Clinical Trial

Surgical excision versus Mohs’ micrographic surgery for basal cell carcinoma of the face: A randomised clinical trial with 10 year follow-up

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Facial

Abstract  Background: Basal cell carcinoma (BCC) is the most common form of cancer among Caucasians and its incidence continues to rise. Surgical excision (SE) is considered standard treatment, though randomised trials with long-term follow-up are rare. We now report the long-term results of a randomised trial comparing surgical excision with Mohs’ micrographic surgery (MMS) for facial BCC.

Methods: 408 facial, high risk (diameter at least 1 cm, H-zone location or aggressive histological subtype) primary BCCs (pBCCs) and 204 facial recurrent BCCs (rBCCs) were randomly allocated to treatment with either SE or MMS between 5th October 1999 and 27th February 2002.

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2002. The primary outcome was recurrence of carcinoma. A modified intention to treat analysis was performed.

**Findings:** For primary BCC, the 10-year cumulative probabilities of recurrence were 4.4% after MMS and 12.2% after SE (Log-rank test $\chi^2 = 2.704, p = 0.100$). For recurrent BCC, cumulative 10-year recurrence probabilities were 3.9% and 13.5% for MMS and SE, respectively (Log-rank $\chi^2 = 5.166, p = 0.023$). A substantial proportion of recurrences occurred after more than 5 years post-treatment: 56% for pBCC and 14% for rBCC.

**Interpretation:** Fewer recurrences occurred after treatment of high risk facial BCC with MMS compared to treatment with SE. The proportion of recurrences occurring more than 5 years post-treatment was especially high for pBCC, stressing the need for long-term follow-up in patients with high risk facial pBCC.

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1. Introduction

Basal cell carcinoma (BCC) is the most common form of cancer among Caucasians worldwide. The incidence has increased with 5.5% per year over the past decades and is predicted to continue rising [1]. In the Netherlands, the lifetime risk of developing a BCC is one in every 5–6 persons [2]. The disease related mortality is very low due to the low rates of metastatic disease [3]. However, morbidity can be high due to local tissue destruction, especially since most tumours occur in functional areas such as the head and neck [4]. Although many therapeutic options are available today, standard surgical excision (SE) is still the most common form of treatment for BCCs [4]. Mohs’ micrographic surgery (MMS) is a specialised surgical technique and its use is increasing [5]. The main difference between both treatments is the method of histological margin examination. In standard SE, surgical margins are mostly examined on random vertical sections, the so-called bread loaf-technique. In MMS, the specimen is flattened and sliced horizontally. This offers the possibility to examine 100% of the resection margins, in contrast to the small percentage of margin control in SE. Therefore, MMS should theoretically lead to fewer recurrences with maximal sparing of surrounding healthy tissue [6].

We previously showed that, after a period of 5 years, treatment with MMS led to significantly fewer recurrences than SE in recurrent facial BCC [7]. However, consensus on treatment is difficult to reach since prospective randomised studies are rare [4]. Furthermore, most non-comparative studies only report 5 year recurrence rates, but there have been reports that recurrences may develop even later [7–13]. BCC located in the H-zone of the face, with positive excision margins in previous resections or with an aggressive histological growth pattern show higher recurrence rates [14,15].

The goal of this study is to provide evidence on the long-term efficacy of MMS and SE in high risk facial BCC. In 1999, a randomised controlled trial was initiated and we previously reported the results after 2 and 5 years of follow-up [7,16]. To our knowledge, this is the first randomised controlled trial on treatment of BCC which provides data that enable estimation of recurrence probability after a 10-year follow-up period.

2. Material and methods

A prospective randomised controlled trial was started at the Maastricht University Medical Centre in 1999, comparing MMS with SE in facial BCC [7,16]. The primary outcome of this trial was recurrence of tumour. Patient selection and techniques were described in the previous publications on this trial, but will be briefly described here [7,16].

