

CLINICAL REPORT

Predictors of Pain Associated with Photodynamic Therapy: A Retrospective Study of 658 Treatments

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Pain is the most common side-effect of photodynamic therapy (PDT). Our main objective was to identify pain predictors in PDT. In total, we performed 658 treatments on 377 patients at our department during 2004. Larger sized treatment areas were the strongest pain predictor, and actinic keratoses were more painful to treat than basal cell carcinomas and Bowen's disease. The most sensitive areas to treat were the face and scalp. Gender and age did not influence pain. Although treatment outcome was not our primary objective, 62% of 95 superficial basal cell carcinomas that were followed for 3 years showed complete clearance. Also, perforation of nodular basal cell carcinomas did not lead to better clinical results. In conclusion, the size of the treatment area, the diagnosis and the lesion location influence pain during PDT. Nevertheless, there is a large variance in visual analogue scale assessment within each group, thereby limiting the ability to predict pain. Key words: actinic keratoses; basal cell carcinoma; field cancerization; pain; photodynamic therapy.

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Since the early 1990s, photodynamic therapy (PDT) has been performed at the Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden, mainly as a treatment for patients with non-melanoma skin cancers, such as basal cell carcinoma (BCC), Bowen's disease (BD) and actinic keratoses (AKs). One of the advantages of PDT is the possibility to treat field cancerization, defined as extensive areas of sun-damaged skin with multiple AKs (1, 2). PDT is also appropriate for treating lesions on poorly healing areas, such as the lower extremities (3). Furthermore, PDT offers excellent cosmetic results (4).

The major side-effect of PDT is pain during treatment (5). The pain is an uncommon type, in which the patient feels a stinging and burning sensation. In general, the pain is most intense at the beginning of the irradiation phase. After a few minutes, the pain reaches its peak and, thereafter, gradually decreases (6). The pain mechanism

during the irradiation phase is not known. Different hypotheses have been presented as possible causes of the pain, such as local hyperthermia, influences of cytotoxic oxygen and inflammation (7, 8). One limitation of PDT is the difficulty of treating thicker lesions.

Our goal is to obtain a deeper understanding of the pain experienced by patients during PDT, in order to better predict the pain and to try to achieve efficacious pain-relieving strategies.

The main objective of this study was to identify predictors of pain during PDT.

MATERIALS AND METHODS

The study was conducted at the Department of Dermatology at Sahlgrenska University Hospital, Gothenburg, Sweden. All 377 patients (197 men and 180 women) treated at our PDT unit during 2004 were included in the study.

The mean age of the men and women was 72 years (range 18–93) and 71 years (range 32–92), respectively. In total, 658 PDT sessions were carried out on 1,155 treatment fields. Patients' demographics, lesion location, size of the treated area, the diagnoses treated, the patients' assessment of pain and the clearance rates were investigated. The study was designed as a descriptive, retrospective study and the electronic patient records were used to assess the clinical data. The study was performed according to the Helsinki ethical principles for medical research.

Pain evaluation

To assess the maximal pain during PDT, the patients used a visual analogue scale (VAS) or the patient was asked verbally to grade the pain experience on a scale from 0 (no pain) to 10 (unbearable pain). Pain assessment generally took place directly after irradiation was completed. The VAS ruler had a 10-cm long line on the side facing the patient, labelled "no pain" and "unbearable pain" at the ends, with a numerical scale ranging from 0 to 10 on the reverse side. No pain or low pain was defined as VAS scores of 0–3, moderate pain as scores of 4–6 and severe pain as scores of 7–10.

The use of a verbal rating on a numerical scale was most commonly used in clinical praxis in 2004. The retrospective nature of the study did not allow for a standardized method of pain assessment for all patients. VAS scores were provided for each PDT session either from a single treatment field (the area covered by a single PDT lamp) or from a group of treatment fields defined as a treatment area (Fig. S1; available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1101>). In 58% of the VAS-assessed patients more than one treatment area was treated under the same PDT session. Each separate VAS score was included in the analysis. When severe pain was expected or present during PDT, pain relief was applied as infiltration, spinal or general anaesthesia.

