Surgical excision versus Mohs' micrographic surgery for primary and recurrent basal-cell carcinoma of the face: a prospective randomised controlled trial with 5-years' follow-up

Klara Mosterd, Gertruud A M Krekels, Fred H M Nieman, Judith U Ostertag, Brigitte A B Essers, Carmen D Dirksen, Peter M Steijlen, Anton Vermeulen, H A M Neumann, Nicole W J Kelleners-Smeets

Summary

Background Basal-cell carcinoma (BCC) is the most common form of skin cancer and its incidence is still rising worldwide. Surgery is the most frequently used treatment for BCC, but large randomised controlled trials with 5-year follow-up to compare treatment modalities are rare. We did a prospective randomised controlled trial to compare the effectiveness of surgical excision with Mohs' micrographic surgery (MMS) for the treatment of primary and recurrent facial BCC.

Methods Between Oct 5, 1999, and Feb 27, 2002, 408 primary BCCs (pBCCs) and 204 recurrent BCCs (rBCCs) in patients from seven hospitals in the Netherlands were randomly assigned to surgical excision or MMS. Randomisation and allocation was done separately for both groups by a computer-generated allocation scheme. Tumours had a follow-up of 5 years. Analyses were done on an intention-to-treat basis. The primary outcome was recurrence of carcinoma, diagnosed clinically by visual inspection with histological confirmation. Secondary outcomes were determinants of failure and cost-effectiveness. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN65009900.

Findings Of the 397 pBCCs that were treated, 127 pBCCs in 113 patients were lost to follow-up. Of the 11 recurrences that occurred in patients with pBCC, seven (4·1%) occurred in patients treated with surgical excision and four (2·5%) occurred in patients treated with MMS (log-rank test χ^2 0·718, p=0·397). Of the 202 rBCCs that were treated, 56 BCCs in 52 patients were lost to follow-up. Two BCCs (2·4%) in two patients treated with MMS recurred, versus ten BCCs (12·1%) in ten patients treated with surgical excision (log-rank test χ^2 5·958, p=0·015). The difference in the number of recurrences between treatments was not significant for pBCC, but significantly favoured MMS in rBCC. In pBCC, Cox-regression analysis showed no significant effects from risk factors measured in the study. In rBCC, aggressive histological subtype was a significant risk factor for recurrence in the Cox-regression analysis. For pBCC, total treatment costs were €1248 for MMS and €990 for surgical excision, whereas for rBCC, treatment costs were €1284 and €1043, respectively. Dividing the difference in costs between MMS and surgical excision by their difference in effectiveness leads to an incremental cost-effectiveness ratio of €23 454 for pBCC and €3171 for rBCC.

Interpretation MMS is preferred over surgical excision for the treatment of facial rBCC, on the basis of significantly fewer recurrences after MMS than after surgical excision. However, because there was no significant difference in recurrence of pBCC between treatment groups, treatment with surgical excision is probably sufficient in most cases of pBCC.

Funding The Netherlands Organisation for Scientific Research ZonMW.

Lancet Oncol 2008; 9: 1149–56

Published Online November 17, 2008 DOI:10.1016/S1470-2045(08)70260-2

See Reflection and Reaction page 1119

Department of Dermatology (K Mosterd MD, Prof P M Steijlen PhD, N W J Kelleners-Smeets PhD), **Department of Pathology** (A Vermeulen MD), **and Department of Clinical Epidemiology and Medical Technology Assessment** (F H M Nieman PhD, B A B Essers PhD, C D Dirksen PhD), **Maastricht University Medical Centre, Maastricht, Netherlands; Department of Dermatology, Catharina Hospital Eindhoven, Netherlands** (G A M Krekels PhD, J U Ostertag PhD); **Department of Dermatology, Erasmus Medical Centre, Rotterdam, Netherlands** (Prof H A M Neumann PhD)

Correspondence to: Dr Klara Mosterd, Department of Dermatology, Maastricht University Medical Centre, PO Box 5800, 6202 AZ Maastricht, Netherlands **k.mosterd@mumc.nl**

Introduction

Skin cancer is an important public health problem in white people. Its incidence has been increasing for decennia and will continue to rise.[1–3] The authors of a recent Cochrane review concluded that, based on the available published work, surgery is the treatment of choice for basal-cell carcinoma (BCC).[4] However, they also noted a paucity of published randomised controlled trials (RCTs) on the treatment of BCC with a 5-year follow-up. Findings of non-comparative and retrospective studies of Mohs' micrographic surgery (MMS) show recurrences of 1–3% for pBCC and 5–7% for rBCC.[5–7] When compared with recurrence rates after surgical excision (3·2–10% in pBCC and >17% in rBCC) MMS seems to be the better option.[6–9] The method of histological assessment is thought to be the main reason for the difference in recurrence: in MMS the complete surgical margins are examined in horizontal sections, whereas in surgical excision, surgical margins are examined in random vertical sections, in a so-called breadloaf-technique.[7]

To our knowledge, no RCT with long-term follow-up has been done to confirm the expected benefit of MMS over surgical excision. We randomly compared MMS

