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# 5-aminolevulinic acid based Photodynamic therapy for basal cell carcinoma: A 10-years follow-up study

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## SUMMARY

*Objective.* This article presents long-term follow-up after use of topical photodynamic therapy (PDT) for basal cell carcinoma. PDT is treatment option for different tumors, involving use of specific agent which is activated by visible light and results in tissue destruction.

*Materials and methods.* Overall 20 patients with 29 tumors were treated at the Latvian Oncology Center. Two illumination techniques were used: superficial for smaller lesions and multifiber contact for nodular tumors. Clinical outcome was evaluated at 1, 7, 44 months and 10 years after procedure.

*Results.* By 10 year follow up, there were 2 tumor recurrences and in one case there was tumor residual tissue after first PDT treatment. Overall after ten years follow-up complete response was 80% of cases.

*Conclusion.* Data in this study supports hypothesis that PDT could be used for the treatment of non-invasive (superficial and nodular) basal cell carcinoma. Results in this study correspond with similar long-term follow-up studies.


**Key words**: photodynamic therapy, 5-aminolevulinic acid, basal cell carcinoma, long-term follow-up.

## INTRODUCTION

Basal cell carcinoma (BCC) – is the most common nonmelanoma skin cancer, which incidence grows every year world-wide. There are a lot of treatment options for this tumor, ranging from Mohs micrographic surgery to topical therapies (1). One of treatment opportunities is photodynamic therapy (PDT).

PDT involves the use of a photoactive dye (photosensitizer, PS) that is activated by exposure to light of a specific wavelength in the presence of oxygen. The transfer of energy from the activated photosensitizer to available oxygen results in the formation of toxic oxygen species, such as singlet oxygen and free radicals. These very reactive chemical species can damage target tissue.

This method is used in many EU countries, USA, Canada, Japan and Russia (2).

PS is typically administered intravenously or topically, followed by illumination using a light delivery system suitable for the anatomical site being treated (3).

First clinical trial in Latvia using PDT with topical photosensitizer 5-aminolevulinic acid (ALA) for treatment of basal cell carcinoma was performed in 2001 (4).

ALA itself has no photosensitizing effect, but is a natural precursor of heme circle. This pathway ends with the conversion of protoporphyrin IX (PpIX), which has photosensitizing properties, into heme by ferrochelatase. Many tumor types have a lower ferrochelatase activity than normal tissue. Therefore, upon administration of ALA, the capacity of ferrochelatase is overwhelmed, resulting in a buildup of PpIX in tumor cells. The absorption spectrum for PpIX is very similar to that of porfimer sodium, and it is usually activated by light of 630-635 nm (5).

*Aim of this study* was to evaluate long-term clinical results after ALA based BCC treatment with photodynamic therapy.

## MATERIAL AND METHODS

The study was approved by local ethic committee. Patients signed informed consent to procedure

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in compliance with Helsinki declaration of 1975 (revised 1983). The study was performed at the Latvian Oncology Center.

Overall 20 patients were selected for procedure (8 male, 12 female; age between 29 and 86, average 70 years) with 29 BCC and treated in spring 2001. Before use of PDT 4 lesions were treated surgically.

All tumors were examined with punch biopsy for cytological and histological analysis for tumor classification. All of them were classified as BCC with minimal thickness 2 mm. Tumor size varied between 5×5 to 40×42 mm$^2$.

More than half of lesions were localized on back, six on a face (4 – H-zone), two on trunk and one on an upper-arm.

For treatment δ-aminolevulinic acid (ALA, Medac, Batch-No.: M01130 AA, diluted in 0,9% saline solution and mixed with water and oil emulsion was used. Concentration for treatment was 20% by weight. Light was exposed to tumor itself and 10 mm beside visible tumor border, where ALA was also applied (4).

