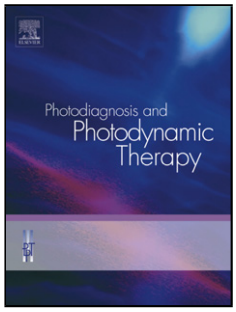


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# Non-metastatic cutaneous squamous cell carcinoma treated with photodynamic therapy using intravenous mTHPC

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Highlights

- PDT achieved high efficacy in the treatment of T1N0 cutaneous squamous cell carcinoma.
- The technique is simple, can commonly be carried out in outpatient clinics, and is highly acceptable to patients.
- The main gains of PDT are its highly satisfactory cosmetic outcome and high remission rates.

**Abstract**

**INTRODUCTION:**
Photodynamic therapy (PDT) is a relatively new method of treating various pathologies. In this retrospective study with prospective intent, a total of 22 patients with T1/T2 N0 cutaneous squamous cell carcinoma (SCC) were treated with intravenous mTHPC (meta-tetrahydroxyphenylchlorin) and surface illumination PDT. Comparisons with the clinical features, rate of recurrence and overall outcome were made.

**MATERIALS AND METHODS:**
Surface illumination PDT was offered under local anaesthesia. 0.05mg/kg mTHPC was administered intravenously into the midcubital vein 48hrs hours prior to tissue illumination. A single-channel 652nm diode laser was used for illumination and light was delivered at 20J/cm$^2$ per site. Lesion response evaluation was carried out according to Response Evaluation Criteria In Solid Tumors (RECIST).

**RESULTS:**
Clinical assessment revealed that 16 patients had lesions of <2cm in size (T1), while the rest were T2. No nodal involvement was identified in any of the patients. None of the patients had a locally recurrent lesion. During the 3-year follow-up, 20/22

patients had complete response (CR) and this was after one round of treatment. Two patients suffered from recurrent disease within 3 years of the follow-up, and they underwent surgical resection.

**CONCLUSION:**
PDT achieved high efficacy in the treatment of T1N0 cutaneous squamous cell carcinoma with greatly reduced morbidity and disfigurement. The technique is simple, can commonly be carried out in outpatient clinics, and is highly acceptable to patients.

**Introduction**

Squamous cell carcinoma (SCC) arises as a result of uncontrolled growth in the squamous epithelial cells. It is the second most common skin cancer, after basal cell carcinoma, and classically present as an elevated nodule with central depression, scaly red patch or an ulcer. Cumulative exposure to ultraviolet light and immunosuppression are the main causes behind its development. Most commonly affected body sites include the ear helix, face, lower lip, scalp and neck. Male to female ratio is 2:1 and tend to affect individuals over 50 years of age.[1-4]

Caucasians have a higher risk of developing cutaneous SCC and the risk is increased in case of substantial sun exposure. It now has been widely accepted that cutaneous SCC is associated with DNA mutations in somatic genes in more than 90% of the cases. Furthermore, more studies have been linking cutaneous SCC to human papilloma virus (HPV) in immunecompromised patients.[3] Other risk factors include ageing patients, smokers and having a history of BCC, cutaneous SCC, cutaneous lupus, xeroderma pigmentosum, albinism as well as post-transplant patients, mainly due to immunosuppressant drugs and patients with certain haematological conditions. [1,2,4]

Skin inflammation and chronic infections have been linked with cutaneous SCC and this pathology was noted to arise in ulcers, scars, thermal burns and sores. Pre-cancerous conditions have been found to be associated with this pathology and they include actinic (solar) keratosis, actinic cheilitis, leukoplakia, Bowen's disease (SCC *in situ*). Cutaneous SCC can metastasize to loco-regional lymph nodes, other skin sites, and organs including lungs, liver, brain as well as bones.[4-5]