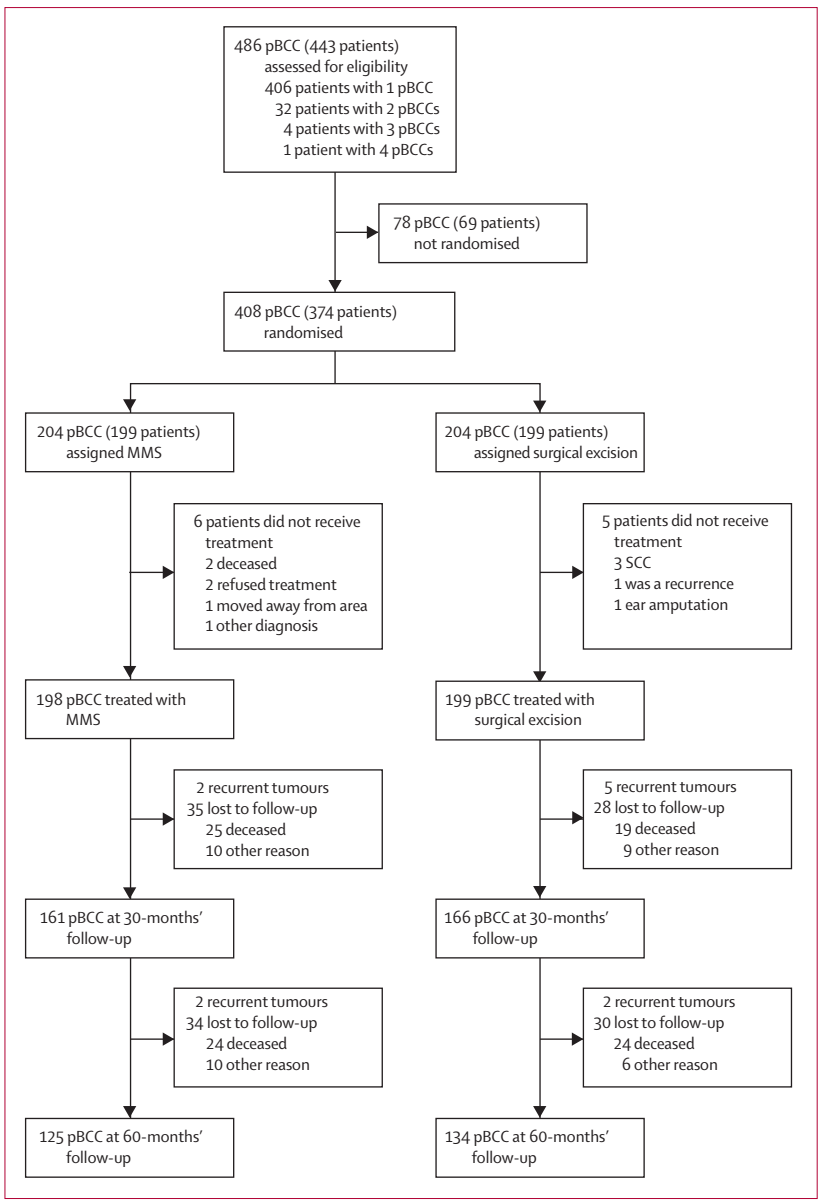

Figure 1: **Trial profile for primary basal-cell carcinoma (pBCC)**
MMS=Mohs' micrographic surgery. SCC=squamous-cell carcinoma.

H-zone
High-risk area of the midface including the temporal areas that might be delineated by drawing an 'H' on the face, with the horizontal line covering the area around the eyes and the nose.

with surgical excision for the treatment of facial pBCC or rBCC. We previously reported the 2-year findings of this RCT, which showed no significant difference in recurrence between the two treatment groups, for either pBCC or rBCC.[10] Here, we present the 5-year follow-up findings.

Methods

Patients and procedures

Patients visiting the dermatology outpatient department at one of the seven participating hospitals in the southern part of the Netherlands between Oct 5, 1999, and Feb 27, 2002, were asked to participate in the trial.

Patients with at least one untreated, histologically confirmed facial pBCC of at least 1 cm in diameter, located in the **H-zone**; or a facial pBCC of an aggressive histological subtype (ie, morpheaform, micronodular, trabecular, infiltrative, or BCC with squamous differentiation) were eligible for inclusion in the pBCC study group. Patients with at least one histologically confirmed facial rBCC (recurring for the first or second time) were eligible for inclusion in the rBBC group. Patients with a life-expectancy of less than 3 years were excluded. The trial was approved by the ethics and scientific committee of the Maastricht University Medical Centre. All patients provided written informed consent.

Randomisation per tumour was done separately for the pBCC and rBCC groups via telephone by a person not involved in the trial, using a computer-generated random allocation scheme (Sampsize 2·0), and eligible patients were assigned to either surgical excision or MMS for each tumour.

Surgical excision was done at the Maastricht University Medical Centre (Maastricht, Netherlands) or at the Laurentius Hospital Roermond (Roermond, Netherlands). The surgical team consisted of two dermatologists (JUO and GAMK), who had equal experience in surgical excision and MMS, and NWJK-S, who was less experienced at the start of the project, but was supervised extensively by JUO or GAMK. After local anaesthesia with an epinephrine (0·001%)-containing lidocaine (1%) solution the BCC was excised at an angle of 90° into the subcutaneous fat, including a 3-mm clinically tumour-free resection margin. In a few patients the procedure was done under general anaesthesia. When the diameter of the excised material was less than 16 mm, standard random histological examination of deep and lateral margins was done on vertical sections of the obtained specimen. For larger diameters, the quadrant method was applied. In most patients, the facial defect was reconstructed immediately, but in selected patients histological examination was awaited. Incomplete excision was followed by a re-excision with a 3-mm margin, and in the case of a second incomplete excision, MMS was done.

