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Photodynamic Therapy for the Treatment of Basal Cell Carcinoma: A Comprehensive Review of Randomized Controlled Trials

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ABSTRACT

Introduction: Basal cell carcinoma (BCC) is the most common skin cancer worldwide and has been reported to have a rising incidence in the last years. Multiple therapeutic modalities are approved for the treatment of BCC, making it difficult for physicians to choose the most suitable option for every patient. Photodynamic therapy (PDT) using either 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) as photosensitizing agents is an established treatment option for low-risk BCC.

Objectives: This review aims to summarize the available evidence from randomized clinical trials (RCTs) that utilize either ALA or MAL PDT and compare it with other treatment modalities. The main outcomes related to the effectiveness, adverse events, cosmetic outcomes and pain sensation, along with data from long-term follow-ups will be presented and discussed.

Methods: Thorough literature searches were conducted through the electronic databases ClinicalTrials.gov and Pubmed/MEDLINE from inception up to 28 March 2023. Only studies in English were included. All relevant data were extracted accordingly from the eligible studies.

Results: Eight RCTs included superficial BCC (sBCC) alone, 7 included nodular BCC (nBCC), 2 included both sBCC and nBCC and 1 included BCC of unspecified subtype. Follow-up duration ranged from 3 months to 5 years. Both ALA-PDT and MAL-PDT demonstrated acceptable efficacy, adverse events, cosmetic outcomes and pain sensation while no major differences were observed between them. PDT was less effective than surgery but with better reported cosmetic outcomes.

Conclusions: PDT is a safe and efficacious treatment option for sBCC and to a lesser extent nBCC.

Introduction

Basal cell carcinoma (BCC) is the most common skin cancer worldwide, with an estimated life risk in fair skinned individuals to be around 30%, and along with squamous cell carcinoma (SCC), they account for the vast majority of non-melanoma skin cancers (NMSCs) [1-3]. BCC has been reported to have a rising incidence globally in the last years, while in the US alone more than 2 million people are diagnosed annually, thus increasing healthcare burden and costs [3-6]. Accordingly, data from Canada, Europe, Australia and Asia exhibit rising incidence rates [6-13]. In terms of histopathology and clinical appearance, BCC has a variety of subtypes including nodular, superficial, infundibulocystic, fibroepithelial, morpheaform and infiltrative while basosquamous and micronodular mainly exhibit distinct histopathologic features and their presence can alter the prognosis and treatment plan [14-16]. In 2012, Arits et al showed that the proportion of superficial BCC (sBCC) has increased significantly with a decrease of nodular BCC (nBCCs) the last years [17]. Despite that, nBCC still remains the most common subtype with sBCC being the second most common [15,17-19]. Between the different subtypes, nBCC and sBCC are considered to be the least aggressive and with the lowest recurrence rates [18]. While proper identification of each subtype aids in management, a significant number of lesions exhibit more than one histopathologic pattern such as nodular-micronodular which could affect response to therapy [20].

Currently, there are many approved treatment modalities for the treatment of BCC. Surgical excision (SE) and Mohs surgery are considered to be the most efficacious with the highest cure rates among the different treatment options but with noteworthy and unwanted side effects in the treated surfaces like infections and scarring [21-23]. Especially for non-aggressive BCC (sBCC and nBCC) non-surgical interventions can be considered like photodynamic therapy (PDT), 5- fluorouracil (5-FU), imiquimod, radiation, cryotherapy and curettage and electrodesiccation with each presenting varying degrees of effectiveness. Careful patient assessment can guide the physician in order to choose the best possible treatment option for each individual since there are special indications (location of lesion, number of lesions, comorbidities, patient preference and contraindications to surgical intervention) for each treatment modality [22-25]. Data from different guidelines suggest that PDT is a safe and effective choice and should be considered in patients with small (less than 2-cm in diameter), thin (not exceeding 2 mm tumour thickness) sBCCs or nBCCs which are not suitable for surgery or because of patient preference [22-27].

PDT works through the combination of 3 key elements: a photosensitizer, a light source and oxygen. It is performed with topical application of the photosensitizer, which is selectively absorbed by neoplastic cells due to their altered metabolism [28-30]. The most commonly used photosensitizing agents are 5-aminolevulinic acid (5-ALA) and its ester, methyl aminolevulinate (MAL) which are both precursors of the heme biosynthetic pathway. Following the application, ALA is converted into photoactivatable porphyrins, specifically protoporphyrin IX (PpIX), in the epidermis and irradiation at pre-defined wavelengths of red, blue or broadband light source causes cytotoxicity mediated by an oxygen-dependent phototoxic reaction and reactive oxygen species (ROS). This process results in the death of the targeted cells through apoptosis, necrosis, or autophagy (Figure 1) [29-32]. A commonly used licensed regimen consists of 2 treatment cycles of PDT, 1 week apart, usually with light curettage of BCCs before the application of the photosensitizer. If the lesions have not fully resolved at the time of the follow-up, re-treatment may be offered [22-27]. PDT is acknowledged as a safe and efficacious option for the treatment of non-aggressive BCC and is utilized in everyday practice. However, since many therapeutic options exist, the decision-making process demands thorough evaluation of the relative effectiveness and safety of the available alternatives.

Objectives

This review aims to summarize and present all the available evidence from randomized controlled trials (RCTs) utilizing either ALA-PDT or MAL-PDT, with an interest in the efficacy, adverse events (AEs), cosmetic outcomes and pain sensation in order to improve clinical decision making. Data from available follow-ups will be presented in order to add to our knowledge of the long-term results of PDT.

Methods

Thorough literature searches were conducted using "photodynamic therapy" AND "basal cell carcinoma" through the electronic databases ClinicalTrials.gov and Pubmed/MEDLINE from inception up to 28 March 2023. The studies that resulted from the search were assessed in order to identify the eligible ones. For inclusion, a study should meet the pre-specified eligibility requirements: the study should be a RCT, one of the studied interventions should be PDT using either MAL or ALA as a photosensitizer and be compared to another type of PDT, different PDT protocol, placebo or other treatment modality and it should be performed on patients with either nBCC or sBCC or both. Studies should be completed with published available results. Only studies in English were included. All relevant data were extracted accordingly from the eligible studies.