Diagnosis is based on clinical examination. However, sub-type histopathological diagnosis is achieved through incisional biopsy or following complete excision. TNM staging started in 2011 after the publication by the American Joint Committee on Cancer (AJCC); the current system is the 8$^{th}$ edition. Cutaneous SCCs are classified into low-risk and high risk depending on clinic-pathological features. Recurrence and mortality has been identified to be associated with high-risk clinic-pathological features including: lesion size ≥2cm in diameter, locally recurrent lesion, arising within scar, sinus, ulcer or burn, rapid growth and immunosuppressed patients, specific anatomical sites, histological thickness ≥2mm, poorly differentiated, peri-neural involvement and intravascular invasion.[4-5]

Treatment includes surgical excision, the gold standard intervention and first line. The resection is carried out with an extra of 3-10mm macroscopic free tumour margin. In case of large lesions, defect reconstruction may follow with skin graft or a flap. Other surgical options include Mohs micrographic surgery (for large facial and recurrent tumours), electrodessication with the curettage (low-risk tumours, mainly affecting the trunk and limbs). Many non-surgical interventions have been employed and found to be successful including topical chemotherapy and radiotherapy (external, adjuvant or brachytherapy). The long-term prognosis of this pathology depends on many factors including its subtype, location, severity, co-morbidities and available interventions. [1-5]

**Photodynamic therapy (PDT)**

This modality is currently being used in the management of various types of tissue pathologies. Superficial disease is usually treated with surface illumination PDT, while deep-seated disease requiring an interstitial intervention (i.e. optical fibres guided deeper into tissues to deliver the light). The photosensitizer is administered topically or intravenously and is activated by non-thermal light of appropriate wavelength. The photodynamic process follows two routes (1) oxygen-free radicals production and (2) intracellular singlet oxygen formation; this causes cell death by intracellular oxygenation and vascular shutdown (i.e. intimal hyperplasia).[6-7]

Adverse events in the immediate post-PDT can occur and include pain and local swelling. This has been linked to the local inflammatory and immunological responses post illumination. Photosensitization and the related skin complications is another problem that can arise in patients receiving this intervention. This usually depends on the photosensitizer, its dose and the mode of administration. The use of topical photosensitizer is the best way to avoid residual systemic photosensitivity, however topically applied photosensitizers can only treat superficial disease due to the small depth of effect (1–2mm).[6-7]

A previous study by Kübler et al.[8], have looked into the possibility of using intravenous mTHPC with surface illumination PDT to treat non-melanoma skin cancers. In this study, 18 patients were treated, mostly with basal cell carcinomas (BCCs). They reported that 92.7% of the treated lesions showed a complete response with an excellent cosmetic outcome and only seven lesions responded by partial success due to low light dosage.[8] We have recently reported a study involving 148 patients with basal cell carcinomas treated with photodynamic therapy. In our study, 80 out of 86 patients with thin BCCs had complete response after one round of topical methyl aminolevulinate (MAL); while 60 out of 62 patients with thick BCCs had complete response after one round of intravenous mTHPC.[9]

We aim in this study, retrospective with prospective intent, to build on these previous studies but mainly target cutaneous squamous cell carcinomas of the head and neck. A total of 22 patients with T1/T2 N0 primary lesions were treated with intravenous mTHPC with surface illumination PDT and follow-up as per our

guidelines. Comparisons with the clinical features, rate of recurrence and overall outcome were made.

**Materials and methods**

Following a number of prospective ethically approved multicenter trials; the European Medicines Advisory Committee approved photodynamic therapy (PDT). Meta-tetrahydroxyphenylchlorin (mTHPC) is approved for the treatment of advanced/recurrent head and neck cancers. The application of photodynamic therapy at the Head and Neck Unit, University College London Hospitals (UCLH) is commonly practiced. Most referrals for this tertiary care unit include patients with advanced or recurrent disease who failed previous conventional interventions as well as patients with skin pathologies. Every patient included in this study was invited to return for a follow-up.

