British Association of Dermatologists guidelines for the management of adults with basal cell carcinoma 2021

I. Nasr,1 E.J. McGrath,2 C.A. Harwood,3,4 J. Botting,5 P. Buckley,6 P.G. Budny,7,8 P. Fairbrother,6 K. Fife,9,10 G. Gupta,11 M. Hashme,1 S. Hoey,12 J.T. Lear,13,14,15 R. Mallipeddi,16,17 E. Mallon,18 R.J. Motley,19 C. Newlands,20,21 J. Newman,22,23 E.V. Pynn,24 N. Shroff,25 D.N. Slater,26 L.S. Exton,1 M.F. Mohd Mustapa1 and M.C. Ezejimofor1 on behalf of the British Association of Dermatologists’ Clinical Standards Unit*

1 British Association of Dermatologists, Willan House, 4 Fitzroy Square, London W1T 5HQ, U.K.
2 Royal Devon and Exeter NHS Foundation Trust, Exeter EX2 5DW, U.K.
3 Barts Health NHS Trust, London E1 1BB, U.K.
4 National Cancer Research Institute’s Skin Cancer Clinical Studies Group and Non-Melanoma Skin Cancer Subgroup
5 Royal College of General Practitioners
6 Independent Cancer Patients’ Voice

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/BJD.20524

This article is protected by copyright. All rights reserved
Corresponding author: ibrahim.nasr@outlook.com
Email: guidelines@bad.org.uk

https://orcid.org/0000-0001-7105-2594 (I.N.); https://orcid.org/0000-0002-1880-9049 (K.F.); https://orcid.org/0000-0002-6322-3901 (G.G.); https://orcid.org/0000-0003-2226-6961 (R.J.M.); https://orcid.org/0000-0003-0073-1885 (L.S.E.); https://orcid.org/0000-0003-4070-0696 (M.F.M.M.); https://orcid.org/0000-0002-2510-9964 (M.C.E.)

Produced in 1999 by the British Association of Dermatologists
Reviewed and updated 2008, 2021

Key words: basal cell carcinoma, guidelines, management, treatment, surgical excision, Mohs surgery, radiotherapy, hedgehog pathway inhibitors, GRADE, systematic review.

This article is protected by copyright. All rights reserved
This article is protected by copyright. All rights reserved
and Evaluation (AGREE II) instrument.\textsuperscript{2} and the Grading of Recommendations Assessment, Development and Evaluation (GRADE).\textsuperscript{3} Recommendations were developed for implementation in the U.K. National Health Service (NHS).

The guideline development group (GDG), which consisted of ten consultant dermatologists (representing England, Northern Ireland, Scotland and Wales; three of whom are also Mohs surgeons), a consultant plastic surgeon, a consultant oral and maxillofacial surgeon, a clinical oncologist, a pathologist, two primary care physicians, a clinical nurse specialist, two patient representatives and a technical team (consisting of an information scientist, two guideline research fellows and a 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 (section 2.1 and Appendix A; see supporting information).

A systematic literature search of PubMed, MEDLINE, EMBASE and Cochrane databases was conducted to identify key articles on BCC published from 1\textsuperscript{st} January 2007 up to 24\textsuperscript{th} January 2020 (publications already included in the 2008 guideline\textsuperscript{4} were evaluated for inclusion). Search terms and strategies can be found in the supplementary information (Appendix K; see supporting information). Additional references relevant to the topic were also isolated from citations in reviewed literature, and where identified, relevant articles published after May 2017 have been included. Evidence from included studies was graded according to the GRADE system (high, moderate, low or very low certainty). Recommendations were based on evidence drawn from systematic reviews of the literature pertaining to the clinical questions identified; the summary of findings with forest plots (Appendices B and C), tables Linking the Evidence To the Recommendations (LETR) (Appendix D), GRADE evidence profiles indicating the quality/certainty of evidence (Appendix E), summary of included comparative studies (Appendix F), narrative findings for non-comparative studies (Appendix G), PRISMA flow diagram (Appendix H) and lists of studies excluded from quantitative analyses with reasons for exclusion (Appendix I) can be found in the supporting information as a web appendix. The strength of recommendation is expressed by the wording and symbols as shown in Table 1.

| Strength | Wording | Symbols | Definition |
|----------|---------|---------|------------|
| Strong   | “Offer” | ↑↑      | Benefits of the intervention outweigh the risks; |
| Recommendation for the use of an intervention | (or similar, e.g. “Use”, “Provide”, “Take”, “Investigate”, etc.) | 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; many 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. |

### 2.1 Low-risk/high-risk BCC criteria

Following review of the literature the GDG agreed to adopt the Royal College of Pathologists’ (RCPath) dataset, which defines pathological low-risk and high-risk BCC based on increased risk for local recurrence and very occasionally metastasis especially if there is perineural invasion in any type of BCC and/or lymphovascular invasion in basosquamous carcinoma. Clinical factors which confer low-risk vs. high-risk BCC are defined as per the National Institute for Health and Clinical Excellence, based on reducing the risks of incomplete excision, recurrence following surgery, and damaging important, proximate anatomical features, to achieve good cosmetic results and reduce post-surgical complications. NICE also considered the skills and training of the surgical operator. The National Comprehensive Cancer Network (NCCN) guidelines gave more precise clinical criteria for clinical low-risk and high-risk BCC. As the Union for International Cancer Control 8th edition (UICC8) version of TNM8 has been endorsed for use in the U.K., and
as NCCN uses the American Joint Committee on Cancer 8th edition cancer staging manual (AJCC8), the NCCN table, on low-risk/high-risk BCC criteria, has been adapted here to equate to the UICC8 and RCPPath dataset.

The GDG’s adopted definition of criteria for low-risk and high-risk BCC is provided in Table 2.

**Table 2. Criteria for low-risk/high-risk BCC**

| Clinical criteria | Low risk | High risk* |
|-------------------|----------|------------|
| Location & size   | Area $L^a \leq 20$ mm (maximum clinical diameter) | Area $L^a > 20$ mm (maximum clinical diameter) |
|                   | Area $M^b \leq 10$ mm (maximum clinical diameter) | Area $M^b > 10$ mm (maximum clinical diameter) |
| Borders           | Well defined | Poorly defined |
| Primary vs. Recurrent | Primary | Recurrent |
| Immunosuppression | No | Yes |
| Site of prior radiotherapy | No | Yes |

**Pathological criteria**

**BCC and stage**

| Growth pattern | Nodular or superficial | Infiltrative (infiltrating, morphoeic, micronodular) |
|----------------|------------------------|----------------------------------------------------|
| Differentiation: basosquamous | Absent | Present (with or without lymphovascular invasion) |
| Level of invasion | Dermis/subcutaneous fat | Beyond subcutaneous fat |
| Depth (thickness) | $\leq 6$ mm | $> 6$ mm |
| Perineural invasion$^d$ | Absent | Present |
| Pathological TNM stage | $pT1 \leq 20$ mm (maximum diameter) | $pT2 > 20$ mm but $\leq 40$ mm (maximum diameter) |
• pT3 >40 mm (maximum diameter), or upstaged\textsuperscript{*} pT1 or pT2, or minor bone invasion
• pT4 major bone invasion

| Margins                      | Histological margins | Not involved (≥1 mm) | Involved (0 mm) or histologically close (<1 mm) |
|-----------------------------|----------------------|---------------------|-----------------------------------------------|

\* One or more criterion equals high risk, unless stated differently in the summary of the recommendations, or in an explanatory note

\textsuperscript{a} Area L = trunk and extremities \textit{but excluding} hands, nail units, genitals, pretibia, ankles and feet

\textsuperscript{b} Area M (see Figure 1) = cheeks, forehead, scalp, neck, and pretibia

\textsuperscript{c} Area H (see Figure 1) = “mask areas” of face (central face, eyebrows, periorbital, nose, lips (cutaneous and vermilion), chin, mandible, preauricular, postauricular, temple, ears); genital areas; hands, nail units, ankles and feet, but \textit{excluding the eyelid}; for tumours <6 mm in size without other high-risk features, standard surgical excision may be considered if at least 4 mm clinical surgical margin can be obtained without significant anatomical or functional distortions

\textsuperscript{d} A named nerve or a diameter at or above 0.1 mm or beyond the dermis

\textsuperscript{e} T1 and T2 can be upstaged to T3 by the presence of one or more high-risk clinical/pathological factors comprising specifically defined perineural invasion or deep invasion representing either a tumour thickness/depth >6 mm and/or invasion beyond/further than the subcutaneous fat.

\textbf{Figure 1. Areas H (darker shade) and M (lighter shade) on the head and neck}

The GDG identified a paper which provided a definition for advanced BCC,\textsuperscript{10} but it was dependent on the AJCC\textsuperscript{7} risk criteria. The GDG adopted the definition with some adaptation to be used in this guideline, as follows:

\textbf{An advanced BCC is a BCC that is either (1) metastatic (mBCC) or (2) locally advanced (laBCC) with one or more high-risk factors, in which current treatment modalities are considered potentially contraindicated by tumour* or patient factors**}.
*Clinical factors that may contribute individually or in combination to a BCC being regarded as locally advanced include:

- Tumour size, location and cosmetic/functional consequences of treatment (e.g. ‘giant’ BCC, which is >5 cm and/or would require extensive surgery such as amputation; and H-zone tumours)
- Large numbers of co-existing tumours
- Tumour subtype (e.g. infiltrative tumours with poorly defined margins)
- Likelihood of successful treatment compromised by previous treatment (e.g. multiple recurrences of BCC after surgery or previous radiotherapy)

**Patient-driven factors that may contribute individually or in combination to a BCC being regarded as locally advanced include:

- Patient performance status (e.g. compromised due to age or frailty)
- Presence of patient comorbidities potentially interfering with surgery (e.g. unsuitability for general anaesthetic)
- Presence of patient factors potentially interfering with radiotherapy (e.g. contraindicated in Gorlin syndrome and relatively contraindicated in younger patients)
- Patient opinions and beliefs regarding treatment and/or their impact on quality of life (e.g. unwilling or reluctant to accept consequences of surgery such as poor cosmetic outcome or adverse effects (AEs) of radiotherapy).

2.2 Clinical questions and outcomes
The GDG established a number of clinical questions pertinent to the scope of the guideline. (Appendix A; see supporting information). The GDG also established a set of outcome measures of importance to patients for each clinical question; these outcomes were ranked by the patient representatives according to the GRADE methodology from 1-9. Outcomes ranked 7, 8 and 9 were critical for decision making; those ranked 4, 5 and 6 were important but not critical for decision making. Data on these outcome measures were extracted from included studies (Table 3 and Appendices B, C, E, F and G; see supporting information).

Table 3. Clinical questions, outcomes and ranking

| Clinical questions | Outcomes | Ranking |
|--------------------|----------|---------|
| Treatment Q1. In people with high-risk BCC, what are the clinical and cost | Complete response or clearance | 9 |
| Surgical margins | Q3. In people with BCC who undergo standard surgical excision, what surgical margin should be used? | Recurrence rate | 9 |
|------------------|-------------------------------------------------------------------------------------------------|----------------|---|
|                   |                                                                                                 | Incomplete excision | 7 |
| Q2. In people with low-risk BCC, what are the clinical and cost effectiveness of surgical (standard and Mohs) and non-surgical techniques (topical therapies, photodynamic therapy, radiotherapy, and biological therapies) compared with each other or with no treatment (observation)? | Recurrence rate (above clavicle) | 9 |
|                   |                                                                                                 | Treatment-related serious AEs (non-surgical), or complications (surgery) | 8 |
|                   |                                                                                                 | Functional outcome (physical or social functioning) | 8 |
|                   |                                                                                                 | Cosmesis | 7 |
|                   |                                                                                                 | Convenience of treatment and patient choice | 7 |
|                   |                                                                                                 | Partial (> 50%) response or clearance | 6 |
| Q3. In people with BCC who undergo standard surgical excision, what surgical margin should be used? | Recurrence rate (below clavicle) | 6 |
|                   |                                                                                                 | Partial (> 50%) response or clearance | 6 |
### 3.0 SUMMARY OF RECOMMENDATIONS

The majority of the recommendations and ratings were agreed upon unanimously by the core members of the GDG and patient representatives following extensive discussions. Where the GDG disagreed on specific issues, votes were cast on all options put forward, and the simple-majority results featured as the final decision. For further information on the wording used for recommendations and strength of recommendation ratings see section 2. The GDG is aware of the lack of high-quality/certainty evidence for some recommendations, therefore, strong recommendations with an asterisk (*) are based on available evidence, as well as informal consensus and specialist experience amongst GDG members. Good practice point (GPP) recommendations are derived from informal consensus amongst GDG members. In general, patient choice should be factored into the decision-making process in applying all the recommendations listed below.

For the relevant recommendations listed below, see †Table 2 for the criteria for low-risk and high-risk BCC, ‡section 2.1 for the definition of advanced BCC, and §Table 7 for levels of community skin cancer services. Where §a patient declines treatment this could also be the patient’s representative with power of attorney.