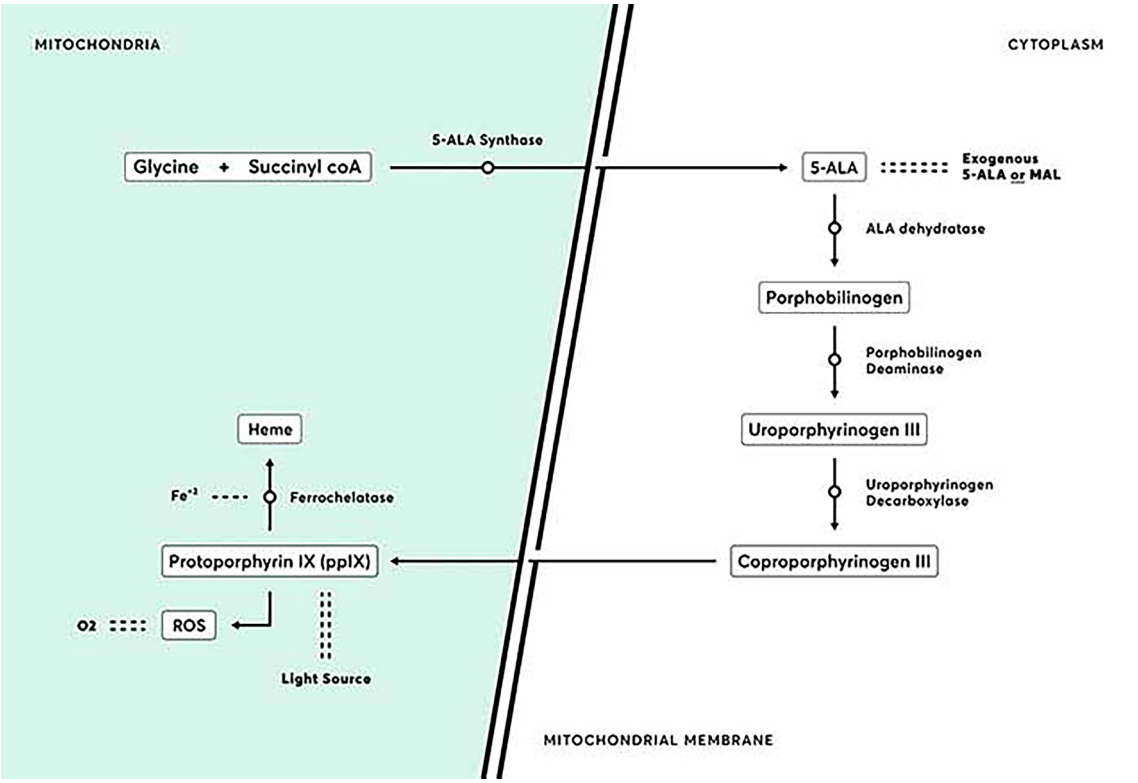

Figure 1. Photodynamic therapy and the heme biosynthetic pathway. Exogenous 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) enter the heme biosynthetic pathway and are gradually converted into Protoporphyrin IX (ppIX). The proper pre-defined wavelength of light, which is produced by the light source, activates ppIX. This reaction eventually produces reactive oxygen species (ROS), which destroy the target cancer cells.

Results

Randomized Controlled Trials of sBCC Treated With PDT

Ten RCTs were identified in our literature search reporting data about sBCCs that were treated with either ALA-PDT or MAL-PDT, and are presented in Tables 1 and 2 [33-48]. Two of the studies include both sBCC and nBCC [45,46], one includes sBCC and Bowen disease (BD) [47] and one study with recurrent BCC without specifying the subtype is presented here [49]. For inclusion, histological confirmation of the BCC was required in all studies [33-47,49] except for one which this was not reported [48]. As presented in table 1, for the assessment of response to treatment, clinical evaluation was the main method with histological confirmation to be utilized only in cases of residual or recurrent lesions [33,34,36-42]. Some trials used clinical evaluation alone [43-45, 47] or clinical and histological together [35,46] for the confirmation of treatment response. Follow-up duration ranged from 1,5 months to 5 years post treatment. MAL-PDT was compared to ALA-PDT in 3 studies. Those studies showed high clearance rates and similar tolerability, AEs and cosmetic outcomes in the patients that attended the follow-ups [33-35,45]. Morton et al, who also included nBCC in their study, showed that the recurrence rates were ≤ 10% at 12 months after the last treatment for both arms of the study [45]. Interestingly, data from another study exhibited lower recurrence rates at 5 years of follow-up after conventional two-stage MAL-PDT compared to fractionated ALA-PDT, although no significant risk of treatment failure was observed in the first 3 years. For both interventions the aesthetic results were rated as good-to-excellent for more than 90% of patients [33,34]. Salimvuory et al compared MAL-PDT, ALA-PDT and hexaminolevulinate (HAL)-PDT and showed no differences in the efficacy and safety between the arms but with a short duration of follow-up at 3 months [35]. SE was compared to 2 sessions, 7 days apart, of MAL-PDT and surgery was statistically more efficacious with better clinical lesion responses at 3 and 12 months. On the other hand, cosmetic outcome, which was assessed by both the investigators and the patients, was significantly better in the MAL-PDT arm. The number of treatment-related AEs was higher in the MAL-PDT arm and those included mostly photosensitivity reactions such as erythema, burning sensation and discomfort. All of the AEs reported were of mild or moderate severity and were well tolerated [41]. Except for PDT, topical treatments like imiquimod and 5-FU are considered to be safe and effective alternatives for sBCC for selected patients [22,23]. The 5-year follow-up results from a RCT indicated the superiority of imiquimod, in

Table 1. Randomized controlled trials of superficial basal cell carcinoma treated with photodynamic therapy

