

## Challenging Approach with Nanoformulation and Photodynamic Therapy in Dermatology

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### Abstract

**Background:** Photodynamic therapy (PDT) holds substantial promise in improving outcomes of patients with a form of cutaneous conditions and dermatological conditions such as keratosis and basal cell carcinoma, etc. Use of 5-aminolevulinic acid (ALA) was sanctioned as secure and effective for use as a treatment.

**Methods:** In our work, we used Photodynamic therapy in patients with selected skin cancerization, and evaluated the fluorescence from photo sensitizer to constitute the field cancerization, which helps in analyzing the efficacy of the technique.

**Results:** From our study, it is clear that use of ALA with PDT against different skin cancerization has significant effects. However, the effect of efficacy varied according to the type of carcinoma. In our study, we observed that nano-ALA with PDT targeted about 70-80% more skin lesion and the mean reduction area of skin cancerization was about 10% greater with nano-ALA and PDT.

**Conclusion:** Our findings suggest use of ALA-PDT as a simple, cost effective, and novel method that can be used for various skin cancerization treatments.

**Keywords:** Skin; Cancerization; Treatment; ALA; Patients

### Introduction

The combination of nanoformulation and Photodynamic therapy (PDT) has become one of the leading research topics [1]. Phototherapy is a promising strategy used in the treatment with activation of photosensitizing drugs of particular wavelengths of lights which produces energy transforming into cytotoxic reactive oxygen which render apoptotic and necrotic cell death [2].

Therapeutic approaches with a novel targeting system with high efficacy and less toxicity are in high demand focusing on drug discoveries, which has clinical approach. Use of nanoformulation is one such approach in novel therapeutic systems [3]. Drugs with nanoparticles have special approach such as smaller size (up to 100 nm) stability, bioencapsulation, biocompatibility etc. that focus on many drawbacks in usage of traditional drugs [4].

Various drug delivery systems, which are widely in use, are nanoliposomes in cancer therapy, theragnostics that are used for diagnosis and treatment of cancer [5]. When compared to other methods of treatment such as radiation therapy, chemotherapy, surgery etc use of nanoformulations and PDT has many advantages like less morbidity, lesser invasive procedures, better tolerance and combination of nanoformulation and PDT can be used repeatedly on the same surface of the affected region [6,7].

There are several reports on the use of nanoformulation for the treatment of skin cancerization. Use of nanoformulation with PDT has better effectiveness [8-10]. Nevertheless, still there are drawbacks in the use of this nanoformulation 5-aminolevulinic acid (ALA) along with PDT such as leakage of drug, instability of the formulation and side effects for a longer duration [11-13].

In our study, use of 5-aminolevulinic acid (ALA) nanoformulation along with Photodynamic therapy has been found to be safe and effective against the treatment in skin cancerization.

### Materials and Methods

The nanoformulation ALA is photosensitized onto a nano-emulsion with polylactide-polyglycerol with a size range of 100-300 nm analyzed using scanning electron microscope as reported in various literatures [14]. The institutional ethical committee approved this study. An informed consent was obtained from the patients after explaining the study procedures.

A total of 100 patients diagnosed of skin cancerization attending the dermatology unit of Shandong Provincial Institute of Dermatology and Venereology, Jinan, China were included in the study. Among the 100 patients, 53 were males and 47 were females in the age group of 35-60 years were taken for the study. Among 53 males, 42 (79.2%) were diagnosed with basal cell carcinoma and 11 (20.8%) with squamous cell carcinoma. Among 47 females, 28 (59.6%) are diagnosed with Bowen's disease and 14 (29.8%) with basal cell carcinoma and 5 (10.6%) with squamous cell carcinoma.

Those patients who are prone to hypersensitivity reactions, patients receiving steroid therapy, and patients with other allergic reaction are excluded from the study. 30 patients with other skin diseases, which may later lead to cancerization, were served as control groups. The control group patients were also treated with the same nano ALA formulation along with Photodynamic therapy. The selected patients

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are taken for therapy with 2-5 weeks apart between each session of treatment.

**Pretreatment**

The areas to be treated in the patients are washed with water and alcohol. The area where treatment to be started was performed with micrdermabrasion which helps in increased penetration of ALA. After applying ALA, it allows for 1-2 hours.