Every treated patient signed an informed consent prior to the intervention and was regularly updated on the treatment progress and outcome. The patients' data were entered into proformas, which were validated and checked by interval sampling. The fields included a range of clinical, operative and histopathological variables. Data collected also included recurrence and last clinic review.

The inclusion criteria were patients with primary (not recurrent) T1/T2 cutaneous SCC. Twenty-two consecutive patients, who presented with suspicious skin lesions and diagnosed with squamous cell carcinoma, were examined and included in this study. The initial recruitment number was twenty-eight, but six patients were excluded (four in the enrolment stage and two were lost to follow-up). Figure 1 highlights the enrolment, allocation, follow-up and analysis process.

The diagnosis of these lesions was made through close skin examination; followed by incisional biopsy. These patients, with 22 SCC lesions, were treated with surface illumination mTHPC-PDT. These treatments were carried out at the UCLH Head and Neck Unit over a 5-year period. Patients were followed-up as part of out UCLH head and neck protocol for skin cancer. This was at the following intervals post illumination: 1 week, 1 month, 3 months, 6 months, 12 months, 24 months, 36 months (3 years) and 60 months (5 years). Patients who fell outside our routine follow-up protocol (had the treatment $>$5 years before) were invited for a last clinic review.

Surface illumination photodynamic therapy was offered under local anaesthesia. 0.05mg/kg mTHPC was administered intravenously into the midcubital vein 48hrs hours prior to tissue illumination. Early introduction of the photosensitizer would allow the agent to accumulate in the pathological area, which would increase the PDT effect. Patients were advised to avoid direct sun light exposure for 2 weeks to avoid residual systemic photosensitisation.

On the day of treatment, shielding of the macroscopically healthy surrounding tissue was employed. A safety margin of 5mm around the suspicious lesion was included

and illuminated as part of the treatment. The laser light delivery fibre, with a core diameter of 400µm, was held directly above the suspect area. The distance from the tip of the fibre to the tumour surface was 5cm with up to 3cm spot diameter. A single-channel 652nm diode laser was used for illumination and light was delivered at 20J/cm$^2$ per site. The treatment was repeated to cover larger lesions.

Post-PDT pain control was applied according to UCLH post-PDT pain protocols. Patients were discharged on the same day unless they were required to stay for other reasons (i.e. marked swelling or pain and any significant medical issues). Lesion response evaluation was carried out according to Response Evaluation Criteria In Solid Tumors (RECIST): complete response (CR): disappearance of all target lesions for at least 4 weeks; partial response (PR): at least a 30% decrease in the sum of the longest diameter (LD) of target lesions confirmed at 4 weeks; stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease taking as references the smallest sum LD; and progressive disease (PD): at least a 20% increase in the sum of LD of target lesions (Figure 2). The assessment, treatment and follow-up protocols were based on previous studies carried out in our unit to treat thick BCCs and thin oral SCCs with intravenous mTHPC and surface illumination PDT.[9,10]

**Statistical analysis**

The results were analysed by an independent statistician using SPSS. The outcomes of the categorical clinic-pathological variables were summarised as frequencies and percentages for the whole group of SCC patients. The numerical variables, “age and follow-up”, were summarised by means, standard deviations, minimal and maximal values.

**Results**

The patients’ population comprised 16 males and 6 females. Their mean age at the 1$^{st}$ diagnosis was 64 years. Chronic sun bathing was the most prominent risk factor, which was reported by 16 patients. The treated lesions involved most of the body sites. Nearly half the cohort had history of actinic keratosis; two-thirds had history of cutaneous SCC, with others reporting problems including history of non-skin SCC, BCC and immunodeficiency (Table 1).