2.1. Patient selection

Patients were recruited during a visit to a dermatology outpatient clinic of one of the seven participating hospitals in the southern part of the Netherlands between 5th October 1999 and 27th February 2002. Patients were included in the primary basal cell carcinoma (pBCC) group if they presented with a primary facial BCC of 1 cm or more in diameter, and were either located in the H-zone of the face or were of an aggressive histological subtype (micronodular, morpheaform, BCC with squamous differentiation, infiltrative). Patients were included in the recurrent basal cell carcinoma (rBCC) group if they had at least one facial BCC recurring for the first or second time. The diagnosis of BCC had to be histologically confirmed before treatment.

Patients with a life expectancy of less than 3 years were excluded from participation. The trial was approved by the ethics and scientific committee of the University Hospital Maastricht and has been carried out in accordance with The Code of Ethics of the World Medical Association. All patients gave written informed consent for study participation.

2.2. Randomisation and masking

Tumours of eligible patients were randomly assigned to either SE or MMS by use of a computer-generated
allocation scheme (Sampsize 2.0). Randomisation occurred by telephone, by an independent person not involved in the trial and separately for the pBCC and rBCC groups. For practical reasons no blinding was performed for the allocated treatment.

2.3. Procedures

Patients with tumours assigned to SE were referred for treatment to either the Maastricht University Medical Centre (Maastricht, the Netherlands) or the Laurentius Hospital Roermond (Roermond, the Netherlands), in which SE was performed under the same conditions and by the same three surgeons (JUO, GAMK and NWJK-S). In most patients the procedure was performed under local anaesthesia. In both the pBCC and rBCC group, a tumour assigned to SE was excised with a 3-mm clinically tumour free resection margin at a 45° angle into the subcutaneous fat. Histological margin examination with the bread loaf-technique was performed if the tumour diameter was 16 mm or less. In larger sized tumours the quadrant method was applied [17]. In case of an incomplete excision the quadrant method was applied [17]. In case of two incomplete excisions, tumours were treated with MMS.

Patients with tumours assigned to MMS were referred for treatment to the Maastricht University Medical Centre and treated by the same three surgeons formerly mentioned. The tumour was excised with a 3-mm clinically tumour free resection margin at a 90° angle in order to obtain a bowl-shaped excision sample. For histological margin examination, this sample was compressed and sliced horizontally. In case of residual tumour the procedure was repeated until no more tumours were seen in the specimen.

2.4. Follow-up information

The primary outcome of this study was tumour recurrence defined as a histologically confirmed BCC in a skin biopsy of a clinically suspect area within 5-mm of the surgical scar. Patients were seen once every year by their own dermatologist, generally until 5 years after treatment. Long-term follow-up was conducted by the patient’s own dermatologist if indicated, e.g. in patients with multiple skin cancers. For this study, the remaining patients who did not complete a follow-up of at least 10 years received an invitation for skin examination by the research physician. At follow-up visits the treatment site was inspected. The collection of follow-up data for pBCC and rBCC groups ended on 19th June 2012.

2.5. Statistical analysis

The sample size calculation for this study has been described in previous publications on this trial [7,16]. For estimation of cumulative probabilities of recurrence, Kaplan–Meier survival analysis was used. Patients were censored at the date of histological confirmation of a recurrence or the date of the last follow-up visit. Differences in cumulative probability of recurrence between treatment groups were tested for statistical significance with the log-rank test. Differences in tumour characteristics between tumours with and without a follow-up period of at least 10-years were tested for statistical significance with the Fisher-exact test (categorical data) or Student’s T-test (continuous data). Unless stated otherwise, analyses were performed per included tumour and not per patient. A p-value below 0.05 was considered to indicate statistical significance. A modified intention to treat analysis was applied: randomised tumours that were not treated were excluded from further analysis. All data analyses were performed with SPSS version 18.0 (SPSS, Chicago, IL, United States of America (USA)) and STATA version 11.0 (StataCorp, USA).

