the next clear surgical plane, and on the scalp the excision should include the galea.

- For deeply infiltrating or fixed lesions at any site, achieving an uninvolved deep histological margin may require inclusion of one or more of the following - fascia, muscle, bone or other underlying structure - which may be determined clinically or by imaging or both.
- Consideration should be given to excision of a further, orientated, deep margin specimen where possible, if there is clinical concern at the time of resection that the resection is close or incomplete.
- Whenever possible confirm uninvolved histological margins by paraffin section analysis prior to reconstruction involving complex tissue rearrangement where dressings or temporizing cover can reasonably be achieved. In the context of extensive ablative resections, however, (e.g., scalp into calvarium/abutting dura, ear-parotid-temporal bone, composite maxillofacial resections etc) this approach is unlikely to be feasible due to immediate reconstructive requirements.
- Where there is extensive disease, and/or involvement of specific anatomical areas, consider liaising with one or more additional MDT depending on the site of the cSCC.

R8 (↑↑): Manage and report excised cSCC specimens according to the Royal College of Pathology dataset.[4]

MDT discussion (see also Figure 1)

R9 (GPP): Document risk status of cSCC tumour as low-risk, high-risk or very high-risk in patient notes (see Figure 1).

R10 (↓↓): T1 cSCC tumours excised with histologically clear margins of **at least** 1 mm, in the absence of other high-risk factors, do not need routine discussion at an MDT (see Figure 1).

R11 (↑↑): Review the histology of people with cSCC with one or more involved or clear-but-close margins (<1 mm) at an appropriate Skin MDT (see Figure 1).

[4] https://www.rcpath.org/uploads/assets/9c1d8f71-5d3b-4508-8e6200f11e1f4a39/Dataset-for-histopathological-reporting-of-primary-invasive-cutaneous-squamous-cell-carcinoma-and-regional-lymph-nodes.pdf

R12 (↑): Consider the risk factors for the patient, margin, site and tumour stage in people with cSCC with one or more clear-but-close margins (<1 mm). Consider observation in immunocompetent people with cSCC with a low-risk tumour (see Figure 1).

R13 (↑↑): Offer further wide local excision (with likely delayed reconstruction), Mohs micrographic surgery, or adjuvant radiotherapy to people with cSCC with one or more involved margins, or close margins (<1 mm) where patient or tumour factors confer higher risk.

R14 (GPP): Offer active treatment to immunosuppressed people with cSCC with one or more clear-but-close (<1 mm) or involved margins with structured follow-up and surveillance.

R15 (↑↑): Discuss at an SSMDT people with cSCC with symptomatic perineural invasion and/or radiologic evidence of perineural invasion. If discussed at Skin MDT, Skull base or H&N MDT opinion may be required. Aggressive surgical excision of the involved nerve should be the first step, where technically possible, followed by consideration of adjuvant radiotherapy.

Figure. 1: Guidance for Referral to LSMDT/SSMDT: this referral guidance relates to primary cSCC where treatment has been excisional surgery with curative intent. Factors associated with risk of poor disease-related outcomes (local recurrence, nodal metastasis, disease-specific death) in multiple studies using univariate or multivariate analysis.[11-16] cSCC, cutaneous squamous cell carcinoma; PNI, perineural invasion; LSMDT, local skin cancer multidisciplinary team; SSMDT, Specialist skin cancer multidisciplinary team; HAART, highly active anti-retroviral therapy; CLL, chronic lymphocytic leukaemia; SCID, severe combined immunodeficiency; *Review of nodal basins in the head and neck should be per the criteria of Head & Neck MDT

Mohs micrographic surgery

R16 (↑): Consider Mohs micrographic surgery in selected people with cSCC following SSMDT discussion, particularly where tumour margins are difficult to delineate or in sites where tissue conservation is important for function.

Radiotherapy: primary and postoperative (adjuvant radiotherapy)

R17 (↑↑): Discuss people with histologically proven cSCC being considered for radiotherapy at an MDT (LSMDT or SSMDT) with a clinical oncologist present.

R18 (↑↑): Offer primary radiotherapy:

- to selected people with cSCC as a treatment option following appropriate discussion at appropriate Skin MDT and/or with a clinical/radiation oncologist, factoring in patient preference
- to people with cSCC when surgery is not feasible or would be challenging or likely to result in an unacceptable functional or aesthetic outcome.

R19 (↑): Consider adjuvant radiotherapy in people with cSCC:

- if pathological excision margins are clear-but-close (<1 mm) following discussion at an appropriate Skin MDT, where a clinical oncologist is present
- with completely excised T3 tumours, where there are multiple high-risk factors including those >6 mm in thickness (depth) and invasion beyond subcutaneous fat invasion.

