Acta Derm Venereol 2014; 94: 431–435

CLINICAL REPORT

Bowen's Disease: A Six-year Retrospective Study of Treatment with Emphasis on Resection Margins

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Bowen's disease is an *in situ* squamous cell carcinoma of the skin with various treatment modalities available. A major advantage of surgical excision is the opportunity to histologically examine the resection margins. There is no consensus about the most appropriate margin. This retrospective study evaluates the clearance rates achieved by excision with a 5 mm margin and estimates how that might change after fictitiously reducing the resection margin by 1 or 2 mm. Patients with histologically confirmed Bowen's disease were selected at the Maastricht University Medical Centre from 2002 until 2007. Surgical margins and complete excision rates were evaluated and histological slides were re-examined. To our knowledge this is the first study investigating the safety margin for Bowen's disease. As Bowen's disease is not an invasive disease, minimisation of healthy tissue excision is desirable. Our data show that a hypothetical reduction of the safety margin from 5 mm to 4 or 3 mm decreases the complete excision rate from 94.4% to 87% and 74.1%, respectively. *Key words: Bowen's disease, squamous cell carcinoma* in situ*, surgical excision, safety margin*.

Accepted Sep 18, 2013; Epub ahead of print Dec 12, 2013

Acta Derm Venereol 2014; 94: 431–435.

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Bowen's disease (BD), originally described by JT Bowen in 1912, is a squamous cell carcinoma (SCC) *in situ* of the skin, restricted to the epidermis and without evidence of dermal invasion (1). It usually appears as a slow growing, sharply demarcated erythematous plaque with irregular edges and surface crusting or scaling. BD is generally asymptomatic, but larger lesions may itch (2). Although BD is usually solitary, multiple lesions may occur in 10–20% of patients (3).

The annual incidence in the UK is 15/100,000 and 14.9–27.8/100,000 in North American populations (3, 4). The peak incidence is in the seventies (5). BD predominantly occurs on areas of the body subjected to chronic sun exposure (head, neck and lower legs). About 75% of patients have lesions on the lower legs (3, 6, 7). The presence of various types of human papilloma virus have been found in extragenital BD including the oncogenic type 16 (7–9). Immunosuppression is a risk factor for BD (10).

Most studies suggest a risk of advancement into invasive SCC in about 3–5% of cases and a further progression to metastasis may occur in 1/3 of those invasive tumours (4, 11–13).

Therapies

Available treatment options for BD are cryotherapy, curettage, surgical excision, photodynamic therapy (PDT), laser therapy, imiquimod 5% cream and 5-fluorouracil cream (3, 7, 12, 14–16). Studies addressing these different treatment modalities are difficult to compare, due to variation in treatment protocols and patient populations. For example, to determine clearance, this may be based on clinical assessment in some studies and histological in others (13). Also, safety margins used for excision vary, based on expert opinion. Because of the diversity in studies, there is no consensus on the optimal treatment for BD (4).

The UK guidelines state that no single treatment modality is superior for all clinical situations. All therapeutic options have failure and recurrence rates in the order of 5–10%. For individual patients the choice of treatment is influenced by patient and tumour characteristics (3, 12). The French guideline recommends surgical excision for BD with a minimal margin, but does not specify what this margin should be. When the tumour is extensive, multifocal or on a body site associated with poor wound healing, PDT or 5-fluorouracil cream are advised (15). In the United States a 4–6 mm margin is advised for low risk SCC including BD, when surgery or radiation is contraindicated or impractical, non-invasive therapy including PDT, imiquimod 5% cream and 5-fluorouracil cream is suggested (16). Other national guidelines do not specify the safety margin (3, 7, 15, 16). In the Netherlands low risk SCC are excised with a 5 mm safety margin, margins for BD are not specified (5). To date, no comparative trials have been published about safety margins in BD.

 doi: 10.2340/00015555-1771
 ISSN 0001-5555

Objectives and importance of the study

The aim of this study is to analyse the safety margins used in conventional surgical excision in BD and evaluate whether a 5 mm margin is appropriate, or whether smaller margins may be sufficient. Because BD is usually a clinically sharply demarcated tumour, we hypothesise that reduction of the safety margin may be possible. Furthermore, we analysed other possible determinants of incomplete excision of BD including clinical and tumour characteristics and the influence of specialist performing surgery (dermatologist, plastic surgeons or GP).

