Pan Birmingham NHS
Cancer Network

Guideline for the Management of Patients with Basal Cell Carcinoma

Version History

Version	Date	Summary of Change/Process
0.1	13.09.07	National guideline adopted by Skin Network Site Specific Group
1.0	04.09.08	Endorsed by Network Governance Committee following confirmation with Skin Network Site Specific Group Chair that this is the current version from the Association
1.1	30.06.11	Skin Network Site Specific Group agreed to continue adoption of National guidance
2.0	11.07.11	Reviewed and endorsed by Guidelines Sub Group

Date Approved by Network Governance	**July 2011**

Date for Review	**July 2014**

1. Guideline Background

Burton Hospitals NHS Trust, Sandwell and West Birmingham Hospitals NHS Trust, Walsall Healthcare NHS Trust and Worcestershire Acute Hospitals NHS Trust have a local specialist multi disciplinary team for skin cancer. The specialist multi disciplinary teams are located at Heart of England NHS Foundation Trust and University Hospitals Birmingham NHS Foundation Trust.

2. Guideline Statement

The British Association of Dermatology Guideline for the Management of Basal Cell Carcinoma has been adopted by the Pan Birmingham Cancer Network to guide the treatment for patients with basal cell carcinomas (see appendix 1).

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Guidelines for the management of basal cell carcinoma

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Summary

This article represents a planned regular updating of the previous British Association of Dermatologists guidelines for the management of basal cell carcinoma. These guidelines present evidence-based guidance for treatment, with identification of the strength of evidence available at the time of preparation of the guidelines, and a brief overview of epidemiological aspects, diagnosis and investigation.

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Conflicts of interest
C.A.M. has received honoraria for speaking and has organized educational events as well as conducted research during the past 5 years from/for Galderma. He has also received travel support from 3M Pharmaceuticals.

There are several effective modalities available to treat basal cell carcinoma (BCC).[1,2] Guidelines aim to aid selection of the most appropriate treatment for individual patients. Careful assessment of both the individual patient and certain tumour-specific factors are key to this process.

Definition

BCC is a slow-growing, locally invasive malignant epidermal skin tumour predominantly affecting caucasians. The tumour infiltrates tissues in a three-dimensional fashion[3] through the irregular growth of subclinical finger-like outgrowths which remain contiguous with the main tumour mass.[4,5] Metastasis is extremely rare[6,7] and morbidity results from local tissue invasion and destruction particularly on the face, head and neck. Clinical appearances and morphology are diverse, and include nodular, cystic, superficial, morphoeic (sclerosing), keratotic and pigmented variants. Common histological subtypes include nodular (nBCC), superficial (sBCC) and pigmented forms in addition to morphoeic, micronodular, infiltrative and basosquamous variants which are particularly associated with aggressive tissue invasion and destruction.[8] Perivascular or perineural invasion are features associated with the most aggressive tumours.

Incidence and aetiology

BCC is the most common cancer in Europe, Australia[9] and the U.S.A.,[10] and is showing a worldwide increase in incidence. Inconsistent data collection unfortunately means that accurate figures for the incidence of BCC in the U.K. are difficult to obtain.[11] The age shift in the population has been accompanied by an increase in the total number of skin cancers, and a continued rise in tumour incidence in the U.K. has been predicted up to the year 2040.[12]

The most significant aetiological factors appear to be genetic predisposition and exposure to ultraviolet radiation.[13] The sun-exposed areas of the head and neck are the most commonly involved sites.[14,15] Sun exposure in childhood may be especially important.[16] Increasing age, male sex, fair skin types I and II, immunosuppression and arsenic exposure are other recognized risk factors[17] and a high dietary fat intake may be relevant.[18] Multiple BCCs are a feature of basal cell naevus (Gorlin's) syndrome (BCNS).[19] Following development of a BCC, patients are at significantly increased risk of developing subsequent BCCs at other sites.

Diagnosis and investigation

Dermatologists can make a confident clinical diagnosis of BCC in most cases. Diagnostic accuracy is enhanced by good lighting and magnification and the dermatoscope may be helpful in some cases.[20] Biopsy is indicated when clinical doubt exists or when patients are being referred for a subspecialty opinion, when the histological subtype of BCC may influence treatment selection and prognosis[8] (Table 1). The use of exfoliative cytology has been described.[21] Imaging techniques such as computed tomography or magnetic resonance imaging

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Table 1 Factors influencing prognosis of basal cell carcinoma

Tumour size (increasing size confers higher risk of recurrence)
Tumour site (lesions on the central face, especially around the eyes, nose, lips and ears, are at higher risk of recurrence)
Definition of clinical margins (poorly defined lesions are at higher risk of recurrence)
Histological subtype (certain subtypes confer higher risk of recurrence)
Histological features of aggression (perineural and/or perivascular involvement confers higher risk of recurrence)
Failure of previous treatment (recurrent lesions are at higher risk of further recurrence)
Immunosuppression (possibly confers increased risk of recurrence)

scanning are indicated in cases where bony involvement is suspected or where the tumour may have invaded major nerves,[22] the orbit[23,24] or the parotid gland.[25] Other techniques, such as ultrasound, spectroscopy and teraherz scanning, are of academic interest but currently have little or no proven clinical role.

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

The likelihood of curing an individual BCC strongly correlates with a number of definable prognostic factors (Table 1). These factors[26,27] should strongly influence both treatment selection and the prognostic advice given to patients. The presence or absence of these prognostic factors allows clinicians to assign individual lesions as being at low or high risk of recurrence following treatment.

