Five-Year Follow-up of a Randomized, Prospective Trial of Topical Methyl Aminolevulinate Photodynamic Therapy vs Surgery for Nodular Basal Cell Carcinoma

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**Objective:** To compare 5-year lesion recurrence rates in primary nodular basal cell carcinoma treated with topical methyl aminolevulinate photodynamic therapy (PDT) or simple excision surgery.

**Design:** Prospective, randomized, multicenter study.

**Setting:** University hospital dermatology departments.

**Patients:** A total of 97 patients, 50 with 53 lesions treated with methyl aminolevulinate PDT and 47 with 52 lesions treated by excision surgery, were included in the per protocol analysis. Of the lesions treated with methyl aminolevulinate PDT and surgery, 49 and 52, respectively, showed complete clinical response at 3 months after treatment and were observed for long-term outcome evaluation.

**Interventions:** Topical methyl aminolevulinate cream, 160 mg/g, applied for 3 hours before illumination (75 J/cm² of red light at 570 to 670 nm) on 2 or 4 occasions (12 [23%] of 53 lesions); or excision surgery.

**Main Outcome Measures:** Histologically confirmed lesion recurrence, sustained lesion complete response rate (time-to-event analysis), and investigator assessment of cosmetic outcome, 5 years after the last treatment.

**Results:** At 5 years, recurrence was documented in 7 (14%) of 49 lesions (95% confidence interval [CI], 6%-27%) treated with methyl aminolevulinate PDT vs 2 (4%) of 52 lesions (95% CI, 1%-13%) treated with excision surgery (P = .09). Estimated sustained lesion complete response rates were 76% (95% CI, 59%-87%) and 96% (95% CI, 84%-99%), respectively (P = .01). More patients treated with methyl aminolevulinate PDT than surgery had an excellent or good cosmetic outcome: 27 (87%) of 31 patients (95% CI, 70%-96%) vs 19 (54%) of 35 patients (95% CI, 37%-71%) (P = .007).

**Conclusions:** Long-term follow-up indicates superior efficacy of surgery to methyl aminolevulinate PDT in nodular basal cell carcinoma. However, methyl aminolevulinate PDT is also an effective treatment for this indication and exhibits a more favorable cosmetic outcome.

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(nodular) BCC. Nearly two-thirds of all recurrent BCC lesions appear in the first 3 years after treatment, with 18% appearing between 5 and 10 years posttreatment. We therefore performed a 5-year follow-up to examine the sustained complete lesion response and recurrence rate over time for methyl aminolevulinate PDT vs excision surgery in patients with nodular BCC.

METHODS

European university hospital dermatology departments participated in a prospective, randomized study of methyl aminolevulinate PDT vs simple excision surgery in patients with nodular BCC. The study design and procedures have been detailed in a prior report. Patients aged at least 18 years with previously untreated primary nodular BCC, suitable for simple excision surgery, were enrolled from the clinics of participating centers. The diagnosis of nodular BCC was confirmed by histological examination. 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 were excluded. Patients were enrolled from October 26, 1999, to August 29, 2000, and were followed up until October 12, 2005. All patients gave written informed consent before enrollment. The study was performed in accordance with the Declaration of Helsinki, with ethical approval obtained from the local ethics committee of each of the participating centers. Eligible patients were randomized to treatment with PDT using methyl aminolevulinate cream, 160 mg/g (Metvix; PhotoCure ASA, Oslo, Norway, and Galderma, Sophia Antipolis, France), or excision surgery. In the PDT group, lesion surface preparation was performed in a standardized manner between centers, before application of methyl aminolevulinate cream. Surface scale or crust was gently removed with a curette or scalpel blade, without anesthesia, insufficient to cause pain or bleeding. An occlusive and light-shielding dressing was applied, and after 3 hours, the area was illuminated with noncoherent red light (wavelength, 670 nm; total fluence, 75 J/cm²; and fluence rate, 50-200 mW/cm²). Patients in the PDT group were treated with either 1 or 2 PDT cycles, each composed of 2 PDT sessions, with an interval of 1 week between sessions. Simple elliptical excision surgery with at least 5-mm margins was performed once under local anesthesia in accordance with the usual practice of the center.

Patients with a complete response at 3 months after the last treatment (ie, complete disappearance of the lesion as evaluated on clinical inspection by the same investigator [M.A.R., V.G., G.A.E.W., or P.W.]) were followed up at yearly intervals for 5 years after the last treatment. Any clinically suspected recurrence was confirmed by histological examination. Investigator-assessed cosmetic outcome was judged yearly for up to 5 years in all patients with a complete response in all lesions, using a 4-point scale as follows: (1) excellent: no scarring, atrophy, or induration of an adverse event; (2) good: no scarring, atrophy, or induration and slight or no redness or change in pigmentation compared with adjacent skin; (3) fair: slight to moderate occurrence of scarring, atrophy, or induration and moderate redness or increase in pigmentation compared with adjacent skin; (4) poor: extensive occurrence of scarring, atrophy, or induration.

