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Guidelines for management of Bowen's disease

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Summary These guidelines for management of Bowen's disease 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: Bowen's disease, treatment, guidelines.

Definition and introduction to the guideline

Bowen's disease (BD) is a form of intraepidermal (*in situ*) squamous cell carcinoma (SCC), originally described in 1912.[1] It is usually persistent and progressive, with a small potential for invasive malignancy, although spontaneous partial regression may occur. Its epidemiology, predisposing factors, disease associations and risk of malignancy are all pertinent to patient management and are discussed in addition to the local treatment options for the disease itself.

Histology

The epidermis is replaced by abnormal keratinocytes with disordered maturation and loss of polarity. Large and atypical mitotic figures are characteristic. Similar changes extend deeply into the pilosebaceous unit and may replace the infundibulum, external root sheath and sebaceous gland[2] (a feature which may explain recurrences after superficial forms of therapy). DNA-ploidy studies also support the malignant nature of BD, although DNA malignancy grades are lower than for SCC.[3] Large cell acanthoma may be a rare cytologic variant of BD.[4]

Clinical description, demographics and variants

Typical BD presents as a gradually enlarging well demarcated erythematous plaque with an irregular border and surface crusting or scaling.[5] Symptoms are minor in the absence of ulceration. BD may occur at any age in adults but is rare before the age of 30 years; most patients are aged over 60.[5–12] In the U.K., the peak age group is the seventh decade.[6,7] Lesions are usually solitary but are multiple in 10–20% of patients.[6–10] Any site may be affected, although involvement of palms[13,14] or soles is uncommon. In the U.K., BD occurs predominantly in women (70–85% of cases),[6,7] and about three-quarters of patients have lesions on the lower leg (60–85%).[6,7]

Specific sites which deserve mention due to the potential for diagnostic confusion include perianal[15–17] and subungual BD.[18–20] Pigmented BD is an uncommon variant, occurring in 1·7% of cases in one series,[21] and is particularly likely at flexural, perianal or subungual sites. Verrucous BD is important as it is likely to raise suspicion of invasive carcinoma.

Genital lesions which have the histology of BD include erythroplasia of Queyrat and Bowenoid papulosis.[22–26] Erythroplasia of Queyrat (penile intraepithelial neoplasia) occurs on the glans penis and under the prepuce, virtually always in uncircumcised men. Comments on vulval BD in these guidelines are drawn from references written over several years, which may have included both lesions morphologically similar to BD at other body sites and other dysplastic lesions which would be classified as vulval intraepithelial neoplasia (VIN) according to current terminology. Reference to original data sources and current vulval disease literature is recommended if treating VIN. Bowenoid papulosis is a different disorder with a viral aetiology, slight female predominance and benign behaviour in most cases, but it may cause extensive multiple lesions.

Rarely, BD may affect other mucosal surfaces such as oral mucosa and the conjunctiva or cornea;[27] these are not discussed further.

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Aetiology

Solar

The age group and body site distribution of BD (head and neck, female lower leg) are suggestive of a relationship with chronic solar damage.[4,9,11] As with other skin cancers, BD is rare in individuals with black skin in whom it predominantly affects non-exposed sites.[28] BD has been reported in patients having psoralen ultraviolet A treatment.[29–31]

Arsenic

Several studies have identified an association between BD and previous arsenic exposure.[32–35] In one large survey, about 50% of arsenical cancers were BD,[32,33] although another study reported that multiple basal cell carcinomas were the commonest arsenical tumour and were more frequent than multiple or solitary BD.[34] There is typically a time lag of over 10 years (often several decades) between exposure and development of BD.

Immunosuppression

There are small numbers of reported cases of BD associated with congenital or acquired immunosuppression, including patients with AIDS. BD is probably not uncommon in transplant patients having therapeutic immunosuppression, but is not separately identified in all studies.

Viral

A number of viral agents have been implicated in the aetiology of BD. The most extensively investigated have been human papilloma viruses (HPV), especially HPV16, which have been detected in up to 20–30% of anogenital lesions,[36,37] although some large studies have reported much lower[38] or negative[39] results. Human herpesvirus type 8 has been reported in up to two-thirds of BD lesions[40,41] but was not found in another study.[42]

Other aetiological agents and pre-existing lesions

Therapeutic and other ionizing radiation has been reported to cause BD, as have various forms of skin injury or chronic dermatoses (such as lupus vulgaris or chronic lupus erythematosus[12]).