The recent development of more effective topical and nonsurgical therapies has increased the treatment options for many low-risk lesions, although surgery and radiotherapy (RT) remain the treatments of choice for the majority of high-risk lesions.[28]

Patient-specific factors which may influence the choice of treatment include general fitness, coexisting serious medical conditions, and the use of antiplatelet or anticoagulant medication. A conservative approach to asymptomatic, low-risk lesions will prevent treatment causing more problems than the lesion itself. Even when dealing with high-risk BCC aggressive management may be inappropriate for certain patients, especially the very elderly or those in poor general health, when a palliative rather than a curative treatment regimen may be in the best interests of the patient.

Finally, factors including patient choice, local availability of specialized services, together with the experience and preferences of the specialist involved may influence treatment selection.

Management

A wide range of different treatments has been described for the management of BCC,[29] and both the British Association of Dermatologists (BAD)[30] and the American Academy of Dermatology[31] have published professional guidelines on their appropriate use. Usually the aim of treatment is to eradicate the tumour in a manner likely to result in a cosmetic outcome that will be acceptable to the patient. Some techniques [e.g. cryosurgery, curettage, RT, photodynamic therapy (PDT)] do not allow histological confirmation of tumour clearance. These techniques are generally used to treat low-risk tumours, although RT also has an important role in the management of high-risk BCC. Surgical excision with either intraoperative or postoperative histological assessment of the surgical margins is widely used to treat both low- and high-risk BCC, and is generally considered to have the lowest overall failure rate in BCC treatment.[28] In rare advanced cases, where tumour has invaded facial bones or sinuses, major multidisciplinary craniofacial surgery may be necessary.[32]

There are few randomized controlled studies comparing different skin cancer treatments, and much of the published literature on the treatment of BCC consists of open studies, some with low patient numbers and relatively short follow-up periods.[33]

Broadly, the available treatments for BCC can be divided into surgical and nonsurgical techniques, with surgical techniques subdivided into two categories: excision and destruction.

Surgical techniques

Excision with predetermined margins

The tumour is excised together with a variable margin of clinically normal surrounding tissue. The peripheral and deep surgical margins of the excised tissue can be examined histologically using intraoperative frozen sections[34] or, more commonly, using postoperative vertical sections taken from formalin-fixed, paraffin-embedded tissue.[35] This approach may be used with increasingly wide surgical margins for primary, incompletely excised and recurrent lesions.

Primary basal cell carcinoma

Surgical excision is a highly effective treatment for primary BCC,[35,36] with a recurrence rate of < 2% reported 5 years following histologically complete excision in two different series.[35,37] The overall cosmetic results are generally good,[36] particularly when excision and wound repair are performed by experienced practitioners. The use of curettage prior to excision of primary BCC may increase the cure rate by more accurately defining the true borders of the BCC.[38,39] The size of the peripheral and deep surgical margins should correlate with the likelihood that subclinical tumour extensions exist (Table 1). Although few data exist on the correct deep surgical margin, as this will depend upon the local anatomy, excision through subcutaneous fat is generally advisable. Studies using horizontal [Mohs micrographic surgery (MMS)] sections which can accurately detect BCC at any part of the surgical

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margin suggest that excision of small (< 20 mm) well-defined lesions with a 3-mm peripheral surgical margin will clear the tumour in 85% of cases. A 4–5-mm peripheral margin will increase the peripheral clearance rate to approximately 95%, indicating that approximately 5% of small, well-defined BCCs extend over 4 mm beyond their apparent clinical margins.[4,40,41] Morphoeic and large BCCs require wider surgical margins in order to maximize the chance of complete histological resection. For primary morphoeic lesions, the rate of complete excision with increasing peripheral surgical margins is as follows: 3-mm margin, 66%; 5-mm margin, 82%; 13–15-mm margin, > 95%.[4] Standard vertical section processing of excision specimens allows the pathologist only to examine representative areas of the peripheral and deep surgical margins, and it has been estimated that at best 44% of the entire margin can be examined in this fashion, which may partly explain why tumours which appeared to have been fully excised do occasionally recur.[42]

Evidence level: *Surgical excision is a good treatment for primary BCC. (Strength of recommendation A, quality of evidence I – see Appendix 1).*

Incompletely excised basal cell carcinoma

Incomplete excision, where one or more surgical margins are involved with (or extremely close to) tumour, has been reported in 4·7%[43] and 7%[44] of cases reported from British plastic surgical units and 6·3%[45,46] in two retrospective studies from Australia. This usually reflects the unpredictable extent of subclinical tumour spread beyond the apparent clinical margins. However, other relevant factors associated with incomplete excision include operator experience, the anatomical site and histological subtype of the tumour[43] and the excision of multiple tumours during one procedure.[47]

When the surgical margins are examined intraoperatively (excision under frozen section control, MMS), further resection of any involved margins can take place prior to wound repair. Using standard surgery, one approach to minimize the risk of incomplete excision is to excise tumours and delay wound repair until an urgent pathology report is received. In the more common situation, when surgical margins are examined routinely postoperatively, the wound has usually been repaired and the only options are further treatment or prolonged follow up to monitor for tumour recurrence.[48]

Various prospective and retrospective reviews of incompletely excised BCC suggest that not all tumours will recur. Studies using approximately 2–5 years of follow up have reported recurrence rates following histologically incomplete excision of 30%,[46] 38%,[49] 39%[50] and 41%.[51]

In a follow-up study of 140 incompletely excised BCCs 21% of lesions recurred; however, as 31% of the cohort died of other causes during the (minimum 5-year) follow-up period this figure could have been significantly higher.[47] Re-excision of incompletely excised lesions revealed the presence of residual tumour in 45%[47] and 54%[44] of cases when the tissue was examined using standard (vertical) tissue sectioning and in 55% of cases re-excised using MMS.[52]

