British Journal of Dermatology 1999; **141:** 415–423.

Guidelines for the management of basal cell carcinoma

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Accepted for publication 30 April 1999

Disclaimer These guidelines on the management of basal cell carcinoma have been prepared for dermatologists on behalf of the British Association of Dermatologists. They 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.

Key words: basal cell carcinoma, management, guidelines

Many different and well-accepted treatments are used in the management of basal cell carcinoma (BCC).[1] These guidelines aim to aid selection of the most appropriate treatment for individual patients.

Definition

BCC is a slow-growing, locally invasive malignant epidermal skin tumour which mainly affects Caucasians. BCC tends to infiltrate tissues in a three-dimensional contiguous fashion through the irregular growth of subclinical finger-like outgrowths.[2] Metastasis is extremely rare,[3] and the morbidity associated with BCC is related to local tissue invasion and destruction, particularly on the head and neck. The clinical appearances and morphology are diverse, including nodular, cystic, ulcerated ('rodent ulcer'), superficial, morphoeic (sclerosing), keratotic and pigmented variants.

Incidence

BCC is the most common cancer in the U.S.A. and Australia[4] and is showing an increase in incidence in the U.K. The most significant aetiological factor is chronic exposure to ultraviolet light and consequently exposed areas such as the head and neck are the most commonly involved sites,[5] although increasing age, male sex and a tendency to freckle are also known risk factors.[4] BCCs may also arise in basal cell naevus (Gorlin's) syndrome and in organoid naevi. Once a person has developed a BCC there is a significantly increased risk of developing subsequent BCCs at other sites.[6–9]

These guidelines were commissioned, developed and edited by the Therapy Guidelines and Audit Sub-Committee of the British Association of Dermatologists, C.E.M.Griffiths (Chairman), C.A.Holden, C.B.Bunker, N.H.Cox, M.R.Judge, H.C.Williams, D.K.Mehta and S.M.Burge.

Diagnostic tests

The treatment of many BCCs is based upon a clinical diagnosis. However, where clinical doubt exists, or when patients are referred for specialized forms of treatment a pre-operative biopsy is recommended. Biopsy will also provide information on the histological subtype of the BCC which has a direct bearing on the prognosis (Table 1).

Concept of 'low-risk' and 'high-risk' basal cell carcinomas

Individual tumours can be divided into relatively low- and high-risk categories by considering the recognized prognostic factors (Table 1). This will allow the clinician to select the most appropriate form(s) of treatment.

Additional factors

Once the tumour has been assessed the most appropriate treatment options can be discussed with the patient. Patients reluctant to consider any form of surgery are best referred for radiotherapy. Similarly, co-existing medical conditions or drug medication may influence the choice between surgical and non-surgical treatment. Not all BCCs require treatment; aggressive treatment might be inappropriate for patients of advanced age or poor general health, especially for asymptomatic low-risk lesions that are unlikely to cause

Table 1. Factors affecting the prognosis of basal cell carcinoma

Tumour size[2,11,12,27,28,34,40,41,48]
Tumour site[5,10–12,16,34,35,58,60]
Tumour type and definition of tumour margins[2,27,41]
Growth pattern/Histological subtype[2,41,42,75–79]
Failure of previous treatment (recurrent tumours)[2,15,17,37,41,50,77,80,81]
Immunocompromised patients[82]

significant morbidity. Furthermore, some elderly or frail patients with symptomatic or high-risk tumours might prefer less aggressive treatments designed to palliate rather than cure their tumours. Local availability of various specialized services, together with the experience and preferences of the dermatologist managing the case are also factors which will influence the selection of therapy.