Details of adverse events, including local phototoxicity reactions reported up to 3 months after last treatment, have been provided. During the 5-year follow-up, any adverse events that led to discontinuation were documented.

The primary statistical analysis was based on the per protocol (PP) population, including all eligible patients who completed surgery or the first PDT treatment cycle and had a response assessment at 3 months or who completed the second PDT treatment cycle and received treatment in accordance with the study procedures. In addition, an intention-to-treat analysis was performed. The analysis populations (intention-to-treat and PP groups) were almost identical and gave similar results in all aspects. Two patients in each treatment group (4 of 101) were excluded from the PP population. The present study therefore focuses on the population of primary interest (ie, the PP population). Analyses were performed independently (PAREXEL International GmbH, Berlin, Germany) using SAS statistical software (SAS Institute Inc, Cary, North Carolina).

Of primary interest during long-term follow-up was the histologically confirmed lesion recurrence rate. Lesion recurrence rates were the proportion of recurrent lesions, of all lesions that were followed up at yearly intervals for 5 years after the last treatment.
had a clinical complete response 3 months after treatment. They were presented with 95% confidence intervals (CIs), and the treatment difference was tested with the Fisher exact test.

A time-to-event approach was used to estimate lesion complete response rates over time, using all available information and keeping the original sample size and randomization scheme. The event of interest was failure, defined as nonresponse at 3 months after the last treatment or recurrence at the follow-up intervals of 1, 2, 3, 4, or 5 years.

Censoring occurred when a patient with a lesion in complete response discontinued for reasons other than treatment failure. Discontinuations or recurrences were only recorded at the yearly follow-up. Thus, the exact time when the event occurred was unknown. Furthermore, some patients had more than 1 lesion. The lesions formed clusters within these patients and therefore could no longer be regarded as independent observations. The interval censoring and the lesion clusters made the data unsuitable for standard procedures, such as the Kaplan-Meier or the life-table approach. Instead, a complementary log-log model suggested by Guo and Lin was used. In a first step, a logistic regression using the complementary log-log link function was run with standard software (PROC LOGISTIC; SAS Institute Inc). In a second step, the standard errors of the estimates were adjusted for the dependencies in the data caused by the lesion clusters, as described using computer software (IML; SAS Institute Inc).

Recurrence rates could not be derived from the time-to-event model because the failure rates were a combination of nonresponse rates at 3 months after the last treatment and recurrence rates during later follow-ups.

The proportions of patients categorized with excellent or good overall cosmetic outcome were summarized with 2-sided 95% CIs. The treatment difference was tested with the Fisher exact test using the categories of excellent or good vs fair or poor.

Of 103 randomized patients, 101 were treated in the study, 52 with methyl aminolevulinate PDT and 49 with surgery. The PP population comprised 97 patients, 50 with 53 lesions treated with methyl aminolevulinate PDT and 47 with 52 lesions treated with excision surgery (Figure 1). Four patients were excluded from the PP population, 1 in the methyl aminolevulinate PDT group with a major protocol violation (received a light dose less than that stipulated) and 3 for whom response at 3 months could not be assessed (in the surgery group, 1 died and 1 withdrew consent; and in the methyl aminolevulinate PDT group, 1 discontinued the study prematurely because of treatment-related pain). Forty-nine lesions in 46 patients treated with methyl aminolevulinate PDT and 52 lesions in 47 patients treated with excision surgery showed complete lesion response at 3 months and were included in the long-term follow-up.

Sixty-six patients, 31 treated with methyl aminolevulinate PDT and 35 treated with surgery, completed the 5-year follow-up evaluation with at least 1 lesion in complete response. Twelve patients, 10 treated with methyl aminolevulinate PDT and 2 treated with surgery, discontinued the study before the 5-year follow-up evaluation, with treatment failure in all lesions (Figure 1). Only 4 patients (2 in each treatment group) were truly lost to follow-up during the 5-year period. Eight patients (4 in each group) died during the follow-up, and 2 discontinued because of intercurrent disease.

