INTRODUCTION

Ultraviolet (UV) therapy or phototherapy is a widely used treatment modality for skin manifestations of psoriasis. Although treatment with UV has proven to be very effective in different modalities, concerns were raised about the safety of these UV treatments when psoralen UVA (PUVA) was shown to be carcinogenic.1,2 Patients treated with PUVA have an elevated risk of developing actinic keratosis3 and squamous cell carcinoma (SCC).1–4 However, the relative risk of developing SCC has varied greatly between studies performed in Europe and the United States.1–4

Although PUVA treatments have now been generally accepted to be potentially carcinogenic, the risk of skin carcinogenesis due to UVB therapy has not been demonstrated.5–7 UVB therapy, especially narrowband UVB (NB-UVB), is still regarded as a safe treatment modality without an elevated risk of non-melanoma skin cancer (NSMC).
Nonetheless, dermatologists are reluctant to prescribe prolonged courses of UV therapy; they limit the number of courses per year or the cumulative dose. This approach is recommendable as NMSC is known to be caused by recurrent and excessive UV exposure and has a predilection for sun-exposed areas of the body. Another argument against excessive UV therapy is that psoriasis patients are likely to exhibit sun-seeking behaviour upon experiencing positive effects of the treatment on their skin disease.

In a recent position statement, van der Kerkhof and de Grujil stood up for revisiting the way phototherapy is prescribed.\(^6\) Intervals of conventional phototherapy might not be the best-fitted treatment in a chronic disease such as psoriasis. The authors therefore advocate further research into prolonged low-dose phototherapy.

Low-dose phototherapy has been described in several skin conditions and with several modalities, such as NB-UVB, UVA1 and BB-UVB.\(^9\)–\(^15\) The majority of studies reported positive results in terms of effectiveness. The definition of ‘low dose’, however, varies widely between these studies. A clinical trial in 2013 with a low-emission phototherapy unit addressed this problem.\(^16\) This unit was designed for treatment at home and emits a fixed dose of UVA and UVB of 1 standard erythemal dose (SED) in 10 min.

Remarkably, the safety of these low-dose treatments has only been sparsely investigated.\(^16\)–\(^20\) Of the safety studies that have been conducted to date, most have been in cell lines or mice, and very few in patients. In a preliminary safety study in psoriasis patients using the ‘fixed’ low-dose phototherapy, no significant elevation in the carcinogenic markers p53 and thymidine dimers was detected.\(^19\) Carcinogenic effects are therefore presumed to be low. These results, however, were acquired after just two months of treatment in a study setting. In practice, many patients in the Netherlands continued this treatment for a prolonged period of time, sometimes up to 5 years, or initiated this type of phototherapy without a clear answer as to the safety risks of prolonged use.

Hence, in this study we aimed to investigate (I) the possible long-term carcinogenic effects of low-emission phototherapy and (II) the treatment adherence during the prolonged use of low-emission phototherapy.

## 2 | MATERIALS AND METHODS

The study design was approved by the Medical Ethics Committee of the Amsterdam UMC (protocol number 2018.490) and was performed in accordance with the Declaration of Helsinki (2008). To investigate the possible carcinogenic effects of prolonged use, an observational cross-sectional cohort study was set up.

### 2.1 | Population

Three groups of psoriasis patients were included:

1. Patients prescribed daily low-dose phototherapy (Dermasun Helios\(^5\)) for a period longer than 18 months.

2. Patients without treatment or with local treatment of their skin disease.

3. Patients with hospital-based NB-UVB for at least 1 month.

Patients included were aged 18 years or older and had a clinical diagnosis of psoriasis, ascertained by a dermatologist.

Exclusion criteria were use of systemic immunosuppressants or prolonged, intentional exposure to any UV non-prescribed source (natural or tanning booth) 2 weeks prior to point of measurement.

### 2.2 | Treatment

Low-dose phototherapy was given using the Dermasun Helios\(^©\) prescribed for a use of 10 min/day. The equipment emits 1 standard erythemal dose (SED) in 10-minute time of UVA and UVB. Hospital-based NB-UVB was given following the normal standard of care for psoriasis patients. Patients were treated in Waldmann 7002 with Waldmann light bulbs TL-01 (for emission spectrum of the lamps, Figure 1).

The start dose was set at 70% of the estimated mean erythemal dose (MED) according to Fitzpatrick skin type with increments of 10%–20% depending on any erythema reactions. NB-UVB was given 3 times per week in an outpatient setting. An overview of the SED values of both groups is given in Table 1.