Data from 120 out of 889 treatment areas was excluded from further analysis, since no VAS scores were available or the patient felt no pain due to anaesthesia.

On the other hand, VAS scores from 58 out of 125 anaesthetized treatment areas were included in the analysis since pain relief was incomplete (VAS scores >0).

Pain-relieving methods

The standard routine during PDT in 2004 was to give the patients appropriate information regarding pain before PDT, to have a continuous conversation during the illumination phase in order to distract the patient, and to combine this with the use of cold water spray and pauses if requested by the patient (9).

If anaesthesia was required, the lesion was anaesthetized by local infiltration. The lesions were anaesthetized prior or during PDT with (Xylocain® 10 mg/ml + adrenalin 5 µg/ml; AstraZeneca AB, Södertälje, Sweden).

Nerve blocks and/or spinal anaesthesia was applied when PDT was performed in the genital area. In exceptional cases, when the pain was expected to be unbearable, the treatment was performed under general anaesthesia.

Diagnosis

A total of 229 patients with AKs, 128 patients with BCCs and 35 with BD were included in this retrospective study. Some patients had a combination of diagnoses. Twenty patients were treated with PDT due to other diagnoses (e.g. Paget's disease and lichen sclerosus).

Lesion location

The patients' lesions were classified as belonging to one of four separate body areas depending on where they were located. These four body areas were: face and/or scalp, the trunk, the upper extremities and the lower extremities. The most frequently treated location was the face and scalp (44%), followed by the trunk (26%), the lower extremities (21%) and the upper extremities (9%).

Size of the treatment field

In this study, irradiation was performed using Aktelite® CL 128 and/or CL 16 lamps (PhotoCure ASA). Aktelite® CL 128 lamps have a maximal illumination area of 8×18 cm (large lamp) and the Aktelite® CL 16 can irradiate an area of 4×5 cm (small lamp). When larger areas were treated, several Aktelite® lamps were used simultaneously.

Lesion preparation

The treatment field or area was prepared according to our hospital routines. A very light curettage causing no bleeding was performed on the lesions before methylaminolaevulinate (MAL) cream 160 mg/g (Metvix®, PhotoCure ASA, Oslo, Norway) was applied on the treatment area. Occlusive dressings (Tegaderm™, 3M Health Care Neuss, Germany and Mefix®, Mölnlycke Health Care AB, Göteborg, Sweden) were used to cover the treatment area. After 3 h, the cream was gently wiped off. When patients with field cancerization were treated, MAL cream was applied to the entire treatment area(s). A very light curettage was performed on the superficial BCCs and BD lesions in order to achieve a good cosmetic result and to avoid hypopigmented scars.

In 20 thick nodular BCCs, perforation was tested in clinical practice prior to PDT theoretically in order to increase penetration of the photosensitizer prodrug in these lesions.

Eleven other nodular BCCs were included, but these were more extensively curettaged prior to PDT instead. The lesions were anaesthetized prior to the extensive curettage.

If the lesions were still anaesthetized when the irradiation was performed 3 h later, the VAS scores were excluded from the pain assessment analysis.

PDT irradiation

Irradiation was performed using visible red light from light-emitting diodes (LEDs) (Aktelite® CL 128 and/or CL 16 lamps, PhotoCure ASA) with a mean wavelength of 635 nm. The fluence rate was 80–90 mW/cm² and irradiation occurred during 7–10 min, resulting in a total light dose of 37–45 J/cm². The standard hospital routine for the treatment of BCC and BD was used. This involved two PDT sessions with an interval of 1–2 weeks between sessions. However, 32 patients with these diagnoses were treated only once, probably due to the small size and/or the mild clinical appearance of the lesions. Patients with AKs were treated 1–2 times depending on the grade of the AKs. Treatment for patients with other diagnoses was individualized.

