

Photodynamic therapy for nodular basal cell carcinoma up to 5mm located on high-risk area: Effectiveness and long-term follow-up results

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ABSTRACT

Significance: Response rates evaluation of photodynamic therapy (PDT) for nodular basal cell carcinoma (BCC) treatment located on high-risk and low-risk areas of the face.

Approach: Two groups of nodular BCC were selected, debulked, and received 20% methyl aminolevulinate (MAL) hydrochloride cream. After 3 h, the first irradiation was performed (20 min, 150 J/cm²). Then, the cream was re-applied, and a second irradiation was performed after 1.5 h (20 min, 150 J/cm²). Clearance at 30 days and recurrence-free survival rate were evaluated.

Results: The clearance at 30 days after PDT was 89% for the low-risk area group and 87% for the high-risk group. The recurrence-free survival at 60 months was 82% and 85% for the high-risk and low-risk groups, respectively.

Conclusions: No significant differences were observed between groups nor for clearance at 30 days, nor recurrence-free follow-up. These results make PDT possible option for nodular BCC less than 5 mm located in high-risk areas.

1. Introduction

Skin cancer is the most frequent cancer type in the world population, and the incidence of basal cell carcinoma (BCC, the most frequent skin cancer type) is increasing worldwide and is predicted to increase until 2040 [1]. More than 70% of BCCs occur in head and neck area [2]. The location of the BCC on the face can predict its behavior, as well as tumor size [3]. Lesions located on high-risk areas defined as tumors on the "mask area" of the face (i.e., nose, lips, eyelids, eyebrows, periorbital skin, chin, mandible, ears, preauricular and postauricular areas, temples) have a higher recurrence risk and, small lesions have low recurrence rate [4]. The gold standard treatment for BCC is surgery, but photodynamic therapy (PDT) can be an option, especially when there are multiple lesions as well as comorbidities that contraindicate surgery [5,6]. In order to support a possible indication of the PDT technique for BCC located on the face, it would be important to evaluate of response rates of small BCC treated with PDT.

2. Materials and methods

This study was conducted from January 2016 to April 2021 in a tertiary dermatology service at an oncology hospital, where 98 lesions of nodular BCC up to 5 mm diameter in 52 adult patients were selected. The lesions were debulked and the material was taken to histological confirmation of BCC. The nodular BCCs were separated into 2 groups according to anatomical risk area of the face: group "high-risk area" (BCC located on nose, eyebrows, periorbital skin, chin, mandible, ears, preauricular, postauricular areas, and temples) and group "low-risk area" (others face areas) as illustrated in Fig. 1.

Then, a 20% w/w concentration of methyl aminolevulinate (MAL) hydrochloride cream (PDT Pharma, Brazil) was applied and the area was covered for 3 h. The first irradiation was performed, using a commercial LED device system emitting at 630 nm (LINCE, MMOptics, Brazil). The lesion was irradiated for 20 min with 125 mW/cm² totalizing 150 J/cm² of fluence. Immediately after the first irradiation, another MAL cream layer was applied and covered, but now for only 1.5 hours (Fig. 2).

After that, a second irradiation was performed using the same

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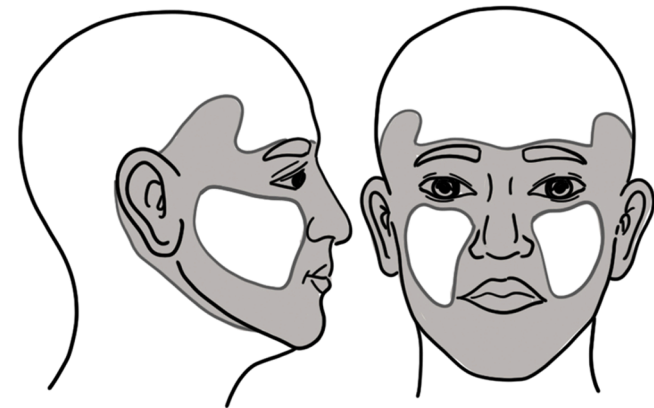


Fig. 1. Representation of high-risk areas of the face (darker shade) and low-risk areas (lighter shade).

parameters [7]. This PDT protocol consisted of two sessions performed in a single day and was previously explored by the authors [7]. Thirty days after treatment, a 2 mm punch biopsy was performed to evaluate the treatment response by histological analysis and estimate the cure rate between the groups which was compared using the *Chi-Square test*. A clinical and dermoscopic evaluation of the remaining cases was performed every 6 months until December 2022. The recurrence-free survival rate was calculated by using the Kaplan-Meier survival curve.

3. Results

Most of the lesions were located in high-risk areas and most of the patients were female. The mean age was 57 years old for the high-risk areas group and 66 for the low-risk group. Both groups had a mean diameter of 4 mm. The cure rate after 30 days confirmed by histological analysis presented no statistical significance between groups, showing 87% of clearance for the high-risk group and 89% for the low-risk group. Patients who were not histologically BCC-free 30 days after PDT were submitted to surgical removal. The clinical profile of the two groups is presented in Table 1.

The histologically BCC-free cases had a mean follow-up of 34 months for the low-risk group (range from 2 to 82 months) and 36 months for the high-risk group (range from 2 to 73 months). The recurrence-free follow-up at 12, 36, 48, and 60 months for the high-risk group was 96.2%, 91.5%, 87.8%, and 82%, respectively. Similarly, the recurrence-free follow-up at 12, 36, 48, and 60 months for the low-risk group was 96.6%, 92.7%, 85.6%, and 85.5%, respectively (Fig. 3).

Table 1

The profile of the 98 BCC lesions up to 5 mm.