There are several cases of BD arising in seborrhoeic keratoses[43] and it has also been reported in porokeratoses (disseminated, Mibelli and linear types) and in a Becker's naevus.

Association with internal malignancy

The apparent relationship between BD and internal malignancy was reported in 1959[44] and several studies subsequently supported this association.[6,45–48] Multiple lesions of BD have been associated with higher risk but not confirmed in a U.K. population.[6] However, some studies found no significant association with internal malignancy for BD overall,[49] or for BD at specific sites such as perianal BD.[50] A critical analysis review of the existing studies in 1987 concluded that there were many methodological concerns,[51] and a subsequent meta-analysis of 12 studies in 1989 indicated that there was no significant association.[52] The overall conclusion from larger studies and meta-analysis is therefore that routine investigation for internal malignancy in patients with BD is not justified (*strength of evidence, E*).

Association with other skin malignancy

In studies which have examined this association, about 30–50% of subjects had other previous or subsequent skin malignancies (mainly basal cell carcinoma).[8,9] The standardised incidence ratio for subsequent non-melanoma skin cancer was 4·3 in a recent study[53]

Risk of progression to squamous cell carcinoma

Although risk of progression to invasive SCC of up to 20% has been suggested, most studies suggest a risk of invasive carcinoma of about 3%.[46,54] Of these, one-third may metastasize.[54] However, both of these figures are drawn from retrospective case series. When invasion occurs it may have sebaceous or eccrine differentiation.[56,57] The degree of aneuploidy in BD has been proposed as a factor to predict risk of invasive carcinoma,[58] but other authors feel that aneuploidy occurs in all BD and is unlikely to have prognostic significance.[59]

The risk of invasion for genital BD or erythroplasia of Queyrat, in the region of 10%,[7,22,23] is greater than for typical sites of BD. In Bowenoid papulosis invasion is extremely rare,[23] but cervical intraepithelial carcinoma (CIN) occurs in 60–90% of affected females or in female sex partners of affected men,[60] and oral papillomas and tumours have been reported in association with

HPV16-positive Bowenoid papulosis. Perianal BD also has higher risk of invasion, recurrence, and an association with cervical and vulvar dysplasia.[16,17]

The risk of invasive carcinoma may also be higher for BD on the neck compared with other sites (10% in one study,[8] compared with an overall risk for all sites of 4% in the same study population).

Investigation and diagnosis

Diagnosis is primarily on the basis of clinical features. Histological confirmation is required for cases with diagnostic doubt, or where there is suspicion of invasive malignancy. Biopsy is probably not required for all small lesions diagnosed by specialists; clinicopathological correlation was good in one study[7] but this has not been extensively investigated.

Treatment

Evaluation of treatment studies of BD is difficult due to potential selection bias to specific forms of treatment. Similarly, healing and success rate may vary with body site. Virtually all authors use visible rather than histological assessment to determine the end-point of clearance. Even for the same treatment modality, there is difficulty in directly comparing studies due to different lesion sites, sizes of lesions and use of different types of equipment and treatment regimens.

No treatment

In some patients with slowly progressive thin lesions, especially on the elderly lower leg where healing is poor, there is an argument for observation rather than intervention.

5-Fluorouracil (strength of evidence B, II-iii [Appendix])

5-Fluorouracil has been used topically for treatment of BD in several studies.[61–66] Most of these are open trials or small case series. It is usually applied once or twice daily as a 5% cream for a variable period of time (between 1 week and 2 months in most studies using this concentration) to achieve disease control, and repeated if required at intervals. Efficacy may be increased by application under occlusion,[62] and a recent study used iontophoresis to improve follicular penetration.[64] In this study,[64] only one of 26 patients had histological evidence of residual disease at 3 months after eight treatments (evidence II-iii). It has been combined with dinitrochlorobenzene (DNCB) to improve penetration, but the DNCB appeared to be the effective constituent.[65] An evaluation of different concentrations of 5FU (in a propylene glycol base) used mainly a 1% strength for 4–18 weeks (most 8–12 weeks) in 41 patients, with an 8% recurrence rate; the authors suggested that at least 2·5% was required for BD at extrafacial sites.[62] As 5FU can be very irritant, less aggressive regimens have been used for disease control rather than cure. A once weekly application of 5% 5FU improved lesions in 24 of 26 patients, although long-term clearance was only achieved in a minority with this regimen.[66]

In erythroplasia of Queyrat, application of 5% cream twice daily for 4–5 weeks has been recommended,[26,67] but inflammation frequently limits this treatment regimen.[22]

None of these studies provide details of the success rate for the currently available preparation available in the U.K. (5% cream to be used once or twice daily for 3–4 weeks) as a first-line option for unselected lesions.