The baseline characteristics of the 2 groups were similar.7 The mean (range) age was 69 (40-95) years in the methyl aminolevulinate PDT group and 67 (38-82) years in the surgery group; there were 32 men and 20 women in the methyl aminolevulinate PDT group and 29 men and 20 women in the surgery group. Most patients in each group had 1 lesion (94% [47 of 50 patients] in the methyl aminolevulinate PDT group and 89% [42 of 47 patients] in the surgery group). In each group, most lesions were less than 20 mm in diameter and were located on the face or scalp or trunk or neck (Table 1). However, the distribution of these lesions differed between the 2 groups. In the surgery group, there were more lesions on the face or scalp than on the trunk or neck, whereas in the methyl aminolevulinate PDT group, the distribution of lesions to these areas was similar (Table 1). Most lesions in the methyl aminolevulinate PDT group were treated with 1 PDT cycle (41 of 53 lesions [77%]).

**RESULTS**

A time-to-event analysis of lesion response over time showed that excision surgery was more favorable than methyl aminolevulinate PDT (Figure 2). At 5 years af-

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**Table 1. Baseline Characteristics of Lesions in the PP Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methyl Aminolevulinate PDT Group (n = 53)</th>
<th>Surgery Group (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face or scalp</td>
<td>21 (40)</td>
<td>32 (62)</td>
</tr>
<tr>
<td>Trunk or neck</td>
<td>27 (51)</td>
<td>15 (29)</td>
</tr>
<tr>
<td>Extremities</td>
<td>5 (9)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Longest lesion diameter, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 10</td>
<td>29 (55)</td>
<td>34 (65)</td>
</tr>
<tr>
<td>&gt; 10 and &lt; 20</td>
<td>19 (36)</td>
<td>14 (27)</td>
</tr>
<tr>
<td>&gt;= 20</td>
<td>2 (4)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Abbreviations: PDT, photodynamic therapy; PP, per protocol.

*Data are given as number (percentage) of lesions for each group.

Percentages may not total 100 because of rounding or because of missing data.

3 Patients in the methyl aminolevulinate PDT group and 1 in the surgery group.

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**Figure 2.** Lesion complete response (CR) over time (time-to-event analysis) for the per protocol population. PDT indicates photodynamic therapy.
ter last treatment, the sustained lesion complete response rate, estimated by the complementary log-log model, was 76% (95% CI, 59%-87%) for methyl aminolevulinate PDT compared with 96% (95% CI, 84%-99%) for excision surgery in the PP population (P = .01). Lesion recurrence was documented in 14% of lesions with complete response after 3 months treated with methyl aminolevulinate PDT, compared with 4% of lesions treated with excision surgery (P = .09) (Table 2). The methyl aminolevulinate PDT group recurrences included 5 of 40 lesions given 1 treatment cycle and 2 of 9 lesions given 2 treatment cycles. No recurrences in the methyl aminolevulinate PDT group were observed from 3 to 5 years, and only 1 lesion treated with excision surgery recurred.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interval After Last Treatment, y</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Methyl Aminolevulinate PDT Group</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Missing, No. (%)</td>
<td></td>
<td>2</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Lesion recurrence (n = 49)</td>
<td></td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>No. of lesions</td>
<td></td>
<td>4</td>
<td>10</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Proportion (95% CI) of lesions, %</td>
<td></td>
<td>1-14</td>
<td>3-22</td>
<td>6-27</td>
<td>6-27</td>
<td>6-27</td>
</tr>
<tr>
<td>Lesion size, mm&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>≤10</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
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<tr>
<td></td>
<td></td>
<td>&gt;10 and &lt; 20</td>
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<td>2</td>
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<td>2</td>
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<tr>
<td></td>
<td>Surgery Group</td>
<td></td>
<td></td>
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<td>Missing, No. (%)</td>
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<td>3</td>
<td>7</td>
<td>10</td>
<td>11</td>
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<td>Lesion recurrence (n = 52)</td>
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<td>0</td>
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<td>2</td>
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</tr>
<tr>
<td>No. of lesions</td>
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<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Proportion (95% CI) of lesions, %</td>
<td></td>
<td>0-100</td>
<td>0-100</td>
<td>1-13</td>
<td>1-13</td>
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<tr>
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<td></td>
<td>≤10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td>&gt;10 and &lt; 20</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PDT, photodynamic therapy.

<sup>a</sup> Complete response at 3 months occurred in 49 of 53 lesions (92%) (95% confidence interval, 82%-98%).

<sup>b</sup> P = .12 for the treatment difference at 3 months in lesion response rate.

<sup>c</sup> P = .09 for the treatment difference at 5 years in lesion recurrence rate.

<sup>d</sup> There were no ≥20-mm or larger lesions in either group.

<sup>e</sup> Complete response at 3 months occurred in 52 of 52 lesions (100%) (95% confidence interval, 93%-100%).