Follow-up

In general, the follow-up time varied between 3 months and 3 years, depending on the patients' diagnoses. Patients with AKs had individualized follow-up visits. Some patients had no scheduled follow-up visits, but were advised to perform self-examination of their skin and contact the clinic if a suspicious skin lesion developed.

Statistical analysis

All data were analysed using R version 2.10.1 (The R Foundation for Statistical Computing, Vienna, Austria).

A mixed-effects logistic regression model with a random intercept for each patient was used. A dichotomous pain response was defined by dividing the VAS at the median (VAS ≤5 vs. >5). The size of the irradiation field (small vs. large irradiation field), the diagnosis (BCC vs. AK) and the lesion location (face and/or scalp vs. trunk or extremities) were used as fixed effects. The unit of analysis was the treatment area.

The follow-up visits of patients treated for BCCs were analysed using survival analysis for interval-censored data. The "lifetime" is defined as the time in which the tumour/operated area is healed and not recurrent. The non-parametric maximum likelihood estimate of the survival function, as defined by Peto (10) and Turnbull (11), was calculated. An exact (permutation form) log-rank test was carried out to compare survival rates for nodular and superficial BCCs.

The exact permutation form of Wilcoxon-Mann-Whitney's test was used for pair-wise comparisons of VAS scores between groups. Bonferroni correction was used to adjust the significance level for multiple pair-wise comparisons. Error limits reported represent standard error of the mean (SEM). Statistical significance was taken as $p < 0.05$.

RESULTS

An overview of the patients' demographics, their diagnoses, and the size and location of their treatment areas is shown in Table I.

Diagnoses

The most common lesions treated during the study period were AKs ($n = 229$ patients). The mean VAS score for AKs was 6.1 ± 0.14 , compared with 4.6 ± 0.15

Table I. Overview of the patients' demographics, their diagnoses, and the size and location of the lesions

Characteristic	n (%)	Age (years)
		Mean \pm SEM
Sex		
Male	197 (52.3)	72.4 \pm 0.95
Female	180 (47.7)	70.6 \pm 1.07
Total	377	71.6 \pm 0.71
Size of irradiation field		
Large	227 (60.2)	
Small	63 (16.7)	
Large+Small	87 (23.1)	
Diagnosis ^a		
Basal cell carcinoma	128 (34.0)	
Actinic keratosis	229 (60.7)	
Bowen's disease	35 (9.3)	
Other	20 (5.3)	
Location ^a		
Face and/or scalp	243 (64.5)	
Trunk	92 (24.4)	
Upper extremities	42 (11.1)	
Lower extremities	79 (21.0)	

^aSome patients had several different treatments/diagnoses/locations, which explains any overlap in the *n* values.

SEM: standard error of the mean.

for patients with BCCs ($n = 128$) ($p < 10^{-11}$). AKs were also significantly more painful than BCCs for patients with lesions on the face and/or scalp independently whether a small irradiation field ($p < 0.0003$) or a larger irradiation field ($p < 0.0002$) was treated. For BD ($n = 35$), the mean VAS score was 5.0 ± 0.34 , which was also significantly lower than the scores obtained when treating AKs ($p = 0.004$).

Lesion location

The location of the lesions was the weakest predictor of pain. Nevertheless, PDT carried out on the face and/or scalp was more painful than on the rest of the body ($p < 0.05$). PDT of AKs on large areas of the scalp and/or forehead was particularly painful, with a mean VAS score of 6.7 ± 0.17 . On the trunk, in general, PDT was well tolerated. An exception to this was treatment in the genital area in both sexes; an area which was more sensitive to pain. Due to our previous clinical

experience with severe pain perception during PDT in the genital area, most patients treated in this area were anaesthetized prior to PDT with nerve blocks or spinal anaesthesia. The patients' VAS assessments for the four different body areas are shown in Table II.

Size of the treatment area

During PDT of larger areas, 2–4 lamps were used simultaneously. The size of the treatment area proved to be crucial regarding the pain experience. This parameter is a good predictor of pain and had the strongest statistical significance ($p < 0.0001$) when compared with the diagnoses and the lesion location, as shown in Table III.