Surgical techniques

The most commonly used surgical techniques can be divided into two main categories:

Destructive

Curettage and cautery/electrodesiccation. There are wide variations in how this technique is performed (e.g. type of curette used, number of cycles of treatment) and both experience in the technique[10] and appropriate selection of cases is crucial to success. Curettage and cautery is best used for selected low-risk lesions (small, well defined primary lesions with non-aggressive histology usually in non-critical sites[11–14] where 5-year cure rates of up to 97% are possible.[11] Curettage and cautery is generally not recommended for the management of recurrent[15] or morphoeic tumours, and tumours in 'high-risk' facial sites such as the nose, naso-labial folds and around the eyes,[10,12,13,16–18] although some reports suggest acceptable results for such tumours.[19]

Tumour size is an important factor as the recurrence rate rises dramatically with increasing tumour size.[20] (Strength of Evidence [Appendix] A, II-iii)

A literature review of all studies published since 1947 suggested an overall 5-year cure rate of 92·3% following curettage and cautery for primary BCC.[21] However, a similar review of all studies published since 1945 suggested an overall 5-year cure rate of 60% following curettage and cautery for recurrent BCC. This supports the view that curettage and cautery is much less useful in the treatment of recurrent BCC, especially in high-risk sites.[17] (Strength of Evidence A, II-ii)

Cryosurgery. Cryosurgery is widely used to treat solitary and multiple BCCs. Individual technique can vary considerably, using the open or closed spray techniques and single, double or triple freeze/thaw cycles.[22] Subcutaneous temperature monitoring using thermocouples is sometimes used.[23]

Many large published series specifically exclude the treatment of very high-risk BCCs, emphasizing the importance of careful selection of appropriate lesions with non-aggressive histology, away from critical facial sites in order to achieve high cure rates.[18,23,24–26] (Strength of Evidence A, II-ii)

There are reports in the ophthalmological literature[27–29] recommending the use of cryosurgery for periocular BCC, although full-thickness eyelid defects may occasionally result and require subsequent plastic surgical reconstruction.[27]

Thorough curettage immediately prior to cryosurgery may help to increase the cure rate.[30] (Strength of Evidence A, II-ii)

As with most treatment modalities, cryosurgery is less useful in the treatment of recurrent BCC.[21]

Post-operative wound care can be a problem. However, the treatment is usually well tolerated when performed on a local anaesthetic, outpatient basis[24] and the cosmetic results can be excellent.[31]

Carbon dioxide laser. Carbon dioxide (CO_2) laser surgery is not a widely used form of treatment and there is little published follow-up data to date. The treatment is mainly recommended for low-risk lesions. When combined with curettage, CO_2 laser surgery may be useful in the treatment of large or multiple superficial BCCs.[32,33]

Excisional

Excision with predetermined margins. The primary objective of any excisional procedure is to remove the tumour entirely. However, there is a confusing literature suggesting that total removal of some BCCs may not be necessary to effect cure. This will be discussed further under the section on management of incompletely excised BCC (positive histological margins).

Discussion of the surgical excision of BCC is divided into the following sections:

1 *Primary (previously untreated) BCC.* Surgical excision

is a highly effective treatment for primary BCC.[34–36] (Strength of Evidence A, II-ii) The excised tissue can be examined histologically[37,38] and the peripheral and deep surgical margins can be grossly assessed. The overall cosmetic results are usually good. The use of thorough curettage prior to excision of primary BCC may help to increase the cure rate by more accurately defining the true borders of the BCC.[39] The size of the surgical margins should correlate with the likelihood that subclinical tumour extensions exist (Table 1). Few data exist on the correct deep surgical margin as this will depend upon the local anatomy. In an average case, excision will extend deeply through subcutaneous fat. Studies using horizontal frozen sectioning—Mohs' micrographic surgery (MMS)—to detect accurately BCC at any part of the surgical margin suggest that, for a small (< 20 mm) well defined BCC 3 mm peripheral surgical margins will clear the tumour in 85% of cases, and a 4–5 mm margin will increase the peripheral clearance rate to approximately 95%, i.e. approximately 5% of small, well-defined BCCs show subclinical spread of > 4 mm.[2,40] In contrast to small primary BCCs, morphoeic and large BCCs require wider surgical margins for complete histological resection. For primary morphoeic BCC, 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%.[2]

2 *Recurrent (previously treated) BCC.* The results of all published series on the surgical excision of BCC show that cure rates for recurrent BCC are inferior to those for primary lesions.[17] Recurrent BCCs require wider peripheral surgical margins than primary lesions with or without standard (non-Mohs) frozen section control.[37] Peripheral excision margins for recurrent BCC of 5–10 mm have been suggested.[41] (Strength of Evidence A, II-ii)

3 *Incompletely excised BCC (positive histological margins).* The management of incompletely excised BCC remains controversial. Some evidence suggests that the total removal of some BCCs may not be necessary to effect cure and that up to two thirds of incompletely excised BCCs that are not re-treated do *not* recur.[42,43] This raises a series of questions.