First Author	Clinical Trial Identifier	BCC Subtype	Method of initial diagnosis and confirmation of CR	PDT Type	Comparator	PDT-N (Lesions-N)	Comparator-N (Lesions-N)	Follow Up (Months)	Results
Kessels 2017 [33] Van Delft 2022 [34]	NCT01491711	sBCC	Diagnosis: Histological CR confirmation: Clinically (only In the event of clinical suspicion of residual tumour at 3 months or recurrent tumour at 12 months, a biopsy was performed for histological examination)	MAL-PDT	ALA-PDT	80	82	3m, 12m, 60m	MAL: 95% 75/79 CR (3m) ALA: 96% 76/79 CR (3m) MAL: 89% 65/74 CR (12m) ALA: 96% 72/75 CR (12m) MAL: 91% 48/53 CR (60m) ALA: 76% 44/58 CR (60m)
Salmivuori 2020 (1) [35]	NCT02367547 EudraCT number: 2014-002746-50	sBCC	Diagnosis: Clinical, dermatoscopic and histological CR confirmation: Histological	MAL-PDT	HAL-PDT	27 (31)	24 (31)	3m	MAL: 97% 30/31 sBCCs CR (3m) HAL: 94% 29/31 sBCCs CR (3m)
Salmivuori 2020 (2) [35]	NCT02367547 EudraCT number: 2014-002746-50	sBCC	Diagnosis: clinical, dermoscopy and histological CR confirmation: Histological	MAL-PDT	ALA-PDT	27 (31)	26 (33)	3m	MAL: 97% 30/31 sBCCs CR (3m) ALA: 91% 30/33 sBCCs CR (3m)
Arits 2013 (1) [36] Roozeboom 2014 (1) [37] Roozeboom 2016 (1) [38] Jansen 2018 (1) [39, 40]	IS-RCTN79701845	sBCC	Diagnosis: Histological CR confirmation: Clinical (In case there was clinical suspicion of basal-cell carcinoma recurrence at the follow-up visits, a 3 mm punch biopsy was taken for histological verification)	MAL-PDT	Imiquimod	202	198	3m, 12m, 36m, 60m	MAL: 84% 165/196 CR (3m) Imiquimod: 90% 170/189 CR (3m) MAL: 87% 135/156 CR (12m) Imiquimod: 93% 153/165 CR (12m) MAL: 92% 116/126 CR (36m) Imiquimod: 99% 143/145 CR (36m) MAL: 70% 107/153 CR (60m) Imiquimod: 84% 124/148 CR (60m)

First Author	Clinical Trial Identifier	BCC Subtype	Method of initial diagnosis and confirmation of CR	PDT Type	Comparator	PDT-N (Lesions-N)	Comparator-N (Lesions-N)	Follow Up (Months)	Results
Arits 2013 (2) [36] Roozeboom 2014 (2) [37] Roozeboom 2016 (2) [38] Jansen 2018 (2) [39, 40]	IS-RCTN79701845	sBCC	Diagnosis: Histological CR confirmation: Clinical (In case there was clinical suspicion of basal-cell carcinoma recurrence at the follow-up visits, a 3 mm punch biopsy was taken for histological verification)	MAL-PDT	5-FU	202	201	3m, 12m, 36m, 60m	MAL: 84% 165/196 CR (3m) 5-FU: 88% 174/198 CR (3m) MAL: 87% 135/156 CR (12m) 5-FU: 91% 154/169 CR (12m) MAL: 92% 116/126 CR (36m) 5-FU: 95% 138/146 CR (36m) MAL: 70% 107/153 CR (60m) 5-FU: 80% 125/157 CR (60m)
Szeimies 2008 [41]	NA	sBCC	Diagnosis: Clinical and histological CR confirmation: Clinical	MAL-PDT	SE	100 (135)	96 (132)	3m, 12m	MAL: 92% 118 /128 sBCCs CR (3m) SE: 99% 117/118 sBCCs CR (3m) MAL:91% 107/118 sBCCs CR (12m) SE: 100% 117/117 sBCCs CR (12m)
Nguyen 2018 [42]	NA	sBCC	Diagnosis: Histological CR confirmation: Clinical (histology in case of suspicion of a residual or recurrent BCC)	MAL-PDT (3h/4h group)	MAL-PDT (3h/5h group)	11 (11)	10 (10)	3m, 12m	MAL (3h/4h): 64% 7/11 CR (3m) MAL (3h/5h): 70% 7/10 CR (3m) MAL (3h/4h): 80% 8/10 CR (12m) MAL (3h/5h): 100% 8/8 CR (12m)
De Haas 2006 [43] de Vijlder 2012 [44]	NA	sBCC	Diagnosis: Clinical and histological CR confirmation: Clinical	ALA-PDT (single illumination 4h)	ALA-PDT (double illumination 4h and 6h)	100 (243)	55 (262)	First year (4 times a year), second year (twice yearly) for up to 5 years. 12m minimum for inclusion	ALA single: FU 12m-41m, mean 21m ALA double: FU 12m-32m, mean 17m ALA single: 32/243 recurrent or non-responding lesions (20 were found not to be sBCC) for overall study ALA double: 10/262 recurrent or non-responding lesions (5 were found not to be sBCC) for overall study

Table1 continues

Table 1. Randomized controlled trials of superficial basal cell carcinoma treated with photodynamic therapy *(continued)*

