

British Association of Dermatologists' guidelines for the management of squamous cell carcinoma *in situ* (Bowen's disease) 2014

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NICE has accredited the process used by the British Association of Dermatologists to produce guidelines. Accreditation is valid for 5 years from May 2010. Full details of our accreditation can be viewed at www.nice.org.uk/accreditation.

1.0 Purpose and scope

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the management of squamous cell carcinoma (SCC) *in situ* (Bowen's disease). The document aims to update and expand on the previous guidelines by (i) offering an appraisal of all relevant literature since January 2006, focusing on any key developments; (ii) addressing important, practical clinical questions relating to the primary guideline objective, i.e. accurate diagnosis and identification of cases and suitable treatment; (iii) providing guideline recommendations and, where appropriate, some health economic considerations; and (iv) discussing potential developments and future directions.

The guideline is presented as a detailed review with highlighted recommendations for practical use in the clinic (see section 16.0), in addition to an updated patient information leaflet [available on the British Association of Dermatologists' (BAD) website, <http://www.bad.org.uk>].

The guideline also reviews erythroplasia of Queyrat (EQ)/penile intraepithelial neoplasia (PIN) and bowenoid papulosis, which have similar histology and are often diagnosed by dermatologists; however, a detailed therapeutic review of these conditions is beyond the scope of this guideline.

1.1 Exclusions

This guideline does not offer treatment recommendations for vaginal intraepithelial neoplasia or perianal SCC *in situ*.

2.0 Stakeholder involvement and peer review

The guideline development group consisted of consultant dermatologists. The draft document was circulated to the BAD membership, the British Dermatological Nursing Group (BDNG) and the Primary Care Dermatological Society (PCDS) for comments, and was peer reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines Subcommittee) prior to publication.

3.0 Methodology

This set of guidelines has been developed using the British Association of Dermatologists' recommended methodology,¹

with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument (www.agreetrust.org).² It represents a planned regular update of the previous BAD guidelines for the management of SCC *in situ* (Bowen's disease).^{3,4} Recommendations were developed for implementation in the U.K. National Health Service (NHS) using a process of considered judgement based on the evidence. The PubMed, Medline and Embase databases were searched for meta-analyses, randomized controlled trials (RCTs) and non-RCTs, case series, case reports and open studies involving SCC *in situ* (Bowen's disease) to September 2013; search terms and strategies are detailed in the Supporting Information. Additional relevant references were also isolated from citations in the reviewed literature, as well as from a specific targeted search for PIN. Each author screened their set of identified titles, and those relevant for first-round inclusion were selected for further scrutiny. The authors then reviewed the abstracts for the shortlisted references, and the full papers of relevant material were obtained; disagreements in the final selections were resolved by discussion within the entire development group. The structure of the 2007 guideline was then discussed and re-evaluated, with headings and subheadings decided; different coauthors were allocated separate subsections. Each coauthor then performed a detailed appraisal of the selected literature, and all subsections were subsequently collated and edited to produce the final guideline.

The authors intend that the recommendations and quality of evidence reflect the full evidence base at the time of writing and may be read without the need for reference to earlier versions, although detailed discussion of older studies is not repeated here. It should be recognized that this new version may give disproportionate weight to references to newer publications and therapies. Where there are direct comparisons between therapies, these are generally discussed in the section relating to those deemed to be most efficacious. Recommendations take into account simplicity, cost and healing, as well as the type and validity of the published evidence base; for any treatment, there may be site-specific differences in the recommended option.

4.0 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. 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.

5.0 Plans for guideline revision

The proposed revision for this set of recommendations is scheduled for 2019; where necessary, important interim changes will be updated on the BAD website.

6.0 Background

6.1 Definition

Bowen's disease is a form of intraepidermal (*in situ*) SCC, originally described in 1912,⁵ although the original lesions, located on sites that were not sun exposed, were possibly arsenic induced. Current practice is to consider Bowen's disease as synonymous with SCC *in situ* for lesions sited on non-genital areas. In line with reduced use of eponyms, we have used the term squamous cell carcinoma *in situ* (SCC *in situ*) throughout this updated guideline.

6.2 Clinical description, demographics and variants

Squamous cell carcinoma *in situ* typically presents as a well-demarcated, erythematous hyperkeratotic plaque with an irregular border, characterized by full-thickness epidermal dysplasia on histology. An annual incidence of 15 per 100 000 has been suggested in the U.K.⁶; however, this was based on U.S. data, which may reflect a higher incidence due to greater sun exposure.⁷

Peak incidence of the disease occurs in the seventh decade of life, and most studies have shown a slight female preponderance.^{8–11} The majority of studies report that SCC *in situ* occurs mainly on sun-exposed sites, with more recent studies suggesting the most common site being the head and neck (29–54%)^{10–13}; however, the lower limbs seem to be affected more in women than in men.^{8,11,14} Older, U.K.-based studies have reported that the majority of patients (60–85%) have SCC *in situ* on the lower legs, which may indicate that the sun exposure pattern is different in countries with lower rates of sunshine.^{8,9} Less common variants include pigmented, subungual, periungual, palmar, genital, perianal and verrucous SCC *in situ*.

7.0 Diagnosis

In routine clinical practice the diagnosis is made on clinical grounds, perhaps with the aid of dermoscopy (showing glomerular vessels and scaling).^{15–17} If there is diagnostic doubt, or if confirmation is required before proceeding with a certain type of treatment, a punch biopsy can be performed. This is preferable to a curette biopsy, as the full thickness of the epidermis and dermis can be viewed to establish whether there is any invasive disease amounting to a cutaneous SCC.