(a) *Do incompletely excised (positive margin) BCCs contain residual tumour?* A study in which 43 incompletely excised BCCs were re-excised and the tissue examined using standard tissue sectioning techniques suggested that only 7% contained residual BCC.[44] However, when 78 incompletely excised BCCs were re-excised and examined using horizontal frozen sectioning (MMS) in order to detect BCC more accurately at any part of the surgical margin, 55% were found to contain residual BCC.[45] (Strength of Evidence A, II-iii)

(b) *Do incompletely excised (positive margin) BCCs recur if they are not retreated?* In a prospective study of 34 incompletely excised BCCs, 41% recurred after a mean follow-up of 2 years.[46] In a review of 60 incompletely excised BCCs, 35 (58%) recurred.[47] In a series of 187 incompletely excised BCCs, with 93% occurring on the head and neck, 119 were immediately retreated with radiotherapy, one was excised and 67 were not treated. After a median follow-up period of 2·7 years, statistical analysis suggested a 5-year probability of cure in the radiotherapy group of 91%, and in the untreated group of 61%.[48]

(c) *Does it matter which surgical margin(s) are involved with tumour?* In a review of 60 incompletely excised BCCs, 35 (58%) recurred.[47] The risk of recurrence was highest in those lesions where both lateral and deep margins were involved with BCC and when the incomplete excision was performed to remove recurrent BCC, especially following radiation therapy.[47] BCCs incompletely excised at the deep margin were considered especially difficult to cure with re-excision.[47] Other authors have calculated that the probability of recurrence of incompletely excised BCC varies when only the lateral margins were involved (17% risk of recurrence) and if the deep margins were involved (33% risk of recurrence).[48]

(d) *Should incompletely excised (positive margin) BCCs be retreated?* Several studies have strongly recommended the immediate re-treatment of incompletely excised BCC[45–47,49] especially those where the surgical defect has been repaired using skin flaps or skin grafts.[50] Overall, an expectant policy would be most appropriate for BCCs that are incompletely excised on a lateral margin only, are of non-aggressive histological type, were not previously recurrent tumours, and involve non-critical anatomical sites. In contrast, it seems most appropriate to re-treat BCCs that are incompletely excised on the deep margin, are of an aggressive histological type, were previously recurrent tumours and involve critical anatomical sites. In this latter situation, re-excision with or without frozen section control or MMS are probably the treatments of choice (Table 2).

Table 2. Basal cell carcinoma (BCC), indications for Mohs' micrographic surgery

Site
Eyes, ears, lips, nose, nasolabial folds[54,55,79,83]
Histological subtype
morphoeic, infiltrative, micronodular
Recurrent BCCs[17,83]
Size
> 2 cm, especially in high-risk sites[17,21,41,55,63,77,83–90]
Special situations
Perineural spread[91]

Mohs' micrographic surgery

MMS[51–57] offers highly accurate yet conservative removal of BCC. It offers high cure rates for even the most difficult of BCCs[58] together with the maximal preservation of normal tissues. The indications for using MMS are summarized in Table 2. (Strength of Evidence A, II-i)

A review of all studies published since 1947 suggested an overall 5-year cure rate of 99% following MMS for primary BCC[21] and a review of all studies published since 1945 suggested an overall 5-year cure rate of 94·4% following MMS for recurrent BCC.[17] MMS is a relatively specialized treatment, is relatively expensive when compared with other outpatient-based treatments for BCC, and is undoubtedly time-consuming.

