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CLINICAL REPORT

# Squamous Cell Carcinoma Following Photodynamic Therapy for Cutaneous Bowen's Disease in a Series of 105 Patients

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**Photodynamic therapy (PDT) is an alternative to surgery for Bowen's disease. This monocentric retrospective study included 105 patients with Bowen's disease, treated with PDT between 2007 and 2013, who received a total of 151 different PDT fields. Comparison of immunocompromised and non-immunocompromised patients revealed that the former often had a previous history of squamous cell carcinoma (SCC; $p=0.004$) and received more PDT fields ($p=0.007$) than the latter. At least one SCC occurred post-PDT in 16 out of 105 patients in a PDT field. However, many of the patients were at risk of SCC and the possibility that the lesion did not have a mixed histology at baseline, but might simply be a transformation of non-PDT-responsive Bowen's disease, cannot be excluded. Although it is rare, patients should be closely monitored for SCC post-PDT.** ***Key words: Bowen's disease; photodynamic therapy; squamous cell carcinoma.***

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Bowen's disease (BD) is an intra-epidermal carcinoma of the skin, which, if untreated, may progress to invasive squamous cell carcinoma (SCC) in 3–5% of cases (1). BD can occur anywhere on the skin in adults, especially in elderly people. BD usually presents as an asymptomatic circular erythematous scaly patch localized on a sun-exposed area. Typically, BD has an excellent prognosis because of its slow evolution and good response to treatment. Although surgery is often the best treatment option for BD, new therapies have emerged in recent years. Alternatives to surgery, such as photodynamic therapy (PDT), cryosurgery, 5-fluorouracil and imiquimod, have been proposed for BD, especially when it is located in sensitive surgical areas (face, fingers, etc.) (1–11). PDT is also used in the treatment of actinic keratoses (AK) and superficial basal cell carcinomas. Its use in other fields of dermatology is under evaluation (12).

PDT is based on the application of a photosensitizing product or its precursor, which is activated by a light source of an appropriate wavelength according to the absorption spectrum of the photosensitizer and offers sufficient penetration. Its activation causes the selective destruction of malignant cells via production of reactive oxygen species (ROS). Methyl aminolevulinate (MAL) in its hydrochloride form is a photosensitizing product for cutaneous application, marketed under the name of Metvixia®. Irradiation is performed using a light source with a wavelength between 570 and 670 nm within the absorption spectrum of porphyrins. PDT using Metvixia® is abbreviated MAL PDT. The light energy absorbed by the photoactive porphyrin is transferred to oxygen, generating ROS. Two MAL PDT sessions 8 days apart are recommended for the treatment of BD.

The effectiveness (complete clearance) of PDT for the treatment of BD is approximately 80%, with recurrences in 10–20% of cases (8, 11, 13). Side-effects are essentially local erythema, oedema, warmth, burning, tingling and painful sensations (13, 14).

PDT is considered to be a safe treatment, although its carcinogenic risk has never been studied. However, several cases of SCC after PDT have been reported in the literature (15, 16). We studied the occurrence of SCC following PDT treatment in a series of 105 patients with BD.

## METHODS

A monocentric retrospective study of patients with cutaneous BD treated by PDT between 2007 and 2013 was conducted in the Department of Dermatology at Saint Louis Hospital, Paris, France. Data studied were the patients' age, sex, history of SCC, immunosuppression, location of BD treated by PDT, number of treated lesions, number of PDT sessions performed, response to PDT at 3 months, and occurrence of SCC on a PDT field or outside a PDT field. The fields treated with PDT were classified into 4 regions: head and neck, trunk, upper limbs and lower limbs. The efficacy of PDT on BD 3 months after therapy was qualified as complete response (CR) when complete regression of the lesion occurred, partial response (PR) when part of the BD lesion persisted, progression (P) in the case of occurrence of a SCC in a PDT field, or stability (S) in the case of PDT failure. The time for SCC to develop, the number of SCCs and their histological character (microinvasive or invasive) were also recorded.

