Photodynamic Therapy Using Topical Methyl Aminolevulinate vs Surgery for Nodular Basal Cell Carcinoma

Results of a Multicenter Randomized Prospective Trial

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Background: Photodynamic therapy (PDT) is increasingly used as a noninvasive treatment for nodular basal cell carcinoma (BCC), without a sound evidence base.

Objective: To compare topical PDT, with the use of the sensitizer methyl aminolevulinate, and standard excision surgery in nodular BCC.

Design: Prospective, randomized study.

Setting: University dermatology departments.

Patients: A total of 101 adults with previously untreated nodular BCC.

Interventions: Patients received methyl aminolevulinate PDT (n=52) or surgery (n=49). The PDT was given twice, 7 days apart, with methyl aminolevulinate cream (160 mg/g) and 75 J/cm² red light (570-670 nm). Thirteen patients with a noncomplete response to PDT at 3 months (24% lesions) were retreated.

Outcome Measures: Primary end point was clinically assessed lesion clearance at 3 months after treatment. Secondary end points were sustained response rate at 12 months and cosmetic outcome at 3 and 12 months. Cosmesis and lesion recurrence were further assessed at 24 months.

Results: Data from 97 patients (105 lesions) were included in the 3-month per-protocol analysis. Complete response rates did not differ significantly between groups (51/52 [98%] lesions with surgery vs 48/53 [91%] lesions with methyl aminolevulinate PDT; difference [95% confidence interval], 4.8% (-3.4% to 13.0%]; P=.25). At 12 months, tumor-free rates were 50 (96%) of 52 lesions with surgery vs 44 (83%) of 53 with methyl aminolevulinate PDT (P=.15). More patients treated with methyl aminolevulinate PDT than surgery had an excellent or good cosmetic outcome at all time points (significant at 12 and 24 months on patient assessment, P<.05, and at 3, 12, and 24 months on investigator evaluation, P<.001). At 24 months, 5 lesions that had initially cleared with methyl aminolevulinate PDT had recurred, compared with 1 after surgery.

Conclusions: Methyl aminolevulinate PDT is an effective treatment for nodular BCC, and while there is a trend for higher recurrence with this modality, it conveys the advantage over surgery of better cosmesis.

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Skin Cancer is the Most Common Cancer in White Populations, with an Estimated Incidence of 1100 per 1 Million Population per Year in Northwest Europe, and Twice and 10 Times this Number in the United States and Australia, respectively. Moreover, the Incidence Continues to Rise. Basal Cell Carcinoma (BCC) is the Most Frequent Form, and the Morbidity Associated with Local Tissue Invasion and Destruction is Significant. Simple Surgical Excision is Regarded as the Treatment of Choice for BCCs of the Nodular Type, however, Cosmetic Outcome May be Less than Optimal.

Photodynamic Therapy (PDT) Offers the Advantages over Surgery of Being a Non-invasive Procedure Causing Minimal Damage to Surrounding Tissue, Because of Relatively Selective Uptake of Photosensitizer by Malignant Cells. Activation by Visible Light Releases Reactive Oxygen Species that Produce Local Tissue Destruction. Topical PDT has been increasingly practiced since the description of 5-aminolevulinic acid, a precursor in heme biosynthesis, as prodrg. Application of excess 5-aminolevulinic acid results in buildup of photosensitive porphyrins at the lesion site, which then bind with light energy to induce tissue destruction. The photosensitizer most commonly used is methyl aminolevulinate, which is applied topically as an ointment to the target lesion and left on for 8-24 hours.
toactive porphyrins including protoporphyrin IX. Any protoporphyrin IX formed, or remaining, after light exposure is metabolized within 48 hours. Ease of application of 5-aminolevulinic acid PDT has resulted in its widespread use in several countries, without license, and in the absence of randomized prospective trials with standard surgical treatment. Large series of BCCs treated with 5-aminolevulinic acid PDT show complete response rates of 34% to 100%, with inferior clearance in nodular compared with superficial BCC. Routine double PDT treatment may improve procedure efficacy.