As light source diode laser was used (CeramOptec Ceralas PDT 635) with wavelength 635 nm and 2W output power. Two light application methods were used:

Superficial, for tumors with small surface area (17 cases)

Multifiber contact (MFC) light application for nodular tumors (12 cases). Fiber amount were 3 for 4 tumors and 6 for 8 tumors. (Figure 1) [4].

In previous studies clinical and cosmetic outcomes were evaluated after 1, 7, 28, 44 months. Clinical outcome was evaluated visually and morphologically by cytological or histopathological examination (for nodular tumors by two independent patologist from Latvia and Sweden). In this study clinical outcome was evaluated 10 years after

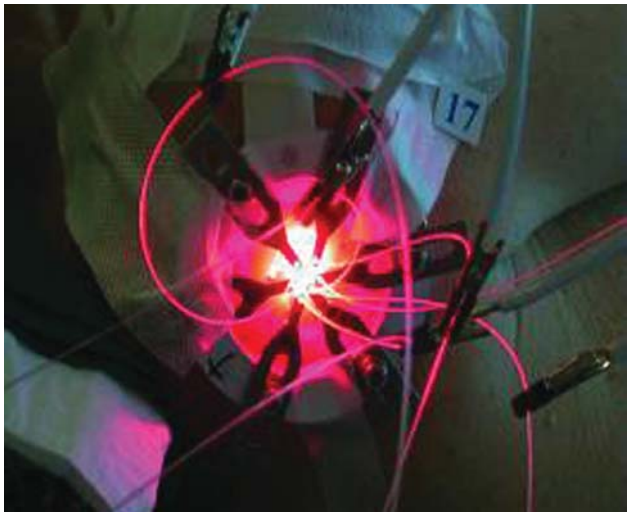


**Fig. 1.** Multifiber contact illumination

treatment. Data about patient clinical condition was gained by follow up or by phone call to patients.

Clinical outcome was evaluated as complete response (CR), partial response (PR), no response (NR) and tumor recurrence (TR). Complete response determined, when disease site is clinically without any evidfence of BCC; partial response – when tumor decreased by 50% or more by seven month follow up; no response – when disease decreased by less than 50%; tumor recurrence was observed, when disease is remained more than six months after treatment (according to WHO, 1979).

For statistical analysis Kaplan-Meier method with help of MedCalc® software was used.

## RESULTS

One month after procedure all patients (except 2, who did not come on recall) were examined his-