R20 (↑↑): Offer adjuvant radiotherapy to people with incompletely excised cSCC, where further surgery is not possible (or is not chosen by the patient) and in those at high risk of local recurrence:

- perineural invasion (multifocal, named nerve and/or diameter of nerve >0.1 mm, below the dermis)
- in recurrent disease
- in those who are immunocompromised (see R21).

R21 (↓↓): Do not offer post-operative radiotherapy to people with completely excised T1 or T2 cSCC and with microscopic, dermal only, nerve diameter <0.1 mm perineural invasion.

R22 (↑): Consider conformal radiotherapy including the entire course of the involved nerve in people with cSCC with symptomatic perineural invasion and/or radiologic evidence of perineural invasion when surgery is inappropriate, after carefully weighing benefits and side effects from radiotherapy to such an extensive radiotherapy treatment field.

R23 (GPP): Inform younger people with cSCC (<60 years), especially if they are an organ transplant recipient, of the very low risk of radiation-induced, in-field malignancy in the future. Take this risk into account when making any treatment decision.

Curettage & cautery

R24 (↑): Consider curettage & cautery with curative intent in immunocompetent people with small (<1 cm), well-defined, non-recurrent, clinically low-risk cSCC.

R25 (GPP): Review the histology of cSCC removed by curettage & cautery to identify high- or very high-risk features. If these are identified, the case should be discussed at an appropriate MDT regarding further management.

Locally advanced, recurrent and metastatic cSCC

R26 (GPP): Do not routinely offer imaging of the draining nodal basin to people with cSCC in the absence of suspected or clinically detectable regional nodal involvement. Very high-risk lesions, such as pT2 or greater lip cSCC, carry a high risk of occult metastasis and consideration can be given to high-resolution USS of the regional nodes in the clinically N0 setting.

R27 (↑↑): Initiate an individualized SSMDT, multi-modality and imaging treatment plan for people:

- with regional lymph node metastasis
- who are immunocompromised and with locally advanced and/or metastatic cSCC
- with in-transit metastases from cSCC
- with metastatic cSCC who have had further locoregional relapse following lymphadenectomy.

R28 (GPP): Where assessment of the anatomical extent of a primary cSCC warrants imaging, consider including regional lymph nodes in the scan.

R29 (GPP): Only consider sentinel lymph node biopsy for specific, high-risk, primary cSCC cases in the context of a clinical trial/SSMDT discussion.[5]

[5] National Comprehensive Cancer Network, NCCN Clinical practice Guidelines in Oncology: Squamous Cell Skin Cancer Version 2.2019 https://www.nccn.org/professionals/physician_gls/default.aspx MS.10.

R30 (GPP): Offer ultrasound-guided fine-needle aspiration cytology to people with cSCC with clinically suspicious nodes. If negative and suspicion remains, this can be repeated, although core or open-biopsy histology may be required.

R31 (GPP): Undertake a high-resolution MRI imaging of the involved area in people with cSCC with in-transit metastasis[6] or regional perineural invasion of named nerves. Discuss with a radiologist if MRI contraindicated.

R32 (↑↑): Offer therapeutic regional lymphadenectomy[7] to people with head and neck cSCC with regional lymph node metastasis. Imaging is required preoperatively to define the extent of locoregional relapse, and to identify distant metastatic disease (also see R36). The head and neck imaging should include locoregional MRI or CT, and CT imaging of the chest as a minimum. The surgery should be performed by a designated surgeon who is a core member of the SSMDT pathway and compliant with prevailing multi-specialty guidance.

- Where the parotid gland has proven nodal metastasis and the neck is cN0, a therapeutic parotidectomy, usually the superficial lobe alone, should be combined with an elective selective neck dissection of levels I-III. If an anterior scalp or temple primary site has proven neck nodal metastasis, consideration should be given to an elective superficial parotidectomy at the time of therapeutic neck nodal dissection.
- Where the neck has proven nodal metastasis, the therapeutic neck dissection should include levels and structures to maximise tumour clearance, whilst minimising unnecessary morbidity. It may be appropriate to preserve a clinically and radiologically uninvolved level I where the primary tumour was posterior, i.e. to carry out a posterolateral neck dissection of levels II-V. Consideration can also be given to preservation of an uninvolved, level V where the primary tumour site was in the central lower face.
- Nodes in the superficial system, such as the occipital nodes, or external jugular node should also be included in a dissection, according to the primary site, and the identified sites of metastasis.

[6] A type of metastasis in which skin cancer spreads through a lymph vessel and begins to grow between the area of previous treatment and the nodal basin

[7] A surgical procedure in which the lymph nodes which drain the site of the tumour are removed to an extent which has therapeutic rather than diagnostic or palliative intent. The tissue is subsequently checked under the microscope for signs of cancer

R33 (↑↑): Offer therapeutic regional lymphadenectomy[c] to people with non-head and neck cSCC with regional lymph node metastases in axillary, inguinofemoral or other peripheral draining nodes. Imaging is required preoperatively to define the extent of locoregional relapse, and to identify distant metastatic disease (also see R36). In the axilla CT imaging should include the neck, chest and axilla as a minimum and the surgery should include levels I-III. In the inguinofemoral region CT imaging should include the chest abdomen pelvis and to mid-thigh level and the surgery should include superficial and deep levels.