All patients assigned to the MMS group received treatment at the Maastricht University Medical Centre. After local anaesthesia with an epinephrine (0·001%)-containing lidocaine (1%) solution and bupivacaine (0·5%), the tumour was excised, including a 3-mm clinically tumour-free resection margin. An incision angle of 45° was used, to obtain a bowl-shaped excision specimen, which is obligatory for the preparation of horizontal slides. The specimen was compressed and subsequently processed into horizontal frozen sections by the laboratory technician. To aid with the compression of the excised specimen, debulking was done before excision in case of a clinically very thick tumour. The frozen section slides were assessed by the Mohs' surgeon together with a pathologist. If residual tumour was noted, the procedure

was repeated until the area was tumour-free. In most cases, reconstruction was done immediately.

Equal defects caused by either MMS or surgical excision were reconstructed in the same way, independent of the treatment modality used. Complications after treatment including wound infections, necrosis of grafts, and postoperative bleeding were assessed for both treatment groups.

The primary outcome was recurrence of carcinoma, diagnosed clinically during visual examination, with histological confirmation. Secondary outcomes were determinants of failure (ie, localisation of the tumour, histological subtype, and mean diameter of the tumour in pBCC and rBCC, plus previous treatment and number of recurrences, in rBCC) and cost-effectiveness.

Clinical assessment

All patients were assessed visually by the research physician (NWJK-S) at 6 and 18 months after surgery. Furthermore, regular follow-up (consisting of visual assessment) was done yearly up to 5 years by the patients' own dermatologist, according to the recommendation by the Dutch Society of Dermatology and Venereology. For practical reasons, the research physician was not blinded to the treatment, nor was the patients' own dermatologist. The site of treatment was examined visually at each follow-up visit. A recurrent tumour was defined as a histologically confirmed carcinoma in a skin biopsy of a clinically suspect area, in, or just next to, the scar (<0·5 cm).

Economic analysis

Similar to the first economic assessment, the costs of both treatments were calculated by multiplying volumes of use with the costs per unit.[11] Direct costs of both treatments included those for the personnel involved in the procedures and materials used during surgery (including the costs of a re-excision) as well as those for pathology research and all out-patient visits. Because the first economic assessment was done after 30 months for pBCC and 18 months for rBCC, the costs of three and four outpatient visits, respectively, were added to the total treatment costs of the pBCC group and rBCC group to capture the follow-up period of 5 years. Both costs and effects occurring after 1 year were discounted at 4% which means that, in accordance with the Dutch guidelines for cost-calculation, costs and effects spent in the future are not weighed equally as in the present.[12] All costs in euros were based on actual costs in 2001, because most of the resources were used in that year. The analysis in which costs and effects were combined, was done according to the intention-to-treat principle in which general mean substitution of the missing cases was applied. An incremental cost-effectiveness ratio (ICER) was calculated by dividing the mean difference in total treatment costs between MMS and surgical excision by their difference in effectiveness. To account for uncertainty of the ICER, a bootstrap analysis was initially done.[13] This method estimates the sampling distribution of a statistic through a large number of simulations (1000 times), based on replacement from original data. The findings from this analysis were used for the calculation of the ICER.

	pBCC		rBCC	
	Surgical excision (n=204), n (%)	MMS (n=204), n (%)	Surgical excision (n=102), n (%)	MMS (n=102), n (%)
H-zone	197 (97)	184 (90)	81 (79)	85 (83)
Frontal/temporal	65 (32)	53 (26)	46 (45)	38 (37)
Cheek/chin	16 (8)	19 (9)	10 (10)	12 (12)
(Peri)nasal	62 (30)	69 (34)	29 (28)	23 (23)
Lips/perioral	8 (4)	14 (7)	1 (1)	6 (6)
Periocular	16 (8)	16 (8)	5 (5)	6 (6)
Ears	16 (8)	9 (4)	4 (4)	8 (8)
Periauricular	21 (10)	24 (12)	7 (7)	9 (9)
1st recurrence	0 (0)	0 (0)	82 (80)	83 (81)
Aggressive histological subtype	88 (43)	105 (52)	49 (48)	60 (59)

pBCC=primary basal-cell carcinoma. rBCC=recurrent basal-cell carcinoma. MMS=Mohs' micrographic surgery.

Table 1: **Tumour characteristics according to study group and treatment**

Statistical analyses

On the basis of the available published work, we expected a difference in the number of recurrences of 6·5% in pBCC and 13·5% in rBCC, favouring MMS. To confirm this difference with 95% confidence and a power of 85%, about 408 pBCCs and 204 rBCCs were needed. The analysis of effects was done according to the intention-to-treat principle. The Log-rank test in Kaplan-Meier analyses was used to analyse postoperative recurrence during follow-up to 60 months. Currently, there is no software available to calculate the confidence interval around an observed percentage difference on cumulative incidences.[14] A Cox regression analysis was done on the 5-year follow-up data to control for important confounding variables. Within this model, localisation of the tumour, histological subtype, and the mean diameter of the tumour were included for pBCC and rBCC. For rBCC, we additionally included the previous treatment and whether the BCC was a first or second recurrence. The log-likelihood χ^2 test was used to test differences in complications between both groups. A p value of less than 0·05 was considered to be statistically significant. All data were analysed by use of the software SPSS, version 15·0. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN65009900.

