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CLINICAL REPORT

Efficacy of Fluorescence Diagnosis-guided Mohs Micrographic Surgery for Pigmented vs Non-pigmented Basal Cell Carcinoma

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Pigmented basal cell carcinoma (PBCC) occurs more frequently in Asian population. The efficacy of fluorescence diagnosis (FD) for PBCCs treated with Mohs micrographic surgery has not yet been determined. This study enrolled 255 patients with 258 biopsy-proven BCC lesions: 199 PBCCs (77.1%) and 59 non-PBCCs (22.9%). We compared the clinicopathological and surgical features of the PBCCs and non-PBCCs. Each group was divided into 2 sub-groups, those assessed and not assessed by FD, to retrospectively analyse surgical features. Aggressive histological subtypes were less prevalent in PBCCs than in non-PBCCs. PBCCs required significantly fewer stages of Mohs excision, with significantly smaller surgical margins and surgical depth, than non-PBCCs. FD did not confer any benefits on PBCCs during Mohs micrographic surgery. However, non-PBCCs assessed by FD required significantly fewer Mohs stages, with significantly smaller surgical margins, than lesions not assessed by FD. These findings suggest that FD should be performed before Mohs micrographic surgery to delineate the margins of non-PBCCs in Asians. *Key words: Asian; Mohs micrographic surgery; fluorescence diagnosis; pigmented basal cell carcinoma.*

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Mohs micrographic surgery (MMS) is the most efficacious modality for treating non-melanoma skin cancers, resulting in better initial outcomes, lower 5-year recurrence rates, and better cosmetic results than other treatment modalities (1, 2). However, the time consuming nature of this procedure, attributable to ill-defined tumour margins and subclinical extension of the lesion, remains a significant disadvantage. The efficacy of MMS may therefore be increased, and the number of surgical steps required to clear the tumour, reduced, by accurately determining tumour margins before surgery. Curettage, high frequency ultrasonography, fluorescence diagnosis (FD), positron emission tomography, spectrophotometric intracutaneous analysis, and laser Doppler velocimetry may be some of the methods currently available for this purpose (3–10).

Amongst these procedures, FD is a relatively simple, non-invasive diagnostic technique, involving the application of a photosensitiser over a lesion, which allows the red fluorescence from selectively accumulated protoporphyrin IX (PpIX) to be observed using Wood's lamp. This in turn reveals the location of the tumour margin (11). FD is easy to perform and does not require advanced training or specialised equipment and has therefore been widely used to determine tumour margins prior to MMS.

Basal cell carcinoma (BCC) is the most common form of skin cancer, with an increasing annual incidence in Asian populations (12, 13). Pigmented BCC (PBCC), one of the most common clinical subtypes in Asian patients, is clinically defined as a BCC with at least some visible pigmentation. PBCCs frequently occur in individuals with darker skin types (14–16). Although several studies have assessed the characteristics of PBCCs (4–6), none have evaluated the efficacy of preoperative FD for locating the margin of PBCCs prior to MMS, possibly because their borders are often more distinct. However, when PBCC tumour borders are indistinct as a result of erythema, and/or ulceration, it becomes difficult to accurately delineate their margins during MMS. Furthermore, visible boundaries determined using FD have been shown to correspond to those determined histologically, suggesting that FD may help determine the required extent of surgery (7, 17).

In this study, we examined the differences in clinicopathological and surgical features between PBCC and non-PBCC cases treated using MMS. In order to determine the clinical significance and efficacy of FD for these lesions, we divided BCC lesions into subgroups that were either assessed or not assessed by FD before MMS and analysed the differences between their surgical outcomes.

MATERIAL AND METHODS

Study design and patients

We reviewed cases of biopsy-proven BCC treated using MMS at the Dong-A University Hospital (Busan, Korea) between January 2001 and December 2011. Amongst these cases, we identified 258 lesions in 255 patients, all of which had associated clinical images, including fluorescence images, facilitating

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a comparison of preoperative tumour size and postoperative defect size. This retrospective, comparative, single-centre study was approved by the institutional review board of Dong-A University Hospital and was performed in accordance with the guidelines set by the Declaration of Helsinki.