The risk of recurrence seems highest in those lesions where both lateral and deep margins were involved with BCC and when the incomplete excision was performed to remove recurrent BCCs, especially those recurrent following radiation therapy.[49] BCCs incompletely excised at the deep margin were considered especially difficult to cure with re-excision.[49] One study calculated the probability of recurrence of incompletely excised BCC and found that it varied according to which margins were involved. When only the lateral margins were involved there was a 17% risk of recurrence, rising to a 33% risk of recurrence if the deep margins were involved.[53]

There is good evidence to support a policy of re-treatment of incompletely excised lesions[44,49,51,52,54–56] especially when they involve critical midfacial sites, where the deep surgical margin is involved, the surgical defect has been repaired using skin flaps or skin grafts[49,57] and where histology shows an aggressive histological subtype. It has been suggested that some incompletely excised lesions may demonstrate a more aggressive histological subtype when the lesion recurs, especially on the central face.[58] If the decision is made to re-treat rather than observe, re-excision (with or without frozen section control) or MMS are the treatments of choice (Table 2). Although there are limited data on the subject, RT appears to have a role in preventing the recurrence of incompletely excised BCC.[53]

Evidence level: *Tumours which have been incompletely excised, especially (i) high-risk lesions; and (ii) lesions incompletely excised at the deep margin, are at high risk of recurrence. (Strength of recommendation A, quality of evidence II-i).*

Recurrent basal cell carcinoma

Recurrent BCC is more difficult to cure than primary disease – the results of all published series on the surgical excision of BCC show cure rates following treatment of recurrent disease that are inferior to those for primary lesions.[59] Recurrent lesions generally require wider peripheral surgical margins than primary lesions with or without standard (non-Mohs) frozen section control.[34] Peripheral excision margins for recurrent BCC of 5–10 mm have been suggested.[60]

Evidence level: *Recurrent tumours, especially on the face, are at high risk of further recurrence following surgical excision even with wide surgical margins. (Strength of recommendation A, quality of evidence II-ii).*

Table 2 Indications for Mohs micrographic surgery

Tumour site (especially central face, around the eyes, nose, lips and ears)
Tumour size (any size, but especially > 2 cm)
Histological subtype (especially morphoeic, infiltrative, micronodular and basosquamous subtypes)
Poor clinical definition of tumour margins
Recurrent lesions
Perineural or perivascular involvement

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Mohs micrographic surgery

This specialized surgical procedure was pioneered (as chemosurgery) by Frederic Mohs in the 1940s and later refined into the modern technique of MMS.[61] MMS combines staged resection with comprehensive surgical margin examination and results in extremely high cure rates for even the most high-risk lesions together with maximal preservation of normal tissues.[62,63] The technique, which is generally reserved for high-risk facial lesions, is based upon the principle that all traces of infiltrating BCC must be identified and excised in order to achieve complete cure.[64,65] The indications for using MMS are summarized in Table 2. A review of studies published since the mid-1940s suggested an overall 5-year cure rate of 99% following MMS for primary BCC[66] and 94·4% for recurrent disease.[59] Two prospective studies have been reported from Australia: in one, 5-year cure rates of 100% and 92·2% for primary and recurrent tumours, respectively, were reported in 819 patients with periocular BCC;[67] in the other, 3370 BCCs on the head and neck treated wth MMS resulted in 5-year cure rates of 98·6% for primary BCC and 96% for recurrent disease.[68] A retrospective review of 620 patients with 720 lesions gave estimated 5-year cure rates of 98·8% for primary BCC and 93·3% for recurrent disease.[69] Five-year cure rates of 93·5% for primary BCC and 90% for recurrent disease have been reported.[64]

MMS for BCC performed under local anaesthesia in an outpatient or day-case setting has a good safety record[70,71] and Mohs surgical defects can be repaired by the Mohs surgeon or by facial reconstructive specialists including plastic,[72] otolaryngeal[73] and oculoplastic[74,75] surgeons. The technique is performed using either frozen tissue sections,[76] when resection can take place over a matter of hours, or with formalin-fixed, paraffin-embedded tissues, when the procedure takes place over a number of days.[77,78] Variations of the technique, based upon different techniques of pathological processing of tissue excised in a standard fashion, have been described.[79–82] Both maxillofacial[83] and ophthalmic[84,85] surgeons have reported good results with staged excision of high-risk BCC using standard vertical (non-Mohs) permanent sections and delayed wound repair, as an alternative to MMS which one group felt was too 'labour-intensive'.[84] Several studies have looked at the comparative cost of MMS,[86–89] which (to produce tumour-free margins) has a similar cost to traditional excision[87] but is less expensive than excision using intraoperative frozen section control.[86] A study from the Netherlands found MMS to be more expensive than traditional surgery; however, as MMS is likely to produce extremely high cure rates, it remains cost-effective. The only study to date which tried to compare cure rates following standard excision and MMS[89] appeared to show little difference between the two treatment modalities. However, a failure to adhere to the study design (with 24 of 301 patients randomized to have standard surgical excision being moved into the MMS treatment group) raises concerns about the conclusions of this study.[90]

Evidence levels: *Mohs micrographic surgery is a good treatment for high-risk primary BCC. (Strength of recommendation A, quality of evidence I).*

Mohs micrographic surgery is a good treatment for high-risk recurrent BCC. (Strength of recommendation A, quality of evidence I).