Comparison between groups

Pair-wise comparisons between groups were performed. The patient data was divided into eight groups using two body area groups (face and/or scalp, trunk/extremities), two diagnoses (AK, BCC) and two sizes of irradiation fields, as seen in Fig. 1. and Table IV.

The treatment of large irradiation fields was significantly more painful for AKs ($p < 0.0002$) and BCCs ($p < 0.0004$) on the face and/or scalp, when compared with the smaller irradiation fields. The large irradiation fields were also found to be more painful for BCCs on the trunk or extremities ($p < 0.005$), when compared with the smaller irradiation fields. When comparing lesion location, AKs treated on large irradiation fields were found to be significantly more painful on the face and/or scalp than on the trunk or extremities ($p < 0.0002$).

Gender and age

The mean VAS scores were 5.7 ± 0.20 for men and 5.2 ± 0.18 for women. No significant differences were seen. Men over the age of 70 years with AKs on the face and/or scalp scored the pain higher than did younger men. However, this trend was not considered relevant, since elderly men were often treated for extensive AKs (field cancerization), whereas younger men received PDT on smaller treatment areas.

Table II. Pain evaluation in relation to body area treated. A: Number of treatment fields (percentage of all 1,155 treatment fields); B: Mean visual analogue scale (VAS) scores of assessed treatment areas (standard error of the mean; SEM); C: Number of VAS assessed treatment areas with severe pain (percentage of areas in the corresponding body area); D: Number of VAS-assessed treatment sessions in which photodynamic therapy was disrupted due to severe pain (percentage of sessions in the corresponding body area)

Body area	A	B	C	D
	Treatment fields <i>n</i> (%)	VAS scores mean \pm SEM	Severe pain VAS 7–10 <i>n</i> (%)	Disrupted treatments <i>n</i> (%)
Face and/or scalp	506 (44)	5.8 \pm 0.14	152 (38)	18 (4)
Trunk	305 (26)	5.2 \pm 0.19	48 (27)	1 (0)
Upper extremities	101 (9)	5.6 \pm 0.36	17 (32)	0 (0)
Lower extremities	243 (21)	4.8 \pm 0.21	40 (28)	0 (0)
Total	1,155	5.4 \pm 0.09	257 (33)	19 (2)

Table III. Mixed effects logistic regression

Predictor	Coefficient estimate (logistic regression)	Coefficient Standard error	p-value (logistic regression)	Univariate R ² statistic ^a
Size (small irradiation field (reference) vs. large irradiation field)	1.13	0.28	<0.0001	0.07
Diagnosis (basal cell carcinoma (reference) vs. actinic keratosis)	0.90	0.30	<0.005	0.08
Location (head (reference) vs. trunk or extremities)	-0.71	0.28	<0.05	0.02

^aThe R² values are from univariate linear normal models, where visual analogue scale values from the same patient and predictors are replaced with their mean. The overall R² for the linear model including all three variables was 0.12.

Pain-relieving methods

In 125 out of 889 treatment areas, infiltration, spinal or general anaesthesia was required. The most common reason for anaesthesia was pain in the treatment area or painful pre-treatment procedures prior to the irradiation, such as perforation of thick nodular BCCs ($n=38$), or extensive curettage ($n=13$) prior to PDT. Dorsal penile nerve blocks were used when performing PDT in the genital area of men ($n=21$) and spinal anaesthesia was applied when treating genital Paget's disease in women ($n=2$). Three PDT sessions were performed on patients with Gorlin's syndrome under general anaesthesia, since they had to endure treatment on very large irradiation areas (12–18 treatment fields).

Follow-up and clinical results

In general, AKs were not followed up, but some patients with field cancerization had a follow-up visit to ensure that no additional PDT was required. Patients with BCCs and BD were followed up after approximately 3 months and for a period of up to 3 years. The results from the superficial BCCs are shown in Figs 2. and 3. Statistical analysis was only carried out on the data that could be retrieved reliably from the patients' clinical history. If at any follow-up visit the clinical outcome was uncertain, the patient was considered to have been lost to follow-up. Patients with a diagnosis of BD or nodular BCCs were few in our data; hence the follow-up and clinical results are not shown.