### 2.3 | Procedure

After informed consent, patients underwent a visual inspection of the skin to ascertain any signs of (pre-)malignant changes in the skin. The inspection was performed by a dermatologist. During this inspection, skin type was also recorded, as well as prior history of skin malignancies or actinic keratosis or lentigines.

Subsequently, patients had two 4-mm skin biopsies from the buttock area, as this is, in most patients, not exposed to natural sunlight. The biopsies were taken from non-lesional skin. In patients undergoing NB-UVB or low-dose UV, the biopsies were taken just before the scheduled UV session. In patients with NB-UVB, this was 2–3 days after their last treatment. The interval just before the next scheduled treatment was chosen to exclude acute effects of UV as the dose of both treatments differed. Patients undergoing low-dose UV therapy were asked to refrain from the therapy the day of biopsy, but to continue their normal routine, whether this be evening treatment or morning treatment.

From the obtained biopsies, one was fixed in formalin to be embedded in paraffin for immunohistochemistry, and the other was snap-frozen in liquid nitrogen for DNA extraction for CPD ELISA.

### 2.4 | Immunohistochemistry—p53 and γH2AX

Paraffin-embedded sections (5 μm) were used for immunohistochemical analysis for histone γH2AX and p53-positive cells. A 1:100
dilution of the H2A.X (Ser139) antibody (clone JBW301, mouse, 
IgG1; Sigma-Aldrich) was used after antigen retrieval using 0.01 M 
citrate buffer, pH 6, boiling step. A 1:50 dilution of the p53 antibody 
(mouse, clone DO-7, IgG2b, Dako, Agilent) was used after antigen 
retrieval using a 10 mM TRIS/1 mM EDTA buffer, pH 9, boiling step. 
Both followed by a 15-min. room temperature (RT) incubation with 
Post-antibody Blocking Gold and a 30-min RT incubation with Poly-
HRP-Goat anti-Mouse/Rabbit/Rat IgG Ruby (Brightvision 2-step 
Colour Detection System; ImmunoLogic) followed by AEC incuba-
tion at RT for 10 min. A background staining with haematoxylin was 
used. Slides were scanned using Vectra Polaris (PerkinElmer) part 
of the Microscopy and Cytometry Research Core Facility at the 
Amsterdam UMC location VUmc, and analysed with QuPath: open 
source software for digital pathology image analysis. Positive cells 
in epidermis were analysed.

**TABLE 1** Approximated SED in low-dose UV treatment vs 
conventional NB-UVB. The NB-UVB group would undergo 
increment of 20%, resulting in culminating values

| Skin type | Low-dose UV | NB-UVB start | NB-UVB after 4 weeks |
|-----------|-------------|--------------|---------------------|
| 1         | 1           | N/A          | N/A                 |
| 2         | 1           | 2.2          | 5.2                 |
| 3         | 1           | 2.6          | 7.4                 |
| 4         | N/A         | 3.3          | 8.7                 |

Note: Biopsies were taken after 4 weeks of NB-UVB. At this time point, 
this would result in the dose demonstrated in the last column.

For γH2AX staining, 5 GJ irradiated skin was used as positive 
control. For p53 staining, a tonsil was used.

### 2.5 | ELISA—cyclobutane pyrimidine dimers

High-Sensitivity Cyclobutane Pyrimidine Dimer (CPD) ELISA (ver2.0 
Cosmo Bio LTD) was performed on 0.4 μg/ml DNA extracted with 
QIAamp DNA Mini Kit (Qiagen) from the snap-frozen 4-mm skin 
biopsy according to the manufacturer’s instructions. Shortly, 50 μl 
0.4 μg/ml of denatured DNA was coated overnight by a 37°C in-
cubation on a pre-coated protamine sulphate 96-well plate. After 5 
washes with wash buffer, the plate was incubated for 30 min at 37°C 
with a primary anti-CPD antibody followed by 5 washes and a bioti-
nylated secondary antibody incubation for 30 min. At 37°C. After 
an additional 5 washes, the plate was incubated for another 30 min 
at 37°C with streptavidin-peroxidase solution, and after another 5 
washes with wash buffer, the plate was incubated for 30 min at 37°C 
with OPD solution. After adding stop solution, absorbance was de-
termined using a Berthold Mithras 940 ELISA reader.

As positive and negative controls, DNA supplied by manufacturer 
was used and DNA of ex vivo skin and UV-treated ex vivo skin was used.