Destructive techniques: surgical

Destructive surgical and nonsurgical techniques are best used for low-risk disease. Unless a confident clinical diagnosis and assessment has been made, a preoperative biopsy is indicated to confirm the diagnosis and to determine the histological subtype. This advice is especially important for facial lesions.

Curettage and cautery

Curettage and cautery (C&C, also known as electrodesiccation and curettage)[91–93] and curettage alone[91,94,95] are traditional methods of BCC removal. Successful outcomes rely heavily on careful selection of appropriate lesions (ideally small nodular or superficial)[94,96] as well as the skill and experience of the operator.[96,97] In a survey of 166 U.K. consultant dermatologists in 1995, 24% of 1597 lesions presenting for the first time were treated by C&C, making it the second most common form of treatment after surgical excision (58%).[98] Variations in technique include the use of different types of curette and the number of cycles of treatment;[93] however, the exact protocol is often unclear in published studies. Curettage and cautery is generally suitable for the treatment of low-risk lesions.[94,96,97,99] Curettage and cautery of high-risk facial lesions is associated with a high risk of tumour recurrence[97,100,101] and is generally contraindicated.

In a study of 69 C&C wounds that were immediately re-excised using MMS, residual tumour was found in 33% of cases overall, with striking differences seen in different body sites (47% of head and neck sites and 8·3% of trunk and limb sites contained residual BCC).[102] This may be one reason why C&C is generally less successful in the treatment of facial lesions. The relatively high incidence of residual BCC but an apparently low incidence of recurrence following C&C has led to suggestions that unidentified wound healing processes following C&C may play a part in tumour destruction, although at least two studies have failed to confirm this theory.[103,104] Tumour debulking by curettage has been combined with various treatment modalities such as imiquimod (IMQ)[105,106] and PDT[107] in attempts to increase efficacy. Curettage has also been combined with cryosurgery – a 5-year follow-up study of 70 noninfiltrative auricular BCCs (not involving the external auditory meatus) treated in this way resulted in one recurrence.[108]

A literature review of all studies published since 1947 suggested an overall 5-year cure rate of 92·3% following C&C for selected primary BCC.[66] Curettage is much less useful for recurrent BCC and a similar review suggested an overall 5-year cure rate of 60%.[59]

Evidence levels: *Curettage and cautery is a good treatment for low-risk BCC. (Strength of recommendation A, quality of evidence II-iii).*

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Curettage and cautery is a poor treatment for high-risk BCC. (Strength of recommendation D, quality of evidence II-iii).

Curettage and cautery is a poor treatment for recurrent BCC. (Strength of recommendation D, quality of evidence II-ii).

Cryosurgery

Liquid nitrogen cryosurgery for the destruction of BCC uses the effects of extreme cold (tissue temperatures of −50 to −60 °C) to effect deep destruction of the tumour and surrounding tissues. Individual treatment techniques vary considerably, with both open and closed spray techniques and single or multiple cycles of freezing (freeze/thaw cycles).[109,110] Double freeze/thaw cycles are generally recommended for the treatment of facial BCC, although superficial truncal lesions may require only a single treatment cycle.[111] One report describes the use of 'fractional cryosurgery' where large lesions are treated on multiple separate occasions.[112] The success of cryosurgery relies upon careful selection of appropriate lesions[113] and the experience of the operator.

In one study 12 small nonfacial nBCCs were treated with single freeze-thaw cryosurgery to a monitored temperature of between −50 and −60 °C. When each treatment site was subsequently excised and examined with horizontal step sections, no residual tumour was detected.[114] Cryosurgery is most useful in the treatment of low-risk BCC.[115,116] Five-year cure rates of 99% have been reported by the same author in both 1991[117] and 2004.[118]

In expert hands, cryosurgery also has a role in the management of high-risk lesions, either as the sole treatment[118] or following curettage.[108,119] A follow-up study of 171 high-risk BCCs treated with combined curettage/cryotherapy reported a 8% recurrence rate after a mean follow up of 5·2 years (range 6 months–9·1 years).[119] Although cryosurgery is less useful for the treatment of recurrent BCC,[59] selected lesions may also respond to aggressive expert treatment.[120]

Some authors consider cryosurgery to be an appropriate treatment for selected periocular BCC[121–124] and one series of 158 periocular BCCs treated with double-cycle cryosurgery reported a 8% recurrence rate after a mean 5-year follow-up period. Careful lesion selection was crucial, as factors associated with recurrence included large size, morphoeic histology and involvement of the lid margin.[123] Other than tumour recurrence, adverse results of cryosurgery to eyelid and periocular BCC include conjunctival hypertrophy and ectropion which may require corrective surgery.[123] Cryosurgery (double 25–30-s treatment cycles) has been compared with 5-aminolaevulinic acid (ALA)-PDT in the treatment of low-risk BCC.[125] Histologically verified recurrence rates in the two groups were statistically comparable: 25% (11 of 44) for PDT and 15% (six of 39) for cryosurgery. Additional treatments had to be performed in 30% of the lesions in the PDT group although the healing time was shorter and the cosmetic outcome better with PDT. Pain and discomfort during and after treatment were the same. Additional studies using methylaminolaevulinic acid (MAL)-PDT with longer follow-up periods and including comparison with surgical excision are detailed in the later section on PDT.