- Therapeutic extended ilio-inguino-femoral lymphadenectomy is indicated in those with additional iliac nodal cSCC on imaging or cytology.
- Elective extended ilio-inguino-femoral lymphadenectomy should also be considered, at the SSMDT, for people with extensive inguino-femoral relapse (multiple nodes, any >3 cm, plus or minus ENE) who do not have concurrent evidence of iliac relapse on imaging or cytology but are deemed to be at high risk of microscopic disease in the extended basin.
- Nodal disease at other ectopic sites should have individualised imaging under guidance from the SSMDT.

The surgery should be performed by a designated surgeon of the SSMDT pathway who is compliant with prevailing multi-specialty guidance.

R34 (↑↑): Offer adjuvant radiotherapy following therapeutic regional lymphadenectomy to people with cSCC with high-risk pathology (e.g. two or more nodes, large nodes and extracapsular extension), i.e. UICC 8 ≥ pN1.

R35 (GPP): Consider surgical resection (+/- adjuvant radiotherapy) or primary radiotherapy in people with locally recurrent cSCC.

R36 (GPP): Consider regional lymphadenectomy or regional lymph node basin irradiation in selected people with cSCC for disease control even in the presence of distant metastases, especially in those undergoing multi-modality treatment.

R37 (↑): Consider immune checkpoint inhibitor treatment in people with locally advanced cSCC where curative surgery or radiotherapy is not reasonable, or those with metastatic cSCC, except organ transplant patients or those who have significant autoimmune conditions.

R38 (↑): Consider systemic chemotherapy or EGFR inhibitors in people with metastatic cSCC with contraindications to immune checkpoint inhibitors.[8] EGFR inhibitors are unlicensed for cSCC in the U.K.

R39 (GPP): Consider electrochemotherapy in people with locally advanced cSCC in palliative settings if other local or systemic therapies are not appropriate.

Follow-up

R40 (↑↑): Offer access to a key worker to people with cSCC, ideally a Clinical Nurse Specialist (CNS), as part of an ongoing treatment prevention package.[9] Provide information on the diagnosis and management of cSCC.

R41 (GPP): Follow up people with cSCC by examining the skin and lymph node basins and any other appropriate clinical examination.

R42 (GPP): Educate people with cSCC on self-examination (skin and lymph nodes) and sun protection by providing appropriate verbal and written information (e.g. www.bad.org.uk/leaflets).

R43 (GPP): Offer people with **low-risk** cSCC a single post-treatment appointment, where appropriate, to check histopathology results, conduct skin and nodal surveillance and facilitate patient education on self-examination and own digital photographic surveillance.[10] Provide information on the 5-year risk of developing further cSCC and on how to access a referral, including the 2-week wait pathway back into the system if they suspect a new lesion.

R44 (GPP): Offer people with **high-risk** cSCC (especially when several risk factors apply) post-treatment follow-up appointments at 4-monthly intervals for 12 months, then at 6-monthy intervals for a further 12 months. The initial follow-up should be with secondary care clinicians to facilitate skin surveillance and patient education on self-examination. Later appointments may be with other clinicians able to recognise recurrences and new skin cancers according to local arrangements approved by the appropriate Skin MDT.

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[8] Responses are generally short-lived and chemotherapy is poorly tolerated in the elderly and frail and consideration for best supportive care should be made.
[9] NICE quality standards on skin cancer https://www.nice.org.uk/guidance/qs130
[10] Patient education could have already taken place at the pre-treatment appointment.

R45 (GPP): Offer people with **very high-risk** cSCC post-treatment follow-up appointments at 4-monthly intervals for 24 months, then at 6-monthy intervals for a further 12 months. The initial follow-up should be with secondary care clinicians to facilitate skin surveillance and patient education on self-examination. Later appointments may be made with other clinicians able to recognise recurrences and new skin cancers according to local arrangements approved by the appropriate Skin MDT. People who have a high risk of developing further high-risk, primary cSCC, such as organ transplant recipients, should remain under life-long skin surveillance.

R46 (GPP): Offer people with **metastatic** cSCC post-treatment follow-up appointments at 3-monthly intervals for 24 months, then at 6-monthy intervals for a further 36 months, with potential longer-term review dependent on patient factors. Imaging should be performed on basis of clinical findings with SSMDT discussion if appropriate.

Insufficient evidence to support any recommendation

Θ There is insufficient evidence to support any recommendation for cryotherapy, CO_2 laser or topical therapies in the treatment of cSCC.

