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"A 10-years follow-up of Photodynamic Therapy for nodular basal cell carcinoma: a randomized comparing the effectiveness of Aminolevulinic acid-PDT, Methyl aminolevulinate-PDT, and surgery"

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ABSTRACT

Background: Topical Photodynamic Therapy (PDT) is a well-studied and effective treatment for basal cell carcinoma (BCC) and pre-malignant lesions. Developing a cheaper approach to this treatment involves local production of aminolevulinic acid (ALA) and methyl aminolevulinate (MAL). Furthermore, a prospective study to verify its clinical effectiveness and advantages was required.
Objective: This randomized, controlled trial evaluated the efficacy of MAL-PDT and ALA-PDT treatments for BCC using photosensitizers produced in Brazil, and compared with surgical treatment as a third arm, all with long-term follow-up.
Methods: 567 patients with small nodular BCCs were randomized for ALA-PDT, MALPDT, or surgical treatment. Both PDT groups had a 30-day post-treatment biopsy for cure rate assessment, and a clinical 10 years-follow-up was performed.
Results: The 30-day post-treatment biopsy showed a complete response of 90.4 % for ALA-PDT (171/189 patients) and 86.1 % for MAL-PDT (161/187), while surgery showed free margins in 97.2 % (177/182). Considering 5 and 10 years of follow-up, 93.7 % and 92.8 % of recurrence-free survival rate for surgery, respectively, while 78.6 % and 74.5 % for ALA-PDT, and 73.1 % and 69 % for MAL-PDT were observed.
Conclusion: Surgery remains the gold standard treatment for nodular BCC; however, if non-surgical treatment is chosen, both ALA-PDT and MAL-PDT achieve similar effectiveness and recurrence-free survival rates. While surgery has already yielded optimal results, PDT still has room for great improvement as discussed here.

1. Introduction

Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer in fair-skinned people in the world, representing the most frequent cancer in many countries, including Europe, the United States, Brazil, and Australia [1–3]. Although it has low mortality, it has high morbidity because of multiple scars from surgery, which is the gold standard treatment for nodular BCC [4,5]. Many patients are not suitable for surgery and require another approach. Another issue to consider is the cost of surgery and potential complications. Although surgery is considered the best treatment globally, access to treatment is often difficult or costly in low-income communities. In this scenario,

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photodynamic therapy (PDT) is a non-invasive option for BCC treatment [6].

Many studies analyze the effectiveness of short-term follow-up for topical PDT.However, the recurrence rates of this non-surgical procedure are a concern. Some studies evaluated the long-term recurrence-free follow-up of lesions treated with PDT. Still, none of them have compared PDT using methyl aminolevulinate (MAL), PDT using aminolevulinic acid (ALA), and surgery [7–11].

In order to turn PDT into a cost-effective and affordable treatment in Brazil, cheaper products are required. A new synthetic route to produce ALA and MAL prodrugs was developed, making it available at a price within the economic reality of the country.

Differences in the effectiveness of the photosensitizer used for PDT treatment are also reported [12]. In Brazil, a randomized controlled trial using national prodrugs was necessary to approve their use by the Brazilian Health Regulatory Agency (ANVISA).

Although a comparison of MAL and ALA has been studied before, a long-term follow-up was performed among MAL-PDT, ALA-PDT, versus surgery (as a third arm) in this study. This randomized controlled trial aimed to show the efficacy of MAL-PDT and ALA-PDT treatment for BCC using prodrugs produced nationally and compared their cure rates with surgical treatment with long-term clinical follow-up.

2. Material and methods

2.1. ALA and MAL syntheses

Brazilian ALA and MAL are derived from an internationally known synthetic route with a reduced number of steps and increased yield. The powders were mixed in a base cream specifically for PDT application (to make a 20 % w/w ALA and MAL hydrochloride cream). The active pharmaceutical ingredient (API) were produced by PDT Pharma (Cravinhos-SP, Brazil) in compliance with Good Manufacturing Practices (GMP), with purity levels ranging from 97 % to 100 % and stability studies supporting a one-year shelf life under refrigerated storage at 2–8 °C, as confirmed by high-performance liquid chromatography (HPLC). The use of these formulations was authorized by the ANVISA for clinical research purposes.