Cryosurgery wounds generally heal with minimal tissue contraction, resulting in good cosmetic results;[113,115,119] however, one study comparing the cosmetic results (but not efficacy) of cryosurgery with excisonal surgery for head and neck found that excision generally gave superior cosmetic results.[126]

Evidence level: *Cryosurgery is a good treatment for low-risk BCC. (Strength of recommendation A, quality of evidence II-ii).*

Carbon dioxide laser

Carbon dioxide (CO_2) laser ablation remains an uncommon form of treatment and there are few published data. When combined with curettage, CO_2 laser surgery may be useful in the treatment of large or multiple low-risk sBCCs. In one small series, the Ultrapulse CO_2 laser appeared effective in treating small BCCs in low-risk areas with minimal post-treatment scarring in three patients with BCNS.[127]

Evidence level: *Carbon dioxide laser ablation may be effective in the treatment of low-risk BCC. (Strength of recommendation C, quality of evidence III).*

Destructive techniques: nonsurgical

Topical immunotherapy with imiquimod

IMQ is an immune-response modifier which acts through toll-like receptors, predominantly expressed on dendritic cells and monocytes, to induce production of cytokines and chemokines which promote both innate and adaptive cell-mediated immune responses.[128] Several studies have reported the efficacy of topical 5% IMQ cream in the treatment of sBCC and dose–response studies indicate that the highest response rates are associated with more frequent or prolonged dosing, together with a significant inflammatory reaction.[129,130]

Pooled results from two randomized vehicle-controlled studies of 5% IMQ cream in the treatment of small sBCC in 724 patients have been reported. Twelve weeks following a 6-week treatment period the histological clearance rates were 82% (application five times weekly, 5x/week), 79% (application seven times weekly, 7x/week) and 3% (vehicle only). An increasing severity of local inflammatory reactions was associated with higher clearance rates. Moderate to severe local site reactions occurred in 87%, including erosion (36%) and ulceration (22%) in subjects in the 5x/week group, with higher figures for the 7x/week group. Rest periods were requested by 10% and 22% of patients in the 5x/week and 7x/week groups, respectively, with resumption of treatment when the reaction had resolved. Eleven patients withdrew from the study due to adverse events.[131]

A multicentre randomized study of the treatment of sBCC with 5% IMQ cream vs. vehicle alone in 84 patients reported similar results. Histological clearance rates following once-daily application for 6 weeks were 80% (IMQ) and 6% (vehicle).[132]

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Topical IMQ is approved by the European Medicines Agency for the treatment of small sBCC, using the 5x/week regimen for 6 weeks. This regimen balances therapeutic efficacy with patient tolerability of the common inflammatory reactions.

Long-term data on clinical recurrence rates are limited. An on-going multicentre open-label study of 182 small sBCCs using the 5x/week regimen resulted in 10% of patients failing to respond at 12 weeks. The 90% who did respond then entered a 5-year follow-up phase. Interim results after 2 years of follow up reported an estimated recurrence rate of 20·6% in this group.[133]

Data on the treatment of nBCC using IMQ are limited. Two randomized dose–response studies (reported in the same paper) each evaluated four dosing regimens over a 6- or 12-week application period. Six weeks following treatment the entire treated areas were excised. Histologically confirmed complete response rates were highest in the groups receiving a once-daily dose, with clearance rates of 71% (25 of 35) and 76% (16 of 21) in the 6- and 12-week studies, respectively. Increasing response rates were associated with increasing frequency of dosing over all regimens, and there was a significant correlation between the most intense inflammatory reactions and complete response rate.[134]

A further randomized trial reported complete clinical clearance in 78% of 90 evaluable patients with nBCC following thrice-weekly application of IMQ for 8 or 12 weeks (no difference in outcome between protocols). The treated areas were excised 8 weeks following treatment, and residual BCC was found in 36% of cases, including 12 of 90 (13%) patients considered to have shown complete clinical clearance.[135]

There are currently limited published data on the long-term recurrence rates following IMQ treatment of nBCC. During 5-year follow up of 55 lesions in an open study of different types of BCC treated with IMQ, the long-term clearance rate for the intention-to-treat dataset was 100% (four of four) for sBCC, 75% (six of eight) for nBCC and 60% (26 of 43) for infiltrative BCC.[136]

Two pilot studies investigated the combination of curettage of nBCC prior to the use of topical IMQ.[105,106] In the first, following a single cycle of curettage, IMQ was applied daily for 6–10 weeks and this produced histological clearance of 94% (32 of 34) when the treatment sites were excised 12 weeks after treatment.[105] In the second study, 20 patients received three cycles of C&C followed by IMQ or vehicle once daily for 1 month. Histological examination revealed residual tumour in 10% (one of 10) in the IMQ group and 40% (four of 10) in the vehicle group.[106]

Occlusion of the treatment site does not appear to be beneficial as no difference in efficacy was demonstrated when 5% IMQ cream with and without occlusion was used to treat both sBCC and nBCC.[137] Three separate studies of topical IMQ in a total of seven patients with BCNS have suggested clinical benefit in treating multiple sBCC and nBCC.[138–140]

To date, there are no published randomized trials comparing topical IMQ with an existing standard therapy. One small study compared the efficacy and tolerability of topical IMQ (three times weekly for 3 weeks followed by a 1-week rest period, repeated for a total of 3 months) with MAL-PDT therapy (one cycle of two treatments). Histological clearance in the IMQ group was reported in six of eight (all sBCC) vs. 12 of 13 (sBCC and nBCC) in the PDT group 12 weeks after treatment. Cosmetic results in both groups were similar, although patients tolerated IMQ therapy less well.[141]

On the basis of the currently available data, topical 5% IMQ cream appears to have a role in treating small sBCC, although 5-year follow-up data are awaited. The role of IMQ in the treatment of nBCC remains unclear, as its use has been studied in only small numbers of patients and there are currently limited long-term follow-up data.

