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An Assessment of Histological Margins and Recurrence of Melanoma In Situ

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Background: Melanoma in situ (MIS) accounts for up to 27% of all melanomas. MIS has no metastatic potential and the aim should be to excise the lesion completely with a clear histological margin, although margin clearance remains undefined. We aimed to assess the relation of histological excision margins of MIS to recurrence and progression to invasive disease.
Methods: We analyzed all patients with MIS excised by wide local excision or staged excision in our institution over a 5-year period from December 2008 to January 2014 using a prospectively maintained database. Clinicopathologic details included patient demographics, anatomical site of lesion, melanoma subtype, histological excision margin, and recurrence.
Results: A total of 410 patients had MIS excised during this time, the majority of which were lentigo maligna subtype (79%). The average histological excision margin was 3.7 mm. The rate of recurrence was 2.2% (9/410), with a median follow-up of 23 months. Lentigo maligna had a similar rate of recurrence to non-lentigo MIS (2.3% vs 1.2%) ($P = 0.69$). The mean excision margin of those that recurred was 1.9 mm compared with an average of 3.8 mm in those that did not. The rate of recurrence of MIS with histological excision margin ≤3.00 mm was 3.8% compared with 0.5% in those with a histological margin >3.00 mm ($P = 0.03$). One case of MIS recurred as invasive disease.
Conclusion: At institutions using wide local excision or staged excision for MIS, a histological margin of >3.0 mm is required to achieve a low recurrence rate. *(Plast Reconstr Surg Glob Open 2015;3:e301; doi: 10.1097/GOX.0000000000000272; Published online 2 February 2015.)*

Melanoma in situ (MIS) is an early form of melanoma with the atypical melanocytes confined to the epidermis. MIS accounts for up to 27% of all melanomas, with over 60,000 cases of MIS diagnosed in the United States in 2013.[1,2] The risk of MIS converting to invasive melanoma, if untreated, is unknown, but the lentigo maligna (LM) subgroup carries a 5–15% lifetime risk of progression.[3]

MIS is becoming increasingly prevalent as the population ages, with risk factors, including sun exposure and immunosuppression, becoming more widespread. Therefore, optimal treatment for patients with MIS is becoming increasingly necessary. Although MIS is a precursor for invasive disease, it has no potential for metastatic spread, and the aim should be to excise the lesion completely with a clear histological margin.[4] LM often has wide invisible extensions resulting in frequent reexcision. Local recurrence of LM occurs in 5% of patients by 2 years.[5]

Current National Comprehensive Cancer Network guidelines for MIS recommend a 5-mm surgical margin of resection, but this margin is frequently

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insufficient to prevent recurrence.[6] A large study by Kunishige et al[7] in 2012 suggested that MIS should be treated similarly to early invasive melanoma, with surgical margins of at least 9 mm. A further study by Akhtar et al[8] suggested that narrow margin excisions are unlikely to lead to recurrence and that wide margins may be unnecessary. The aim of this study was to assess the impact of histological excision margins to recurrence and progression to invasive disease for MIS.

MATERIALS AND METHODS

We reviewed a prospectively maintained pathology database of all patients with MIS excised at our institution over a 5-year period from December 2008 to January 2014. Selection criteria included all patients who had biopsy-proven (excisional or incisional) primary MIS. The finding of single scattered atypical melanocytes was not considered sufficient for diagnosis of LM. All patients were treated by wide local excision (WLE) or staged excision. Patients undergoing staged excision only had the final histologic margin included in the analysis of margins. Mohs micrographic surgery is not performed at our institution. Specimens were formalin fixed and underwent serial sectioning and immunohistochemical staining. All cases were discussed at a skin cancer multidisciplinary meeting, and consensus was reached for each individual case.

Clinicopathologic details recorded included patient demographics, anatomical location, melanoma subtype, histological excision margin, and recurrence. Histological excision margins were measured by the pathologist in formalin-fixed specimens following surgical excision. Surgical margins of excision were not recorded given the retrospective nature of the study. The standard margin of excision for MIS in our institution was 5 mm when possible, as per recommended guidelines.[4] For those who underwent a WLE that was clear of disease, the narrowest width of the specimen was taken as the histological margin of excision. Recurrence was defined as reappearance of tumor within or adjacent to the scar, with an intraepidermal component, and represented inadequate initial excision. Follow-up period was determined by the last outpatient review. Those patients lost to follow-up were excluded. Statistical analyses were performed using Fisher's exact test, with statistical significance determined as $P < 0.05$.

RESULTS

From 2009 to 2014, 458 patients were treated for primary MIS. Forty-eight patients (10.5%) were lost to follow-up and were excluded from the study. These patients were followed up by their referring physician. The final cohort consisted of 410 patients (52.2% female, 47.8% male) with a median age of 69 years (range, 22–98 years). The median follow-up was 23 months (range, 1–65 months). The number of MIS excised per year increased over the study period, with 45 cases in 2009 compared to 111 cases in 2013 (Fig. 1).