**General**
Offer verbal and written information about BCC to all adults with BCC, including the nature and prognosis of BCC, available treatment options and the ongoing need for sun protection and self-surveillance of their skin as part of prevention/early detection of future skin tumours.

Referral from primary care

Refer to a local skin multidisciplinary team (LSMDT) or a specialised skin cancer multidisciplinary team (SSMDT) member all adults with high-risk BCC, and all adults with low-risk BCC in the absence of an accredited General Practitioner with Enhanced Role (GPwER) or if the primary care facility is not suitable for surgery. See Table 7 for levels of community skin cancer services.

Surgical treatment

Offer standard surgical excision as a first-line treatment option to adults with low-risk BCC.

Offer standard surgical excision with immediate reconstruction as a first-line treatment option to adults with primary BCC with a high-risk factor, if the BCC has well-defined clinical margins under bright lighting and magnification or dermoscopy.

Offer standard surgical excision with delayed definitive reconstruction, or Mohs micrographic surgery (MMS), as first-line treatment option to adults with high-risk BCC within a high-risk anatomical site if the BCC has poorly defined clinical margins under bright lighting and magnification or dermoscopy.

Excise low-risk BCC using a 4 mm peripheral clinical surgical margin.

Excise primary BCC with a high-risk factor using at least a 5 mm peripheral clinical surgical margin (also, see R4 and R5).

Excise BCC by ensuring adequate excision at the deep margin to a clear plane, including a fat layer where present, and other deeper structures if needed.

Consider Mohs micrographic surgery in adults with primary BCC with at least one high-risk factor.
R10 Offer* Mohs micrographic surgery as a first-line treatment option to adults with recurrent BCC with at least one other high-risk factor,\textsuperscript{†} especially if the tumour is at a high-risk site.

R11 Following discussion at MDT, consider standard surgical excision with at least a 5 mm margin and delayed definitive reconstruction as a treatment option to adults with recurrent BCC with at least one other high-risk factor.\textsuperscript{†}

R12 Offer* standard surgical excision or radiotherapy as treatment option to adults with advanced\textsuperscript{†} BCC (also, see R14).

R13 Consider Mohs micrographic surgery as a treatment option to adults with advanced\textsuperscript{†} BCC.

Systemic therapy
R14 Offer* vismodegib, subject to availability, as treatment option to adults with advanced\textsuperscript{†} BCC who are unsuitable for Mohs micrographic surgery, standard surgical excision or radiotherapy, including patients with Gorlin syndrome, following discussion at MDT (also, see R12 and R13).

Radiotherapy
R15 Offer* radiotherapy as a treatment option to adults (suggested age \(\geq 60\) years) with low-risk and high-risk BCC who are unsuitable for or decline\textsuperscript{§} Mohs micrographic surgery or standard surgical excision and who express a preference for radiotherapy, and in whom the lesion is a:
- nodular BCC
- infiltrative BCC subtypes provided a sufficient planning margin is used
- excised BCC with involved margins.

R16 Do not offer* radiotherapy as a treatment option to adults with BCC who are unsuitable for or decline\textsuperscript{§} Mohs micrographic surgery or standard surgical excision, and in whom the lesion is:
- a recurrent BCC following previous radiotherapy
• associated with certain genetic syndromes predisposing to skin cancers, e.g. Gorlin syndrome, xeroderma pigmentosum.

Discuss alternative treatment modalities at MDT (see R1, R3-R5, R9-14, R18-23).

R17 Do not routinely offer* radiotherapy as a treatment option to adults with BCC who are unsuitable for or decline Mohs micrographic surgery or standard surgical excision, and in whom the lesion is:
• on areas of poor blood supply, e.g. the lower limbs
• in younger patients in whom the late effects of radiotherapy could be an issue (suggested age < 60 years)
• a BCC invading bone or cartilage.

Discuss alternative treatment modalities at MDT (see R1, R3-R5, R9-14, R18-23).

Other treatment options

R18 Offer* topical imiquimod, topical 5-fluorouracil, cryosurgery, or topical PDT as treatment options to adults with low-risk† BCC who are unsuitable for or decline§ standard surgical excision.

R19 Do not offer* topical imiquimod, topical 5-fluorouracil, cryosurgery, curettage & cautery, or topical PDT as treatment options to adults with high-risk† BCC who are unsuitable for or decline§ Mohs micrographic surgery or standard surgical excision.

R20 Do not offer* topical imiquimod, topical 5-fluorouracil, cryosurgery, or topical PDT as treatment options to adults with advanced¶ BCC unless for palliation of symptoms, following discussion at MDT.

R21 Advise* adults with BCC who decline all treatments that the risk of significant progression of the tumour is at least 25% over 2-5 years.

Θ1 There is insufficient evidence to support any recommendation for the following interventions for low-risk (including recurrent, low-risk) BCC†:
• Mohs micrographic surgery
• vismodegib.

This article is protected by copyright. All rights reserved
There is insufficient evidence to support any recommendation for the following interventions for BCC:

- topical ingenol mebutate gel
- topical curaderm-BEC5 cream
- electrochemotherapy (ECT)
- CO₂ laser
- pulsed dye laser
- combinations of:
  - topical diclofenac + calcitriol
  - topical imiquimod + Mohs micrographic surgery
  - intralesional interferon-α + standard surgical excision
  - topical PDT + Mohs micrographic surgery
  - laser therapy + topical PDT.

There is insufficient evidence to recommend 'no treatment' as an option for adults with:

- recurrent BCC with at least one other high-risk factor
- advanced BCC who are not suitable for or decline Mohs micrographic surgery or standard surgical excision.

**Management following primary treatment**

**R22** Following discussion at MDT, offer further standard surgical re-excision to adults with excised high-risk BCC with involved histological margin unless there is a contraindication (also, see R4, R5, R7-R21, Θ1, Θ2 and Θ3).

**R23** Refer all adults with excised high-risk BCC with a close histological margin (<1 mm) for MDT discussion of management options. These may include surgical re-excision, Mohs micrographic surgery, radiotherapy, or monitoring. Patient choice should especially be factored into the decision-making process in such situation.

**R24** Do not routinely offer follow-up to patients with adequately treated isolated BCC, unless for a post-operative review (also, see R25 and R26).

**R25** Offer if possible, a post-operative review of adults with adequately treated BCC by an appropriate healthcare professional, either in secondary or primary care.
R26 GPP Offer if possible, at least a yearly follow-up to adults with a history of multiple BCCs who are likely to develop further tumours or recurrence within 12 months.

Summary of future research recommendations
The following list outlines future research recommendations (FRRs).

FRR1 Randomized controlled trials comparing standard surgical re-excision of high-risk BCC excised with close (<1 mm) or involved histological margin versus Mohs micrographic surgery, radiotherapy, or no treatment. Primary outcomes should include recurrence rate over at least 5 years.

FRR2 Randomized controlled trials directly comparing various treatment modalities with primary outcomes to include U.K. health economic assessment (including treatment of recurrences) and patient-reported outcome measures.

FRR3 Randomized controlled trials comparing standard surgical excision versus Mohs micrographic surgery for high-risk BCC, with longer follow-up periods of at least 5 years

4.0 ALGORITHM
The recommendations, discussions in the LETR sections (Appendix D; see supporting information) and consensus specialist experience were used to produce management pathways for adults with BCC – see Figure 2.

Figure 2. BCC management pathway in primary, secondary and tertiary care

Table 4a. Primary BCC suitable for surgery: influence of tumour risk on the selection of treatment

| Treatment                          | Low-risk BCC | High-risk BCC |
|-----------------------------------|--------------|---------------|
|                                   | Strength of recommendation | Strength of recommendation |
| Excisional surgery                | ↑↑           | ↑↑**          |
| Mohs micrographic surgery         | Θ            | ↑↑            |

**Please refer to summary of recommendations R4, R5, R7 and R8 for details
### Table 4b. Primary BCC not suitable for or patient declines surgery: influence of tumour risk on the selection of treatment

| Treatment                                      | Low-risk BCC | High-risk BCC |
|------------------------------------------------|--------------|---------------|
| Radiotherapy                                   | ↑↑**         | ↑↑**          |
| Vismodegib                                     | ⊙            | ↑↑††          |
| Topical agents (imiquimod or 5-fluorouracil)   | ↑↑           | ↓↓            |
| Cryosurgery                                    | ↑↑           | ↓↓            |
| Curettage & cautery without subsequent surgery | ↑↑           | ↓↓            |
| Photodynamic therapy                           | ↑↑           | ↓↓            |
| No treatment (patient declines\(^\text{§§}\) treatment) | ↑            | ⊙‡‡          |

**Please refer to summary of recommendations R15, R16 and R17 for details**

††Please refer to summary of recommendations R14 for details

\(^{\text{§§}}\)Or patient’s representative with power of attorney

‡‡Please refer to summary of recommendations R21 for details

### Table 5a. Recurrent BCC suitable for surgery: influence of tumour risk on the selection of treatment

| Treatment                               | Low-risk BCC | High-risk BCC |
|-----------------------------------------|--------------|---------------|
| Excisional surgery                      | ↑↑           | ↑**           |
| Mohs micrographic surgery               | ⊙            | ↑↑            |

**Please refer to summary of recommendations R4, R5, R7, R8, R9, R10 and R11 for details**

### Table 5b. Recurrent BCC not suitable for or patient declines surgery: influence of tumour risk on the selection of treatment

| Treatment | Low-risk BCC | High-risk BCC |
|-----------|--------------|---------------|
|           | Strength of recommendation | Strength of recommendation |

This article is protected by copyright. All rights reserved
Table 6. Advanced BCC (metastatic or locally advanced): strength of recommended treatments

| Treatment                             | Strength of recommendation |
|---------------------------------------|----------------------------|
| Excisional surgery                    | ↑↑                        |
| Mohs micrographic surgery             | ↑                         |
| Radiotherapy                          | ↑↑                        |
| Vismodegib                            | ↑↑                        |
| Topical agents (imiquimod or 5-fluorouracil) | ↓↓                    |
| Cryosurgery                           | ↓↓                        |
| Curettage & cautery without subsequent surgery | ↓↓                    |
| Photodynamic therapy                  | ↓↓                        |
| No treatment (patient declines§§ treatment) | Θ**        |

**Please refer to summary of recommendations R15, R16 and R17 for details
††Please refer to summary of recommendations R21 and Θ3 for details
§§Or patient’s representative with power of attorney

5.0 BACKGROUND

5.1 Definition

BCC is the most common keratinocyte cancer / non-melanoma skin cancer (NMSC).11-15 It is a slow-growing, locally invasive malignancy that very rarely metastasizes.7,10,14 Usually, it develops on sun-exposed areas such as the head and neck,13,14 although potentially any cutaneous site
can be affected. Clinically and pathologically, BCC is heterogenous. The commonest subtype is nodular BCC (>60%),\textsuperscript{10} and other variants include superficial, infiltrative (morphoeic, sclerosing, micronodular), keratotic and pigmented are also described, with frequent histological overlap between types.\textsuperscript{11} The basosquamous variant is the most aggressive type, which has a tendency for lymphovascular or perineural invasion, and can rarely metastasize.\textsuperscript{7,11} BCC usually develops as a sporadic tumour but rarely can develop in chronic scars\textsuperscript{16} or be part of a genodermatosis, for example Gorlin syndrome, xeroderma pigmentosum, Bazex-Dupré-Christol syndrome and Rombo syndrome.\textsuperscript{10,11,13}

5.2 Incidence and aetiology

The exact incidence of BCC globally is not accurately known because it is not included in cancer registries in most countries.\textsuperscript{13-15} However, recent improvements to registry data collection in England has enabled more accurate analysis, which has confirmed a rise in incidence of the first BCC per person per year from 268,565 in 2013 to 410,716 in 2015.\textsuperscript{15} Incidence increases with age and is more common in men.\textsuperscript{15}

BCC is an epidermal keratinocyte cancer. The exact cell of origin is not known, although it is considered to originate from pluripotent cells in the interfollicular epidermis and infundibulum of the hair follicle distributed along the basal layer.\textsuperscript{17,18} It is believed to be caused by a combination of genetic predisposition and exposure to ultraviolet radiation (UVR), and the risk is increased in the context of immunosuppression, for example organ transplantation,\textsuperscript{19} HIV\textsuperscript{20} and haematologic malignancy.\textsuperscript{11,13} The hedgehog (Hh) intracellular signalling pathway is critical for the regulation of cell growth and differentiation in embryonic development. Development of BCC is associated in the most cases with loss of inhibition of Hh signalling. This is the result of inactivating mutations in the tumour-suppressor protein patched homologue 1 (PTCH1) gene in 90% and activating mutations in smoothened (SMO) trans-membrane protein gene in 10% of sporadic BCC, with germline mutations in PTCH1 and occasionally PTCH2, SMO and suppressor of fused (SUFU) gene in Gorlin syndrome. The importance of this pathway is highlighted by the successful use in advanced BCC of hedgehog pathway inhibitors (e.g. vismodegib).\textsuperscript{10,11,14,18}

6.0 DIAGNOSIS AND INVESTIGATION

6.1 Diagnosis

Dermatologists and other skin cancer specialists can usually diagnose BCC clinically, without the need for biopsy. Diagnostic accuracy is enhanced by good lighting, the skin stretch test,\textsuperscript{21} and dermoscopy.\textsuperscript{22,23} Specialist non-invasive skin imaging tools including reflectance confocal
microscopy and optical coherence tomography may also help in diagnosis of difficult cases, although these are not widely available.24-26

Biopsy is indicated if there is clinical doubt about the diagnosis, for potentially high-risk types (e.g. based on clinical risk factors of size and/or location), if the treatment will be influenced by histological subtype (e.g. infiltrative versus superficial) and to confirm recurrences after treatment.7,11,12,14 In most cases, shave or curette biopsy should be sufficient to make a positive diagnosis of BCC.11 If the histological subtype is in doubt, a deep incisional or excisional biopsy (to include the dermis or fat, if possible) is recommended.12,14

If there is clinical suspicion that the tumour is attached to or extends deep to the underlying deep fascia, and/or if there is suspected involvement of muscle, large nerves or blood vessels or bone, then cross-sectional imaging of the area using either computerised tomography (CT) scanning or magnetic resonance imaging (MRI) should be considered, and the case should be discussed at an SSMDT meeting prior to treatment.7,12,14 In the case of involvement of deeper structures of the head and neck area, a referral to the Head & Neck MDT may be considered.7,12,14

6.2 Low-risk and high-risk tumours, patient factors and treatment selection

The management of BCC depends on a number of factors including the size, site and histological subtype of the tumour (Table 2), patient comorbidities, previous treatment history and patient preference.10 It is also important to consider whether the intention of treatment is curative or palliative, where and by whom treatment should be delivered to ensure the best possible outcome (see section 7), and availability of treatment within the treating healthcare provider’s service.