Non-surgical techniques

Radiotherapy

Radiotherapy (RT) is an extremely useful form of treatment,[48,59,60] but faces the same problem of accurately identifying tumour margins as standard excisional surgery. RT includes a range of treatments using different types of equipment, each with its own specific indications and side-effects. It is, therefore best performed by clinical oncologists with a specialist interest in skin cancer. Collaboration between dermatologists, plastic surgeons and clinical oncologists in the management of patients with high-risk BCC is a common and valuable feature of dermatological care in the U.K. (Strength of Evidence A, II-i)

Careful patient selection can result in very high cure rates; in a series of 412 BCCs treated with RT, 5-year cure rates of 90·3% were achieved.[34] In a prospective trial, where 93 patients with BCC were randomized to receive either cryosurgery or radiation therapy; the 2-year cure rate for the RT group was 96%.[26] A review of all studies published since 1947 suggested an overall 5-year cure rate of 91·3% following RT for primary BCC,[21] and a review of all studies published since 1945 suggested an overall 5-year cure rate of 90·2% following RT for recurrent BCC.[17]

Radiotherapy can be used to treat many types of BCC, even those overlying bone and cartilage, although it is probably less suitable for the treatment of large tumours in critical sites, as very large BCC masses are often both resistant and require radiation doses that closely approach tissue tolerance.[61] It is also not indicated for BCCs on areas subject to repeated trauma such as the extremities or trunk[61] and for young patients as the late-onset changes of cutaneous atrophy and telangiectasis may result in a cosmetic result inferior to that following surgery.[59] It can also be difficult to use RT to re-treat BCCs that have recurred following RT. Modern fractionated dose therapy has many advantages but requires multiple visits to a specialist centre.[62] Late-onset fibrosis may cause problems such as epiphora and ectropion following treatment of lower eyelid and inner canthal lesions, where cataract formation is also a recognized risk,[62] although this can be minimized by the use of protective contact lenses.

There is some suggestion that BCCs recurring following RT may behave in a particularly aggressive and infiltrative fashion,[47,63,64] although this may simply reflect that these lesions were of an aggressive, high-risk type from the very beginning.

Topical therapy

This mainly involves topical 5-fluorouracil (5FU). Treatment is especially useful for low-risk, extrafacial BCC but it cannot be expected to eradicate invasive BCC or lesions with follicular involvement.[65] Topical 5FU therapy can be particularly helpful in the management of multiple superficial BCCs on the trunk and lower limbs. (Strength of Evidence A, II-ii)

Intralesional interferon

In a pilot study of low-risk BCCs, thrice-weekly intralesional injections of human recombinant interferon α2 (IFN-α2) were given for 3 weeks with histological evidence of tumour clearance.[66] The same authors later reported a placebo-controlled study in which 172 nodular or superficial BCCs were treated with intralesional IFN-α2, resulting in a 14% immediate treatment failure rate and a 19% recurrence rate at 1 year.[67] Other studies have confirmed a 20%[68]–45%[69] failure rate 3

months following treatment. Treatment of BCC with intralesional IFN-α2 is still essentially investigational and is unlikely to prove useful in high-risk tumours. It is also very expensive, time consuming and long-term cure rates are not yet available. (Strength of Evidence C, II-iii)

Photodynamic therapy

The use of topical photodynamic therapy (PDT) in the management of BCC is still essentially investigational and is not widely available in the U.K. In a study of 151 BCCs treated with PDT without long-term follow-up, 88% demonstrated a complete response.[70] (Strength of Evidence C, II-iii) Long-term follow-up data on large series is needed to demonstrate whether or not topical PDT has a role in the management of BCC. However, as depth of penetration of the photosensitizer appears to be a limiting factor with topical PDT,[71] it is only likely to be of benefit for the treatment of superficial BCC in low risk areas.[72] (Strength of Evidence C, III)

Chemotherapy

Chemotherapy has been used both for the management of uncontrolled local disease and for patients with metastatic BCC,[73] which is both an extremely rare and a rapidly fatal condition.[3]

Palliative therapy

In the debilitated patient aggressive treatment may be inappropriate for asymptomatic or low-risk BCC. Otherwise, palliative (non-curative) treatment may be

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

Basal cell carcinoma ● histology ● size ● site	Topical therapy including photodynamic therapy	Curettage and cautery	Radiation therapy	Cryosurgery	Excision	Mohs micrographic surgery
Superficial, small and low-risk site	*	**	?	**	?	x
Nodular, small and low-risk site	–	**	?	**	***	x
Morphoeic, small and low-risk site	–	*	*	*	***	?
Superficial, large and low-risk site	*	**	*	***	*	?
Nodular, large and low-risk site	x	**	**	**	***	?
Morphoeic, large and low-risk site	x	–	*	*	***	**
Superficial, small and high-risk site	x	*	**	**	***	*
Nodular, small and high-risk site	x	*	**	**	***	**
Morphoeic, small and high-risk site	x	–	*	*	**	***
Superficial, large and high-risk site	x	–	**	*	**	**
Nodular, large and high-risk site	x	x	**	*	**	***
Morphoeic, large and high risk site	x	x	*	x	*	***