2.6. Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

3. Results

3.1. Primary basal-cell carcinomas

Between October 1999 and January 2001, 408 pBCCs in 374 patients were randomly assigned to treatment with SE or MMS (Fig. 1). 11 allocated patients were not treated. A total of 363 patients with 397 tumours were treated. Of the 374 randomised patients, 30 patients had two and two patients had three tumours. Treatment characteristics, nature and prevalence of complications were described previously [7,16]. Baseline characteristics were comparable between the randomised groups (Table 1). The median follow-up period for pBCC was 79.2 months (range 0.0–150.3). Follow-up data for at least 10 years post-treatment were available for 140 (35.3%) of 397 treated tumours in 129 patients. Reasons for not completing the 10-year follow-up were: death due to causes unrelated to BCC or treatment, refusal to attend follow-up visits, and other reasons such as inability to contact the patient or inability of the patient to visit the hospital (Fig. 1). Reasons for loss to follow-up were comparable between SE and MMS treatment groups (Fig. 1). The mean age of patients lost to follow-up was significantly higher than that of patients who completed a 10-year follow-up period (72.1 versus 60.3 years respectively, p < 0.001).
There was no significant difference in the mean age of patients lost to follow-up between the two treatment groups. Comparison of other characteristics such as tumour location, allocated therapy, gender and aggressive histological subtype did not reveal any important differences.

During the 10-year follow-up period, 21 recurrences were registered in the pBCC group; 15 after SE and...
Six after MMS. Two more recurrences occurred in each treatment group more than 10-years post-treatment. The 10-year cumulative probability of recurrence is 4.4% (95% confidence interval (CI): 1.9–9.8%) after MMS and 12.2% (95% CI: 7.3–19.8%) after SE (log-rank test $\chi^2 = 2.704$, $p = 0.10$, Table 2, Fig. 2).

Of all recurrences, 11 (44.0%) were registered in the first 5-years after treatment, 10 (40.0%) were registered between 5 and 10-years post-treatment and another 4 (16.0%) even past 10-year follow-up. Of the patients who had more than one pBCC, none had more than one recurrence. Characteristics of recurrent tumours are shown in Table 3.

### 3.2. Recurrent basal-cell carcinomas

Between October 1999 and February 2002, 204 rBCCs in 191 patients were assigned to one of the treatment groups (Fig. 3). Two patients, randomised to MMS, deceased before treatment so 202 patients were treated. Of the 191 randomised patients with rBCC, 10 patients had two and one had four rBCCs. Previous treatments of rBCC consisted mainly of SE (53.9%), cryotherapy (28.9%) or radiotherapy (5.4%). Baseline characteristics are presented in Table 1.

The median follow-up period for rBCC was 85.0 months (range 0–149.3). 10-year follow-up data were complete for 78 (38.6%) of 202 treated tumours in 74 patients (Fig. 3).

### Table 1

Baseline patient and tumour characteristics separated for primary and recurrent BCC and treatment group.

<table>
<thead>
<tr>
<th></th>
<th>pBCC $n = 204$</th>
<th>rBCC $n = 102$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMS (n, %)</td>
<td>SE (n, %)</td>
</tr>
<tr>
<td>Mean age at treatment, y</td>
<td>67.4 (SD 12.7)</td>
<td>68.7 (SD 12.2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>123 (60.3)</td>
<td>126 (61.8)</td>
</tr>
<tr>
<td>Female</td>
<td>81 (39.7)</td>
<td>78 (38.2)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal/temporal</td>
<td>53 (26.0)</td>
<td>65 (31.9)</td>
</tr>
<tr>
<td>Cheek/chin</td>
<td>19 (9.3)</td>
<td>16 (7.8)</td>
</tr>
<tr>
<td>(Peri)nasal</td>
<td>69 (33.8)</td>
<td>62 (30.4)</td>
</tr>
<tr>
<td>Lips/perioral</td>
<td>14 (6.9)</td>
<td>8 (3.9)</td>
</tr>
<tr>
<td>Periocular</td>
<td>16 (7.8)</td>
<td>16 (7.8)</td>
</tr>
<tr>
<td>Ears</td>
<td>9 (4.4)</td>
<td>16 (7.8)</td>
</tr>
<tr>
<td>Periauricular</td>
<td>24 (11.8)</td>
<td>21 (10.3)</td>
</tr>
<tr>
<td>H-zone</td>
<td>184 (90.0)</td>
<td>197 (97.0)</td>
</tr>
<tr>
<td>Aggressive histological subtype</td>
<td>105 (51.5)</td>
<td>88 (43.1)</td>
</tr>
<tr>
<td>First recurrence</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

pBCC, primary basal cell carcinoma; rBCC, recurrent basal cell carcinoma; MMS, Mohs’ micrographic surgery; SE, surgical excision; BCC, basal cell carcinoma; Y, years; SD, standard deviation.