Methyl aminolevulinate, the methyl ester of 5-aminolevulinic acid, may offer advantages over 5-aminolevulnic acid in terms of improved skin penetration because of enhanced lipophilicity and specificity for neoplastic cells. Initial experience suggests that methyl aminolevulinate PDT is a promising treatment for BCC. The aim of this first multicenter, randomized, parallel-group, prospective study was to compare the efficacy and cosmetic outcome of topical methyl aminolevulinate PDT with standard simple excision surgery in primary nodular BCC.

METHODS

PATIENTS

Between October 29, 1999, and September 8, 2000, 103 patients were enrolled from the specialist dermatology clinics of participating centers. All subjects were 18 years or older and had previously untreated primary nodular BCC suitable for simple excision surgery. Diagnosis of clinically apparent nodular BCC was confirmed histologically. Excluded from the study were patients with more than 10 eligible lesions; lesions in the midface region, orbital areas, and ears; lesions with a longest diameter of less than 6 mm or more than 15 mm (face or scalp), more than 20 mm (extremities or neck), or more than 30 mm (trunk); and pigmented, or morpheaform BCCs. Patients with porphyria, Gorlin syndrome, or a history of arsenic exposure; those who had participated in any other investigational study in the past 30 days; those likely to be poor compliers; those taking immunosuppressive medication; and women who were pregnant or breastfeeding were excluded. The study was approved by the local ethics committee responsible for each center and conducted in accordance with the Declaration of Helsinki (South Africa, 1996). Patients gave written informed consent before study entry.

STUDY DESIGN

Within 4 weeks of the screening visit, eligible patients were randomized consecutively to treatment with PDT with the use of methyl aminolevulinate cream, 160 mg/g (Metvix; PhotoCure ASA, Oslo, Norway) or excision surgery. The randomization list was kept centrally, and investigators called or faxed to the monitor when a new patient was included to find out the treatment allocated to that patient number. Randomization was stratified by center and number of eligible lesions per patient (1-3 and ≥4). Patients randomized to PDT were treated with either 1 or 2 PDT cycles, each comprising 2 PDT sessions, with an interval of 1 week between sessions. Before application of methyl aminolevulinate cream to the lesion, surface crust or scale was gently removed with a curette or scalpel blade. This superficial lesion preparation was performed in a standardized manner between centers, without anesthesia, such as to be insufficient to cause pain or bleeding. A 1-mm-thick layer of methyl aminolevulinate cream was applied to each lesion and 5 mm of surrounding tissue and covered with an adhesive occlusive dressing (eg, Tegaderm; 3M Corp, St Paul, Minn) for 3 hours. Dressings were then removed and the cream was washed off with 0.9% saline solution, immediately before illumination with noncoherent red light from a standard light source (Curelight; PhotoCure ASA), with emission spectrum of 570 to 670 nm, total fluence of 75 J/cm², and fluence rate of 50 to 200 mW/cm². Fluence rate depended on distance of the lamp from the lesion, which was adjusted to achieve field sizes 3.5 to 3.5 cm in diameter, as appropriate. Simple elliptical excision surgery with at least 5-mm margins was performed with the patient under local anesthesia in accordance with the usual practice of the center.