First Author	Clinical Trial Identifier	BCC Subtype	Method of initial diagnosis and confirmation of CR	PDT Type	Comparator	PDT-N (Lesions-N)	Comparator-N (Lesions-N)	Follow Up (Months)	Results
Morton 2018 [45]	EudraCT number: 2013-003241-42	sBCC, nBCC	Diagnosis: Histological CR confirmation: Clinical	MAL-PDT	ALA-PDT	110 (127 sBCCs and nBCCs)	121 (148 sBCCs and nBCCs)	3m, 12m	MAL: 92% 101/110 CR (3m) ALA: 93% 113/121 CR (3m) MAL: 91% 86/94 CR (12m) ALA: 92% 98/107 CR (12m)
Wang 2001 [46]	NA	sBCC, nBCC	Diagnosis: Histological CR confirmation: Clinical and histological	ALA-PDT	Cryotherapy	47 (22 sBCC, 25 nBCC)	41 (17 sBCCs, 24 nBCCs)	12m	ALA: 38% 8/21 sBCCs and 13% 3/23 nBCCs recurred (12m) Cryotherapy: 7% 1/15 sBCCs and 21% 5/24 nBCCs recurred (12m)
Ibbotson 2022 [47]	NCT02872909	sBCC, BD	Diagnosis: NA CR confirmation: Clinical	MAL-PDT (CPDT)	MAL-PDT (APDT)	18 (8 patients with sBCC)	34 (19 patients with sBCC)	3m, 6m, 12m	Of the APDT group, 77.8% (–6.6%, 95% confidence interval for difference –30% to 16%) were clear at 1 year compared with 84.4% with CPDT (P = 0.56) (data for both sBCC and BD patients)
Basset-Seguin 2008 [48]	NCT00469417	sBCC	Diagnosis: Histological CR confirmation: NA	MAL-PDT	Cryotherapy	60 (114)	58 (105)	3m, 5y	MAL: 88% 100/114 CR 3m Cryotherapy:89% 93/105 CR 3m 5-year recurrence rates: 20% with cryotherapy versus 22% with MAL PDT, P = 0.86
Osiecka 2012 [49]	NA	Recurrent BCC (unknown subtype)	Diagnosis: Histologically CR confirmation: Clinical and photodynamic diagnosis	ALA-PDT + Imiquimod	PDT + Placebo	24	10	1,5m	ALA+imiquimod: 75% 18/24 CR 1.5m Placebo: 60% 6/10 CR 1.5m

ALA = aminolevulinic acid; APDT = ambulatory PDT; BCC = basal cell carcinoma; BD = Bowen disease; CPDT = conventional PDT; CR = complete response; FU = follow-up; sBCC = superficial basal cell carcinoma; HAL = hexaminolevulinate; m = months; MAL = methyl aminolevulinate; NA = not available; nBCC = nodular basal cell carcinoma; ; PDT = photodynamic therapy; SE= surgical excision; 5-FU = 5-Fluorouracil.

Table 2. Adverse events, Cosmetic outcomes and Pain of superficial basal cell carcinoma treated with photodynamic therapy

First author	Adverse events	Cosmetic outcomes	Pain
Kessels 2017 [33] Van Delft 2022 [34]	• Moderate/severe erythema MAL: 28/73, ALA: 59/80 swelling MAL: 5/73, ALA: 9/80 crusts MAL: 6/73, ALA: 15/80 vesicles MAL: 5/73, ALA: 18/80 pruritus MAL: 13/73, ALA: 16/80	• Good-to-excellent MAL: 48/72 (end of initial evaluation) ALA: 58/73 (end of initial evaluation) MAL: 56/59 (as judged by patients 5 years after) ALA: 61/63 (as judged by patients 5 years after)	• Pain score, mean NRS ± SD PDT1 MAL: 2.25 ± 2.54 ALA: 1.88 ± 2.36 PDT2 MAL: 2.48 ± 2.57 ALA: 3.36 ± 2.57
Salmivuori 2020 [35]	• Moderate-to-severe post treatment reactions MAL: 22/31 HAL:25/31 ALA: 24/33 1 treatment-related withdrawal from the trial, as one patient from the MAL group experienced remarkable swelling, edema, erythema, and hematoma in the treatment area after PDT I.	• Good-to-excellent by number of lesions MAL: 24/31 HAL: 19/31 ALA: 25/33	No differences in pain during illumination (MAL vs BF-200 ALA vs HAL; PDT I 4 min P=0.21, 8 min P=0.18; PDT II 4 min P=0.47, 8 min P=0.87). In the HAL group, the second session was more painful than the first session (PDT I vs PDT II; 4 min P=0.006, 8 min P=0.005). No difference in pain between sessions in the other arms (PDT I vs PDT II; MAL 4 min P=0.17, 8 min p=0.79; BF-200 ALA 4 min P=0.45, 8 min P=0.43).
Arits 2013 [36] Jansen 2018 [39,40]	• Moderate-to-severe patient reported AEs First week redness MAL: 70/191, Imiquimod 68/189, 5-FU: 59/191 swelling MAL: 6/191, Imiquimod: 26/189, 5-FU: 5 /191 erosion MAL: 10/191, Imiquimod: 9/189, 5-FU: 10/191 crusts MAL: 16/191, Imiquimod: 9/189, 5-FU: 6/191 vesicles/bullae MAL: 12/191, Imiquimod: 9/189, 5-FU: 8/191 squamae MAL: 12/191, Imiquimod: 1/189, 5-FU 3/191 itching MAL: 18/191, Imiquimod: 35/189, 5-FU 20/191 tingling MAL: 7/191, Imiquimod: 7/189, 5-FU: 3/191	• Good-to-excellent at 12 months MAL: 116/186 (lesions) Imiquimod: 113/184 (lesions) 5-FU: 111/ 193 (lesions) 5 years MAL: 137/153 (patients) Imiquimod: 121/148 (patients) 5-FU: 133/157 (patients)	• Moderate-to-severe First treatment MAL: 54/191, Imiquimod: NA, 5-FU: NA First week MAL: 23/191, Imiquimod: 6/189, 5-FU: 3/192 Second treatment MAL: 58/190 Imiquimod: NA, 5-FU: NA Second week MAL: 27/190, Imiquimod: 9/189, 5-FU: 14/192

Table2 continues

Table 2. Adverse events, Cosmetic outcomes and Pain of superficial basal cell carcinoma treated with photodynamic therapy *(continued)*

