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CLINICAL REPORT

5-year Recurrence Rates of Mohs Micrographic Surgery for Aggressive and Recurrent Facial Basal Cell Carcinoma

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Mohs micrographic surgery allows for complete microscopic examination of the surgical margin when treating aggressive and recurrent facial basal cell carcinomas. This leads to the highest cure rates and maximal preservation of healthy tissue. The 5-year recurrence rates of 587 aggressive and/or recurrent facial basal cell carcinomas treated during 1993 to 2003 at our centre were studied retrospectively. The resulting 5-year recurrence rates using Kaplan–Meier survival analysis were 2.1% for primary (previously untreated) tumours, 5.2% for recurrent basal cell carcinomas and 3.3% overall. In total, 87.9% of the tumours required at least two stages of Mohs micrographic surgery. The surgical defect's size after complete excision was, on average, approximately twice the size of the defect after excision of the clinically visible tumour with a 2–3 mm margin. Mohs micrographic surgery is underused in Scandinavia despite being the treatment of choice for aggressive and recurrent facial basal cell carcinomas. ***Key words: Mohs micrographic surgery; basal cell carcinoma; recurrence rates; skin cancer; therapy.***

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Basal cell carcinomas (BCCs) are by far the most common form of cancer among the Swedish population, with more than 36,500 histopathologically proven cases per year (1). Surgery is generally considered the treatment of choice (2, 3). Even with surgery, there are several tumour characteristics that are associated with higher recurrence rates. These include: tumours located around the eyes, nose, lips and ears; morphoeic, infiltrative, micronodular and basosquamous histopathological subtypes; BCCs with ill-defined margins; recurrent lesions; incompletely excised lesions and perineural or perivascular involvement (3, 4). BCCs with these characteristics are preferably treated with Mohs micrographic surgery (MMS), which allows for complete examination of all tissue margins, minimizing the risk of recurrence and avoiding unnecessary removal of healthy tissue (3, 5).

MMS using the "fresh-tissue technique" (6), a modification of the "chemosurgical" technique originally described by Frederic Mohs in 1941 (7), has been carried out on the above-mentioned indications at the Department of Dermatology, Sahlgrenska University Hospital in Gothenburg, Sweden, since 1983. Until 2009, Gothenburg was the only centre regularly performing MMS in Sweden. We have previously published the results of MMS on 228 aggressive facial BCCs performed during 1983 to 1992 at our hospital. The 5-year recurrence rates (using Kaplan–Meier survival analysis) were 6.5% for primary BCCs and 10% for recurrent BCCs (8).

The aim of the current study was to analyse the 5-year recurrence rates in patients treated with MMS at our department during the period 1993 to 2003 to determine whether these had changed compared with our previous report. A secondary objective was to describe the clinical and histopathological characteristics of the tumours and the outcome of the surgical procedure, which might be associated with recurrence after MMS.

METHODS

The study was conducted at the Department of Dermatology, Sahlgrenska University Hospital in Gothenburg, Sweden. Approval of the study was granted by the local ethics committee, and procedures were carried out in accordance with the ethical standards on human experimentation and the Declaration of Helsinki of 1975, as revised in 1983.

We retrospectively analysed all patients who had undergone MMS at our clinic between 1 January 1993 and 31 December 2003. A description of the surgical technique used at our department (MMS using the "fresh-tissue technique") has been published previously (8). In summary, the bulk of the tumour may be removed initially by curettage for further delineation and for reducing the number of MMS stages (9). The tumour is then excised with a 2–3 mm margin as a saucer-shaped layer of tissue with a 45º angle at the lateral margins. The specimen is processed in an adjacent laboratory into horizontal sections of frozen tissue that theoretically allow for inspection of 100% of the lateral and deep resection margins. The slides are examined by both a dermatopathologist and the Mohs surgeon to ascertain whether the margins are tumour-free. If residual tumour deposits are noted, the above-mentioned procedure is repeated until complete tumour removal has been achieved. Finally, reconstruction of the surgical defect is carried out by the Mohs surgeon. The whole procedure is generally performed under

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local anaesthesia as a day case procedure. A 5-year clinical follow-up is recommended to all patients.