END POINT ASSESSMENTS

At 3 months after the initial treatment, lesions were evaluated by clinical inspection by the same investigator and rated as either complete response, ie, complete disappearance of the lesion, or noncomplete response, ie, noncomplete disappearance of the lesion. Lesions with noncomplete response to PDT at 3 months received a second treatment cycle and were reevaluated 3 months later. Further treatment of patients who did not show complete response to surgery at 3 months depended on the standard practice of the center concerned. Investigator-assessed cosmetic outcome was evaluated 3 months after surgery or the last PDT treatment (ie, at 3 months for patients who required 1 PDT cycle and 6 months for patients who required 2 PDT cycles), in all patients who had shown a complete response in all lesions, and on the basis of a 4-point scale: (1) excellent: no scarring, atrophy, or induration; slight or no redness or change in pigmentation compared with adjacent skin; (2) good: no scarring, atrophy, or induration, moderate redness or increase in pigmentation compared with adjacent skin; (3) fair: slight to moderate occurrence of scarring, atrophy, or induration; and (4) poor: extensive occurrence of scarring, atrophy, or induration. Evaluation of cosmetic outcome was repeated at the 12-month and 24-month follow-up visits. In addition, patients gave a global assessment of cosmetic outcome on a similar 4-point scale (ranging from excellent to poor) at 3, 12, and 24 months. Clinical evaluation for detection of lesion disease involvement or recurrence was performed at 12 and 24 months after treatment.

ADVERSE EVENTS

Local skin reactions during and after cream application and illumination were documented. Adverse events (ie, any unfavorable and unintended sign, symptom, or disease) either reported spontaneously by the patient or elicited after nonleading questioning were noted at each follow-up visit, together with their severity, duration, and need for additional therapy. The severity of the adverse event was rated as follows: mild, transient and easily tolerated; moderate, caused the patient discomfort and interrupted usual activities; and severe, caused considerable interference with usual activities and may have been incapacitating or life-threatening. Local phototoxicity reactions were graded in accordance with the National Cancer Institute Common Toxicity Criteria relevant to the skin. The clinician assessed the causal relationship of the event to the study treatment as related, uncertain, or not related.

STATISTICAL ANALYSIS

The primary variable in the study was complete response based on investigator assessments of the lesions 3 months after the last PDT treatment or surgical excision. Lesion response was
regarded as independent between lesions, even within the same patient. Assuming that an estimated 95% of lesions would show complete response to simple excision surgery, and that the response to PDT would be the same in this study population, it was estimated that approximately 50 lesions per treatment group would be required to demonstrate with 95% confidence and a power of 90% that methyl aminolevulinate PDT was no more than 15% inferior to simple excision therapy. The 15% difference was agreed on before study commencement as being clinically relevant by the dermatologists who participated in the study.

Per-protocol analysis of pooled data including all eligible patients who completed surgery or the first PDT cycle and had at least 1 response assessment at 3 months, or who completed a second PDT cycle and received treatment in accordance with the protocol procedures, was performed independently by Parexel GmbH, Berlin, Germany, using SAS software (SAS Institute Inc, Cary, NC). Two-sided 95% confidence intervals for the complete response rate were calculated for the difference between treatment groups. If the upper limit of this interval was less than 15%, it was concluded that methyl aminolevulinate PDT was not inferior to surgery. Since this was a multicenter study involving 13 centers, a Mantel-Haenszel analysis was also performed to account for center differences in complete response. The numbers of patients with excellent or good overall cosmetic outcome were compared between the treatment groups. Sustained tumor-free response rates at 12 months were reported for each treatment group.

**RESULTS**

**PATIENTS**

A total of 101 of 103 randomized patients received the study treatment; 52 patients were treated with methyl aminolevulinate PDT and 49 patients were treated with simple excision surgery. Two patients, 1 patient in each treatment group, withdrew consent before receiving treatment and were therefore excluded from the study (Figure 1). The baseline characteristics of the 2 treatment groups were similar (Table 1). The majority of patients in each group had 1 lesion (49/52 [94%] in the methyl aminolevulinate PDT group and 43/49 [88%] in the surgery group); most lesions were less than 15 mm in diameter and were located on the face and scalp or the trunk and neck (Table 1). Most lesions in the methyl aminolevulinate PDT group were treated with 1 PDT cycle (42/55 [76%]). Patients received a light dose of 75 J/cm², at mean light intensity of 127 mW/cm² (range, 50-200 mW/cm²).