2.2. Clinical study

This phase III study was carried out following Good Clinical Practice Standards approved by the Human Research Ethics Committee of the Amaral Carvalho Hospital (N° 140/11) and by ANVISA for medication approval (N° 24/2012, 07 Feb 2012). This study was registered at Universal Trial: U1111–1215–2068/main ID: RBR-4bdbpk (available at https://apps.who.int/trialsearch). Informed consent was obtained before participating in the study. This was a single-center, controlled, randomized, double-blinded (for PDT treatments), closed-label, recruiting patients from February 2012 to December 2014, and with follow-up until December 2024.

2.3. Patients

A total of 567 adult patients were selected for the study. Each patient had a nodular BCC, with only one lesion per patient, clinically diagnosed by a dermatologist and confirmed through dermatoscopic analysis. Based on a randomization chart, the patients were assigned to receive either ALA-PDT treatment, MAL-PDT treatment, or surgery.

The inclusion criteria were patients aged over 18, male and female, who presented a nodular BCC measuring up to 15 mm in diameter. The lesion site was not restricted. The exclusion criteria were recurrent BCC, known allergies to any ingredients of the cream, porphyria, systemic lupus erythematosus disease, pregnancy or lactation, and pigmented or sclerodermiform BCC.

2.4. Randomization and sample size

This study included three treatment protocols: the standard surgical treatment and two related to the prodrugs: MAL-PDT and ALA-PDT. To determine the group size, we used the method described by Blackwelder et al., which considered a surgery cure rate of 95 %, a PDT cure rate of 90 %, a non-inferiority limit of 2 %, and a 95 % confidence level ($\alpha = 0.05$), and 80 % power. This calculation indicated that 172 patients would be required per group. However, considering that 10 % of the population might not complete the treatment for various reasons, we proposed a sample size of 189 patients for each group [13]. Block randomization was performed with a four-block size, using an algorithm in MATLAB® software (MathWorks, USA) to generate the treatment sequences. The PDT protocols remained double-blinded until the analysis of the results was completed.

2.5. Surgical treatment protocol

Surgery was performed under local anesthesia, and the nodular BCC was excised with 5 mm margins. This was followed by histological analysis and surgical margin assessment.

2.6. PDT treatment protocol

All the BCC lesions treated with either ALA-PDT or MAL-PDT protocol were initially debulked by removing all the tumor tissue above the skin level using a blade. The excised tissue was promptly sent for histological evaluation to confirm the initial diagnosis of nodular BCC. Following this, as this was a double blinded treatment for both PDT groups, a cream (containing MAL or ALA) was applied to the lesion and covered with aluminum foil to protect it from light for 3 h. After this incubation period, the lesions were cleaned and illuminated with a commercial LED device emitting light at a wavelength of 630 nm (LINCE®- MMOptics, Brazil), delivering an irradiance of 125 mW/cm^2 for 20 min, totaling 150 J/cm^2 of fluence. A second treatment session was performed one week later using the same parameters.

2.7. Outcome assessment

The primary endpoint was a comparison of treatment effectiveness among the three groups. Thirty days after PDT treatments, the treated area was clinically and dermatoscopically evaluated to guide a 2 mm punch biopsy to provide the treatment result. Treatment failure was considered if residual BCC was observed at the 30-day follow-up after biopsy. Margin assessment and clinical evaluation of the treated area were performed 30 days after surgery. Patients whose lesions presented compromised margins after surgery were considered treatment failures.

Regarding the three protocols, the remaining patients were evaluated clinically and dermatoscopically every six months, and the recurrence of BCC was assessed as a secondary endpoint. If recurrence was suspected, a punch biopsy was taken. If histologically confirmed, the patient was excluded from follow-up.