List of key future research recommendations

The following list outlines future research recommendations (FRRs)

FRR1: Research should identify which clinicopathological or molecular factors predict poor outcome, which may facilitate a scoring system (1-5) for risk.

FRR2: Future cancer-related RCTs need to include more people with cSCC, with stratification of the results by risk factors.

FRR3: Future Skin cancer clinical studies need to clearly differentiate outcomes by histopathology (i.e. SCC/BCC) and stage

FRR4: Prospective, head-to-head RCTs for primary cSCC reporting the following outcomes: 1) 5-year recurrence rates, 2) quality of life, 3) long- and short-term adverse effects, including pain, function and cosmetic appearance.

- comparing surgical interventions with modern standardised 2D histopathology

- evaluating the role of adjuvant radiotherapy in resected primary cSCC
- comparing further surgery versus radiotherapy in incompletely resected primary cSCC
- comparing adjuvant radiotherapy (margins, techniques) after surgical excision of higher risk cSCC

FRR5: All future RCTs involving cSCC need to report standardised outcome measures (e.g. time to recurrence, standardised quality of life scales, etc.) to facilitate comparisons and pooling of data across studies.

FRR6: A study evaluating the cost and resource implications of different treatment options for people with cSCC in the U.K. NHS healthcare setting.

FRR7: Alternative immunotherapy strategies suitable for people with inoperable, locally advanced cSCC, not amendable to radical radiotherapy, or metastatic cSCC in whom immune checkpoint inhibitors are contraindicated.

FRR8: There is a need for a review of the treatments of cSCC in those who are at increased risk (e.g. those with impaired immunity or genetic conditions) of developing SCC.

FRR9: The role of sentinel lymph node biopsy in the staging of very high-risk cSCC given the propensity of these tumours to metastasise.

4.0 Algorithms

The recommendations, discussions in the LETRs (Appendix D; see Supplementary Information) and consensus specialist experience were used to inform the algorithm/pathway of care (Figure 2 and Figure 3).

Figure 2. Staging and management pathway of primary cutaneous squamous cell carcinoma. LSMDT, local skin cancer multidisciplinary team; SSMDT, specialist skin cancer multidisciplinary team

Figure 3. Treatment pathway for primary cutaneous squamous cell carcinoma in adults. D, diameter; ART, adjuvant radiotherapy; laSCC, locally advanced squamous cell carcinoma; mSCC, metastatic squamous cell carcinoma

5.0 Background

5.1 Definition

Primary cutaneous squamous cell carcinoma (cSCC) is a malignant tumour which arises from the keratinocytes of the epidermis or its hair follicles. It is locally invasive and has the potential to metastasise.[17]

5.2 Incidence and aetiology

The rate of non-melanoma skin cancer is at least 2.4 times higher than the next commonest tumour in the UK which is breast cancer.[18] Recent evidence suggests that this is still an underestimate for skin cancer due to under reporting.[19] cSCC is the sixth most common cancer in the UK[18,19] and it's incidence continues to rise, not only in the UK but also in many other countries.[19-21] This will have an increasing impact on planning for NHS services and on histopathology services.[19,22]

Its occurrence is usually related to chronic ultraviolet light exposure and is therefore especially common in people with sun-damaged skin, fair skin, albinism and xeroderma pigmentosum. Additionally, increasing longevity may also be responsible for increasing incidence of these tumours. It may develop de-novo, as a result of previous exposure to ultraviolet and ionising radiation, chemicals such as pesticides/herbicides or arsenic; within chronic wounds, scars, burns, ulcers or sinus tracts; and from pre-existing lesions such as SCC *in situ* (Bowen's disease).[20,21] A high incidence of aggressive cSCC is found in individuals with recessive dystrophic epidermolysis bullosa (RDEB), where it is a major cause of death. In RDEB, the aetiology of cSCC is chronic wounding, not UV-exposure. Individuals with impaired immune function, for example those receiving immunosuppressive drugs following allogeneic organ transplantation or for inflammatory disease, and those with lymphoma or leukaemia, are at increased risk of this tumour. Some cSCCs are associated with human papillomavirus infection.[23] The risk of cSCC with the 'biologic' therapies (for inflammatory or haematological disease) has yet to be accurately quantified.[24,25]

There is good evidence linking cSCCs with chronic actinic damage, (including that from the use of tanning devices)[26] and to support sun avoidance, use of protective clothing and effective sun blocks[27] in the prevention of actinic keratoses and cSCCs. These measures are particularly important for people receiving long term immunosuppressive medication.[28] People who have had PUVA therapy for skin conditions may also be at higher risk.[29]

cSCC may also occur in patients who are being treated with BRAF inhibitors for melanoma.[30]

People with organ transplants are at high-risk of developing cSCC. Skin surveillance to allow early detection and treatment, and measures to prevent cSCC should be part of their routine care. In patients with multiple, frequent or high-risk cSCCs consideration should be given to modifying immunosuppressive regimens[31,32] and the prophylactic use of systemic retinoids[33-35] which may also be valuable in other high-risk groups.[36] Nicotinamide should also be considered in this situation.[37] Therapies such as topical 5-fluorouracil[38] and imiquimod[39] and photodynamic therapy[40] may have useful roles in preventing skin dysplasia and therefore decreasing the risk of skin cancers in high-risk renal transplant recipients, but substantive evidence is awaited.