Clinical assessment revealed that 16 patients had lesions of <2cm in size (T1), while the rest was T2. No nodal involvement was identified. None of the patients had a locally recurrent lesion; however 4 patients reported lesions arising with a scar, sinus, ulcer or thermal burn. Seven patients reported rapid lesional growth, while 2 patients were actively taking immunosuppressant agents. Histopathological features acquired from the incisional biopsy revealed that 5 patients SCC depth of invasion ≥2mm, 4 had poorly differentiated SCC, 2 patients biopsies showed features of perineural involvement and 1 patient with intravascular invasion (Table 1).

Side effects showed that one patient developed local paraesthesia and another developed local hyperesthesia. Both patients recovered full sensation within 3 months post-PDT. Furthermore, 3 patients reported hypopigmentation of the treatment site (Table 2).

All the 22 patients at the first follow-up assessment achieved complete response (based on clinical examination). Small biopsies were taken from the area of the previous PDT-treated lesion in all cases to assess for recurrence. Within 6-18 months post-PDT, 2 patients reported ulceration at the border of the previously treated lesions. Incisional biopsy confirmed the diagnosis of cutaneous SCC (recurrence). These 2 patients were further discussed at our multi-discipline meeting and it was recommended to have these lesions surgically excised. Surgical excision resulted in clear margins. At 3-year, 5-year and last clinic follow-up, all patients continued to be in remission (Table 3). The complete response rate of PDT (alone) was 91% with recurrence of 9%.

Using visual analogue scale (VAS), 20 patients reported that this treatment gave them “excellent” cosmetic outcome (VAS 9-10) and 2 patients reported it to be “good” (VAS 7-8).

**Discussion**

The main purpose of treating cutaneous SCC is to completely eliminate the tumour and improve form and function of tissues as well as prevent any loco-regional or distant spread. The UK guidelines continue to recommend surgical excision as the primary intervention. For many years and due to the fear of metastatic disease, conventional interventions (i.e. surgery, radiotherapy and chemotherapy) where the only treatment options offered to patients.[11] As a result, patients with cutaneous cancers were only referred for non-conventional therapies when they develop recurrence and fail a conventional treatment more than once. This has resulted in patients treated by non-conventional interventions (i.e. lasers and photodynamic therapy) to have less than adequate outcome compared to the conventional cohort and this led to the conclusion that lasers and PDT are not the treatment of choice for skin cancers.[1]

Over the years there has been a number of prospective studies reporting on the use of PDT in the management of cutaneous SCC.[1,2,6,7] A systematic review by Lansbury et al.[12] identified 14 small prospective studies (comprising 297 patients) in this category. Their analysis reported a complete response 72.0% and recurrence rate of 26.4%. The review also reported that few studies confirmed histological clearance in apparently completely responsive SCCs, and in those that attempted to do so, residual tumour remained in several biopsies. This extensive review of these PDT studies reached a conclusion about complete response and recurrence rate but failed to explain the results. On further examination, it was noted that 11 of the 14 reported studies involved using topical photosensitisers [ALA (aminolevulinic acid) and MAL (methylaminolevulinate)] with limited penetration depth and light

properties.[13-22] The remaining three studies used systemic photosensitisers [haematoporphyrin and mTHPC].[8,23-24] Hence combining the results of these studies and reporting their outcome under one umbrella was neither fair nor accurate for PDT. The only study reported, in this extensive systematic review, which was comparable to ours was that of Kübler et al.[8] which involved treating BCCs and cutaneous SCCs using mTHPC-PDT with complete response rate of 92.7% at average follow-up of 15 months.

The result in our study was very promising. For example at 3-year follow-up, complete response following PDT was 91% and recurrence rate was 9%. Only 2 patients suffered from recurrent disease and these were the patients with clinical features of tumour size >2cm, both arose in scar/ulcer site and grew rapidly. Furthermore, histopathological features of these two recurrence cases showed tumour depth of >2mm, poorly differentiated carcinoma with perineural invasion, and one of them had intravascular invasion reported. It is fair to say that recurrence in such high-risk cutaneous SCC in not uncommon and after multidiscipline discussion we proceeded and removed them surgically.