2.8. Statistical analysis

The primary statistical analysis was based on the per-protocol (PP) population, including all the eligible patients who completed surgery or PDT treatment and had a histological evaluation at 30 days after treatment. In addition, an intention-to-treat analysis was performed. The analysis populations (intention-to-treat and PP group) were almost identical and gave similar results. The histologically confirmed lesion recurrence rate was particularly interesting during the long-term follow-up.

The Kaplan-Meier survival curve estimated the proportion of treatment failures and the recurrence-free survival rates [14]. The three groups were compared using time-to-event analysis of the cumulative

probability of recurrence-free survival, considering differences in the follow-up among patients. The log-rank test (Mantel-Cox) was used to evaluate the significance of the divergence between the recurrence-free survival plots. Differences between these plots were considered statistically significant for a *p-value*<0.05. The analyses were performed on Statistical Package for the Social Sciences, version 17.0(SPSS Inc., Chicago, IL, USA). The recurrence-free survival rate was estimated at 5 and 10 years of follow-up.

3. Results

All groups had 189 patients and presented a similar gender distribution, with a predominance of females in the three treatment groups (Table 1). The average age of the ALA-PDT group was 64.2 years, 65 for the MAL-PDT group, and 68.3 for the surgery group. Most of the lesions were located on the head and neck area, followed by trunk, upper limbs, and lower limbs, with similar distribution in all groups (Table 1).

After randomization, nine patients did not return for treatment, seven of them belonged to the surgical procedure group, and the other 2 to the PDT treatment group (Fig. 1).

At 30 days post-treatment, a complete cure of 97.2 % for surgery (177/182 patients), 90.4 % for ALA-PDT (171/189), and 86.1 % for MAL-PDT (161/187), showing no statistical significance between MAL-PDT and ALA-PDT. No significant side effects were reported and no pattern was observed among the lesions with treatment failure.

At long-term follow-up, the recurrence-free follow-up rates, respectively, at 5 and 10 years of follow-up, were 93.7 % and 92.8 % of recurrence-free survival rates for surgery, while 78.6 % and 74.5 % for ALA-PDT, and, 73.1 % and 69 % for MAL-PDT. Fig. 1 shows the diagram of randomization and the overall results, along with the analysis of the first follow-up (30 days after treatment) and long-term follow-up (5 and 10 years after treatment).

The surgical group showed an average follow-up of 76 months (0 to 173 months). The ALA-PDT group had an average follow-up of 77 months (0–151 months), and the MAL-PDT group had an average follow-up of 68 months (1 to 151 months) (Fig. 2).

The Kaplan-Meier curves (Fig. 2) illustrate the recurrence-free survival of BCC lesions treated with PDT and surgery. Although there was a significant statistical difference between surgery and both PDT long-term follow-ups, there was no statistical difference between ALA-PDT and MAL-PDT.

Fig. 3 shows the follow-up of three patients. The first lesion corresponds to a patient with a nodular BCC on the nasal area, treated with MAL-PDT with no recurrence after 54 months of follow-up. The second case was a patient with a nodular BCC on the eyebrow area who was treated surgically. No recurrence was observed after 57 months of follow-up, but an evident scar is notable. The third nodular BCC was in the right arm of a 75-year-old woman, who was clinically followed up to 10 years from the PDT treatment, with no recurrence and an excellent cosmetic outcome.

Table 1
"Characterization of treatment groups (surgery, ALA-PDT, and MAL-PDT) according to age, sex, and location of BCC".

	Mean age (years)	Sex		BCC location			
		male	*female*	*head and neck*	*lower limb*	*upper limb*	*trunk*
SURGERY	68.3	90 47.6 %	99 52.4 %	129 68.3 %	1 0.5 %	22 11.6 %	37 19.6 %
ALA-PDT	64.2	92 48.7 %	97 51.3 %	122 64.5 %	3 1.6 %	21 11.1 %	43 22.8 %
MAL-PDT	65	93 49.2 %	96 50.8 %	116 61.4 %	2 1.1 %	22 11.6 %	49 25.9 %

4. Discussion

Surgery remains the gold standard procedure for nodular BCC treatment. However, some patients are not suitable for surgery sometimes because of poor clinical performance or because of further scarring as a result of multiple surgeries. Multiple scars may occur in basal cell nevus syndrome, where multiple BCCs arise early in life. Topical PDT can be considered the best treatment option in those cases [15].

