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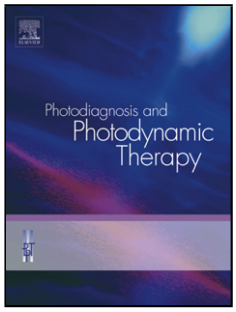

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Photodynamic therapy in the management of actinic keratosis: Retrospective evaluation of outcome

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Highlights

- Management of actinic keratosis lesions is usually based on the clinical characteristics of the lesion and the patient's choice.
- PDT offers an effective treatment for actinic keratosis lesions.
- With this technique (PDT) it is possible to treat multiple lesions at the same visit.

Abstract

Introduction

Photodynamic therapy (PDT) is a minimally invasive intervention used in the management of tissue disorders. In this retrospective study, a total of 62 patients with actinic keratosis (AKs) were treated with surface illumination PDT. Comparisons with the clinical features, rate of recurrence as well as malignant transformation and overall outcome were made.

Materials and methods

The medical records of 62 consecutive patients who presented with suspicious skin lesions and diagnosed with AKs were examined. These patients with 178 AKs lesions were treated with surface illumination methyl aminolevulinate – photodynamic therapy (MAL-PDT). The 16% strength cream (MAL) was applied topically 3 hours prior to tissue illumination. A single-channel 628nm diode laser was used for illumination and light was delivered at 100J/cm^2 per site. These patients were followed-up for a mean of 7.4 years.

Results

Eight recurrences were reported after the first round of MAL-PDT, and two recurrences after the second round. Malignant transformation to squamous cell carcinoma (SCC) was noted in 2 patients only. The 3-year outcome resulted in 60 patients with complete response (CR), and this was maintained at the final outcome (last clinic review). Assessment of lesional outcome vs. response showed that 175/178 treated lesions had complete response (CR) at 3-year follow-up, which increased to 176/178 lesions at the last clinic follow-up.

Conclusion

MAL-PDT offers an effective treatment for AKs lesions with excellent cosmetic outcome.

Keywords: 5-ALA, MAL, PDT, actinic keratosis, NMSC, photodynamic therapy, pre-cancer, recurrence

Introduction

Actinic keratosis (AKs), also known as solar keratosis, is considered to be precancerous skin condition and can be present in thick patchy, crusty, or scaly form. They are commonly known to occur in Caucasians. Frequent exposure to direct sunlight is notably a risk factor, due to the damage caused by ultraviolet radiation. If left untreated, AKs can progress into squamous cell carcinoma. The malignant transformation risk can be up to 20%[1,2].

Diagnosis is based on physical examination of the lesion and rarely histopathological confirmation is required. Clinically they are often described as having sandpaper–like texture with a variety of pigmentary alterations, (i.e. light, dark, tan, red or a combination of all) [1,2]. Scattered telangiectasias are one of its characteristics, similar to basal cell carcinoma. They are generally asymptomatic but many patients described lesions with tenderness, itchiness or burning sensation and in some cases they tend to bleed. They have been graded clinically depending on their visibility and palpability during clinical examination[2]. There are numerous clinical variants of AKs with the "classic" and "hypertrophic" ones being the most common. Others include atrophic form, pigmented, AKs with cutaneous horn, actinic cheilitis and Bowenoid form. Concern is raised about progression to malignancy if there is induration, inflammation, rapid enlargement, bleeding, erythema or ulceration. When there is uncertainty during clinical examination, then an incisional biopsy is recommended; it is usually taken from the thickest part of the lesion[3].

Management of AKs lesions is usually based on the clinical characteristics of the lesion and the patient's choice[2]. Medical management was proven to be successful when applying topical fluorouracil cream as it blocks the methylation of thymidylate synthetase; furthermore, a topical immune-enhancing agent (Imiquimod cream) was found to be of use in eliminating these lesions[3]. Disrupting cell membranes and cellular organelles causing cell death was achieved by Ingenol mebutate gel, while the diclofenac sodium gel was found to be beneficial as it causes inhibition of the arachidonic acid pathway. Retinoids have been introduced and found to be advantageous in treating these lesions[4].