The most common site for the primary lesion was the face (67.1%), followed by the upper limb (9%) and scalp and neck (8.3%) (Fig. 2). The anatomical distributions of primary lesions varied according to gender, with men having a greater proportion on the scalp and neck area (14.8% vs 2.3%) ($P = 0.001$), whereas women had a greater proportion on the lower limb (14.0% vs 1.5%) ($P < 0.001$). Within our cohort, 324 cases of MIS were LM subtype (79%), with the majority of these occurring on the face (81.4%) and scalp and neck (5.9%).

The average histological excision margin was 3.7 mm (range, 0.2–14 mm). The rate of recurrence was 2.2% (9/410), with a mean time to recurrence of 29.6 months (range, 8–47 months). This is comparable to recent international studies (Table 1). LM had a similar rate of recurrence compared with nonlentigo MIS (2.3% vs 1.2%) ($P = 0.69$). The majority of recurrences occurred on the face (Table 2). The mean excision margin of those that recurred was 1.9 ± 1.3 mm compared with a mean of 3.8 ± 2.3 mm in those that did not. There was no case of recurrence with a histological excision margin of ≥5 mm (Table 3). The rate of recurrence of lesions with histological margin ≤3.00 mm was 3.8% compared with 0.5% in those lesions with a histological margin >3.00 mm ($P = 0.03$). One case of MIS recurred as invasive disease. Initial excision showed a LM MIS with involved peripheral resection margins. This recurred after 6 months, and further excision showed a pT1a LM melanoma of Breslow thickness 0.5 mm.

DISCUSSION

Worldwide, MIS is becoming increasingly prevalent. Contributing to this increase is an ageing pop-

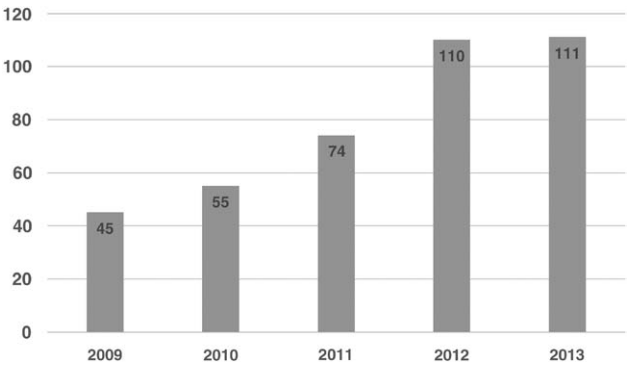

Fig. 1. Number of MIS excised per year.

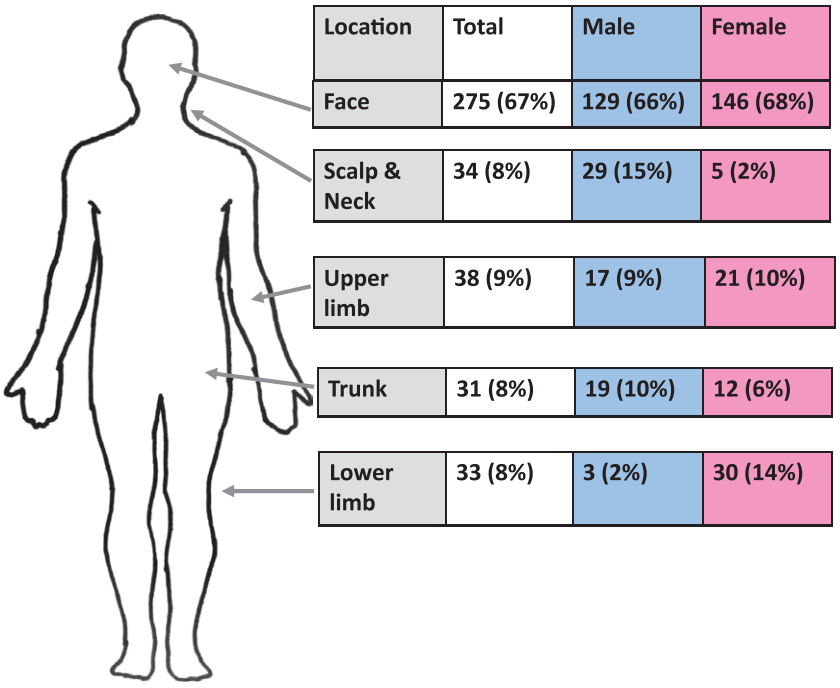

Fig. 2. Location of primary melanoma in situ.

