Outcome of Patients with Buruli Ulcer after Surgical Treatment with or without Antimycobacterial Treatment in Ghana

Mirjam Schunk,* William Thompson, Erasmus Klutse, Jörg Nitschke, Kwame Opare-Asamoah, Ruth Thompson, Erna Fleischmann, Vera Siegmund, Karl-Heinz Herbinger, Ohene Adjei, Bernhard Fleischer, Thomas Loscher, and Gisela Bretzel

Department of Infectious Diseases and Tropical Medicine (DITM), Ludwig-Maximilians University of Munich, Munich, Germany; Agogo Presbyterian Hospital, Agogo, Ghana; Dunkwa Governmental Hospital, Dunkwa-on-Offin, Ghana; Bernhard Nocht Institute for Tropical Medicine (BNITM), Hamburg, Germany; Kumasi Centre for Collaborative Research and Tropical Medicine (KCCR), Kwame Nkrumah University of Science and Technology Kumasi, Ghana

Abstract. This study assesses the frequency of recurrences and treatment outcome after surgery of buruli ulcer disease (BUD) with or without concomitant antimycobacterial treatment. Of 129 laboratory-confirmed BUD patients who underwent surgery in two treatment centers in Ghana, 79 (61%) were retrieved for follow-up 4–29 months after the initial treatment. Among 7 (9%) recurrent cases no significant association was found between recurrences and clinical or treatment specific factors including antimycobacterial treatment. In 21 (27%) patients, a reduced range of motion (ROM) of one or more joints was detected. Lesions other than nodules, joint involvement, and skin grafting were identified as independent risk factors. Functional limitations hampering daily activities were perceived by 22% of the patients. Compared with other studies the recurrence rate was relatively low, functional limitations were, however, frequent. This emphasizes the need for improvement of pre- and post-treatment wound care as well as rehabilitation programs.

INTRODUCTION

Mycobacterium ulcerans, the causative agent of buruli ulcer disease (BUD), has a wide geographical distribution in the tropical and subtropical belt, yet the clinical manifestation occurs in focal disease clusters. BUD is most common in humid, remote rural areas that are close to stagnant or slow moving bodies of water. Only in the last decade, with dramatically growing numbers of cases reported mainly from West African countries, BUD assumed importance as an emerging infectious disease. This prompted the establishment of the Global Buruli Ulcer Initiative by the World Health Organization (WHO) in 1998. Presently BUD is acknowledged to be the third most frequent mycobacterial disease in humans after tuberculosis and leprosy. The condition has been reported or suspected in > 30 countries worldwide. West Africa is the most affected region. In Ghana, a national case search was conducted in 1999, and cases of BUD were detected in all 10 regions of the country with a peak prevalence rate of 150.8 per 100,000 in the Amanfie West district. Children between 2 and 15 years of age are most affected, the lesions occur predominantly on the limbs. The mode of transmission is not certain, although transmission through aquatic insects has been suggested. After inoculation of M. ulcerans into the subcutaneous tissue the infection initially presents as painless papule, nodule, plaque, or—a rare—as an extensive edema. Later, ulcerative skin lesions develop. The ulcers progress slowly, they are usually painless and there are, besides bone involvement, no systemic signs of infection. Although mortality is very low, the frequency of long-term sequelae is high. Contractures and deformities causing restricted movements of affected limbs are often the result of uncontrolled self-healing processes or surgical treatment at a late, far progressed stage of disease.

Until recently wide surgical excision of BUD lesions was the only treatment option. Because there was evidence that a combined antibiotic treatment with rifampicin and streptomycin has the potential to inhibit growth of M. ulcerans WHO issued provisional guidelines recommending standard antimycobacterial therapy in 2004. Presently, prospective drug trials are being conducted comparing the efficacy of different dosages and durations of antimycobacterial treatment in different stages of BUD. According to the lesion category (category I, single lesion < 5 cm; category II, single lesion 5–15 cm; category III, single lesion > 15 cm and multiple lesions), different treatment schemes are applied (antibiotic treatment alone or in combination with surgery). To improve the quality of clinical management, the need for follow-up studies to monitor the treatment outcome has been emphasized.