Role of the funding source

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

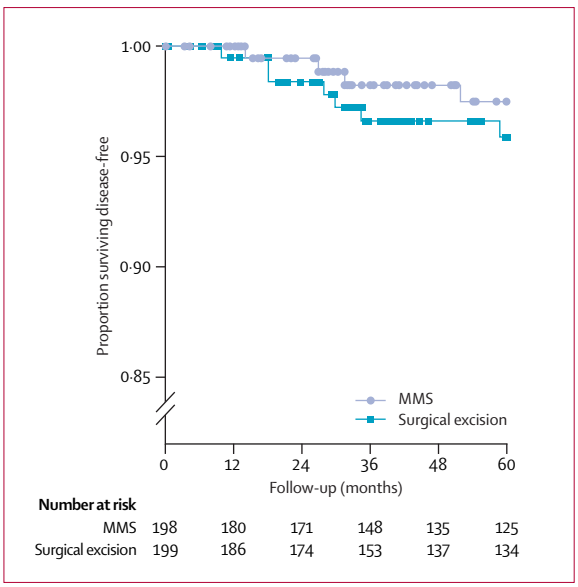

Figure 2: **Kaplan-Meier survival analysis of primary basal-cell carcinoma (pBCC) treated with Mohs' micrographic surgery (MMS) or surgical excision**

	Age (years)	Sex	Histological subtype	Tumour location	Assigned treatment	Survival (months)
1	69	M	Non-aggressive	Frontal/temporal	Surgical excision	9
2	73	M	Non-aggressive	Ears	Surgical excision	18
3	52	F	Non-aggressive	Frontal/temporal	MMS	15
4	59	M	Aggressive	(Peri)nasal	MMS	52
5	72	M	Non-aggressive	Frontal/temporal	Surgical excision	18
6	75	M	Non-aggressive	Frontal/temporal	Surgical excision	59
7	71	F	Non-aggressive	Frontal/temporal	MMS	27
8	54	M	Aggressive	Frontal/temporal	MMS	9
9	63	F	Non-aggressive	Frontal/temporal	Surgical excision	34
10	41	M	Non-aggressive	Frontal/temporal	Surgical excision	30
11	82	F	Aggressive	(Peri)nasal	Surgical excision	28

pBCC=primary basal-cell carcinoma. M=male. F=female. MMS=Mohs' micrographic surgery.

Table 2: **Tumour and patient characteristics for pBCCs that recurred during the study period**

	Mean cost (SD), €	Effectiveness*	Incremental cost-effectiveness ratio, €
pBCC (60 months)			
MMS (n=198)	1248 (350)	0·967	..
Surgical excision (n=199)	990 (347)	0·956	..
Mean difference	258	0·011	23 454
rBCC (60 months)			
MMS (n=100)	1284 (409)	0·968	..
Surgical excision (n=102)	1043 (521)	0·892	..
Mean difference	241	0·076	3171

pBCC=primary basal-cell carcinoma. rBCC=recurrent basal-cell carcinoma. MMS=Mohs' micrographic surgery.
*1=effective; 0=not effective.

Table 3: **Incremental cost-effectiveness ratio for primary and recurrent BCC**

Results

Between October, 1999, and January, 2001, 408 pBCCs in 374 patients were randomly assigned to treatment with surgical excision (204 tumours) or MMS (204 tumours; figure 1). 69 patients with 78 pBCCs were not randomised, mostly because they specifically preferred surgical excision or MMS. Of the 374 patients who had tumours randomised, 342 had one pBCC, 30 had two pBCCs, and two patients had three pBCCs. The mean age of the patients was 67·7 years (SD 12·7; range 23–92). Tumour characteristics are shown in table 1.

Of the patients with 397 tumours (198 MMS, 199 surgical excision) that received treatment, 251 patients with 270 tumours (129 MMS, 141 surgical excision) completed the follow-up of 5 years. 83 patients with 92 tumours (23%) died of causes not related to the tumour or to the treatment. A further 35 tumours (9%) in 30 patients were lost to follow-up due to other reasons, such as an inability to visit the hospital, moving out, or refusing further follow-up at our department. The median follow-up of the total pBCC study population was 60 months (range 0–60; 5% percentile: 10·9 months, 10% percentile: 18·4 months, and 25% percentile: 37·8 months).

Of the 199 pBCCs that were assigned surgical excision, 35 (18%) were incompletely excised after the first excision; 31 were re-excised, three were treated with MMS, and one did not receive further treatment because the patient refused. Four tumours were still incompletely excised after two excisions and were re-treated with MMS.[10] Of 88 aggressive pBCCs, 21 tumours (24%) were incompletely excised. 24 of 198 tumours (12%) had complications after MMS and 27 of 199 (14%) had complications after surgical excision (p=0·681). The most common complication included wound infection, necrosis of grafts or flaps, or a combination of both. Aesthetic outcome did not differ significantly between MMS and surgical excision.[10]

11 recurrences of pBCC were registered during the 60-month follow-up period; four (2·5%) after MMS and seven (4·1%) after surgical excision. Percentages of recurrence are 5-year estimated Kaplan-Meier results from the full dataset (figure 2). The Kaplan-Meier log-rank test statistic amounts to 0·718 (p=0·397), and in the Cox-regression analysis the effect parameter of MMS versus surgical excision is 1·690 (95% CI 0·495–5·775; p=0·397).

Of the patients who had more than one pBCC, none had more than one recurrence. Recurrence of tumours was diagnosed between 9·9 and 58·8 months after treatment. An additional recurrence after surgical excision appeared after more than 5-years' follow-up. This late recurrence was not included in the survival analysis.