Table 1. Comparison of Recurrence Rates in the Literature

Study	No. MIS	Follow-up (months)	Recurrence Rate (%)
Kunishige et al[7]	1072	56	0.3
Current study	410	26	2.2
Bricca et al[16]	331	58	0.3
Akhtar et al[8]	192	31	2.9
Bene et al[17]	167	63	1.8
Huilgol et al[18]	125	38	2.0

ulation with a significant history of sun exposure. In our institution, the number of cases excised increased by over 160% in the time period studied. National melanoma statistics show that overall there is an increasing prevalence of melanomas being diagnosed; however, the rate of increase of MIS is greater than that of invasive disease.[9] This may reflect the benefit of public awareness campaigns.

The anatomical distributions of primary lesions varied according to gender, with men having a greater proportion on the scalp and neck area, whereas women had a greater proportion on the lower limb. This may be explained, in part, by the differences in clothing between men and women. Rates of melanoma tend to be highest on intermittently exposed sites among people under 40 years old (ie, trunk or lower limbs), whereas for men and women over 60 years, melanoma is most commonly found on more chronically exposed sites such as the head and neck.[10]

The rate of recurrence in our study is similar to recent international studies. There was no significant difference in the rate of recurrence of LM versus non-LM lesions. All excisions of MIS in this study were carried out by WLE or staged excision, which is common practice in many plastic surgery units in Great Britain and Ireland. Mohs micrographic surgery provides the advantages of complete margin assessment, tissue conservation, and high cure rates, but this technique is not carried out at our institution. Controversy exists regarding the use of Mohs surgery for the treatment of MIS, with some authors highlighting the difficulties in recognizing MIS on frozen sections.[11]

The histological evaluation of MIS, particularly LM, presents a challenge for pathologists as certain histological criteria are often difficult to distinguish from benign changes that occur secondary to sun exposure. The presence of widespread atypical melanocytes in the background of long-standing sun damage is highly indicative of LM.[12] However, the significance of individual melanocytes at the tumor margin that remain after surgical excision is unclear. Gorman et al[13] demonstrated that for LM, melanocyte count at the excision margin was predictive of recurrence. The propensity for LM to recur after apparently adequate surgery is associated with significant morbidity. Clinical recurrence may relate to both wide subclinical extension of atypical melanocytes and limitations in margin assessment. Our results demonstrate that for WLE or staged excision, a

Table 2. Clinicopathological Details of Lesions That Recurred

No.	Age (years)	Histological Subtype	Location	Histological Excision Margin	Time to Recurrence (months)
1	74	LM	Face	Involved	6
2	41	LM	Face	0.5 mm	47
3	32	LM	Face	1.0 mm	18
4	79	LM	Face	1.0 mm	24
5	71	LM	Face	2.0 mm	30
6	90	LM	Face	2.0 mm	41
7	68	LM	Neck	3.0 mm	40
8	74	LM	Neck	3.0 mm	30
9	67	Non-LM	Upper limb	4.5 mm	28

Table 3. Histological Excision Margin and Number of Recurrences

Histological Margin (mm)	No. Patients	Recurrence	Recurrence Rate (%)
<0.3	2	1	50.0
0.3–1.0	52	3	5.8
1.1–2	90	2	2.2
2.1–3	67	2	3.0
3.1–4	51	0	0
4.1–5	65	1	1.5
5.1–6	35	0	0
6.1–7	15	0	0
7.1–8	14	0	0
8.1–9	5	0	0
9.1–10	9	0	0
>10	6	0	0

histological margin of >3.0 mm is required to achieve a low recurrence rate.

The rate of progression of MIS to invasive disease is poorly understood, yet it has been reported that LM carries a 5–15% lifetime risk of developing an invasive disease.[3] This risk of invasive progression may be related to the size of the primary lesion, with large lesions harboring invasive nests.[3] In our study, there was one case of MIS that recurred as invasive melanoma 6 months after initial excision. This was a pT1a LM melanoma. Previously reported studies have shown that 23% of recurrent MIS have an invasive component, with a mean Breslow thickness of 0.94 mm.[14] It has also been postulated that recurrent lesions may track along the original scar, thereby resulting in larger wounds.

Several limitations exist within this study. Surgical margins of excision were not recorded due to the retrospective nature of the study. Furthermore, all lesions excised were by staged excision and not by Mohs micrographic surgery. In Mohs surgery, the entire margin of the specimen is examined compared to standard pathological assessments where only 0.5–5% of the margin is examined.[15] Ideally, all specimens should be excised by Mohs, but this would be far too laborious and resource depleting.

CONCLUSIONS

In conclusion, this study demonstrates that, at institutions using WLE or staged excision, a histological margin of >3.0 mm is required to achieve a low recurrence rate. The difference in recurrence rates of LM and non-LM subtypes was not significant, and so we conclude that they do not require different histological clearance. Future prospective, randomized controlled trials comparing surgical treatment options and excision margins for MIS are warranted to develop evidence-based guidelines.

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