***, Probable treatment of choice; **, generally good choice; *, generally fair choice; ?, reasonable, but not often needed; –, generally poor choice; x, probably should not be used.

appropriate, using simple debulking procedures or RT to gain local control of the BCC and improve the quality of life in the short term.

Retinoids

Oral retinoid therapy may prevent or delay the development of new BCCs. Such therapy has mainly been used in patients with the basal cell naevus (Gorlin's) syndrome and may also have a lesser effect in producing partial regression of existing BCCs.[74] Unfortunately, the relatively high doses necessary mean that compliance may be poor, and relapse occurs following the discontinuation of treatment.[74] (Strength of Evidence B, III)

Follow-up

Long-term hospital-based follow-up of all patients after treatment of BCC is neither necessary nor recommended. However, follow-up can be important for selected patients, although there is no clear consensus on either the frequency or total duration or such review. The main arguments for follow up are: (i) early detection of tumour recurrence; (ii) early detection and treatment of new lesions; and (iii) patient education, especially regarding sun protection measures. Most evidence suggests that the majority of BCCs which recur will present within 5 years of treatment,[75] although up to 18% will recur after this.[21] A review of all studies published since 1947 suggested that for primary (previously untreated) BCCs treated by a variety of modalities less than one-third of all recurrences occurred in the first year following treatment, 50% appear within 2 years, and 66% within 3 years.[21] Patients who have had one BCC are at significantly higher risk of developing new primary lesions,[6–8] many of which may go unnoticed by patients. In a 5-year

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

Basal cell carcinoma ● histology ● size ● site	Topical therapy including photodynamic therapy	Curettage and cautery	Radiation therapy	Cryosurgery	Excision	Mohs micrographic surgery
Superficial, small and low-risk site	x	*	*	**	***	?
Nodular, small and low-risk site	x	**	**	**	***	?
Morphoeic, small and low-risk site	x	–	**	**	***	*
Superficial, large and low-risk site	x	*	**	***	*	*
Nodular, large and low-risk site	x	–	*	*	***	*
Morphoeic, large and low-risk site	x	–	*	*	**	**
Superficial, small and high-risk site	x	–	*	*	**	**
Nodular, small and high-risk site	x	–	*	*	***	**
Morphoeic, small and high-risk site	x	x	*	*	**	***
Superficial, large and high-risk site	x	x	*	–	**	**
Nodular, large and high-risk site	x	x	*	–	**	***
Morphoeic, large and high-risk site	x	x	*	–	*	***

***, Probable treatment of choice; **, generally good choice; *, generally fair choice; ?, reasonable, but not often needed; –, generally poor choice; x, probably should not be used.

prospective follow-up study of 1000 patients following treatment for BCC, 36% developed new primary BCCs[9] and 20% of patients with very fair skin types and frequent sun exposure went on to develop multiple BCCs.[9] Consequently, some authors have recommended long-term, even lifetime follow-up, particularly for patients with high-risk or multiple lesions.[8,21]

The early detection and appropriate re-treatment of either recurrent BCCs or new primary BCCs may help to increase the chances of permanent cure and to minimize morbidity. Patient education together with close collaboration with colleagues in primary care should allow the vast majority of adequately treated patients to be discharged back to the care of their general practitioners.

The relative value of the available forms of therapy for BCCs of different sizes, clinical and histological subtypes and involving both high- and low-risk body sites are summarized in Table 3 (primary BCCs) and Table 4 (recurrent BCCs).

Appendix

Table A1. 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

Table A2. Quality of evidence

I	Evidence obtained from at least one properly designed, randomized control trial
II-i	Evidence obtained from well-designed controlled trials without randomization
II-ii	Evidence obtained from well-designed cohort or case–control analytic 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 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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