### 2.6 | Use of low-dose phototherapy

Patients using daily low-dose phototherapy were asked to fill in a 
survey about their actual use of the phototherapy installation. This 
was a retrospective survey.
The survey comprised of questions about the time the low-dose therapy was used per session, the number of sessions per day or week, changes in use and the number of months patients already had access to this treatment modality.

2.7 | Statistics

2.7.1 | Sample size calculation

The sample size calculation was done assuming that the smallest difference is consistent with prior results (no UV treatment vs low-dose UV treatment patients; difference of 5 points with σ = 5), and the groups are distributed in a 2:1:1 fashion (daily low-dose UV treatment: local treatment: conventional NB-UVB). The power (1-β) was set to 90%, and the significance level α to 0.05/3 to correct for multiple testing.

With these parameters, 88 participants were necessary. Correcting for technical failures, analytical failure and dropout of 20% of 110 patients would be needed. The anticipated number of patients would be (daily low-dose UV treatment: local treatment: conventional NB-UVB) 55:28:28.

2.8 | Statistical analysis

Categorical variables are described by frequency and percentage, and continuous variables by mean and standard deviation (SD) in case of normal distribution and by median and range in case of non-normal distribution. The categorical variables were compared between the three treatment arms (controls with local treatment only, patients undergoing low-dose UV treatment and patients undergoing conventional UV treatment) using a chi-squared test, and continuous variables were compared with each other with an ANOVA test after ln-transformation, as the values of the markers were not normally distributed. In case of significant difference between the three treatments arms, a post hoc analysis was carried out with the Bonferroni correction for multiple testing.

Correlation between markers and the use of low-dose UV treatment and correlation between the markers were analysed using a Spearman correlation test.

3 | RESULTS

Patients were included from May 2019 up to March 2020. Due to the outbreak of the COVID-19 pandemic, downscaling of outpatient care and restrictions, further inclusions were not feasible. Due to these circumstances, the sample size was not met.

Thirty-nine patients with daily low-dose UV treatment, 15 patients using only local treatment and 8 patients undergoing conventional NB-UVB were included in the study. Patient characteristics are shown in Table 2. There was no significant difference in gender, age or Fitzpatrick skin type between the groups.

3.1 | Use of daily low-dose UV treatment

Patients using the daily low-dose UV treatment had access to the cabin for a median time of 30 months. The machine was used for a median of 40 min/week, although a large range was seen varying from 5 up to 140 minutes. Table 3 gives a clear overview of the self-reported use of the low-dose UV treatment. Of note is that all patients but 1 reported to comply with the instructions not to exceed a daily treatment frequency. Sixty-one per cent reported not to use the treatment on a daily basis. None exceeded the maximum of 10 min/session.

3.2 | Skin inspection

All patients underwent a complete visual skin assessment during their study visit. In 12 patients, a sign of photoageing was found in the current inspection or had a prior diagnosis of skin malignancies (Table 4): nine patients in the low-emission phototherapy group, 2

| TABLE 2 | Patient characteristics |
|----------|--------------------------|
|          | Low-dose UV (n = 39) | Local treatment (n = 15) | NB-UVB (n = 8) | p-value |
| Age      |                        |                        |               |         |
| Mean (SD)| 48.3                   | 14.3                   | 48.7          | 16.5    | 51.3 | 18.0 | .89    |
| Gender   |                        |                        |               |         |
| Male     | 29                     | 74.4%                  | 7             | 46.7%   | 6    | 75.0% | .13    |
| Female   | 10                     | 25.6%                  | 8             | 53.3%   | 2    | 25.0% |         |
| Skin type fitzpatrick |            |                        |               |         |
| 1        | 5                      | 12.8%                  | 1             | 6.7%    | 0    | 0.0%  | .30    |
| 2        | 26                     | 66.7%                  | 10            | 66.7%   | 5    | 62.5% |         |
| 3        | 8                      | 20.5%                  | 2             | 13.3%   | 2    | 25.0% |         |
| 4        | 0                      | 0.0%                   | 1             | 6.7%    | 1    | 12.5% |         |
| 5        | 0                      | 0.0%                   | 1             | 6.7%    | 0    | 0.0%  |         |
in the local therapy group and 1 in the NB-UVB. The difference between the findings was not significant (p = .63).