The purpose of this study was to assess the frequency of recurrences after surgical treatment of BUD with or without concomitant antimycobacterial treatment in two treatment centers in highly endemic areas in Ghana and to record the treatment outcome with regard to functional limitations as late sequelae of BUD.

MATERIALS AND METHODS

Study area and treatment procedures. The follow-up was conducted in the catchment area of two treatment centers for BUD in Ghana. One center, the Agogo Presbyterian Hospital, is located in the Asante Akim North District in the Ashanti Region; the other, Dunkwa Governmental Hospital, is situated in Dunkwa-on-Offin, Upper Denkyira District in the Central Region. BUD is highly prevalent in both areas. In each treatment center one surgeon especially trained and experienced in surgical treatment of BUD performed the operations on all study subjects. For wound closure mesh skin grafting was considered the standard technique; in some cases, however, primary suturing was applied or the wound was left open for spontaneous healing. When surgery was carried out physiotherapy could not yet be offered; therefore, prevention of disability strategies were limited to providing adequate wound care and promoting early movement. Splints were not routinely applied.

*Address correspondence to Mirjam Schunk, Department of Infectious Diseases and Tropical Medicine (DITM), Ludwig-Maximilians University of Munich, 80802 Munich, Germany, E-mail: schunk@lrz.uni-muenchen.de
**Patients and inclusion criteria.** One hundred twenty-nine patients with a laboratory-confirmed BUD infection who received surgical treatment in the period from September 2003 to September 2005 in one of the two sites were included in the study. Laboratory confirmation was carried out by microscopy of Ziehl-Neelsen–stained smears, culture on Loewenstein-Jensen media, IS2404 polymerase chain reaction (PCR), or histopathological examination according to standardized procedures.

Data collection. Subject-specific epidemiological and clinical data was extracted from WHO “BU 01” BUD surveillance forms and hospital records, if available.

In total 16 field trips were conducted in February and March 2006: 11 in the area of Agogo and 5 in the Dunkwa area. We conducted participant interviews using a semi-structured questionnaire to collect information on the pre- and post-treatment history with special focus on possible recurrences and sequelae. For children, the guardian was interviewed.

To record the delay in seeking medical care, the time period from noticing a possible BUD lesion to presentation in a treatment center was documented. In addition, the site of the initial BUD lesion was examined and information on the size and the state of healing was recorded. For documentation, a photograph was taken. In case of joint involvement, the passive range of motion (ROM) was measured using a standard goniometer (E-Z Read Goniometer 30 cm; Rolyan Jamar, Russka, Germany). ROMs were recorded by two observers according to the Neutral-Zero Measuring Method and SFTR (sagittal, frontal, and transverse rotation) documentation. If any skin lesion was present, the site was clinically assessed according to WHO BUD case definition and documented. In case of an ulcer, swab specimens for laboratory confirmation (microscopy/culture/PCR) were collected. At the time of the study, assessment of punch biopsies or fine needle aspirates were not among the established methods for the routine diagnosis of BUD in Ghana; therefore, the collection of tissue specimens from non-ulcerative lesions was not possible in the field. All patients with new or not healed lesions were referred to the respective treatment center.

**Definition of recurrence.** In accordance to the definition of recurrences established by WHO in 2001, a recurrent case was defined as a patient with previous surgical treatment with or without concomitant antimycobacterial therapy for *M. ulcerans* who presented with a further BUD lesion at the same or a different site within 1 year after the end of the last treatment.

Lesions that were present at follow-up were judged as BUD recurrences if the clinical features matched the BUD case definitions and the diagnosis was confirmed with at least one positive laboratory test. Clinically diagnosed BUD lesions that developed after the initial surgical excision and were subjected to surgery before follow-up were counted as interim recurrences. All clinically diagnosed interim recurrences were included, even if laboratory confirmation was not performed.