MATERIAL AND METHODS

Patients and procedures

This is a retrospective study of patients selected from the Dutch nationwide network and registry of pathology, PALGA, database at the Maastricht University Medical Centre (MUMC), a tertiary referral centre, specialised in dermatological oncology.

All patients with a histologically confirmed and previously untreated BD from January 2002 until December 2007 were included. Not only patients who visited the dermatology department were included, but also patients treated by the general practitioners who sent their specimen to the pathology department of the MUMC.

Tumours found on mucous membranes or genitalia (e.g. erythroplasia of Queyrat and Bowenoid papulosis) or found within and at the margins of an invasive skin malignancy, were excluded. Patient and tumour characteristics and information about the treatment were obtained from (electronic) patient files. Tissue was obtained from the Maastricht Pathology Tissue Collection (MPTC). Before the start of our study the research protocol was approved by the Medical Ethical Committee of our hospital.

Histological evaluation

All histological slides were retrospectively re-examined by the same 2 independent investigators, a 4th year pathology resident (BL) and a 6th year medical student (FH) who had been intensively trained by a dermatopathologist (VW). Resection margins were measured in mm. Mitotic activity was categorised as mild, moderate or severe by the number of mitoses per microscopic field (mild <5, moderate 5–10 and severe >10 mitoses per microscopic field). Viral features were scored as present or absent. The maximum thickness of the epidermis was measured in mm. Growth along hair follicle was documented as present or absent and the depth of this growth was measured in mm. Grade of atypia was based on the number of atypically formed epithelial cells, including large cells, atypically formed nuclei and large number of mitosis. This was classified as mild, moderate or severe.

Effect of surgical excision

The effect was rated as successful or failed. Complete clearance was defined as histologically tumour free resection margins. Therapy failed when resection margins were tumour positive.

We analysed the following potential determinants of incomplete excision: clinical resection margins, clinical characteristics (Table I), grade of atypia, grade of mitotic activity, thickness of the epidermis, expansion of the tumour along hair follicles, viral features and influence of different specialists performing the excision (dermatologist, plastic surgeons or GP).

Reduction of surgical margin

To investigate if a reduction of our standard clinical safety margin would be possible, the histological excision margin (the distance of the tumour to the resection border) was measured in the microscopic slides with a ruler. The theoretical implication of a reduction of the clinical safety margin by 1 mm or 2 mm was investigated by fictitiously reducing the histological resection margin of the excision specimen by either 1 or 2 mm. Because of known post excision tissue shrinkage of approximately 12%, we subtracted 0.88 mm on both sides to simulate a clinical safety margin reduction of 1 mm and 1.76 mm to simulate a 2 mm margin reduction (17).

Statistical analyses

Distributions of patient characteristics, clinical tumour aspects and histopathological data were described as means with standard deviations or as proportions and absolute numbers. Univariate and multivariate analysis were performed to identify determinants of incomplete surgical excision in BD. Odds ratios with corresponding 95% confidence intervals and *p*-values are presented. Furthermore percentages of incomplete excision after hypothetically reducing the surgical safety margin are shown. All data analyses were performed with SPSS (Statistical Package for Social Sciences) version 18.0 (SPSS, Chicago, IL, USA).