First author	Adverse events	Cosmetic outcomes	Pain
Szeimies 2008 [41]	• Photosensitivity reaction (all expected reactions such as skin discomfort, burning sensation, erythema, stinging, among others, reported with MAL-PDT) MAL: 31/100, SE: NA wound infection MAL: NA, SE: 5/96 milia MAL: 2/100, SE: NA wound dehiscence MAL: NA, SE: 2/96	• Investigator assessment (12m) MAL: 77/83 success (mean cosmetic outcome across lesions at least good) SE: 44/86 success (mean cosmetic outcome across lesions at least good)	• Pain MAL: 2/100 SE: 1/96 • Post procedural pain: MAL: NA, SE: 3/96
Nguyen 2018 [42]	NA	NA	• Median VAS score after 1st illumination (range) MAL-PDT (3h/4h group): 3 [0-7.0] MAL-PDT (3h/5h group): 4.5 [2.0-7.0] • Median VAS score after 2nd illumination (range) MAL-PDT (3h/4h group): 4 [0-8.0] MAL-PDT (3h/5h group): 4 [2.0-8.0]
De Haas 2006 [43]	In the 2-fold illumination, crusts formed following therapy in 15 lesions in six patients. In the single illumination group, crusts were seen in two lesions in two patients. One patient showed a pustular skin reaction in 11 of 16 lesions, which lasted 5 days. A small number (19) showed persistent hypopigmentation at the illumination site 1 year after therapy.	Cosmetic outcome was good in all lesions.	In the single illumination group, five patients required pain relief for six of 32 treated lesions. In the 2-fold illumination group, 15 patients required pain relief for 44 of 64 treated lesions
Morton 2018 [45]	MAL: Patients with related TEAEs rated as local skin reaction 130/143 ALA: Patients with related TEAEs rated as local skin reaction 121/138 Most commonly reported TEAEs in both groups were local reactions at the application site (pain, erythema, pruritus, and edema). The majority of related TEAEs were of mild-to-moderate intensity.	MAL EOS: 36/74 good or very good, 24/74 satisfactory, 14/74 unsatisfactory or impaired MAL 1yFUP: 39/57 good or very good, 8/57 satisfactory, 10/57 unsatisfactory or impaired ALA EOS: 42/70 good or very good, 16/70 satisfactory, 12/70 unsatisfactory or impaired ALA 1yFUP: 41/56 good or very good, 8/56 satisfactory, 7/56 unsatisfactory or impaired	Maximal pain sensation during PDT (means and (SD)) PDT1 MAL: 3.6 (2.22), ALA: 3.7 (2.42) PDT2 MAL: 4.1 (2.66), ALA: 4.5 (2.69) PDT3 MAL: 2.5 (2.23) ALA: 2.8 (2.55) PDT4 MAL: 2.9 (2.75) ALA: 3.9 (2.97)

First author	Adverse events	Cosmetic outcomes	Pain
Wang 2001 11298545 [46]	• Time and course of healing. Significantly shorter healing time after ALA-PDT as compared with cryosurgery and was manifested by less edema and leakage, but not erythema, 1 week after treatment. None of the PDT treated lesions was classified as severe concerning leakage, edema and erythema. In the cryosurgery group, four lesions had severe leakage, one severe edema and one severe erythema. At the first follow-up, 12 crusts were necrotic following cryosurgery compared with only six after PDT.	• 1 year assessment ALA: 21/42 excellent, 18/42 good, 1/42 acceptable, 2/42 blemished Cryosurgery: 3/37 excellent, 17/37 good, 7/37 acceptable, 10/37 blemished.	• mean ± SD VAS scores ALA: 43 ± 31 mm Cryosurgery: 32 ± 27 mm A few hours and 7 days after the treatment, the average VAS scores were 9.4 mm and 1.4 mm, respectively, for PDT. The corresponding numbers were 8.3 and 1.8 for cryosurgery.
Ibbotson 2022 34545565 [47]	Erythema was slightly greater with APDT (median 2) (CPDT median 1; 95% confidence interval for difference 1 to 0, P =0.025) (erythema: 0–3; none, mild, moderate, severe) (data for both sBCC and BD patients)	The geometric mean patient satisfaction scores at 1 year (available for 24 APDT, 14 CPDT) were 9,63 and 9,27 for APDT and CPDT, respectively (P = 0.34). (data for both sBCC and BD patients)	The geometric mean VAS pain scores were 1.55 for APDT and 2.62 for CPDT (P = 0.36) (data for both sBCC and BD patients)
Basset-Seguin 2008 18693158 [48]	NA	Excellent cosmetic outcome with MAL PDT (60% versus 16% with cryotherapy, P = 0.00078)	NA

ALA = aminolevulinic acid;BD = Bowen disease; EOS = end of clinical study; FUP = follow-up MAL = methyl aminolevulinate; HAL = hexaminolevulinate; NA = not available; NRS = numeric rating scale; ; PDT = photodynamic therapy;SD = standard deviation; SE = surgical excision; TEAE = treatment emergent adverse event; VAS = visual analog scale; 1yFUP =1 year follow-up; 5-FU = 5-Fluorouracil.

terms of effectiveness, when compared to 5-FU and MAL-PDT while no major AEs were reported for any arm [36-40]. Data regarding cosmetic outcome suggest that those 3 non-invasive options are better than retreatment of recurrent BCC with excision or an alternative treatment, with PDT having the best cosmetic results at 5 years in recurrence-free patients [39]. A trial tested a combination of ALA-PDT and imiquimod vs placebo for recurrent unspecified BCC and the results of the combination treatment showed a 75% complete response (CR) at 6 weeks with the remaining lesions significantly reducing in size. Interestingly, in this study photodynamic diagnosis (PDD) was used to detect and visualize suspicious sites (including cancer lesions) that were not detected during routine clinical assessment [49]. NBCCs and sBCCs were treated with ALA-PDT and with cryotherapy in a different RCT [46]. At 12 months, cryotherapy showed to be more effective in the treatment of sBCC with lowest clinical recurrence rates than ALA-PDT, which was not the case in the treatment of nBCC. Retreatments were required more often with PDT, which can more easily be repeated since it proved significantly shorter healing times and better cosmetic outcomes than cryotherapy [46]. Cryotherapy was compared to PDT in another study but this time, the results showed no difference in 5-year recurrence rates with either treatment, and PDT yielded better cosmetic outcomes [48]. Different illumination regimens were tested in two trials [42-44]. One trial compared a single illumination ALA-PDT scheme performed at 4 hours after the application of ALA to a 2-fold illumination ALA-PDT scheme performed at 4 and 6 hours after application. Follow-ups ranged from 12 to 41 months. CR was higher in the 2-fold illumination protocol but with a higher number of patients requiring pain relief during or after illumination. In general, good tolerability and cosmetic outcomes were reported by both arms [43,44]. A 3 and 4-hour illumination scheme after application of MAL was compared to a 3 and 5-hour illumination scheme after