The GDG identified only one publication27 that addresses the needs and preferences of patients regarding BCC and SCC treatment. The qualitative study found that of particular importance to patients with BCC were to receive relevant information tailored to their specific situation, to be seen by the same physician during treatment and follow-up, to have a full-body skin examination during follow-up, and to participate in shared decision-making.

Factors that should be considered in making a joint decision regarding treatment include:

- performance status of the patient
- risk of the particular tumour in causing harm if not treated (e.g. the presence of ulceration, bleeding, rapid growth, proximity to or involvement of important structures, e.g. the eye and bony orifices)
• presence of comorbidities, including serious, life-limiting conditions
• presence of genodermatoses (e.g. Gorlin syndrome)
• presence of compromised immune status
• regular medications taken by patient, especially anticoagulants and those that adversely modify wound healing
• risk of morbidity/mortality associated with treatment of the BCC
• the likelihood of treatment success.
• if the patient has an implanted cardiac device.

Since BCC is a slow-growing, often asymptomatic tumour that rarely metastasizes, in certain circumstances the option of ‘no treatment’ arises. This may seem an attractive option if the patient has a short life expectancy, but the healthcare provider needs to ensure that the patient fully understands the risks of locally advanced disease.\textsuperscript{10,12} A case series of five patients with low-risk BCC demonstrated that they progressed to advanced BCC within 2 years.\textsuperscript{28} Retrospective studies of patients who did not have re-excision for incompletely excised BCCs showed recurrence rates of at least 25% over 5 years.\textsuperscript{29,30}

6.3 Eyelid
For several editions of TNM, staging of the eyelid has been specifically excluded from staging of BCC of the entire skin. Eyelid has been allocated its own specific and different staging system for the primary tumour and lymph nodes. For many reasons (including clinical, pathological and cancer registration) it is essential that this different system for eyelid is better recognised and used by clinicians, pathologists, and skin cancer MDTs. Regarding its management, a BCC of the eyelid of combined lowest pT1 stage and low-risk histological status still constitutes a high-risk BCC as it is situated in area H. This would mandate management considerations similar to all high-risk BCCs in area H, i.e. with either Mohs micrographic surgery or standard surgical excision with delayed definitive reconstruction – see R4, R5, R9-R21 and \Theta3.

6.4 Digital photography
The diagnosis and management of skin disorders can be aided by digital photography for clear documentation, and to monitor treatment response.\textsuperscript{31} Basal cell carcinoma is no exception to this, where healthcare professionals can utilize it with or without digital dermoscopy photography. Digital photography is also useful in helping patients with regular self-examination of their skin.\textsuperscript{32}
Total-body digital photography can be available for use in clinic, while patients can use digital applications to store these photographs on their personal devices.\textsuperscript{33}

However, some limitations and challenges have been reported, such as the lack of standardization in ensuring the same position, imaging angle and lighting every time, highly expensive devices and equipment, and the time needed to have the photographs taken.\textsuperscript{34} It is envisaged that in the future, advances in technology might make digital photography for skin cancer, including basal cell carcinoma, more efficient and cheaper.\textsuperscript{34}

The GDG agrees with the utility of digital photography, where possible, in the management of BCC, and highlights the following:

- No image should be kept without the patient’s express consent, and in line with the NHS data protection and information governance requirements.
- As remote consultations (e.g. teledermatology) increasingly become the new norm, even prior to the COVID-19 pandemic, patients should be informed of the risks associated with forwarding of digital images. Information governance and data protection rules do not apply until the images have reached the healthcare provider.\textsuperscript{35}
- Images should become part of the patient’s life-long clinical records.
- Images should demonstrate both anatomical location and close-to-detail features (plus dermoscopic detail, if available).
- Where multiple lesions exist, each should be annotated separately.

7.0 MANAGEMENT

Overview

In most cases of primary BCC, surgery is the recommended treatment modality.\textsuperscript{11} ‘Surgery’ includes those forms of surgical treatment with postoperative margin assessment such as standard surgical excision and Mohs micrographic surgery; and those without postoperative margin assessment, such as curettage and cautery (C&C), cryosurgery and laser therapy.\textsuperscript{11,12,14} Each surgical technique has its own indications and contraindications (see sections 7.4, 7.5, 7.6 and 7.7). Other treatment modalities such as radiotherapy, topical therapies and photodynamic therapy (PDT), may be offered if the patient is not suitable for or declines surgery; selection of each modality depends on the precise clinical scenario. In advanced BCC (mBCC and laBCC), surgery may not be feasible, and alternative options include radiotherapy and hedgehog pathway inhibitors.
7.1 Considerations: the patient
The patient, or the person with the power of attorney for health matters, should be counselled sufficiently on all aspects of the treatment approach being considered and post-treatment care, especially with respect to the possibility of developing a scar. Patients should be informed of methods to improve cosmetic outcome following primary treatment. If psychological need has been identified, a referral should be made to appropriate services and a key worker should be identified to support the patient during this process.

At diagnosis, all patients with BCC should be given tailored advice in the forms of verbal and written information. This should include information regarding the nature, prognosis, and treatment options for BCC; predisposing factors (especially sun exposure); advice on photoprotection (with accompanying advice on implications of photoprotection for vitamin D status); risk of recurrence or development of new primary skin cancers and the importance of early detection of recurrence or new tumours by self-skin examination. All patients should be directed as to how to access clinical assessment rapidly should a suspicious lesion arise.

7.2 Considerations: the clinical practitioner
One important issue in management of BCC in the U.K. is that not all clinicians involved in providing treatment have the same specific skills. For example, some are competent in treating low-risk BCC in the primary care setting, while others in the secondary care setting have advanced surgical skills either for all anatomic areas affected (L, M, H), or for particular areas only, e.g. area L and M. Others are clinical or medical oncologists who treat advanced BCC with radiotherapy and/or with systemic agents, respectively.

Primary care/community-based practitioners can choose to develop the necessary knowledge and skills to undertake skin cancer diagnosis and treatment. All general practitioners (GPs) providing skin cancer treatment should demonstrate the necessary knowledge and skills commensurate with their level of activity. Those currently known as a GP with Extended Role (GPwER) are accredited by a team appointed by the Royal College of General Practitioners, to meet the skills described in the current NICE guidance 2010 and the RCGP framework 2018 (see Table 7).

Table 7. Levels of community skin cancer services
| Groups of GPwER                              | Status                                                                 | Range of activity*                                                                 |
|---------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Group 1 - GPwER in General Dermatology      | a GP who has suitable training and has demonstrated competency in General Dermatology | Diagnosis and management of inflammatory skin disease, diagnosis of skin lesions and their non-surgical management, including topical therapy, and PDT, and non-excisional surgical procedures, including cryosurgery and C&C, depending on their training level and availability of treatment, for low-risk BCC (and also precancerous lesions, e.g. actinic keratoses, SCC in situ (Bowen’s disease). |
| Group 2 - GPwER in Skin Lesion Management   | a GP who has suitable training and has demonstrated competency in skin lesion management | Diagnosis and management of skin lesions, including low-risk BCC (well defined bordered primary nodular or superficial BCC on area L ≤ 20 mm (maximum clinical diameter) and on area M ≤ 10 mm (maximum clinical diameter), using both surgical and non-surgical techniques, relevant to their clinical training. In addition, Group 2 & 3 GPwERs are expected to follow those aspects of the NICE recommendations** relevant to their agreed scope of practice. |
| Group 3 - GPwER in General Dermatology and Skin Lesion Management | a GP who has suitable training and has demonstrated competency in General Dermatology and skin lesion management | This group combines groups 1 and 2.                                                                 |
Model 2 Practitioner | a skin surgeon who might be a GP, nurse specialist or secondary care specialist working in the community under the governance of an acute Trust | Management of skin lesions discussed with a core LSMDT member and within the practitioner’s competencies recognized by the LSMDT

* No community practitioner should knowingly treat high-risk BCC, especially on areas M<sup>b</sup> or H<sup>c</sup>, recurrent BCC, BCC with high-risk pathological criteria, except after discussing it with the LSMDT.

** NICE<sup>6</sup> recommends that, for all groups of GPs managing BCC in the community, the patient is not aged 24 years or younger, is not immunosuppressed and does not have Gorlin syndrome, and also that the lesion:

- is located below the clavicle (see definition of area L<sup>a</sup> below)
- is less than 1 cm in diameter with clearly defined margins
- is not a recurrent BCC following incomplete excision
- is not a persistent BCC that has been incompletely excised according to histology
- is not morphoeic, infiltrative or basosquamous in appearance
- is not located:
  - over important underlying anatomical structures (for example, major vessels or nerves)
  - in an area where primary surgical closure may be difficult (for example, digits or front of shin)
  - in an area where difficult excision may lead to a poor cosmetic result
  - at a highly visible anatomical site (for example, anterior chest or shoulders) where a good cosmetic result is important to the patient.

If the lesion is thought to be a superficial BCC the GP should ensure that the patient is offered the full range of medical treatments (including topical therapy, and PDT) and non-excisional surgical procedures, including cryosurgery and C&C, which may require referral to a member of the LSMDT.

<sup>a</sup> Area L = trunk and extremities **but excluding** hands, nail units, genitals, pretibia, ankles and feet.

<sup>b</sup> Area M = cheeks, forehead, scalp, neck, and pretibia.
Area H = “mask areas” of face (central face, eyebrows, periorbital, nose, lips (cutaneous and vermilion), chin, mandible, preauricular, postauricular, temple, ears); genital areas; hands, nail units, ankles and feet, but excluding the eyelid.

7.3 Multidisciplinary team

One of the main service provisions for management of skin cancers, including BCC, in the U.K. is the MDT. It was first recommended by NICE in 2006\textsuperscript{37} to be in two forms: the Local hospital Skin cancer MDT (LSMDT) and the Specialist Skin cancer MDT (SSMDT). NICE described in the guidance the types of patients to be referred to each level of MDT, the roles required from the MDT, and the core and the extended membership of each MDT. This guidance was updated in 2010\textsuperscript{6} (and currently under review), the referral process was reviewed in 2015 and the quality standard published in 2016.\textsuperscript{38} A report was published in 2018 by the BAD\textsuperscript{39} in response to NHS England reform of cancer MDT meetings.\textsuperscript{40}

The main points that these guidance documents recommend for BCC are:

- **To refer for discussion at an LSMDT meeting:**
  - All patients with high-risk BCCs that involve the excision margins or are recurrent.
  - Patients suitable for Mohs micrographic surgery.
  - Immunocompromised patients (e.g. organ transplant recipients, patients with haematologic malignancy and HIV/AIDS) with skin cancers and patients who have Gorlin syndrome or other genetic conditions in which predisposition occurs.
  - All patients with low-risk BCCs that should not be treated in primary care as per Table 7 above.

- **To refer for discussion at an SSMDT meeting:**
  - Patients with metastatic BCCs.
  - For periodic review, patients developing skin cancers who are immunocompromised, have Gorlin syndrome or other genetic predisposition syndromes.
  - Patients who may be eligible for entry into clinical trials.
  - Patients who require adjuvant treatment (where this is shown to be beneficial).