6.0 Diagnosis and investigation

6.1 Clinical presentation

SCC usually presents as an indurated nodular keratinising or crusted tumour that may ulcerate, or it may present as an ulcer without evidence of keratinisation. All patients in whom there is a possibility of a cSCC should be referred urgently to an appropriately trained specialist who is attached to a local multidisciplinary skin cancer team (LSMDT) usually in their local Dermatology Department, rapid access skin cancer clinic.[41]

6.2 Diagnosis and Staging

The handling of skin cancer specimens, their histopathological diagnosis and reporting should conform to the Royal College of Pathologists (RCPath) dataset for primary cutaneous squamous cell carcinoma.[42] The RCPath and Public Health England have adopted UICC TNM8[7] for the staging of melanoma and non-melanoma skin cancer.

7.0 Recommended audit points

In the last 20 consecutive patients with cSCC is there clear documentation for/evidence of the:

1 Name and grade of the surgeon who carried out the surgery?
2 Patient being instructed in self-examination and provided with written patient information, e.g. www.bad.org.uk/leaflets?
3 Site and maximum dimension (usually diameter) of the lesion?
4 Lesion being fixed or mobile beneath the skin (head, neck, trunk and limbs)?
5 Lesion having tarsal plate / lid margin involvement, or not (eyelid)?
6 Immunosuppressive status of the patient?
7 Risk status of the lesion (low-risk, high-risk or very high-risk)?
8 Lesion having associated clinically detectable nodes, or clinically N0?
9 Standard surgical excision detailing:
    a. Surgical margins of excision (R6 – see below)?
       N.B. ≥4 mm for low-risk; ≥6 mm for high-risk; ≥10 mm for very high-risk cSCC
    b. Anatomical description of deep margin?
10 Histology margins in all planes following standard surgical excision?
       N.B. Clear (≥1 mm); clear but close (<1 mm) or involved (0 mm)
11 Appropriate follow-up protocols (R43, R45, R46 – see below) by different members of the MDT, including clinical nurse specialists?
   N.B. low-risk: one appointment for diagnosis and education; high-risk: a follow-up every 4 months in the first year; every 6 months in the second year; very high-risk: a follow-up every 4 months in the first and second year; every 6 months in the third year
12 Recording and review of histologically proven recurrence of cSCC during follow-up periods following both surgical and non-surgical treatments?

The audit recommendation of 20 cases per department is to reduce variation in the results due to a single patient and allow benchmarking between different units. See Appendix L; Supplementary information.

Stakeholder involvement and peer review

The draft document and Supporting Information was made available to the BAD membership, Royal College of General Practitioners (RCGP), the Royal College of Pathologists (RCPath), the Royal College of Radiologists (RCR), the British Association of Oral & Maxillofacial Surgeons (BAOMS), the British Association of Head and Neck Oncologists (BAHNO), the British Association of Plastic Reconstructive & Aesthetic Surgeons (BAPRAS), the British Society for Dermatological Surgery (BSDS), the British Dermatological Nursing Group (BDNG), the British Association of Skin Cancer Nurse Specialists (BASCNS) and the Primary Care Dermatological

Society (PCDS) . The comments received were actively considered by the GDG. Following further review, the finalised version was sent for peer-review by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines Sub-committee) prior to submission for publication.

Limitations of the guideline

This document has been prepared on behalf of the BAD and is based on the best data available when the document was prepared. It is recognized that under certain conditions it may be necessary to deviate from the guidelines and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence. Limiting the review to English and German language references was a pragmatic decision but the authors recognize this may exclude some important information published in other languages.

Plans for guideline revision

The proposed revision date for this set of recommendations is scheduled for 2025; where necessary, important interim changes will be updated on the BAD website.