3.3 Skin biopsies

In skin biopsies, the percentage of p53 cells showed a clear difference between the groups (p < .001; Table 5). The low-dose UV treatment group had a significantly lower percentage of p53-positive cells (p = .015) than the NB-UVB group. As p53 is upregulated in psoriatic skin, patients were only included if the diagnosis of psoriasis had been confirmed. The group using only local therapy, the baseline group, were also found to have a significantly lower percentage of p53-positive cells compared with NB-UVB (p < .001). The difference between the low-dose treatment group and the local therapy group was not significant (p = .065). The staining of the skin biopsies is shown in Figure 2.

CPDs were measured in optical units. Again, a difference was found between the groups (p < .001): low-dose UV showed a lower amount of CPDs than NB-UVB (p = .016) and local therapy (p < .001). CPDs in local therapy, which can be considered background activity, were significantly lower than NB-UVB (p < .001).

To ascertain whether the self-reported frequency of low-dose UV therapy could be a factor in the lack of significant difference between the low-dose UV treatment group and the control group undergoing local therapy only, a subselection of low-dose treatment patient using the treatment more intensively was chosen (Figures 3 and 4). When patients using the low-dose UV treatment 3× per week or more were selected, post hoc analysis showed a marked difference in the amount of CPDs and percentage of p53-positive cells in the epidermis between low-dose UV treatment and NB-UVB (percentage of p53, p = .039; CPD, p = .034), low-dose UV treatment and controls with local therapy only (percentage of p53, p = .011; CPD, p < .001) and lastly, as reported before, between the controls without UV treatment and the group with conventional NB-UVB (percentage of p53, p < .001; CPD, p < .001). Table 6 shows the specifics of the analysis. Patients reporting a strict adherence to the low-dose UV treatment (ie daily use) showed similar significant results of CPDs (NB-UVB vs controls, p = .022; low-dose UV vs NB-UVB, p < .001; and low-dose UV treatment vs controls, p < .001). For the percentage of p53-positive cells, a significant difference was found between NB-UVB and controls (p < .001), but not between low-dose UV treatment and NB-UVB (p = .053) or low-dose UV treatment and controls (p = .17).

To evaluate whether the chosen markers for carcinogenicity showed a correlation to each other within the patients, Spearman’s test was used. This showed a clear correlation between the markers with the exception of CPDs and γH2AX. The results are shown in Table 7.

In patients using low-dose UV therapy, a clear link was found in the amount CPDs when correlated to the self-reported time of use per session (p = .009). This is demonstrated in Table 8.

No such correlation was found with p53 markers or γH2AX. A correlation was found, however, in the time patients had access to the low-dose UV therapy unit and the absolute amount of γH2AX.

4 DISCUSSION

This study sets out to investigate safety aspects of prolonged use of low-dose phototherapy in psoriasis patients, focusing on possible carcinogenic effects. Low-dose phototherapy is used at home. Treatment adherence was therefore an important parameter, more specifically that patients did not overexpose themselves. Although the calculated sample size was not met, the power reached with current included patients in the study was 94% for p53 results and 99% for CPD results.

4.1 Carcinogenic effects

To measure the carcinogenic effects of phototherapy on the skin p53 activation, cyclobutane pyrimidine dimers (CPDs) and γH2AX were selected as markers.

p53 is a well-known tumour suppressor gene. It regulates cell-cycle control after DNA damage, activates DNA-repair mechanisms or initiates apoptosis. It is activated after cell damage of different kinds, and mutations in p53 have been found in many different tumours, including NMSC.22

Activation of p53 provides information on DNA damage and the need for repair (or apoptosis) in tissue.

UV light causes direct genotoxic effects as DNA is a strong chromophore of UVB. UVB energy is readily absorbed by DNA and can cause mutations as covalent bonds are formed between adjacent pyrimidines. Mutations occur especially in dipyrimidine sites, causing the two most characteristic UVR lesions: pyrimidine (6-4) pyrimidine photoproducts and CPD. They are known as UVR-signature
mutations when a C→T or CC→TT mutation occurs. CPDs are not evenly distributed in genomic DNA. There seem to be preferential hot spots, in particular in the p53 gene. In NMSC, mutations at these sites appear to be frequent and have been associated with a UV signature.

The phosphorylated variant of histone H2Ax, γH2AX, is known to be produced in response to DNA damage that involves the formation of DNA double-stranded breaks (DSB) after ionizing radiation. It has also been observed in UVB-irradiated cells, but reports on the occurrence of γH2AX after UVA irradiation have been conflicting. Several studies have implicated oxidative stress due to UVR as a cause of the phosphorylation of γH2AX, instead of the direct genotoxic effect seen in ionizing radiation.