### *Statistical analysis*

Quantitative variables were described as median and interquartile range (IQR) and qualitative variables as number and

percentage. Categorical variables were compared between 2 groups using Fisher's exact tests and continuous variables were compared using Wilcoxon rank-sum tests. The main endpoint was the delay time of occurrence of at least one SCC post-PDT in a PDT field, defined as the difference between the date of first SCC post-PDT and the date of first PDT session. Delay has been censored at the date of the last follow-up. The probability of SCC post-PDT-free follow-up was obtained using the Kaplan–Meier estimator, and is presented as an estimate and 95% confidence interval (95% CI). To determine the association between the characteristics of patients or of BD and the occurrence of at least one SCC post-PDT in a PDT field, we used a Cox proportional hazards model. In order to take into account the fact that several areas of BD could have been treated by PDT in a single patient, we included a patient's random effect in the Cox model. The proportionality hazards assumption was tested by computing Schoenfeld residuals and using Grambsch and Therneau's lack-of-fit test (17). Univariate analyses were performed initially. Factors included in the multivariate regression model were selected as clinically relevant variables or as variables yielding *p*-values smaller than 0.10 by univariate analysis. The association of factors with the probability of occurrence of at least one SCC post-PDT in a PDT field was expressed in terms of the hazard ratio (HR) (95% CI).

All tests were 2-sided, and $p$-values $< 0.05$ were considered statistically significant. Analyses were performed using R statistical software version 3.0.2 (available online at: http://www.R-project.org, free software distributed under a GNU style copyleft).

## RESULTS

A total of 105 patients were enrolled (64 women, 41 men; median age 75 years (IQR 63–81 years)). Among them, 35 (35%) had a prior history of SCC and 25 (24%) were immunocompromised (Table I). Median follow-up was 14 months (IQR 6–30). Because some of these patients had several fields with BD, a total of 151 PDT fields out of the 105 patients were studied. Most patients had one PDT field ($n = 79$) and 26 patients had more than one PDT field (Table II). Patients with multiple PDT fields had a significantly greater prior history of SCC ($p = 0.008$) and were more immunocompromised ($p = 0.007$) than those who had only one PDT field. In most cases, only one BD was present in the PDT field, but 28 patients had more than one BD in the same PDT field. Immunocompromised patients were more likely to have a prior history of SCC than non-immunocompromised patients (15 (60%) vs. 20 (27%), respectively; $p = 0.004$). They were also more likely to have more than one PDT field than non-immunocompromised patients (12 (48%) vs. 14 (18%), respectively $p = 0.007$) (Table SI[1]).

Table I. *Patient characteristics (*n*=105)*

| Patient characteristics | |
|---|---|
| Median age at first photodynamic therapy session, years (IQR) | 75 (63–81) |
| Sex, *n* (%) | |
| Women | 64 (61) |
| Men | 41 (39) |
| History of squamous cell carcinoma, *n* (%) | |
| No | 65 (65) |
| Yes | 35 (35) |
| Missing values | 5 |
| Immunosuppression, *n* (%) | |
| No | 79 (76) |
| Yes | 25 (24) |
| Missing values | 1 |

IQR: interquartile range.

Table II. *Patient characteristics according to the number of photodynamic therapy (PDT) fields*

| Variable | 1 PDT field ($n = 79$) | > 1 PDT field | *p*-value |
|---|---|---|---|
| Number of patients | 79 | 26 | |
| Median age at first photodynamic therapy, years (IQR) | 76 (66–82) | 69 (59–80) | 0.064 |
| Sex, *n* (%) | | | 0.65 |
| Women | 47 (60) | 17 (65) | |
| Men | 32 (40) | 9 (35) | |
| History of squamous cell carcinoma, *n* (%) | | | 0.008 |
| No | 54 (73) | 11 (42) | |
| Yes | 20 (27) | 15 (58) | |
| Missing values | 5 | 0 | |
| Immunosuppression, *n* (%) | | | 0.007 |
| No | 65 (83) | 14 (54) | |
| Yes | 13 (17) | 12 (46) | |
| Missing values | 1 | 0 | |