Lucena et al.[25] undertook a comprehensive search of the available literature and concluded that PDT could be applied in combination with immunomodulatory and chemotherapeutic agents, inhibitors of some molecules implicated in the carcinogenic process, surgical techniques, or even radiotherapy as a new strategy to open the way to a wider improvement of the prevention and eradication of skin cancer.

It is essential to understand that PDT, at this stage, is not the answer for all cutaneous SCCs but only certain cases. The gold-standard intervention for cutaneous SCCs remains surgery. We have chosen our cases carefully, by ensuring that all were primary lesions. The majority of our cases was low risk (73%) and classified as T1N0. We did have 6 cases as T2 (lesion size ≥2cm) and arguably these are considered high-risk but were managed by PDT following multi-discipline discussion. Unfortunately 2 of these 6 cases resulted in recurrent disease and were managed surgically. These six T2 patients were scanned for nodal disease at 2 stages (initial presentation and recurrence) and at both times were disease free.

It is worth highlighting the fact that photodynamic therapy is not an option that is available in every head and neck or dermatology unit. It is an intervention that requires the involvement of a specialized and trained team, including surgeons, physicians and physicists as well as specialist nurses. Furthermore the adverse reactions, for example the prolonged photosensitivity in case of intravenous application of the photosensitizer may not be suitable for certain patients or in certain geographic locations. The next step, here, is to compare intravenous PDT to the gold standard surgical excision, mainly to compare recurrence, metastasis, overall prognosis and cosmetic role. Furthermore to look into the patient's treatment choice and potential effect on the quality of life.

Our study confirms the advantage of using PDT in the management of T1N0 cutaneous squamous cell carcinoma. High cure rates have been achieved using mTHPC as the photosensitiser with no report of any recurrence after 6 years of follow-up. The technique is simple, can be easily applied in outpatient setting and have superior cosmetic results when compared to other conventional interventions.

**Competing interests and conflict of interests**
We declare none.

**Authors' contributions**
All authors designed and carried out the literature search and manuscript preparation. All authors were responsible for critical revision of the scientific content and manuscript review. All authors approved the final version of the manuscript.

