

Additional review of Mohs slides to optimize Mohs micrographic surgery

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Br J Dermatol 2015;173:123-27

ABSTRACT

Background: One significant risk factor for recurrence after Mohs micrographic surgery (MMS) is misinterpretation of slides.

Objectives: To determine how often pathologists detected incompletely excised basal cell carcinoma (BCC) on MMS slides and to determine risk factors for incompletely excised BCCs.

Methods: This retrospective study included 1,653 BCCs treated with MMS in a university hospital between 2007 and 2011. For routine quality assurance, all slides were additionally reviewed by a pathologist within one week of the procedure. For this study, all cases that had divergent interpretations were re-evaluated by a MMS surgeon and a pathologist. Mixed-effects logistic regression models with MMS surgeon effects as random effects were used to determine risk factors for incompletely excised BCC.

Results: Incompletely excised BCCs were detected in 2% (31/1,653), in which defects > 20 mm in diameter were an independent risk factor (OR 3.6, 95% CI 1.6-8.3). Other studied variables (i.e. aggressive subtype, previously treated BCC, location on nose and > 2 MMS stages) did not affect the risk of incompletely excised BCCs.

Conclusions: The additional review of MM slides might increase accurate interpretation, especially in large BCCs.

INTRODUCTION

Due to a low recurrence rate and preservation of healthy tissue, Mohs micrographic surgery (MMS) is a superior treatment for aggressive or recurrent basal cell carcinomas (BCCs) located on the face.^{1,2} These benefits are achieved because all margins are reviewed microscopically. Therefore, the success of MMS depends on correct interpretation of slides. At least 30% of skin cancer recurrences after MMS are due to misinterpretation of slides by the MMS surgeon.^{3,4} It is unknown how often MMS surgeons miss tumour cells on slides and, to date, no study has been performed on methods to reduce the number of cases with missed tumour. In pathology, an additional review to detect slide misinterpretation is considered the gold standard.⁵ The purpose of our study was to determine how often a pathologist detected misinterpreted slides that included incompletely excised BCCs. We also aimed to determine risk factors for these incompletely excised BCCs.

METHODS

This retrospective study included BCCs treated with MMS at the Department of Dermatology, Erasmus University Medical Center Rotterdam (EMC), between 2007 and 2011. Each month, the first 60% of BCCs treated with MMS were included. Other types of skin cancers were excluded. Included cases were operated on by one of 11 MMS surgeons. MMS surgeons were certified by the European Society for Micrographic Surgery and each had over five years' experience in MMS. During the study period, four of the MMS surgeons operated on a regular basis; the other six only operated for approximately six months. Well-trained histotechnicians prepared MMS slides, which were stained with haematoxylin and eosin; the distance between each section was 100 µm and the sections themselves were eight µm thick. The number of slides made per MMS procedure depended on the size of excised tissue and number of stages. For each tissue block, at least six slides were prepared and reviewed. The MMS surgeon reviewed slides intraoperatively and recorded the findings in a standard digital file. For a margin to be considered tumour free, at least two complete slides should be without tumour. For routine quality assurance, all slides and files were additionally reviewed by one of five pathologists within one week of the MMS procedure. Slides and files were additionally reviewed for the absence or presence and correct mapping of BCC. Whenever the pathologist's review diverged from that of the MMS surgeon, this was recorded by the pathologist in the pathology report.

We examined patient records, MMS files and pathology reports of the included BCCs. Whenever a pathologist's interpretation diverged from that of the MMS surgeon, this was recorded in our database. For this study, an MMS surgeon and a pathologist were appointed to re-evaluate the cases with divergent interpretations. The MMS surgeon and the pathologist appointed both had > 15 years' experience in the interpretation of MMS slides. They jointly determined if the cases with divergent interpretations were truly misinterpreted by the initial MMS surgeon. If they determined that the initial MMS surgeon had truly misinterpreted a slide, it was specified whether this resulted in an incompletely excised BCC. Incompletely excised BCCs were defined as follows: BCC present on slides at the margin but not marked on the MMS map; marking of BCC on wrong portions of the map; an inadequately sized specimen to encompass previous areas of BCC completely.⁶ In the case of an incompletely excised BCC, the BCC subtype was specified. In the case of a mixed subtype, the case was categorized on the basis of the worst pattern: perineural invasion (PNI) > morpheaform > micronodular > nodular > superficial. If the subtype on the MMS slide differed from the biopsy, it was specified whether this subtype was more aggressive than the biopsy. Aggressive subtypes were considered to be morpheaform, micronodular, adenoid, basosquamous and BCC with PNI. Less aggressive subtypes were considered to be superficial and nodular BCC.⁷