In this study, psoriasis patients treated with low-dose phototherapy showed a significantly lower amount of p53 activation and CPDs as compared to patients undergoing conventional NB-UVB. No significant difference was found in p53 activation and CPDs in patients treated with low-dose phototherapy as compared to a control group using local therapy only, when all patients were taken into account. When patients using the low-dose phototherapy thrice weekly or more were selected, the difference between the control group and the patients undergoing low-dose phototherapy became significant. This demonstrates a clear dose-effect ratio: when used more frequently, low-dose phototherapy causes p53 activation and CPDs. This corroborates findings of previous studies that the extent of UV exposure correlates with induced 'damage' in keratinocytes. This damage is, however, clearly lower in prolonged use of low-dose phototherapy than in conventional NB-UVB.

These findings suggest that the prolonged use of low-dose phototherapy for at least 18 months is not more harmful for psoriasis patients than conventional NB-UVB. Further research into the effects of even longer treatment of low-dose UV therapy is warranted, as are studies to evaluate the longevity of the current markers after cessation of (conventional and low-dose) phototherapy.

### 4.2 | Visual signs of photodamage

Patients undergoing NB-UVB, low-dose phototherapy and controls using local treatment only underwent visual skin examination to ascertain any signs of photodamage. Although the groups were small, no difference was found in the presence of these signs. A
prospective study registering these signs after any form of (medical) phototherapy could shed more light on the clinical meaning of elevated markers such as p53 and CPDs. Is there a possible cut-off value (ie cumulative UV dose, specific p53 values) when these signs appear? Such a study would be extremely valuable, albeit very hard to undertake as it would be difficult to take into account the sun-seeking behaviour of psoriasis patients. Advocating due caution, regular (eg biannual) visual skin examination should be considered when prescribing any kind of phototherapy.

4.3 | Correlation between the markers

The p53 and CPDs significantly differed between the treatment groups. Surprisingly, the last marker, γH2AX, did not show a significant activation, even when patients using the therapy >3x per week were selected. To further investigate the relevance of this immunohistochemical staining, the correlation between all carcinogenic markers was assessed. A significant correlation was found between
all groups, with the exception of CPDs and γH2AX. There was, however, a clear trend for correlation (p = .06 and p = .09) between those. This implies mutual coherence between the markers, and the test was valid. A possible explanation for the lack of correlation or statistically significant activation in the examined biopsies could lie in the relatively small sample size, the timing of the samples or a different activation pathway.

4.4 | Use of low-dose phototherapy

Due to the carcinogenic risks associated with UV exposure, dermatologists are reluctant to prescribe prolonged and repeated courses of phototherapy. In-hospital treatment provides a sense of control over the treatment use and facilitates adjustments of the treatment. Home-based treatment lacks these benefits. In this study, all patients used low-dose phototherapy for at least 18 months but one reported not to overuse their home-based treatment. Although a retrospective survey was used to ascertain this phenomenon, the immunohistochemical and ELISA findings support this phenomenon.

There was a clear correlation between the amount of CPDs and the reported amount of time the machine was used per week. The CPDs rose when low-dose phototherapy was used more frequently. The CPDs, however, remain significantly lower compared with conventional NB-UVB. Overall, the low-dose phototherapy is safe when compared to one course of conventional NB-UVB and it is not notably ‘overused’. On the contrary, 61% of patients who filled out the survey indicated using the low-dose phototherapy less than originally prescribed. Only one (2.7%) reported overuse. It seems desirable, however, for such a home-based unit to have a control mechanism monitoring its use.

5 | CONCLUSION

Patient safety is the primary obstacle in home-based phototherapy: patients have unsupervised access to the UV-emitting device. Excessive or prolonged use causes photodamage and, in the long run, skin malignancies. The current results show that patients using low-dose phototherapy at home for at least 18 months had significantly lower activation of p53 and CPDs than patients undergoing conventional NB-UVB. Patients also did not show more signs of photoageing (lentigines, actinic keratosis) or skin malignancies.
The groups in our study, however, were small. Only 68 patients participated. Although this was enough to demonstrate the significant difference, further studies are warranted to evaluate the risks of even longer use. Ideally, these studies would be performed prospectively, including an electronic system monitoring the actual use of the home-based phototherapy device.

Conventional NB-UVB is generally accepted as a safe treatment in psoriasis. Overall, the current findings show that low-dose UV during a period of 18 months causes less p53 and CPDs (of damage) than this ‘safe’ NB-UVB. It can therefore be considered as a safe treatment in psoriasis patients.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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