As inclusion criteria we used the main indications for MMS at our clinic during this period: BCCs located on or in close proximity to the nose, eyelids, eyebrows, lips or ears, which also presented an aggressive histopathological subtype, had ill-defined clinical margins, were recurrent or had previously been incompletely excised. Patients were excluded if they had undergone MMS for an unknown diagnosis or any diagnosis other than BCC. BCCs were classified as primary BCCs if they were previously untreated or had undergone failed surgery (i.e. incomplete surgical excision). BCCs were defined as recurrent if they had been treated previously with apparent success (clinically or histopathologically) with a single treatment modality or a combination of the following measures: surgical excision, cryosurgery, curettage and electrodesiccation, radiotherapy, photodynamic therapy and/or laser ablation.

In total, MMS was carried out on 558 patients with 591 lesions during these 11 years. Three patients with 4 lesions were excluded from further analysis, since the lesions were not BCCs or had an unknown diagnosis (one squamous cell carcinoma *in situ* and three lesions of uncertain histopathological diagnosis). Thus, 555 patients with 587 aggressive or recurrent facial BCCs fulfilled the inclusion criteria. The median age of the 315 women and 240 men included in the study was 69 years (range 26–89 years) for both sexes. All surgery was performed or supervised by a Mohs surgeon certified by the European Society for Micrographic Surgery (BS).

Data concerning the results of clinical follow-up were collected. Furthermore, we recorded the number of MMS stages, the defect sizes after MMS and the reconstructive techniques used. The available data regarding the postoperative defect sizes were the length and width of the surgical defect (measured in mm) after the initial stage of MMS and the respective measurements after the final stage. Since surgical defects can theoretically be described as circular or oval in shape, these measurements were used to calculate the probable area of the defect using the formula:

$$\text{Area} = \Pi \times (\text{major axis}/2) \times (\text{minor axis}/2).$$

The 5-year recurrence rates were calculated using the Kaplan–Meier survival analysis method. All data were analysed using "R" version 2.10.1 (The R Foundation for Statistical Computing, Vienna, Austria). Exact (permutation form) logrank tests were performed in order to find possible factors that could predict a recurrence following MMS. The tested parameters were primary vs. recurrent BCC, histopathological subtype, number of MMS stages and postoperative defect sizes.

RESULTS

Among the 587 BCCs, 56% were primary ($n = 328$) and 44% were recurrent BCCs ($n = 258$). Data on the primary or recurrent nature of the tumour was not available for one case. Recurrent BCCs had been treated previously with a variety of treatment modalities, sometimes repeatedly, and often in combination (e.g. prior treatment with cryosurgery and surgical excision). Most commonly, patients had undergone one or more failed surgical excision(s) prior to MMS (67.4%). However, destructive or medical modalities (i.e. cryosurgery, curettage and electrodesiccation, radiotherapy, photodynamic therapy and/or laser ablation) had led to recurrence in 20.2% of the patients. The mean number of previously tested methods was 1.58 (95% confidence interval (CI), 1.46–1.70), with a number of failed treatments ranging from 1 to 8. Data regarding the histopathological subtype of BCC was available for 457 BCCs. Among these, 84.2% were morphoeic or infiltrative (aggressive subtypes) and the rest were nodular or superficial (non-aggressive subtypes). The nose was the most common location of the tumours included in the study (42.6%). Fig. 1 shows the anatomical distribution of the lesions.