Cryotherapy (strength of evidence A, II-i)

The varied results reported may reflect differences between studies in equipment and regimen used. Thestrup-Pedersen *et al.*[8] reported a 33% failure rate in 56 patients but the regimen was not provided. The studies discussed below all used liquid nitrogen (LN_2) cryotherapy.

Plaza de Lanza and colleagues using LN_2 in 28 patients with BD[68] demonstrated that a single freeze–thaw cycle (FTC) of 30 s was as effective as 2×30 s (no failures or recurrences in either group) but more effective than 1×15 s (two failures and one recurrence). Graham and Clark[69] reported one recurrence in 30 patients treated with a single FTC of LN_2 of sufficient duration to produce a clinical thaw time of at least 90 s. Holt[70] treated 128 lesions of BD (including 20 lesions > 2 cm diameter) in 85 patients under lignocaine local anaesthesia, with the same single 30 s FTC of LN_2. There was only 1 in 128 recurrence during a minimum 1-year follow-up period, in a 2-cm lesion on the calf which was later demonstrated to have a focus of invasive cancer. Slow healing of the lower leg was noted.

Cox and Dyson[71] used LN_2 with two FTC of 20 s for 82 lesions on the lower leg in 49 patients (including 17 lesions > 2 cm diameter), and demonstrated recurrence in five patients (6%) after a minimum 1-year follow-up; one of these had a focus of invasive cancer which was

not apparent in a pretreatment incisional biopsy. No anaesthesia was required, and there were no treatment-related failures of healing, but lesions of > 2 cm were treated in a staged manner at 2-month intervals.

Morton *et al.*[72] reported 100% clearance in 20 patients with one to three treatments of LN_2 using one FTC of 20 s on each occasion (50% success after a single treatment). There were two (10%) recurrences in the 1-year follow-up period. In this study, photodynamic therapy was more effective than cryotherapy but the FTC duration was less than in the studies detailed above; despite this, five lesions ulcerated following cryotherapy.

The combination of intermittent cryotherapy before and during 4 weeks of 5FU was used for a technically difficult ear lesion with success, but in a single case and with focal recurrences.[73]

Cryotherapy therefore appears to have a good success rate (recurrences less than 10% at 12 months) but healing may be slow for broad lesions and discomfort may limit treatment of multiple lesions.

Curettage with cautery/electrocautery (strength of evidence A, II-iii)

Veien *et al.* did not report any recurrences within 2 years among 33 cases of BD treated with curettage and electrocautery, compared with 36 of 508 basal cell carcinoma recurrences in the same treatment period.[75] However, recurrence rates of 20% were reported by both Thestrup-Pedersen *et al.*[8] (65 of 345 cases) and by Sturm[62] (four of 20 cases) with this modality, and a 73% failure rate was recorded by Graham and Helwig,[45] although these studies do not give details of the treatment regimens or equipment. Healing has recently been demonstrated to be faster after curettage than after cryotherapy with less early pain,[74] but the variable and possibly suboptimal cryotherapy in this study (some lesions treated with 2FTC of 5 s) does not permit firm conclusions regarding recurrence rates.

Excision (strength of evidence A, II-iii)

Thestrup-Pedersen *et al.* reported a 4·5% recurrence rate (three of 65 cases) with simple excision.[8] Graham and Helwig[45] treated 62% of 155 patients by excision only, and had a 19% recurrence rate within 5 years. The risk of recurrence after simple excision is greater at some sites, such as perianal BD (discussed later).