Additionally, the GDG recommends that the following cases be referred to an LSMDT member:

- Low-risk BCC in the absence of a competent General Practitioner with Enhanced Role (GPwER) or if the primary care facility is not suitable for surgery (see R2).
• Recurrent BCC with high-risk factors when Mohs micrographic surgery is not appropriate, or the patient or the patient’s representative with power of attorney declines it (see R11).
• Patients unsuitable for Mohs micrographic surgery or standard surgical excision but suitable for radiotherapy and patients who may prefer radiotherapy as an alternative treatment option (see R15, R16 and R17).
• Excised high-risk BCC with a close histological margin (<1 mm; see R23).
• If deep extension of BCC to underlying tissue (e.g. named nerve, muscle or bone) is suspected, following a computerized tomography (CT) scan or magnetic resonance imaging (MRI).

In advanced cases of BCC, consider referral to one or more other MDT(s), as clinically appropriate.

7.4 Excision techniques with postoperative margin assessment
7.4.1 Standard surgical excision with predetermined margins
For the indications for standard surgical excision with predetermined surgical margins, please refer to recommendations R3, R4, R5, R6, R7, R8, R11, R12, R22 and R23. For a more detailed discussion on the evidence that underpins these recommendations please refer to Appendix D1 and D2 (LETR, pp 62-77 and 84-87 in the supporting information).

Standard surgical excision is an empirical treatment suitable for the majority of primary BCCs with reported 5-year, recurrence rates between 3-8%; higher recurrence rates have been reported in more historic papers. Standard surgical excision with complete margin control showed a 0.5% recurrence at 5 years for primary tumours and 2.9% at 5 years for recurrent tumours in a single study. For Mohs micrographic surgery, recurrence rates for primary tumours of the head and neck range from 0.3-6.5%. Treating already recurrent tumours is associated with higher subsequent recurrent rates, ranging from 4-10%.

Expertly performed, definitive standard surgical excision can therefore have low recurrence rates. Evidence for clinically significant sparing of tissue, which thereby enables less extensive reconstruction by using complex margin-controlled techniques, is limited.

Evidence from case series involving standard excision margins of 4-5 mm in high-risk BCC (head and neck) reports lower incomplete excision rates (3.74%) compared with excision margins of 3-4 mm (4.10%) or <4 mm (11.31%) (Appendices C and D for proportional meta-analysis forest plots.
and LETR discussions, respectively; see supporting information). Similarly, evidence from case series involving standard excision margins of 4-5 mm in high-risk BCC (whole body) reports lower incomplete excision rates (3.66%) compared with excision margins of 3-4 mm (4.49%) or <4 mm (9.72%). Dhepnorrarat et al.\textsuperscript{49} reports a very high volume (21,677) of BCCs excised and data prospectively collected over a period of 6 years by a defined group of 25 plastic surgeons in Western Australia showing an incomplete excision rate of 4.01%, although no reference was made to the margins involved.

Standard surgical excision consists of three stages: (1) excision of the tumour with a predetermined margin of normal-appearing skin beyond the visible edge of the tumour; (2) surgical repair of the wound; and (3) subsequent histological analysis of the excised tissue.

For a list of good surgical practice points please refer to the ‘Other considerations’ section in Appendix D1.1 (LETR, pp 78-82 in the supporting information).

7.4.2 Mohs micrographic surgery
For the indications for Mohs micrographic surgery please refer to the recommendations R5, R9, R10, R13 and \Theta1. For a more detailed discussion on the evidence that underpins these recommendations please refer to Appendix D1 (LETR, pp 62-64 in the supporting information).

All the general good medical advice for standard surgical excision still applies to Mohs micrographic surgery, namely the operator should be qualified and working in an accredited centre for such surgery, with sufficient time allocation, high-standard (theatre) lighting, and patient counselling for an informed consent. Recently, the British Association of Dermatologists published service guidance and standards for Mohs micrographic surgery performed in the U.K.\textsuperscript{50}

For key features of Mohs micrographic surgery and the differences in technique with standard surgical excision please refer to the ‘Other considerations’ section in Appendix D1.1 (LETR, pp 78-82 in the supporting information).

Only one RCT to date has compared Mohs micrographic surgery and standard surgical excision, with only 3 mm margins being used for the latter in the study. The two publications for the RCT showed the recurrence rate with Mohs micrographic surgery to be lower at both 5-year and 10-year follow-up; however, this was not statistically significant (p>0.05) for primary, high-risk BCC\textsuperscript{43} (Mohs micrographic surgery RR 2.5% vs. standard surgical excision RR 4.1%\textsuperscript{51} after 5 years;
Mohs micrographic surgery RR 4.4% vs. standard surgical excision RR 12.2% after 10 years). With regard to recurrent BCC, the same publications showed that the recurrence rate for Mohs micrographic surgery was statistically significantly better (p<0.05) than that for standard surgical excision (Mohs micrographic surgery RR 2.4% vs. standard surgical excision RR 12.1%; Mohs micrographic surgery RR 3.9% vs. standard surgical excision RR 13.5%).

Mohs micrographic surgery can be considered for all high-risk primary BCC, and offered for recurrent, high-risk BCC. In such cases, either Mohs micrographic surgery is offered or the wound from standard surgical excision should be kept open for delayed reconstruction until the margins are confirmed clear, by paraffin sections.

7.5 Radiotherapy
For the indications for radiotherapy please refer to recommendations R15, R16 and R17. For a more detailed discussion on the evidence that underpins these recommendations please refer to Appendix D1 (LETR, pp 64-66 in the supporting information).

Primary treatment of BCC with radiotherapy is a well-established, definitive treatment. It is considered as an acceptable modality in the previous iteration of the BAD guidelines as well as in international guidelines such as those of the European Dermatology Forum 2019, U.S. National Comprehensive Cancer network (NCCN) 2019, and American Academy of Dermatology 2018.

Standard surgical excision or Mohs micrographic surgery is the usual primary treatment for BCC; however, radiotherapy can be considered on an individual patient basis especially when older patients may prefer radiotherapy as an alternative treatment option, usually after MDT discussion for high-risk BCCs and usually with a diagnostic biopsy. There is evidence for its role as an alternative primary treatment modality for nodular BCC, particularly in older patients with poorer performance status, those (or their representative with power of attorney) who decline surgery or for patients in whom surgery may result in significantly adverse cosmetic or functional outcomes, and to patients who may prefer radiotherapy as an alternative treatment option. It may be an effective post-operative treatment for BCC with involved (microscopic or macroscopic) histological margins for which further surgery is inappropriate.

When managing BCC with perineural invasion (PNI), an MDT team including a cutaneous surgeon and a radiation oncologist familiar with PNI is recommended. Where there is one or more
close or involved margin and PNI, further excision should be offered, or radiotherapy if excision is not feasible. The evidence for the role of adjuvant radiotherapy in a completely excised BCC with PNI is weak.\textsuperscript{14,53}

There is a single randomized trial evaluating standard surgical excision vs. radiotherapy for facial BCCs of less than 4 cm in 347 patients. The 4-year actuarial failure rate was 0.7\% (0.1-3.9\%) for surgery, and 7.5\% (4.2-13.1\%) for radiotherapy (p=0.003). Patients were assessed for cosmetic result at 4 years, which was rated as ‘good’ in 87\% of those having undergone surgery and 69\% radiotherapy.\textsuperscript{54,55}

In retrospective case series, 5- and 10-year local recurrence rates of 4\% and 6\%, respectively, were reported in a series of 720 head and neck BCCs,\textsuperscript{56} with 5-year recurrence rate of 4.2\% reported in another series of 712 patients.\textsuperscript{57} In a systematic review of patients with NMSC treated with hypofractionated radiotherapy (i.e. fraction size over 2 Gy) local recurrence rate did not exceed 7.9\% in 33/36 studies with follow-up ranging from 2-77 months.\textsuperscript{57} However, an older retrospective study of 148 patients with 175 BCC of different subtypes treated with radiotherapy found an overall 5-year recurrence rate of 15.8\%; 86.4\% of all recurrences appeared within 3 years following treatment.\textsuperscript{58} In the same study, compared with nodular BCC, sclerosing (morphoeic, infiltrative) BCC was a significant risk factor for recurrence after radiotherapy; therefore, surgery is generally preferable for these subtypes.\textsuperscript{58} If radiotherapy is used for poorly defined BCCs, then a wider planning margin is advised.\textsuperscript{58} Surgery is also preferred to radiotherapy in areas of potential poor healing, particularly the leg,\textsuperscript{59} and for BCC invading bone or cartilage and recurrent BCCs that have recurred following radiotherapy.\textsuperscript{7,12,14}

The acute complications of radiotherapy include moist and dry desquamation, acute/erosive dermatitis, while the longer term, cosmetic effects of radiotherapy (e.g. hypopigmentation, telangiectasia, fibrosis and rarely, skin/cartilage/bone radionecrosis) may worsen over time, and are likely to be worse with high dose per fraction;\textsuperscript{60} however, there is growing clinical evidence that hypofractionation (larger than standard 2-2.5 Gy per fraction) does not compromise cosmesis and is particularly appealing to older or frail patients, as fewer treatments are required. Most guidelines therefore recommend reserving radiotherapy for patients aged 60 or over.\textsuperscript{7} Radiotherapy should also not be used in genetic syndromes predisposing to skin cancers such as Gorlin syndrome and xeroderma pigmentosum, as it can predispose to secondary carcinomas.\textsuperscript{7,61-64}
For discussions on radiotherapy regimens please refer to the ‘Other considerations’ section in Appendix D1.1 (LETR, pp 82 in the supporting information).

7.6 Other surgical techniques without postoperative margin assessment

For the indications for other surgical techniques without postoperative margin assessment, please refer to recommendations R18, R19, R20 and Ø2. For a more detailed discussion on the evidence that underpins these recommendations please refer to Appendix D1 (LETR, pp 71-73 in the supporting information).

7.6.1 Curettage and cautery

Curettage, in combination with cautery or electrodessication, up to three cycles has been used as a treatment modality for many years for BCC. Although it is an expedient and cost-effective technique for superficial lesions, it does not allow histological margin assessment.

Curettage and cautery undertaken by experienced practitioners for well-defined, low-risk nodular and superficial BCCs produces 5-year recurrence rates of 4-8%. If it is used for high-risk BCC it was reported to have recurrence rates of 19% which carries significant morbidity to patients and may make subsequent treatment more complicated and cure more difficult to achieve.

Curettage may be used prior to standard surgical excision to define the extent of tumour margins more accurately (see section 7.4.1), prior to Mohs micrographic surgery (see section 7.4.2), prior to cryotherapy (see section 7.6.2), or prior to PDT (see section 7.7.2).

In the event that the curette enters the subcutaneous fat, curettage should be abandoned, and the wound excised surgically.

7.6.2 Cryosurgery

Although ‘cryotherapy’ is a common synonym for ‘cryosurgery’, the GDG agreed to use the latter because in the UK, the term ‘cryotherapy’ often refers to cold therapy for destructive and non-destructive purposes. The term ‘cryosurgery’ refers to the destruction of BCC by using liquid nitrogen specifically.

Cryosurgery with liquid nitrogen spray in freeze-thaw cycles is an effective treatment for selected low-risk, well-defined BCCs. However, the reported 5-year recurrence rates vary significantly, ranging from 7.5% to 20%. This variability might be a result of wrong patient
selection, different techniques, and different clinician skills, as reported by a single clinician who treated 7,338 patients (primary and recurrent BCC and SCC) by cryosurgery over 30 years with a total recurrence rate of 1%.

Thissen et al. compared the cosmetic outcome of cryosurgery compared to standard surgical excision of superficial BCC and reported that both clinicians and patients were in favour of standard surgical excision over cryosurgery. Similarly, in an RCT comparing cryotherapy with MAL-PDT, recurrence rates at 5 years were similar, but cosmetic outcomes were significantly better with MAL-PDT.

7.6.3 Laser therapy
Laser destruction of low-risk superficial or thin nodular BCCs has been employed using several different laser types, including pulsed dye, and CO₂ laser. The latter study randomised patients to CO₂ laser, standard surgical excision and cryosurgery. Complete remission with CO₂ laser was similar to cryotherapy but significantly lower than surgery, although these data were reported after a follow-up period of only 3 months and so are not sufficient to adequately determine efficiency.

7.7 Nonsurgical
For the indications for non-surgical treatments please refer to recommendations R14, R18, R19, R20, Θ1 and Θ2. For a more detailed discussion on the evidence that underpins these recommendations please refer to Appendix D1 (LETR, pp 68-72 in the supporting information).

