Recurrence rates of cutaneous squamous cell carcinoma of the head and neck after Mohs micrographic surgery vs. standard excision: a retrospective cohort study

C. van Lee
B. Roorda
M. Wakkee
Q. Voorham
A. Mooyaart
H. de Vijlder
T. Nijsten
R. van den Bos

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ABSTRACT

Background: Recurrent cutaneous squamous cell carcinoma (cSCC) has been associated with an increased risk of local functional and aesthetic comorbidity, metastasis and mortality.

Objectives: To compare the risk of recurrence between Mohs micrographic surgery (MMS) and standard excision (SE) for cSCC of the head and neck.

Methods: This was a retrospective cohort study of all patients with a cSCC treated with MMS or SE at the departments of dermatology of a secondary or tertiary care hospital in the Netherlands between 2003 and 2012. To detect all recurrences, patients were linked to the Dutch pathology registry. To compare the risk of recurrence between MMS and SE, hazard ratios (HRs) were used adjusted for clinical tumour size > 2 cm and deep tumour invasion.

Results: A total of 579 patients with 672 cSCCs were included: 380 cSCCs were treated with MMS and 292 with SE. The risk of recurrence was 8% (22/292) after SE during a median follow-up of 5.7 years (IQR 3.5-7.8), which was higher than the 3% (12/380) after MMS during a median follow-up of 4.9 years (IQR 2.3-6.0). The cumulative incidence of recurrence was higher for SE than for MMS during the entire follow-up period of 8.6 years. Carcinomas treated with MMS were at a three times lower risk of recurrence than those treated with SE when adjusted for tumour size and deep tumour invasion (adjusted HR 0.31, 95% confidence interval 0.12-0.66).

Conclusion: MMS might be superior to SE for cSCCs of the head and neck because of a lower rate of recurrence.

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) represent 20% of all skin cancers. CSCC is the second most common skin cancer after basal cell carcinoma. At least one in 15 white people will develop a cSCC before the age of 85 and the incidence is still rising.[1-4] CSCCs rarely metastasize (4%) and the disease specific death rate is low (2%).[2,5] However, because of the frequent localization in the head and neck, treatment can lead to major functional and aesthetic comorbidity.

In the Netherlands, cSCC is commonly treated with standard excision (SE). In the Dutch cSCC guideline, Mohs micrographic surgery (MMS) is noted as an alternative for SE for stage ≥ II, especially when SE would lead to substantial functional or aesthetic comorbidity.[6] In the United States it is generally accepted that MMS is indicated in high risk cSCC and the American 'appropriate use criteria for MMS' state that it is also appropriate to use MMS for stage I cSCC.[7]

MMS is superior to SE for facial aggressive or recurrent basal cell carcinomas, because of the low recurrence rate and maximum preservation of healthy tissue.[8-10] Studies on cSCC recurrence rates after surgery are sparse and it therefore remains unclear if MMS is better than SE for cSCC. This large retrospective cohort study was conducted to determine if the risk of cSCC recurrence is lower after MMS than SE.

METHODS

This was a retrospective, comparative cohort study of cSCC treated with MMS or SE at the dermatology departments of a tertiary (Erasmus University Medical Center) or a secondary care hospital (Isala Hospital), both in the Netherlands, between 2003 and 2012. The study was exempted from approval by both institutional review boards.

Inclusion criteria were all histologically confirmed invasive cSCCs of the head and neck that were completely excised with MMS or SE; multiple cSCCs per patient were included. The cSCCs that were incompletely excised with MMS or SE were excluded from the analysis and described separately. For SE, incomplete excision was postoperatively defined by a pathologist with the standard vertical bread loaf technique if cSCC was detected on the excision margin (stage I) or if a tumour free margin was ≤ 2 mm (≥ stage II).[6] For MMS, incomplete excision was postoperatively defined by a pathologist within the routine quality check if cSCC was detected on the outermost fresh frozen MMS slide. The study involved four pathologists; all had special training in skin cancer pathology and MMS.