Although topical PDT has lower success rates than surgery in BCC treatment, it is important to highlight several aspects. There are great aesthetic and psychological benefits attributed to PDT due to its noninvasive characteristic of avoiding scars caused by surgery. PDT, as an ambulatory procedure, is more comfortable than surgery, especially for elderly patients with comorbidities. The mode of action of PDT significantly reduces the risk of infection compared to surgery [16]. BCC is the most common skin cancer in fair-skinned people, with an estimated >180,000 new cases per year in Brazil and about 1 million worldwide [17]. This scenario may result in an overcrowded health system, requiring other and cheaper treatment options than surgery.

Pain is one of the most reported side effects of PDT, although its intensity is highly subjective and may vary depending on individual sensitivity and lesion location. In clinical settings, when patients report significant discomfort during irradiation, mainly at the beginning of irradiation due to the higher PS concentration, brief pauses may be introduced to improve tolerability. Environmental measures, such as maintaining a comfortable room temperature and providing supportive interaction, can also help minimize discomfort. With these strategies, PDT is generally well tolerated, and treatment interruption due to adverse effects is uncommon [18].

Complete responses from BCC treated through PDT are effective and well documented in short-term studies as well as in this study (90.4 % for ALA-PDT and 86.1 % for MAL-PDT). However, a significant recurrence was observed when the patients were monitored for extended periods. Rhodes et al. compared their short and long-term success rate obtained in 105 nodular BCC lesions treated using MAL-PDT (75 J/cm^2 fluence-3 h, 16 % MAL cream incubation) or surgery, showing that after three months, there was a success rate of 92.5 % for PDT compared to 100 % for surgery, and, that at the end of 5 years, these values changed to 76 % and 96 % respectively [11]. Even though these values still have shown a higher success rate for surgery, the excellent cosmetic results achieved by PDT should be considered once it avoids undesirable scars and reduces costs compared with surgical procedures [18]. In studies by Jansen et al., there is a lower recurrence-free rate for MAL-PDT (62.7 %) using 37 J/cm^2 of fluence compared to imiquimod (80.5 %) and 5-fluorouracil (70.0 %) [19].

More potent drugs could increase the complete response rate of PDT. Still, these are expensive, using other ways of administration, such as intravenously, where the patient shows high phototoxicity, and there is light protection [20].

To reduce bias, this was a randomized, double-blinded study (in the case of PDT protocols) where the same dermatologist performed all the diagnoses and treatments. In this current study, the lesion was treated with a higher fluence (150 J/cm^2), achieving a result of 82.0 %, surpassing other PDT data. Lindberg-Larsen *et al.* used MAL-PDT (37 J/cm^2 of fluence with 3 h of 16 % MAL occlusion) and showed that after 12 months, a significantly higher recurrence rate for nodular BCC (28 %) compared to superficial BCC (13 %) [7]. The same protocol was used in another study performed by Szeimies *et al.*, which showed that surgery was a little more efficient than PDT, but 92.2 % of the PDT cases did not have a recurrence, while the surgery cases had a 94.1 % success rate [21].

There are some limiting factors in PDT, such as the light delivery and the penetration of the photosensitizers into the deeper layers of the skin. Although nodular BCC was treated in the present study, a higher success