Methods

The 258 BCC lesions were divided into 2 groups according to the presence of pigmentation: the PBCC group ($n = 199$, 77.1%) and the non-PBCC group ($n = 59$, 22.9%). In this study, we arbitrarily defined PBCCs as lesions with visible pigmentation covering at least 1% of the tumour. PBCC and non-PBCC groups were each further divided into 2 subgroups, depending on whether the lesion was assessed by FD prior to MMS. Tumours with ill-defined margins on visual inspection were examined by FD before surgery to delineate their margins. Of the 199 PBCCs, 113 (56.8%) were assessed by FD and 86 (45.2%) were not, and of the 59 non-PBCCs, 22 (37.3%) were assessed by FD and 37 (62.7%) were not.

Fluorescence diagnosis-guided Mohs micrographic surgery using aminolevulinic acid

Patients underwent FD approximately 6 h before MMS in order to delineate tumour margins. Before the application of a photosensitiser, any excessive scales and crusts were scraped off gently so as not to cause bleeding. The lesions were cleansed with gauze soaked in physiological saline. A 1 mm layer of cream containing 20% aminolevulinic acid (ALA) was applied on each lesion and 0.5–1 cm of surrounding normal skin (7), and the area was covered with polyurethane film (Tegaderm; 3M, Minneapolis, USA) and aluminium foil to prevent exposure to light. This was left on for 6 h (18), after which the occlusive dressing was removed, and the lesion was cleansed with saline to remove excess photosensitiser cream. To determine the margin of BCCs for MMS, red fluorescence was marked with gentian violet under Wood's lamp (Ultraviolet Examination Light, model no. 31602, 356 nm; Burton Medical Products Corp., Chatsworth, USA) in the operating room (Fig. 1). The margins of those lesions not assessed by FD were determined instead by visual inspection.

Data collection

Data were collected by reviewing patient medical records, including clinical photographs, pathology slides, and MMS operation sheets. Clinicopathological data on demographic characteristics including patient age and sex; whether the lesion was primary or recurrent; time to pathologically confirmed diagnosis; tumour size, depth, and location; the presence or absence of ulceration; and the histologic subtype were collected. Surgical data included the surgical margin, surgical depth, and the number of MMS stages required to clear the tumour.

Pathology slides were obtained from the archives of the Department of Dermatology and Pathology, Dong-A University Hospital, and were evaluated histologically by 2 dermatologists blinded to clinical information. Most BCCs were nodular or nodulocystic, superficial, micronodular, infiltrative, morphoeic, or of a mixed type (19). Although a mixed subtype has been strictly defined as noduloinfiltrative, nodulomicronodular, micronoduloinfiltrative, and nodulomicronoduloinfiltrative (19), in this study, this was defined simply as the presence of 2 or more tumour types. Several histological subtypes with poor prognosis owing to their aggressive nature and high recurrence rate were placed into an 'aggressive group', including micronodular, infiltrative, morphoeic, and mixed type tumours.

Tumours were located at a number of different sites including the nose, periorbital area, cheek, auricle, forehead/scalp/temple, lip, neck, and chin. Tumour size in patients who were not assessed by FD was defined as the largest diameter that could be measured with the naked eye, whereas tumour size in patients assessed by FD was defined as the largest diameter of red fluorescence. Post-MMS defect size was defined as the largest diameter of the postoperative defect and was measured after removal by MMS. Surgical margins were calculated by subtracting the largest diameter of a tumour from the largest diameter of the postoperative defect. The preoperative tumour area, fluorescence area, postoperative defect area, and marginal area (mm^2), were calculated using Photoshop CS software (version 8.0, Adobe Systems, Inc., San Jose, CA). The surgical depth was classified as subcutaneous layer (down to the subcutaneous fat), muscle fascia/muscular layer (down to the muscle fascia or muscular layer), or perichondrium/cartilage (down to the perichondrium or cartilage).

Statistical analysis

Differences were analysed using SPSS software (version 18.00, SPSS, Inc, Chicago, IL, USA). Categorical variables were analysed using Pearson's chi-square test or Fisher's exact test, and continuous variables were analysed using one-way analysis of variance or Student's *t*-test. All *p*-values < 0.05 were considered statistically significant.