application in a different study. This study sought to examine the effects of a single day, double illumination protocol since it would be less expensive and more practical. Results seemed to be promising for both groups with CR at 3 months after treatment to be between 64 and 70%. Some of the failures/recurrences were attributed to the presence of a more aggressive BCC subtype, because of sampling errors of the primary punch biopsy and primary clinical assessment. In this study in four punch biopsies (three initial and one post-treatment), other BCC subtypes were detected after additional sectioning [42]. Pain was well tolerated in both groups and no serious AEs were reported. The study main limitation was the small number of participants, which was 11 and 10 respectively, for each group [42]. A novel low-irradiance ambulatory PDT (APDT) was compared to conventional PDT, with both arms using MAL as the photosensitizing agent for the treatment of sBCC and BD. Both interventions showed similar efficacy at 12 months and a good safety profile. There were no significant differences in the pain scores while erythema was slightly greater in the APDT group. Both treatments were well tolerated, but the results refer to the treatment of both sBCC and BD [47].

In the examined studies, dropouts related to the use of either MAL-PDT or ALA-PDT were very low to none, without life threatening AEs and with the deaths that occurred not attributed to the studied interventions after careful examination. Most commonly, for both ALA and MAL, AEs included topical reactions such as vesiculation, crusting, erythema, swelling, pruritus and edema. Pain and discomfort occurred frequently during and after treatment but eventually both were well tolerated with or without the use of analgesic medication (Table 2) [33-49].

Randomized Controlled Trials of nBCC Treated With PDT

Nine RCTs were identified in our literature search reporting data about nBCCs that were treated with either ALA-PDT or MAL-PDT and are presented at Tables 3 and 4 [50-58], with two of those studies which included both nBCC and sBCC already discussed above and presented at Tables 1 and 2 [45,46]. Similar to sBCC trials, for inclusion histological confirmation was required [50-58]. For the assessment of response to treatment (Table 3), clinical evaluation, with histological confirmation to be utilized only in cases of residual or recurrent lesions, was the preferred method [50-54,57]. One study relied to clinical evaluation alone [56] and two studies used both clinical and histological assessment [55, 58]. Follow-ups ranged from 3 months to 5 years. MAL cream was compared to placebo cream in one trial. For inclusion, histological examination of a 2–3-mm punch biopsy was performed. Both clinical and histological confirmations were required for the evaluation of the treatment outcome. After the application of the photosensitizer, illumination followed for both groups. The higher CR rates were observed with MAL-PDT and concurrently with excellent cosmetic outcomes for both treatment arms. As expected, the incidence of treatment-related AEs and pain was higher with MAL-PDT, with most of them being of mild-to-moderate severity and, resolving within one day. The serious AEs reported were considered not to be related to either treatment modality [55]. 3 trials randomized patients to receive either PDT or SE [51-54,56]. In two of them, ALA cream was utilized, and the results exhibited higher recurrence rates in comparison with SE, especially at 5 years after treatment [51,52,56]. No serious AEs were reported and cosmetic outcomes were equally good for both studies [51,56], but with pain scores being higher in one study, during and immediately after treatment with PDT, which at later assessments had resolved completely [56]. SE was compared to MAL-PDT and the long-term results indicated the superiority of SE in lesion response but with a more favorable cosmetic outcome with PDT. However, more patients experienced pain and topical AEs in the PDT group. In addition, skin infection occurred in 3 patients in the surgery group while no patient in the PDT group had a similar AE [53, 4]. In a different study, Choi et al found that Er:YAG ablative fractional laser with MAL-PDT (Er:YAG AFL-PDT) had notably higher clearance rates than conventional MAL-PDT at 12 months. In this study, the reported short-term efficacy of conventional MAL-PDT was significantly lower than the one reported by previous studies. Despite the better efficacy of Er:YAG AFL-PDT, the cosmetic outcomes, pain scores and AEs were similar for both studied groups. All AEs were of mild to moderate severity and mostly self-limiting, with no patient to discontinue the particular study. Crusting was the most common AE in both groups, followed by erythema, burning sensation and post-inflammatory hyperpigmentation [50]. Another study with 258 patients in total, compared Er:YAG laser-MAL-PDT with MAL-PDT and with Er:YAG laser alone. Patients with at least 3 nBCCs were recruited and all interventions were applied at every patient. At 12 months the group of Er:YAG laser-MAL-PDT had only 2 recurrences, while the MAL-PDT group had 8 and the Er:YAG laser had 16 with all treatments having acceptable aesthetic results. Despite its effectiveness, the Er:YAG laser-MAL-PDT combined therapy was described as very complicated and long-lasting by the participants [58]. High-risk nBCCs were treated with ablative fractional laser (AFXL)-MAL-PDT and conventional MAL-PDT. The AFXL-MAL-PDT showed comparable efficacy with conventional MAL-PDT at 12 months follow-up with a histological assessment despite the fact that short-term results were in favor of AFXL-MAL-PDT which exhibited higher CR at 3 months. For both interventions, cosmesis was very satisfying and no serious AEs

Table 3. Randomized controlled trials of nodular basal cell carcinoma treated with photodynamic therapy