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Declarations of interest

The following interests were declared over the duration of the guideline development:

PGB: RCSEng RSPA Plastics South Central (demitted 2016) Deputy Chair TVCN Skin Cancer TSSG (demitted 2020) (specific); **KF:** (1) advisory boards – ESAI, IPSEN, Roche, Novartis, Merck, Pfizer, Eusa (specific); (2) speaker fees and consultancy – BMS, Pfizer, MSD (non-specific); (3) conference hospitality – Novartis, Ipsen (specific); (4) institutional research funding – Roche, MSD, Exelixis (specific) **CAH**: (1) Speaker and honoraria for Sanofi (specific); (2) Member of the NCRI Skin Group (specific); member of the EADO guidelines development group for cSCC (specific); **JRM**: member of the NCRI non-melanoma skin cancer subgroup (specific)

CN: (1) member of the NCRI non-melanoma skin cancer subgroup (specific); (2) shares in a private GP web based company (non-specific); **CP**: (1) Chair of the Scottish Dermatological Society Skin Cancer Group (specific), (2) member of the NCRI Skin Group (specific), (3) member of the NCRI non-melanoma skin cancer subgroup (specific), (4) clinical expert for appraisal of Cemiplimab for cSCC for NICE (April 2019) (specific) **DNS**: Royal College of Pathologists Lead on Skin Cancer Datasets (specific). **AR**: (1) member of the NCRI Skin Group (specific), (2) member of the NCRI non-melanoma skin cancer subgroup (specific), (3) Non-Melanoma Skin Cancer Advisory Board prior to ESMO 2018 on Cemiplimab for Sanofi (specific).

SGK, JB, OD, RM, RJM, CN, JS, PB, PF, MH, MFMM, LSE: None

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix A: Review Protocol
Appendix B: Forest plots
Appendix C: Clinical Evidence summary
Appendix D: Linking Evidence To Recommendations (LETR)
Appendix E: GRADE evidence tables
Appendix F: Summary of included studies
Appendix G: Narrative findings for non-comparative studies
Appendix H: Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram – study selection
Appendix I: Papers excluded from quantitative analysis
Appendix J: Methodology
Appendix K: Search strategy
Appendix L: Audit standards, data items and data collection methodology

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T categories	
T1	≤2 cm in greatest dimension
T2	>2 to 4 cm in greatest dimension
T3	>4 cm in greatest dimension or minor bone erosion or specified perineural invasion (≥0.1 mm diameter and/or deeper than the dermis and/or a named nerve) or deep invasion (thickness >6 mm and/or beyond the subcutaneous fat)
T4a	Tumour with gross cortical bone/marrow invasion
T4b	Tumour with skull base or axial skeleton invasion including foraminal involvement and/or vertebral foramen involvement to the epidural space
N categories for non-head and neck	
N1	Metastasis in a single node ≤3 cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm or in multiple ipsilateral nodes none >6 cm in greatest dimension
N3	Metastasis in a lymph node >6 cm in greatest dimension
N categories Head and neck region	
N1	Metastasis in a single ipsilateral lymph node ≤3 cm in greatest dimension without extranodal extension (ENE)†
N2a	Metastasis in a single ipsilateral lymph node >3 cm but <6 cm in greatest dimension without ENE
N2b	Metastasis in multiple ipsilateral lymph nodes, where none are >6 cm in greatest dimension without ENE
N2c	Metastasis in bilateral or contralateral lymph nodes, where none are >6 cm in greatest dimension without ENE
N3a	Metastasis in a single or multiple lymph nodes >6 cm in greatest dimension without ENE
N3b	Metastasis in a single or multiple lymph nodes with extranodal extension

M categories for metastasis	
M0	No distant metastasis
M1	Distant metastasis (including contralateral nodes in non-head and neck cSCC)

† ENE can be clinical or pathological.

Table 1: TNM8 classification for cSCC[7]

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1, T2, T3	N1	M0
IVA	T1, T2, T3	N2, N3	M0
	T4	Any N	M0
IVB	Any T	Any N	M1

Table 2: TNM8 stage groups for cSCC[7]

Strength	**Wording**	**Symbols**	**Definition**
Strong recommendation *for* the use of an intervention	"Offer" *(or similar, e.g. "Use", "Provide", "Take", "Investigate", etc.)*	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention whilst only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policy makers, it would be a useful performance indicator.
Weak recommendation *for* the use of an intervention	"Consider"	↑	Risks and benefits of the intervention are finely balanced; most patients would choose the intervention but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policy makers it would be a poor performance indicator where variability in practice is

			expected.
No recommendation		Θ	Insufficient evidence to support any recommendation.
Strong recommendation *against* the use of an intervention	"Do not offer"	↓↓	Risks of the intervention outweigh the benefits; most patients would *not* choose the intervention whilst only a small proportion would; for clinicians, most of their patients would *not* receive the intervention.