Of the 105 patients, 16 developed at least one SCC in a PDT field (ranging from 1 to 7 SCC per patient) and 16 developed at least one SCC outside a PDT field (ranging from 1 to 10). Of the 16 patients with SCC in a PDT field (Table III), 8 patients were immunocompromised and 8 had a history of SCC including in the PDT field in 5 patients. The development of SCC was not necessarily preceded by complete remission of the BD after PDT. More precisely, SCC developed on a PDT field after CR at 3 months in one patient, PR in 2 patients and P for 6 patients, whereas the data were missing for the other 7 patients. The median time for the development of the first SCC on a PDT field after the first PDT session was 6.0 months (IQR 2.7–11.8). Considering the 16 patients who developed SCC outside the PDT fields, the median time to SCC development after the first PDT session was 10.3 months (IQR 4.3–21.1). Of these patients, 5 (31%) were immunocompromised and 12 (75%) had a prior history of SCC. SCC located outside a PDT field was single in 8 patients or multiple in 8 other patients (2 SCC for 3 patients, 4 SCC for 1, 6 SCC for 2, 8 SCC for 1 and 10 SCC for 1). Among all the 48 observed SCC outside PDT fields, 34 (74%) were invasive and 12 (26%) were microinvasive; histology was not available in 2 SCC cases.

Of the 151 treated BD, 34 (23%) were located on the upper limbs, 37 (25%) on the lower limbs, 59 (39%) over the head and neck area and 20 (13%) on the trunk.

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Table III. *Summary of the 16 patients who developed squamous cell carcinoma (SCC) in photodynamic therapy (PDT) fields*

| Case number/sex/ age, years | History of SCC | Immuno–suppression | BD, *n* | Location | PDT sessions, *n* | SCC on PDT fields | SCC outside PDT fields | Histology of SCC in PDT fields | Follow-up since first PDT, months |
|---|---|---|---|---|---|---|---|---|---|
| 1/M/66 | No | No | 1 | HN | 2 | 1 | 0 | Microinv | 64 |
| 2/F/87 | No | No | 4 | HN | 2 | 2 | 0 | 2 Inv | 53 |
| 3/M/57 | No | Yes | 1 | UL | 3 | 1 | 0 | Inv | 9 |
| | | | 1 | UL | 1 | 1 | | Inv | 7 |
| 4/F/62 | No | Yes | 42 | LL | 6 | 2 | 0 | Inv, Microinv | 72 |
| 5/F/75 | Yes | No | 3 | LL | 2 | 7 | 1 | 7 Inv | 6 |
| 6/M/69 | Yes | No | 1 | HN | 2 | 1 | 6 | Inv | 76 |
| 7/F/56 | No | No | 4 | UL | 2 | 1 | 0 | Inv | 16 |
| | | | 50 | LL | 2 | 1 | | Inv | 16 |
| 8/M/72 | Yes | Yes | 1 | HN | 2 | 2 | 6 | 2 Inv | 56 |
| 9/F/77 | Yes | No | 25 | LL | 2 | 1 | 1 | Inv | 12 |
| 10/F/62 | Yes | Yes | MV | UL | 1 | 1 | 0 | Inv | 12 |
| 11/F/48 | Yes | Yes | 10 | UL | 4 | 4 | 4 | 4 Inv, 3 Microinv | 49 |
| | | | 10 | UL | 4 | 1 | | Inv | 49 |
| 12/F/85 | Yes | No | MV | HN | 2 | 2 | 0 | Microinv, Inv | 5 |
| 13/M/60 | Yes | Yes | 10 | UL | 2 | 5 | 10 | 5 Inv | 25 |
| 14/F/79 | No | Yes | 3 | LL | 2 | 1 | 0 | Inv | 5.8 |
| 15/F/84 | No | Yes | 1 | Trunk | 2 | 1 | 0 | Microinv | 21 |
| 16/M/75 | No | No | 10 | HN | 2 | 2 | 2 | 2 Inv | 47 |

BD: Bowen's disease; MV: missing value; UL: upper limb; LL: lower limb; HN: head and neck; Inv: invasive; Microinv: Microinvasive; F: female; M: male.