The secondary outcome was to determine if the characteristics of the BCCs and MMS procedures were an independent risk factor for incompletely excised BCCs. A mixed-effects logistic regression model was used to test the effect of variables on incompletely excised BCCs. MMS surgeon effects were taken into account as random effects. Variables in the model were presumed to increase the risk of an incomplete BCC excision and included: aggressive BCC subtype; previously treated BCC; BCC located on the nose; final defect size > 20 mm in diameter; and total number of MMS stages > 2. To check if our sample size was sufficient, a simulation for power calculation based on the mixed-effects logistic regression model was performed. The simulation study indicated > 80% power to detect at least one of five risk factors for incompletely excised BCCs. To indicate significance, a two-sided P-value < .05 was used. Statistical analyses were performed using R version 3.1.1 (<http://www.r-project.org>).

RESULTS

A total of 1,653 cases were examined (50% men, 50% women). The median age of the patients was 69 years (IQR 59-77). BCCs were most frequently morpheaform or nodular (Table 1). The median number of MMS stages was two (IQR 1-2; range 1-6).

Table 1. Subtypes of completely and incompletely excised basal cell carcinoma with Mohs micrographic surgery.

BCC Subtype	Completely excised BCC, BCC subtype in biopsy prior to MMS n = 1,662 (%)	Incompletely excised BCC, BCC subtype in biopsy prior to MMS n = 31 (%)	Incompletely excised BCC, BCC subtype in outer MMS slide n = 31 (%)
Morpheaform	922 (57)	16 (52)	13 (42)
Nodular	552 (34)	13 (42)	3 (10)
Micronodular	76 (5)	1 (3)	1 (3)
Superficial	14 (1)	0 (0)	13 (42)
Adenoid	10 (1)	1 (3)	0 (0)
Basosquamous	3 (0)	0 (0)	0 (0)
Perineural invasion	0 (0)	0 (0)	1 (3)
Unknown	45 (3)	0 (0)	0 (0)

Percentages were rounded.

BCC, Basal cell carcinoma; MMS, Mohs micrographic surgery; n, number.

Of the 1,653 cases, a pathologist's review diverged from the initial interpretation of the MMS surgeon in 6% cases (n = 104) (Figure 1). These 104 cases were re-evaluated by the MMS surgeon and the pathologist appointed for this study. They jointly determined that 99 of these 104 cases were truly misinterpreted by the initial MMS surgeon. In 4% (68/1,653), initial misinterpretation did not result in an incompletely excised BCC (e.g. benign structures were misinterpreted as BCC). Benign structures that were interpreted as BCC were inflammatory cells; pronounced hair follicles; fibrotic cells; actinic keratosis; syringoma; and seborrheic keratosis. In 2% (31/1,653), initial misinterpretation resulted in an incompletely excised BCC.

The 31 incompletely excised BCCs were superficial in 42% (n = 13); morpheaform in 42% (n = 13); nodular 10% (n = 3); micronodular in 3% (n = 1); and with perineural invasion in 3% (n = 1) (Table 1). Subtypes of incompletely excised BCCs differed from their biopsy in 58% (n = 18). In 10% (n = 3), subtypes of incompletely excised BCCs were more aggressive than demonstrated in their biopsy, while in 48% (n = 12) incompletely excised BCC were less aggressive. The 13 incompletely excised superficial BCCs demonstrated different subtypes in their biopsy: 77% (10/13) biopsies demonstrated nodular BCCs; 15% (2/13) demonstrated morpheaform BCCs; and 8% (1/13) demonstrated adenoid BCC. The 13 incompletely excised morpheaform BCCs demonstrated consistent subtypes in 85% (11/13) biopsies and nodular BCCs in 15% (2/13) biopsies. The three incompletely excised nodular BCCs demonstrated a consistent subtype in 33% (1/3) biopsy and morpheaform BCCs in 67% (2/3) biopsies. The incompletely excised micronodular BCC was consistent with the biopsy. The incompletely excised BCC with PNI occurred in a case where the biopsy demonstrated a morpheaform BCC without PNI.