Cryotherapy is commonly used to treat AKs. It is usually recommended to treat the mild forms of this pathology. Despite having high cure rates, this intervention is not commonly advocated nowadays due to side effects including destruction of surrounding healthy tissue, skin pigmentation, scarring and blistering. PDT is now commonly used to treat these lesions[3]. Both topical methyl aminolevulinate (MAL) and 5-aminolevulinic acid (5-ALA) have been used as part of this intervention. The MAL cream is applied topically over the lesion and the light therapy is delivered after few hours. High cure rates have been achieved using this technique with superior cosmetic outcomes[3,4]. Surgery can always be employed to deal with complex lesions. The surgical choices include surgical excision, shave excision and curettage and dermabrasion. Laser therapy is another alternative. Carbon dioxide (CO2) and

erbium:yttrium aluminum garnet (Er:YAG) lasers have been used and AK lesions have been dealt with by either resection or ablation[5].

The clinical course of these lesions varies depending on their characteristics and methods of intervention. Regression is most common in patients with few thin lesions, while recurrence is higher in patients with thicker symptomatic lesions. Patients with complex lesions and high recurrence rate tend to suffer from progression to malignancy[1,2,3].

In this retrospective study, a total of 62 patients with AKs were treated with surface illumination MAL-PDT. Comparisons with the clinical features, rate of recurrence as well as malignant transformation and overall outcome were made.

Materials and methods

Following a number of prospective ethically approved multicenter trials, PDT was approved by the European Medicines Advisory Committee. MAL is approved for the use in the management of AK and superficial BCC. The application of PDT 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 interventions (i.e. surgery, radiotherapy and/or chemotherapy) as well as patients with skin pathologies.

PDT is provided as a regular NHS treatment for several superficial and deep-seated tissue pathologies. 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, malignant transformation and last clinic review.

The medical records of 62 consecutive patients who presented with suspicious skin lesions and diagnosed with AKs were examined. All patients attending at our department undergo full assessment of their skin lesions, which includes physical examination, grading, anatomical diagrams and clinical photography as well as polarized contact dermoscopy. A surgical biopsy is employed when the diagnosis remains uncertain after the clinical assessment. This approach is also employed at every follow-up visit.

These 62 patients with 178 AKs lesions were treated with surface illumination MAL-PDT. These treatments were carried out at the Head and Neck Unit, University College Hospital, London between 2006 and 2008. Currently 15-20% of the patients we see jointly with our dermatology colleagues elect to receive PDT rather than receive conventional therapies.

We used Metvix, which is manufactured by Penn Pharmaceutical Services Ltd. and supplied by Galderma. Metvix cream contains methyl aminolevulinate (MAL), which is an ester of 5-aminolevulinic acid (5-ALA). It is available as a 16% strength cream in a 2g tube. Common side effects include: pain, mild swelling, skin redness, burning sensation and crusting; whilst the least common side effects include blister formation, ulceration, skin infection, hyper/hypopigmentation. The manufacturer of the laser is Diomed Ltd., Cambridge, UK

These patients were followed-up for a mean of 7.4 years, and biopsies taken in case of changes indicative of malignant development. Smoking status was classified into 5 categories each: life long smoker <20cig/year, life long smoker >20cig/year, ex-smoker <20cig/year, ex-smoker >20cig/year and non-smoker (Table 1).

A MAL cream was applied topically 3 hours prior to tissue illumination. Early application 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 few days after treatment to avoid local tissue photosensitive reactions and to allow gradual exposure afterwards.

Very few patients suffering from multiple/extensive AKs were offered the option to have the procedure under general anesthetics. It was offered as a day case where the patient is brought in the morning and the MAL cream applied and then after achieving the drug light interval (DLI), then a treatment is carried out in theatres. If the patient recovers well, then plan is set for discharge on the same day after giving the full discharge instructions.

On the day of treatment, shielding of the macroscopically healthy surrounding tissue is employed. A safety margin of 2mm around the suspicious lesion is included and illuminated as part of the treatment. The laser light delivery fibre, with a core diameter of 400µm, is usually held directly above the suspect area. A fibre holder has been used during all our treatments. The distance from the tip of the fibre to the tumour surface is 5cm with up to 3cm spot diameter. A single-channel 628nm diode laser was used for illumination and light is delivered at 100J/cm^2 per site with a dose rate of 50mW/cm^2 (Figure 1).

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, pain, medical issues).