For each PDT field, the patients received a median of 2 sessions (ranging from 1 to 6 sessions). The evolution of disease at 3 months after the first PDT session was available for 64 patients. At 3 months, CR was observed in 33 (52%) fields, PR in 17 (26%) fields, P in 8 (13%) fields and S in 6 (9%) fields (Table IV). In the 151 PDT fields, the development of at least one SCC was observed in 19 (12.6%). A single SCC was observed in 11 out of 151 PDT fields (Fig. 1), whereas 8 PDT fields presented several SCC (Fig. 2), (5 (3.3%) with 2 SCC, 1 (0.7%) with 4 SCC, 1 (0.7%) with 5 SCC and 1 (0.7%) with 7 SCC). Overall, 37 SCC in PDT fields were observed.

Of the 37 post-PDT SCC that developed in PDT fields, 30 (81%) were invasive and 7 (19%) were microinvasive. For each PDT field, the probability of occurrence of at least one SCC at one year was estimated at 11%. Comparison of the characteristics of BD patients who developed at least one SCC in a PDT field, and those who did not develop SCC in a PDT field are shown in Table V.

In univariate analysis, the number of BD lesions in one PDT field was associated with a higher risk of occurrence of at least one SCC in a PDT field (hazard

Table IV. *Evolution of photodynamic therapy (PDT) fields (*n*=151)*

| Variable | *n* (%) |
|---|---|
| At least one SCC in one PDT field | |
| No | 132 (87) |
| Yes | 19 (13) |
| SCC in 1 PDT field | |
| 0 | 132 (87) |
| 1 | 11 (7) |
| 2 | 5 (3) |
| 4 | 1 (1) |
| 5 | 1 (1) |
| 7 | 1 (1) |
| Evolution of BD at 3 months | |
| Complete response | 33 (52) |
| Partial response | 17 (26) |
| Progression | 8 (13) |
| Stability | 6 (9) |
| Missing values | 87 |

SCC: squamous cell carcinoma; BD: Bowen's disease.

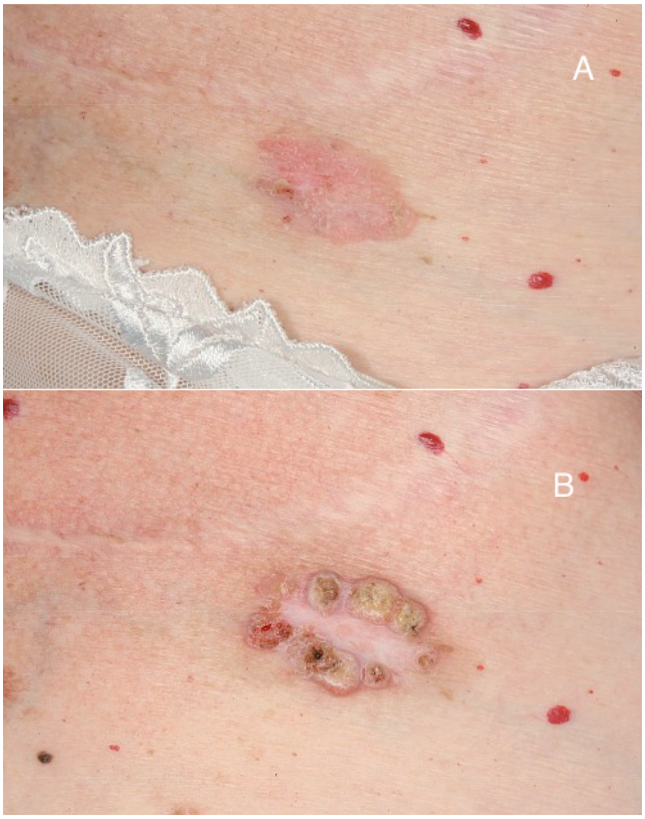


*Fig. 1.* Case 1. Bowen's disease on the left breast. (A) Before photodynamic therapy. (B) Five months after 2 methyl aminolevulinate photodynamic therapy sessions: microinvasive squamous cell carcinoma.