The clinical and histopathological characteristics of the tumours and their surgical outcome are shown in Table I. Overall, the mean number of MMS stages carried out to obtain histopathological clearance of the lesions was 2.39 (95% CI, 2.32–2.47). In total, 77.2% of the BCCs were eradicated in 2–3 stages and only 12.1% were completely removed in a single stage (Fig. 2). The median area of the initial surgical defect was 1.98 cm^2 (range 0.19–32.8 cm^2). Meanwhile, the median area of the final defect after complete removal of the tumours was 3.90 cm^2 (range 0.19–53.4 cm^2), approximately twice the initial size (Table I). When reconstructing the surgical defects, primary closure was used in 95 cases (16.2%), grafts were carried out in 239 tumours (40.7%), flaps were performed in 171 BCCs (29.1%), secondary intention healed 38 wounds (6.5%) and 39 patients were managed using combinations of these techniques (6.6%). The remaining five patients (0.9%) were referred to other specialists for surgical reconstruction.

Data regarding follow-up was available for 486 BCCs (306 primary BCCs, 179 recurrent BCCs and 1 unknown) in 457 patients (82.8% of all cases). The median follow-up for these patients was 5 years (range 0.5–11.5 years).

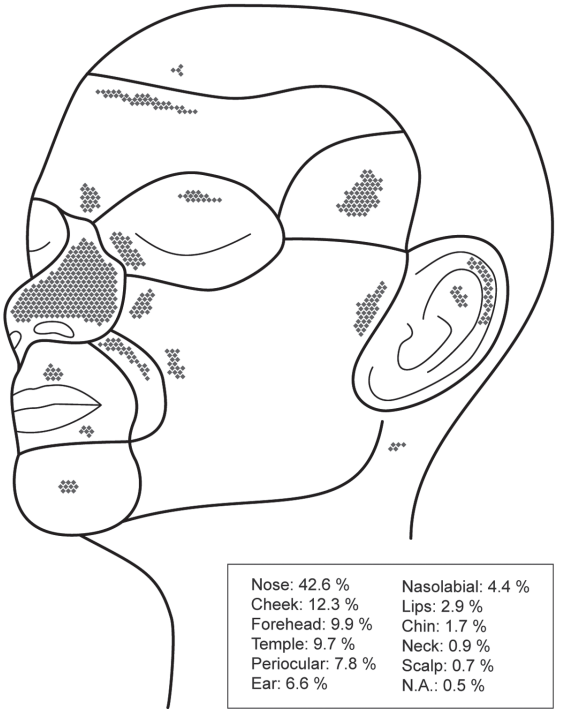

Fig. 1. Anatomical distribution of the 587 basal cell carcinomas. Each rhomb corresponds to a single lesion. The placement of each rhomb is approximate. Data not available (NA) for 3 lesions.

Table I. *Characteristics of the 587 basal cell carcinomas (BCCs)[a], the number of stages and the resulting size of the defects*

	Cases *n* (%)	No. of MMS stages Mean	Area of initial defect (cm^2) Median	Area of final defect (cm^2) Median
Primary BCCs (328 cases)				
Morphoeic	223 (68)	2.35	1.77	3.46
Infiltrative	20 (6.1)	2.24	1.84	2.67
Nodular or superficial	33 (10.1)	2.25	1.73	3.71
Unspecified	52 (15.9)	2.17	1.80	3.46
Recurrent BCCs (258 cases)				
Morphoeic	121 (46.9)	2.55	2.12	4.52
Infiltrative	20 (7.8)	2.54	2.57	4.43
Nodular or superficial	39 (15.1)	2.60	2.14	5.11
Unspecified	78 (30.2)	2.38	2.20	4.08
Overall	587 (100)	2.39	1.98	3.90

[a]Data was not available for one basal cell carcinoma regarding its primary or recurrent nature.
MMS: Mohs micrographic surgery.

Clinical follow-up was carried out for at least 5 years in 289 cases (59.5%). Follow-up was shorter in some cases due to the patients choosing to conclude follow-up visits at an earlier stage, change of residence, concomitant diseases or death. No deaths could be attributed to the treated tumours or to the surgical procedures. Follow-up information for the remaining 22 primary and 79 recurrent BCCs (101 BCCs in 98 patients) was unfortunately not available. Most of these cases (91 BCCs) were patients who lived outside of the Gothenburg region and were therefore followed by their referring physician instead.