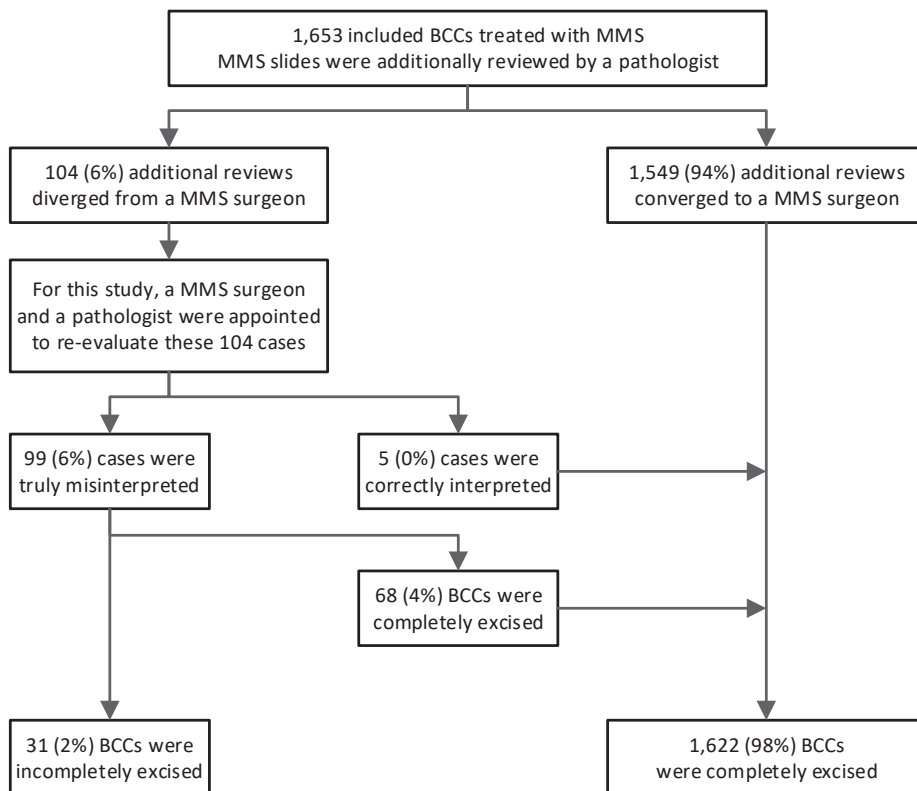


Figure 1. With the additional review of a pathologist, incompletely excised basal cell carcinomas were detected in 2% (31/1,653) Mohs micrographic surgery procedures. BCC, Basal cell carcinoma; MMS, Mohs micrographic surgery.

Mixed-effects logistic regression models with MMS surgeon effects as random effects showed that a final defect > 20 mm in diameter was an independent significant risk factor for incompletely excised BCCs (OR 3.6, 95% CI 1.6-8.3) (Table 2). Other studied variables (i.e. aggressive BCC subtype; previously treated BCC; location on the nose; and total number of MMS stages > 2) did not impact the risk of incompletely excised BCCs (P > .05).

Table 2. Descriptive statistics and the results of variables in the mixed-effects logistic regression model with incompletely excised basal cell carcinomas as response and Mohs surgeons effects as random effects.

Variables	Completely excised BCC n = 1,622 (%)	Incompletely excised BCC n = 31 (%)	Adjusted OR (95% CI)
Previously treated BCC			
Yes	390 (24)	14 (45)	1.9 (0.9-4.2)
No	1,232 (76)	17 (55)	
Aggressive BCC subtype ^a			
Yes	1,011 (62)	15 (48)	0.6 (0.3-1.2)
No	611 (38)	16 (52)	
Location on nose			
Yes	640 (40)	14 (45)	0.5 (0.3-1.1)
No	982 (61)	17 (55)	
Number of stages > 2			
Yes	219 (14)	7 (23)	1.1 (0.4-2.7)
No	1,403 (87)	24 (77)	
Defect > 20 mm in diameter			
Yes	516 (32)	19 (61)	3.6 (1.6-8.3)
No	1106 (68)	12 (39)	

Percentages were rounded.

BCC, Basal cell carcinoma; CI, confidence interval; MMS, Mohs micrographic surgery; n, number; OR, odds ratio.

^a Aggressive subtypes included: morpheaform, micronodular, adenoid, basosquamous and perineural invasion.

DISCUSSION

This study shows that pathologists detected incompletely excised BCCs on MMS slides in 2% of cases. This is in line with two other studies, although these studies included fewer cases than we did (207 and 102, respectively, vs. 1,653).^{8,9} In our study, incompletely excised BCCs were most frequently morpheaform (42%) or superficial (42%) and, less frequently, nodular (10%). Both morpheaform and superficial BCCs were probably missed because both can be subtle in their appearance. Although superficial BCCs grow less aggressively than other BCC subtypes, they must be recognized on the MMS slides and treated (e.g. with nonsurgical therapies adjuvant to the MMS procedure) to prevent evolution to a more aggressive subtype. Micronodular BCCs and BCCs with PNI are less common; in our study, they counted for only 6% of the incompletely excised BCCs. Subtypes of incompletely excised BCCs differed from their biopsy in 58%. This is in line with two other studies, which show that biopsy subtypes differed from MMS slides in 41% and 51% of cases, respectively.^{10,11} It is known that about 30% of BCCs demonstrate

mixed subtypes.¹² MMS surgeons might miss BCCs with mixed subtypes more easily if they focus on the detection of the subtype seen in the biopsy.