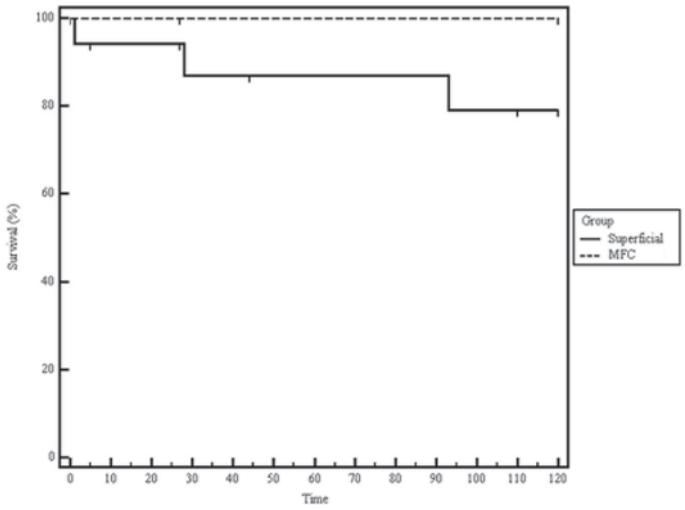


**Fig. 2.** Kaplan-Meier method for lesions divided in two groups – MFC group and Superficial illumination group

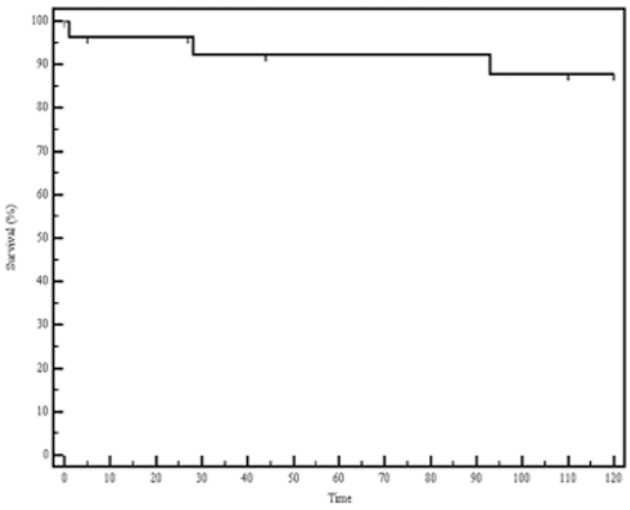


**Fig. 3.** Kaplan-Meier statistical method for all lesions

tologically and visually. All histological samples with CR are without BCC. CR was observed in 25 of 27 tumors (93%), PR was observed in 2 tumors.

After 7 months 16 patients were examined in Latvian Oncological center. 20 tumors (85%) showed CR, 3 tumors – PR. Punch excisions converted two PR to CR (4).

Interestingly that complete response was achieved in all cases, treated with multifiber light application PDT.

After 44 months 12 out of 20 patients came for recall, three died from disease not related to this study. Clinical outcome was following: in 17 sites CR, in one TR, in 1 residual tissue after PR. During follow-up one TR and one residual tumor was observed.

10 years after treatment clinical data were collected from 15 patients (five excluded because of disease nonspecific death). Clinical outcomes were as follows: there was one tumor recurrence, other 14 patients denied the existence of the disease. Again all patients, who gone through multifiber contact PDT, were disease free. Overall during 10 year follow-up, two TR and one residual tumor were observed.

**Table 1.** Overall clinical outcome by 10 years

| Patient | Age | Gender | Tumor data | | | PDT Mode | | Clinical outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lesion | Locali-zation | Earlier treatment | MFC | Sup | 1 month | 7 months | 44 months | 10 years |
| 1 | 43 | F | 1 | Back | Surgery | | X | CR | PR | Residual tissue | |
| 2 | 40 | M | 2 | Back | None | | X | CR | CR | TR | |
| 3 | 65 | M | 3 | Back | None | | X | PR | CR | - | TR |
| 4 | 69 | F | 4 | Back | None | X | | - | CR | CR | CR |
| 5 | 70 | M | 5 | Back | None | | X | CR | Disease nonspecific death | | |
| | | | 6 | Back | None | X | | CR | | | |
| | | | 7 | Back | None | | X | CR | | | |
| 6 | 70 | M | 8 | Back | None | X | | CR | CR | CR | CR |
| 7 | 73 | F | 9 | Back | None | | X | CR | CR | - | CR |
| | | | 10 | Back | None | X | | CR | CR | - | CR |
| 8 | 75 | M | 11 | Back | None | | X | CR | CR | - | Disease non-specific death |
| 9 | 59 | F | 12 | Face | None | | X | CR | CR | CR | CR |
| 10 | 65 | F | 13 | Trunk | None | X | | CR | CR | CR | CR |
| 11 | 76 | F | 14 | Back | Surgery | | X | CR | - | CR | CR |
| | | | 15 | Back | Surgery | | X | CR | - | CR | CR |
| | | | 16 | Back | Surgery | | X | CR | - | CR | CR |
| 12 | 29 | F | 17 | Back | None | X | | CR | CR | CR | CR |
| 13 | 48 | F | 18 | Trunk | None | X | | CR | CR | CR | CR |
| 14 | 73 | F | 19 | Face | None | | X | CR | CR | CR | CR |
| 15 | 73 | F | 20 | Face | None | | X | CR | CR | CR | CR |
| | | | 21 | Face | None | | X | CR | CR | CR | CR |
| | | | 22 | Face | None | | X | CR | CR | CR | CR |
| 16 | 86 | F | 23 | Face | None | | X | CR | - | Disease nonspecific death | |
| 17 | 82 | M | 24 | Arm | None | | X | CR | Disease nonspecific death | | |
| 18 | 79 | M | 25 | Back | None | X | | - | - | - | Disease non-specific death |
| 19 | 79 | F | 26 | Back | None | X | | CR | CR | CR | CR |
| 20 | 77 | M | 27 | Face | None | X | | CR | CR | CR | CR |
| | | | 28 | Back | None | X | | PR | PR | CR | CR |
| | | | 29 | Back | None | X | | PR | PR | CR | CR |