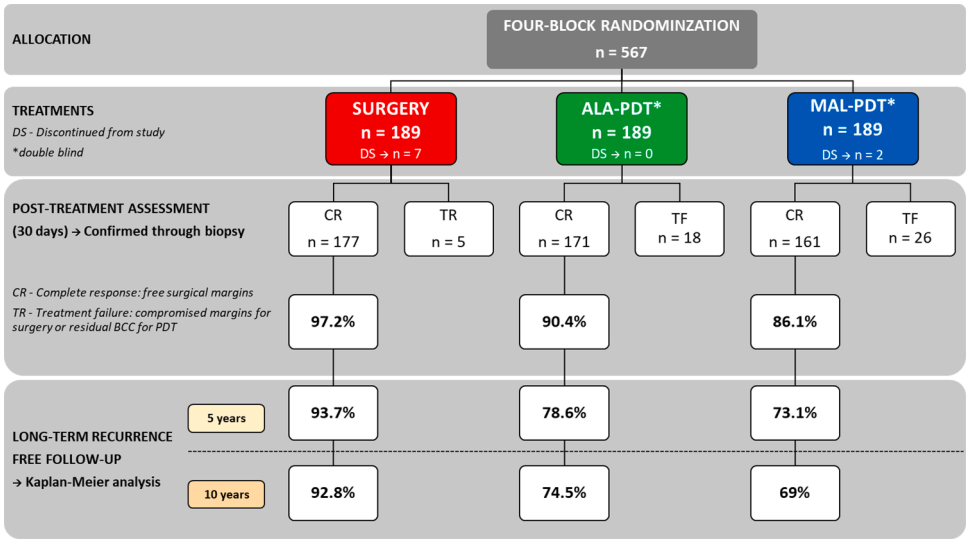

Fig. 1. "Randomization blocks illustrate the allocation of treatments (surgery, ALA-PDT, and MAL-PDT), along with the post-treatment and the long-term follow-up recurrence-free survival results".

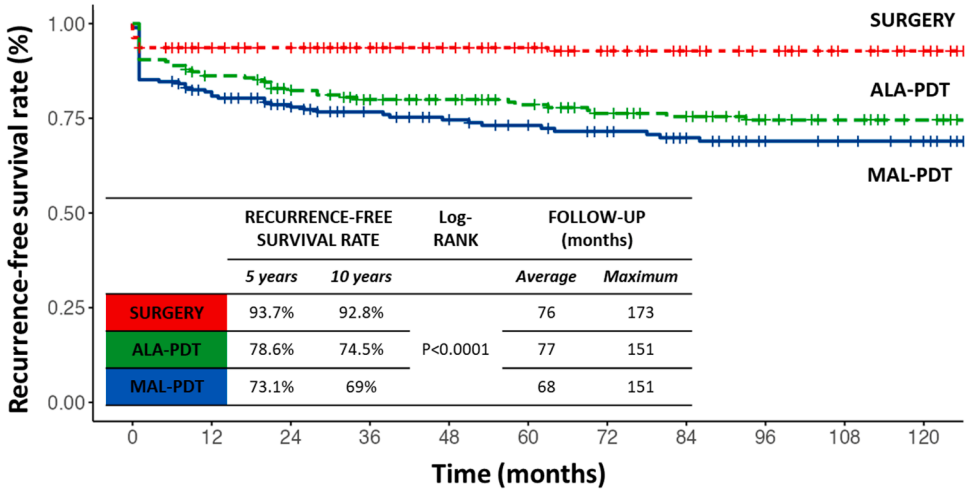

Fig. 2. "Recurrence-free survival rate, median, and a maximum follow-up for lesions treated with surgery, ALA-PDT, and MAL-PDT".

clearance rate (90.1 %) was reached compared to other studies. A complete cure of 67 % in superficial BCC was reported by Tehranchinia et al., who used ALA-PDT with 120 J/cm^2 after 6 to 8 h of incubation [10]. An alternative approach that could be easily implemented is a treatment break, which could increase the depth of the treatment effect [22]. Roozeboon *et al.* demonstrated a 69.5 % cure rate using ALA-PDT with 150 J/cm^2 in fractional lighting 15 min apart [23].