8.0 Aetiology

Aetiological factors for SCC *in situ* include (i) irradiation: ultraviolet radiation (solar, iatrogenic and sunbeds)^{14,18} and radiotherapy; (ii) carcinogens: arsenic (lesions may arise in sun-protected areas)¹⁹; (iii) immunosuppression: in particular, therapeutic^{20,21}; (iv) viral: there is an association between human papillomavirus (HPV), especially HPV16, and the development of anogenital SCC *in situ*,^{22–24} but this is by no

means conditional for its development.²⁵ HPV DNA has been demonstrated in extragenital SCC *in situ* in varying amounts from 4.8–60%.^{24,26–28} It appears that HPV16 may be particularly relevant with regard to development of SCC *in situ* on the hands and feet; it has been implicated in 60% of palmoplantar and periungual lesions²⁹; and (v) others: chronic injury or dermatoses (such as lupus vulgaris or chronic lupus erythematosus) have been implicated.³⁰

9.0 Skin malignancy

Previous studies have suggested that about 30–50% of subjects with SCC *in situ* may have previous or subsequent nonmelanoma skin cancer (NMSC), mainly basal cell carcinoma (BCC).^{18,31} The NMSC risk after an index SCC *in situ* is probably similar to the overall risk of NMSC following any index NMSC (3-year overall risk of 35–60%).³² In the study by Jaeger *et al.*,¹⁰ NMSC had a standardized incidence ratio of 4.3, and lip cancer a ratio of 8.2, in patients with SCC *in situ* (calculated as ratios of observed-to-expected numbers of cancer, derived from cancer registration data in Denmark). These increased risks of further SCC *in situ* or of other NMSCs probably reflect a common solar aetiology.

10.0 Risk of progression to squamous cell carcinoma

Most studies suggest a risk of invasive carcinoma of about 3–5% for typical SCC *in situ*,^{33,34} and about 10% for EQ.³ In bowenoid papulosis, invasion is extremely rare.³⁵ Perianal SCC *in situ* has a higher risk of invasion and recurrence. However, these estimates are drawn from retrospective case series, may be biased by different referral patterns of lesions to different disciplines, and do not take account of subjects with SCC *in situ* who have either not requested medical advice or who have been treated in primary care.

11.0 Treatments

Evaluation of treatment studies of typical SCC *in situ* is difficult due to potential selection bias in relation to specific forms of treatment. Moreover, healing and clearance rates may vary with body site. Earlier studies used clinical appearance rather than histological assessment to determine the end point of lesion clearance and, in practice, most dermatologists will instigate treatment without first resorting to a biopsy. Even for the same treatment modality, there is difficulty in directly comparing studies due to different lesion site and size, and use/availability of different types of equipment and treatment regimens.³⁶ Retrospective studies in particular may have several inherent problems; in 'real-world' treatment of SCC *in situ*, clinicians may select several different types of treatment,³⁷ with decisions potentially being influenced by several factors, such as lesion size and thickness, equipment available, and the perceived potential for poor wound healing (e.g. at sites such as the lower leg).³⁸

Current U.K. product licences for many of the drugs listed do not include treatment of SCC *in situ*; all recommendations in this guideline are extrapolated from literature on SCC *in situ* and knowledge of other neoplastic skin lesions, and are presented on the understanding that neither the authors nor the BAD can formally recommend an unlicensed treatment.

Treatments are presented in a sequence that discusses the least invasive and topical therapies first, then surgical approaches, and finally treatments that require more complex or expensive equipment or are not widely available. A summary of advice incorporating these issues, and related to lesion sites and sizes, is provided in Table 1.

A recent review of interventions for SCC *in situ* by the Cochrane Skin Group³⁹ identified nine RCTs, but noted limited data for surgery and topical cream therapies. The review concluded that photodynamic therapy (PDT) using methyl aminolaevulinate (MAL) is an effective treatment, more efficacious than cryotherapy, but not significantly different from topical 5-fluorouracil (FU). PDT using aminolaevulinic acid (ALA) achieved a significantly higher clearance rate than 5-FU, but there was no significant difference in clearance between 5-FU and cryotherapy.

11.1 No treatment [strength of recommendation D (good practice point); level of evidence 4]

In some patients with slowly progressive thin lesions, especially on the lower leg of elderly patients where healing is poor, there is an argument for observation rather than intervention. In these cases use of an emollient (especially one containing urea) can reduce the scaling and make it less obvious (see Appendix 1).

11.2 5-Fluorouracil (strength of recommendation B; level of evidence 1+)

Topically applied 5-FU is a well-recognized treatment option for SCC *in situ* and is commercially available in the U.K. as a 5% cream. Many of the original studies were performed using different concentrations and various regimens. The typical regimen in current clinical use is once- or twice-daily application for 3–4 weeks, repeated if required. There have been a number of good-quality studies in recent years comparing the efficacy of 5-FU with that of PDT. Topical 5-FU cream, applied once daily for 1 week, then twice daily for 3 weeks, was compared with both MAL-PDT and cryotherapy in a large European multicentre RCT.⁴⁰ At 3 months following the last treatment, 83% of lesions treated by 5-FU showed complete response, compared with 93% with PDT and 86% with cryotherapy, with follow-up rates discussed below. A smaller RCT of 40 patients comparing 5-FU, applied in the same manner and repeated if required, with ALA-PDT showed a 67% response rate, compared with 88% with PDT.⁴¹ At 12 months, following two recurrences in patients receiving PDT and six in patients treated with 5-FU, only 48% of patients treated with 5-FU were clear compared with 82% with PDT.

Table 1 Summary of the main treatment options for squamous cell carcinoma (SCC) *in situ*. The suggested scoring of the treatments listed takes into account the evidence for benefit, ease of application or time required for the procedure, wound healing, cosmetic result and current availability/costs of the method or facilities required. Evidence for interventions based on single studies or anecdotal cases is not included

Lesion characteristics (small, < 2 cm)	Topical 5-FU	Topical imiquimod ^b	Cryotherapy	Curettage	Excision	PDT	Radiotherapy	Laser
Small, single/few, good healing ^a	3	3	2	1	3	3	5	4
Large, single, good healing ^a	3	3	3	4	5	2	4	–
Multiple, good healing ^a	2	3	2	3	5	3	4	4
Small, single/few, poor healing site ^a	2	2	3	2	2	2	5	–
Large, single, poor healing site ^a	3	2	5	4	5	1	6	–
Facial	3	3	4	2	4	3	4	–
Digital	3	3	4	5	2	3	3	3
Nail bed	–	4	–	–	2 ^c	3	4	4
Penile	3	3	4	5	4 ^c	3	3	3
Lesions in immunocompromised patients	5	4	3	3	4	3	–	–

FU, fluorouracil; PDT, photodynamic therapy; 1, probably treatment of choice; 2, generally good choice; 3, generally fair choice; 4, reasonable but not usually required; 5, generally poor choice; 6, probably should not be used; –, insufficient evidence available. ^aRefers to the clinician's perceived potential for good or poor healing at the affected site. ^bDoes not have a product licence for SCC *in situ*. ^cConsider micrographic surgery for tissue sparing or if poorly defined or recurrent.