Four patients, 2 in the methyl aminolevulinate PDT group and 2 in the surgery group, were excluded from per-protocol analysis of the 3-month efficacy data. In the methyl aminolevulinate PDT group, 2 patients withdrew consent before receiving treatment and 1 patient died from a non-dermatologic cause. In the surgery group, 1 patient was excluded due to adverse event (death) and 1 patient withdrew consent before treatment.
come at the 12-month follow-up. However, tumor-free re-

sions in the surgery group, were assessed for cosmetic out-

aminolevulinate PDT group and 45 patients with 50 le-

nine patients, 44 patients with 46 lesions in the methyl

aminolevulinate PDT group and 47 patients with 52 le-

tions treated with methyl aminolevulinate PDT and 47 pa-

3 months per-protocol analysis population. Eighty-

tions treated with surgery, were included

sions with methyl aminolevulinate PDT and 47 pa-

2 patients were withdrawn and had missing response as-

fore had no assessment of response. In the surgery group,

protocol violator (received a light dose less than that stipu-

None of the patients treated with methyl aminolevuli-

tion by 12 months. There were 8 discontinuations before

disease at 12 months, whereas all lesions cleared by sur-

was anticipated because local anesthesia was provided

three patients in this group rated their outcome

gery group had a poor outcome as judged by the inves-

investigator or patient, whereas 4 patients in the sur-

nate PDT had a poor cosmetic outcome as judged by the

Two lesions that appeared completely cleared at 3 months

tive of the site or size of the lesion (Table 2).

12- AND 24-MONTH DISEASE STATE

Three months after the last PDT treatment or surgery, 48

(91%) of 53 lesions treated with methyl aminolevulinate

PDT and 51 (98%) of 52 lesions treated with surgery showed

a complete clinical response. When center differences were

accounted for by means of a Mantel-Haenszel analysis, the

estimated treatment difference was 4.8% (95% confidence

interval, −3.4% to 13.0%) (P = .25). The upper bound of

the 95% confidence interval was less than 15%, thereby

providing support for the hypothesis that methyl ami-

nolevulinate PDT was not inferior to surgery. Lesion re-

sponse rates in each group were high and similar irrespec-

tive of the site or size of the lesion (Table 2).

COSMETIC OUTCOME

Assessment of cosmesis favored methyl aminolevulinate

PDT over surgery at all time points, whether rated by clinician or subject (Table 4). All preferences were

statistically significant (Cochran-Mantel-Haenszel test)

except for the 3-month assessment by subjects. An ex-

ample of the response at 12 months is shown in Figure 2.

None of the patients treated with methyl aminolevulinate

PDT had a poor cosmetic outcome as judged by the

investigator or patient, whereas 4 patients in the sur-

gery group had a poor outcome as judged by the inves-

tigator and 3 patients in this group rated their outcome as poor (Figure 3).

SAFETY AND TOLERABILITY

More patients treated with methyl aminolevulinate PDT

than surgery reported adverse events (27/52 [52%] com-

pared with 14/49 [29%]) (P = .03, Fisher exact test). This

was anticipated because local anesthesia was provided

with surgery, but not with methyl aminolevulinate PDT.

Most of these adverse events were transient local reac-

tions commonly associated with this treatment modal-

ity, such as burning sensation of the skin, pain in the skin,
or erythema (Table 5). One patient in the methyl aminolevulinate PDT group discontinued treatment because of a severe burning sensation of the skin; the pain resolved later that day without medical intervention. All other local adverse events were of mild to moderate intensity, and all resolved in less than 1 day.

Three patients had skin infections after surgery; there were no infections in the methyl aminolevulinate PDT group. Three patients died during the first 12 months of the study; 1 patient treated with methyl aminolevulinate PDT had a fatal myocardial infarction after removal of a kidney tumor, and 2 patients treated with surgery died of myocardial infarction. In each case, the cause of death was considered unrelated to the study treatment. An additional patient treated with surgery was hospitalized after confirmation of breast carcinoma and underwent a total right mastectomy with lymph node clearance.