### Table 2

Estimated cumulative probabilities of recurrence for primary and recurrent basal cell carcinoma treated with Mohs’ micrographic surgery (MMS) or surgical excision.

<table>
<thead>
<tr>
<th>Follow-up (months)</th>
<th>Kaplan–Meier cumulative probability of recurrence (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary basal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>MMS</td>
</tr>
<tr>
<td>12</td>
<td>0.005 (0.001–0.037)</td>
</tr>
<tr>
<td>24</td>
<td>0.011 (0.003–0.043)</td>
</tr>
<tr>
<td>60</td>
<td>0.024 (0.009–0.063)</td>
</tr>
<tr>
<td>120</td>
<td>0.044 (0.019–0.098)</td>
</tr>
</tbody>
</table>

Fig. 2. Kaplan–Meier survival analysis of primary basal cell carcinoma (pBCC) treated with Mohs’ micrographic surgery (MMS) or surgical excision.
The most common reasons for not completing follow-up were death and inability to reach the patient or no-show at appointments (Fig. 3). Percentages of reasons for loss to follow-up were comparable between treatment groups.

Patients lost to follow-up were older than patients who completed a 10-year follow-up period (mean age 70.4 versus 64.5 years respectively, \( p < 0.001 \)). The mean age of patients lost to follow-up did not differ significantly between treatment groups. Other characteristics such as histological subtype, tumour location, gender, Fitzpatrick skin type and number of recurrence showed no statistical differences between patients with and without a complete 10-year follow-up.

During the 10-year follow-up period, 14 recurrences were registered in the rBCC group, 11 after treatment with SE and three after treatment with MMS. The cumulative probability of recurrence after MMS was 3.9% (95% CI: 1.2–11.7%) and after SE 13.5% (95% CI: 7.6–23.2%) at 10-years post-treatment (log-rank \( \chi^2 = 5.166; p = 0.023 \), Table 2, Fig. 4). Of the cumulative number of recurrences, 12 (86%) were registered in the first 5-years and 2 (14%) between 5 and 10-years post-treatment. No recurrences were registered more than 10-years post-treatment. Of the patients who had more than one rBCC, none had more than one recurrence. Characteristics of recurrences are shown in Table 4.

### 3.3. Subgroup analyses

Additional analyses were performed within subgroups according to histological subtype. Results are presented in Table 5, which shows that 10 year risk of recurrence was consistently higher after treatment with SE when compared to treatment with MMS. The largest difference between SE and MMS was found for aggressive rBCC.

### 4. Discussion

To our knowledge, this is the first prospective randomised study that compares SE and MMS for treatment of high risk primary and recurrent facial BCC with a long-term follow-up of 10 years. We observed substantial differences in estimated 10-year recurrence rates of 7.8% for pBCC and 9.6% for rBCC, favouring MMS. Our results show that, compared to SE, MMS is more effective in preventing recurrences for both high-risk pBCC and rBCC in the face.

Several prospective, non-randomised studies reported a 5-year recurrence percentage for MMS of 1.0–6.5% for primary and 4.0–10.0% for recurrent tumours [8,10–13,18–21]. The 5-year percentages in our study are comparable for pBCC and somewhat lower for rBCC (Table 2). For SE, reported 5-year recurrence rates are 1.3–10.1% for pBCC and 11.6–17.4% for rBCC.
The 5-year percentages of recurrences after SE in this study are comparable.