Group	Number of lesions	Female	Male	Mean age (years)	Cure rate (30 days)
High-risk area	62	19	17	57	87%
Low-risk area	36	13	6	66	89%
p-value*					0.946

* Chi-Square test with significant differences for $p < 0.05$.

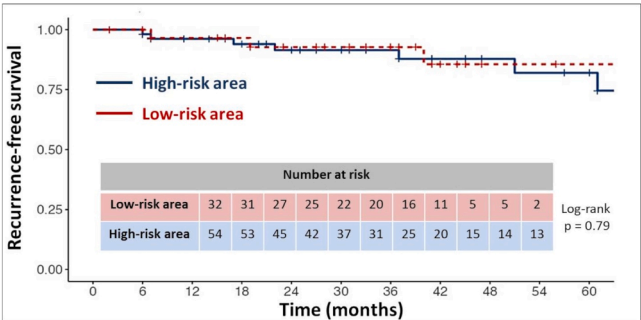


Fig. 3. Recurrence-free survival rate of the two groups of nodular BCC (the high-risk and the low-risk areas groups).

4. Discussion

It is undoubtful that the first choice of treatment for a nodular BCC is surgical excision. But, sometimes the dermatologist may use a non-surgical treatment due to patient's performance status as well as the presence of some comorbidities [4,6]. In this scenario, PDT is raised as a non-surgical option, but it has to be precisely indicated to achieve excellent results.

When treating skin cancer it must be considered many characteristics of the tumor, specifically the location and the size of the BCC. According to National Comprehensive Cancer Network (NCCN) guidelines, the tumor located on the mask has a higher potential of recurrence, independent of size [8]. Even knowing that size is not an independent factor of prognosis for BCC located on the face, we selected for this study only small tumors (up to 5 mm), and both groups had a homogeneous distribution and the same median size (4 mm). Besides, the diagnosis of nodular BCC was proven in all the lesions by histological evaluation. It is important to have a similar profile when considering the response to treatment.

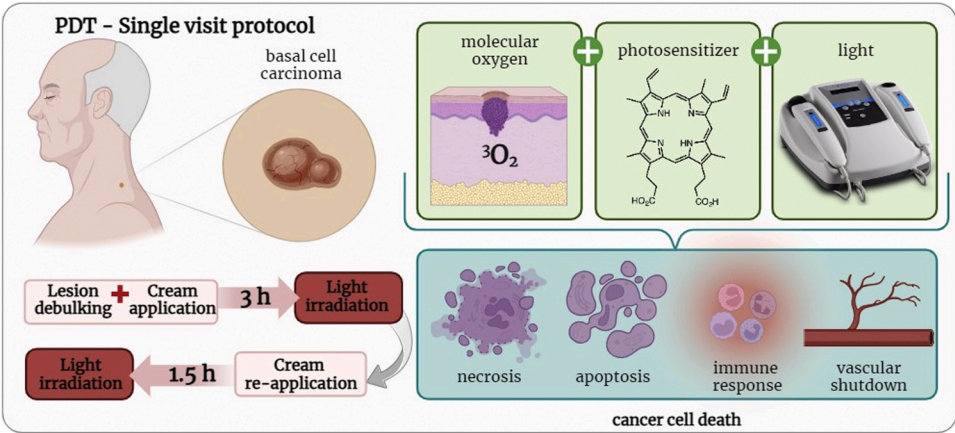


Fig. 2. Steps of PDT treatment performed on one day and representative images of the main PDT components (molecular oxygen, photosensitizer, and light to promote cell death).

Considering 62 nodular BCC located in the high-risk area and 32 nodular BCC located in the low-risk area, the cure rate after the 30-days-after biopsy showed a clearance of 87% for the high-risk group and 89% for the low-risk group, with no statistically significant difference among them. Those values are the same as those observed in some studies that involved multiple and different areas and do not consider specific areas of treatment like ours [9,10].

The PDT protocol used in this study where all the treatment is performed on one single day has proved to be more efficient than the 2 sessions performed with a two-week interval [11].

Another important point is the follow-up after treatment. The cured lesions of this study both the high-risk and the low-risk groups had similar recurrence-free follow-up at 60 months (82% and 85.5%, respectively), with no statistical significance between the groups. Those data were higher than those observed in other long-term follow-up studies (Roozeboom et al. observed a 69.3% recurrence-free follow-up in 60 months and Rhodes et al. 76%) [12,13].

PDT typically induces minimal side effects. Patients may experience transient discomfort, including pain or a burning sensation, during the light activation phase. Post-PDT, the treated area may undergo erythema followed by crusting and peeling during the healing process. However, considering the old age of the patients and their comorbidities, these data demonstrate that this single-visit PDT treatment protocol is a safe treatment choice for nodular BCC up to 5 mm diameter, even for those located in high-risk areas of the face. The high cure rates and low recurrence in long-term follow-up make PDT an excellent treatment choice for dermatologists, with advantages such as aesthetic results and low side effects when compared to surgery.

CRediT authorship contribution statement

Ana Gabriela Salvio: Writing – original draft, Visualization, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Michelle Barreto Requena:** Writing – review & editing, Validation, Software, Investigation, Formal analysis, Data curation. **Mirian Denise Stringasci:** Writing – review & editing, Validation, Software, Investigation, Formal analysis, Data curation. **Bianca A. Fregolenti:** Methodology, Funding acquisition, Data curation, Conceptualization. **Maira M.C. Medero:** Methodology, Funding acquisition, Data curation, Conceptualization. **Rosilene G.S. Silva:** Methodology, Funding acquisition, Data curation, Conceptualization. **Vanderlei Salvador Bagnato:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Conceptualization.

Declaration of Competing Interest

No conflicts of interest to be declared

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