This, to our knowledge, is the first prospective, randomized study to compare treatment of primary nodular BCC with topical PDT and simple excision surgery, conventionally regarded as the treatment of choice. The results of the study support that treatment with methyl aminolevulinate PDT is as effective as excision surgery, in terms of clinical complete response rate at 3 months (91% vs 98%, respectively). It should be noted that the study was powered to detect a 15–percentage point difference at 3 months, and therefore smaller differences in response, which might still be important to some clinicians, will not be apparent. The confidence interval was wider for tumor-free rate at 12 months, and at this time a 15–percentage point advantage in favor of surgery cannot be excluded.

Topical PDT is generally reported to be nonscarring or minimally scarring, but formal evaluation of cosmetic outcome of PDT against standard excision surgery has not previously been reported. Assessments made by both patient and investigator showed that more patients achieved

| Table 3. Long-term Lesion Response Rates* |
|----------------|----------------|--------------------|
|               | **12 mo After Treatment** | **24 mo After Treatment** |
| Response Category | MAL-PDT, No. (%) | Surgery, No. (%) | Estimated Difference (95% CI) | MAL-PDT, No. (%) | Surgery, No. (%) | Estimated Difference (95% CI) |
| Nonresponse or recurrence | 7 (13) | 1 (2) | 8 (−1 to 18) | 10 (19) | 2 (4) | 8 (−1 to 22) |
| Tumor free | 44 (83) | 50 (96) | 9 (−3 to 20) | 32 (60) | 44 (85) | 18 (3 to 34) |
| Missing/ discontinued | 2 (4) | 1 (2) | NA | 11 (21) | 6 (11) | NA |
| **Total No. of Lesions** | **53** | **52** | **NA** | **53** | **52** | **NA** |

Abbreviations: CI, confidence interval; MAL-PDT, methyl aminolevulinate photodynamic therapy; NA, not applicable.

*Three patients in each group died; in addition, 2 patients in the MAL-PDT group withdrew their consent to participate in the trial. Six patients with 9 lesions (6 in the MAL-PDT group and 3 in the surgery group) did not attend the 24-month follow-up visit.

| Table 4. Excellent or Good Cosmetic Outcome Over Time* |
|----------------|----------------|----------------|
| Time From Last Treatment, mo | Treatment Group, No. (%) | P Value |
| **MAL-PDT** | **Surgery** | **Investigator Rated** |
| 3 | 36/44 (82) | 15/45 (33) | .001 |
| 12 | 33/42 (79) | 17/45 (36) | .001 |
| 24 | 24/29 (83) | 18/39 (41) | .001 |
| **Patient Rated** |
| 3 | 39/41 (95) | 37/44 (84) | .10 |
| 12 | 41/42 (98) | 36/43 (84) | .03 |
| 24 | 28/29 (97) | 27/36 (75) | .04 |

Abbreviation: MAL-PDT, methyl aminolevulinate photodynamic therapy.

*Cochran Mantel-Haenszel test showed a significant difference in favor of MAL-PDT at all time points for the investigator ratings and at 12 and 24 months for the patient ratings. See “End Point Assessments” subsection of the “Methods” section for explanation of rating scale.

Figure 2. A male patient with a nodular basal cell carcinoma on the forehead, in facial (A) and close-up (B) view (scale in millimeters). The untreated lesion is shown on the left, while on the right, complete clinical response with no scarring is seen at 12 months after methyl aminolevulinate photodynamic therapy.
an excellent or good cosmetic result with methyl aminolevulinate PDT than surgery (Figure 2). Even at 2 years, allowing time for full healing after surgery, 97% of patients receiving methyl aminolevulinate PDT assessed their outcome as excellent or good, compared with 75% after surgery ($P = .04$), while the corresponding investigator assessment was 83% vs 41% ($P = .001$). Differences in scoring between investigators and patients may be attributable to the investigators’ assessment being based on detailed evaluation of treatment site characteristics, including presence or absence of a scar, while patients gave a global assessment. Patient evaluation clearly has priority over unblinded investigator assessment, although the overall conclusions are the same. Interestingly, it can also be seen (Figure 3) that many more subjects scored their cosmesis as the highest (excellent) grade with methyl aminolevulinate PDT than with surgery. Given the importance of avoidance of scarring caused by the treatment of BCC, which predominantly occurs on exposed sites,$^5$ methyl aminolevulinate PDT may have an important advantage over surgery for some patients.