All recurrences appeared in the H-zone of the face. Three of 11 recurrent tumours were of an aggressive histological subtype (table 2). Further Cox-regression analyses showed no significant effects from risk factors

measured in the study (webtable 1). Of the seven tumours that were randomly assigned surgical excision, but were treated with MMS due to one or two incomplete excisions, none has recurred.

As shown in table 3, dividing the mean difference in total treatment costs between MMS and surgical excision (€258) by their difference in effectiveness (0·011) leads to an ICER of €23 454 per recurrence avoided.

Of the 204 rBCCs in 191 patients, 102 were assigned to each treatment group (figure 3). 42 patients with 42 rBCCs were randomised in the study, mainly because the patient or referring physician preferred MMS. Between October, 1999, and April, 2002, 100 rBCCs were treated with MMS and 102 with surgical excision. Two patients with tumours assigned MMS died just before treatment. Four patients, each with one tumour, were treated by MMS although randomly assigned to the surgical-excision group.[10] Of all 204 patients, 180 had one BCC, ten had two BCCs, and one patient had four BCCs. The mean age of the patients was 67·9 years (SD 11·7; range 31–95).

146 of 202 tumours (72%) in 137 patients completed the follow-up period of 5 years. 33 patients with 35 tumours (17%) died due to causes not related to the tumour or to the treatment. 21 tumours (10%) in 20 patients were lost to follow-up due to other reasons. The median follow-up time of the rBCC study population was 60 months (range 0–60; 5% percentile: 15·2 months, 10% percentile: 20·2 months, 25% percentile: 45·8 months).

In the surgical-excision group, 31 of the 102 rBCCs (30%) were not completely eradicated after the first excision; 25 were re-excised, five were treated with MMS, and one was treated with photodynamic therapy. Eight tumours were still incompletely excised after two excisions and re-treated with MMS.[10] The most common complication included wound infection, necrosis of grafts or flaps, or postoperative bleeding. There were 19 complications after surgical excision (19%) and eight after MMS (8%; p=0·021). Aesthetic outcome did not differ significantly between MMS and surgical excision.[10]

After the follow-up period of 5 years, there were 12 recurrences in the rBCC study population. Two recurrences (2·4%) appeared after treatment with MMS and ten (12·1%) after surgical excision. According to the Kaplan-Meier analysis of disease-free survival (figure 4), this percentage difference is statistically significant (log-rank test χ^2 5·958, p=0·015). The Cox regression analysis effect of MMS versus surgical excision is 5·390 (95% CI 1·180–24·615; p=0·015).

Of the patients with more than one rBCC, none had more than one recurrence of the tumours treated. Recurrences were diagnosed between 18·0 months and 53·1 months after treatment. Two additional recurrences appeared after the 5 years' follow-up; one after surgical excision and one after MMS. These late recurrences were not included in the analysis.

Ten of the 12 recurrences in patients with rBCC were of an aggressive histological subtype (table 4). Inclusion of

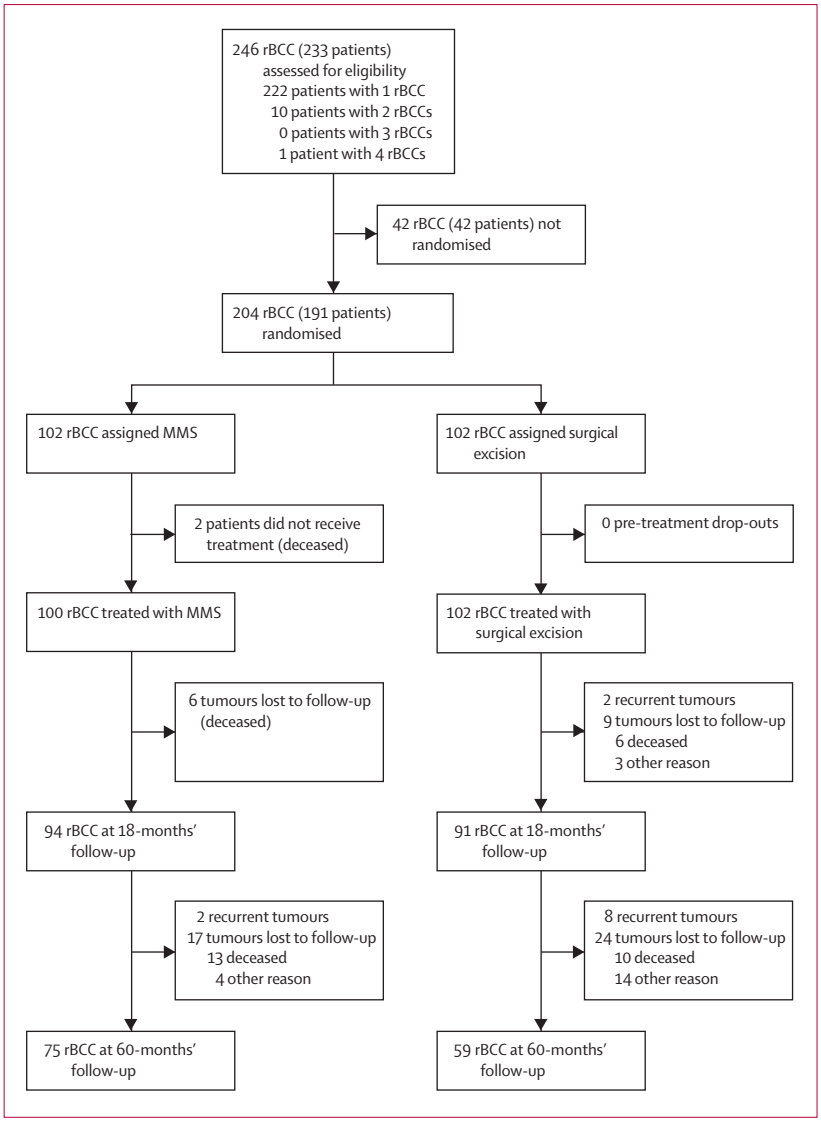

Figure 3: **Trial profile for recurrent basal-cell carcinoma (rBCC)**
MMS=Mohs' micrographic surgery.