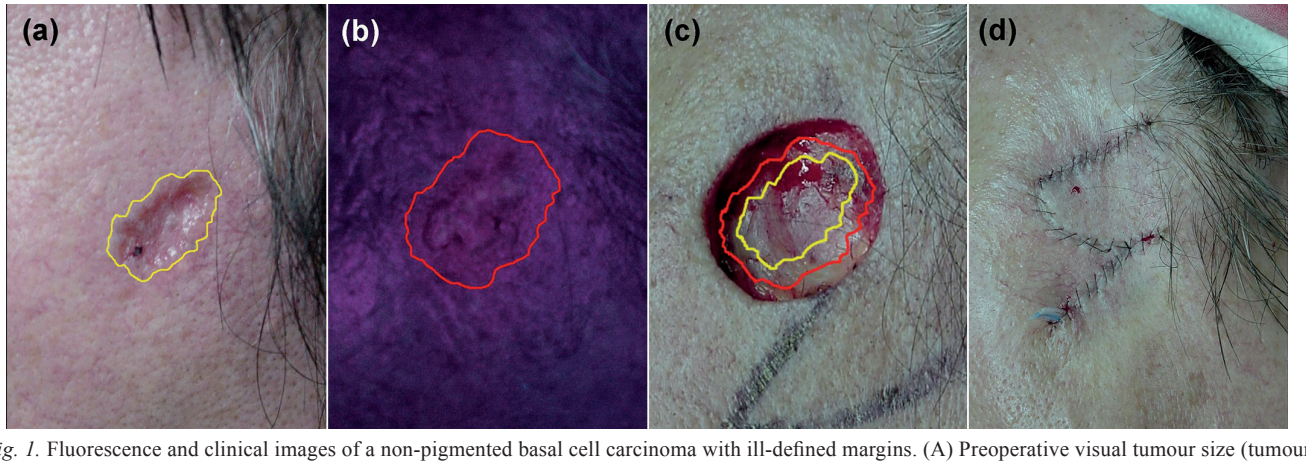

Fig. 1. Fluorescence and clinical images of a non-pigmented basal cell carcinoma with ill-defined margins. (A) Preoperative visual tumour size (tumour area: 167 mm^2; clinical margin: yellow line). (B) Fluorescence image after application of 20% aminolevulinic acid cream (fluorescence area: 409 mm^2; fluorescence diagnosis margin: red line). (C) The final defect after the first step of Mohs micrographic surgery (defect area: 595 mm^2; clinical margin: yellow line; fluorescence diagnosis margin: red line). (D) The defect covered by a local flap.

RESULTS

Clinicopathological and surgical features of pigmented basal cell carcinomas and non-pigmented basal cell carcinomas treated using Mohs micrographic surgery

The clinical features of PBCCs and non-PBCCs are summarised in Table I. No statistically significant differences were observed between these 2 groups. However, the histologic subtypes did differ significantly ($p = 0.006$, Table SI[1]), with the micronodular type occurring more frequently in the PBCC (12.6%, $n = 25$) than in the non-PBCC (3.4%, $n = 2$) group ($p = 0.043$) and the infiltrative type occurring more frequently in the non-PBCC (30.5%, $n = 18$) than in the PBCC (12.1%, $n = 24$) group ($p = 0.001$). A significantly higher proportion of non-PBCCs (66.1%, $n = 39$) than PBCCs (46.7%, $n = 93$) could be classified as aggressive lesions ($p = 0.009$).

The surgical features of PBCCs and non-PBCCs are compared in Table SI[1]. The mean number of Mohs stages required for complete tumour removal was significantly higher for non-PBCCs (2.34 ± 1.15) than for PBCCs (1.80 ± 0.98; $p = 0.001$). Division of each group into 4 classes according to Mohs stages also resulted in a significant inter-group difference ($p < 0.001$). Of the 199 PBCCs, 92 (46.2%) were completely removed by 1 Mohs stage, whereas 107 (53.8%) required 2 or more stages. In contrast, of the 59 non-PBCCs, only 19 (32.3%) were completely removed by 1 Mohs stage, and the other 40 (67.7%) required 2 or more stages for complete excision.