Another important result of this study is that either MAL-PDT or ALA-PDT can provide significant cure rates, but with no statistical significance between them. Besides this, the recurrence rate related to the difference between the long-term follow-up and the 30-day evaluation showed more similarity between surgery and MAL-PDT rates. These data lead our group to choose MAL as the main photosensitizer in another national study with PDT for BCC [8]. It is also important to mention that the Brazilian pro-drug used in this study has the same amount of active compounds (ALA and MAL) when compared to the worldwide well-known commercialized brands Levulan Kerastick®(Dusa Pharmaceuticals, Inc.) and Metvix® (Galderma S.A.), respectively. The 200 mg of MAL hydrochloride in 1 g of cream corresponds to 20 % of MAL hydrochloride content, whose molar mass is 181.62 g/mol. When only the MAL molecule is considered (whose molar mass is 145.12 g/mol), 1 g of MAL cream corresponds to 16 % MAL.

In this randomized clinical study, 5 years of recurrence-free survival rates of 78.6 % for ALA-PDT and 73 % for MAL-PDT were achieved, and 10 years of recurrence-free survival was 74.5 % for ALA-PDT and 69 % for MAL-PDT. These results, added to the fact that there is no statistical difference at 30 days between ALA-PDT and MAL-PDT, allow the dermatologist to choose any of these photosensitizers to perform the PDT treatment. Seven patients from the surgery group gave up the treatment, while only two patients from the PDT group dropped out of the treatment. This might suggest that patients have a greater preference for PDT. Besides the surgery group showing a higher recurrence-free survival, it is important to emphasize the economic and social benefits to the public health system of PDT, as it can be easily used in offices and outpatient clinics, even in remote and underprivileged regions, without the need for special rooms, reducing surgical waiting times. Photodynamic Therapy has significant opportunities for enhancement through the integration of new technologies and methodologies. As drug penetration is a limitation in PDT, primarily due to the natural barrier of the skin, ongoing developments, such as dissolving microneedles, aim to enhance drug delivery to greater depths within the skin [24]. There are also several efforts to improve PDT's efficacy with treatment protocol

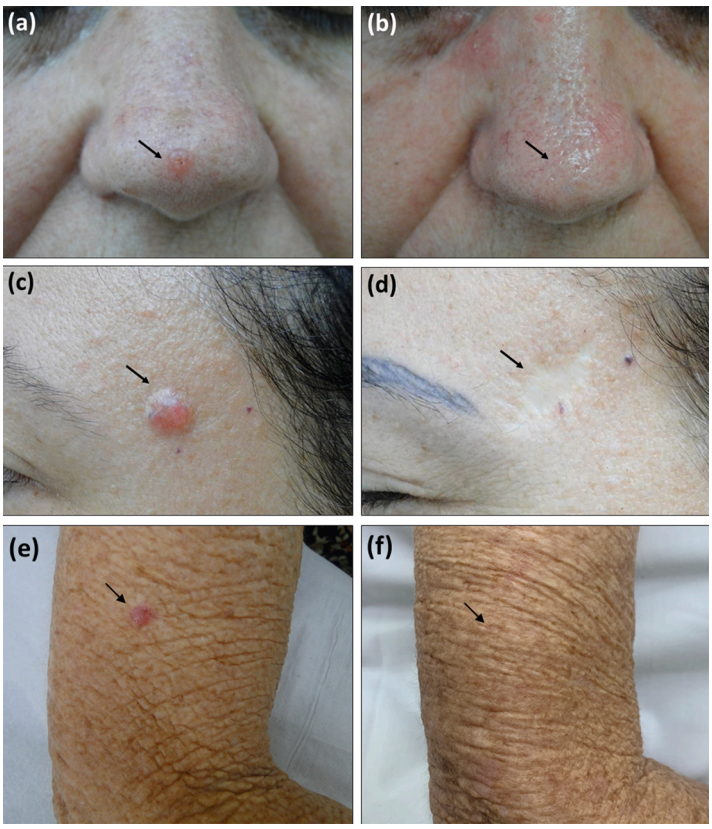

Fig. 3. "Clinical results from long-term follow-up: (a) Female patient, 57 years old, with a nodular BCC before MAL-PDT treatment; (b) the same patient after 54 months of follow-up showing no recurrence. Another female patient, 38 years old, with (c) a nodular BCC on eyebrow area before surgery; (d) the same patient, 57 months after surgery, showing no recurrence; (e) Female patient 75 years old, before MAL-PDT treatment of a nodular basal cell carcinoma in the right arm; (f) and 10 years after, showing no recurrence".

changes. One of these solutions was to perform the two PDT sessions on the same day, which resulted in a treatment rate for MAL-PDT up to 95.4 % at 30-day evaluation [25].