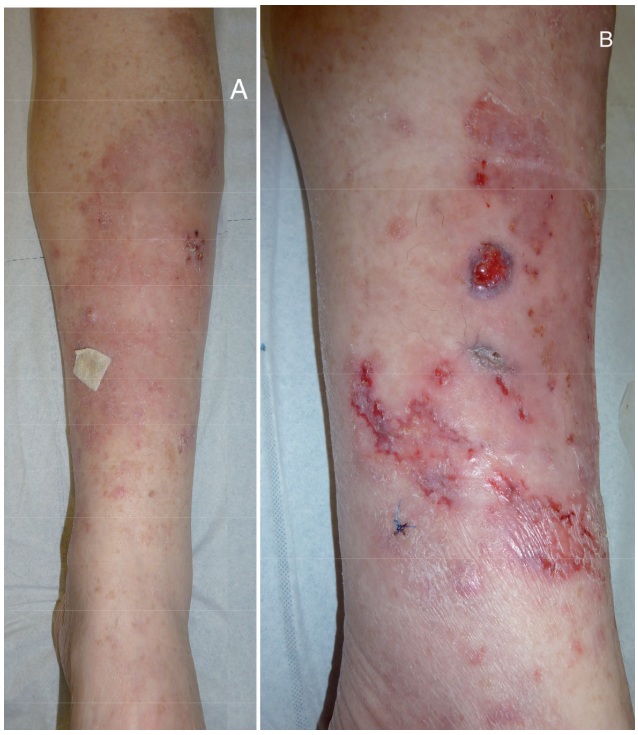


*Fig. 2.* Case 5. Several Bowen's disease lesions on the left leg. (A) Before photodynamic therapy (PDT). (B) Between 2 and 6 months after 2 sessions of PDT therapy: 7 squamous cell carcinomas developed.

ratio (HR) 1.06 (95% CI 1.02–1.11); $p<0.01$). However, this association did not remain statistically significant in multivariate analysis (HR 1.05 (95% CI 1.00–1.12); $p<0.07$). The estimation of the risk of occurrence of at least one SCC in a PDT field was higher in immunocompromised patients compared with non-immunocompromised patients (HR = 3.0); however, this difference was not statistically significant either in univariate analysis ($p=0.09$) or in multivariate analysis ($p=0.12$).

## DISCUSSION

This paper presents an analysis of 16 patients who developed one or more SCC after PDT treatment, out of a study total of 105 patients with BD. The potential role of PDT in the occurrence of SCC in these patients was evaluated. Observations of cases of BD or AK treated by PDT that have been followed by the development of skin cancers have been reported in the literature, suggesting a possible role of PDT in promoting carcinogenesis. Liang et al. (15) reported 2 cases of SCC on BD treated by PDT, respectively, 2 months and 4 months after PDT. Calista (16) recently reported that, out of 15 patients consecutively treated by PDT for AK of the scalp, 5 developed SCC on an area treated by PDT with a median time to onset of 6 months. A case of keratoacanthoma of the face developed after treatment of AK with PDT, and an invasive SCC of the penis was reported after treatment for erythroplasia of Queyrat by PDT (18, 19).

However, these cases should be analysed with caution, as they may simply reflect that the patient is at risk for the development of skin cancer and that PDT is not directly involved in this process. Our observations of SCC after PDT for BD prompted us to look more closely at the relationship between these factors in our series of patients.