Evidence levels: *Topical imiquimod appears effective in the treatment of primary small superficial BCC. (Strength of recommendation A, quality of evidence I).*

Topical imiquimod may possibly have a role in the treatment of primary nodular BCC. (Strength of recommendation C, quality of evidence I).

Photodynamic therapy

Previous BAD guidelines have rated topical PDT using ALA as suitable for the treatment of low-risk sBCC, but a relatively poor option for the treatment of high-risk lesions.[30,142]

ALA-PDT has been compared with cryosurgery in the treatment of both sBCC and nBCC.[125] Clinical recurrence rates at 12 months of 5% (PDT) and 13% (cryotherapy) were underestimates, as histology demonstrated residual BCC in 25% (PDT) and 15% (cryotherapy) of cases, raising concerns both over clinical observation rather than histology as proof of tumour clearance and over the long-term efficacy of PDT. Two further studies of double-cycle ALA-PDT treatment of sBCC reported initial clinical clearance rates of 95% (60 of 62)[143] and 90% (76 of 87),[144] with subsequent recurrence rates of 18%[143] and 4·8%,[144] respectively, after 12 months of follow up.

Since the last BAD guidelines were published,[30] studies have increasingly reported the use of topical MAL, a more lipophilic methyl ester of ALA, which may demonstrate better tumour selectivity. There are currently limited data comparing these two agents, with no difference in tumour response (by histology) in one study of patients with nBCC receiving either ALA-PDT (n = 22) or MAL-PDT (n = 21) using identical regimens including surgical debulking of half of the tumours in each group prior to treatment.[145] MAL-PDT is currently the only licensed form of topical PDT for the treatment of BCC.

The use of MAL-PDT has been compared with both cryotherapy and surgery in the treatment of BCC. Clinical clearance at 3 months of 97% of 102 sBCCs treated by MAL-PDT compared with 95% of 98 lesions treated with cryotherapy in a randomized multicentre study was described in a review article.[146] The cosmetic outcome was superior following PDT, with a good or excellent outcome reported in 89% (PDT) and 50% (cryotherapy). During 48 months of follow up, recurrence rates of 22% (PDT) and 19% (cryotherapy) were reported. In another study previously mentioned in the

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curettage section, 91% of 131 sBCCs cleared following MAL-PDT, with 9% of these recurring during 35 months of follow up.[107] The same study also treated nBCCs with MAL-PDT (following curette debulk), with initial clearance of 89% of 168 lesions. Subsequently, 12 thick and six thin tumours (14% and 7%, respectively) recurred during 35 months of follow up.

MAL-PDT (following nonpainful superficial curette or scalpel surface preparation) has been compared with surgical excision (> 5 mm margin) in the treatment of 105 nonfacial nBCCs in a multicentre randomized study. Clearance rates at 3 months were 91% (PDT) and 98% (surgery), and cosmetic outcome rated as good/excellent in 83% (PDT) and 33% (surgery).[147] The same researchers reported long-term (60 months) recurrence rates of 14% (PDT) and 4% (surgery).[148]

A multicentre study of patients considered to be at high risk of complications, poor cosmesis, disfigurement and/or recurrence reported histologically confirmed initial (3 months) clearance rates following MAL-PDT treatment of 85% (40 of 47) for sBCCs and 75% (38 of 51) for nBCCs, with long-term (24 months) recurrence rates of 22% and 18%, respectively.[149] In a similar multicentre study, 148 sBCCs and nBCCs regarded by the authors as 'difficult-to-treat' (defined as large and/or central facial lesions, or patients at increased risk of surgical complications) received MAL-PDT treatment.[150] Histologically confirmed clearance rates at 3 months were 93% (sBCC) and 82% (nBCC). The authors used a time-to-event approach to estimate sustained lesion clearance rates of 82% (sBCC) and 67% (nBCC) at 24 months. These data suggest that MAL-PDT may be an option for high-risk disease when other more effective treatments are either contraindicated or unacceptable to patients.

Some patients with BCNS responded to PDT using either red (~630 nm) or blue (~417 nm) light sources, but experience is limited to case reports.[151,152] To date, there is no good evidence to support the use of PDT for infiltrative or recurrent BCC. Topical PDT can be a time-consuming procedure, especially if performed on multiple occasions. Pain during the illumination phase is significant for some patients and ranges from a stinging or burning sensation to occasionally severe discomfort. A number of measures can reduce this pain, including the use of fans, directed cool air, simple analgesia or local anaesthesia. Following PDT the area tends to swell and then form a crust which takes a few weeks to separate.[153]

Evidence levels: *Photodynamic therapy is a good treatment for primary superficial BCC. (Strength of recommendation A, quality of evidence I).*

Photodynamic therapy is a reasonable treatment for primary low-risk nodular BCC. (Strength of recommendation B, quality of evidence I).