**Post treatment**

Patients were instructed to apply moisturizers and advised to avoid exposure to direct sunlight for up to 48 hours. There may be mild side effects like rashes and redness after treatment between 24 to 72 hours.

**Software analysis**

Field cancerization and the exposure to PDT therapy is analyzed and quantified with color image segmentation software. Using this software fluorescent area treated can be recorded using digital techniques, which estimates the skin area fluorescing under light.

**Results**

The particle size of the ALA was examined using scanning electron microscope which showed ALA nano-particle in spherical shape (Figure 1 and Table 1). Our study used both fluorescent and non fluorescent areas (Figure 2). The changes were noted among the patients. The images obtained are recorded after treatment with nano ALA and PDT using wood lamp illumination. The fluorescent area is linear to field cancerization.

Invariable to the severity of cancerization ALA with PDT were given

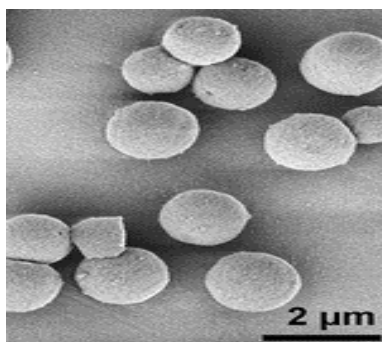


Figure 1: Scanning electron micrograph showing the size of the Nano ALA.

Properties	Nano ALA
Size dispersion	0.14
Size (nm)	172.2
Potential	-48.4
Soluble	Aqueous
Self life	100 days
Pathway	Type II PDT (singlet O <sub>2</sub> )

Table 1: Properties of Nano ALA.

Types of skin cancerization	Age group in years	Male
Basal cell carcinoma	40-55	42
Squamous cell carcinoma	35-45	11
Bowen's disease	45-50	-

Table 2: Age wise distribution of different cancer group patients among male.