A small randomized inpatient comparative study compared 5-FU, twice daily for 3 weeks, with MAL-PDT in organ transplant recipients (OTRs) with epidermal dysplasia.⁴² Only five patients had SCC *in situ* and the baseline data were not equivalent, with the lesions treated with 5-FU being about a third larger than those treated with PDT. Four of the five patients treated with PDT had a complete response at 6 months, with the fifth having a partial response, whereas all five patients treated with 5-FU had only a partial response. Despite this, the difference was nonsignificant once a multiple regression analysis had been performed.

Of 406 biopsy-proven SCCs *in situ* treated at a single centre in the U.S.A. between 1999 and 2003, 24 lesions were treated with 5-FU (the vast majority were treated using surgical techniques).¹¹ Only one lesion recurred after a mean follow-up period of 23.6 months, comparing favourably with the subset of lesions treated by surgery, with three recurrences out of 109 patients following elliptical excision, and two of 83 following Mohs micrographic surgery. These data are similar to those of another follow-up study (26 patients, 2.4–204 months of clinical follow-up) in which recurrences had occurred in only two patients (8%).⁴³

It has been reported that the efficacy of 5-FU may be increased by application under occlusion,⁴⁴ use of dinitrochlorobenzene as a vehicle,⁴⁵ iontophoresis⁴⁶ (to improve follicular penetration) or pretreatment with a laser (to ablate the stratum corneum and thus enhance penetration of 5-FU).⁴⁷

11.3 Imiquimod (strength of recommendation B; level of evidence 1+)

Imiquimod stimulates both the innate and acquired immune systems, resulting in antitumour and antiviral activity. It is available as a topical 5% cream and has been used to treat SCC

in situ, although its licence in the U.K. is only for superficial BCCs, actinic keratoses and genital warts. It is generally well tolerated, but it does cause significant erythema and crusting, so appropriate counselling needs to be given prior to treatment.

The best evidence remains a small RCT demonstrating 73% histologically proven resolution with once-daily application for 16 weeks, vs. zero response in the placebo group.⁴⁸ An interesting observation from the study was that the nonresponders had hyperkeratotic lesions, suggesting that the drug was unable to penetrate the thick keratin layer.

An open-label clinical trial on five patients who were deemed unsuitable for surgery used imiquimod once daily, five times a week until the lesions clinically cleared, for up to a maximum of 16 weeks. After 8–12 weeks of treatment, four of the five SCC *in situ* lesions showed complete clinicopathological resolution, with no recurrence after a mean of 31 months of follow-up.⁴⁹ Another open study on 16 patients with previously untreated lesions (15 on the lower leg) who used imiquimod once daily for up to 16 weeks reported that 93% (14/15) of patients who completed the study had clinicopathological resolution 6 weeks after the treatment period.⁵⁰ Five lesions had an area of ≥ 5 cm².

One retrospective study from Texas reported that 86% (42/49) of patients (96% were male) with SCC *in situ* (11% were genital lesions) treated for ≥ 6 weeks had complete response to topical imiquimod applied once daily for extragenital lesions (mean duration 9 weeks) and every other day for genital lesions.⁵¹ Another study from Brazil reported that only 57% of patients (four of seven) with SCC *in situ*, without any significant comorbidities such as immunosuppression, cleared following a mean of 6.1 weeks of treatment.⁵²

Single cases or small case series suggest that different regimens such as cyclical treatment⁵³ might be useful, and also

that imiquimod might be effective for large facial lesions.⁵⁴ These, along with lower-leg lesions,⁵⁰ are typically those that pose the greatest therapeutic challenge. Some studies suggest that shorter treatment periods may be adequate.⁵⁰ Due to its method of action, imiquimod has the potential to exacerbate pre-existing autoimmune disease. In the second open study discussed above, 38% of patients (six of 16) discontinued treatment early due to side-effects, but still had lesion clearance.⁵⁰

Benefit has been reported in the treatment of SCC *in situ* in immunosuppressed patients, although many of these reports have been of imiquimod use in combination with another therapy, making interpretation of its role difficult.^{55–57} Combinations of therapies are discussed in section 11.10.1.

11.4 Cryotherapy (strength of recommendation B; level of evidence 1+)

Cryotherapy is a simple, inexpensive and quick method of treating SCC *in situ*, with the advantage of accessibility in the outpatient setting. Clearance rates for cryotherapy vary widely, probably reflecting differences in the techniques and regimens used, with failure rates in the order of 5–10% in the larger series, provided that adequate cryotherapy is used [e.g. liquid nitrogen cryotherapy, using a single freeze–thaw cycle (FTC) of 30 s, two FTCs of 20 s with a thaw period, or up to three single treatments of 20 s at intervals of several weeks].^{58–61} However, such doses do cause discomfort and may cause ulceration, especially on the lower leg.

In the largest, prospective open study, a single 30-s FTC on between one and eight lesions, more than half of which were on the calf, achieved a clearance rate of 100% and recurrence rate of 0.8%, with follow-up periods ranging from 6 months to 5 years.⁵⁹ In contrast, in a retrospective comparison study the use of a 20-s freeze on 91 lesions resulted in lower clearance rates of 68% after one treatment and 86% after retreatment of lesions, with partial response 12 weeks later.⁶⁰ From the available studies it would appear that the more aggressive approach consisting of a freeze of 30 s at least once, or 20 s at least twice, yields better results, but the optimum freeze time, the number of freezes in one treatment cycle and the role of retreatment visits are not clear. Although lesions treated with cryotherapy healed better than those with radiotherapy,⁶⁰ they did not heal as well as those treated with curettage or PDT. Cryosurgery may be useful in low-risk situations for patients who prefer to avoid surgery or cumbersome topical treatment, but one must balance the need of a cure against the potential adverse effects of aggressive FTCs.

Cryotherapy was compared with MAL-PDT and 5-FU in a large European RCT, discussed in section 11.7. In an earlier RCT of ALA-PDT vs. cryotherapy, the latter produced 100% clearance in 20 patients following one to three treatments of liquid nitrogen using one FTC of 20 s on each occasion (50% success after a single treatment), but ulceration was observed following cryotherapy in 25% of lesions.⁶¹

A prospective, nonrandomized case-comparison study comparing curettage vs. cryotherapy found better healing, less discomfort, fewer complications and a lower recurrence rate with curettage.⁶²

Cryotherapy appears to have a moderate success rate with prolonged freezing times (recurrences < 10% at 12 months), but complications such as poor healing and hypopigmented scarring are more likely to occur, particularly in poorly vascularized areas. PDT and curettage both have higher success rates and less discomfort overall, but are more time consuming and/or expensive to perform.