Lesion response evaluation was carried out according to RECIST (Figure 2)- 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.

Statistical analysis

The results were analysed by an independent statistician using SPSS 17. The outcomes of the categorical clinicopathological variables were summarised as frequencies and percentages for the whole group of AKs patients. The numerical variables, "age and follow-up", were summarised by means, standard deviations, minimal and maximal values. The results were, also, cross-tabulated to test for differences in the case-mix.

Results

The patients' population comprised 43 males and 19 females. Their mean age at the 1st diagnosis was 58.9 years. Chronic sun bathing was the most prominent risk factor, which was reported by 50 patients. The treated lesions involved most of the body sites, with many located over the scalp (n=48), nose (n=32), forehead and peri-auricular area. Nearly half the cohort had history of AKs, with others reporting problems including history of BCC, skin SCC and immunodeficiency. Incisional biopsy was required in 18 patients to confirm the diagnosis. Eight recurrences were reported after the first round of MAL-PDT, and two recurrences after the second round. Malignant transformation to SCC was noted in 2 patients only (Table 1). After the first round of treatment, 3 patients reported hypoesthesia and 4 others reported hypopigmentation (Table 2).

The 3- year outcome resulted in 60 patients with complete response (CR), and this was maintained at the final outcome (last clinic review), (Table 3). Assessment of lesional outcome vs. response showed that 175/178 treated lesions had complete response (CR) at 3-year follow-up, which increased to 176/178 lesions at the last clinic follow-up (Table 4).

Using visual analogue scale (VAS), 53 patients reported that this treatment gave them "excellent" cosmetic outcome (VAS 9-10), 5 patients reported it to be "good" (VAS 7-8), 2 patients as "fair" (VAS 4-6) and the 2 patients who suffered from malignant transformation reported this intervention to be poor (VAS<4).

Discussion

PDT is an attractive treatment option for AKs. With this technique it is possible to treat large affected skin areas at the same visit. This intervention resulted in high cure rates. Wiegell postulated that the efficacy of 5-ALA-PDT and MAL-PDT has been established in multiple studies and recommended PDT as a first line therapy in the management of these AKs [2].

Treatment outcome in our study utilizing MAL-PDT of 62 patients with AKs showed that the majority of patients had complete response (CR) after the first round (58/62) and second round (10/12) of treatment. These results were consistent with a previous study[3]; which included 38 patients with AK, subjected to ALA-PDT, were

randomized to receive a light dose of 70 or 100 J/cm^2 as their first split face/scalp treatment. Remission at 3 months was 100% and at 6 months was 92.1% for the 70 J/cm^2 cohort; while it was 92.1% (at 3 months) and 84.2% (at 6 months) for the 100 J/cm^2 cohort. The study by Buinauskaite et al. concluded that topical ALA-PDT with the red light dose of 70 J/cm2 is an effective treatment for mild and moderate face/scalp AKs.

Unpublished data from our institute suggests that light delivery at 100J/cm^2 per site seems to be leading to a more favourable outcome when managing AK lesions and as such we modified the light parameters after discussion with our medical physicists (from the licensed protocol of the MAL cream) to ensure enhancing the effect of the photochemical process leading to a satisfactory clinical and a cosmetic outcome, especially when dealing with the severe face and scalp AKs. From our clinical experience and unpublished data, the 100J/cm^2 light dose appears to cause more satisfactory effect clinically and cosmetically compared to 37 J/cm^2 (MAL cream licensed protocol) and the 75 J/cm^2 recommended by the comparative study of Buinauskaite et al., which had a smaller cohort size and based its conclusions on mild and moderate face and scalp AKs.