During follow-up, 16 recurrences were observed among the 486 BCCs that were followed at our department after MMS (Table II). Six of these BCCs were registered as primary and 10 were recurrent BCCs. In the great majority of these 16 cases, 2 or more MMS stages were needed (87.5%). Recurrences were generally observed within the first 3 years (81.2%), although one recurrence was noted as late as 7 years after MMS. The Kaplan–Meier model yielded 5-year recurrence rates of 2.1% for primary BCCs (95% CI 0.4–3.8%) and 5.2% for recurrent BCCs (95% CI 1.6–8.7%), as shown in Fig. 3. The overall 5-year recurrence rate was 3.3% (95% CI 1.6–5.0%), as presented in Fig. 4.

Exact (permutation form) logrank tests showed no statistically significant correlations between recurrences after MMS and primary vs. recurrent BCC, histopathological subtype, number of MMS stages and size of the postoperative skin defect. Nevertheless, there was a trend towards higher risk of recurrence after MMS when treating recurrent BCCs ($p=0.06$), morphoeic BCCs ($p=0.14$) and in tumours demanding >4 MMS stages ($p=0.17$).

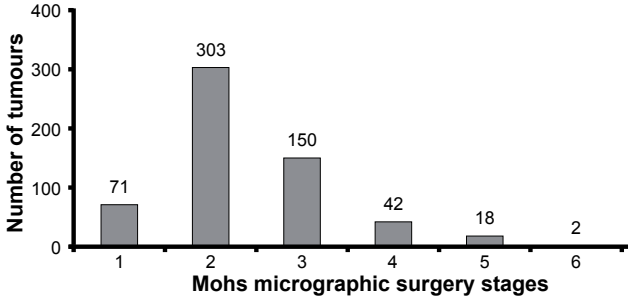

Fig. 2. Number of stages required per tumour.

Table II. *Recurrences after Mohs micrographic surgery*

Patient number	Age, years/ sex	Location	Histopathological type of BCC	Stages *n*	Years until recurrence
Primary BCCs					
1	82/F	Nose	Infiltrative	2	0.5
2	51/F	Forehead	Morphoeic	2	1
3	72/M	Cheek	Morphoeic	2	1.5
4	74/F	Temple	Morphoeic	2	1.5
5	72/F	Forehead	Unknown	1	1.5
6	54/F	Temple	Morphoeic	2	2
Recurrent BCCs					
1	75/M	Nose	Morphoeic	2	1
2	47/M	Temple	Unknown	2	1
3	63/F	Forehead	Morphoeic	2	1.5
4	74/M	Nose	Morphoeic	1	2
5	59/F	Eye	Unknown	2	2
6	70/M	Temple	Morphoeic	5	2.5
7	67/M	Forehead	Unknown	5	2.5
8	75/M	Eye	Morphoeic	3	5
9	54/M	Nose	Morphoeic	4	5.5
10	72/F	Forehead	Morphoeic	2	7

BCCs: basal cell carcinomas; M: male; F: female.

DISCUSSION

The use of MMS in our department during this 11-year period resulted in 5-year recurrence rates of 2.1% for primary BCCs and 5.2% for recurrent BCCs, with an overall recurrence rate of 3.3%. At first glance, we appear to have improved on our previous results from 1983 to 1992, in which the rates for primary and recurrent BCCs were 6.5% and 10%, respectively (8). Even though these results are not completely comparable, the surgical procedure and the indications for MMS remained the same during both periods. Also, the pro-