7.7.1 Topical therapy
Two topical agents are licensed for BCC, namely imiquimod and 5-fluorouracil (5-FU).

7.7.1.1 Imiquimod
Imiquimod is a toll-like receptor 7 agonist and induces a tumour-directed cellular immune response. Several studies support its use in sBCC, and it is licensed in a regimen of 5 days per week over 6 weeks. Many studies support its efficacy in treating single or multiple small, superficial, low-risk BCCs, particularly those on the trunk and limbs, with two non-inferiority RCTs comparing imiquimod to standard surgical excision in low-risk BCC and to PDT and topical 5% 5-FU cream. In these RCTs, topical imiquimod was inferior to standard surgical excision: 3-year follow-up cure rates were 84% with imiquimod and 98% with standard surgical excision, (P<0.0001), with comparable data at 5 years: 5 year follow-up cure rates were 82.5% for
imiquimod versus 97.7% for surgery, \( p<0.001 \), but superior to MAL-PDT and topical 5-FU.\(^{81}\) 1-year follow-up cure rates were 83.4% with imiquimod, 72.8% with PDT, and 80.1% with 5-FU), indicating that topical imiquimod was superior to MAL-PDT and that 5-FU was non-inferior to MAL-PDT for treatment of sBCC.\(^{79,81}\) Five-year follow up data confirmed the superiority of imiquimod to both MAL-PDT and 5-FU, with 5 year BCC-free survivals of 80.5% for imiquimod, 70.0% for 5% 5-FU, and 62.7% for MAL-PDT.\(^{82}\)

Arits et al.\(^{81}\) noted that topical treatments are associated with very high rates of local AEs, with up to 56% of subjects experiencing severe local skin reactions and discomfort. This is variable between patients and may necessitate alterations to treatment regimens to achieve maximal efficacy without unacceptable side effects. Around 5% of subjects treated with topical imiquimod also experienced systemic flu-like symptoms.\(^{81}\)

In terms of cosmesis, if the BCC does notrecur, then topical therapy is associated with comparable or superior cosmetic outcomes to standard surgical excision at 3 years.\(^{79}\)

### 7.7.1.2 5-Fluorouracil cream

5-FU, a topical chemotherapeutic agent, is licensed for treatment of sBCC in a treatment regimen of once or twice daily for 3-4 weeks.\(^{83}\) As mentioned above, 5-FU is inferior to imiquimod but is non-inferior to MAL-PDT.\(^{79-82}\) Rates of local AEs are similar to those seen with imiquimod, but flu-like systemic symptoms are not seen with 5-FU use in one study; one study suggested that 5-FU treatment was associated with higher rates of wound infection than imiquimod treatment.\(^{81}\)

### 7.7.1.3 Other agents

A low-quality/certainty, randomised, vehicle-controlled clinical study involving 94 participants, of which 62 patients with superficial, nodular, cystic and pigmented BCCs were treated with solasodine glycoalkaloids, reported 66% efficacy compared with vehicle group (25%) at the end of an 8-week treatment period, which was reduced to 47% by the end of the year.\(^{84}\) The results in this single study are not sufficient to determine the safety and efficacy of the studied cream compared with more established topical agents.

### 7.7.2 Photodynamic therapy

Topical PDT is a widely studied treatment option for low-risk, superficial BCC.\(^{89,81,82,85,86}\) In these studies PDT was compared to cryosurgery,\(^{87}\) standard surgical excision,\(^{86}\) and topical therapy (imiquimod, and 5-FU).\(^{81,82,88}\) The studies showed that PDT was not inferior to cryosurgery,
standard surgical excision, or 5-FU, while imiquimod was superior to it; and the cosmetic outcome of PDT was better than cryosurgery and standard surgical excision, but equal to imiquimod and 5-FU.\textsuperscript{69,81,82,85,86}

PDT is associated with few AEs, of which some are expected e.g. pain during and after treatment and an acute local reaction, whereas some are unexpected e.g. urticaria in the treated area, hyper- and hypo-pigmentation, and rarely, scarring and contact sensitisation.\textsuperscript{69}

Some studies indicate a possible role for PDT in treating nodular BCC, although 5-year follow-up studies indicate efficacy rates of no more than 76\% at best;\textsuperscript{90} 2-year cure rate of 94\% for standard surgical excision and 74\% for PDT;\textsuperscript{91} 5-year cure rate of 96\% for standard surgical excision and 76\% for PDT;\textsuperscript{90} 12-month cure rate of 79\% for standard surgical excision and for 62\% PDT;\textsuperscript{68} 3-year cure rate of 97.7\% for standard surgical excision and 69.7\% for PDT;\textsuperscript{92} and 5-year cure rate of 98\% for standard surgical excision and 72\% for PDT.\textsuperscript{93}

Guidelines regarding use of PDT in BCC can be found in the British Association of Dermatologists and British Photodermatology Group updated guidelines for topical PDT.\textsuperscript{94}

7.7.3 Hedgehog pathway inhibition

For a more detailed discussion on the evidence that underpins these recommendations please refer to Appendix D1 (LETR, pp 67 in the supporting information).

Vismodegib and sonidegib are Hedgehog pathway inhibitors and specifically target oncogenic smoothened receptors. Both vismodegib and sonidegib are approved by the European Medicines Agency (EMA) and the USA Food and Drug Administration (FDA) for treatment of adults with locally advanced disease (laBCC) who are not candidates for surgery or radiotherapy, while vismodegib is also approved for patients with metastatic BCC (mBCC). Currently in the U.K., vismodegib has a marketing authorisation but did not attain NICE approval for treating symptomatic metastatic BCC in the NHS, whereas sonidegib does not have a marketing authorisation.

Vismodegib has demonstrated efficacy in patients with laBCC and mBCC in the pivotal ERIVANCE clinical trial,\textsuperscript{95-97} and was confirmed in a subsequent global safety study STEVIE clinical trial,\textsuperscript{96,99} and was also demonstrated in a separate RCT in patients with Gorlin syndrome.\textsuperscript{100,101}
In total, 104 patients were treated in ERIVANCE; at 39 months, response rates were 60.3% (laBCC) and 48.5% (mBCC, all partial responses), and median response durations were 14.8 months (mBCC) and 26.2 months (laBCC). During treatment, class-specific AEs were common and included muscle spasm, taste alterations, hair loss, fatigue, and weight loss. These AEs appeared in the majority of patients and led to a treatment discontinuation in 21% of all treated patients. In the primary analysis of STEVIE, 1215 recruited patients were evaluable (1119 laBCC; 96 mBCC). Investigator-assessed response rates were 68.5% for laBCC and 36.9% for mBCC and the AEs were consistent with those identified in ERIVANCE. Treatment was associated with improvement in health related quality of life.

In patients with Gorlin syndrome: a randomised, placebo-controlled trial showed a significant reduction in the number of new, surgically eligible BCCs when treated with vismodegib compared with placebo (2 vs. 29 cases per group per year, P<0.001).

The MIKIE study showed that two intermittent dosing regimens of vismodegib were effective in the control of patients with multiple BCCs, including Gorlin syndrome. The regimen with a shorter induction period of 12 weeks (followed by 8 weeks placebo alternating with 12 weeks of treatment) showed a similar adverse effect profile to the group with a 24-week induction period (followed by 8 weeks of placebo alternating with 8 weeks of treatment).

Studies of neoadjuvant vismodegib in patients with locally advanced BCC, especially in the periocular and orbital area followed by Mohs micrographic surgery, are promising.

Sonidegib, the other smoothened inhibitor, was also shown to be clinically effective in a pivotal prospective randomized double blinded clinical trial (BOLT).

7.7.4 Electrochemotherapy (ECT)

NICE recognised ECT as an ablative treatment to metastases in the skin from tumours of non-skin origin and melanoma, and in 2014 produced a guidance on ECT for primary BCC and primary SCC. With regard to primary BCC, NICE advised that ‘evidence on its efficacy is limited in quantity and quality’, and that the clinician should ‘ensure that patients understand the uncertainty about the procedure’s efficacy and why it is being offered as an alternative to other established methods of treatment’. Since then, four non-randomised comparative and non-comparative studies, and one RCT have been published. The quality/certainty of these
studies is generally very low, and none provided additional evidence to update NICE recommendations in its guidance for treating primary BCC.

Campana et al.\textsuperscript{116} and Gehl et al.\textsuperscript{117} produced recommendations and minimal requirements for reporting clinical data on ECT and updated the standard operating procedures for ECT, which, if the future trials followed these, would help provide further evidence for clinical practice. For a more detailed discussion on the GDG’s decision not to recommend ECT for treating BCC please refer to Appendix D1 (LETR, pp 73-74 in the supporting information).

7.7.5 Other treatments

There are other treatments that were reported in literature to treat BCC, but they are either historic or with currently insufficient evidence to recommend their use for treating BCC.

7.7.5.1 Chemotherapy

Literature on chemotherapy for BCC is old and limited to case reports\textsuperscript{7} that would not comply with the guideline’s inclusion criteria. Moreover, since the introduction of Hh inhibitors, chemotherapy is rarely used in practice (personal communications).

7.7.5.2 Systemic immunotherapy

Literature on systemic immunotherapy is fairly new but still limited to a phase II study and case reports. These reports indicate that anti-PD-1 drugs, namely pembrolizumab\textsuperscript{118,119} and nivolumab\textsuperscript{120,121} might be promising agents to treat advanced BCC, although one\textsuperscript{121} of the two reports on nivolumab showed that new superficial and nodular BCCs appeared during successful treatment of a metastatic tumour.

7.7.5.3 Combination therapy

There were few very low-quality/certainty studies evaluating a number of different combination therapy to treat nodular BCC such as a combination of (diclofenac + calcitriol),\textsuperscript{122} (imiquimod + Mohs micrographic surgery),\textsuperscript{123,124} (interferon-α + standard surgical excision),\textsuperscript{125} (topical PDT + Mohs micrographic surgery),\textsuperscript{126} and (lasers + topical PDT).\textsuperscript{127-129} In order to assess such combination therapies, they need to be followed up for at least 5 years.

7.8 Basal cell carcinoma in children and young people

BCC is extremely rare in children under 15 years of age\textsuperscript{130} and when seen is generally in the context of inherited conditions such as Gorlin syndrome (prevalence 1 per 40,000 -60,000).\textsuperscript{131}
Childhood BCC may also be seen in association with xeroderma pigmentosum, Bazex syndrome, Rombo syndrome, albinism, previous radiotherapy and naevus sebaceous.\textsuperscript{11,130, 132} Sporadic idiopathic BCC in childhood is also reported in the literature, with a total of 107 cases reported worldwide.\textsuperscript{130,132}

All childhood BCC should be managed within the context of a specialist MDT including specialists experienced in treating skin cancer in children.\textsuperscript{131,133}

The first-line treatment option for childhood BCC is surgery, either with standard surgical excision and Mohs micrographic surgery\textsuperscript{130-132,133} Other treatments described for treating childhood BCC include RT (contra-indicated in inherited BCC syndromes)\textsuperscript{14,62,133}, topical therapy, C&C, PDT, and cryosurgery \textsuperscript{130-133}, but in view of the high recurrence rates for childhood BCC (18\% overall\textsuperscript{132}), these treatment options are not recommended.

Vismodegib has proven efficacy in treating BCCs associated with Gorlin syndrome, but its use in children is limited by side effects and a high recurrence rate and incidence of new tumours on cessation of treatment.; in addition vismodegib is currently not recommended by NICE guidance in the UK.\textsuperscript{131,133}

Reducing the risk of future development of BCC should start in childhood with UV protection, particularly in those with predisposing conditions. Early detection is important, so for children with a high risk of BCC education on skin surveillance and regular follow up with a dermatologist is recommended.\textsuperscript{14,131-133}

8.0 FOLLOW-UP

Please refer to recommendations R24-R26 and Appendix D3, pp 87-90 in the supporting information. R24 is underpinned by higher-certainty evidence against routinely following up adequately treated BCC, whereas R25 and R26 are recommendations based on good practice points (GPP). There are many specialties that treat BCCs and other skin cancers, and each specialty will have their own clinics and policies to govern the follow-up process.

The possible reasons for follow-up after initial diagnosis and treatment include (1) detection of local recurrence for tumours at high risk for recurrence; (2) monitoring of advanced BCC following conservative or palliative treatment; (3) surveillance for subsequent development of new BCCs
and/or other skin cancers; (4) repeat the advice on BCC verbally and in written format (as mentioned in section 7.1).

At present there is no evidence that follow-up is required for patients with a single, adequately treated low risk BCC. However, for patients with inadequately treated BCC at high risk for recurrence or for patients with a past history of multiple primary or recurrent BCCs or for those who are at high risk of developing multiple BCC (e.g. in the setting of Gorlin syndrome or immunosuppression), then long-term follow-up may be justified. There is no evidence to support how often this should be, but 6-monthly follow-up for the first year, then annually for at least 5 and possibly up to 10 years or longer, may be appropriate. This may need to be more frequent in selected high-risk patients such as those with Gorlin syndrome or immunosuppressed organ transplant recipients. For patients with advanced BCC, follow-up is likely to be required and should be decided as part of management discussions within the SSMDT and on a case-by-case basis.