The inclusion period differed per treatment modality and study centre. Patients treated with MMS were included at the tertiary care hospital between 1 January 2009 and 31 December 2012 because in the Netherlands MMS for cSCC was only offered at the tertiary care hospital since 2008. Inclusion started from 2009 to exclude the effect of a presumed learning curve during the first MMS year and continued until 2012 to have at least 5 years of follow-up. To prevent selection bias, cSCCs treated with SE were included at the tertiary care hospital between 1 January 2003 and 31 December 2007. At the secondary care hospital, SE was the only surgical treatment option during the entire study period and patients were included from 1 January 2008 to 31 December 2012. Selection bias because of the different inclusion periods was not expected because the Dutch cSCC guideline did not change during the entire study period (2003-2012).[6] In both hospitals, it was recommended that patients should visit a dermatologist routinely postoperatively for the following 5 years.[6]

The following variables were extracted from electronic patient files including pathology reports and standardized digital MMS files[11]: patient age and sex, tumour location (in the H-zone), recurrence before MMS or SE, clinical tumour size > 2 cm, defect size > 2 cm and deep tumour invasion (i.e. beyond the subcutaneous fat). These tumour characteristics were recorded because they have been associated with a high risk of cSCC recurrence.[12] Vital status, including date of death, was obtained from the Dutch Municipal Population Register until 1 August 2017.

Study outcome

The main outcome was cSCC recurrence. Recurrence was defined as a histologically proven cSCC in or within 1 cm of the scar. Furthermore, histologically confirmed cSCC metastasis was recorded. To detect all histopathologically proven recurrences and metastases, patients were linked to the nationwide network and registry of histology and cytopathology (Dutch acronym: PALGA) on 1 August 2017.[13] In the Netherlands, all histopathology reports from every biopsy, excision or MMS procedure are recorded in this database.

Follow-up

As explained above, the inclusion period for SE started earlier (2003) than for MMS (2009). Therefore, the median follow-up time after SE was suspected to be longer than after MMS. This was accepted because all patients had a follow-up of at least 5 years and the majority of cSCC recurrences occur within 5 years.[14] The maximum follow-up time for patients treated with SE was restricted to the maximum follow-up possible for patients treated with MMS (i.e. 8.6 years, which was the time between the start of MMS inclusion on 1 January 2009 until the PALGA search on 1 August 2017).

Surgical procedures

SE was performed in a standard manner by a dermatologist (n = 7), or a resident (n = 10) under supervision of a dermatologist. The cSCCs were excised with margins of five mm for stage I and ten mm for ≥ stage II.[6] Specimens were postoperatively assessed by a pathologist with the standard vertical bread loaf technique and haematoxylin and eosin staining.

MMS was performed in a standard manner by experienced MMS surgeons (n = 6, all dermatologists certified by the European Society for Micrographic Surgery), or a resident (n = 10) under supervision of a MMS surgeon. The cSCCs were excised with a minimal margin of clinically tumour free tissue. The sample was directly compressed, frozen and sliced horizontally by a trained MMS technician. The entire excision margins were microscopically examined on the fresh frozen slides by a MMS surgeon. Residual tumour was mapped and subsequently excised. The procedure was repeated until tumour clearance was achieved.

Statistics

Differences between MMS and SE regarding the studied variables were assessed with an exact test for binary variables and with an independent sample T-test with bootstrapping for continuous variables, to take within-patient correlation into account. The length of follow-up per patient was calculated as the number of years between surgery and end of study (linkage to PALGA on 1 August 2017) or date of recurrence or date of death, whichever occurred first. Difference between the rate of recurrence after MMS and SE was assessed with a cumulative incidence curve to take into account the competing risk of death. Comparison of the risk of recurrence after MMS and SE was assessed with univariable and multivariable Cox proportional hazards regression adjusted for clinical tumour size > 2 cm and deep tumour invasion. The 95% confidence interval (CI) and P-value for the univariable and multivariable regression were obtained by applying bootstrapping to take within-patient correlation into account. The proportional hazards assumption was confirmed by log minus log plots. P-values less than 0.05 (2-sided) were considered significant. SPSS 24.0 for Windows (IBM, Armonk, NY, U.S.A.) and SAS 9.4 (SAS Institute Inc., Cary, NC, U.S.A.) were used for statistical analyses.