Multiple retrospective studies have reported on recurrences more than 5 years post-treatment [7–13]. In the current prospective study more than half of all recurrences in the pBCC group occurred more than 5 years post treatment, a finding which justifies the assumption that longer follow-up periods are required for evaluation of treatments for high-risk facial BCC. For pBCC, the effect of MMS appears visually more impressive in the late study period since a relatively large number of events occurred (in the SE group) in a smaller number of patients.
at risk. However, after testing we found that the proportional hazards assumption was met for the whole study period, hence the relative efficacy remains constant also for the whole study period. Notably, in the rBCC group only few extra recurrences occurred between 5 and 10 years post-treatment. We hypothesise that primary tumours and their first recurrences show less aggressive biological behaviour than tumours recurring for the second time or more, and therefore first recurrences of pBCC are discovered after a longer period of time.

Our study has several limitations. In the trial, a total of 13 patients received no treatment after randomisation and were excluded from analysis. For this reason, a modified intention to treat analysis had to be applied. Bias of results is unlikely, because reasons for exclusion were not related to tumour characteristics. A second limitation of our study is that only around 35–40% of all patients completed a 10-year follow-up. BCC generally affects people at higher age and it is known that loss to follow-up in older patient populations is substantial. In this study, death (unrelated to BCC) occurred in 30–40% of all patients. Another 20% of cases was lost to follow-up because of other reasons. However, these percentages still compare favourably to loss to follow-up rates reported in some of the few available long-term studies on BCC, in which percentages range from approximately 36% with more than 5-years of follow-up to 88% loss to follow-up at 10-years post-treatment [21,24]. The substantial loss to follow-up may have resulted in less precise estimates of recurrence-free survival, but the comparable loss to follow-up percentages in both treatment groups make biased comparison of the recurrence estimates unlikely.

At present times, a clinically tumour free margin of at least 4–5 mm is generally chosen in these high risk primary and recurrent facial BCCs. However, when this study was designed (in 1998) guidelines were lacking and an appropriate excision margin was based on the available literature at that time. [25,26] The benefit of larger margins (less incomplete excisions) was carefully weighed against the disadvantage of larger defects. Furthermore, the same resection margin (3 mm) was chosen for both SE and MMS to standardise both treatments and enhance comparability. We aimed at clear margins in both treatments, without an additional histological

![Graph](image.png)

**Figure 4.** Kaplan–Meier survival analysis of recurrent basal cell carcinoma (rBCC) treated with Mohs’ micrographic surgery (MMS) or surgical excision.

![Graph](image.png)

**Table 4**

<table>
<thead>
<tr>
<th>Survival (months)</th>
<th>Sex</th>
<th>Age (years)</th>
<th>1st/2nd recurrence</th>
<th>Histological subtype</th>
<th>Tumour location</th>
<th>Allocated treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.0 M</td>
<td>44.0</td>
<td>1st</td>
<td>Non-aggressive</td>
<td>(Peri)nasal</td>
<td>SE</td>
</tr>
<tr>
<td>2</td>
<td>18.2 F</td>
<td>75.2</td>
<td>1st</td>
<td>Aggressive</td>
<td>Cheek/chin</td>
<td>SE</td>
</tr>
<tr>
<td>3</td>
<td>20.7 F</td>
<td>82.6</td>
<td>1st</td>
<td>Non-aggressive</td>
<td>Frontal/temporal</td>
<td>SE</td>
</tr>
<tr>
<td>4</td>
<td>25.3 M</td>
<td>73.3</td>
<td>1st</td>
<td>Aggressive</td>
<td>Frontal/temporal</td>
<td>SE</td>
</tr>
<tr>
<td>5</td>
<td>27.1 M</td>
<td>60.4</td>
<td>2nd</td>
<td>Aggressive</td>
<td>(Peri)nasal</td>
<td>MMS</td>
</tr>
<tr>
<td>6</td>
<td>29.2 F</td>
<td>74.0</td>
<td>1st</td>
<td>Aggressive</td>
<td>Cheek/chin</td>
<td>SE</td>
</tr>
<tr>
<td>7</td>
<td>29.2 F</td>
<td>82.0</td>
<td>1st</td>
<td>Aggressive</td>
<td>Frontal/temporal</td>
<td>SE</td>
</tr>
<tr>
<td>8</td>
<td>31.9 F</td>
<td>82.2</td>
<td>1st</td>
<td>Aggressive</td>
<td>(Peri)nasal</td>
<td>MMS</td>
</tr>
<tr>
<td>9</td>
<td>39.1 M</td>
<td>71.7</td>
<td>2nd</td>
<td>Aggressive</td>
<td>Periocular</td>
<td>SE</td>
</tr>
<tr>
<td>10</td>
<td>45.8 F</td>
<td>71.4</td>
<td>1st</td>
<td>Aggressive</td>
<td>Frontal/temporal</td>
<td>SE</td>
</tr>
<tr>
<td>11</td>
<td>46.9 M</td>
<td>47.9</td>
<td>1st</td>
<td>Aggressive</td>
<td>Frontal/temporal</td>
<td>SE</td>
</tr>
<tr>
<td>12</td>
<td>53.1 M</td>
<td>56.8</td>
<td>1st</td>
<td>Aggressive</td>
<td>(Peri)nasal</td>
<td>SE</td>
</tr>
<tr>
<td>13</td>
<td>74.6 M</td>
<td>61.8</td>
<td>1st</td>
<td>Non-aggressive</td>
<td>Frontal/temporal</td>
<td>MMS</td>
</tr>
<tr>
<td>14</td>
<td>77.1 F</td>
<td>54.7</td>
<td>1st</td>
<td>Non-aggressive</td>
<td>Periocular</td>
<td>SE</td>
</tr>
</tbody>
</table>