A total of 7 patients only had adverse effects, which included pigmentation changes and altered sensation This agreed with previous findings which also suggested minimal side effects of PDT[3]. The reason for these unwanted effects could be due to irritation or damage to pigment-producing cells and/or nerve endings at the treated site. Efficiency of PDT in treating AK was also reported by retrospective study by Oh et al., data analysis of 13 East Asian patients treated with topical MAL-PDT showed an overall clearance rate at 3 months of 81.8%[4]. In addition to high rate of AK clearance, malignant transformation was only recorded in 2 patients. Furthermore, comparative studies favored PDT over other AK-therapeutic measures. In a meta-analysis of 641 participants, with a total of 2174 AKs treated with cryotherapy and 2170 AKs treated with PDT identified PDT to have a better chance (14%) of complete lesion clearance at 3 months compared to cryotherapy for thin face and scalp AKs lesions[5]. A Comparative study for the effect of PDT, imiquimod immunotherapy and combination of both therapies on 40 lesions of AKs in Japanese patients were assessed by Tanaka et al.[6]. Here severe AK cases were found to respond favorably to a combination therapy. Another privilege of PDT was concluded from feedback from patients enrolled in this study using VAS, 53 patients (~85%) indicated excellent cosmetic outcome, the evaluation by other patients (7) ranged between fair and good. Poor results were reported by the 2 patients who suffered malignant transformation.

PDT can be delivered under local or general anesthesia and the delivery technique can include surface illumination or interstitial application. The selective uptake and retention of a locally applied photosensitizer in pathological tissue is an important factor in the process[7,8]. When tumor:normal tissue differentiation has reached an optimum, the photosensitizer is activated by non-thermal light of the appropriate wavelength. This results either in the production of oxygen free radicals (type I mechanism) or the formation of intracellular singlet oxygen (type II mechanism),

which causes tumor cell death by intracellular oxygenation and vascular shutdown mechanisms[8-10].

MAL is applied topically. The advantage of topically applied photosensitizer is the complete lack of systemic photosensitivity and the fact that MAL-treated patients do not have to avoid exposure to light for 2-4 weeks following treatment[7,8]. The major disadvantage of a topically applied photosensitizer is the small treatment depth of only 1–2 mm that can be obtained. Therefore, only very superficial lesions of less than 1 mm can be treated successfully[10-12].

We believe that higher response rates can be achieved using PDT. By careful planning and application of the photodynamic process, the cure rates can be very high with a very low malignant transformation. The results from this modality are comparable to other modalities in achieving excellent clinical and cosmetic outcome. However, with PDT the risk of tissue scarring and volume loss are minimal. At this stage, there is no evidence to suggest that PDT reduces recurrence rates or malignant transformations when compared to other conventional interventions.

In summary, AKs lesions, which are often widespread, can be treated successfully with PDT with high cure rate, excellent cosmetic outcomes and minimal adverse events.

Competing interests and conflict of interests

We declare none.

Authors' contributions

All authors designed and performed the study, 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.

References

1. Schmitt AR, Bordeaux JS. Solar keratoses: photodynamic therapy, cryotherapy, 5-fluorouracil, imiquimod, diclofenac, or what? Facts and controversies. Clin Dermatol. 2013 Nov-Dec;31(6):712-7.

2. Wiegell SR. Update on photodynamic treatment for actinic keratosis. Curr Probl Dermatol. 2015;46:122-8.

3. Buinauskaite E, Maciulaitis R, Buinauskiene J, Valiukeviciene S. Topical photodynamic therapy of actinic keratoses with 5-aminolevulinic acid: randomized controlled trial with six months follow-up. J Dermatolog Treat. 2014 Dec;25(6):519-22.

4. Oh CC, Theng TS, Chong WS. A study of topical methyl-aminolaevulinate red-light photodynamic therapy in the treatment of actinic keratosis in Chinese patients: a Singaporean experience. Clin Exp Dermatol. 2015 Jul;40(5):502-6.

5. Patel G, Armstrong AW, Eisen DB. Efficacy of photodynamic therapy vs other interventions in randomized clinical trials for the treatment of actinic keratoses: a systematic review and meta-analysis. JAMA Dermatol. 2014 Dec;150(12):1281-8.

6. Tanaka N, Ohata C, Ishii N, Imamura K, Ueda A, Furumura M, Yasumoto S, Kawakami T, Tsuruta D, Hashimoto T. Comparative study for the effect of photodynamic therapy, imiquimod immunotherapy and combination of both therapies on 40 lesions of actinic keratosis in Japanese patients. J Dermatol. 2013 Dec;40(12):962-7.

7. Hopper C. Photodynamic therapy: A clinical reality in the treatment of cancer. Lancet Oncol 2000;1:212–219.

8. Jerjes W, Upile T, Betz CS, El Maaytah M, Abbas S, Wright A, Hopper C. The application of photodynamic therapy in the head and neck. Dent Update 2007;34(8):478–480, 483–484, 486.