RESULTS

In total, 631 patients with 738 cSCCs of the head and neck were reviewed of which 383 cSCCs were treated with MMS and 355 with SE (Figure 1). Of the 355 cSCCs that were treated with SE, 34% (n = 122) were included at the tertiary care hospital and 66%

(n = 233) at the secondary care hospital. The baseline characteristics, the rate of incompletely excised cSCCs and the rate of recurrences did not differ between the included cases at the tertiary care hospital and secondary care hospital.

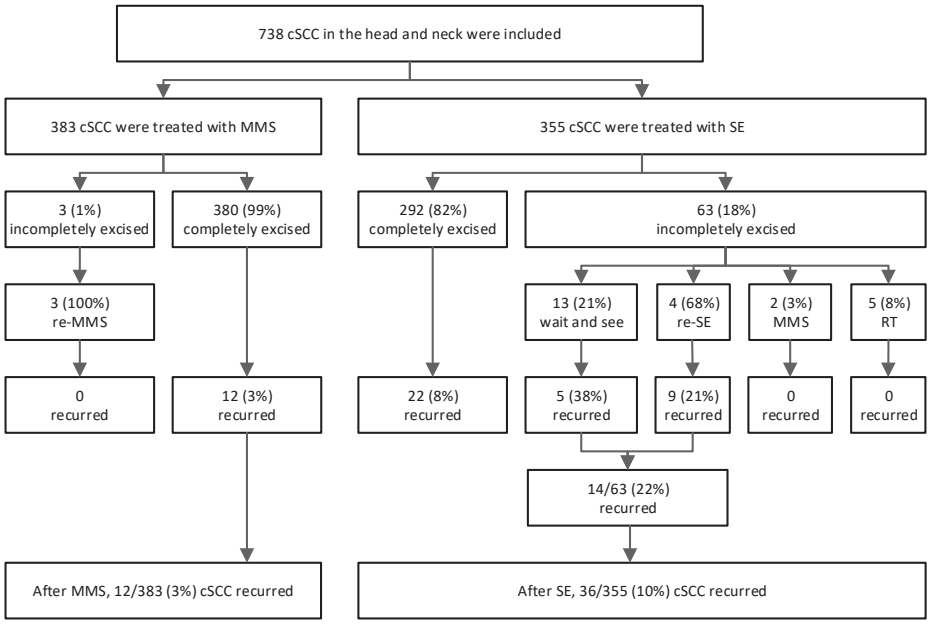


Figure 1. Flowchart of the cutaneous squamous cell carcinomas of the head and neck that were treated with Mohs micrographic surgery or standard excision.
cSCC, cutaneous squamous cell carcinoma; MMS, Mohs micrographic surgery; RT, radiotherapy; SE, standard excision.

Of the 738 cSCCS, three treated with MMS and 63 treated with SE were excluded because of an incomplete cSCC excision. All three treated with MMS were additionally completely excised with re-MMS and did not recur or metastasize. Of the 63 incomplete SE cases, no additional treatment was given in 21% (13/63), after which 38% (5/13) developed a recurrence and 15% (2/13) metastasized. Of the incomplete SE cases, an additional treatment was given in 79% (50/63): 68% (43/68) were re-excised with SE, 8% (5/63) received radiotherapy, and 3% (2/63) were re-excised with MMS. Of the 43 incomplete SE cases which were re-excised with SE, 21% (9/43) developed a recurrence and 2% (1/43) metastasized. Of the incomplete SE cases which were additionally treated with radiotherapy (n = 5) or MMS (n = 2), none developed a recurrence or metastasis.