First author	Clinical trial identifier	BCC subtype	Method of initial diagnosis and confirmation of CR	PDT type	Comparator	PDT-n (lesions-n)	Comparator-n (lesions-n)	Follow up (months)	Results
Choi 2016 [50]	NCT02018679	nBCC	Diagnosis: Histological CR confirmation: Clinical and dermoscopy (in case of suspicion of recurrence or treatment failure, histological assessment was performed)	MAL-PDT	YAG-AFL-MAL-PDT	19 (21)	20 (21)	3m, 12m	MAL: 50% CR (3m) YAG-AFL-MAL-PDT: 84.2% CR (3m) MAL: 22.2% CR (12m) YAG-AFL-MAL-PDT: 78.9% CR (12m)
Mosterd 2008 [51] Roozeboom 2013 [52]	NA	nBCC	Diagnosis: Histological CR confirmation: Clinical (in case of suspicion of recurrence or treatment failure, histological assessment was performed)	ALA-PDT	SE	NA (83)	NA (88)	3m, 12m, 36m, 60m	ALA: 2 treatment failures (3m), 11 treatment failures (12m), 21 treatment failures (36m), 23 treatment failures (60m) SE: 2 treatment failures (3m) which remained throughout the study
Rhodes 2004 [53] Rhodes 2007 [54]	NA	nBCC	Diagnosis: Clinical and histological CR confirmation: Clinical (in case of suspicion of recurrence or treatment failure, histological assessment was performed)	MAL-PDT	SE	53 (60)	50 (58)	3m, 12m, 24m, 60 m	MAL: 91% 48/53 nBCCs CR (3m) SE: 98% 51/52 nBCCs CR (3m) MAL: 83% 44/53 nBCCs CR (12m) SE: 96% 50/52 nBCCs CR (12m) MAL: 76% 32/42 nBCCs CR (24m) SE: 96% 44/46 nBCCs CR (24m) At 5 years (60m) after last treatment, the sustained lesion complete response rate, estimated by the complementary log-log model, was 76% (95% CI, 59%-87%) for MAL-PDT compared with 96% (95% CI, 84%-99%) for SE in the PP population (P = 0.01).

Table3 continues

Table 3. Randomized controlled trials of nodular basal cell carcinoma treated with photodynamic therapy *(continued)*

First author	Clinical trial identifier	BCC subtype	Method of initial diagnosis and confirmation of CR	PDT type	Comparator	PDT-n (lesions-n)	Comparator-n (lesions-n)	Follow up (months)	Results
Foley 2009 [55]	NA	nBCC	Diagnosis: Histological CR confirmation: Clinical and histological	MAL-PDT	Placebo	66 (75)	65 (75)	3m, 6m	MAL: 75% 55/75 nBCCs CR for overall study Placebo: 27% 20/75 nBBCs CR for overall study
Berroeta 2007 [56]	NA	nBCC	Diagnosis: Histological CR confirmation: Clinical	ALA-PDT	SE	NA (21)	NA (19)	3m, 6m, 12m	ALA: 62% 13/21 CR (12m) SE: 79% 15/19 CR (12m)
Haak 2015 [57]	EudraCT number: 2010-020179-22	nBCC	Diagnosis: Histological CR confirmation: Clinical (non complete response, clinical recurrence or any uncertainty, a diagnostic biopsy was taken for confirmation or clarification)	MAL-PDT	AFXL-MAL-PDT	16 (16)	16 (16)	3m, 6m, 9m, 12m	MAL: 88% 14/16 clinical CR 3m AFXL: 100% 16/16 clinical CR 3m MAL: 56% 9/16 histological CR 12m AFXL: 63% 10/16 histological CR 12m
Smucler 2008 (1) [58]	NA	nBCC	Diagnosis: Clinical and histological CR confirmation: Clinical, dermoscopy and histological	MAL-PDT	Er:YAG laser	286 (286)	286 (286)	3m, 6m, 12m	MAL: 99% 246/248 CR 3m Er:YAG: 98% 244/248 CR 3m MAL: 95% 184/194 CR 12m Er:YAG: 92% 178/194 CR 12m
Smucler 2008 (2) [58]	NA	nBCC	Diagnosis: Clinical and histological CR confirmation: Clinical, dermoscopy and histological	MAL-PDT	Er:YAG laser-MAL-PDT	286 (286)	286 (286)	3m, 6m, 12m	MAL: 99% 246/248 CR 3m Er:YAG-MAL: 100% 248/248 CR 3m MAL: 95% 184/194 CR 12m Er:YAG-MAL: 99% 192/194 CR 12m

AFL = ablative fractional laser; AFXL = Ablative fractional laser; ALA = aminolevulinic acid; BCC = basal cell carcinoma; CI = confidence interval; CR = complete response; m = months; MAL = methyl aminolevulinate; NA = not available; nBCC = nodular basal cell carcinoma; PP = per-protocol; PDT = photodynamic therapy; SE = surgical excision.

Table 4. Adverse events, Cosmetic outcomes and Pain of nodular basal cell carcinoma treated with photodynamic therapy

First author	Adverse events	Cosmetic outcomes	Pain
Choi 2016 [50]	crust YAG-AFL-MAL-PDT:17/18, MAL-PDT 14/16 erythema YAG-AFL-MAL-PDT: 17/18, MAL-PDT: 14/16 burning sensation YAG-AFL-MAL-PDT: 15/18, MAL-PDT 12/16 hyperpigmentation YAG-AFL-MAL-PDT: 12/18, MAL-PDT: 9/16 itching YAG-AFL-MAL-PDT: 4/18, MAL-PDT: 3/16 scale YAG-AFL-MAL-PDT: 3/18, MAL-PDT: 2/18 bullae YAG-AFL-MAL-PDT: 3/18, MAL-PDT 2/16 oozing YAG-AFL-MAL-PDT: 2/18, MAL-PDT 1/16 bleeding YAG-AFL-MAL-PDT: 2/18, MAL-PDT 1/16	• Combined excellent/ good cosmetic outcome rates at 12 months MAL-PDT: 100% YAG-AFL-MAL-PDT: 93.8%	VAS scores during illumination were similar with Er:YAG AFL-PDT: 4.632 ± 1.257 and MAL-PDT: 4.222 ± 1.865
Rhodes 2004 [53] Rhodes 2007 [54]	erythema MAL: 7/52, SE: 1/49 skin infection MAL: 0/52, SE: 3/49 crusting MAL: 2/52, SE: 0/49 itching MAL: 2/52, SE: 0/49	• Investigator rated excellent or good cosmetic outcome MAL: 36/44 (3m) SE: 15/45 (3m) MAL: 33/42 (12m) SE: 17/45 (12m) MAL: 24/29 (24m) SE: 16/39 (24m) MAL: 27/31 (60m) SE: 19/35 (60m) • Patient rated excellent or good cosmetic outcome MAL: 39/41 (3m) SE: 37/44 (3m) MAL: 41/42 (12m) SE: 36/43 (12m) MAL: 28/29 (24m) SE: 27/36 (24m)	• Burning sensation of skin MAL: 16/52, SE: 0/49 • Skin pain MAL: 7/52, SE:3/49 (1 patient discontinued due to severe burning sensation which resolved without medical intervention)
Foley 2009 [55]	erythema MAL: 14/66, Placebo: 4/65 stinging of skin MAL: 10/66, Placebo: 5/65 crusting MAL: 5/66, Placebo: 3/65 bleeding skin MAL: 4/65, Placebo: NA	Assessed by investigator as excellent or good MAL: 42/43 (completely responding lesions) Placebo: 14/15 (lesions with clinical and histologic complete response assessment.	• Skin pain MAL: 12/66, Placebo: 3/65 • Burning sensation of skin MAL: 19/66, Placebo: 8/65