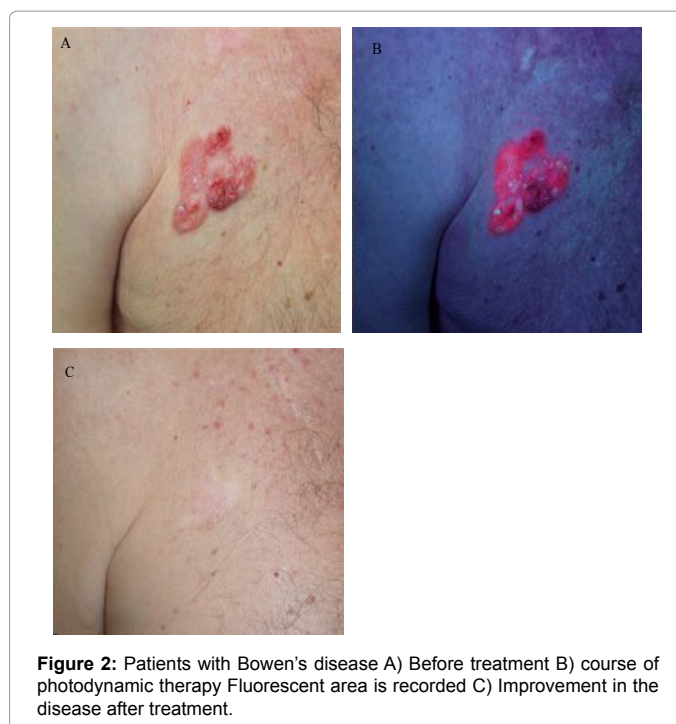


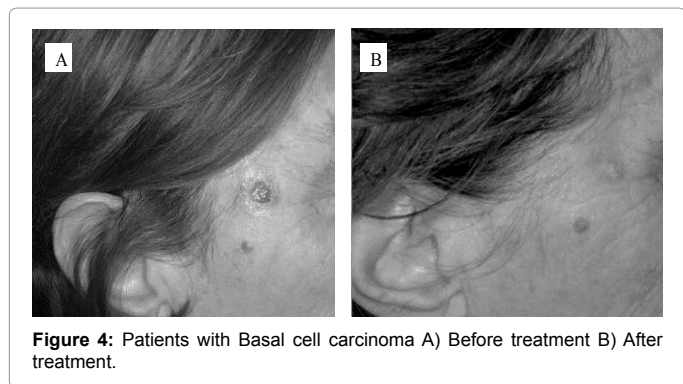
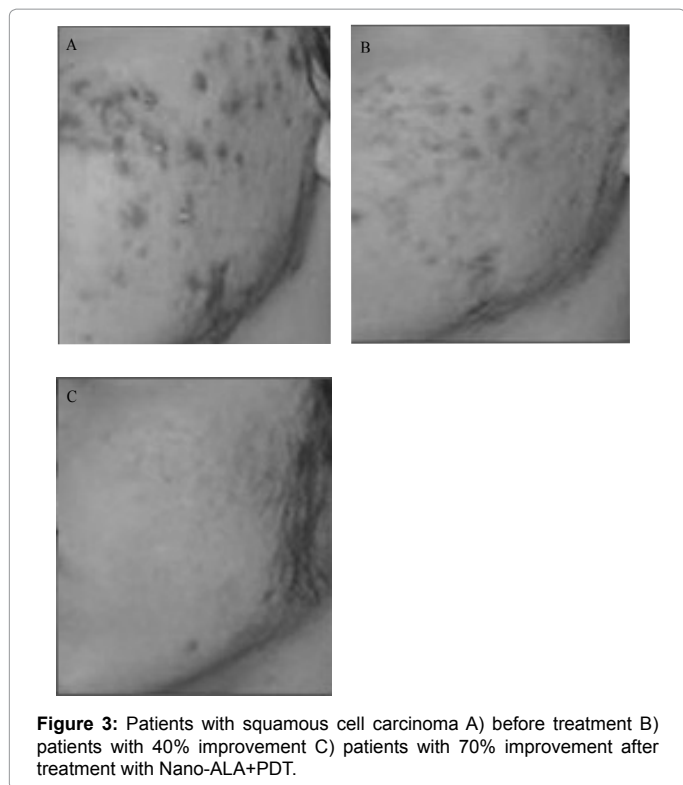
Figure 2: Patients with Bowen's disease A) Before treatment B) course of photodynamic therapy Fluorescent area is recorded C) Improvement in the disease after treatment.

for patient's upto six months and followed for 1 year after treatment to observe for the side effects. Nano ALA was used in the treatment of patients with severe skin cancerization and also in patients with less severity to compare the efficacy of the nano ALA. The exposure time was 1-3 hours after applying the formulation. Nano ALA was found to be more efficient in patients all most all carcinoma patients expect in very few who did not respond to therapy properly and also in patients who had discontinuous in there visit for the treatment.

Among 42 (79.2%) males diagnosed with basal cell carcinoma 28 (66.7%) had up to 75% reduction were as 10 (23.8%) patients had only 55% improvement and 4 (9.5%) patients had less than 20% of improvement. Those patients with less effectiveness either the therapy were prolonged for 5 weeks or the time of exposure was extended to 4 hours, which showed better improvement. All the male patients who showed significant improvement were in the age group of 40-55 years. The Less effective group was 55-65 years of age. In 11 (20.8%) patients with squamous cell carcinoma 6 (54.5%) showed effective improvement of 70%, whereas 5 (45.5%) showed only 40% improvement (Figure 3). All these patients were in the 35-45 years of age (Table 2 and Figure 5).

Among 47 females 28 (59.6%) were diagnosed with Bowen's disease among which only 18 (64.3%) showed improvement of 65% in 45-50 years of age group. Ten (35.7%) showed 45% in improvement in age 50-55 years (Figure 2). 14 (29.8%) with basal cell carcinoma 8 (57.1%) showed 80% improvement were as 6 (42.9%) showed 55% improvement in the age group 35-50 years (Figure 4). Among the 5 (10.6%) squamous cell carcinoma affected females 3 (60%) showed 35% improvement. 2 (40%) showed less than 10% improvement. All the 5 were in the age group 45-50 years (Table 3 and Figure 5).

Patients who had less improvement were given a prolonged therapy up to 4 hours. In those patients, we observed significant side effects such as rashes, allergic response, and hypersensitivity reactions mostly seen among basal and squamous cell carcinoma affected patients than in other patients like Bowen's disease.



Types of skin cancerization	Age group in years	Female
Basal cell carcinoma	45-50	14
Squamous cell carcinoma	35-50	5
Bowen's disease	45-55	28

**Table 3:** Age wise distribution of different cancer group patients among Female.

Among the 30-control group, patients with other skin disease the same therapy were given showed significant improvement of 85%. All the control groups were in 40-50 years of age.