Baseline characteristics

A total of 579 patients (69% men, overall median age 76 years, IQR 69-82) with 672 completely excised cSCCs were included; 380 cSCCs were treated with MMS and 292 with SE. There were 513 patients with one included cSCC, 50 patients with two cSCCs, eight patients with three cSCCs, six patients with four cSCCs, one patient with five cSCCs and one patient with six cSCCs.

For MMS, most cSCCs were located on the nose (22%), forehead (19%) and scalp (17%) followed by the auricular region (15%), cheek and maxilla (11%), periocular region (8%), perioral region and lips (6%) and neck (2%). For SE, most cSCCs were located on the auricular region (24%), scalp (21%), cheek and maxilla (20%) and forehead (20%), followed by the nose (7%), perioral region and lips (5%), neck (3%) and periocular region (2%).

The cSCCs treated with MMS were significantly more often: located in the H-zone, previously recurrent tumours, clinically > 2 cm and more often had deep tumour invasion (Table 1). Defects after MMS were more often ≤ 2 cm than after SE. Median number of MMS stages needed for tumour clearance was one (range 1-4).

Cutaneous squamous cell carcinoma recurrence

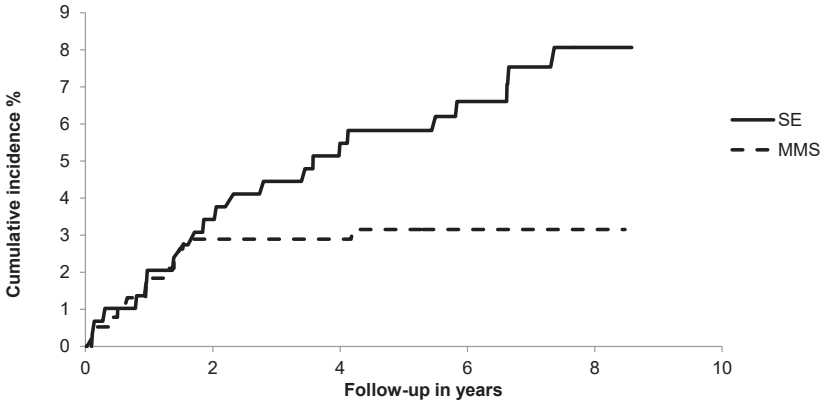
The risk of recurrence was 8% (22/292) after SE during a median follow-up of 5.7 years (IQR 3.5-7.8), which was higher than the 3% (12/380) after MMS during a median follow-up of 4.9 years (IQR 2.3-6.0). The cumulative incidence of recurrence was higher for SE than for MMS during the entire follow-up period of 8.6 years (Figure 2).

After adjusting for tumour size and deep tumour invasion, cSCCs treated with MMS were at a three times lower risk of recurrence than SE (adjusted HR 0.31, 95% CI 0.12-0.66) (Table 2). Of the 12 cSCC recurrences after MMS, 33% (n = 4) were located in the H-zone, 50% (n = 6) were previously recurrent tumours, 58% (n = 7) had a clinical tumour size > 2 cm, 67% (n = 8) had a defect size > 2 cm, 67% (n = 8) had a deep tumour invasion and none metastasized. Of the 22 cSCC recurrences after SE, 32% (n = 7) were located in the H-zone, 9% (n = 2) were previously recurrent tumours, 9% (n = 2) had a clinical tumour size > 2 cm, 77% (n = 17) had a defect size > 2 cm, 27% (n = 6) had a deep tumour invasion and 5% (n = 1) metastasized.

Table 1. Differences between cutaneous squamous cell carcinomas that were treated with Mohs micrographic surgery or standard excision regarding the characteristics and events during follow-up.