clinically relevant, potentially confounding variables or factors within the Cox regression analysis, such as tumour localisation in the H-zone, previous therapy, first or second rBCC, and tumour size, corroborated the statistically significant difference in recurrence between both groups of the study (webtable 2). Inclusion of aggressive histological subtype within the model resulted in a significant risk factor for recurrence (p=0·038), and the treatment modality remained statistically significant (Cox regression effect of MMS *vs* surgical excision: 6·146 [95% CI 1·343–28·122]; p=0·019). Of the 17 tumours that were randomly assigned to the surgical-excision group, but were treated with MMS, two have recurred. According to the intention-to-treat principle of our protocol, the results of these tumours were included in the analysis for the surgical-excision group. The incremental cost-

See Online for webtables 1 and 2

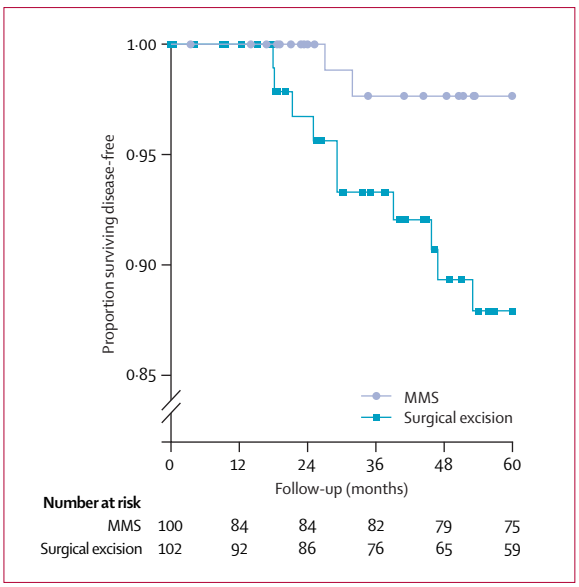

Figure 4: **Kaplan-Meier survival analysis of recurrent basal-cell carcinoma (rBCC) treated with Mohs' micrographic surgery (MMS) or surgical excision**

	Age (years)	Sex	1st/2nd recurrence	Histological subtype	Tumour location	Assigned treatment	Survival (months)
1	73	M	1st	Aggressive	Frontal/temporal	Surgical excision	25
2	71	F	1st	Aggressive	Frontal/temporal	Surgical excision	46
3	44	M	1st	Non-aggressive	(Peri)nasal	Surgical excision	42
4	83	M	1st	Aggressive	(Peri)nasal	MMS	32
5	74	F	1st	Aggressive	Cheek/chin	Surgical excision	29
6	61	M	2nd	Aggressive	(Peri)nasal	MMS	28
7	57	M	1st	Aggressive	(Peri)nasal	Surgical excision	53
8	48	M	1st	Aggressive	Frontal/temporal	Surgical excision	46
9	82	F	1st	Aggressive	Frontal/temporal	Surgical excision	29
10	83	F	1st	Non-aggressive	Frontal/temporal	Surgical excision	21
11	75	F	1st	Aggressive	Cheek/chin	Surgical excision	18
12	72	M	2nd	Aggressive	Periocular	Surgical excision	39

rBCC=recurrent basal-cell carcinoma. M=male. F=female. MMS=Mohs' micrographic surgery.

Table 4: **Tumour and patient characteristics for rBCCs that recurred during the study period**

effectiveness ratio amounts to €3171 per recurrence avoided.

Because some patients had more than one tumour randomised, clustering was a possibility. We therefore randomly sampled one of two, three, or four BCCs, respectively, to obtain a patient-based data file, and analysed the results in the same way as in the intention-to-treat analysis. In 374 patients with pBCCs, three (2·1%) recurred after treatment with MMS and seven (4·4%) after treatment with surgical excision (p=0·230). In the Cox regression analysis, the effect is 2·240 (p=0·223; 95% CI 0·579–8·663). In the 191 patients with rBCCs, two tumours (2·6%) treated with MMS recurred versus ten tumours (12·7%) after surgical excision (p=0·018). In the Cox regression analysis, the effect is 5·180 (p=0·014; 95% CI 1·134–23·653). As before, percentages of recurrence are 5-year estimated Kaplan-Meier results from the full dataset.