9. JerjesW,UpileT,HamdoonZ,NhembeF,BhandariR,Mackay S, Shah P, Mosse CA, Brookes JA, Morley S, Hopper C. Ultrasound-guided photodynamic therapy for deep seated pathologies: Prospectivestudy.LasersSurgMed2009;41(9):612–621.

10. Jerjes W, Upile T, Hamdoon Z, Mosse CA, Akram S, Hopper C. Photodynamic therapy outcome for oral dysplasia. Lasers Surg Med. 2011 Mar;43(3):192-9.

11. Grant WE, Speight PM, Hopper C, Bown SG. Photodynamic therapy: An effective, but non-selective treatment for superficial cancers of the oral cavity. Int J Cancer 1997; 71(6):937–942.

12. Hopper C, Kubler A, Lewis H, Tan IB, Putnam G. mTHPCmediated photodynamic therapy for early oral squamous cell carcinoma. Int J Cancer 2004;111(1):138–146.

Figure Captions

Figure 1: Surface illumination PDT of multiple AK lesions of the scalp.

Figure 2: Clinical images showing response of thick actinic keratosis lesion to photodynamic therapy.

Table 1: Demographic details of 62 patients with actinic keratosis treated with photodynamic therapy.

	Frequency		Frequency
Age at diagnosis		**Site (**178 lesions)	
Minimum	45	Forehead	12
Maximum	74	Nose	32
Mean ±SD (years)	58.9±11.3	Periorbital area	5
		Upper lip	2
Gender		Lower lip	7
Male	43	Cheek	5
Female	19	Pre-auricular are	15
		Auricular area	17
Race		Post-auricular area	8
Caucasian	58	Scalp	48
Indian	2	Neck	3
Middle-Eastern	1	Anterior chest wall	8
Oriental	1	Posterior chest wall	4
		Upper limbs	7
Smoking status		Lowers limbs	5
Life long smoker <20	12		
Life long smoker >20	11	**Relevant Medical history**	
Ex-smoker <20	13	Hx of actinic keratosis	27
Ex-smoker >20	6	Hx of BCC	13
Non-smoker	20	Hx of skin SCC	19
		Immunodeficiency	7
Risk factors			
Chronic sun bathing	50	**Need for incisional biopsy**	18
Chronic non-healing wounds	4	Hyperkeratotic AK	7
Genetic syndromes	0	Pigmented AK	1
HPV infection	0	Lichenoid AK	9
Ionizing radiation	2	Atrophic AK	1
Environmental carcinogens	0		
Artificial UV radiation	0	**Primary Rx**	
		5-MAL-PDT	62
Clinical description			
Macules	42	**Recurrence after 1st round**	8
Papules	20	**Recurrence after 2nd round**	4
		Overall recurrence	3
Presenting complaint/concern		**Overall Malignant transformation**	2
Pain	7		
Itchiness	53	**Follow-up**	
Bleeding	4	Minimum	48
Cosmetic	17	Maximum	93
Fear of malignancy	36	Mean ±SD (months)	88±26.8

Table 2: Side effects reported by patients following treatment of their actinic keratosis lesions using 5-MAL photodynamic therapy.