Mohs micrographic surgery has been used for lesions at special sites such as the penis, where tissue sparing is important, with good results in the small number of reported cases.[76]

Laser (strength of evidence B, III)

Lasers used to treat BD include CO_2, argon and Nd:YAG.[77–79] They have particularly been used to treat lesions at difficult sites such as the finger or genitalia, and CO_2 laser has also been used to treat Bowenoid papulosis. Results are generally stated to be good, but the published results are of small numbers, or are considered with other epidermal neoplasia and difficult to analyse specifically.

Photodynamic therapy (strength of evidence A, II-iii)

This modality requires the activation of a photosensitizer, usually a porphyrin derivative, by visible light. Systemic photosensitization was used with excellent results in early studies[80,81] but this summary refers to aminolaevulinic acid (ALA)–photodynamic therapy (PDT) (PDT using topical ALA derivatives).

Svanberg *et al.* reported complete response in nine of 10 cases of BD (2–5 cm diameter) treated with δ-ALA and 60 J/cm^2 of 630 nm laser light.[82] Epithelialization was established at 3–6 weeks and there were no recurrences over 6–14 months. Cairnduff *et al.*[83] achieved initial clearance of 35 of 36 lesions of BD (one partial response) using 5-ALA and 125–150 J/cm^2 of 630 nm laser light; three cases relapsed at a median follow-up of 18 months (overall success 89%). Stables *et al.*[84] reported a complete clinical response in 73 of 77 lesions in 54 patients at 12 months (71 of 77 at 24 months) using ALA and either 125 J/cm^2 white light from a modified slide projector or 100–125 J/cm^2 of 630 nm laser light. The same authors have reported the successful use of ALA–PDT for broad lesions of BD in three patients[85] (each required two treatments) and for erythroplasia of Queyrat.[86]

Morton *et al.*[72] demonstrated clearance in 20 of 20 lesions of BD (75% with one, 25% with two treatments) using 5-ALA and 125 J/cm^2 xenon arc irradiation (630 ± 15 nm), with no recurrences at 12 months. Varma *et al.* have recently used a non-laser red light source[87] to treat 38 lesions of BD, with 95% complete response after two treatments which was sustained at 12 months in 15 of 19 who were reviewed.

The currently reported overall initial clinical clearance rate for ALA–PDT is therefore 90–100%, and recurrence rate 0–11% in studies with completed 12-month follow-up. Good cosmesis and healing is likely, but availability is limited.

Radiotherapy (strength of evidence B, II-iii)

A variety of radiotherapy techniques and regimens have been used to treat BD, including external beam irradiation, strontium 90, proton radiotherapy and beta-emitting radionuclides. Although Graham and Helwig reported an 88% failure rate in 12 patients,[45] complete response rates of 100% were reported in 77 lesions treated with X-irradiation by Blank and Schnyder,[88] and in 59 patients treated by Cox and Dyson.[71] In one of these studies,[88] two patients (both with genital lesions) relapsed at 8 and 16 months. The patients reported by Cox and Dyson all had lower leg lesions, and poor healing (which was related to age, diameter of field and radiotherapy dose) was a feature in 12 of 59 (20%). Thus the high cure rate may be offset by impaired healing.

Other treatments

The combination of isotretinoin and interferon alpha has been used in one patient with multiple lesions of BD (over 50 plaques) and all except two cleared after 3 months of treatment with sustained remission at 15 months.[89] Etretinate and interferon gamma have both also been used for treatment of Bowenoid papulosis.

Site-specific treatment

Digits. Excision has usually been recommended at digital/subungual sites.[18,19] A study of seven cases recommended Mohs surgery for optimal tissue sparing.[19] CO_2 laser may also be useful, with 80% cure in a series of five patients.[78]

Genital. Erythroplasia of Queyrat has higher risks of invasion compared with ordinary BD, and treatment may need to be more aggressive. Mohs surgery has been advised for tissue sparing, and CO_2 laser for good healing. However, radiotherapy, 5FU, PDT[86] and cryotherapy[90] are all potentially useful.

Bowenoid papulosis has very low risk, and treatment is dictated by the multiplicity of lesions; the risk of CIN in women is important.

Perianal Bowen's disease. Treatment is usually surgical or with radiotherapy. Wide local excision is usually adequate[15–17] but has a recurrence rate of 10–30%; the rate after simple excision may be over 50%.[17] In one study of 47 cases, the recurrence rate after CO_2 laser was 80% (four of five cases) but after wide excision was 23% (six of 26 cases).[17] A study of 57 cases of epidermoid carcinoma of the anal margin[91] suggested that radiotherapy is the treatment of choice for BD but did not specifically present any results for this disorder. PDT has been used in a small number of cases.