At 24 months, 5 recurrences of previously cleared lesions were seen in the methyl aminolevulinate PDT group vs 1 in the surgical group. The study was not powered to examine long-term recurrence rate, but the findings were consistent with previous reports for these respective treatments.$^{17-20}$ Soler et al$^{17}$ reported a recurrence rate of 8% at 1 year, after combined treatment of lesions with debulking followed by single 5-aminolevulinic acid PDT. More recently, Wang et al$^{20}$ reported a clinical recurrence rate of 5% at 1 year for single 5-aminolevulinic acid PDT treatment, but the histologically confirmed recurrence rate was higher at 25%. A recent retrospective study of recurrence of superficial and nodular BCC after 2 methyl aminolevulinate PDT treatments, involving a mean follow-up of 35 months (range, 2-4 years), showed that 89% of a total of 310 lesions remained in complete remission.

![Figure 3. Cosmetic outcome at 3, 12, and 24 months on investigator and patient assessment. MAL-PDT indicates methyl aminolevulinate photodynamic therapy.](image)

**Table 5. Adverse Events to Treatment**

<table>
<thead>
<tr>
<th>Treatment Group, No. (%)</th>
<th>MAL-PDT (n = 52)</th>
<th>Surgery (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>27 (52)</td>
<td>14 (29)</td>
</tr>
<tr>
<td>Total No. of adverse events</td>
<td>61</td>
<td>24</td>
</tr>
<tr>
<td>Any local adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First cycle, first treatment</td>
<td>20/52 (38)</td>
<td>8/49 (16)</td>
</tr>
<tr>
<td>First cycle, second treatment</td>
<td>18/49 (37)</td>
<td>NA</td>
</tr>
<tr>
<td>Second cycle, first treatment</td>
<td>1/12 (8)</td>
<td>NA</td>
</tr>
<tr>
<td>Second cycle, second treatment</td>
<td>3/10 (30)</td>
<td>NA</td>
</tr>
<tr>
<td>Common local adverse events*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning sensation of skin</td>
<td>16 (31)</td>
<td>0</td>
</tr>
<tr>
<td>Pain in skin</td>
<td>7 (14)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Erythema</td>
<td>7 (14)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Skin infection</td>
<td>0</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Crusting</td>
<td>2 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Itching</td>
<td>2 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: MAL-PDT, methyl aminolevulinate photodynamic therapy; NA, not applicable.

*Reported by more than 1 patient.
events were consistent with the profile of adverse events associated with an invasive procedure is an important factor. Unlike surgery, cosmetic outcome over the inconvenience of making additional visits to the clinic, or where avoidance of an invasive procedure is an important factor. Unlike surgery, there is no routine need for local anesthesia. Methyl aminolevulinate PDT is well tolerated; in this study, adverse events were consistent with the profile of adverse events previously reported with PDT using topical 5-aminolevulinic acid and topical methyl aminolevulinate, generally of mild to moderate intensity, and resolving the same day without the need for medical treatment.

In conclusion, this study supports that treatment of primary nodular BCC with methyl aminolevulinate PDT is effective and has cosmetic advantages over surgery. Long-term follow-up is advised in view of the trend for higher recurrence rate. Since topical methyl aminolevulinate PDT has recently become licensed for the treatment of nodular BCC in 14 countries, experience with this new agent continues to grow. Methyl aminolevulinate PDT is a promising treatment option in nodular BCC that may have particular application when avoidance of scarring is a priority.

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