The time period was calculated using the date of initial surgery (as documented in the BU 01 form) and the date of follow-up. For interim recurrences, information from the patients was correlated with the documentation in the corresponding treatment center.

It must be noted that following the WHO recommendation and implementation of antimycobacterial treatment, the definition of recurrence was revised by the WHO technical advisory group. Since 2007, only new and culture confirmed BUD lesions occurring > 3 months after completion of a full course of antibiotic treatment (possibly followed by surgery), which resulted in complete healing of the initial lesion, are considered recurrences. In contrast, lesions occurring within 3 months after completion of a full course of antibiotics in the same or adjacent area are regarded ongoing cases (i.e., non-healers). In both cases, a patient is considered to have completed treatment after 56 doses of antibiotics in 8 weeks.

Because treatment of our study subjects was primarily surgical, and none of the patients received a full course of the standardized antimycobacterial treatment according to the current WHO definitions, we consider the revised definition of recurrence not applicable.

**Treatment outcome.** Outcome was assessed by recording the frequency of a reduced ROM in one or more joints and the perceived functional limitations caused by BUD sequelae.

A reduced ROM was recorded when the ROM deviated from the international standardized normal range of motion. A functional limitation was recorded if the patient reported to have difficulties with daily activities because of sequelae of the BU infection.

**Statistical analysis.** For categorical data analysis, the χ² test and Fisher exact test were used, and for continuous variables, Student’s t tests were applied. In addition, we constructed multiple logistic regression models for detecting potential confounders among the analyzed variables. Records with missing data for a particular variable were excluded from analysis of that variable. Calculations were done by software package SAS version 9.1.19 χ² values < 0.05 were considered as statistically significant.

**Ethical clearance and informed patient consent.** Ethical clearance for the study was obtained through the Ethics Committee of Human Research Publication and Ethics, School of Medical Sciences, University of Science and Technology, Kumasi, Ghana. Informed consent was obtained from the participants or their guardians before beginning any study-related interventions.

**RESULTS**

**Followed up patients.** Of a total of 129 laboratory-confirmed BUD patients, 79 (61%) were retrieved for follow-up examination within a study period of 2 months. In the catchment area of Agogo, 56 (63%) of 89 patients could be followed up; in the catchment area of Dunkwa, 23 (58%) of 40 patients were retrieved. Of the 50 lost patients, 29 had a wrong address, 11 moved from the region, 3 died, and 7 could not be followed up for other reasons. The group lost to follow-up was comparable with the study participants in terms of sex, age, and year of initial treatment (data not shown).

Baseline characteristics of the followed-up patients are shown in Table 1. Of the 79 followed-up patients, 65 (82%) received antibiotic treatment in addition to surgery as recorded in BU 01 forms and/or hospital records. In 11 of these cases, no records could be retrieved on the type and duration of treatment; however, in the BU 01 form, it was stated that the respective patients were treated with antimycobacterial drugs. In 54 cases, hospital records with precise documentation were available: 13 patients were treated with rifampicin only, one was treated with streptomycin only, and 40 patients were treated with a combination of both. The mean duration of ther-
apy was 39.2 ± 32.4 (SD) days for streptomycin and 26.2 ± 21.4 days for rifampicin. In 70% (N = 38) of these patients, antymycobacterial treatment was started on the day of excision of the primary lesion, in 24% (N = 13) treatment was started before surgery (minimum, 3 days; maximum, 24 days), and in 6% (N = 3) of the cases, treatment was started after surgery (minimum, 2 days; maximum, 21 days). Concerning the use of drug treatment, there is less precise information of the patients in the Dunkwa region, with 43% (N = 10) missing entries in the BU 01 forms on this topic. Records with missing data were not included in the analysis. There was no significant difference between the two treatment centers.

The time interval between the first BUD treatment and the follow-up assessment ranged between 4 and 29 months (mean, 18 months; median, 20 months). In 25% (N = 20) of the patients, the time interval between the first BUD treatment and the follow-up assessment was <12 months, in 38% (N = 30) was 12–23 months, and in 37% (N = 29) was >23 months (range, 4–29 months).