The 20 nodular BCCs that underwent perforation were assumed to be difficult to treat with PDT because of their thickness and were therefore followed up clinically for up to 3 years. After one year, only 8 out of 19 lesions (42%) had responded clinically (one patient with one BCC was deceased and could not be followed up). At 3 years, only 6 out of 19 lesions (32%) remained without recurrence. There was a lower clearance rate for nodular

BCCs compared with superficial ones ($p<0.0001$).

DISCUSSION

The major side-effect during PDT is pain during irradiation. In clinical praxis the patients' pain experience is sometimes unbearable, especially when treatment is performed in the face and/or scalp area. Due to this experience they are unable to complete the treatment session as shown in Table II. In addition, a high number of patients assessed the pain as severe (VAS score 7–10). Our aim was to identify pain predictors in order to attain more specific pain-relieving methods in the future. In order to perfect PDT, the aim should be to lower patients' pain assessment to VAS scores below 4 during treatment.

With regard to our primary objective, several predictors of pain have been identified. The size of the treated area is crucial, but the level of pain also depends on the diagnosis and the location that is treated. Our results show that PDT of extensive AKs (field cancerization) on the scalp and face cause the most severe pain (12, 13). This is not surprising, due to the fact that the three above-mentioned pain predictors are present when performing PDT in these cases.

Our study shows that AKs are more painful to treat than BCCs, regardless of the size of the irradiation field. However, one may argue that the true area of a group of AKs within a small irradiation field, for example, does not necessarily have to be exactly the same as the area occupied by a single BCC treated with the same PDT lamp. Thus, the difference in pain between BCCs and AKs may still be due to the size of the treated area.

Other factors besides the size of the treated area, the diagnosis and the lesion location have and should be discussed. One study concluded that an intense redness of AKs influences the pain experience negatively, but also renders better treatment outcome (12). Grapengiesser et

Table IV. VAS scores for patients grouped by size of irradiation field, diagnosis and location

	Face and/or scalp		Trunk or extremities	
	Small irradiation field Mean \pm SEM (SD)	Large irradiation field Mean \pm SEM (SD)	Small irradiation field Mean \pm SEM (SD)	Large irradiation field Mean \pm SEM (SD)
Actinic keratosis	5.14 \pm 0.33 (2.40)	6.66 \pm 0.17 (2.54)	4.55 \pm 0.94 (2.96)	5.47 \pm 0.26 (2.46)
Basal cell carcinoma	3.41 \pm 0.35 (2.33)	4.86 \pm 0.39 (2.23)	4.01 \pm 0.33 (2.61)	5.14 \pm 0.21 (2.56)

SEM: standard error of the mean; SD: standard deviation.