Table I. *Clinical features of non-pigmented and pigmented basal cell carcinomas (PBCC)*

Characteristics	Non-PBCC ($n = 59$)	PBCC ($n = 199$)	p-value
Age, year, mean ± SD	53.66 ± 13.08	56.64 ± 13.80	0.143
Sex, *n* (%)			0.777
Male	30 (50.9)	97 (48.7)	
Female	29 (49.1)	102 (51.3)	
Primary or recurrent, *n* (%)			0.097
Primary	45 (76.3)	170 (85.4)	
Recurrent	14 (23.7)	29 (14.6)	
Duration, month, mean ± SD	71.44 ± 90.83	63.20 ± 78.74	0.497
Tumour location, *n* (%)			
Nose	28 (47.4)	83 (41.7)	0.433
Periorbital area	12 (20.3)	36 (18.1)	0.697
Cheek	10 (17.0)	30 (15.1)	0.727
Auricle	1 (1.7)	6 (3.0)	0.584
Forehead/scalp/temple	6 (10.2)	29 (14.6)	0.386
Lip	2 (3.4)	7 (3.5)	0.963
Neck/chin	0 (0.0)	3 (1.5)	0.796
Others	0 (0.0)	5 (2.5)	0.219
Tumour size, mm, mean ± SD	16.34 ± 11.64	14.36 ± 9.77	0.193
Tumour area, mm^2, mean ± SD	143.3 ± 99.2	129.6 ± 76.9	0.514
Tumour depth, mm, mean ± SD	3.74 ± 2.68	3.73 ± 1.86	0.962
Ulceration, *n* (%)			0.956
No ulcer	37 (62.7)	124 (62.3)	
Ulcer	22 (37.3)	75 (37.7)	

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1783

The mean surgical margin was significantly smaller in the PBCC than in the non-PBCC group (6.28 ± 2.04 mm vs. 6.97 ± 2.15 mm; $p = 0.026$). Similarly, when lesions were divided into 4 classes according to the surgical margin, at 5 mm intervals, the inter-group difference was also statistically significant ($p = 0.021$). In addition, the mean margin area was significantly smaller in the PBCC than in the non-PBCC group (128.6 ± 108.7 mm^2 vs 194.4 ± 179.9 mm^2; $p = 0.001$), and the inter-group difference was significant when the lesions were divided into 4 classes according to area ($p = 0.005$).

When lesions were divided into 3 classes according to surgical depth, a significant difference was noted between the PBCC and non-PBCC groups ($p = 0.036$). Of the 199 PBCCs, 115 (57.8%) were completely removed at the level of subcutaneous fat, compared with 24 of the 59 (40.7%) non-PBCCs ($p = 0.021$). In contrast, 37.3% ($n = 22$) of non-PBCCs were completely removed at the level of the perichondrium/cartilage, compared with only 22.1% ($n = 44$) of PBCCs ($p = 0.019$).

Surgical features of PBCCs and non-PBCCs assessed visually or by fluorescence diagnosis prior to Mohs micrographic surgery

The surgical features of MMS did not differ significantly between PBCCs that were assessed by FD and those assessed visually (Table II). Among non-PBCCs, however, the mean number of Mohs stages required for complete tumour removal was significantly lower for lesions assessed by FD than for those assessed visually (1.77 ± 0.87 vs. 2.68 ± 1.18, $p = 0.003$), and the inter-group difference was statistically significant when each group was divided into 4 classes according to the number of Mohs stages ($p = 0.016$) (Table II). Of the 22 lesions assessed by FD, 10 (45.5%) were completely removed by a single Mohs stage, whereas 12 (54.5%) required 2 or more stages. Of the 37 lesions not assessed by FD, however, only 9 (24.3%) were completely removed by a single Mohs stage, whereas 28 (75.7%) required 2 or more stages. Lesions evaluated by FD had significantly smaller mean surgical margins (5.73 ± 1.86 mm vs. 7.76 ± 3.41 mm, $p = 0.013$) and smaller mean margin areas (118.6 ± 114.4 mm^2 vs 239.5 ± 197.2 mm^2; $p = 0.013$; Fig. 1) than lesions not evaluated by FD, although the surgical depth was similar in these subgroups ($p = 0.115$).