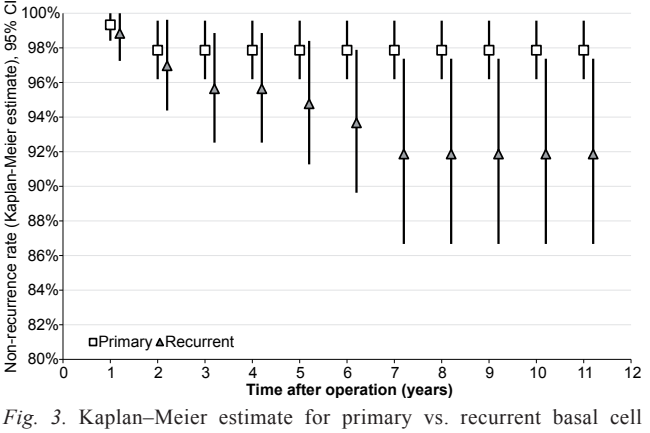

Fig. 3. Kaplan–Meier estimate for primary vs. recurrent basal cell carcinomas.

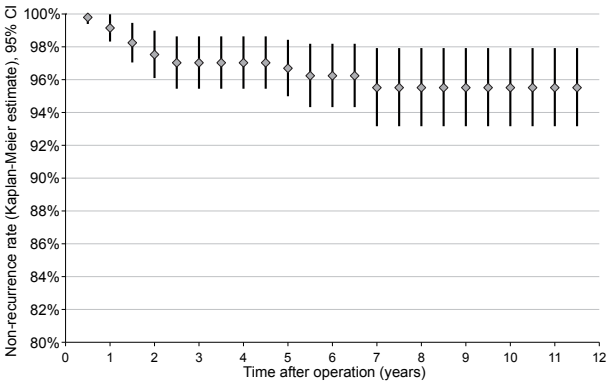

Fig. 4. Kaplan–Meier estimate for all basal cell carcinomas.

portions of primary and recurrent BCCs, the anatomical distribution of the lesions and the number of MMS stages were fairly similar in both studies. Despite these apparent similarities, the differences in the recurrence rates may still be due to dissimilar levels of surgical difficulty among the included cases. Another explanation may simply be that years of practice and a larger number of cases performed each year at a single centre are beneficial in improving the outcome of MMS.

Other European centres with similar indications for MMS have reported 5-year recurrence rates of 1.7–3.2% for primary BCCs and 4.8–6.7% for recurrent BCCs using the same MMS technique and similar indications (10, 11). Variants of micrographic surgery that also allow for complete examination of all tissue margins have shown comparable 5-year recurrence rates: 3.3% for primary BCCs and 7.3% for recurrent BCCs (12). Thus, we seem to have succeeded in obtaining similarly excellent results when comparing our 5-year recurrence rates with those shown by these centres.

In order to put these recurrence rates in perspective, one should consider the difficulty involved in treating the tumours included in our study. In summary, almost all BCCs were located in the so-called "H-zone" of the face, more than five out of six lesions (in which data was available) were of an aggressive histopathological subtype and almost half of the tumours were recurrent BCCs. Postoperatively, it was noted that more than seven out of eight cases required more than one stage of MMS and the size of the final skin defect was approximately double that of the initial defect. These results indirectly suggest that the clinical examination of aggressive and recurrent BCCs in the facial area through inspection, dermoscopy and palpation are insufficient in predicting the full extent of the tumours, even when carried out by experienced dermatologists. The complexities of the tumours included in the study are a natural consequence of the strict indications that we use for patients to qualify for MMS at our centre. These indications, in turn, are due to the limited resources that are available to carry out this procedure in Sweden.

Recurrent BCCs, histopathologically aggressive BCCs, >4 stages of MMS and large size of the skin defect (>4 cm in diameter) have previously been found to have predictive value for recurrence after MMS (11). Although our study did not show statistical significance for any predictors of recurrence, morphoeic BCCs, recurrent BCCs and a large number of MMS stages may have some relevance in this context. Until further studies show clearer results in recurrence prediction, all patients treated with MMS should be recommended a follow-up of 5 or more years. The importance of clinical follow-up should be emphasized even more for those patients treated for recurrent BCCs. Currently, we check our MMS patients at 1, 3 and 5 years postoperatively, with extra visits planned if the patient suspects a recurrence or new lesions.