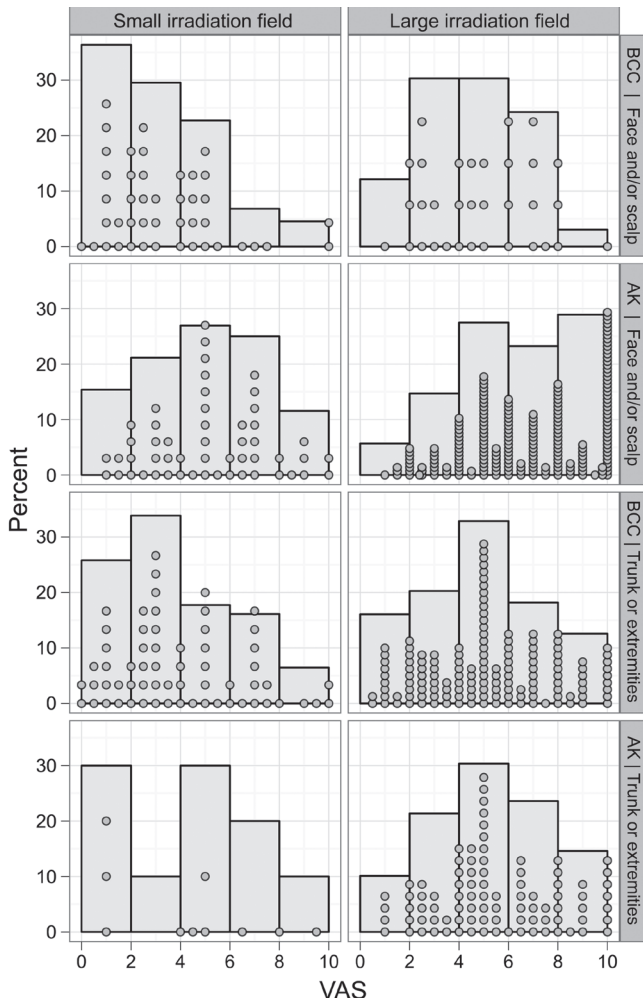


Fig. 1. Histograms for subjective pain measured on a visual analogue scale (VAS) grouped by size of irradiation field, diagnoses and location. The bins of the histograms are [0–2], [2–4], [4–6], [6–8] and [8–10]. The stacked points are VAS scores for the individual treatment areas. AK: actinic keratosis; BCC: basal cell carcinoma.

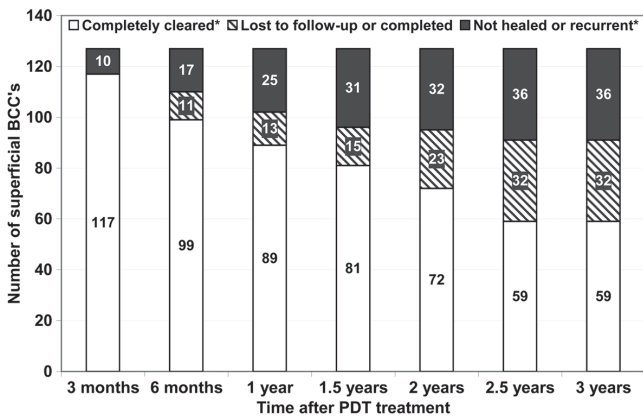


Fig. 2. Clinical results of photodynamic therapy (PDT) for superficial basal cell carcinomas (BCCs). *The status is given for the visit closest to the respective time given in the x-axis.

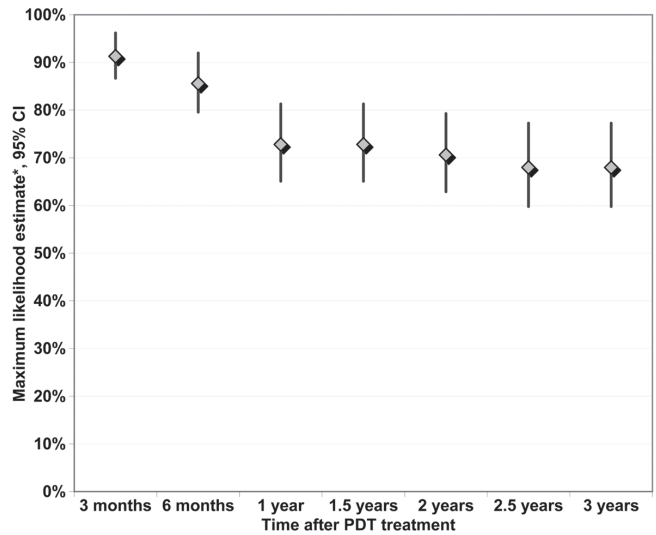


Fig. 3. Estimated clearance rates for superficial basal cell carcinomas. *Non-parametric maximum likelihood estimate of the probability of being cleared for interval censored data, as defined by Peto (10) and Turnbull (11). PDT: photodynamic therapy; 95% CI: 95% confidence interval.

al. (5) concluded that men experienced more pain during PDT than did women. On the other hand, Sandberg et al. (12) found no significant difference in pain due to gender, in concordance with our results in this study. Moreover, Steinbauer et al. (14) found no significant differences in the pain experienced during PDT when considering the patients' age. Our study concurs with these findings, and we conclude that gender and age are poor predictors of pain.