**Characteristics of the recurrent cases.** Of the 79 patients available for follow-up, there were 11 possible recurrent cases (Table 2). According to the definitions of this study, seven (9%) patients with recurrences were detected.

During the physical examination at follow-up, five patients presented with skin lesions. In four cases, small excoriation with a maximum diameter of 2 cm were located in the scar area of the previous BUD lesion. None of these lesions showed the typical clinical features of a BUD lesion, and the reported duration of the lesions was in no case >4 weeks. The laboratory examinations (microscopy, culture, and PCR) were negative for *M. ulcerans*.

One patient stated at follow-up that the initial wound never fully closed after surgery 7 months earlier. On inspection, we found a 2 × 13-cm purulent wound without under-mined edges on the left flank. In the Ziehl-Neelsen–stained smear of the swab sample, acid-fast bacilli were detected; culture and IS2404 PCR were negative. Therefore, a superinfection with other mycobacteria, as well as the possibility of a persistent, slowly healing lesion with dead bacilli, can not be excluded. In this patient, no antymycobacterial treatment had been documented.

Six patients reported interim recurrences (i.e., they had developed a recurrent lesion that was clinically diagnosed as BUD and surgically removed in the period between excision of the primary lesion and follow-up). Two of these patients came from Dunkwa and four patients were from Agogo. The median time period of the occurrence of the new lesions after excision of the primary lesion was 3 months (range, 0.5–5 months). In four cases, the patients received antymycobacterial treatment in addition to surgery for at least 14 days starting on the date of excision; in two cases, there was no written documentation of drug treatment, yet the patients remembered receiving oral and intramuscularly medication for treatment. At the time of follow-up, the patients with interim recurrences had no acute medical complaints.

In the analysis of factors possibly influencing the probability of recurrence, no significant difference was found between recurrence and size or type of lesions, use of antymycobacterial treatment, duration of disease before treatment, and place of treatment.

In eight patients from the follow-up group, an assessment of the margins of the excised tissue was conducted after surgical resection of the primary lesion.20 In all of these specimens, *M. ulcerans* infection was detected even in the macroscopically unaffected tissue at the periphery. However, none of these patients showed a recurrence at follow-up. All had received antibiotic therapy started on the day of excision either as monotherapy with rifampicin (N = 5) or as combination therapy with rifampicin and streptomycin (N = 3) over at least 30 days.

**Treatment outcome.** Reduced ROM of one or more joints as a consequence of the BUD infection and treatment was detected in 21 (27%) patients. In nine of these (43%), a disability caused by the primary lesion was already documented before surgical excision. The wrist was most often affected (7.6%, N = 6), followed by the joints of the hand and the ankle (6.3%, N = 5), the elbow (3.8%, N = 5), and the knee (2.5%, N = 2). Clinical features and their association to reduced ROM are summarized in Table 3.

In 30 patients, the primary lesion was located over one or more joints, resulting in a reduced ROM of the involved joints in 60% (N = 18) of these patients. The association between these two variables is highly significant (P < 0.001).