11.5 Curettage with cautery/electrocautery (strength of recommendation C; level of evidence 2+)

Curettage and cautery has been advocated as one of the simplest, least expensive,⁶³ safest and most effective methods of dealing with SCC *in situ*, but its success is determined by the skill of the operator.⁶⁴

Studies using curettage and cautery give a wide range of cure rates, with larger series suggesting a recurrence rate of 20%, but they often lack details of treatment regimens and equipment used.^{3,31} High cure rates can be achieved; one study showed a recurrence rate of 2% (one out of 52) over 4 years,⁶⁵ while another study reported a recurrence rate of 10% (eight of 83) after a follow-up of 2 years.⁶⁶ These smaller studies have shown recurrence rates similar or superior to excision.

In a prospective but nonrandomized trial of curettage and cautery (44 lesions) compared with cryotherapy (36 lesions) involving 67 patients, curettage was preferable in terms of pain, healing and recurrence rate⁶²; 74% of lesions were on the lower leg. Median time to healing with cryotherapy was 46 days (90 days on the lower leg), compared with 35 days (39 days on the lower leg) for curetted lesions, and reported pain was significantly greater with cryotherapy. Recurrences were more likely following cryotherapy (30%, 13/44) compared with curettage (11%, four of 36) during a median follow-up period of 2 years, although the cryotherapy regimen was less aggressive than that used by the authors in most studies of this technique. In another comparative retrospective study, clearance rates were 93% for curettage and cautery, 87% for 5-FU and 61% for cryotherapy,³⁷ and the authors also observed that curettage and cautery required the fewest clinic visits for these treatment modalities.

11.6 Excision (strength of recommendation C; level of evidence 2+)

This is a simple, rapid and effective treatment for SCC *in situ* of limited size and located in suitable areas. It allows for verification of the diagnosis and confirmation of the intraepithelial nature of the lesion. Cosmetic outcome, body site, healing properties and vascularity of the area need to be considered. The largest retrospective study reported to date, of 155 patients, showed recurrence rates of 19.4% over an

unspecified period.⁶⁷ Two other studies reported lower recurrence rates of 2.8% (three of 109 lesions) over a mean follow-up period of 31 months,¹¹ and 5% (three of 65 lesions) after a follow-up period of 1–5 years.³¹ While it is logical that excision should be an effective treatment, the evidence base is limited. Additionally, lower-leg excision wounds may be associated with considerable morbidity.³⁷

11.6.1 Mohs micrographic surgery (strength of recommendation D; level of evidence 3)

Mohs micrographic surgery may be indicated for digital SCC *in situ* (around the nail in particular) and for some cases of genital (especially penile) SCC *in situ* for its tissue-sparing benefits. There may also be a role for Mohs in recurrent or incompletely excised lesions. A large national 10-year retrospective study of 270 patients has reported on micrographic surgery for tissue sparing at head and neck sites;¹² this study included 128 cases of previously treated head and neck SCC *in situ*. Among the 270 cases analysed, 94 had had previous cryotherapy, 18 curettage and cautery, 44 excision (10 incomplete) and one radiotherapy (some had been treated with more than one modality); nearly all referrals cited poorly defined tumour, recurrent or incompletely excised tumour, or tumour site as the rationale for micrographic surgery, so it cannot be assumed to be routinely necessary or cost-effective. The overall 5-year recurrence rate for the 95 patients was 6.3% (3% for primary tumours and 9% for recurrent tumours).

11.7 Photodynamic therapy (strength of recommendation A; level of evidence 1++)

PDT for SCC *in situ* involves topical application of the photosensitizer prodrug ALA or its more lipophilic methyl ester MAL.⁶⁸ MAL is applied under occlusion for 3 h followed by illumination using red light, with narrowband light-emitting diode (LED) sources in routine use. Treatment is repeated 7 days later and again after 3 months, if required. Several protocols have been described for ALA-PDT in SCC *in situ* as outlined below, with nonformulary ALA often used. Fluorescence diagnosis, the identification of lesions using the fluorescence detectable after MAL/ALA occlusion, achieved 100% sensitivity (higher than clinical evaluation alone) and a specificity of 85.7% in a recent study in SCC *in situ*.⁶⁹ The opportunities for lesion delineation and detection of recurrences using fluorescence, and more detail on treatment protocols and light sources used in PDT are reviewed in the BAD British Photodermatology Group guidelines on PDT.⁶⁸

Complete clinical clearance rates of 88–100% are reported 3 months after one cycle of MAL-PDT, with 68–89% of treated lesions remaining clear over follow-up periods of 17–50 months.^{40,70–73}

A multicentre, randomized study compared MAL-PDT with cryotherapy or 5-FU in 225 patients with 275 SCCs *in situ*.⁴⁰ MAL was applied for 3 h then the sites were illuminated with

broadband red light, with treatment repeated after 7 days (16% of lesions required retreatment after 3 months). The lesion complete response rates 3 months after the last treatment were similar with all regimens (93% for MAL-PDT, 86% for cryotherapy, 83% for 5-FU). PDT gave superior cosmetic results compared with cryotherapy or 5-FU. Clearance rates for all three therapies were similar after 2 years, with 68% of lesions cleared following PDT, 60% after cryotherapy and 59% after 5-FU.⁷⁰ A similar 3-month efficacy rate of 88% was observed in an open study of MAL-PDT (only one cycle of two treatments, 7 days apart), for 41 SCCs *in situ*, using a narrowband red LED source, with sustained clearance of 71% at 24 months.⁷¹ Further open studies of 51 and 43 lesions treated by the same MAL-PDT protocol observed 76% and 89% sustained clearance after 17 and 50 months, respectively.^{72,73}

Efficacy rates for ALA-PDT of 80–100% reported in previous guidelines remain valid, with a 90% clearance of 19 lesions in an open study in patients unsuitable or unwilling to have surgery, with 77% still clear at 2 years, but only 53% at 5 years following only one session of ALA-PDT with a nonformulary ALA, and with two penetration enhancers added.^{4,74} PDT may be particularly appropriate for large lesions (> 3 cm diameter), with two treatments of MAL-PDT, 1 week apart, clearing 96% (22/23) of lesions at 3 months, with sustained clearance after three recurrences of 83% at 1 year.⁷⁵