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**Figures**

**Figure 1:** Enrolment, allocation, follow-up and analysis process.

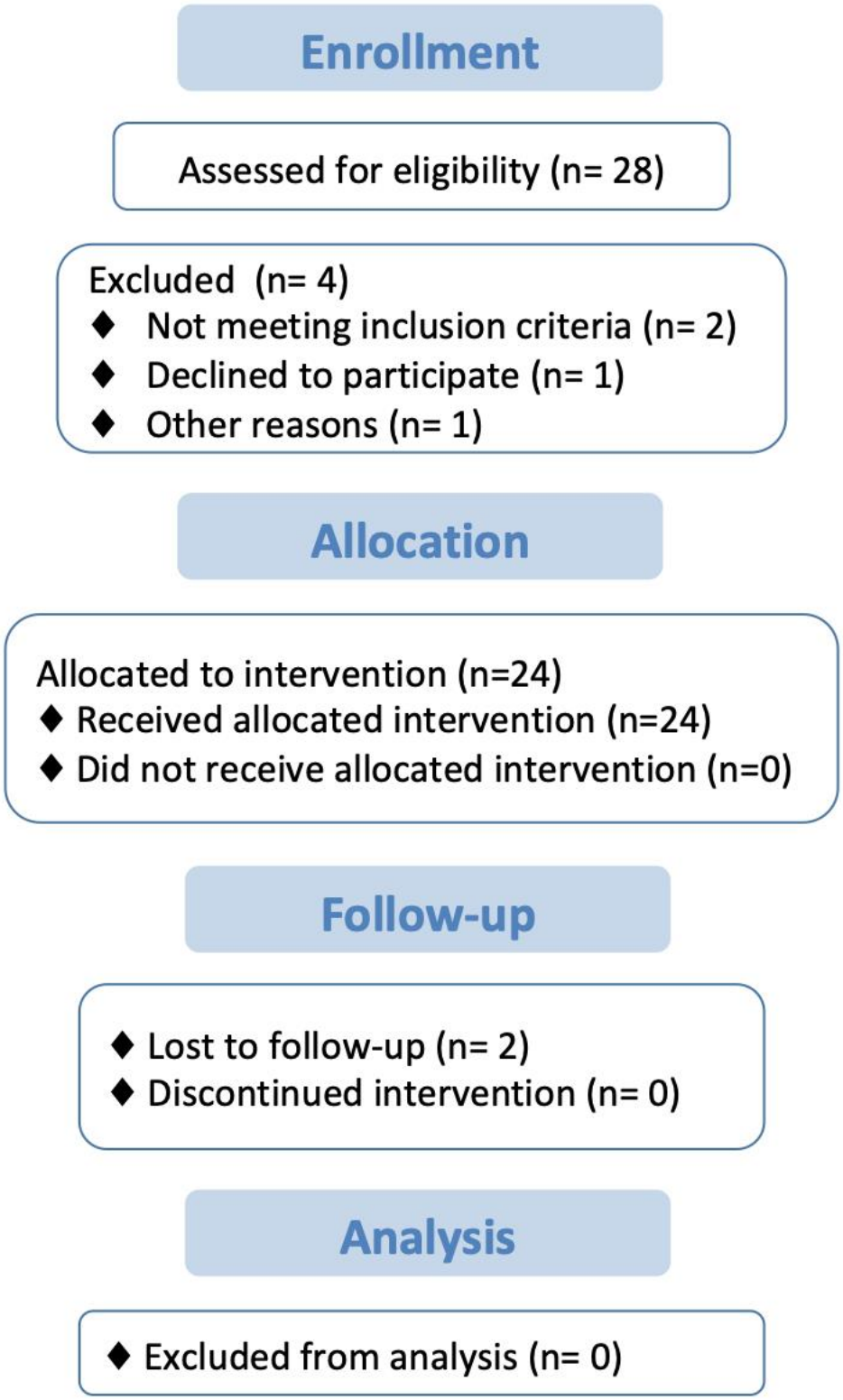
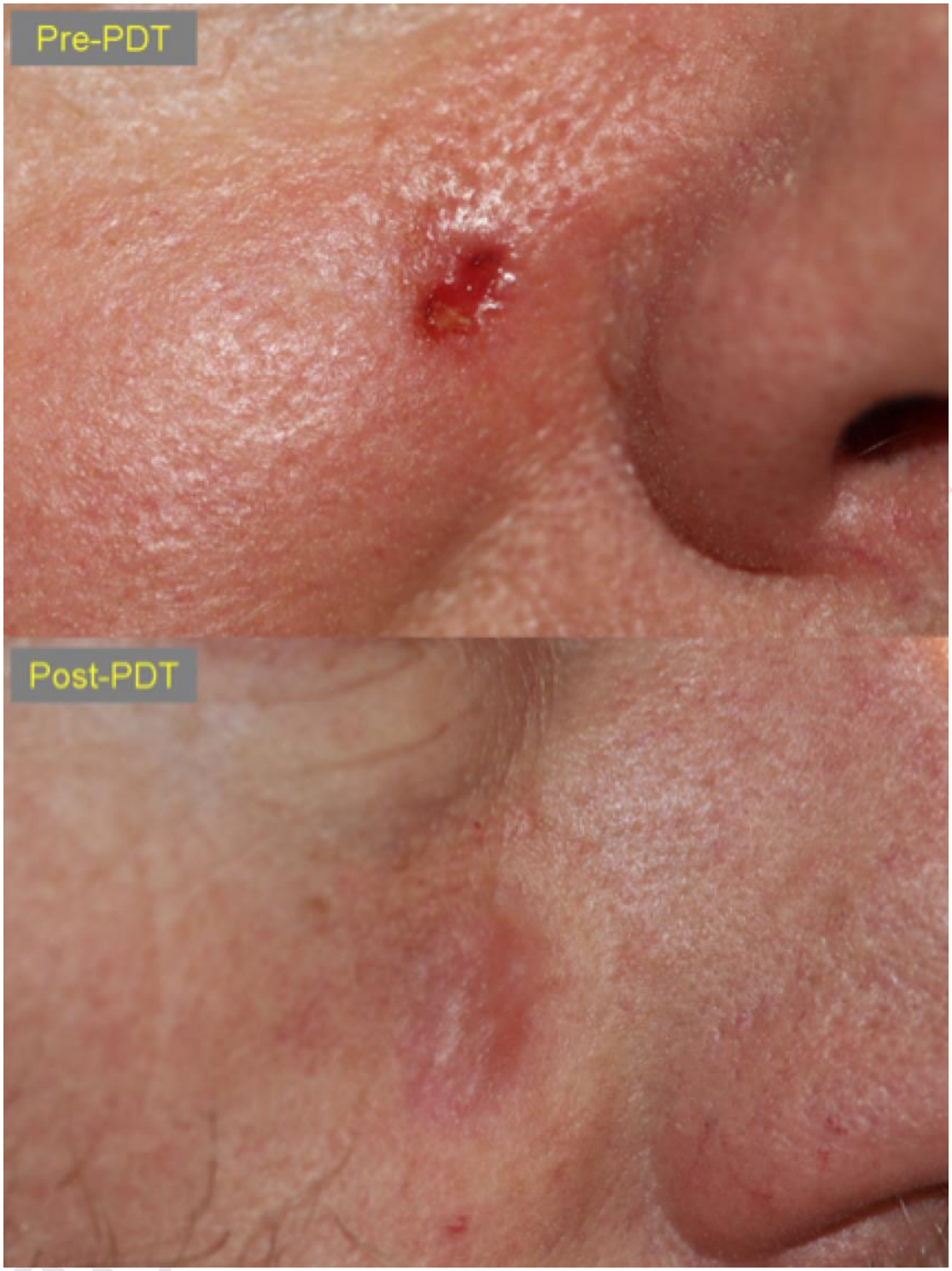