### Table 1

Baseline characteristics of the follow-up samples

<table>
<thead>
<tr>
<th>Variables</th>
<th>Agogo (N = 56)</th>
<th>Dunkwa (N = 23)</th>
<th>Total (N = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female), N (%)</td>
<td>28 (50)</td>
<td>10 (43)</td>
<td>38 (48)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range (minimal-maximal)</td>
<td>2–72</td>
<td>3–43</td>
<td>2–72</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>17.1 (15.1)</td>
<td>18.3 (11.3)</td>
<td>17.5 (14.0)</td>
</tr>
<tr>
<td>Median</td>
<td>11</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Delay in seeking medical care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range (minimal-maximal)</td>
<td>7–180</td>
<td>7–120</td>
<td>7–180</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>41.8 (35.5)</td>
<td>46.2 (38.1)</td>
<td>43.0 (34.7)</td>
</tr>
<tr>
<td>Median</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Kind of medical care, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>2 (4)</td>
<td>10 (43)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Ambulant operation and post treatment</td>
<td>3 (5)</td>
<td>6 (26)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Treatment as in-patient</td>
<td>51 (91)</td>
<td>7 (30)</td>
<td>58 (73)</td>
</tr>
<tr>
<td>Type of lesion, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodule</td>
<td>8 (14)</td>
<td>4 (17)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Plaque</td>
<td>8 (14)</td>
<td>5 (22)</td>
<td>13 (16)</td>
</tr>
<tr>
<td>Ulcer</td>
<td>35 (63)</td>
<td>14 (61)</td>
<td>49 (62)</td>
</tr>
<tr>
<td>Edema</td>
<td>5 (9)</td>
<td>0 (0)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Localization of lesion, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extremity</td>
<td>30 (54)</td>
<td>10 (43)</td>
<td>40 (51)</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>16 (29)</td>
<td>9 (39)</td>
<td>25 (32)</td>
</tr>
<tr>
<td>Trunk</td>
<td>10 (18)</td>
<td>4 (17)</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Head/neck</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Size of lesion, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category I (&lt;5 cm maximal diameter)</td>
<td>30 (54)</td>
<td>11 (48)</td>
<td>41 (52)</td>
</tr>
<tr>
<td>Category II (5–15 cm maximal diameter)</td>
<td>18 (32)</td>
<td>8 (35)</td>
<td>26 (33)</td>
</tr>
<tr>
<td>Category III (&gt;15 cm maximal diameter)</td>
<td>8 (14)</td>
<td>4 (17)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Wound closure technique, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suturing</td>
<td>5 (9)</td>
<td>7 (30)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Skin grafting</td>
<td>48 (86)</td>
<td>3 (13)</td>
<td>51 (65)</td>
</tr>
<tr>
<td>Spontaneous healing</td>
<td>3 (5)</td>
<td>13 (57)</td>
<td>16 (20)</td>
</tr>
<tr>
<td>Antimycobacterial therapy, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>3 (5)</td>
<td>10 (43)</td>
<td>13 (16)</td>
</tr>
<tr>
<td>No</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Yes</td>
<td>52 (93)</td>
<td>13 (57)</td>
<td>65 (82)</td>
</tr>
<tr>
<td>With rifampicin*</td>
<td>13</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>With streptomycin*</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>With combination streptomycin/rifampicin*</td>
<td>38</td>
<td>2</td>
<td>40</td>
</tr>
</tbody>
</table>

*P documented in hospital record and/or BU 01 forms (N = 54).
In the factor analysis, no correlation between size of the primary BUD lesion and a reduced ROM was found ($P = 0.064$). There was, however, a significant association between the type of primary BUD lesion and the occurrence of a reduced ROM ($P = 0.025$). In contrast to other types of lesions, nodules did not result in a reduced ROM.

There was also a significant association ($P < 0.01$) between the wound closure technique and the risk of a reduced ROM. From the 28 patients who received suturing after surgical intervention or where the lesion was left to heal spontaneously, 2 (7%) presented with a reduced ROM. Of the 51 patients where skin grafting was used, 19 (37%) showed a reduced ROM at follow-up.

From 21 patients at increased risk of a reduced range of motion (lesion other than nodule, joint involvement, skin graft for wound closure), 76% ($N = 16$) presented a reduced ROM at follow-up. Multiple logistic regression models including the four above-mentioned independent variables have shown that the size of the lesion ($P = 0.71$) and the type of lesion ($P = 0.93$) were not significantly associated with the dependent variable reduced ROM. On the other hand, the involvement of joints ($P < 0.001$) and the methods of wound closure ($P = 0.011$) were significantly associated with the dependent variable. Multiple logistic regression detected that the association between the dependent variable and the size of lesion was confounded by involvement of joints. These two independent variables were highly associated ($P = 0.010$), because larger lesions were significantly more often situated over joints and vice versa. Other confounding was not found.