9.0 PREVENTION

Patients with a history of BCC have an increased risk of developing further skin cancers of all types. For this reason, advice regarding the avoidance of excessive exposure to UV light, including from sunbeds, and regular skin surveillance is recommended for all BCC patients. Practical guidance in this regard, including on vitamin D supplementation, is well described in the NICE guidance “Sunlight exposure: risks and benefits” and in conjunction with another NICE guidance on “Vitamin D: supplement use in specific population groups”. Although excessive UV light exposure is strongly associated with the development of BCCs, there is no good evidence for the benefit of sunscreens in preventing further BCC (in contrast to actinic keratosis and cutaneous squamous cell carcinoma). Despite the lack of firm evidence for the role of sunscreens in preventing BCC, it is still considered an important part of general advice on sun protection. Specific agents that have been studied for the chemoprevention of BCC include:

**NSAIDs (other than aspirin):** a large RCT found that oral celecoxib 200 mg twice daily significantly reduced the mean number of BCCs in a high-risk population. However, there is a known risk of cardiovascular events in long-term use of COX-2 inhibitors, therefore, routine use in the prevention setting is not currently recommended.
Oral retinoids: acitretin has long been used in transplant/immunocompromised patients with a high keratinocyte tumour burden. Its use is limited due to a high rate of mucocutaneous side-effects and hyperlipidaemia. No large RCTs have been carried out in the non-immunosuppressed population, although a small study demonstrated that acitretin 25 mg once daily was associated with 25% fewer keratinocyte cancers (both BCC and SCC) compared with placebo.\textsuperscript{141} However, the results lacked statistical significance for the study size (designed to pick up a difference of 33% or more).

Oral nicotinamide: an RCT involving nicotinamide 500 mg twice daily in patients with a history of NMSC showed a relative reduction in BCC incidence of 20% at 12 months.\textsuperscript{142} This result was modest, not statistically significant, and the reduction in BCC incidence was not maintained upon cessation of the drug. A clinician wishing to advise on oral nicotinamide should highlight to their patients that it gives no more than 20% relative reduction in the number of BCCs, the effect is not long-lasting following treatment cessation, and is based on only one trial that has not been repeated.

Other oral agents: both α-difluoromethylornithine (DFMO)\textsuperscript{143} and selenium\textsuperscript{144} have been studied for effects on BCC prevention, but no significant risk reduction has been found.

Topical retinoids: neither tazarotene\textsuperscript{145} nor tretinoin\textsuperscript{146} have been shown to significantly reduce the risk of BCC.

In conclusion, aside from sun protection\textsuperscript{147} and regular skin self-surveillance, which should be recommended for all patients following a BCC diagnosis, there is some evidence for a small preventative effect of oral acitretin, nicotinamide and non-aspirin NSAIDS. Due to the commitment of life-long medication and the potential for side effects, these are likely to be recommended only for those with a history of multiple BCCs.

10.0 RECOMMENDED AUDIT POINTS
All clinicians treating skin cancer should audit their histological concordance and complete excision rate. Current examples available for use include:

- For dermatologists who are core MDT members: the British Society for Dermatological Surgery (BSDS) audit tool www.bsdso.org.uk/imagelib/downloads/Dr-Brays-Surgical-Log-Book.zip,
• For primary care clinicians involved in skin cancer surgery: the Community Based Surgery Audit (CBSA) tool www.rcgp.org.uk/clinical-and-research/our-programmes/quality-improvement/community-based-surgery-audit.aspx, to document all surgically treated NMSC cases including BCC.

• Other secondary care specialists may have alternative arrangements for auditing their practice.

These tools calculate the statistics while adding the histology results. It presents the results for the whole department or for the individual surgical operators in the department.

For all cases of BCC, is there documentation of the following (modified BSDS audit tool)?

• Surgeon identity
• Patient identity without any identifiable personal data entry
• Site of lesion
• Primary vs. recurrent lesion
• Type of surgery
• Clinical surgical margins
• Closure
• Growth pattern, deep invasion, perineural invasion, and TNM stage
• Histological margin clearance
• Complications
• Follow-up plan

For all cases of BCC managed in primary care, is there documentation of the following (CBSA audit tool)?

• Surgeon
• Patient
• Procedure type
• Location of lesion
• Closure
• Histology service usage
• Histological diagnoses
• Comparison of clinical and histological diagnoses
• Histological margin completeness
• Complications
• Management information
  o waiting time for surgery
  o waiting time for histology results
  o consent for surgery
  o post-operative information
  o onward referral

Individual operators and units should regularly audit their outcomes with a target of ≥95% complete excision rate being defined as acceptable.\textsuperscript{148,149}

11.0 STAKEHOLDER INVOLVEMENT AND PEER REVIEW
The GDG consisted of representatives from the National Cancer Research Institute (NCRI) Skin Cancer Clinical Studies Group and Non-melanoma skin cancer subgroup (CAH), the Royal College of General Practitioners (RCGP) (JB), the Royal College of Pathologists (RCPath) (DNS), the Royal College of Radiologists (RCR) (KF), the British Association of Oral & Maxillofacial Surgeons (BAOMS) (CN), the British Association of Plastic Reconstructive & Aesthetic Surgeons (BAPRAS) (PGB), the British Society for Dermatological Surgery (BSDS) (RM), the British Society for Skin Care in Immunocompromised Individuals (BSSCII) (JTL), the British Dermatological Nursing Group (BDNG) (JN) and the Primary Care Dermatological Society (PCDS) (NS). The draft document and supporting information were made available to the BAD membership, the RCGP, RCPath, RCR, BAOMS, BAPRAS, BSDS, BSSCII, BDNG, PCDS and British Association of Head & Neck Oncologists (BAHNO), which were actively considered by the GDG. Following further review, the finalized version was sent for peer-review by the Clinical Standards Unit of the BAD, made up of the Therapy & Guidelines Sub-committee (T&G), prior to submission for publication.

12.0 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. Additionally, it is acknowledged that limited cost effectiveness data in the context of U.K. healthcare setting may impact on the availability of a given therapy within the NHS, despite evidence of efficacy. 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 language references was a pragmatic decision but the authors recognize this may exclude some important information published in other languages.

13.0 PLANS FOR GUIDELINE REVISION
The proposed revision date for this set of recommendations is scheduled for 2026; where necessary, important interim changes will be updated on the BAD website.

SUPPORTING INFORMATION
Additional supporting information may be found in the online version of this article at the publisher’s website:
Appendix A: Systematic review protocols
Appendix B: Forest plots for comparative studies
Appendix C: Forest plots for non-comparative studies
Appendix D: Linking Evidence To Recommendations (LETR)
Appendix E: GRADE evidence tables
Appendix F: Summary of included comparative studies
Appendix G: Narrative findings for non-comparative studies
Appendix H: PRISMA 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

ACKNOWLEDGEMENTS
We are very grateful to the patient representatives for their input in formulating the clinical questions, ranking of the outcomes, reviewing the evidence and subsequent draft guideline, clinical oncologist Agata Rembielak, as well as all those who commented on the draft during the consultation period.

DECLARATIONS OF INTEREST
PB: Employed within healthcare industry (2003-2013) – specific; KF: (1) honoraria (advisory board and speaker) – Roche – specific; (2) sponsorship to attend meeting – Roche – specific; GG: (1) honoraria (advisory board and speaker) – Almirall, Leo Pharma, Meda – specific; Novartis – non-specific; (2) research support – Biofrontera – specific, Leo Pharma, Meda – non-
specific; **CAH**: honoraria (advisory board and speaker) – Roche, Leo Pharma, Novartis – specific; Sanofi, Merck – non-specific; (2) clinical trial investigator – PellePharm Inc. – specific; Novartis, Leo Pharma, Meda – non-specific; **JTL**: honoraria (advisory board and speaker) – Leo Pharma, Meda, Novartis, Roche – specific; **EM**: sponsorship to attend meeting – Leo Pharma – specific. **CN**: Investor in a private GP web-based company – non-specific; **DNS**: lead on skin cancer dataset – specific; **EVP**: education sponsorship to attend a dermatology course – Leo Pharma – specific; **PGB**: Deputy Chair TVCN Skin Cancer TSSG – specific; **SH**: honoraria (advisory board and speaker) – Abbvie, Janssen – non-specific. IN, EJM, JB, PB, PF, RM, EM, RJM, JN, NS, LSE, MFMM and MCE have no interests to declare.

**REFERENCES**

1. Mohd Mustapa M, Exton L, Bell H *et al.* Updated guidance for writing a British Association of Dermatologists clinical guideline: the adoption of the GRADE methodology 2016. *Br J Dermatol* 2017; 176:44-51.

2. Brouwers MC, Kho ME, Browman GP *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *Can Med Assoc J* 2010; 182:E839-42.

3. Guyatt GH, Oxman AD, Vist GE *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924-6.

4. Telfer N, Colver G, Morton C. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 2008; 159:35-48.

5. Slater D, Barrett P, Durham C. Standards and datasets for reporting cancers Dataset for histopathological reporting of primary invasive cutaneous squamous cell carcinoma and regional lymph nodes February 2019 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. Last access 20th July 2020. [Last update: 2019].

6. National Institute for Health and Clinical Excellence (NICE). Improving outcomes for people with skin tumours including melanoma (update). In: *The management of low-risk basal cell carcinomas in the community*. London: National Institute for Health and Clinical Excellence (NICE), 2010.

7. National Comprehensive Cancer network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Basal Cell Skin Cancer Version 1.2019 https://www.nccn.org/about/news/ebulletin/ebulletindetail.aspx?ebulletinid=1510. [Last access 20th May 2020]. 2016 [Last update: 2019].
Gospodarowicz MK, Brierley JD, Wittekind C. TNM classification of malignant tumours: John Wiley & Sons. 2017.

Califano JAL, William M.; Nehal, Kishwer S.; O'Sullivan, Brian; Schmults, Chrysalyne; , Seethala RRW, Randal S.; Shah, Jatin P. Cutaneous squamous cell carcinoma of the head and neck. In: AJCC Cancer Staging Manual: Springer. 2017; 171-81.

Lear JT, Corner C, Dziewulski P et al. Challenges and new horizons in the management of advanced basal cell carcinoma: a UK perspective. Br J Cancer 2014; 111:1476-81.

Dika E, Scarfi F, Ferracin M et al. Basal Cell Carcinoma: A Comprehensive Review. International Journal of Molecular Sciences 2020; 21:5572.

Bichakjian C, Armstrong, A., Baum, C. et al. Guidelines of care for the management of basal cell carcinoma. J Am Acad Dermatol 2018; 78:540-59.

Reinau D, Surber C, Jick SS et al. Epidemiology of basal cell carcinoma in the United Kingdom: incidence, lifestyle factors, and comorbidities. Br J Cancer 2014; 111:203-6.

Peris K, Fargnoli MC, Garbe C et al. Diagnosis and treatment of basal cell carcinoma: European consensus–based interdisciplinary guidelines. Eur J Cancer Care (Engl) 2019; 118:10-34.

Venables Z, Nijsten, T., Wong, K., Autier, P., Broggio, J., Deas, A., Harwood, C., Hollestein, L., Langan, S., Morgan, E., Proby, C., Rashbass, J. and Leigh, I. Epidemiology of basal and cutaneous squamous cell carcinoma in the UK 2013–15: a cohort study. Br J Dermatol 2019; 181:474-82

Kowal-Vern A, Criswell BK. Burn scar neoplasms: a literature review and statistical analysis. Burns 2005; 31:403-13.

Tan ST, Ghaznawie, M., Heenan, P.J. and Dosan, R.,. Basal Cell Carcinoma Arises from Interfollicular Layer of Epidermis. J Oncol 2018; 2018;1-5

Sehgal VN, Chatterjee K, Pandhi D et al. Basal cell carcinoma: pathophysiology. Skinmed. 2014; 12:176-81.

Matinfar M, Shahidi S, Feizi A. Incidence of nonmelanoma skin cancer in renal transplant recipients: A systematic review and meta-analysis. J Res Med Sci 2018; 23:14.

Omland SH, Ahlstrom MG, Gerstoft J et al. Risk of skin cancer in patients with HIV: A Danish nationwide cohort study. J Am Acad Dermatol 2018; 79:689-95.

Mellor RH, Bulstrode N, Withey S et al. The stretch test in basal cell carcinoma: a clinical indicator of tumour. Br J Plast Surg 2002; 55:594-5.

Carducci M, Bozzetti M, De Marco G et al. Usefulness of margin detection by digital dermoscopy in the traditional surgical excision of basal cell carcinomas of the head and neck including infiltrative/morpheaform type. J Dermatol 2012; 39:326-30.
23 Caresana G, Giardini R. Dermoscopy-guided surgery in basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2010; **24**:1395-9.

24 Kadouch DJ, Leeftlang MM, Elshot YS et al. Diagnostic accuracy of confocal microscopy imaging versus punch biopsy for diagnosing and subtyping basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2017; **31**:1641-48.

25 Yucel D, Themstrup L, Manfredi M et al. Optical coherence tomography of basal cell carcinoma: density and signal attenuation. *Skin Res Technol* 2016; **22**:497-504.

26 Iftimia N, Peterson G, Chang EW et al. Combined reflectance confocal microscopy-optical coherence tomography for delineation of basal cell carcinoma margins: an ex vivo study. *J Biomed Opt* 2016; **21**:16006.

27 van Egmond S, Marlies Wakkee, Mirjam Droger, M. T. Bastiaens, A. van Rengen, K. P. de Roos, Tamar Nijsten, and M. Lugtenberg. Needs and preferences of patients regarding basal cell carcinoma and cutaneous squamous cell carcinoma care: a qualitative focus group study. *Br J Dermatol* 2019; **180**:122-9.