Radiotherapy

RT is effective in the treatment of primary BCC,[154–158] surgically recurrent BCC,[159] as adjuvant therapy, and is probably the treatment of choice for high-risk disease in patients who are unwilling or unable to tolerate surgery.[159,160] RT is a complex mix of different techniques including superficial RT (generated at up to 170 kV) which is suitable for lesions up to ~6 mm in depth, electron beam therapy (generated at higher energies) which penetrates deeper tissues, and brachytherapy which is useful for lesions arising on curved surfaces. Due to the expensive nature of the equipment involved, RT is usually available only at major hospital centres. RT can be used in an adjuvant role, for example following incomplete excision of high-risk BCC. Poor long-term cosmetic results which were once a significant problem are much less likely following treatment using modern techniques. Fractionated treatment regimens (which repeatedly exploit the difference in radiosensitivity between malignant and normal tissues) generally produce superior cosmetic outcomes compared with single-fraction treatment, although this obviously requires multiple hospital visits. In the elderly, infirm patient, single-fraction regimens are still used, as the long-term cosmetic result of treatment is less of a concern. All RT treatments are a careful compromise between the likelihood of tumour destruction and an acceptable risk of radionecrosis (a 5% level being generally accepted as a maximum, and most clinical oncologists aiming for a much lower level). Different anatomical areas have different RT tolerances, with the head and neck generally tolerating RT well. However, certain areas such as the upper eyelid can be difficult to treat. The bridge of the nose, where thin skin overlies bone and is often subjected to repeated minor trauma from spectacles, is an area historically associated with a particularly high risk of radionecrosis. However, RT can be used successfully on many facial sites and studies have reported good outcomes following treatment of BCC on the nose,[155,158,159,161] lip,[162] ear[155,163] and periorbital[155,164] skin.

Unfortunately, some studies of RT for facial BCC report treatment of all nonmelanoma cancers (BCC, squamous cell carcinoma and basosquamous cancer), and do not clearly differentiate tumour-specific outcomes. However, in all these studies, BCC was generally the single largest tumour group and consequently some of these studies are referenced in these guidelines.

Review articles have reported overall 5-year cure rates following RT of 91·3%[66] for primary BCC and 90·2%[59] for recurrent disease. Other studies suggest long-term (> 4 years) local control rates of 84%,[165] 86%,[157] 88%,[166] 92·5%[167] and 96%.[158]

Attempts have been made to compare RT with other treatment modalities. A randomized comparison trial of RT against cryotherapy (93 patients) resulted in 2-year cure rates of 96% and 61%, respectively.[168]

Surgical excision (91% with frozen section margin control) of 174 primary facial BCCs < 4 cm in diameter has been compared with RT (mix of interstitial brachytherapy, contact therapy and conventional RT) for 173 lesions.[167] The 4-year recurrence rates were 0·7% (surgery) and 7·5% (RT). Cosmetic outcome at 4 years was significantly superior following surgery (good cosmesis in 79%) compared with RT (good cosmesis in 40%), with altered pigmentation and telangiectasia in over 65% of RT patients, and radiodystrophy in 41%.[169]

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RT is contraindicated in the re-treatment of BCC that has recurred following previous RT. RT may promote the growth of new BCC in patients with BCNS, and consequently should either be avoided or used with extreme caution in this patient group.[170]

Evidence levels: *Radiotherapy is a good treatment for primary BCC. (Strength of recommendation A, quality of evidence I).*

Radiotherapy is a good treatment for recurrent (but not radiorecurrent) BCC. (Strength of recommendation A, quality of evidence I).

Follow up

Following treatment of a BCC, all patients are at some degree of risk of both local recurrence (treatment failure) and the development of further primary BCC at other sites (new lesions). These risks form the basis of the arguments both for and against long-term specialist follow up.

The risk of local recurrence is an individual risk, based upon the tumour characteristics and the treatment used. However, for primary BCC treated appropriately by experienced practitioners, the recurrence rate should be low. This is not true for recurrent BCC, where recurrence rates are universally higher than for primary BCC. Patients who have had recurrent (especially multiply recurrent) lesions treated are particularly worthy of follow up in view of their relatively high risk of further recurrence. The timing of follow-up visits should take into account the generally slow growth rate of BCC. Evidence suggests that recurrent disease may take up to 5 years to present clinically, and that up to 18% of recurrent BCC may present even later.[100] In a review of all studies published since 1947 looking at the treatment of primary BCC by various modalities, less than one third of all recurrences presented in the first year of follow up, 50% presented within 2 years, and 66% within 3 years.[66]

The risk of developing further BCC has been studied in a number of ways. Marcil and Stern[171] conducted an English language literature review and meta-analysis and found seven studies assessing the risk of developing a second BCC. Overall, the 3-year cumulative risk ranged from 33% to 70% (mean 44%), representing an approximately 10-fold increase over the rate expected in a comparable general population. The highest rates (60–70%) came from studies including large populations of patients with at least two (sometimes more than two) previous BCCs, suggesting that as the number of BCC lesions increases, so does the risk of developing more. In contrast, patients with only their index BCC who remain disease free for 3 years appear to have a decreased ongoing risk of further BCC. There was no general agreement on particular risk factors which might confer a higher risk of subsequent BCC.

The findings have been supported by the results of a prospective study of two cohorts (total 1183) of private patients in Denmark[172] in whom 299 (25·3%) developed at least 777 new skin cancers during 2 years of follow up, 89·5% of these being BCC. A study based upon data stored by the Swiss Cancer Registry[173] suggested the risk of a second BCC was 8·45 times higher (measured over an unlimited time period) than expected in a comparable general population.

Various authors have tried to identify specific risk factors which might be associated with an increased risk of developing further BCC. Van Iersel *et al.*[174] confirmed an overall increase of subsequent BCC over a 5-year period and identified a possible higher risk in older patients, those with multiple BCC at first presentation, and those with an index tumour > 1 cm in size.