A BUD-related functional limitation in daily activities was perceived by 22% ($N = 17$) of the patients or their guardians. Of the 21 patients with a reduced ROM, 52% ($N = 11$) stated that they had difficulties in their daily tasks. Another six patients indicated functional restrictions, although objectively reduced ROM could not be measured.

**DISCUSSION**

Because there is no causative prevention of BUD, early case detection and optimization of treatment and rehabilitation are the major objectives to reduce morbidity and disability. Data on the long-term outcome after treatment are essential to evaluate treatment strategies and to adapt them according to needs identified. Despite being identified as a major public health concern in endemic areas, implementing routine aftercare and follow-up is still a major problem because people affected with BUD live mostly in remote and poorly accessible rural areas.

The recurrence rate of 9% as detected in our study is relatively low compared with the results of most other published studies where recurrence rates vary from 2% to 35%. However, because of variation in study design, sample sizes, follow-up periods, and diagnostic tools applied for confirmation of cases, the comparability of these studies is limited. In one study from Benin reporting a similar low recurrence rate of 6% ($N = 4$), in total 15% ($N = 10$) of the followed-up patients including two of the recurrent cases had received antimycobacterial treatment with rifampicin and streptomycin for up to 14 days in addition to surgical treatment. A study conducted in Ghana detected a recurrence rate of 35% ($N = 27$) among patients treated between 1994 and 2001 in the same two treatment centers as in our study. Fifty-eight percent of the patients
discrepancy between our and previously reported results may be explained by ongoing training efforts and the implementation of standardized surgical management in both treatment centers.

Another important factor contributing to the low overall recurrence rate and the diminishing difference between the two treatment centers might be the increasing use of antimycobacterial treatment supplementary to surgery. Recent data suggest that antibiotic treatment decreases recurrence rates to 1–4% 13,17,18,21. Even before the WHO recommendations on antimycobacterial treatment were released, 26 both of our treatment centers introduced the use of a combination of streptomycin and rifampicin in their treatment of BUD. In total, 29% of the patient cohort treated between 1994 and 2001 in Agogo and Dunkwa received antimycobacterial drugs consisting of monotherapy with rifampicin. In contrast, 82% of patients retrieved in our follow-up study were treated with antimycobacterial drugs. Although the analysis of the available records showed that the treatment scheme has not yet been standardized, the majority of patients in both centers received a combination of rifampicin and streptomycin for a variable period of time.

The use of antimycobacterial treatment could also explain why there were no recurrences observed in the eight cases where M. ulcerans infection was detected in the macroscopically unaffected tissue of the outer margin of the excised lesions.20 However, in our study, four of the seven patients that experienced recurrences had also received antimycobacterial treatment. However, considering the lack of precise data on the actual adherence to the prescribed medication and the variable duration of therapy, a positive effect of antimycobacterial treatment on treatment outcome can not be excluded.

Because no single factor proved to have an essential influence on the occurrence of recurrent cases in the presented study, the overall reduced incidence of recurrences in this area is attributed to the multifactorial quality improvement of clinical management of BUD in the field of surgical as well as antimycobacterial treatment.

Although the low incidence of recurrences is promising, adverse sequelae (measurable ROM and/or functional limitations that hampered the daily activities of the patients) were frequent. The measurement of a reduced ROM of joints can be difficult in the field, and there are no validated normal ranges of motion adjusted to African populations. However, it is a useful tool to assess and document treatment outcomes.27 In our study, 9 of 21 patients with reduced ROM at follow-up had presented with reduced ROM before the beginning of treatment. No reduced ROM was observed in cases with nodules as primary lesions, emphasizing the importance of early detection and treatment. Whereas lesion over joint and lesion other than nodule and skin grafting for wound closure were identified as risk factors for a reduced ROM, there was no statistically significant association between occurrence of functional limitations and the size of lesion. This is a surprising result because it is obvious that large, far progressed lesions with soft tissue and bone involvement are prone to cause ankylosis and require extensive surgery, leading to significant scarring. A possible explanation for this finding is that the absolute lesion size was not related to actual body surface area. Because most patients are children, the assumed size categories do not apply equally in all patients. Also, the multiple logistic regression