Table4 continues

Table 4. Adverse events, Cosmetic outcomes and Pain of nodular basal cell carcinoma treated with photodynamic therapy *(continued)*

First author	Adverse events	Cosmetic outcomes	Pain
Berroeta 2007 [56]	NA	• Mean scar severity following treatment assessed by male assessor ALA: 1,94, SE: 2.07 • Mean scar severity following treatment assessed by female assessor ALA: 2,23, SE: 2,53 (no detectable difference in cosmesis between the two groups)	• During treatment (median) ALA: 5/10, SE: 0/10 • Immediately after treatment (median) ALA: 5/10, SE: 0/10 • At later assessments, with a median pain of 0/10 for both treatments
Haak 2015 [57]	AEs were predominantly mild with mild scarring being the most frequently observed reaction at 3 months. AEs in terms of scarring pigmentary changes were observed to similar extents after AFXL-PDT and PDT at 3, 6, 9 and 12 months.	Good-to-excellent cosmetic outcome rated by physicians at 3 months MAL: 13/14 AFXL: 15/16 Good-to-excellent cosmetic outcome rated by patients at 3 months MAL: 14/14 AFXL: 15/16	• First treatment AFXL-PDT median 3 (IQR 2–55) versus PDT 35 (25–5) • Second treatment AFXL-PDT 35 (3–65) versus PDT 3 (3–45), (P > 0.519).

AE = adverse event; ALA = aminolevulinic acid; EOS = end of clinical study; FUP = follow-up; HAL = hexaminolevulinate; IQR = interquartile range; MAL= methyl aminolevulinate; NA = not available; NRS =numeric rating scale; PDT = photodynamic therapy; SD = standard deviation; SE = surgical excision; TEAE = treatment emergent adverse event; VAS = visual analog scale; 5-FU 5-Fluorouracil.

were observed. The AFXL pre-treatment did not influence pain sensation during illumination [57].

Conclusions

According to the data reviewed, both ALA-PDT and MAL-PDT can be termed as generally effective and well-tolerated treatment modalities for the treatment of thin and small sBCC and nBCC. In terms of efficacy, similar CR were observed between PDT and most of the other interventions, except for SE and imiquimod which demonstrated better results [36-41,51-54,56]. The main weakness of surgery, especially when compared to PDT, was the cosmetic outcome, with PDT being superior and exhibiting more often good or excellent aesthetic results. Pain during intervention was higher with PDT [41,51-54,56]. PDT was more effective than placebo for nBCC [55]. No major differences were observed between MAL-PDT and ALA-PDT in terms of efficacy, AEs, pain and cosmetic outcomes for sBCC in 3 RCTs implying their equality [33-35,45]. The combination of imiquimod with ALA-PDT showed promising results but with a short-term follow-up in one study [49]. Interestingly, the laser pretreatment along with PDT combination showed favorable outcomes and good clearance rates in 3 studies with nBCC. Despite that, further comparative clinical testing is necessary to achieve more clarity [50,57,58]. Cryotherapy yielded better results regarding CR than PDT in one study with a 12m follow-up [46], while in another with a 5 year follow-up, it did not [48]. For sBCC, different illumination protocols that were tested showed that a regimen of a double illumination at 4 and 6 hours after application of ALA was more effective than a single illumination protocol, while both exhibited a good safety profile. Those regimens however require longer hospital visits which could affect patient adherence negatively [43,44].

For most studies the main concern with PDT, was the pain and feeling of discomfort that was experienced during and/or immediately after illumination. In most cases though, it was well tolerated without the administration of analgesic medication. In the rare cases of intolerable pain during treatment, medication can be offered in order to achieve pain relief. A wide range of treatment-related AEs were observed including erythema, edema, pruritus, crusting and vesiculation with most to be of mild or moderate severity and usually self-limiting. No life-threatening AEs were attributed to

PDT and no substantial dropout rates were detected during the observation period. These data suggest that PDT exhibits a very good safety profile with the only concern to be the treatment-related pain. PDT exhibited favorable aesthetic results in the various studies, assessed by both patients and physicians in some, and especially in comparison to different treatments.

Main limitations of some of the examined studies were the small number of participants, a follow-up of less than 12 months, the heterogeneity of the assessment of clinical outcomes and that not all studies reported treatment-related AEs. The follow-up duration was important for the assessment of efficacy of the various treatment modalities since lesions may recur years after treatment and thus short-term follow-ups could be misleading. In addition to that, lesions that did not respond to therapy were in some cases misdiagnosed as nodular or superficial BCCs when in fact they were a more aggressive subtype which required a different therapeutic approach. This supports the need of biopsy for the evaluation of treatment response, especially for recurrent or residual lesions, while clinical assessment and dermoscopy as diagnostic and assessment tools have some limitations. For the assessment of pain, AEs and cosmetic outcomes shorter duration of observation is generally sufficient although some of the examined studies provided long term results.

Our data suggest that PDT poses as a great tool among the various available treatment modalities for the treatment of small and thin sBCC and to a lesser extent nBCC. Since many alternatives exist, with comparable efficacy, patient preference should be taken under consideration. After thorough patient assessment, PDT should be considered the first option for select patients with special concerns about the cosmetic results, long lasting and unwanted AEs, with multiple lesions, and with evident contraindications to surgery and the other alternatives including previous allergic and topical reactions. Further research in clinical and preclinical settings is warranted since novel approaches such as lasers, novel lightning sources, different illumination protocols and different combinations of PDT with other treatments could improve responses to therapy and eventually patient care.

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