28 Varga E, Korom I, Rasko Z et al. Neglected Basal cell carcinomas in the 21st century. *J Skin Cancer* 2011; **2011**:392151.

29 Sherry K, Reid L, Wilmshurst A. A five year review of basal cell carcinoma excisions. *J Plast Reconstr Aesthet Surg* 2010; **63**:1485-9.

30 Codazzi D, Van Der Velden J, Carminati M et al. Positive compared with negative margins in a single-centre retrospective study on 3957 consecutive excisions of basal cell carcinomas. Associated risk factors and preferred surgical management. *J Plast Surg Hand Surg* 2014; **48**:38-43.

31 Giuffrida R, Conforti C, Di Meo N et al. Use of noninvasive imaging in the management of skin cancer. *Curr Opin Oncol* 2020; **32**:98-105.

32 Marek AJ, Chu EY, Ming ME et al. Piloting the Use of Smartphones, Reminders, and Accountability Partners to Promote Skin Self-Examinations in Patients with Total Body Photography: A Randomized Controlled Trial. *Am J Clin Dermatol* 2018; **19**:779-85.

33 Schneider SL, Kohli I, Hamzavi IH et al. Emerging imaging technologies in dermatology: Part I: Basic principles. *J Am Acad Dermatol* 2019; **80**:1114-20.

34 Schneider SL, Kohli I, Hamzavi IH et al. Emerging imaging technologies in dermatology: Part II: Applications and limitations. *J Am Acad Dermatol* 2019; **80**:1121-31.

35 Rimmer A. Can I store any images sent during remote consultations? *BMJ (Online)* 2020; **2020**:370.

36 Cunliffe. T.; Schofield J. Guidance and competences to support the accreditation of GPs with Extended Roles (GPwERs): Dermatology and Skin Surgery
https://www.rcgp.org.uk/training-exams/practice/guidance-and-competences-for-gps-with-
extended-roles-in-dermatology-and-skin-surgery.aspx. In. London. 2018; 1-37.

37 National Institute for Health and Clinical Excellence (NICE). Improving outcomes for people
with skin tumours including melanoma [CSG8]: https://www.nice.org.uk/guidance/csg8.
[Last accessed 20th June 2019]. London, United Kingdom: National Institute for Health and
Clinical Excellence. 2006 [Last update: May 2010].

38 National Institute for Health and Clinical Excellence (NICE). Skin cancer [QS130]
https://www.nice.org.uk/guidance/qs130. [Last accessed 30th July 2019]. London, United
Kingdom: National Institute for Health and Clinical Excellence (NICE). 2016.

39 British Association of Dermatologists (BAD). National Reform of Cancer MDT Meetings
https://www.bad.org.uk/healthcare-professionals/clinical-services/national-reform-of-cancer-
mdt-meetings. [Last accessed 20th May 2020]. United Kingdom, London. 2018; 1-24.

40 Gore M. Transforming multidisciplinary team meetings (MDTMs).
https://www.england.nhs.uk/south/wp-content/uploads/sites/6/2018/10/Transforming-
MDTM-Martin-Gore-August-2017.pdf. In. United Kingdom, London. 2017; 1-3.

41 Thissen MR, Neumann MH, Schouten LJ. A systematic review of treatment modalities for
primary basal cell carcinomas. Arch Dermatol 1999; 135:1177-83.

42 Smeets NW, Krekels GA, Ostertag JU et al. Surgical excision vs Mohs' micrographic
surgery for basal-cell carcinoma of the face: randomised controlled trial. Lancet 2004;
364:1766-72.

43 Mosterd K, Krekels GA, Nieman FH et al. Surgical excision versus Mohs' micrographic
surgery for primary and recurrent basal-cell carcinoma of the face: a prospective
randomised controlled trial with 5-years' follow-up. Lancet Oncol 2008; 9:1149-56.

44 Griffiths R, Suvarna S, Stone J. Do basal cell carcinomas recur after complete conventional
surgical excision? Br J Plast Surg 2005; 58:795-805.

45 Wetzig T, Woitek M, Eichhorn K et al. Surgical excision of basal cell carcinoma with
complete margin control: outcome at 5-year follow-up. Dermatology 2010; 220:363-9.

46 Macfarlane L, Waters A, Evans A et al. Seven years' experience of Mohs micrographic
surgery in a UK centre, and development of a UK minimum dataset and audit standards.
Clin Exp Dermatol 2013; 38:262-9.

47 Leibovitch I, Huilgol SC, Selva D et al. Basal cell carcinoma treated with Mohs surgery in
Australia II. Outcome at 5-year follow-up. J Am Acad Dermatol 2005; 53:452-7.

48 Wennberg AM, Larko O, Stenquist B. Five-year results of Mohs' micrographic surgery for
aggressive facial basal cell carcinoma in Sweden. Acta Derm Venereol 1999; 79:370-2.
Dhepnorrarat RC, Lee MA, Mountain JA. Incompletely excised skin cancer rates: a prospective study of 31 731 skin cancer excisions by the Western Australian Society of Plastic Surgeons. *J Plast Reconstr Aesthet Surg* 2009; 62:1281-5.

British Association of Dermatologists (BAD). Mohs Micrographic Surgery (MMS). https://www.bad.org.uk/shared/get-file.ashx?itemtype=document&id=6346. In: *Mohs Micrographic Surgery Services Guidance and Standards*. London, United Kingdom: British Association of Dermatologists (BAD), Clinical Standard Unit. 2020; 1-46.

van Loo E, Mosterd K, Krekels GA et al. Surgical excision versus Mohs' micrographic surgery for basal cell carcinoma of the face: A randomised clinical trial with 10 year follow-up. *Eur J Cancer* 2014:3011-20.

Likhacheva A, Awan M, Barker CA et al. Definitive and postoperative radiation therapy for Basal and Squamous cell cancers of the skin: An ASTRO clinical practice guideline. *Pract Radiat Oncol* 2020; 10:8-20.

Jackson JE, Dickie GJ, Wiltshire KL et al. Radiotherapy for perineural invasion in cutaneous head and neck carcinomas: toward a risk-adapted treatment approach. *Head Neck* 2009; 31:604-10.

Avril MF, Auperin A, Margulis A et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. *Br J Cancer* 1997; 76:100-6.

Bath-Hextall FJ, Perkins W, Bong J et al. Interventions for basal cell carcinoma of the skin. *Cochrane Database Syst Rev* 2007; 1:CD003412.

Marconi DG, Da Costa Resende B, Rauber E et al. Head and neck non-melanoma skin cancer treated by superficial x-ray therapy: An analysis of 1021 cases. *PLoS ONE* 2016; 11.

Gunaratne DA, Veness MJ. Efficacy of hypofractionated radiotherapy in patients with non-melanoma skin cancer: Results of a systematic review. *J Med Imaging Radiat Oncol* 2018; 62:401-11.

Zagrodnik B, Kempf W, Seifert B et al. Superficial radiotherapy for patients with basal cell carcinoma: recurrence rates, histologic subtypes, and expression of p53 and Bcl-2. *Cancer*. 2003; 98:2708-14.

Podd T. Treatment of lower limb basal cell and squamous cell carcinomas with radiotherapy. *Clin Oncol* 1992; 4:44-5.

Pampena R, Palmieri T, Kyrgidis A et al. Orthovoltage radiotherapy for nonmelanoma skin cancer (NMSC): Comparison between 2 different schedules. *J Am Acad Dermatol* 2016; 74:341-7.
61 Cooper JS. Radiotherapy in the treatment of skin cancers. In: Cancer of the skin (Friedman RJ, Rigel DS, Kopf AW et al., eds). Philadelphia: WB Saunders. 1991; 553-68.
62 Silverman MK, Kopf AW, Gladstein AH et al. Recurrence rates of treated basal cell carcinomas. Part 4: X-ray therapy. J Dermatol Surg Oncol 1992; 18:549-54.
63 Smith SP, Foley EH, Grande DJ. Use of Mohs micrographic surgery to establish quantitative proof of heightened tumor spread in basal cell carcinoma recurrent following radiotherapy. J Dermatol Surg Oncol 1990; 16:1012-6.
64 Smith SP, Grande DJ. Basal cell carcinoma recurring after radiotherapy: a unique, difficult treatment subclass of recurrent basal cell carcinoma. J Dermatol Surg Oncol 1991; 17:26-30.
65 Rowe DE, Carroll RJ, Day CL, Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. J Dermatol Surg Oncol 1989; 15:315-28.
66 Barlow JO, Zalla MJ, Kyle A et al. Treatment of basal cell carcinoma with curettage alone. J Am Acad Dermatol 2006; 54:1039-45.
67 Chiller K, Passaro D, McCalmont T et al. Efficacy of curettage before excision in clearing surgical margins of nonmelanoma skin cancer. Arch Dermatol 2000; 136:1327-32.
68 Berroeta L, Clark C, Dawe R et al. A randomized study of minimal curettage followed by topical photodynamic therapy compared with surgical excision for low-risk nodular basal cell carcinoma. Br J Dermatol 2007; 157:401-3.
69 Basset-Seguin N, Ibbotson SH, Emettestam L et al. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. Eur J Dermatol 2008; 18:547-53.
70 Kuflik EG. Cryosurgery for skin cancer: 30-year experience and cure rates. Dermatol Surg 2004; 30:297-300.
71 Thissen MR, Nieman FH, Ideler AH et al. Cosmetic results of cryosurgery versus surgical excision for primary uncomplicated basal cell carcinomas of the head and neck. Dermatol Surg 2000; 26:759-64.
72 Roozeboom MH, Arits AH, Nelemans PJ et al. Overall treatment success after treatment of primary superficial basal cell carcinoma: a systematic review and meta-analysis of randomized and nonrandomized trials. Br J Dermatol 2012; 167:733-56.
73 Tran HT, Lee RA, Oganeyan G et al. Single treatment of non-melanoma skin cancers using a pulsed-dye laser with stacked pulses. Lasers Surg Med 2012; 44:459-67.
74 Zane C, Facchinetti E, Arisi M et al. Pulsed CO2 Laser Ablation of Superficial Basal Cell of Limbs and Trunk: A Comparative Randomized Clinical Trial With Cryotherapy and Surgical Ablation. *Dermatol Surg* 2017; **43**:920-7.

75 Schön M, Schön M. Imiquimod: mode of action. *Br J Dermatol* 2007; **157**:8-13.

76 Geisse J, Caro I, Lindholm J et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. *J Am Acad Dermatol* 2004; **50**:722-33.

77 Gollnick H, Barona CG, Frank RG et al. Recurrence rate of superficial basal cell carcinoma following treatment with imiquimod 5% cream: conclusion of a 5-year long-term follow-up study in Europe. *Eur J Dermatol* 2008; **18**:677-82.

78 Quirk C, Gebauer K, De’Ambrosis B et al. Sustained clearance of superficial basal cell carcinomas treated with imiquimod cream 5%: results of a prospective 5-year study. *Cutis* 2010; **85**:318-24.

79 Bath-Hextall F, Ozolins M, Armstrong SJ et al. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial. *Lancet Oncol* 2014; **15**:96-105.

80 Williams HC, Bath-Hextall F, Ozolins M et al. Surgery Versus 5% Imiquimod for Nodular and Superficial Basal Cell Carcinoma: 5-Year Results of the SINS Randomized Controlled Trial. *J Invest Dermatol* 2017; **137**:614-9.

81 Arits AH, Mosterd K, Essers BA et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. *Lancet Oncol* 2013; **14**:647-54.

82 Jansen MHE, Mosterd K, Arits A et al. Five-year results of a randomized controlled trial comparing effectiveness of photodynamic therapy, topical imiquimod and topical 5-fluorouracil in patients with superficial basal cell carcinoma. *J Invest Dermatol* 2018; **138**:527-33

83 Mylan Products Ltd. Efudix 5% cream: Package leaflet: Information for the user. https://www.medicines.org.uk/emc/files/pil.9260.pdf. In. 2016.

84 Punjabi S, Cook LJ, Kersey P et al. Solasodine glycoalkaloids: a novel topical therapy for basal cell carcinoma. A double-blind, randomized, placebo-controlled, parallel group, multicenter study. *Int J Dermatol* 2008; **47**:78-82.

85 Roozeboom MH, Arits A, Mosterd K et al. Three-Year Follow-Up Results of Photodynamic Therapy vs. Imiquimod vs. Fluorouracil for Treatment of Superficial Basal Cell Carcinoma: A Single-Blind, Noninferiority, Randomized Controlled Trial. *J Invest Dermatol* 2016; **136**:1568-74.
86 Szeimies RM, Ibbotson S, Murrell DF et al. A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8-20 mm), with a 12-month follow-up. J Eur Acad Dermatol Venereol 2008; 22:1302-11.

87 Basset-Seguin N. Topical photodynamic therapy for superficial and nodular basal cell carcinoma. Expert Rev Dermatol 2010; 5:61-6.