Discussion

Our findings show that treatment with MMS leads to a significantly lower number of recurrences than treatment with surgical excision in facial rBCC. This difference in recurrence between the two surgical treatment groups might be because of the use of different histopathological assessments in the two groups. In MMS, horizontal slides show the complete surgical margins, whereas in surgical excision, surgical margins are examined in random vertical sections. To our knowledge, this is the first prospective RCT with long-term follow-up that confirms data from non-comparative retrospective and prospective studies, that MMS has greater efficacy than surgical excision for the treatment of facial rBCC.[15,16] A possible confounding factor is that more aggressive BCCs were included in the MMS group for both pBCC and rBCC; because aggressiveness is a significant risk factor in rBCC, this might have affected the difference noted in the two surgical groups in recurrence, disavantaging MMS. Including aggressiveness in the Cox model did not change the relative efficacy of the treatment modalities noted in our study. However, in non-linear models there is a possibility that models adjusting for covariates and those not adjusting for covariates can be inconsistent.[17,18]

rBCC is a high-risk tumour that recurs more frequently than pBCC.[19,20] In a large non-comparative prospective study, including 1483 rBCCs treated by MMS, 4·0% of the tumours recurred after 5 years of follow-up, which is comparable to the 5-year recurrence of 3·2–4·8% the same researchers found in other prospective non-comparative studies.[15] In retrospective non-comparative studies, the recurrence of rBCC has been shown to vary between 4·4% and 24% after surgical excision.[7,9] Findings of a recent retrospective study investigating MMS in rBCC show an estimated overall 5-year recurrence of 6·7%.[16]

Different treatment modalities are difficult to compare because most studies are non-comparative and use different inclusion criteria or treatment protocols.[5] Furthermore, the current study shows that recurrences can still occur after more than 5 years of follow-up. The overall number of recurrences after 5 years of follow-up can be twice as high as the number after a follow-up period of 2 years in pBCC and rBCC.[6,16] This underlines the necessity for long-term follow-up.

Although recurrence after surgical excision for pBCC is shown to be higher than after MMS in our study, the difference is not statistically significant. The power analysis for our study was based on retrospective or non-comparative studies that showed cumulative recurrence in 5·3–10·1% of the pBCCs treated with

surgical excision,[5,6] which is higher than the recurrence rate seen in our study. Two other prospective RCTs that compared surgical excision with a different treatment for pBCC also showed a lower long-term recurrence of 4% (two of 52 tumours) in (low-risk) nodular BCC and 0·6% (one of 174) in facial BCC after surgical excision.[21,22] Furthermore, in a recently published retrospective study, only one of 90 (cumulative 5-year rate 1·7%) of the pBCCs treated with surgical excision recurred.[23] Recent research generally shows fewer recurrences of pBCC after surgical excision, which is possibly explained by evidence-based standardisation of surgical procedures throughout the years. Data obtained in an RCT are probably better than those obtained from daily practice, because of the meticulously executed procedures used in an RCT. In a prospective non-comparative study of the treatment of pBCC, 26 of 1886 (1·4%) tumours treated with MMS recurred.[15] Because the recurrence in our study was lower than estimated at the start of the study, and the number of drop-outs was higher than expected, the study might have been underpowered to detect such small treatment differences. The number of recurrences in our study might still be relatively high compared with other studies, because only high-risk, facial pBCCs were included.

When choosing between two equally effective treatments, other factors such as cost, cosmetic outcome, preference, and practical use should also be considered. Because of the continuing rise in incidence of BCC, it is important to consider treatment costs. A previous study, in which the cost-effectiveness of MMS was compared with surgical excision for both pBCC and rBCC, showed that implementation of MMS on a large scale was not cost effective.[12] However, because a 5-year period is usually needed to determine a definite number of recurrences, the researchers argued that MMS might become a cost-effective treatment for rBCC. On the basis of our data for the 60-month follow-up period, the ICER for pBCC is €23 454 per recurrence avoided, and the ratio for rBCC is €3171. Comparing these figures with ICERs of €29 231 for pBCC and €8094 for rBCC calculated in the previous cost-effectiveness study,[12] shows that both ratios have decreased. Up to now, a threshold value for the treatment costs of BCC has not been established, which makes the interpretation of the ratios difficult. However, one could argue that an acceptable threshold value should at least include the hospital costs of treating a recurrence. If we calculate two-times the costs of MMS (ie, treating a tumour and a recurrence; €2568) for determining the threshold value, then MMS is definitely not cost-effective for pBCC, but might well be considered a cost-effective treatment for rBCC, because this amount does not differ much from the ICER of €3171.

As the number of young patients with BCC is increasing, the importance of a favourable cosmetic outcome should also be considered when treating facial BCC. In recurrent and large, aggressive facial BCC, we showed previously the defects after treatment were significantly larger after multiple surgical excisions compared with MMS with more than one Mohs' stage, which resulted in worse cosmetic outcome.[10] For this reason, we recommend MMS for facial pBCC of an aggressive subtype. In this study, we started our Mohs' procedure with a 3-mm margin. Because smaller margins are normally used to start MMS, critics have commented that our larger margin might have led to larger defects and, therefore, a worse cosmetic outcome, which minimised the difference in cosmetic result with surgical excision. We chose a standardised margin for both treatments to make comparison easier. An additional advantage of starting with a 3-mm margin is the reduction of Mohs' stages, thereby decreasing the duration of the procedure. In our study, 78 rBCCs (78%) were completely eradicated after two stages. In other words, only 22% of the tumours needed three or more stages of MMS, compared with 43% of rBCCs reported in the published work.[24] Use of a standardised margin of 3 mm in both treatment groups could have affected cosmetic outcome in either direction. For example, in aggressive pBCC or rBCC, the use of a wider margin with surgical excision might have prevented an extra excision, which would have improved the cosmetic results of this group. Conversely, a wider margin could have resulted in larger defects in patients who would have had complete tumour clearance with a 3-mm margin.

In addition to the proportion of recurrence, costs, and cosmetic outcome, other factors need to be considered when choosing a treatment for an individual. These factors should be weighed against the difference in recurrence. For example, physicians and patients might choose surgical excision instead of MMS on the basis of age and comorbidity.