The selection of photosensitizer could also influence the pain experience for the patients. Kasche et al. (13) concluded that MAL-PDT is less painful than 5-aminolevulinic acid (ALA) PDT.

Another factor that influences pain is the light source. Blue and green light sources are less painful compared with red light, but these light sources do not penetrate the tissue as deeply as the red light (15). The lesser penetration depth with blue and green light can therefore limit the use of PDT for thicker lesions. Von Felbert et al. (16) recently compared MAL-PDT on AKs using a halogen lamp emitting a visible light (VIS) plus a water-filtered Infrared A light (wIRA) (Hydrosun® radiator type 505, Hydrosun Medizintechnik GmbH, Mullheim, Germany) with the use of light-emitting diodes (LEDs) (Aktilite® CL 128, Galderma, Bruchal, Germany). The results in this study show that VIS + wIRA PDT was less painful compared with LED PDT, when no spray-cooling was allowed during irradiation.

Furthermore, decreasing the intensity of the irradiation could theoretically reduce pain. The light source and its intensity were not variables in our study, but in clinical praxis, doubling the distance between the light source and the treatment area decreases the intensity of the irradiation. The remaining treatment time is then doubled according to the LED lamp manufacturer's

recommendations. In order to determine the efficacy of this method, further studies are needed.

Once we have elucidated the factors that may predict a painful experience during PDT, the search for pain-relieving solutions begins. If we start by considering the size of the treatment area, one could consider trying to reduce the pain by simply treating smaller areas separately. Nevertheless, our clinical experience is that patients prefer one visit with the whole affected area treated at once even though the pain level is much higher. Meanwhile, the diagnosis and location of the lesions is obviously not something we can influence as easily, thus individualized pain-relieving methods should be our aim.

Several studies have investigated topical anaesthesia (12, 17–19), cold air analgesia (20) and transcutaneous electrical nerve stimulation (TENS) (21) with no or limited effect on pain relief during PDT. Fortunately, there are now pain-relieving alternatives available for field cancerization in the face and scalp.

Nerve blocks effectively relieve pain during PDT in these areas, they are easy to perform and they are well tolerated by the patients (22–24). At our clinic, nerve blocks are used routinely as pain relief when PDT is performed on extensive AKs in these areas. In addition, daylight PDT also seems to provide a certain degree of pain relief (25).

Our follow-up results for BCCs and BD show rather low cure rates after 3 years compared with other studies (26, 27). However, it must be emphasized that 25% (BCCs) and 46% (BD) of the patients were not followed up for 3 years and the treatment protocols were not standardized. If a patient was not healed at the first follow-up visit, then the patient was considered a failure in the survival analysis even if subsequent PDT sessions were performed.

One can only speculate on the outcome of the patients who did not return for their follow-up visits. As we mentioned earlier, a very light curettage was performed on the superficial BCCs. A deeper debulking procedure as pre-treatment might increase the clearance rates, but would also risk worsening the good cosmetic outcome.

Regardless of the clinical results in this study, PDT has proven effective in the treatment of AK, BCCs and BD (1, 2), but better pain-relieving strategies should be developed in order to make PDT acceptable for the patient. We conclude that physicians using PDT as a treatment for non-melanoma skin cancers should be aware of the pain predictors found in this study in order to provide correct patient information and adequate pain management.

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Conflicts of interest. C. B. Halldin has received fees from Galderma and Photocure for giving lectures. M. Gillstedt has no conflicts of interest to declare. J. Paoli has received fees from Meda, Leo Pharma, Photocure, Galderma, Astellas and Schering-Plough for giving lectures. A-M Wennberg has taken part in clinical trials with Galderma, PhotoCure, 3M and Fujisawa. She has received fees from Galderma, PhotoCure, 3M, Fujisawa and Schering-Plough for giving lectures. H. Gonzalez has received fees from Meda, Schering-Plough, Galderma and Astellas for giving lectures.

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