	MMS n = 380 (%)	SE n = 292 (%)	P-value
Sex[a]			
Men	262 (69)	219 (75)	0.101
Women	118 (31)	73 (25)	
Age in years, median (IQR)[a]	76 (69-81)	76 (68-82)	0.694
Anatomical location			
Head and neck, not H-zone	153 (40)	161 (55)	<0.001
H-zone	227 (60)	131 (45)	
Surgical history			
Primary cSCC	311 (82)	266 (91)	0.001
Previously recurrent cSCC	69 (18)	26 (9)	
Tumour size			
≤ 2 cm	256 (67)	274 (94)	<0.001
> 2 cm	124 (33)	18 (6)	
Defect size			
≤ 2 cm	231 (61)	93 (32)	<0.001
> 2 cm	149 (39)	199 (68)	
Tumour invasion			
Dermis	153 (40)	250 (86)	<0.001
Deep	227 (60)	42 (14)	
Events during follow-up			
Follow-up in years, median (IQR)	4.9 (2.3-6.0)	5.7 (3.5-7.8)	0.001
Recurrence			
No	368 (97)	270 (92)	0.013
Yes	12 (3)	22 (8)	
Metastasis			
No	377 (99)	287 (98)	0.304
Yes	3 (1)	5 (2)	
Deceased (cause unknown)			
No	209 (55)	133 (46)	0.016
Yes	171 (45)	159 (55)	

Percentages were rounded.
cm, centimetre; cSCC, cutaneous squamous cell carcinoma; IQR, inter quartile range; MMS, Mohs micrographic surgery; n, number; SE, standard excision.
[a] 575 Patients with 672 cSCC were included. Numbers in the table represent cSCCs.



MMS					
N at risk	380	291	246	96	17
N of recurrences	0	11	12	12	12
SE					
N at risk	292	246	206	134	71
N of recurrences	0	10	16	19	22

Figure 2. Cumulative incidence curve of recurrence of cutaneous squamous cell carcinoma of the head and neck after Mohs micrographic surgery compared with standard excision.
MMS, Mohs micrographic surgery; N number; SE, standard excision.

Table 2. Cox regression for the recurrence risk of cutaneous squamous cell carcinoma of the head and neck.

	Non-recurred cSCC n = 638 (%)	Recurred cSCC n = 34 (%)	Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Intervention						
SE	270 (42)	22 (65)	1	0.031	1	0.004
MMS	368 (58)	12 (35)	0.49 (0.23-0.94)		0.31 (0.12-0.66)	
Tumour size						
≤ 2 cm	504 (79)	26 (77)	1	0.346	1	0.119
> 2 cm	134 (21)	8 (24)	0.70 (0.32-1.82)		1.89 (0.64-4.06)	
Tumour invasion						
Dermis	383 (60)	20 (59)	1	0.593	1	0.164
Deep	255 (40)	14 (41)	0.82 (0.41-1.69)		1.80 (0.71-4.13)	

Percentages were rounded.
CI, confidence interval; cm, centimetre; cSCC, cutaneous squamous cell carcinoma; HR, Hazard ratio; MMS, Mohs micrographic surgery; n, number; SE, standard excision.

DISCUSSION

Until now, a wide range of cSCC recurrence rates after MMS (0-6%) and SE (0-15%) has been reported.[15] One systematic review with pooled analysis by Lansbury et al. showed a lower, but nonsignificant average recurrence rate after MMS (3.0%, 95% CI 2.2-3.9%; ten studies, n = 1,572) compared with SE (5.4%, 95% CI 2.5-9.1%; 12 studies, n = 1,144).[15]

However, the included studies had heterogeneous inclusion criteria, small numbers of included patients and a short follow-up duration with limited information on those lost to follow-up.