Contributors

KM and NWJK-S did the data collection and independent outcome assessment. GAMK, HAMN, and CDD designed the protocol and coordinated the study. JUO, BABE, AV, and PMS took part in data collection. FHMN and BABE were involved in the statistical analysis. All authors took part in writing the report.

Conflicts of interest

The authors declared no conflicts of interest.

Acknowledgments

We thank the patients who agreed to participate in this study. The study was financed by "the Netherlands Organization for Scientific Research ZonMW", a governmental institution financing research to improve health care in the Netherlands. We also thank M H Prins, Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Netherlands. We also thank the doctors of the Dermatology Departments of the Laurentius Hospital Roermond, Viecurie Hospital Venlo, Atrium Hospital Heerlen, St Jans Gasthuis Weert, Catharina Hospital Eindhoven, and Maxima Medisch Centrum Veldhoven for their cooperation.

References

1 de Vries E, Louwman M, Bastiaens M, de Gruijl F, Coebergh JW. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. *J Invest Dermatol* 2004; **123:** 634–38.

2 de Vries E, van de Poll-Franse LV, Louwman WJ, de Gruijl FR, Coebergh JW. Predictions of skin cancer incidence in the Netherlands up to 2015. *Br J Dermatol* 2005; **152:** 481–88.

3 Holme SA, Malinovszky K, Roberts DL. Changing trends in non-melanoma skin cancer in South Wales, 1988-98. *Br J Dermatol* 2000; **143:** 1224–29.

4 Bath-Hextall FJ, Perkins W, Bong J, Williams HC. Interventions for basal cell carcinoma of the skin. *Cochrane Database Syst Rev* 2007: **1:** CD003412.

5 Thissen MR, Neumann MH, Schouten LJ. A systematic review of treatment modalities for primary basal cell carcinomas. *Arch Dermatol* 1999; **135:** 1177–83.

6 Rowe DE, Carroll RJ, Day CL Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol* 1989; **15:** 315–28.

7 Rowe DE, Carroll RJ, Day CL Jr. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. *J Dermatol Surg Oncol* 1989; **15:** 424–31.

8 Kuijpers DI, Thissen MR, Neumann MH. Basal cell carcinoma: treatment options and prognosis, a scientific approach to a common malignancy. *Am J Clin Dermatol* 2002; **3:** 247–59.

9 Silverman MK, Kopf AW, Bart RS, Grin CM, Levenstein MS. Recurrence rates of treated basal cell carcinomas. Part 3: surgical excision. *J Dermatol Surg Oncol* 1992; **18:** 471–76.

10 Smeets NW, Krekels GA, Ostertag JU, et al. Surgical excision *vs* Mohs' micrographic surgery for basal-cell carcinoma of the face: randomised controlled trial. *Lancet* 2004; **364:** 1766–72.

11 Zhang M, Fine J. Summarizing differences in cumulative incidence functions. S*tat Med* 2008; **27:** 4939–49.

12 Essers BA, Dirksen CD, Nieman FH, et al. Cost-effectiveness of Mohs micrographic surgery vs surgical excision for basal cell carcinoma of the face. *Arch Dermatol* 2006; **142:** 187–94.

13 Oostenbrink J, Bouwmans CAM, Koopmanschap MA, Rutten FFH. The Dutch manual for costing in economic evaluations. Amstelveen: Dutch Health Insurance Board, 2000.

14 Efron B,Tibshirani R. An introduction to the bootstrap. London: Chapman and Hall, 1993.

15 Leibovitch I, Huilgol SC, Selva D, Richards S, Paver R. Basal cell carcinoma treated with Mohs surgery in Australia II. Outcome at 5-year follow-up. *J Am Acad Dermatol* 2005; **53:** 452–57.

16 Smeets NW, Kuijpers DI, Nelemans P, et al. Mohs' micrographic surgery for treatment of basal cell carcinoma of the face—results of a retrospective study and review of the literature. *Br J Dermatol* 2004; **151:** 141–47.

17 Ford I, Norrie J, Ahmadi S. Model inconsistency, illustrated by the Cox proportional hazards model. *Stat Med* 1995; **14:** 735–46.

18 Ford I, Norrie J. The role of covariates in estimating treatment effects and risk in long-term clinical trials. *Stat Med* 2002; **21:** 2899–908.

19 Telfer NR, Colver GB, Bowers PW. Guidelines for the management of basal cell carcinoma. British Association of Dermatologists. *Br J Dermatol* 1999; **141:** 415–23.

20 Silverman MK, Kopf AW, Grin CM, Bart RS, Levenstein MJ. Recurrence rates of treated basal cell carcinomas. Part 1: overview. *J Dermatol Surg Oncol* 1991; **17:** 713–18.

21 Rhodes LE, de Rie M, Leifsdottir R, et al. Five-year follow-up of a randomized prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. *Arch Dermatol* 2007; **143:** 1131–36.

22 Avril MF, Auperin A, Margulis A, et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. *Br J Cancer* 1997; **76:** 100–06.

23 Werlinger KD, Upton G, Moore AY. Recurrence rates of primary nonmelanoma skin cancers treated by surgical excision compared to electrodesiccation-curettage in a private dermatological practice. *Dermatol Surg* 2002; **28:** 1138–42.

24 Batra RS, Kelley LC. Predictors of extensive subclinical spread in nonmelanoma skin cancer treated with Mohs micrographic surgery. *Arch Dermatol* 2002; **138:** 1043–51.