Figure 3. The appearance of the nodular basal cell carcinoma in a study participant in the photodynamic therapy group (a 72-year-old woman) at baseline (A) and at 5 years, showing an excellent cosmetic outcome and complete lesion response (B). In A and B, the inset shows a close-up.
within this period. In the methyl aminolevulinate PDT group, there was no evidence that lesion recurrence was higher in larger lesions because recurrence was documented in 5 lesions with a maximum diameter of up to 10 mm and in 2 lesions with a diameter between 11 and 20 mm (Table 2). Recurrence rates at 5 years were identical in the intention-to-treat population.

**COSMETIC OUTCOME**

In the PP population, outcome at 3 months rated as excellent or good was found in 36 of 44 patients (82%) (95% CI, 67%-92%) in the methyl aminolevulinate PDT group vs 15 of 45 patients (33%) (95% CI, 20%-49%) in the surgery group (P < .001). The overall cosmetic outcome 5 years after last treatment was also superior with methyl aminolevulinate PDT compared with excision surgery. At final assessment, outcome as rated by the investigators [L.E.R., M.A.R., R.L., R.C.Y., I.B., V.G., M.-A.R., A.A., and P.W.] was good or excellent in 27 of 31 patients (87%) (95% CI, 70%-96%) treated with methyl aminolevulinate PDT compared with 19 of 35 patients (54%) (95% CI, 37%-71%) treated with excision surgery (P = .007) (Figure 3).

**COMMENT**

Findings from this long-term follow-up study add to evidence supporting a role for methyl aminolevulinate PDT in the treatment of primary nodular BCC. The cumulative 5-year lesion recurrence rate with methyl aminolevulinate PDT was 14% compared with 4% for excision surgery, the latter being consistent with the published low rate for this modality.8,10,11 We anticipate that we have captured all relevant events and that a longer than 5-year follow-up would be unlikely to yield further recurrences because only 2 recurrent lesions were observed in the methyl aminolevulinate PDT group and 1 in the surgical group between 2 and 3 years’ follow-up. There were no recurrent lesions observed in the methyl aminolevulinate PDT group and only 1 in the surgical group from 3 to 5 years’ follow-up.

While the sustained lesion complete response rate at 5 years was statistically superior with excision surgery compared with methyl aminolevulinate PDT (96% vs 76%; P = .01), lesions treated with methyl aminolevulinate PDT showed a substantially better cosmetic outcome at 5 years, as assessed by the investigator, than those treated with surgery (P = .007). Thus, the results of our study indicate that, whereas simple excision surgery will generally remain the treatment of choice for nodular BCC amenable to this intervention, methyl aminolevulinate PDT is also an effective treatment. There are a number of instances (eg, when there are multiple lesions; when there are lesions in sites such as the lower leg, where there is poor healing; and when there are patients undergoing anticoagulation) in which excision can be challenging. Moreover, methyl aminolevulinate PDT may be more suitable for the treatment of lesions in cosmetically sensitive areas, such as the face (involving approximately 50% of lesions in the present study), where optimal cosmetic outcome is an important clinical consideration.

Systematic reviews of treatment modalities for BCC highlight the lack of published long-term follow-up data from controlled clinical trials and advocate evaluation of 5-year lesion recurrence rates as a primary outcome in clinical studies. The lack of long-term data from randomized PDT studies has been a particular concern among dermatologists.12 To our knowledge, we present the first randomized study to report cumulative 5-year recurrence rates in nodular BCC comparing topical PDT with the standard treatment of excision surgery. We conclude that the moderately low 5-year lesion recurrence rate with methyl aminolevulinate PDT documented in this study, together with the favorable long-term cosmetic outcome, supports a clinical role for this modality in the treatment of nodular BCC, particularly when avoidance of scarring is a priority.

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**Author Contributions:** Dr Rhodes had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Rhodes, de Rie, Goulden, and Wong. Acquisition of data: Rhodes, de Rie, Leifsdottir, Yu, Bachmann, Goulden, Wong, Richard, Anstey, and Wolf. Analysis and interpretation of data: Rhodes, de Rie, Yu, Anstey, and Wolf. Drafting of the manuscript: Rhodes, Yu, and Richard. Critical revision of the manuscript for important intellectual content: Rhodes, de Rie, Leifsdottir, Yu, Bachmann, Goulden, Wong, Richard, Anstey, and Wolf. Statistical analysis: Rhodes. Obtained funding: Rhodes. Administrative, technical, and material support: Rhodes, de Rie, Yu, Richard, Anstey, and Wolf. Study supervision: Rhodes, Yu, and Wolf.

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**Additional Contributions:** Parexel GmbH, Berlin, Germany, performed the data analysis.
REFERENCES


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