MMS procedures with misinterpreted slides that did not result in an incompletely excised BCC were found in 4% of cases, which is less than the 9% and 20% reported in two previous studies, respectively.^{8,9} In some of these cases, healthy tissue might have been excised unnecessarily. In the falsely positive interpreted cases studied, areas with dense inflammation were, in some cases, misinterpreted as BCC. Areas of dense inflammation are suspicious for the presence of BCC as inflammation surrounds BCC in 52% of cases.^{13,14} However, inflammation does not mask areas of tumour and therefore dense inflammation alone is no indication for a following MMS stage.

A final defect > 20 mm in diameter was found to be a significantly independent risk factor for incompletely excised BCCs (OR 3.6, 95% CI 1.6-8.3). This is probably because the number of slides to review is higher when the defect is larger and therefore the chance of misinterpretation is higher. Incompletely excised BCCs had a defect > 20 mm in diameter in only 61% of all cases. To detect the other 39% of incompletely excised BCCs, all MMS slides must be reviewed again.

Our results show that MMS surgeons should review slides carefully, paying special attention to morpheaform and superficial BCC. MMS surgeons should review slides with an open mind, without the limiting focus of the biopsy subtype, as some BCCs demonstrate mixed subtypes. In case of large defects, MMS surgeons should stay focused through the entire procedure. To verify their interpretations, they should record their findings and considerations in detail.

This study included 11 MMS surgeons and five pathologists; they were all trained in the Netherlands. Therefore, it is uncertain if our results can be generalized to other international MMS services. The percentage of incompletely excised BCCs found (2%) meets the MMS audit standard in the U.K., where a target rate of < 2% is suggested.¹⁵ One can question if MMS training and the requirements for MMS credentials are sufficient to achieve a rate of incompletely excised BCCs of < 2%. An interesting study showed that approximately 1500 MMS procedures were required before one fellow reduced his misinterpretations to a minimum acceptable level of fewer than 1 per 100.¹⁶ The number of MMS procedures required for MMS credentials is far fewer than 1,500 for both the American College of MMS Surgery and the European Society for Micrographic Surgery. Higher quantitative directives may be needed to ensure the quality of MMS surgeons. In addition to the quantitative directive, we suggest adding a qualitative directive for

MMS credentials (e.g. histopathological examination of MMS slides wherein a low level of misinterpretations must be achieved).

Although labour-intensive, the additional review has several important advantages. Firstly, detection and correction of incompletely excised BCCs will prevent recurrences. Secondly, detection of misinterpretations provides the MMS surgeon with the opportunity to learn from his or her mistakes, which is essential for personal quality improvement.^{5,16} Thirdly, the number of misinterpretations and incompletely excised tumours are an excellent indicator for quality assurance and control for individual MMS surgeons and MMS services.^{5,9} At the EMC, additional reviews were performed by a pathologist, which increased costs. Other studies show that the rate of slides interpreted in concordance by a MMS surgeon and a pathologist is high (95- 100%).^{15,17-20} These studies conclude that MMS surgeons are able to review MMS slides as well as pathologists do. This suggests that the additional review can be performed by another MMS surgeon as well.

Even if all MMS slides were additionally reviewed in MMS practices, tumour will be missed and skin cancer recurrences will occur in some cases. Besides misinterpretation of slides, other risk factors for skin cancer recurrences are acceptance of poor-quality slides and incorrect initiation of later MMS stages.^{3,4,6,14} These factors are under the control of the MMS surgeon. To further improve the effectiveness of MMS, research is needed to minimize all risk factors for skin cancer recurrence.

There are two limitations of this study. Firstly, this study was limited to retrospective data. However, for this study, slides with divergent interpretations were re-evaluated. Secondly, data was extracted from a single centre. However, the study involved several MMS surgeons and pathologists, and a large number (n = 1,653) of BCCs treated with MMS were included.

This study determined that a pathologist detected incompletely excised BCCs on MMS slides in 2% of cases. An independent risk factor for incompletely excised BCCs was a defect size > 20 mm in diameter. The additional review of MMS slides by pathologists and/or MMS surgeons optimizes the quality of MMS and may therefore prevent skin cancer recurrence.

Acknowledgments

We would like to thank Loes Zandwijk-Hollestein for her statistical advice.

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