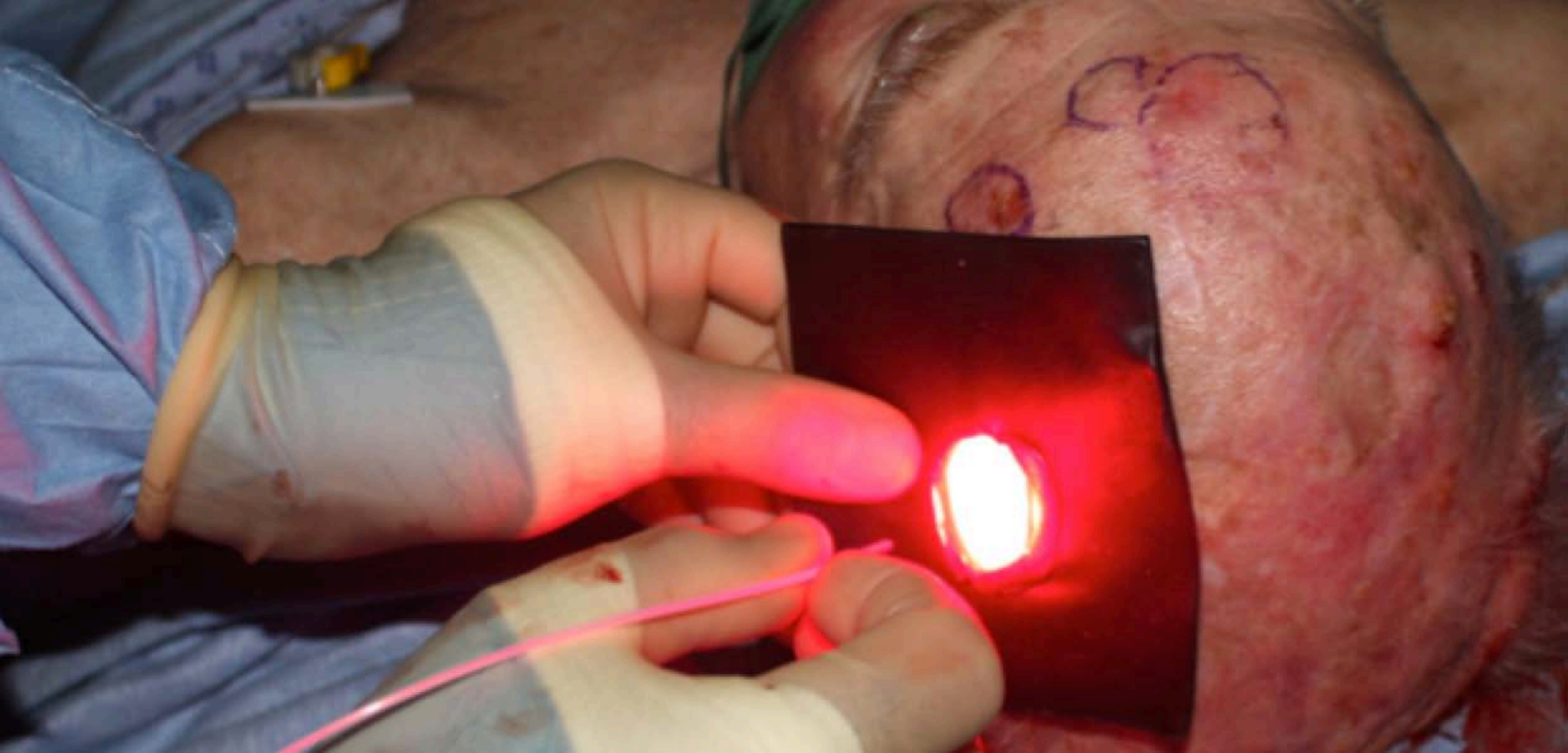
Side effects – per patient after 1st round of treatment	
Anaesthesia	0
Paraesthesia	0
Hypoesthesia	3
Hyperesthesia	1
Dysesthesia	0
Hypopigmentation	4
Hyperpigmentation	1
Scarring	0
Ulceration	0
Transient milia	0
Rosacea	0
Recurrence	9
Malignant transformation	0