Treatment failures and relapses

Treatment failure may be related to indistinct margins (marginal recurrences), concern about healing and minimizing damage to normal tissues, extension of BD down follicles (a typical histological feature) and unrecognized foci of invasive tumour (usually not marginal). Attempts to identify margins more accurately using acetowhitening were reported as useful in one study of 12 lesions[92] but unreliable in another study of eight patients.[93]

Table 1. Summary of the main treatment options for Bowen's disease. The suggested strengths 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 availability of the method or facilities required

Lesion characteristics	Cryotherapy	Curettage	Excision	Topical 5-fluorouracil	Photodynamic therapy	Radiotherapy
Small, single, good healing[a]	1	2	3	4	3	5
Large, single, good healing[a]	3	5	5	3	2	4
Multiple, good healing[a]	2	3	5	3	3	4
Small, poor healing site[a]	3	2	2	2	2	5
Large, poor healing site[a]	5	4	5	3	2	6
Facial	2	2	4	4	3	4
Digital	3	5	4	3	3	3
Perianal	6	6	1	6	7	3
Penile	3	5	4	3	3	3

[a] Refers to the clinician's perceived potential for good or poor healing at the affected site.
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; 7, insufficient evidence available.

Summary of treatment modalities

Most of the above treatments have good success rates, but all have a risk of slow healing at the characteristic lower leg site of BD seen in the U.K. The potential benefits of each treatment are offset by limitations. Thus, for example: laser and PDT treatments have high cost and/or limited availability; simple excision and Mohs surgery are time-consuming and wound closure is difficult on the lower leg; cryotherapy and PDT cause discomfort; and radiotherapy has a high success rate but significant failure to heal on the lower leg. Cryotherapy and curettage are the cheapest and most available of the surgical modalities. The relative status of the available treatment options is summarized in Table 1. This takes into account the evidence for benefit, ease of application and time required for the technique, wound healing, cosmetic result and availability of the method or facilities required.

Follow-up

Required duration of follow-up is uncertain, in part because many studies have used 12-month follow-up periods and clinical assessment for the detection of recurrences. In a series of various epidermal tumours treated with cryotherapy, Holt recommended a 2-year follow-up period on the basis that only one recurrence was after 18 months; however, this series included several different tumour types, and the one BD recurrence was at 6 months.[70] Most recurrences after PDT have been detected within 2 years. In a series of 19 patients with perianal BD[16] the recurrence rate increased from 16% at 1 year to 31% at 5 years; longer follow-up may therefore be appropriate for BD at less common and less visible sites, or where HPV infection is likely to have been relevant. However, in determining follow-up it is not simply the index lesion which is relevant, as a significant proportion of patients have multiple lesions or other epidermal neoplasia at presentation or subsequently.

In uncomplicated cases of solitary BD we suggest that review at about 3 months to confirm clearance and healing is prudent. The requirement for subsequent review should take into account the presence of multiple lesions, previous recurrence, other skin neoplasia, the reliability of the patient and the degree of primary care support.

Conclusions

1 There is no convincing evidence to support routine screening for internal cancer in patients with BD.
2 The risk of progression to invasive cancer is about 3%.
3 There is a significant frequency of multiple lesions and an association of BD with other skin cancers, which may reflect the predominantly solar aetiology or, in some cases, arsenic exposure.
4 Genital, and particularly perianal, BD have higher risks of invasive cancer.
5 Treatment options for BD include cryotherapy, curettage, excision, laser, photodynamic therapy and topical 5FU; all of these have recurrence rates in the order of 5–10%, and no treatment modality appears to be superior for all clinical situations.
6 Direct comparison between treatment modalities is difficult as there are few randomized clinical trials with comparable patient subgroups; other factors such as treatment-related morbidity and the costs and availability of the treatment options need to be considered.

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Appendix 1. 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

Appendix 2. Quality of evidence

I Evidence obtained from at least one properly designed, randomized control trial
II-i Evidence obtained from well designed control 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 results of 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 of comprehensiveness of follow-up or conflicts in evidence).