In Brazil, developing nationwide technologies for pro-drug production and illumination systems was necessary to decrease PDT costs. A multicenter study covering the entire national territory and other centers in Latin America was carried out with funding from the Brazilian government [26]. As a result of this initiative, PDT has become an acceptable option for treating non-melanoma skin lesions.

Surgery is often considered the gold standard for BCC treatment, but it has limited potential for improvement. In contrast, PDT has significant opportunities for enhancement through the integration of new technologies and methodologies. Oxygenation in the treatment area presents a unique challenge in PDT, which is not a concern in surgery. This issue can be exacerbated in patients over 65 years of age, who often experience peripheral vascular deficiencies leading to poor oxygen supply. One possible solution to improve oxygenation is the application of slight negative pressure before and during the application of the light treatment [27]. Additionally, drug penetration is a limitation in PDT, primarily due to the natural barrier of the skin. Ongoing developments, such as dissolving microneedles, aim to enhance drug delivery to greater depths within the skin [24].

Furthermore, the production rate of protoporphyrin IX (PpIX), which is crucial for the success of PDT, can be supported by specific drugs and procedures that promote its accelerated production. This enhancement could improve penetration and compensate for natural losses to circulation, resulting in a higher concentration at greater depths.

These advancements could significantly enhance the effectiveness of PDT with the topical application of ALA/MAL. Our research group is actively pursuing these studies to improve long-term outcomes and reduce recurrence rates, bringing PDT outcomes closer to those achieved through traditional surgery.

5. Conclusions

Surgery remains the gold standard treatment for nodular BCC; however, when the dermatologist chooses a non-surgical treatment, both ALA-PDT and MAL-PDT achieve similar effectiveness and recurrence-free survival rates. ALA and MAL creams developed with Brazilian technology are as effective as worldwide products. PDT is a cost-effective and affordable treatment option in Brazil. Surgery remains the gold standard procedure for nodular BCC. However, the present results represent great significance when deciding and considering the type of treatment according to its cost-effectiveness analysis and cure rates.

Furthermore, it is evident that PDT can and should receive significant innovations to improve its effectiveness, aiming to achieve outcomes similar to those of successful surgical procedures.

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draft, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Michelle Barreto Requena:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Mirian Denise Stringasci:** Writing – original draft, Formal analysis, Investigation, Data curation. **Ana Paula Silva:** Methodology, Writing – original draft, Data curation. **Hilde Barb Buzza:** Writing – original draft, Formal analysis, Investigation, Conceptualization. **Donaldo Botelho Veneziano:** Software, Data curation. **Elisangela Ramos Oliveira:** Validation, Investigation. **Maira Monique Medero:** Investigation, Validation, Data curation. **Natalia Mayumi Inada:** Writing – original draft, Formal analysis, Conceptualization, Writing – review & editing, Investigation, Data curation. **Cristina Kurachi:** Writing – original draft, Formal analysis, Conceptualization, Supervision, Data curation. **Lilian Tan Moriyama:** Writing – original draft, Data curation, Investigation, Conceptualization. **Marcelo Saito Nogueira:** Investigation, Writing – original draft, Data curation. **Dora Patricia Ramirez Angarita:** Investigation, Data curation, Formal analysis. **Dirceu Volet-Filho:** Validation, Investigation, Data curation, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Vanderlei Salvador Bagnato:** Writing – review & editing, Supervision, Methodology, Conceptualization, Validation, Resources, Funding acquisition.

Declaration of competing interest

The author Ana Paula Silva is employed at PDT Pharma Company, working as a pharmaceutical and researcher.

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