RESULTS

In the study period from January 1st 2002 until December 31st 2007, a total of 218 patients with 248 tumours were identified in the pathology database. Of these tumours 36 BDs were excluded: 18 patients had genital BD; in 2 patients with BD, the tumour had already been unsuccessful treated before the first visit to the outpatient clinic and 16 BDs were found within or at the margins of an invasive skin malignancy. In total 212 BDs in 185 patients were

Table I. *Clinical and tumour characteristics*

Characteristics	Study population ($n=212$)	Excision and re-excision group ($n=96$)
Age, years, mean (SD)	70 (11.2)	70 (12.0)
Range	40–93	40–92
Gender, *n* (%)		
Male	90 (42.5)	42 (43.8)
Female	122 (57.5)	54 (56.2)
Immunosuppressive medication, *n* (%)		
Yes	29 (13.7)	15 (15.6)
No	183 (86.3)	81 (84.4)
Tumour diameter, mm, mean (SD)	10 (10.2)	13.9 (9.5)
<10 mm, *n* (%)	51 (24.0)	20 (20.8)
≥ 10 mm, *n* (%)	114 (53.8)	45 (46.9)
Unknown diameter, *n* (%)	47 (22.2)	31 (32.3)
Location of Bowen's disease, *n* (%)		
Upper extremity	44 (20.8)	22 (22.9)
Lower extremity	63 (29.7)	27 (28.1)
Trunk	44 (20.8)	19 (19.8)
Ears	10 (4.7)	4 (4.2)
Other head/neck	51 (24.1)	24 (25.0)

included in this study. Twenty-one patients (11.5%) had more than one BD during the study period. Patient and tumour characteristics are shown in Table I.

Treatment modality

Surgical excision, PDT, 5-fluorouracil cream, imiquimod 5% cream, radiotherapy and laser therapy were the treatments used for BD. The most common treatment in the study population was PDT ($n = 98$, 46.2%), followed by surgical excision ($n = 86$, 40.6%), 5-fluorouracil cream ($n = 11$, 5.2%) and cryotherapy ($n = 3$, 1.4%). In the remaining 14 cases (6.6%) another treatment modality was performed or treatment was either not applied or not registered. In case of therapy failure, a second treatment was registered. An excision was performed after failure of another therapy in 4.7% ($n = 10$) of cases. Surgical excision was mostly performed by dermatologists ($n = 68$, 71.0%), followed by general practitioners ($n = 11$, 11.5%) and plastic surgeons ($n = 12$, 12.5%). The remaining patients ($n = 5$, 5.2%) were operated on by a general surgeon or the operator was unknown.

Effect of surgical excision

In 79 (82.3%) of 96 excised BDs the lesion was completely excised. Patient and tumour characteristics of this subpopulation are shown in Table I. After incomplete excision, patients were treated with re-excision ($n = 15$) or 5-fluorouracil cream ($n = 2$). The mean follow-up of our patients was 35 months (range 0–99, median 34 months). In this period 2 recurrent BD were found.

Determinants of incomplete excision

Univariate and multivariate regression analyses of possible determinants of incomplete excision, namely safety margin, clinical and histological characteristics and operating specialist are shown in Table II. Due to low incidence of viral features ($n = 2/88$), univariate analysis could not be calculated.

In univariate analyse, significantly more incomplete excisions were found when plastic surgeons (OR 12.4) or other specialists (OR 5.2) operated compared to dermatologists. Success rates of different operating specialists can be found in Table III.

In the study population 71 BDs were excised with a known clinical safety margin. In the other 25 cases the margin was not registered in the patient files. In this group of unknown margins the therapy failure rate is significantly higher (48%) than in the group of patients with known margins (7.0%) in univariate and multivariate analysis. These excisions with unknown margins were mainly done by physicians other than dermatologists, 40% were general practitioners and 40% were plastic surgeons.