88 Roozeboom MH, Arits AH, Mosterd K et al. Three year follow-up results of photodynamic therapy versus imiquimod versus fluorouracil for treatment of superficial basal cell carcinoma: a single blind, non-inferiority, randomized controlled trial. J Invest Dermatol 2016; 136:1568-74.

89 Ibbotson SH, Wong TH, Morton CA et al. Adverse effects of topical photodynamic therapy: a consensus review and approach to management. Br J Dermatol 2019; 180:715-29.

90 Rhodes LE, de Rie MA, Leifsdottir R et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. Arch Dermatol 2007; 143:1131-6.

91 Rhodes LE, de Rie M, Enstrom Y et al. Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. Arch Dermatol 2004; 140:17-23.

92 Mosterd K, Thissen MR, Nelemans P et al. Fractionated 5-aminolaevulinic acid-photodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma: results of a randomized controlled trial. Br J Dermatol 2008; 159:864-70.

93 Roozeboom MH, Aardoom MA, Nelemans PJ et al. Fractionated 5-aminolevulinic acid photodynamic therapy after partial debulking versus surgical excision for nodular basal cell carcinoma: a randomized controlled trial with at least 5-year follow-up. J Am Acad Dermatol 2013; 69:280-7.

94 Wong TH, Morton CA, Collier N et al. British Association of Dermatologists and British Photodermatology Group guidelines for topical photodynamic therapy 2018. Br J Dermatol 2019; 180:730-9.

95 Sekulic A, Migden MR, Oro AE et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N Engl J Med 2012; 366:2171-9.

96 Sekulic A, Migden MR, Lewis K et al. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC. J Am Acad Dermatol 2015; 72:1021-6 e8.

97 Sekulic A, Migden MR, Basset-Seguin N et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. BMC Cancer 2017; 17:332.
Basset-Seguin N, Hauschild A, Grob JJ et al. Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial. *Lancet Oncol* 2015; **16**:729-36.

Basset-Seguin N, Hauschild A, Kunstfeld R et al. Vismodegib in patients with advanced basal cell carcinoma: Primary analysis of STEVIE, an international, open-label trial. *Eur J Cancer* 2017; **46**:334-48.

Tang JY, Mackay-Wiggan JM, Aszterbaum M et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *N Engl J Med* 2012; **366**:2180-8.

Tang JY, Ally MS, Chanana AM et al. Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2016; **17**:1720-31.

Hansson J, Bartley K, Karagiannis T et al. Assessment of quality of life using Skindex-16 in patients with advanced basal cell carcinoma treated with vismodegib in the STEVIE study. *Eur J Dermatol* 2018; **28**:775-83.

Dreno B, Kunstfeld R, Hauschild A et al. Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): a randomised, regimen-controlled, double-blind, phase 2 trial. *Lancet Oncol* 2017; **18**:404-12.

Gonzalez A. Neoadjuvant vismodegib for the treatment of periocular basal cell carcinoma. *Ann Surg Oncol* 2018; **25**:S181.

Sagiv O, Nagarajan P, Ferrarotto R et al. Ocular preservation with neoadjuvant vismodegib in patients with locally advanced periocular basal cell carcinoma. *Br J Ophthalmol* 2019; **103**:775-80.

Wong KY, Fife K, Lear JT et al. Vismodegib for locally advanced periocular and orbital basal cell carcinoma: a review of 15 consecutive cases. *Plast Reconstr Surg Glob Open* 2017; **5**.

Chen L, Aria AB, Silapunt S et al. Treatment of advanced basal cell carcinoma with sonidegib: perspective from the 30-month update of the BOLT trial. *Future Oncol* 2018; **14**:515-25.

Lear JT, Migden MR, Lewis KD et al. Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study. *J Eur Acad Dermatol Venereol* 2018; **32**:372-81.

National Institute for Health and Clinical Excellence (NICE). Electrochemotherapy for metastases in the skin from tumours of non-skin origin [IPG446] https://www.nice.org.uk/guidance/ipg446. [Last accessed 30th July 2019]. London United Kingdom: National Institute for Health and Clinical Excellence. 2013.
110 National Institute for Health and Care Excellence (NICE). Electrochemotherapy for primary basal cell carcinoma and primary squamous cell carcinoma [IPG478] https://www.nice.org.uk/guidance/ipg478. [Last accessed 30 October 2019]. London, United Kingdom: National Institute for Health and Care Excellence (NICE) 2014.

111 Bertino G, Sersa G, De Terlizzi F et al. European Research on Electrochemotherapy in Head and Neck Cancer (EURECA) project: Results of the treatment of skin cancer. *Eur J Cancer* 2016; 63:41-52.

112 Campana LG, Marconato R, Valpione S et al. Basal cell carcinoma: 10-year experience with electrochemotherapy. *J Transl Med* 2017; 15:122.

113 Kristiansson S, Reizenstein J, von Beckerath M et al. Long-term follow-up in patients treated with electrochemotherapy for non-melanoma skin cancer in the head and neck area. *Acta Otolaryngol* 2019; 139:195-200.

114 Rotunno R, Campana L, Quaglino P et al. Electrochemotherapy of unresectable cutaneous tumours with reduced dosages of intravenous bleomycin: analysis of 57 patients from the International Network for Sharing Practices of Electrochemotherapy registry. *J Eur Acad Dermatol Venereol* 2018; 32:1147-54.

115 Clover AJP, Salwa SP, Bourke MG et al. Electrochemotherapy for the treatment of primary basal cell carcinoma; A randomised control trial comparing electrochemotherapy and surgery with five year follow up. *Eur J Surg Oncol* 2020; 46:847-854.

116 Campana LG, Clover AJ, Valpione S et al. Recommendations for improving the quality of reporting clinical electrochemotherapy studies based on qualitative systematic review. *Radiol Oncol* 2016; 50:1-13.

117 Gehl J, Sersa G, Matthiessen LW et al. Updated standard operating procedures for electrochemotherapy of cutaneous tumours and skin metastases. *Acta Oncol* 2018; 57:874-82.

118 Lipson EJ, Lilo MT, Ogurtsova A et al. Basal cell carcinoma: PD-L1/PD-1 checkpoint expression and tumor regression after PD-1 blockade. *J Immunother Cancer* 2017; 5:23.

119 Chang ALS, Tran DC, Cannon JGD et al. Pembrolizumab for advanced basal cell carcinoma: An investigator-initiated, proof-of-concept study. *J Am Acad Dermatol* 2019; 80:564-6.

120 Sabbatino F, Marra A, Liguori L et al. Resistance to anti-PD-1-based immunotherapy in basal cell carcinoma: a case report and review of the literature. *J Immunother Cancer* 2018; 6:126.
121 Cohen PR, Kato S, Goodman AM et al. Appearance of New Cutaneous Superficial Basal Cell Carcinomas during Successful Nivolumab Treatment of Refractory Metastatic Disease: Implications for Immunotherapy in Early Versus Late Disease. *Int J Mol Sci* 2017; **18**.

122 Brinkhuizen T, Frencken K, Nelemans P et al. The effect of topical diclofenac 3% and calcitriol 3 μg/g on superficial basal cell carcinoma (sBCC) and nodular basal cell carcinoma (nBCC): a phase II, randomized controlled trial. In: *J Am Acad Dermatol*, 2016; **75**:126-34.

123 Butler DF, Parekh PK, Lenis A. Imiquimod 5% cream as adjunctive therapy for primary, solitary, nodular nasal basal cell carcinomas before Mohs micrographic surgery: a randomized, double blind, vehicle-controlled study. *Dermatol Surg* 2009; **35**:24-9.

124 van der Geer S, Martens J, van Roij J et al. Imiquimod 5% cream as pretreatment of Mohs micrographic surgery for nodular basal cell carcinoma in the face: a prospective randomized controlled study. *Br J Dermatol* 2012; **167**:110-5.

125 Wettstein R, Erba P, Itin P et al. Treatment of basal cell carcinoma with surgical excision and perilesional interferon-alpha. *J Plast Reconstr Aesthet Surg* 2013; **66**:912-6.

126 Al-Niaimi F, Sheth N, Kurwa HA et al. Photodynamic Therapy Followed by Mohs Micrographic Surgery Compared to Mohs Micrographic Surgery Alone for the Treatment of Basal Cell Carcinoma: Results of a Pilot Single-Blinded Randomised Controlled Trial. *J Cutan Aesthet Surg* 2015; **8**:88-91.

127 Carija A, Puizina-Ivic N, Vukovic D et al. Single treatment of low-risk basal cell carcinomas with pulsed dye laser-mediated photodynamic therapy (PDL-PDT) compared with photodynamic therapy (PDT): A controlled, investigator-blinded, intra-individual prospective study. *Photodiagnosis Photodyn Ther* 2016; **16**:60-5.

128 Haak CS, Togsverd-Bo K, Thaysen-Petersen D et al. Fractional laser-mediated photodynamic therapy of high-risk basal cell carcinomas--a randomized clinical trial. *Br J Dermatol* 2015; **172**:215-22.

129 Smucler R, Vlk M. Combination of Er:YAG laser and photodynamic therapy in the treatment of nodular basal cell carcinoma. *Lasers Surg Med* 2008; **40**:153-8.

130 Kuvat SV, Gucin Z, Keklik B et al. Basal cell carcinoma in a child. *J Skin Cancer* 2011; **2011**.

131 Spiker AM, ; Troxell, T.; Ramsey, M.L. Gorlin Syndrome (Basal Cell Nevus). https://www.statpearls.com/articlelibrary/viewarticle/22375/. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing:. 2020.

132 Griffin JR, Cohen PR, Tschen JA et al. Basal cell carcinoma in childhood: case report and literature review. *J Am Acad Dermatol* 2007; **57**:S97-S102.
133 Evans DGF, P.A. Farndon. Nevod Basal Cell Carcinoma Syndrome. https://www.ncbi.nlm.nih.gov/sites/books/NBK1151/.
Seattle (WA): University of Washington, Seattle; 2020.

134 Cameron MC, Lee E, Hibler BP et al. Basal cell carcinoma: Contemporary approaches to diagnosis, treatment, and prevention. Journal of the American Academy of Dermatology 2019; 80:321-39.

135 Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Archives of dermatology 2000; 136:1524-30.

136 Kiiski V, de Vries E, Flohil SC et al. Risk factors for single and multiple basal cell carcinomas. Archives of dermatology 2010; 146:848-55.

137 National institute for Health and Care Excellence (NICE). Sunlight exposure: risks and benefits NICE guideline [NG34] https://www.nice.org.uk/guidance/ng34. [Last accessed 30th July 2019]. London, United Kingdom: National institute for Health and Care Excellence. 2016.

138 National institute for Health and Care Excellence (NICE). Vitamin D: supplement use in specific population groups [PH56] https://www.nice.org.uk/guidance/ph56. [Last accessed 30th July 2019]. London, United Kingdom: National Institute for Health and Clinical Excellence. 2014 [Last update: August 2017].

139 Green A, Williams G, Neale R et al. Daily sunscreen application and beta-carotene supplementation in prevention of BCC and SCC of the skin: a randomised controlled trial. Lancet 1999; 354:723-9.

140 Elmets CA, Viner JL, Pentland AP et al. Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial. J Natl Cancer Inst 2010; 102:1835-44.

141 Kadakia KC, Barton DL, Loprinzi CL et al. Randomized controlled trial of acitretin versus placebo in patients at high-risk for basal cell or squamous cell carcinoma of the skin (North Central Cancer Treatment Group Study 969251). Cancer 2012; 118:2128-37.

142 Chen AC, Martin AJ, Choy B et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. N Engl J Med 2015; 373:1618-26.

143 Kreul SM, Havighurst T, Kim K et al. A phase III skin cancer chemoprevention study of DFMO: long-term follow-up of skin cancer events and toxicity. Cancer Prev Res (Phila) 2012; 5:1368-74.
144 Duffield-Lillico AJ, Slate EH, Reid ME et al. Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. *J Natl Cancer Inst* 2003; 95:1477-81.

145 Tang JY, Chiou AS, Mackay-Wiggan JM et al. Tazarotene: randomized, double-blind, vehicle-controlled, and open-label concurrent trials for basal cell carcinoma prevention and therapy in patients with basal cell nevus syndrome. *Cancer Prev Res (Phila)* 2014; 7:292-9.

146 Weinstock MA, Bingham SF, DiGiovanna JJ et al. Tretinoin and the prevention of keratinocyte carcinoma (Basal and squamous cell carcinoma of the skin): a veterans affairs randomized chemoprevention trial. *J Invest Dermatol* 2012; 132:1583-90.

147 Olsen C. Chemoprevention of keratinocyte cancers. *Br J Dermatol* 2018; 179:233-4.

148 Keith D, Bray A, Brain A et al. British Association of Dermatologists (BAD) National Audit on Non-Melanoma Skin Cancer Excision 2016 in collaboration with the Royal College of Pathologists. *Clin Exp Dermatol* 2020; 45:48-55

149 Keith D, de Berker D, Bray A et al. British Association of Dermatologists’ national audit on nonmelanoma skin cancer excision, 2014. *Clin Exp Dermatol* 2017; 42:46-53.