Body site does not appear to impact the efficacy of PDT, with protoporphyrin IX accumulation identical in SCC *in situ* located on acral and nonacral sites.⁷⁶ Digital SCC *in situ* was treated with ALA-PDT in four patients, with good cosmetic and functional results (one recurrence at 8 months responded to retreatment).⁷⁷ Case reports identify successful treatment of SCC *in situ* on the nipple, subungual, in poor healing sites on the lower legs, and in the setting of epidermolysis bullosa and radiation dermatitis.^{38,78–82}

In a trial comparing ALA-PDT for actinic keratoses or SCC *in situ* in OTR compared with immunocompetent controls, despite comparable cure rates of 86% at 4 weeks, significantly more recurrences occurred in the OTR group over 48 weeks.⁸³ A comparison of MAL-PDT with topical 5-FU in only five OTRs with SCC *in situ* is discussed in section 11.2.⁴²

PDT is normally delivered in a hospital setting, but novel light sources that can be worn by patients have also been used to treat SCC *in situ*, although published numbers are small.^{84,85} A recent open study of ambulatory PDT in NMSC included 30 patients with SCC *in situ*, with an overall 84% lesion response reported at 1 year (including 10 SCCs *in situ* with follow-up).⁸⁶ Red narrowband LED light is used most often; however, a square wave intense pulsed light, with reduced dose variability, cleared all nine SCCs *in situ* in one case series, with all lesions remaining clear after a follow-up period of 4 months.⁸⁷

Pain is a common side-effect, but PDT for SCC *in situ* has been observed as less painful compared with PDT for actinic keratoses.⁸⁸ In a large series reporting the prevalence of severe pain during a standardized ALA-PDT, 21% of 1015 treated SCCs *in situ* were associated with severe pain, similar

to 20% for superficial BCC (sBCC), with a direct association between lesion size and pain.⁸⁹ A comparison of pain with ALA-PDT or MAL-PDT, in 20 SCCs *in situ* and 20 sBCCs, failed to show any difference between the photosensitizing agents.⁹⁰ In a national survey of usage of topical PDT across 12 sites in Scotland, 104/382 lesions included were SCC *in situ*. Severe PDT-induced pain occurred overall in 10% of treatments, moderate pain in 18% and mild to no pain in 72%.⁹¹

Detailed assessment of adverse events associated with PDT is discussed elsewhere, but PDT appears a safe and generally well-tolerated therapy.⁶⁸ Although one patient with clinically diagnosed SCC *in situ* treated with PDT was diagnosed with melanoma at the same site a few months following treatment, it is uncertain whether the treatment contributed, given the lack of initial histology.⁹²

11.8 Radiotherapy (strength of recommendation D; level of evidence 2+)

Various radiotherapy techniques have been used to treat SCC *in situ*, with no standardized protocol, and a recent literature review concluded that both high- and low-dose regimens appear equally efficacious.⁹³ Disadvantages include cost, patient inconvenience and poor healing, particularly on the leg. Advantages are that it can be used to treat areas where surgical modalities are difficult, and it can be used even on the scalp.⁹⁴

Complete clearance of lesions is widely reported following radiotherapy, but impaired healing on the lower leg was observed in a large retrospective study, leaving the authors to recommend that radiotherapy should not be used on lower-leg lesions.⁶⁰ Cox and Dyson⁶⁰ reviewed the use of external beam radiotherapy (26 total dose combinations) in 59 SCC *in situ* lesions, with poor healing or failure to heal in 33%, which was related to patient age, diameter of field and the dose and energy of radiotherapy used, with no apparent effect of fractionation on healing. By comparison, in another cohort of patients treated in this study by cryotherapy, only 2% of lesions failed to heal. Poor healing of the lower legs was supported by a smaller retrospective series of 11 patients with 16 lower-leg lesions, in which a 100% cure rate was obtained, but with 25% failure to heal even though the fraction sizes used were relatively low (2.5–3.5 Gy per fraction for 13–22 fractions).⁹⁵ Complete clearance of SCC *in situ* has also been reported following soft X-ray in 77 treated lesions, with healing in all cases and relapse in only two patients with genital disease over a mean 3-year follow-up period.⁹⁶

In a retrospective review of nine patients with digital SCC *in situ*, lesions were immersed in a water bath and treated with photon irradiation. The total median radiation dose delivered was 50 Gy (range 25–66 Gy) in 2.5-Gy fractions (range 2–3 Gy). All lesions were locally controlled, with a median follow-up of 25 months with only mild-to-moderate erythema, desquamation or oedema acutely following radiotherapy, which resolved within 1 month.⁹⁷

A patient with giant unilateral SCC *in situ* of the scalp, with only partial responses following curettage, cryotherapy and PDT, and aborted therapy with 5-FU and imiquimod due to irritation, achieved clearance following electron beam therapy (8 MeV, 50 Gy, over 25 fractions), with disease persisting only outside the radiotherapy fields.⁹⁴

11.9 Laser (strength of recommendation D; level of evidence 3)

Experience of laser for SCC *in situ* is restricted largely to case reports and small series; it is considered for potentially more challenging treatment sites including the digits and genitalia. One retrospective review included six cases of digital SCC *in situ* treated with CO₂ laser, achieving histologically confirmed clearance and no recurrence over a follow-up period of 6–92 months, although one recurrence was noted in another small series of five patients with digital SCC *in situ*.^{98,99}

A larger retrospective study that used a CO₂ laser in super-pulsed mode (2 W cm⁻²), to treat SCC *in situ* in 44 patients, reported clearance after one treatment in 86% of patients, with all but one of the remaining lesions cleared after a total of two to four treatments.¹⁰⁰ A recurrence rate of only 7% (three of 44) over a follow-up period of 8–52 months was more encouraging than the 12% (two of 16) progression to invasive SCC within 1 year of discharge in a smaller study of 16 patients (25 lower-leg SCCs *in situ*) treated by CO₂ laser, with initial complete response maintained for up to a 6-month follow-up period.¹⁰¹

As deep follicular epithelium is typically spared with the CO₂ laser, there is the clear potential for failure of complete clearance and recurrence. One solution trialled was to perform CO₂ laser treatment (three passes) immediately followed by a long-pulsed 810-nm diode laser used as a final pass, with skin biopsies confirming deeper ablation of the follicular epithelium. In a case series of three, all lesions cleared and remained clear after a follow-up period of 6 months.¹⁰²

11.10 Other approaches

This review of the literature identified certain combinations of treatments and additional therapies, predominantly in case reports and series, where evidence is currently insufficient to permit a specific treatment recommendation.