Table II. *Univariate and multivariate analyses of determinants of incomplete excision*

		Univariate analysis			Multivariate analysis		
Determinant	*n*	OR*	95% CI	*p*-value	OR*	95% CI	*p*-value
Age, years	96	1.0	0.9–1.0	0.644			
Gender (male or female)	96	2.1	0.7–6.1	0.173			
Immunosupression (absent or present)	96	2.9	0.8–9.9	0.094			
Tumour diameter (mm)	65	1.0	0.9–1.1	0.808			
Localization							
Upper extremity	22	1					
Lower extremity	27	1.1	0.3–4.5	0.876			
Trunk	19	0.7	0.2–2.8	0.575			
Ears	4	0.2	0.0–2.0	0.174			
Other head/neck	24	3.8	0.4–34.1	0.233			
Grade of atypia							
Mild	21	1					
Moderate	49	3.9	0.5–33.4	0.214			
Severe	18	2.5	0.2–30.1	0.471			
Mitotic activity							
Low	29	1					
Moderate	30	1.4	0.3–6.8	0.688			
High	29	1.3	0.3–6.5	0.723			
Thickness epidermis (mm)	88	0.3	0.0–2.3	0.243			
Expansion along hair follicle (absent or present)	88	1.0	0.3–3.8	1.000			
Resection margin							
5 mm	54	1			1		
< 5 mm	17	2.3	0.3–14.8	0.393	2.2	0.3–14.7	0.402
Unknown	25	15.7	3.8–63.9	**0.000**	12.8	1.4–113.8	**0.022**
Surgeons							
Dermatologist	68	1			1		
Plastic surgeon	11	12.4	2.9–53.0	**0.001**	1.8	0.2–18	0.593
General practitioner	12	5.2	0.4–65.7	0.206	1.1	0–27	0.938
Other	5	5.2	1.2–22.3	**0.028**	0.8	0.1–7.6	0.854

*Odds ratios (OR) > 1 indicate increased risk of incomplete excision.

Table III. *Success rate of surgical excision in different operators*

	Complete excision *n* (%)	Incomplete excision *n* (%)	Total *n* (%)
Dermatologist	62 (91.2)	6 (8.8)	68
Plastic surgeon	5 (45.5)	6 (54.5)	11
General practitioner	8 (66.7)	4 (33.3)	12
Other	4 (80.0)	1 (20.0)	5
Total	79 (82.3)	17 (17.7)	96

A clinical safety margin of 5 mm was used in 54 BDs. A smaller margin, usually 3 mm, was taken in 17 tumours. There were different and not always clearly documented reasons to opt for a smaller margin, including sharp demarcation of the tumour. The 5 and <5 mm safety margin groups were compared with regard to complete excision rates. In the 5 mm cohort ($n=54$) 51 lesions (94.4%) were excised completely. In the cohort with a <5 mm margin ($n=17$) 15 of the tumours (88.2%) were completely excised.

Reduction of safety margins

The theoretical implication of reducing the clinical safety margin was evaluated. The number of complete excisions in lesions excised with a 5 mm margin is 51 out of 54. If the safety margin had been 4 mm, the histological margin would have been 0.88 mm less on both sides in the specimen and 47 out of 54 excisions (87.0%) would have been complete. If the safety margin had been 3 mm, the histological margin would have been 1.76 mm less on both sides of the specimen. 40 out of 54 (74.1%) excisions would have been complete.

In the group of BD with a known clinical safety margin of 5 mm, 7 patients use immunosuppressive medication. The complete excision rate was 100%. When we theoretically reduced this safety margin to 3 mm, the success rate would have decreased to 42.9%.

DISCUSSION

Of all 96 excised BDs with a variation in safety margins, 17.7% were incompletely excised. The success rates were 94.4% in the 5 mm clinical margin group, 88.2% in the <5 mm margin group and 52% in the unknown margin group. We found that a theoretical safety margin reduction from 5 mm to 4 or 3 mm potentially reduces the complete excision rate from 94.4% to 87.0% and 74.1%, respectively. After incomplete excision, a re-excision or additional non-invasive treatment is necessary. Although a re-excision is often easily performed technically, it is time consuming and it leads to higher costs and the extra burden of risks.