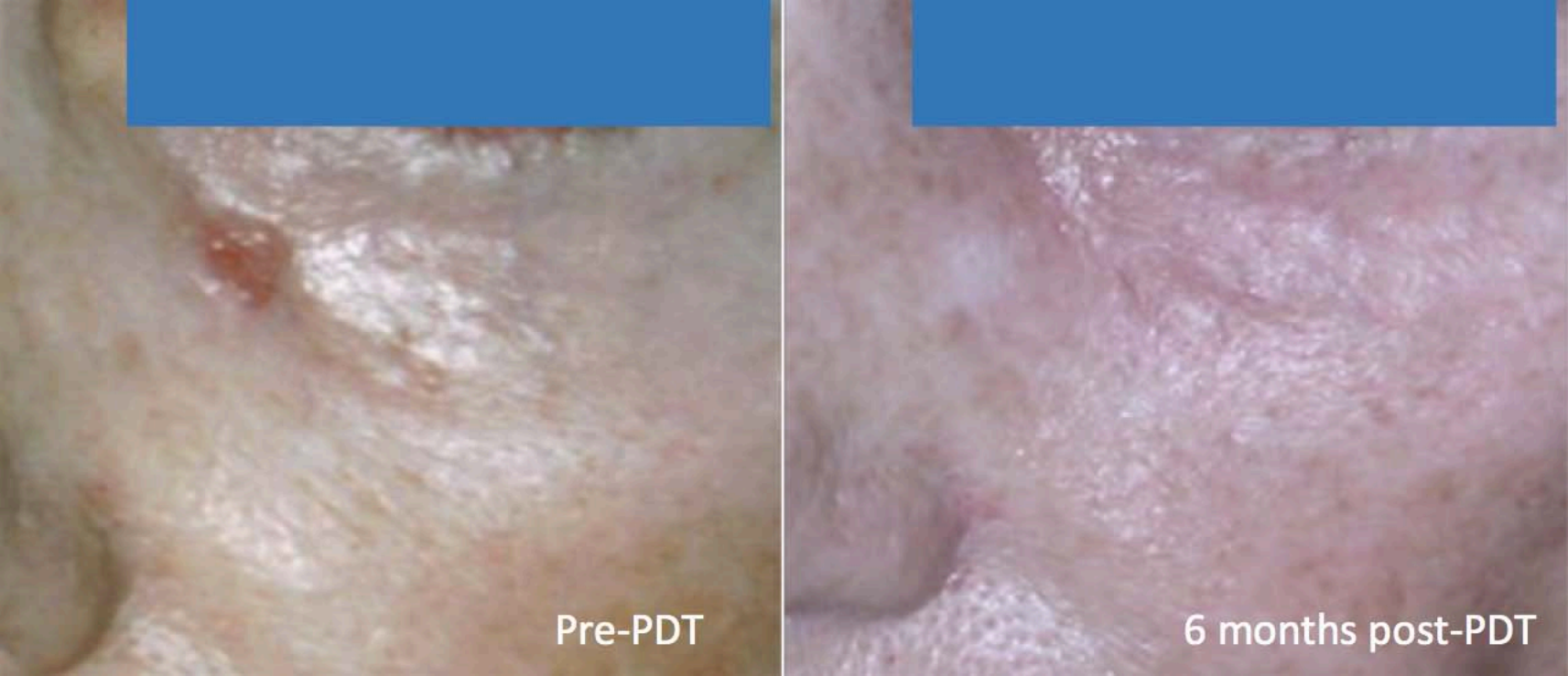
Table 3: Treatment of actinic keratosis using photodynamic therapy: comparing patients versus response.

	Frequency
Treatment 1	**Total of 62 patients**
Complete response	58
Partial response	2
Stable disease	2
Progressive disease (malignant transformation)	0
Recurrence	8
Treatment 2	**Total 12 patients**
Complete response	10
Partial response	0
Stable disease	1
Progressive disease (malignant transformation)	1
Recurrence	4
3-year outcome	**Total of 62 patients**
Complete response	60
Partial response	1
Stable disease	0
Progressive disease (malignant transformation)	1
5-year outcome	**Total of 62 patients**
Complete response	59
Partial response	2
Stable disease	0
Progressive disease (malignant transformation)	1
Final outcome	**Total of 62 patients**
Complete response	60
Partial response	0
Stable disease	0
Progressive disease (malignant transformation)	2
Overall recurrence	3

Table 4: Treatment of actinic keratosis using photodynamic therapy: comparing number of lesions versus response.

	Frequency
Treatment 1	**Total of 178 AKs**
Complete response	167
Partial response	8
Stable disease	3
Progressive disease (malignant transformation)	0
Recurrence	9
Treatment 2	**Total of 20 AKs**
Complete response	18
Partial response	0
Stable disease	1
Progressive disease (malignant transformation)	1
Recurrence	5
3-year outcome	**Total of 178 AKs**
Complete response	175
Partial response	2
Stable disease	0
Progressive disease (malignant transformation)	1
5-year outcome	**Total of 178 AKs**
Complete response	173
Partial response	4
Stable disease	0
Progressive disease (malignant transformation)	1
Final outcome	**Total of 178 AKs**
Complete response	176
Partial response	0
Stable disease	0
Progressive disease (malignant transformation)	2
Overall recurrence	5




Pre-PDT
6 months post-PDT