Table 3: Strength of recommendation ratings

	Low risk	High risk	Very high risk
Tumour Factors	Tumour diameter ≤20 mm (= pT1) Tumour thickness ≤4 mm Invasion into dermis No perineural invasion Well differentiated or moderately differentiated histology No lymphovascular invasion (ALL ABOVE FACTORS SHOULD APPLY to denote a low-risk tumour)	Diameter >20 – 40 mm (= pT2) Thickness >4 mm – 6 mm Invasion into subcutaneous fat Perineural invasion present – dermal only; nerve diameter <0.1 mm Poorly differentiated histology Lymphovascular invasion Tumour site ear or lip Tumour arising within scar or area of chronic inflammation (ANY SINGLE FACTOR denotes a high-risk tumour)	Diameter >40 mm (= pT3) Thickness >6 mm Invasion beyond subcutaneous fat Any bone invasion Perineural invasion present in named nerve; nerve ≥0.1 mm; or nerve beyond dermis High-grade histological subtype – adenosquamous, desmoplastic, spindle/ sarcomatoid/metaplastic In-transit metastasis (ANY SINGLE FACTOR denotes a very high-risk tumour)
Margin status	Clear pathology margins in all dimensions (≥1 mm)	One or more involved or close (<1 mm) pathology margin in a pT1 tumour. Close pathology margins (<1 mm) in a pT2 tumour.	One or more involved or close (<1 mm) pathology margin in a high-risk tumour
Patient Factors	Immune-competent	Iatrogenic immunosuppression or biological therapies; frailty &/or co-morbidities likely to cause some degree of immune compromise; HIV infection stabilised on HAART	AS FOR HIGH-RISK especially: solid organ transplant recipients; haematological malignancies such as chronic lymphocytic leukaemia or myelofibrosis; other significant immunosuppression
Referral to MDT *(Scotland has no LSMDT/ SSMDT division)*	LSMDT discussion not needed	LSMDT discussion of patients with close or involved pathology margins; if margins are not involved other factors alone may not require LSMDT discussion unless more than one factor pertains. Patient factors increase risk, but do not mandate LSMDT discussion in absence of tumour risk factors.	SSMDT discussion should be considered for all patients with very high-risk tumours except those which require straightforward standard surgical excision. A referral to or opinion from an appropriate site-specific MDT may be required to ensure the best management.
Follow-up	Follow-up in secondary care not needed after single post-treatment appointment, where appropriate. Full skin check, examination of regional lymph node basin, discussion of diagnosis and patient education, this may take place before the histological diagnosis. Patient education about sun protection and skin surveillance is advised. Patients and their GPs should be informed of the risk of further cSCCs. There is a 40% risk of a further keratinocyte cancer within 5 years. If this is suspected, refer via the 2-week wait pathway.	4-monthly for 12 months (+ 6-monthly for the second year) especially if several risk factors apply. Full skin check, examination of regional lymph node basin,* discussion of diagnosis and patient education. Advise patient education about sun protection and skin surveillance. Patients with more than one prior keratinocyte carcinomas have a 80% risk of a further keratinocyte cancer within 5 years.	4-monthly for 2 years and 6-monthly for a third year. Full skin check, examination of regional lymph node basin,* discussion of diagnosis and patient education. Advise patient education about sun protection and skin surveillance. Patients with more than one prior keratinocyte carcinomas have a 80% risk of a further keratinocyte cancer within 5 years.