MFC – multifiber contact light application, Sup – superior light application, CR – complete response, PR – partial response, TR – tumor recurrence.

Three lesions that were previously treated with surgery showed CR after PDT. One lesion – residual tumor tissue after first PDT treatment.

Clinical outcome after 1, 7, 44 months and 10 years are shown in table (Table) and graphically by Kaplan-Maier method (Fig 2 and 3).

## DISCUSSION

There are lacks of studies that provide long-term clinical outcome after ALA based PDT. None of them report about 10 year follow-up. The main finding in our study is that ALA-based PDT provides good clinical results. Type of tumor should be kept in mind for choice of illumination technique. We have found following results in few similar studies. Star *et al.* (2006) reported ALA based PDT with two light fractions with two hour interval. At mean follow-up of 59 months 67 superficial BCC were evaluated, CR was achieved in 56 cases (86%) (6).

Another long-term study show results 6 years after ALA based PDT. In this study BCC treated with one or two sessions of dimethylsulfoxide (DMSO)-supported 5-aminolaevulinic acid – PDT following curettage. 43 lesions were evaluated clinically and cosmetically 72 months after treatment. CR was achieved in 81% cases (43/53). More that 90% long-term CR were cleared 3 months after two-session therapy. Interestingly, that more than a half of recurrences occurred in face H-zone (7).

Sauza *et al.* (2009) treated non-melanoma skin cancers with ALA based PDT; also Bowen's disease treatment was included in this study. Different types of BCC were included in this study. After 60 months follow-up CR was achieved in 7 out of 11 cases of BCC: 4/6 superficial and 3/5 nodular (8).

Mosterd *et al.* (2008) compared two treatment modalities for nodular BCC. One was surgical excision, another ALA based PDT with two times illumination at the same day and 3 weeks after debulking. 173 primary BCC were randomly assigned either to PDT either surgery. Failure rates were higher for PDT, 30.3% of all tumors after 3 year follow-up (9). Rhodes at el (2007) prepared similar study, but methylated ALA based PDT was compared to surgery. After 5 year follow-up, surgery group had lower reccurence rate (4% versus 14%). Cosmetical outcome was better in PDT group (10).

ALA is modified to improve penetration abilities and reduce side-effects. One of these modifications is methyl ester of ALA (m-ALA, Metvix®) (5). Schleier *et al.* (2007) compared methylated ALA with non modified molecule clinical effects. One group included 13 patients with 72 tumors, another 11 patients with 40 tumors. After 12 months results were approximately same for both groups – 61% CR for ALA group and 57.5% for m-ALA. There are no studies that provide long-term comparison (11).

Our long-term results are similar to other studies. There are differences from study to study between illumination parameters, procedures amount, application field, drug use, etc.

In our study there are no significant differences between 5 and 10 year follow-up results, except one case. Probably, a bigger group of patients is required to support this assumption. All tumor recurrences or partial response occurred in back, other sites are clear.

## CONCLUSION

Data in this study supports hypothesis that PDT could be used for the treatment of non-invasive (superficial and nodular) basal cell carcinoma. Results in this study correspond with similar long-term follow-up studies.

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