11.10.1 Combination therapies

A variety of combination therapies have been reported in case reports or small series. Pretreatment of SCC *in situ* using an erbium-doped yttrium aluminium garnet laser was shown to accelerate response to topical 5-FU in a small half-side comparison study in one patient with multiple plaques.⁴⁷ Laser ablation of the stratum corneum of one-half of three plaques, prior to twice-daily application of 5-FU to both sides of the lesions, achieved biopsy-confirmed clearance within 2 weeks, while clearance on the nonablated side took 4 weeks of cream application.

A retrospective study of 29 patients with 31 biopsy-proven SSC *in situ* lesions treated with two 5-s FTCs of cryotherapy, followed a week later with imiquimod 5% applied 5 days a week for 6 weeks, showed complete clearance and no recurrences during a mean follow-up of 43.5 months.¹⁰³ Patients were excluded if they were not followed up for at least 2 years or were unable to tolerate treatment. It was suggested that the cryotherapy damages the integrity of the stratum corneum, thus enhancing penetration of the cream.

Ondo *et al.*¹⁰⁴ reported that four patients with SCC *in situ* involving a digit, who had previously failed to respond to imiquimod cream as monotherapy, and two who had also failed with 5-FU alone, all responded completely to 5-FU in the morning and 5% imiquimod cream at night as combination therapy, until significant inflammation developed (between 4 and 8 weeks). There were no recurrences at 1 year and 15, 18 and 23 months.

In a patient with radiation-induced extensive multifocal SCC *in situ* of both hands, a complex regimen involving overnight occlusion with imiquimod, topical tazarotene 0.1% and topical 5-FU ultimately achieved clearance after 18 months, although the 5-FU was discontinued due to irritation during a period when all three agents were applied daily.¹⁰⁵

A patient with a large 10 × 10-cm SCC *in situ* saw clearance (histologically confirmed) with one cycle of MAL-PDT followed by a 6-week course of topical imiquimod 5% cream applied 5 days per week.¹⁰⁶ In a further case where SCC *in situ* failed to clear with imiquimod, the lesion cleared subsequently with MAL-PDT, leading the authors to suggest that immunotherapy followed by the chemotherapy of PDT may have been complementary.¹⁰⁷

Topical ALA-PDT combined with electron beam therapy (total dose of course 12 Gy), with both therapies repeated every 2–3 days for a total of four treatments, completely cleared four SCCs *in situ*, but no comparison data for monotherapy were assessed.¹⁰⁸ The authors suggest that synergistic effects might be achieved by reaction with electron beam and residual protoporphyrin IX after the first PDT, causing greater tissue damage and permitting reduction in the radiation dose required.

11.10.2 Miscellaneous therapies

Two patients with SCC *in situ* were successfully treated with topical diclofenac 3% in hyaluronan 2.5% gel. Following treatment twice daily for 90 days (stopped in one case after 62 days due to local irritation), both lesions were confirmed clear on biopsy, without recurrence after a follow-up period of 10–12 months.¹⁰⁹ Inhibition of the cyclooxygenase (COX) enzymes results in a decrease in the downstream by-products of arachidonic acid metabolism, with metabolites playing a pivotal role in promoting epithelial tumour growth. An oral COX inhibitor was combined with topical imiquimod 5% cream to treat SCC *in situ* in five patients with chronic lymphocytic leukaemia, with 100% clinical and

histological clearance after 16 weeks of therapy, but the contribution of the inhibitor to successful clearance is unclear.⁵⁶

Phenol peels were applied to 14 patients with SCC *in situ*, with a complete response after one to eight treatment sessions in 71% (10/14), all remaining clear over a 1-year follow-up period.¹¹⁰ Hypopigmentation was observed in certain cases and was more common with increased sessions.

Topical tazarotene 0.1% gel, an acetylenic retinoid, was applied daily for up to 6 months to SCC *in situ* in 15 patients, with histologically confirmed clearance in seven patients after 3–5 months of treatment.¹¹¹ Oral acitretin was used to treat arsenical keratoses and SCC *in situ* in two patients, with near-total clearing in one patient at 1 mg kg⁻¹ dose for 10 months, but retinoid-related side-effects led to discontinuation of therapy in the other patient after 5 months.¹¹²

Treatment of SCC *in situ* using an ultrasonic surgical aspirator cleared 20 SCCs *in situ* with no recurrences over a mean period of 20 months.¹¹³ The treatment field included about 1 cm of normal skin, and the treatment required local anaesthesia. Hyperthermic treatment was performed using disposable chemical pocket warmers applied under pressure during waking hours for 4–5 months.¹¹⁴ There was initial clinical clearance in 75% of patients (six of eight), but histological clearance was confirmed in only three patients.

12.0 Specialized or difficult areas

12.1 Squamous cell carcinoma *in situ* of the nail unit

Squamous cell carcinoma *in situ* can present in any part of the nail unit or periungual tissue and can present as hyperkeratotic, papillomatous or warty proliferations, erosions or scaling of the nail fold, whitish cuticle, periungual swelling, paronychia and fissure or ulceration of the lateral nail groove, sometimes with granulation-like tissue beneath and scabbing. Sometimes the nail bed becomes dystrophic or ingrown. Subungual involvement is the most common presentation,^{115,116} and it may also present with onycholysis and extensive hyperkeratosis of the nail bed. Longitudinal melanonychia has been a presenting feature of SCC *in situ* of the nail.^{117–122}

The presence of ulceration, bleeding or a nodule is indicative of the transformation to invasive carcinoma. When invasive malignancy does develop, the rate of metastases does seem to be low, i.e. in the order of 2%. The diagnosis tends to be delayed because of an initial diagnosis of a benign lesion or a delay in performing a biopsy.¹²³ Biopsies can be open to misinterpretation, and if the condition persists the threshold for a repeat biopsy should be low.¹²² Because a histopathological diagnosis of SCC vs. SCC *in situ* may be difficult with periungual lesions because of the three-dimensional nature of the nail bed, it has been suggested that biopsy specimens indicating SCC *in situ* are best treated as if there is a concurrent invasive component.¹²⁴