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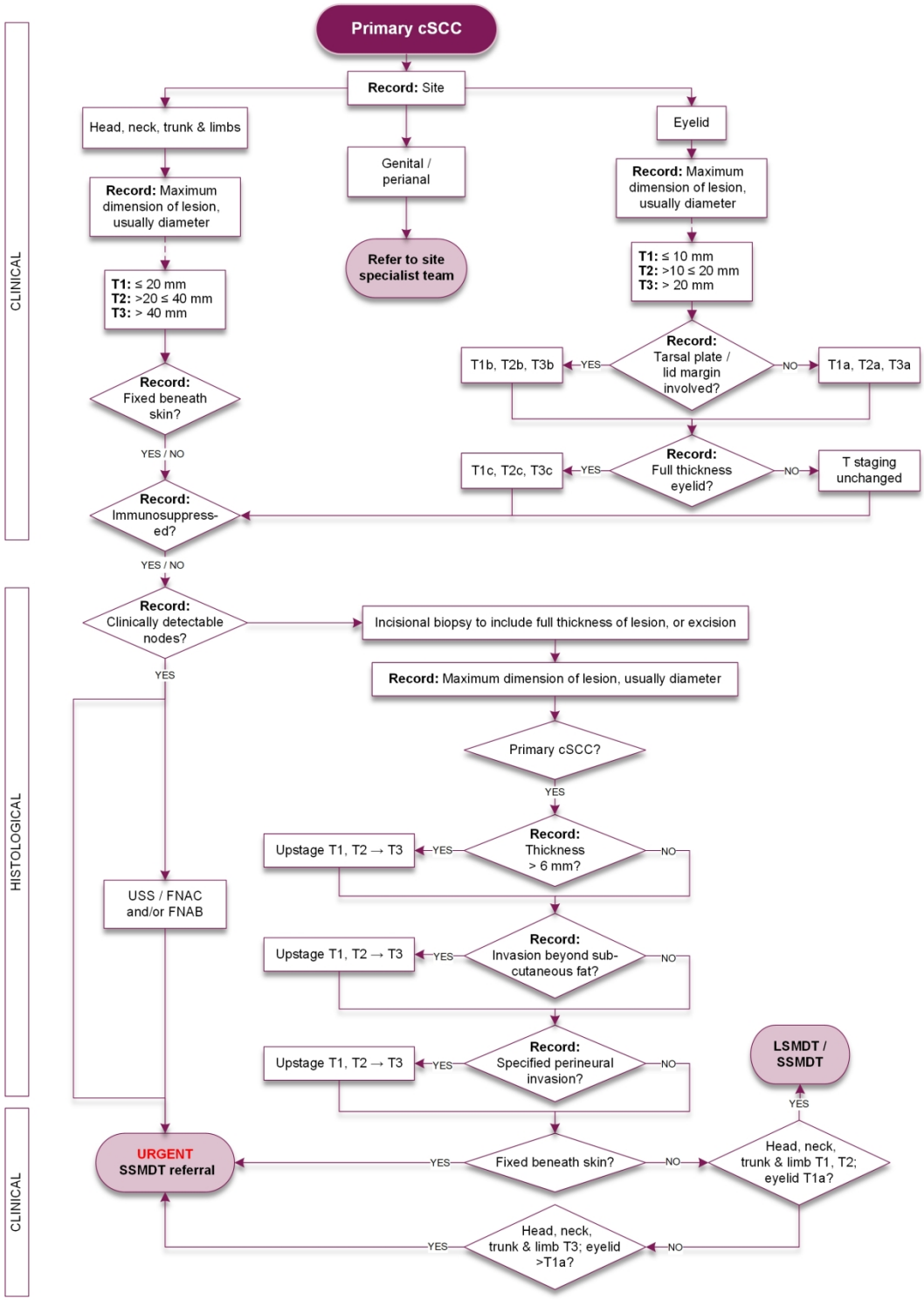
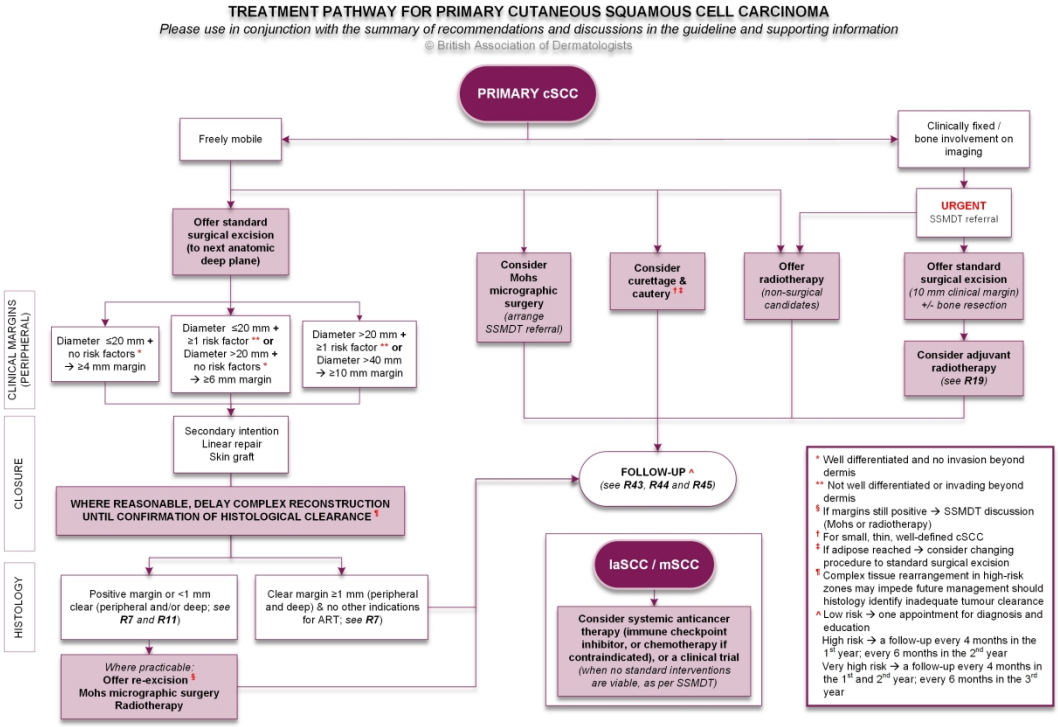
ASSESSMENT, STAGING & MANAGEMENT FLOW CHART FOR PRIMARY CUTANEOUS SQUAMOUS CELL CARCINOMA

Please use in conjunction with the summary of recommendations and discussions in the guideline and supporting information





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