A clinical study of 1200 patients also suggested that the presence of multiple BCC at presentation was associated with increased risk of further BCC[175] and the same group also reported that an index BCC arising on the trunk appeared strongly associated with the development of further (usually also truncal) BCC;[176] this group has suggested that different mechanisms may determine the development of truncal BCC and head and neck BCC.[177]

Two studies have looked at current U.K. practice regarding BCC follow up. Dermatologists in Belfast[178] offered follow up at 12 and 24 months following surgical excision of midfacial primary BCC. They reported attendance rates of 78% at 12 months, falling to 53% at 2 years. A recurrence rate of $< 2\%$ (two of 121) over 2 years was reported, and new BCCs were detected in 11·6% of patients during the first year and 6·3% during the second year of follow up. In 2001 a survey of British dermatologists (68% response) asked about routine follow-up practice following the excision of a primary midfacial BCC. No follow up at all was offered by 27% of responders, 37% would offer one follow-up clinic visit, while 36% would offer more than one hospital-based review.[179]

Clearly, within the British healthcare system it is not possible to offer long-term follow up to all patients who have had their first and only primary BCC treated. Provided treatment has been selected appropriately and performed competently, these patients should, by definition, be at low risk of local recurrence and would benefit from sensible sun protection advice and counselling on the significant (possibly up to 44%) 3-year risk of the development of a second primary lesion. Such patients are probably suitable (with appropriate education and advice) for self-monitoring or follow up in primary care.[50] The case for follow up in either a primary or secondary care setting is stronger for patients who have been treated for recurrent disease (increased risk of further recurrence following all types of treatment) and those with a history of multiple BCCs (significantly increased risk of further BCC), although this would possibly need to be for at least 3 years, to reflect the available evidence base.

Conclusions

Many treatments are known to be effective in the treatment of BCC, ranging from topical therapy (e.g. IMQ) and minimally invasive procedures (e.g. PDT), through destructive modalities (e.g. C&C, cryosurgery) to more specialized treatments such as RT, wide surgical excision and MMS. An assessment of the relative risk of recurrence of an individual lesion will generally

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Table 3 Primary basal cell carcinoma (BCC): influence of tumour type, size (large = > 2 cm) and site on the selection of treatment

BCC type: histology, size and site	PDT	Topical imiquimod	Curettage and cautery	Radiation therapy	Cryosurgery	Excision	Mohs surgery
Superficial, small and low-risk site	**	**	**	?	**	?	X
Nodular, small and low-risk site	*	–	**	?	**	***	X
Infiltrative, small and low-risk site	X	X	*	*	*	***	?
Superficial, large and low-risk site	***	**	**	*	**	*	?
Nodular, large and low-risk site	–	–	**	**	**	***	?
Infiltrative, large and low-risk site	X	X	–	*	*	***	**
Superficial, small and high-risk site	*	*	*	**	*	**	*
Nodular, small and high-risk site	–	–	*	**	**	***	**
Infiltrative, small and high-risk site	X	X	–	*	*	**	***
Superficial, large and high-risk site	*	*	–	*	*	**	**
Nodular, large and high-risk site	–	X	X	–	*	**	**
Infiltrative, large and high-risk site	X	X	X	X	X	*	***

PDT, photodynamic therapy; ***, probable treatment of choice; **, generally good choice; *, generally fair choice; ?, reasonable, but not often needed; –, generally poor choice; X, probably should not be used.

Table 4 Recurrent basal cell carcinoma (BCC): influence of tumour type, size (large = > 2 cm) and site on the selection treatment

BCC type: histology, size and site	PDT	Topical imiquimod	Curettage and cautery	Radiation therapy	Cryosurgery	Excision	Mohs surgery
Superficial, small and low-risk site	**	*	*	*	**	**	–
Nodular, small and low-risk site	–	X	**	**	**	***	–
Infiltrative, small and low-risk site	X	X	–	**	**	***	*
Superficial, large and low-risk site	**	*	*	**	**	*	*
Nodular, large and low-risk site	X	X	–	*	*	***	*
Infiltrative, large and low-risk site	X	X	–	*	*	**	**
Superficial, small and high-risk site	?	X	*	*	*	**	**
Nodular, small and high-risk site	X	X	*	*	*	***	**
Infiltrative, small and high-risk site	X	X	X	*	*	**	***
Superficial, large and high-risk site	?	X	X	*	–	**	**
Nodular, large and high-risk site	X	X	X	–	–	**	***
Infiltrative, large and high-risk site	X	X	X	–	–	*	***

PDT, photodynamic therapy; ***, probable treatment of choice; **, generally good choice; *, generally fair choice; ?, reasonable, but not often needed; –, generally poor choice; X, probably should not be used.

be a useful way of identifying the most appropriate treatment modalities. For example, low-risk disease is generally suitable for topical therapy, C&C, cryotherapy, simple excision and PDT, while high-risk BCC is generally better managed with wide surgical excision, RT and MMS.

An indication of the relative value of the various treatment modalities covered in these guidelines is summarized in Table 3 (primary BCCs) and Table 4 (recurrent BCCs). While heavily based upon the overall likelihood of cure, these recommendations also take into account practicality of use, side-effects, cosmetic outcomes, and patient acceptability.

Disclaimer

These guidelines have been prepared for dermatologists on behalf of the British Association of Dermatologists and are based on the best data available at the time the report was prepared. Caution should be exercised when interpreting the data where there is a limited evidence base. The results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

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Appendix 1

The consultation process and background details for the British Association of Dermatologists guidelines have been published elsewhere.[180,181]

Strength of recommendations

A There is good evidence to support the use of the procedure.
B There is fair evidence to support the use of the procedure.
C There is poor evidence to support the use of the procedure.
D There is fair evidence to support the rejection of the use of the procedure.
E There is good evidence to support the rejection of the use of the procedure.

Quality of evidence

I Evidence obtained from at least one properly designed, randomized controlled trial.
II-i Evidence obtained from well-designed controlled trials without randomization.
II-ii Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group.
II-iii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.
IV Evidence inadequate owing to problems of methodology (e.g. sample size, or length or comprehensiveness of follow-up or conflicts of evidence).

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