Table V. *Factors associated with the occurrence of at least one post-photodynamic therapy (PDT) squamous cell carcinoma (SCC) in a PDT field*

| Variable | No SCC post-PDT $n=132$ | At least 1 SCC post-PDT $n=19$ | Univariate analysis | | Multivariate analysis* | |
|---|---|---|---|---|---|---|
| | | | Crude HR (95% CI) | *p*-value | Adjusted* HR (95% CI) | *p*-value |
| Median age at first PDT session, years (IQR) | 75 (64–81) | 66 (57–76) | 0.98 (0.93–1.04) | 0.51 | | |
| Sex, *n* (%) | | | | 0.80 | | |
| Women | 83 (63) | 12 (63) | 1 | | | |
| Men | 49 (37) | 7 (37) | 1.17 (0.33–4.15) | | | |
| Immunosuppression, *n* (%) | | | | 0.094 | | 0.12 |
| No | 93 (71) | 9 (47) | 1 | | 1 | |
| Yes | 38 (29) | 10 (53) | 3 (0.83–10.88) | | 3.31 (0.73–15.13) | |
| Missing values | 1 | 0 | | | | |
| History of SCC, *n* (%) | | | | 0.27 | | 0.95 |
| No | 80 (63) | 9 (47) | 1 | | 1 | |
| Yes | 47 (37) | 10 (53) | 2.01 (0.58–6.93) | | 1.05 (0.26–4.25) | |
| Missing values | 5 | 0 | | | | |
| Median BD on a PDT field (IQR) | 1.0 (1.0–1.0) | 4.0 (1.0–10.0) | 1.06 (1.02–1.11) | 0.0096 | 1.05 (1–1.12) | 0.069 |
| Missing values | 9 | 2 | | | | |
| Location, *n* (%) | | | | | | |
| Lower limbs | 32 (24) | 5 (26) | 1 | | 1 | |
| Upper limbs | 27 (21) | 7 (37) | 1.03 (0.26–4.07) | 0.97 | 1.11 (0.19–6.46) | 0.91 |
| Head–neck | 53 (40) | 6 (32) | 0.59 (0.13–2.37) | 0.43 | 0.66 (0.11–4.01) | 0.65 |
| Trunk | 19 (15) | 1 (5) | 0.18 (0.018–1.79) | 0.14 | 0.23 (0.02–3.21) | 0.28 |
| Missing values | 1 | 0 | | | | |

*Multivariate model was adjusted on immunosuppression, history of SCC, number of BD on the PDT field, location.
BD: Bowen's disease; HR: hazard ratio; CI: confidence interval; IQR: interquartile range.

We hypothesized that a potential role of PDT in the development of SCC can be suspected only when SCC appears in the PDT field. In our study, patients treated for BD were often at risk of SCC (due to immunosuppression, prior history of SCC, multiple treatment fields and multiple BD). Sixteen patients who developed SCC in the PDT field were observed. However, 7 of these patients also developed SCC outside a PDT field. The efficacy of PDT in our series (CR = 52%) was lower than that classically reported in the literature and was not significantly different between immunocompromised and non-immunocompromised patients. This may be due to differences between clinical trials with selected patients and real-life data with more severe patients, such as those seen in our department. The risk of occurrence of at least one SCC in a PDT field was not significantly different between immunocompromised and non-immunocompromised patients, but we cannot exclude that this could be due to a lack of power of our study because of the relatively small number of events. Therefore, we recommend caution in the use of PDT in immunocompromised patients.

The main question raised by our current study is whether the SCC occurring in such situations are related to the natural evolution of BD with failure of PDT or if they are directly induced by PDT. A diagnostic biopsy prior to PDT was performed with sampling of the most suspicious area. Due to sampling error the possibility that the BD was more invasive at baseline cannot be excluded. We also hypothesize that, if cells are not killed during PDT, there may be a risk of enhancing carcinogenesis.