### Table 3

<table>
<thead>
<tr>
<th>Type and size of lesion*</th>
<th>Reduced ROM (N = 21)</th>
<th>ROM not reduced (N = 58) total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suturing</td>
<td>Skin graft</td>
</tr>
<tr>
<td>Nodule, N = 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint involvement:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>By size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category I</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Category II</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Category III</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ulcer, N = 49</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Joint involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>By size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category I</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Category II</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Category III</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Edema, N = 5</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Joint involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>By size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category I</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Category II</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Category III</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Plaque, N = 13</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Joint involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>By size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category I</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Category II</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Category III</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>19</td>
</tr>
</tbody>
</table>

*All lesions were single lesions.
analysis indicated that the size of lesion was confounded by involvement of joints as larger lesions were significantly more often situated over joints.

Although disfigurement and joint deformities as late sequelae of treated BUD patients are described as a common outcome, there is sparse information on its actual incidence and its social and economic impact. It has been emphasized that besides the high direct and indirect treatment costs, the impact of long-term care for disabled and handicapped BUD patients places an enormous burden on the family members. The frequency of functional impairment after BUD treatment varies from 49% as observed in Ghana, 37% as reported from the Democratic Republic of Congo, to 25% as assumed by WHO. The detection of a reduced ROM in a joint, however, does not necessarily correspond to the perceived individual functional impairment. In our study, 52% (N = 11) of the patients where a reduced ROM had been recorded stated that they had difficulties fulfilling daily tasks, whereas six patients without objectively reduced ROM indicated functional impairments. A BUD functional limitation score questionnaire (BULFS) was recently developed to assess the severity of functional limitations. After treatment of BUD, 57% (N = 362) of the interviewed patients experienced one or more functional limitations according to the BULFS score. In our study only 22% (N = 17) of the patients indicated a functional impairment in daily activities. However, we did not apply the BULFS score, which may have resulted in a higher proportion of functional impairments.

The relatively high incidence of functional limitations as sequelae after BUD observed in our study sample emphasizes the need to re-evaluate the impact of different wound closure techniques on the long-term outcome and the importance of providing rehabilitative care after primary wound treatment. A main concern of follow-up activities should therefore be the establishment of programs for the prevention of disability (POD) on community level. As advised by WHO, POD activities should have a high priority in national BUD control programs.

This study had several limitations, and some conclusions should be interpreted with caution. Epidemiologic and clinical baseline data were retrieved retrospectively from BU 01 forms and hospital records. This retrospective nature of data collection is prone to errors such as potential interobserver variability and assessment bias. In addition, written information on the baseline data were retrieved retrospectively from BU 01 forms. The diagnosis of recurrence in our study patients was always established by clinicians with long-standing experience in BUD. However, we concede that in view of the revised WHO definition, the recurrent cases identified in this study may not fully meet the criteria and may rather be referred to as clinically suspect recurrences.

Received October 30, 2008. Accepted for publication April 15, 2009.

Authors’ addresses: Mirjam Schunk, Erna Fleischmann, Vera Siegmund, Karl-Heinz Herbinger, Thomas Loscher, and Gisela Brezel, Department of Infectious Diseases and Tropical Medicine (DITM), Ludwig-Maximilians University of Munich, Leopoldstrasse 5, 80802 Munich, Germany. William Thompson, Agogo Presbyterian Hospital, Agogo, Ghana. Erasmus Klutse, Dunkwa Governmental Hospital, Dunkwa-on-Offin, Ghana. Jörg Nitschke and Bernhard Flesicher, Bernhard Nocht Institute for Tropical Medicine (BNITM), Bernhard-Nocht Strasse 74, 20359 Hamburg, Germany, Kwame Opare-Asamoah, Ruth Thompson, and Ohene Adjei, Kumasi Center for Collaborative Research in Tropical Medicine (KCCR), Kwame Nkrumah University of Science and Technology (KNUST), University Post Office, Kumasi, Ghana.

REFERENCES