HPV16 has been detected *in situ* in periungual SCC *in situ*, and at least 50 cases have been reported to be associated with HPV16.^{117,125–138} HPV-associated digital SCC suggests the possibility of genital digital spread as a mechanism of tumour induction,¹¹⁵ and patients and partners should be followed up for digital and genital HPV-associated lesions.¹³⁸

Management of periungual SCC is usually local excision, Mohs micrographic surgery or distal phalanx amputation. Mohs micrographic surgery is proposed for SCC *in situ* in the nail apparatus to allow adequate excision of the matrix, but to preserve normal tissue and function, even when healing takes place by secondary intention.^{115,139–142}

Alternatively, excisional surgery may be used for the complete removal of the nail apparatus, allowing healing by either secondary intention, grafting or repair with a bridge flap. Electrosurgery is possible in some cases, as is cryotherapy, but neither allows for adequate histological control of the tumour margins. A multidisciplinary approach to resection and reconstruction is required. This can be done by either conventional surgical instruments or CO₂ laser, the latter reducing bleeding and postoperative discomfort. Radiotherapy has been employed with good functional and cosmetic benefit for isolated or multiple lesions where progression to SCC has occurred.^{143,144} Other recently described treatments are represented in case reports of the use of imiquimod,¹⁴⁵ PDT^{79,80} and CO₂ laser ablation.¹⁴⁶

12.2 Penile intraepithelial neoplasia

PIN is a term that has been used to encompass the three pre-malignant clinical entities of EQ, Bowen's disease of the penis (BDP) and bowenoid papulosis (BP).^{147,148}

Although EQ and BDP are sometimes used interchangeably, they are clinically distinct. EQ presents as one or more red, moist plaques on the mucosal surfaces of the glans and inner aspect of the foreskin, while BDP should be used to describe red, sometimes slightly pigmented, scaly patches and plaques of the keratinized penis.¹⁴⁷ EQ seems to have a higher propensity than BDP to undergo malignant transformation into SCC.¹⁴⁹ In contrast to EQ, the lesions of BP occur in a younger age group, occurring in young, sexually active men. They are most common on the glans over the shaft, prepuce and groin, and can also be seen around the anus.

Lack of circumcision, HPV,¹⁵⁰ infection and genital lichen sclerosis^{151–154} are important risk factors in all forms of PIN.^{147,155} Circumcision is therefore an essential component of the management of most cases of PIN.¹⁴⁷ PIN that is associated with HPV tends to be more undifferentiated, and histologically associated with full-thickness dysplasia (bowenoid), while PIN associated with lichen sclerosis is differentiated, and can therefore be more subtle histologically and easily overlooked on histopathology.¹⁵⁵ There are increasing reports of PIN in association with biologics for the treatment of rheumatology and dermatology patients.¹⁵⁶

Treatment can be difficult, especially in cases with urethral involvement. Early biopsy is clearly indicated to establish the

diagnosis and should be carried out before treatment. Circumcision removes a major risk factor for cancer and provides more extensive tissue for histology.¹⁴⁹

5-FU as a 5% cream is a well-established conventional option for the treatment of BDP, EQ and BP,^{147,149,157} but there have not been any clinical trials.

Treatment options for EQ include the use of topical 5-FU, imiquimod or PDT, although much of the evidence of efficacy depends on case reports. Other treatments that have been recorded in the literature include laser ablation (CO₂ or neodymium-doped yttrium aluminium garnet laser), excisional surgery, Mohs micrographic surgery or, rarely, cryotherapy and radiotherapy. Therapy choice requires a balance between efficacy (in view of the higher risk of invasion for genital *in situ* lesions), tolerability and preservation of appearance and function. Clearance, supported by post-treatment biopsy, without recurrence for up to 70 months was observed in a series of seven men treated with topical 5-FU applied under occlusion twice daily for 4–5 weeks.¹⁵⁸

Standard-protocol MAL-PDT cleared 83% of patients (19/23) with EQ of the glans and/or prepuce, with treated sites remaining clear for an average 18 months of follow-up; however, 22 patients suffered severe or very severe discomfort during therapy.¹⁵⁹ A similar response was noted following MAL-PDT in clearing seven of 10 of patients (70%) either with primary PIN, or undergoing atypical postsurgery treatment for carcinoma of the penis.¹⁶⁰ A poorer response was noted following MAL-PDT in a series of 11 patients, with only six requiring no further treatment.¹⁶¹ In a study using ALA-PDT and MAL-PDT in 10 patients with PIN, clearance was achieved in seven patients, but with recurrence in four. There was sustained clearance in the remaining patients over 46 months, including clearance of human HPV DNA.¹⁶²

In difficult cases, Mohs micrographic surgery has been used to include tissue taken from the distal urethra and the defect covered by a flap repaired from the external part of the prepuce. Total glans surgical resurfacing was reported to be effective in a series of 10 patients, with good cosmesis.¹⁶³

Patients and their sexual partners should be counselled and screened for HPV and other sexually transmitted diseases including HIV. The treatment should be conservatively ablative. Follow-up should be long term.¹⁶⁴

For BP, treatment options include cryotherapy,¹⁶⁵ curettage and cautery,¹⁶⁶ topical 5-FU,^{44,167,168} topical imiquimod cream, topical cidofovir, laser therapy^{169,170} and PDT.^{171,172}

13.0 Practical and health economic considerations

Choice of therapy for SCC *in situ* will be affected by patient and clinician access to therapy, patient preference for home-based vs. hospital-delivered therapies, and therapy cost to the patient and healthcare provider. Standard excisional surgery, curettage and cryotherapy are widely available for the treatment of SCC *in situ* in secondary care along with the opportunity to prescribe the topical agents in both primary

and secondary care. Topical PDT is becoming more widely available, but is most often located in specialist departments, with Mohs, radiotherapy and laser restricted to tertiary specialist centres. Therapy costs will vary depending on the location of services, staffing, volume of procedures and local protocols (e.g. frequency of biopsies prior to nonsurgical therapies). Comparative data remain limited and dependent on assumptions over therapy protocol and pathways of care.