| M, male; F, female; MMS, Mohs’ micrographic surgery; SE, surgical excision.

**Table 5**

<table>
<thead>
<tr>
<th>% cumulative recurrence free survival</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMS</td>
<td>SE</td>
</tr>
<tr>
<td>Aggressive histological subtype</td>
<td>97.5</td>
</tr>
<tr>
<td>Non-aggressive histological subtype</td>
<td>93.7</td>
</tr>
</tbody>
</table>

| rBCC                                 |         |
| Aggressive histological subtype     | 96.1    | 80.7   | 0.021 |
| Non-aggressive histological subtype | 96.0    | 91.8   | 0.362 |
margin. However, if there was any doubt on the completeness of the SE, we performed a second excision with again 3 mm margin. The large number of incomplete excisions (18% of pBCC and 32% of rBCC assigned to SE were incompletely removed after the first excision) shows that a surgical margin of 3 mm is not sufficient in these high risk BCCs [7]. Although surgery was repeated in the SE group until histological tumour free margins were obtained, it may be possible that less long term recurrences would have occurred in the SE group if a larger resection margin had been chosen. Nevertheless, the consequence of a larger surgical margin is a larger defect. This worsens aesthetic outcome and may in some cases lead to reduced functionality. Clinicians that treat facial skin tumours, face that dilemma on daily basis.

Indications for MMS have been broadened in the past years and if we would perform MMS on all indications that are mentioned in a recent published article on indications for MMS, this would mean a great burden on the dermatologists practice [5]. Furthermore, as the incidence of BCC still increases, there is a huge rise in treatment costs of this tumour. Since costs of MMS are higher than costs of SE, MMS should be reserved for indications for which superior effectiveness has been proven [27]. In this study, we included only high risk facial primary BCC and facial recurrent BCC. A high risk facial primary BCC is defined in this study as a BCC of at least 1 cm diameter either located in the H-zone of the face or being of an aggressive histological subtype. At this moment, only for these indications we consider MMS superior to SE. We think that more research is needed before MMS is introduced on a much larger scale.

In conclusion, we showed that recurrences after surgical treatment of both rBCC and pBCC can still occur up to and even after 10-years post treatment. In BCC treated with MMS, fewer tumours recurred during long-term follow-up. We therefore consider MMS as the most effective treatment for rBCC and high risk pBCC located in the face for prevention of recurrence on the long-term.

Contributors

KM, NK-S, JO, PN, GK, PS, CD and MN took part in designing the protocol and literature search. NK-S, KM and EvL coordinated the study. NK-S, MR and EvL took part in the follow-up of patients. EvL and MR took part in data collection. All authors took part in writing of the report. NK-S, KM, EvL, JO and GK took part in enrolment of patients. EvL and PN were involved in the statistical analysis. All authors reviewed and approved the final version of the manuscript.

Conflict of interest statement

None declared.

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