Our study showed a lower recurrence risk of cSCC of the head and neck after MMS (3%) than after SE (8%) during a median follow-up of 5 years (IQR 3-7). Although the median follow-up after SE was longer (5.7 years, IQR 3.5-7.8) than after MMS (4.9 years, IQR 2.3-6.0), the cumulative incidence of recurrence was higher for SE than for MMS during the entire follow-up period of 8.6 years (Figure 2). When adjusted for tumour size and deep tumour invasion, cSCCs treated with MMS were found to be at a three times lower risk of recurrence than SE (adjusted HR 0.31, 95% CI 0.12-0.66) (Table 2). The difference in risk of recurrence was probably underestimated because we could not adjust for all high risk tumour characteristics. However, because of confounding by indication of MMS (i.e. selection bias), cSCCs treated with MMS were more often high risk tumours than cSCCs treated with SE (Table 1).

The lower risk of recurrence after MMS than SE is most likely because of the fact that with MMS the entire excision margin is histologically reviewed. In contrast, for SE only a small portion of the excision margin is histologically reviewed, increasing the risk of a false negative result (i.e. an undetected incomplete cSCC excision).

The excluded 18% of incompletely excised cSCCs with SE in our study was higher than expected based on the study of Lansbury et al., which showed a pooled average estimate of 8.8% (95% CI 5.4-13.0%; 11 studies, n = 2,343).[15] However, the included studies had heterogeneous inclusion criteria (e.g. cSCC on the head and neck and elsewhere) and used a wide range of excision margins (2 to > 10 mm, or unspecified). A recent retrospective review of cSCCs of the head and neck reported 14% (51/364) of incompletely excised cSCCs. However, this study included invasive as well as in situ cSCCs.[16]

We found an extremely high recurrence rate (38%) and metastasis rate (15%) for incompletely excised cSCCs that did not receive additional treatment. This underlines the importance of a complete cSCC excision. In only 1% of the MMS cases, an incomplete cSCC excision was found with the routine postoperative external histological quality check. This shows that the MMS surgeons were very well able to detect cSCC on fresh frozen MMS slides and that MMS is an excellent treatment to achieve tumour clearance.

Another advantage of MMS compared with SE, beside the lower risk of cSCC recurrence and the excellent tumour clearance, is the maximum preservation of healthy tissue.[10] Consistently, we found that after MMS, defects were more often ≤ 2 cm (60%) compared

with after SE (32%), while cSCCs treated with MMS were more often > 2 cm (33%) compared with SE (6%).

Strengths of this study are the comparative design, the large number of included cSCCs, the precise detection of recurrences (elimination of loss to follow-up by the use of PALGA), the long-term follow-up and the use of the cumulative incidence curve. This study shows that it is important to report follow-up data of at least five years: after SE, 77% (17/22) of the recurrences occurred within five years whereas only 45% (10/22) of the recurrences occurred within the first two years.

Our study was limited to a retrospective design. As a result of missing data, we could not determine: tumour stage (mm of tumour invasion, perineural invasion, lymphovascular invasion and cSCC differentiation), disease specific death, and high risk patients (i.e. immunosuppressed patients). We excluded all SCCs that were treated with MMS during the first year that MMS was performed for SCC at the tertiary care hospital. It is uncertain if the learning period of one year was long enough to exclude the presumed bias of a learning curve.

It is uncertain if our results can be generalized to other international dermatology and MMS services. Firstly, in this study MMS and SE were performed by dermatologists, residents and MMS surgeons who were trained in the Netherlands. Secondly, the recommended excision margins in the Dutch cSCC guideline are wider (i.e. five mm for stage I and ten mm for ≥ stage II) than the British and American guidelines recommend (i.e. four mm for stage I and six mm for ≥ stage II).[6,17,18]

In conclusion, this study shows that MMS is an excellent treatment option for patients with cSCC of the head and neck. Although the results imply superiority of MMS compared with SE for cSCC of the head and neck as a result of fewer recurrences, conclusions must be made carefully because of the limitations of the study design.

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