DISCUSSION

PBCC occurs more frequently in individuals with darker skin tones, probably because the peri- and intratumoural depositions of melanin are affected by the pigmentation of the normal surrounding skin (14). Correspondingly, PBCCs are more frequent in Asian than in Caucasian populations, with visible pigmentation

Table II. *Surgical features of pigmented and non-pigmented basal cell carcinomas (BCC) assessed visually or by fluorescence*

	Pigmented BCC			Non-pigmented BCC		
Characteristics	Non-FD group ($n=86$)	FD group ($n=113$)	p-value	Non-FD group ($n=37$)	FD group ($n=22$)	p-value
Mohs stage, mean ± SD	1.66 ± 0.90	1.86 ± 0.89	0.125	2.68 ± 1.18	1.77 ± 0.87	0.003
Mohs stage, *n* (%)			0.073			0.016
1st	48 (55.8)	44 (38.9)		9 (24.3)	10 (45.5)	
2nd	24 (27.9)	50 (44.3)		6 (16.2)	8 (36.4)	
3rd	9 (10.5)	10 (8.8)		10 (27.0)	3 (13.6)	
≥4th	5 (5.8)	9 (8.0)		12 (32.5)	1 (4.5)	
Surgical margin, mm, mean ± SD	6.19 ± 1.75	6.38 ± 2.67	0.562	7.76 ± 3.41	5.73 ± 1.86	0.013
Surgical margin, *n* (%)			0.126			0.206
≤5 mm	53 (61.6)	61 (54.0)		16 (43.3)	10 (45.5)	
6–10 mm	25 (29.1)	35 (31.0)		8 (21.6)	8 (36.3)	
11–15 mm	7 (8.1)	9 (8.0)		7 (18.9)	2 (9.1)	
≥16 mm	1 (1.2)	8 (7.0)		6 (16.2)	2 (9.1)	
Marginal area, mm^2, mean ± SD	121.0 ± 111.0	134.3 ± 107.0	0.391	239.5 ± 197.2	118.6 ± 114.4	0.011
Marginal area, *n* (%)			0.302			0.029
≤100 mm^2	48 (55.8)	49 (43.4)		11 (29.7)	13 (59.1)	
101–200 mm^2	27 (31.4)	50 (44.2)		9 (24.3)	7 (31.9)	
201–400 mm^2	7 (8.1)	9 (8.0)		10 (27.1)	1 (4.5)	
≥401 mm^2	4 (4.7)	5 (4.4)		7 (18.9)	1 (4.5)	
Surgical depth, *n* (%)			0.112			0.115
Subcutaneous layer	51 (59.3)	64 (56.6)		12 (32.4)	12 (54.5)	
Muscle fascia/muscular layer	12 (14.0)	28 (24.8)		11 (29.7)	2 (9.1)	
Perichondrium/cartilage	23 (26.7)	21 (18.6)		14 (37.9)	8 (36.4)	

FD: fluorescence diagnosis.

seen in approximately 75% of BCCs in Asian patients, (16, 20, 21) compared with fewer than 10% of BCCs in Caucasian patients (14–16). Most BCCs with visible pigmentation do not require preoperative methods to delineate the incision line prior to MMS because the tumour margins are already distinct. However, boundaries determined with the naked eye may not always correspond to the actual tumour margins.

Our finding that 77.1% of BCCs in Korean patients have visible pigmentation was similar to that of previous studies (16, 20, 21).

The most common histological growth pattern of PBCCs is the nodular/micronodular type (22). A study analysing histological patterns of 1,039 BCCs revealed a negative association between infiltrative type lesions and the presence of pigmentation (19). Pigmentation has been reported to be present in all histologic subtypes of BCC, except for the infiltrative and morphoeic types (23), reflecting its subtype-specific expression. We found that the infiltrative type lesion occurred less frequently, whereas the nodular or nodulocystic type was more frequent in PBCCs than in non-PBCCs and that the percentage of the aggressive type was lower in PBCCs. These findings suggest that PBCCs may be associated with a lower risk of invasion and less aggressive behaviour than non-PBCCs.

BCCs with a more aggressive histological pattern require more aggressive treatment (19). A retrospective study of 342 BCCs treated using MMS showed that lesions with a more aggressive histology required significantly more surgical stages to achieve clear tumour margins (24). PBCCs are more likely to be excised completely than non-PBCCs, because their margins are more readily discernible because of the presence of melanin, and are therefore less likely to recur (14, 22). We found that excision of PBCCs required fewer Mohs stages, thereby resulting in narrower surgical margins, smaller margin areas, and less surgical depths than excision of non-PBCCs. These findings suggest that the PBCCs were narrower, situated less deeply, and/or were less invasive than the non-PBCCs. Our histologic and surgical findings indicate a relationship between pigmentation and biological behaviour such that subclinical infiltration is less for PBCCs than for non-PBCCs. Hence, pigmentation may be associated with a better prognosis of BCCs in Asian patients treated using MMS.