MMS is globally recognized as the treatment of choice for high-risk BCCs due to its lower recurrence rates and tissue-sparing benefits (3, 5). In the USA, the 5-year recurrence rate for primary BCCs after MMS is as low as 1.0%, in comparison with other modalities, such as: surgical excision, 10.1%; cryosurgery, 7.5%; curettage and electrodesiccation, 7.7%; and radiotherapy, 8.7% (13). The corresponding rates for recurrent BCCs are: MMS, 5.6%; surgical excision, 17.4%; cryosurgery, 13.0% (followed up for <5 years); curettage and electrodesiccation, 40.0%; and radiation therapy, 9.8% (14).

Only one randomized controlled study has been carried out comparing MMS with surgical excision (15). After a 5-year follow-up, MMS achieved statistically significant lower recurrence rates than surgical excision for recurrent BCCs. The recurrence rates for primary BCCs were also lower in the MMS patients, but statistical significance was not reached (16). However, this study has been criticized, since several patients with positive margins after the first or second surgical excision were subsequently treated with MMS, but analysed as belonging to the surgical excision group, constituting a rescue bias. Furthermore, randomization unfortunately led to more histopathologically aggressive BCCs among the patients treated with MMS (17). Finally, 50% of the tumours included in their study were of a non-aggressive subtype, which could also have benefitted the results of surgical excision. In our study, 11 of the 12 recurrences in which the histopathological subtype of BCC was known, occurred in patients with BCCs of the morphoeic subtype. This highlights the relevance of including more or less BCCs with an aggressive histopathological subtype in MMS studies.

Regarding the tissue-sparing benefits of MMS, Smeets et al. (15) showed that surgical excision caused significantly larger defects than MMS for primary and recurrent BCCs needing more than one surgical excision or at least two stages of MMS for complete tumour removal. Moreover, a randomized controlled study showed significantly larger defects after surgical excision of nodular BCCs compared with those obtained after MMS. In this study,

a 4 mm margin was applied during surgical excision to guarantee 95% clearance rates, whereas a 2 mm margin was used for the initial stage during MMS (18). Nevertheless, the size of the surgical defect can be affected by the anatomical site of the tumour or diathermy used during surgery and is therefore not always equivalent to the actual size of the tumour (19).

We should not underestimate the value of physician continuity that can be obtained with MMS. Patients who undergo surgical excision of an aggressive BCC instead of MMS can end up needing to see several physicians in the process of making a correct diagnosis, excising the lesion, reconstructing the defect and ruling out a recurrence postoperatively. In the case of MMS, the Mohs surgeon follows the patient from beginning to end. In fact, less than 1% of our patients required referral to another surgeon for reconstruction.

In Scandinavia, MMS for the aforementioned indications is underused. During the study period (1993 to 2003), Gothenburg was the only active MMS centre in Scandinavia. Our resources for MMS are currently insufficient and limited to approximately 70 cases per year. The most common issue hindering the more extensive use of MMS in Sweden is the opinion that the procedure is time-consuming and expensive.

Several attempts have been made to study the cost-effectiveness of MMS in comparison with surgical excision, rendering disparate results depending on the country's reimbursement systems, the indications applied and the clinical settings of the procedure (16, 20–23). Given the difficulty in interpreting these studies and the fact that cost-effectiveness studies that apply to Scandinavian healthcare systems are lacking; it is our viewpoint that MMS should be offered to all patients with aggressive and recurrent facial BCCs in which preservation of aesthetics and function is important, regardless of their place of residence or their socioeconomic background. Thus, we conclude that our indications for MMS (aggressive, ill-defined, recurrent or incompletely excised BCCs located in the "H-zone") should be maintained.

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