A cost-minimization analysis based on costs incurred by the U.K. NHS was published in 2003, comparing cryotherapy, curettage and cautery, excision, laser ablation, PDT and 5-FU, in the treatment of SCC *in situ*.⁶³ Assumptions included the expectation of diagnostic biopsy in all cases managed by nonsurgical options. Cryotherapy was costed at three visits to achieve clearance, while PDT was costed on two treatments. Curettage or excision biopsy were the cheapest treatments (£200), followed by 5-FU (£287), laser (£312) then cryotherapy (£392), with PDT being the most expensive (£457), although this was costed on more expensive light sources than in current use. This did not include the costs of complications or costs incurred by the patient or their relatives. A cost comparison based on published clearance/morbidity data (excluding the cost of a diagnostic biopsy) estimated the cost of successfully treating a single SCC *in situ* to be £119 for PDT, £145 for cryotherapy and £171 for topical 5-FU, which included additional clinic visits to manage complications.¹⁷³

In one small, retrospective study from Spain, of lesions located on the lower limbs, surgical excision of SCC *in situ* ($n = 54$) and sBCC ($n = 32$) provided high cure rates, but was more expensive than nonsurgical modalities following calculation of the total medical cost, as well as direct and indirect costs.¹⁷⁴ This study was costed on currently licensed MAL-PDT, compared with earlier studies that costed ALA-PDT. After 2 years of follow-up, a complete response was observed in 89.5% of the PDT group, 87.5% of the imiquimod group and 97.5% of the surgery group, but the average total cost for each treated tumour was €536 for surgery, €214 for PDT and €229 for imiquimod. Even allowing for reduced efficacy of the topical therapies, the cost per complete response was also lower with PDT and imiquimod than with surgery. In view of variations in drug pricing as well as service delivery, costings will vary between countries.

In the absence of new therapies, and with limited variation in treatment recommendations since the last guideline update, there should be no significant organizational or financial barriers to the treatment recommendations contained in this guideline. Cost pressures are most likely from increased prevalence of the condition and organizational changes impacting the availability of hospital-delivered therapies.

14.0 Future directions

We present updated evidence to assist therapy choice in SCC *in situ*, although substantial gaps remain in direct evidence of comparison, especially between the surgical approaches, topical therapies and PDT. RCTs for difficult-to-treat sites such as

around the nail apparatus would likely require multicentre design, but offer improved guidance to clinicians on therapy choice. We summarize case reports and small series concerning novel or combination therapies, but formal comparison studies are required if we are to be able to offer sound guidance and recommendations on therapy selection. Accepting that all reviewed therapies have nonresponders and recurrences, it is timely to consider the potential for increased efficacy by combination therapy, perhaps combining initial destructive therapy with topical immuno- or chemotherapy, although a large multicentre trial design is likely to be required. Further study of novel therapies, including emerging therapies for actinic keratoses and sBCC, could be considered for SCC *in situ*. Evaluation of the true cost of each therapy remains limited and would benefit from more rigorous assessment. The preventive potential of field therapies in reducing SCC *in situ* and subsequent invasive SCC requires urgent study.

15.0 Recommended audit points

- In the last 20 consecutive patients seen with SCC *in situ* is there clear documentation of the therapy type and treatment regimen?
- In the last 20 consecutive patients seen with SCC *in situ* is there clear documentation that a choice of therapy was discussed with the patient?
- In the last 20 consecutive patients seen with SCC *in situ* occurring below the knee was a therapy other than radiotherapy used?

The audit recommendation of 20 cases per department is to reduce variation in the results due to a single patient, and to allow benchmarking between different units. However, departments unable to achieve this recommendation may choose to audit all cases seen in the preceding 12 months.

16.0 Summary

This guideline update reviews the evidence level for treatments in common use for SCC *in situ*, as well as identifying novel and combination therapies where the evidence level is typically restricted to case reports/series. The quality of evidence is strongest for PDT, 5-FU and imiquimod, as well as cryotherapy (often a comparator in trials), but this may be influenced by the more rigorous assessment required for newer therapies seeking regulatory approvals. Surgical excision and curettage remain in common use, although with lower quality evidence available. Treatment choice (Table 2) should take into account evidence of efficacy and tolerability, access to the therapy, cost-effectiveness and patient preferences. Specific therapeutic challenges are observed for SCC *in situ* located around the nail and for genital disease.

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Table 2 Summary of treatment choice

Treatment	Strength of recommendation
Cryotherapy: simple, inexpensive and quick method of treating SCC <i>in situ</i> . Lesions heal better than with radiotherapy, but not as well as those treated with curettage or PDT	B
Success (of curettage with cautery): simple, inexpensive, safe and effective method of treating SCC <i>in situ</i> . Preferable to cryotherapy in terms of pain, healing and recurrence rate	C
Excision: simple, rapid and effective treatment for SCC <i>in situ</i> of limited size, located in suitable areas. Cosmetic outcome, body site, healing properties and vascularity of the area need to be considered	C
5-Fluorouracil: commercially available in the U.K. as a 5% cream. Less effective than PDT but not significantly different from cryotherapy (protocol dependent). It is more practical than surgery for large lesions, especially at potentially poor healing sites	B
Imiquimod: available as a topical 5% cream but is currently unlicensed for SCC <i>in situ</i> . It is generally well tolerated, but it does cause significant erythema and crusting, so appropriate counselling needs to be given prior to treatment	B
Laser: limited evidence, considered for potentially more challenging treatment sites including the digits and genitalia	D
Mohs micrographic surgery: may be indicated for digital SCC <i>in situ</i> (around the nail in particular) and for some cases of genital (especially penile) SCC <i>in situ</i> for its tissue-sparing benefits	D
No treatment: in some patients with slowly progressive thin lesions, especially on the lower leg of the elderly, there is an argument for observation. In these cases regular use of an emollient (especially one containing urea) can reduce the scaling and make it less obvious	D (GPP)
PDT: more effective and superior cosmesis than cryotherapy and 5-fluorouracil (protocol dependent). It may be of particular benefit for lesions that are large (> 3 cm diameter), on the lower leg, or at otherwise difficult sites. Pain is a common side-effect	A
Radiotherapy: can be used to treat areas where surgical modalities are difficult. Disadvantages include cost, patient convenience and poor healing, particularly on the leg	D

SCC, squamous cell carcinoma; PDT, photodynamic therapy; GPP, good practice point.

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Supporting Information

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

Table S1. Strength of recommendations and quality of evidence.

Appendix

Table A Levels of evidence

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias ^a
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal ^a
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

RCT, randomized controlled trial. ^aStudies with a level of evidence ‘–’ should not be used as a basis for making a recommendation.

Table B Strength of recommendation

Class	Evidence
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results Evidence drawn from a NICE technology appraisal
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2+, or Formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group

RCT, randomised controlled trial; NICE, National Institute for Health and Clinical Excellence.