Several pathophysiological hypotheses for the carcinogenic potential of PDT have been raised in the literature. It has been shown in mice that ROS are involved in skin carcinogenesis (20). PDT photosensitization mediated by porphyrins generates a large number of ROS. ROS can induce DNA breaks and mutations, chromatin exchanges, chromosomal abnormalities, cell transformation, and could lead to oncogene activation. Giri et al. (21) reported that, after exposure to an inappropriate dose of light, photosensitization mediated by protoporphyrins may have a double dose-dependent effect in mice treated by PDT. Indeed, a 5 mg/kg dose of haematoporphyrin causes destruction of tumour cells and, on the contrary, a lower dose (2.5 mg/kg) could have a pro-tumoural effect with the occurrence of DNA damage in normal epithelial cells. In the spectrum of lung cancers where PDT has also been studied, Miyazu et al. (22) found that the expression of telomerase in the bronchial epithelium may precede transformation into cancer. The authors suggest that PDT is useful for eradicating lung cancer, but does not destroy normal cells at risk of developing SCC that are from healthy regions of the bronchial epithelium and express telomerase. This reminds us of the phenomenon described by Giri et al. of the double dose-dependent effect of the photosensitizer protoporphyrin in mice (21). A PDT-stressed cell that expresses telomerase could lead to SCC development. Indeed, it has been shown that telomeres play an important role in skin carcinogenesis (23).

In our study, 16 out of 105 patients developed SCC in PDT areas, after a median time for appearance of the first SCC after the initial PDT session of 6.0 months. This delay is shorter than that of SCC that developed outside a PDT field, and suggests that if PDT is involved, it might accelerate tumour growth. Indeed BD is an *in situ* carcinoma and the time to become more invasive can be shorter than the time for a carcinogen to induce the initial BD. However, we cannot exclude the possibility that the lesion had a mixed histology (*in situ* and invasive) at baseline and was misdiagnosed on the initial biopsy. Interestingly, a comparable delay was observed in previously reported post-PDT SCC reported cases (15, 16). This growth promotion might be explained by the existence of local immunosuppression after PDT, as suggested by Hayami et al. (24), who showed that PDT induces an early and significant reduction in Langerhans epidermal cells, which play a major role in antigen presentation and thus in the recruitment of immune effectors.

Twenty-five out of the 105 patients in the current study were immunocompromised. The Munich University Hospital transplant team has reported a 20.5% cumulative incidence of non-melanoma skin cancer in 2,419 kidney transplant patients, corresponding to a relative risk of 52.7 (25). The risk is correlated with the level of immunosuppression in the transplant (heart>kidney>liver) (26). In our study, of the 25 immunocompromised patients, 10 developed SCC (5 (50%) in PDT fields and 2 (20%) outside PDT fields, and 3 (30%) in both PDT and outside PDT fields). Of the 37 post-PDT SCC, 30 (81%) were invasive and 7 (19%) were microinvasive and, of the 48 SCC outside a PDT field, 34 (74%) were invasive and 12 (26.09%) microinvasive. However, no experimental studies have demonstrated an excess risk of developing SCC after PDT in that patient population (14, 27–29). In addition, as we observed more SCC outside the PDT field than in the PDT field, this emphasizes that our population had a higher risk of SCC development. Our data do not support our initial hypothesis that PDT has a role in promoting SCC in human skin. In a randomized controlled study searching for a preventive effect of PDT on the development of SCC, de Graaf et al. (30) compared the 2 upper limbs (one treated with 1 or 2 PDT sessions, the other left untreated) of 40 transplant patients followed over a period of 2 years after PDT. A total of 15 SCC was observed in 9 of the 40 patients receiving PDT and 10 SCC in 9 of the 40 untreated patients (not significantly different). Moreover, the number of PDT sessions (1 or 2) did not influence the risk of SCC.

PDT remains a good treatment for BD, especially in difficult locations or in elderly patients, but it is important

to consider its potential effects at the cellular level. Although rare, these cases of SCC should alert clinicians to follow their patients carefully. The carcinogenic effect of PDT requires further research; prospective studies must be conducted on larger cohorts of patients to examine the incidence of SCC after PDT for BD.

*The authors declare no conflict of interest.*

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