**Figure 2:** SCC of the R mid face treated with surface illumination mTHPC-PDT. Pre-PDT (top) and post-PDT at 1 month (bottom).


Pre-PDT
Post-PDT

## Tables

**Table 1:** Demographic details of 22 patients with 22 thin squamous cell carcinoma of the skin treated with photodynamic therapy.

| | Frequency (%) | | Frequency (%) |
|---|---|---|---|
| **Age at diagnosis** | 64±9.6 | Bleeding | 4 (18.2) |
| Min-Max | 58-75 | Cosmetic | 15 (68.2) |
| | | Fear of malignancy | 21 (95.5) |
| **Gender** | | | |
| Male | 16 (72.7) | **Site (**22 lesions) | |
| Female | 6 (27.3) | Forehead | 2 (9.0) |
| | | Nose | 2 (9.0) |
| **Race** | | Periorbital area | 3 (13.6) |
| Caucasian | 14 (63.6) | Upper lip | 2 (9.0) |
| Indian | 4 (18.2) | Lower lip | 1 (4.5) |
| Middle-Eastern | 3 (13.6) | Cheek | 3 (13.6) |
| Oriental | 1 (4.6) | Pre-auricular are | 2 (9.0) |
| | | Auricular area | 1 (4.5) |
| **Smoking status** | | Post-auricular area | 0 (0.0) |
| Life long smoker <20 cig/d | 7 (31.8) | Scalp | 2 (9.0) |
| Life long smoker >20 cig/d | 6 (27.3) | Neck | 0 (0.0) |
| Ex-smoker <20 cig/d | 0 (0.0) | Anterior chest wall | 1 (4.5) |
| Ex-smoker >20 cig/d | 4 (18.2) | Posterior chest wall | 0 (0.0) |
| Non-smoker | 5 (22.7) | Upper limbs | 2 (9.0) |
| | | Lowers limbs | 1 (4.5) |
| **Drinking status** | | | |
| Life long drinker <21 unit/w | 1 (4.6) | **Relevant Medical history** | |
| Life long drinker >21 unit/w | 2 (9.0) | Hx of actinic keratosis | 12 (54.6) |
| Ex-drinker <21 unit/w | 6 (27.3) | Hx of BCC | 7 (31.8) |
| Ex-drinker >21 unit/w | 1 (4.5) | Hx of skin SCC | 16 (72.7) |
| Non-drinker | 12 (54.6) | Immunodeficiency | 3 (13.6) |
| | | Hx of non-skin SCC | 4 (18.2) |
| **Risk factors** | | | |
| Chronic sun bathing | 16 (72.7) | **Size** <2cm in diameter | 16 (72.7) |
| Chronic non-healing wounds | 1 (4.5) | **Size** ≥2cm in diameter | 6 (27.3) |
| Genetic syndromes | 0 (0.0) | **Locally recurrent** | 0 (0.0) |
| HPV infection | 0 (0.0) | **Within scar, sinus, ulcer or burn** | 4 (18.2) |
| Ionizing radiation | 1 (4.5) | **Rapid growth** | 7 (31.8) |
| Environmental carcinogens | 0 (0.0) | **Immunosuppressed patient** | 2 (9.0) |
| Artificial UV radiation | 0 (0.0) | | |
| | | **Histological features** (biopsy) | |
| **Clinical description** | | Depth ≥2mm | 5 (22.7) |
| Macules | 4 (18.2) | Poorly differentiated | 6 (27.3) |
| Papules | 5 (22.7) | Perineural involvement | 2 (9.0) |
| Ulcers | 13 (59.1) | Intravascular invasion | 1 (4.5) |
| | | | |
| **Presenting complaint/concern** | | **Recurrence post PDT** (no. patients) | 2 (9.0) |
| Pain | 1 (4.5) | **Follow-up** | 72±18.5 |
| Itchiness | 1 (4.5) | Min-Max | 45-108 |

**Table 2:** Side effects reported by patients following treatment of their subcutaneous SCC using photodynamic therapy.

| Side effects – per patient post-PDT (%) | |
|---|---|
| Anaesthesia | 0 (0.0) |
| Paraesthesia | 1 (4.5) |
| Hypoesthesia | 0 (0.0) |
| Hyperesthesia | 1 (4.5) |
| Dysesthesia | 0 (0.0) |
| Hypopigmentation | 3 (13.6) |
| Hyperpigmentation | 0 (0.0) |
| Scarring | 0 (0.0) |
| Ulceration | 0 (0.0) |
| Transient milia | 0 (0.0) |
| Rosacea | 0 (0.0) |
| Recurrence | 2 (9.0) |

**Table 3:** Treatment of skin squamous cell carcinoma using photodynamic therapy: comparing patients versus response.

| | Frequency (%) |
|---|---|
| **Treatment 1 (PDT)** | **Total of 22 patients** |
| Complete response | 22 (100.0) |
| Partial response | 0 (0.0) |
| Stable disease | 0 (0.0) |
| Progressive – locoregional spread | 0 (0.0) |
| Progressive – distant spread | 0 (0.0) |
| **Recurrence within 6-18 months** | 2 (9.0) |
| **Treatment 2 (Surgery)** | **Total 2 patients** |
| Complete response | 2 (100.0) |
| **Recurrence** | 0 (0.0) |
| **3-year, 5-year and last clinic review outcome** | **Total of 22 patients** |
| Complete response: mTHPC-PDT alone | 20/22 (91.0) |
| Complete response: mTHPC-PDT and surgery | 22/22 (100.0) |