## Discussion

ALA with PDT are used for various treatments of skin across the world. Application of ALA with PDT is modality used on several skin cancerization treatments [6,15,16]. However, because of the non-bioavailability locally, instable, less penetrating capacity into the cell membranes leads to limited activity of ALA with PDT. This limitation has to be overcome to enhance the efficacy of ALA with PDT. There are various modes of delivering ALA such as by patch method, applying

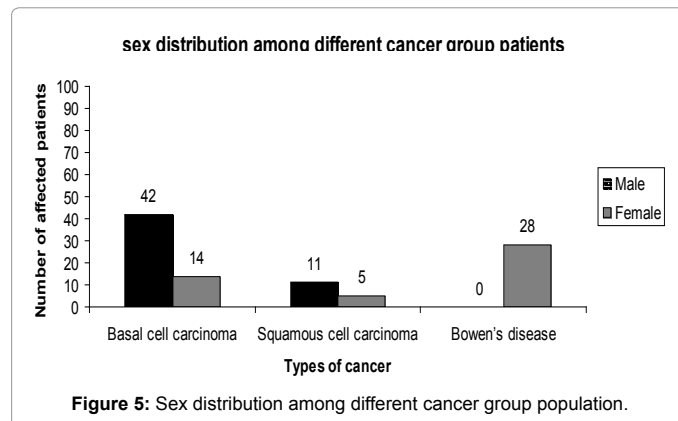
laser, microneedles, microemulsion [17-20]. A lot of research studies have been carried out to know the drug delivering systems for ALA [21-24].

In our study, we used double emulsion system to entrap nano-ALA. There are various factors, which contribute to the stability of the drug ALA such as pH, temperature, concentration. In terms of clinical aspects, the area treated with nano-ALA, which showed improvement more than 60%, and least improvement range of less than 20% favors ALA nanoformulation. For better approach, there should be a balance between the application and need to be monitored by the dermatologist [25].

Basal cell carcinoma is the commonest carcinoma of skin mainly affecting the areas, which are exposed to sun. There are many reports available on the effects of PDT on basal cell carcinoma [26,27]. Our study showed 75% improvement among male patients in the age group of 40-55 years and 80% improvement in female patients in 35-50 years of age, which is slightly less compared to a study, which reports 87% of improvement in basal cell carcinoma patients invariable to their sex, and age [28]. This difference in the improvement rate can be difference in the number patients studied in their study and in ours. In another study which reports 92% of improvement among basal cell carcinoma with ALA-PDT therapy [29].

Bowen's disease is a precancerous skin disease, which appears as scaly patches, and these are more common among females. Generally, the lesions develop as a slow creeping disease with less mortality rate as it responds well for treatment [30]. From our study none of the males who attended our hospital was diagnosed with Bowen's disease supporting the literatures in our study we also observed that only females were diagnosed with Bowen's disease. Among 47 females, 28 were diagnosed with Bowen's disease in which efficacy rate of 65% were observed among 45-50 years of age when they were treated with ALA-PDT. Least efficacy of 45% was observed in 50-55 years of age in females with this Bowen's disease, which are slightly low compared to another study, which reported 89% to 100% of efficacy [28]. Whereas another study reports efficacy rate of only 50% of ALA-PDT against Bowen's disease [31].

Squamous cell carcinoma seconds the basal cell carcinoma among the non-melanoma skin cancer. Uses of ALA-PDT against basal cell carcinoma are increased in the recent years but it is only emerging in case of squamous cell carcinoma. In a study by a researcher who reported 50% efficacy which is slightly higher in our study with 70-40% efficacy rate among males in 35-45 years of age whereas in females only 35% efficacy was observed in 45-50 years of age when ALA-PDT was





used as a therapeutic options [32,33]. The control group population who had other skin diseases responded to ALA-PDT therapy of upto 85% improvement in the age group of 40-50 years.

From our study, it is clear that use of ALA with PDT against different skin cancerization has significant effects. However, the effect of efficacy varied according to the type of carcinoma. Our study also highlights the efficacy of ALA with PDT among male and females with respect to age, which is one of the few studies, which had reported efficacy of ALA with PDT based on age and sex of the patients. In addition, our study suggests use of ALA-PDT as a simple, cost effective, and novel method that can be used for various skin cancerization treatments.

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