The findings of our study also suggested that FD using topical ALA increased the surgical efficacy of MMS by delineating margins in non-PBCCs, although this was not the case for PBCCs. Non-PBCCs assessed by FD required fewer Mohs stages and resulted in narrower surgical margins and smaller margin areas after complete tumour removal than non-PBCCs evaluated only visually, with 45.5% and 24.3%, respectively, requiring a single Mohs stage for complete tumour excision. These results concur with those of previous studies (7, 17) and indicate that the fluorescence pattern generated by FD is more strongly associated with tumour histopathology than clinical demarcation. Thus, FD may help detect occult tumour borders of ill-defined non-PBCCs prior to MMS.

Several previous studies found that clinical detection of tumour margins is equal or superior to that achieved using FD (25–27). In contrast, we found that FD was

superior for non-PBCCs in this respect. The better correlation between fluorescence and microscopic margins in this study was probably attributable to a number of factors, including the specific clinical subtypes of the BCCs assessed and the longer period for which the photosensitiser was left on before the fluorescence margins were measured (3 vs 6 h) (28). However, surgical depth was not significantly different between the 2 groups for non-PBCCs. Therefore, further evaluation of FD, including a comparison with new techniques, for defining tumour depth is needed if the efficacy of MMS is to be further increased.

In addition, we also compared recurrence rate, wound repair and functional outcomes between the FD and non-FD group for patients with PBCCs and non-PBCCs in terms of Mohs complexity (data not shown). However, there were no differences between the groups, and our results show that FD did not confer any benefit in this respect, despite resulting in fewer Mohs stages and a smaller mean surgical margin.

Although FD is generally a robust and effective technique, it can still give rise to both false-positive and false-negative findings. The former may occur due to a fluorescent signal generated in benign tissue, including scars, and sites of infection and inflammation (29–31). Conversely, false-negative results can occur if the tumours are deeply located or have low cellularity (7). Melanin in PBCCs can also result in false-negative FD results as it prevents the penetration of red light (32). In agreement with these findings, we observed that FD using topical ALA did not enhance surgical outcomes for PBCCs treated using MMS.

In our study, although FD using topical ALA improved surgical outcomes (fewer Mohs stages and a smaller mean surgical margin) for the non-PBCCs during MMS, it also seems to be an impractical and inefficient technique due to its long incubation time (6 h). The need to apply FD 6 h prior to MMS clearly presents a practical challenge if patients need to be admitted in order to have this applied at 2 AM to allow the MMS procedure to start at 8 AM, or alternatively, surgery may be completed very late if the necessary multiple stages of Mohs commence at 2 PM. Further, in order to simplify fluorescent imaging to make it as realistic and relevant as possible to the clinical situation, fluorescence borders on Wood lamp examination were read by eye by a dermatologic surgeon. Thus, the fluorescent boundaries are clearly observer dependent. Previous reports have indicated that the fluorescence peak and vanishing points are very difficult to ascertain (33, 34), so we recently performed FD combined with spectrophotometry in order to define more accurate fluorescence margins and to reduce the incubation time of photosensitisers. Thus, although FD improves surgical outcomes in non-PBCC cases, future larger scale studies using a Wood lamp, computed imaging technology, and spectrophotometric readings with variable incubation times for photosensitisers, are needed to overcome this major limitation of FD and make it clinically applicable prior to MMS.

This study had several limitations, including its retrospective design, in which the lesions additionally examined by FD were not randomly allocated. In addition, all of the patients in our study were Korean. Further prospective studies that include different ethnic groups (e.g. Caucasians, Africans, and Asians) are therefore required to confirm our results. Another limitation of this study was the bias introduced by comparing tumour fluorescence with postoperative defect size after MMS. After surgery, scars tend to expand because of changes in skin elasticity and retraction. Thus, the actual excision size and free margins are often 10% to 20% smaller than the size of the resulting scar, depending on tumour location. An additional bias related to the mechanics of MMS may have resulted in the underestimation of margins on using fluorescence. Furthermore, as Mohs layers are extracted with 2-mm margins, the final MMS layer includes a perimeter of normal tissue, increasing the size of the defect when margins are based on microscopic evaluation. This may have resulted in us significantly underestimating tumour size, both clinically and by fluorescence, relative to the Mohs margins.

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The authors declare no conflict of interest.

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