Currently, surgical margins for excision of BD vary from minimal margin to 4–6 mm based on expert opinion (15, 16). In the Netherlands low risk SCCs are usually excised with a 5 mm margin. This margin is also used for BD at the dermatology department in our hospital (5). As BD is a premalignant disorder with no invasive growth, it was hypothesised that minimising the surgical margin is safe and may be desirable for aesthetic reasons.

In our study 2.1% ($n=2$) of all excised BDs recurred during a mean follow-up of 35 months. To our knowledge, clearance rates of surgical excision for BD are not documented in literature. Recurrence rates of 4.5–19% are reported (5). Clinical characteristics of BD in our study population were comparable to the literature (5).

Clinical clearance rates were higher in excisions performed by dermatologists, compared to GPs and other specialists in secondary care. This confirms the results of Goulding et al. (18) reporting significant differences between complete excision rates in nonmelanoma skin cancer between dermatologists versus plastic surgeons and GPs.

In the group of patients with unknown margins there is more therapy failure (48%) than in the group of patients with identified margins (7% failure). This may be explained by the fact that most lesions with unknown margins were excised by physicians other than dermatologists, 40% being GPs and 40% plastic surgeons. Less experience with diagnosis and treatment of BD could have led to smaller resection margins. In most tumours excised by other specialists, the diagnosis was not made by a punch biopsy ($n=22$, 78.6%) prior to the excision. Dermatologists operated without prior punch biopsy in 10 cases (14.7%). Some of these lesions might have been treated without suspecting BD. Furthermore, tumour borders may not have been identified correctly by other specialists, due to less experience with this disease and perhaps with less awareness of recommended excision margins. Preferably, excision of skin tumours is performed by dermatologists. However, with the growing incidence of non-melanoma skin cancer, it is likely that in the future a growing number of lesions will be diagnosed and excised by other physicians. Intensive training on recognition and treatment of skin malignancies is therefore indispensable. The dermatologist must continue to have a leading role in diagnosis and (surgical) treatment of non-melanoma skin cancer, as advised by Goulding et al. (18).

Interestingly, when theoretically reducing the safety margin, the frequency of failure is higher in patients who take immunosuppressive medication compared to immune competent patients. It is well known that immunocompromised patients are more predisposed to skin cancer, which is often more aggressive and multifocal in nature and has a higher risk of recurrence and metastasis (8, 16, 19, 20). Drake & Walling (10) showed that immunosuppressed patients are also at risk for BD, they are more likely to have multiple lesions and their behaviour is more aggressive. Compared to immune competent patients, Smith et al. (21) found a

greater amount of BD occurring together with invasive SCC in organ transplant recipients. The aggressive growth pattern in this population may require a larger excision margin. In our study we found a success rate of 100% ($n = 7$) in this specific subgroup when using a 5 mm clinical margin. When treating BD in patients with immunosuppression, theoretically reducing the clinical safety margin to 3 mm potentially decreases the success rate to 42.9%.

A limitation of our study is the retrospective study design. Unfortunately tumour diameter and safety margin were not documented in all charts of different operators. Furthermore, tumour free margins to the border were measured in conventional histological slides. These slides are samples of the excision, when it was unclear if the excision was complete, extra slides were evaluated. A strong feature of our study is the re-examination of all histopathological slides by the same 2 investigators, excluding inter-observer variability.

This retrospective study of 96 BD treated with surgical excision showed an overall complete excision rate of 82.3% with various safety margins and a complete excision rate of 94.4% in the group of patients with a 5 mm clinical safety margin. Theoretically reducing the safety margin from 5 mm to 3 mm potentially decreases the complete excision rate from 94.4% to 74.1%. We recommend that a safety margin of 5 mm should be used in treating BD patients to reach a high complete excision rate. In delicate areas where tissue maintenance is important for cosmetic results and non-invasive treatment modalities are unsuitable, a smaller safety margin with a higher risk of incomplete excision or Mohs micrographic surgery should be considered. A prospective study is necessary to confirm these results and to evaluate the long-term effects of different excision margins for BD.

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