ORIGINAL ARTICLE

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Association between excision margins and local recurrence in 1407 patients with primary in situ melanomas

Licata Gaetano, MD,[a] Birra Domenico, MD,[b] Serigne N. Lo, PhD,[c,d] Tasnia Hamed, MS,[c] Alison J. Potter, MD,[c,d,e] John F. Thompson, MD,[c,d,f] Richard A. Scolyer, MD,[c,d,e,g] and Pascale Guitera, MD, PhD[c,d,h]

Background: Reliable evidence to guide the management of melanoma in situ (MIS) and minimize the risk of recurrence is lacking.

Objective: To identify clinicopathological predictors of local recurrence (LR) in patients with MIS and evaluate long-term outcomes according to pathological excision margins.

Methods: A case-control study of patients with MIS treated at a large Australian melanoma treatment center from January 2008 to December 2012 was undertaken. Clinicopathological characteristics of patients who developed LR and those who did not were compared.

Results: LR developed in 34 of 1407 patients with MIS (2.5%). Median time to LR was 20 months. The primary lesion was removed with pathological margins <4 mm ($P < .001$) in 67.6 % of patients with LR. Four patients died of metastatic melanoma following LR. Comparing patients with pathological margins <4 mm and ≥4 mm, the former were older (>60y, $P < .001$), more frequently had MIS on the head or neck ($P < .001$), had a greater LR rate ($P < .001$), and had a higher mortality from all causes ($P < .001$).

Limitations: Retrospective, single-institution study.

Conclusions: Pathological margins of ≥4 mm should be considered for patients with MIS who are treated with standard surgical excision and assessed by examining serial slices taken from the formalin-fixed, paraffin-embedded specimen. (JAAD Int 2022;8:102-8.)

Key words: excision margins; in situ melanoma; local recurrence; melanoma; wider excision.

INTRODUCTION

In melanoma in situ (MIS), malignant melanocytes are present but confined to the epidermis. The reported incidence of MIS is steadily increasing worldwide. In Australia, a country with one of the highest age-standardized incidence rates, new cases of MIS increased by 115%, from 32 per 100,000 persons in 2004 to 68 per 100,000 persons in 2015, and the rate was estimated to have reached 81 per 100,000 persons in 2019.[1] Lentigo maligna (LM) is a subtype of MIS that arises on chronically sun-damaged skin and is most commonly diagnosed in older people.[2] LM may represent 50% of MIS in Australia and New Zealand because of high UV exposure.[3] In this article, we will use the term MIS to encompass all subtypes of MIS and the term LM only when the subtype of the MIS was known and categorized as LM in the pathology report.

Postulated reasons for the increasing incidence of MIS include increased patient awareness, better detection methods, overcalling benign lesions as MIS, and an increase in average life span. Increasing longevity means that it has become common for patients with MIS to have many and/or significant comorbidities, particularly those with LM because they are generally older.[3]

Surgical excision is the gold standard for the treatment of MIS because it allows pathological evaluation of the entire lesion, giving some confidence that the MIS does not have an invasive component and indicating that the margins are likely to be sufficient.[4-6] Mohs surgery and complete circumferential peripheral and deep margin assessment (CCPDMA) are techniques that can be used to better evaluate margins. All national guidelines recommend treatment by wide local excision including the skin around the MIS with a clinical safety margin of at least 5 mm.[7,8] There is often confusion between clinical (surgical) margins and pathological margins. Most guidelines recommend clinical excision margins, with the aim of achieving complete histological clearance. Correlation between clinical and pathological margins is generally poor: Crouch et al,[8] for example, reported that >3 mm pathological margins corresponded to >6.5 mm margins clinically (and resulted in a local recurrence rate of 2.6 % compared to a 27.2%

recurrence rate for pathological margins <3 mm) in a series of Australian patients with LM. However, the evidence supporting excision margin recommendations for MIS is not strong and most guidelines recommended surgical excision margins ≥5 mm from the clinically apparent border of the lesion, in particular for LM, because of the frequency of subclinical peripheral extension of atypical melanocytes, which are associated with an increased risk of local recurrence.[9] However, wider margins, especially on the face, may result in unsatisfactory esthetic and functional outcomes for the patient. Other treatments such as topical imiquimod cream and radiotherapy have been proposed to treat LM involving large areas of skin, and it has been suggested that these modalities may achieve lower long-term recurrence rates than surgery and avoid surgical disfigurement.[10-12] Moreover, these treatments are options for patients who are not eligible for surgery or not willing to undergo it.[13] Another option for management of LM occurring late in life is to simply "watch-and-wait", as the reported rate of transformation to invasive melanoma is low: 3.5% per year (95% confidence interval [CI]: 2.5% to 5.0%).[14]

The purpose of this study was to identify clinicopathological predictors of local recurrence in a large cohort of patients with MIS and assess the effect of excision margins on long-term outcomes for patients with MIS.

CAPSULE SUMMARY

- To provide more reliable evidence to guide the management of melanoma in situ, clinicopathological and follow-up data for 1407 patients were analyzed

- The risk of recurrence, which occurred in 2.5% of the patients overall, was substantially lower if pathological excision margins of ≥4 mm were achieved

METHODS

Patients who had MIS diagnosed between January 2008 and December 2012 and who had complete clinical, pathologic, and follow-up data available were identified from the Melanoma Institute Australia (MIA) research database. Because our objective was to assess LR, we did not exclude patients with previous or subsequent in situ or invasive melanomas from the study cohort. We then identified the subgroup of MIS patients with histologic margins <4 mm and therefore deviating from the clinically determined surgical excision margin of ≥5 mm recommended in the Australian Melanoma Management Guidelines and several other national guidelines.[1-5]

The peripheral histologic margin of 4 mm was selected because we have previously shown a 14% shrinkage rate of histologic margins compared with precisely measured clinical excision margins in wide excision specimens. This shrinkage was consistent among melanomas across all patients and excision sites.[10] Our hypothesis was that a 4-mm histological margin approximates the minimum 5-mm surgical/clinically determined excision margin recommended in most melanoma management guidelines and that it was the appropriate threshold to assess differences in local recurrence outcomes.

We then selected 2 cohorts for comparison: (1) all patients with LR (defined as recurrence either as in situ or as invasive melanoma, arising <5 cm from the edge of the primary tumor wide excision margins), and (2) all patients with no LR irrespective of the pathologic margins (Table I). To reduce the imbalance in terms of selected patient characteristics and lesions' features between the 2 cohorts, we used propensity score matching to adjust for confounding between MIS patients with and without LR. Each LR case was directly matched with 1 non-LR control case using individual propensity scores based on a multivariable binary logistic regression analysis that included sex, age, anatomic site, and duration of follow-up. Patient characteristics and clinical outcomes for the 2 excision margin groups (<4 vs ≥4 mm) were compared using the cohorts before and after matching. Patient outcomes were examined using information recorded in the database and their medical records, and the types of treatment that the patients received (ie, surgery, radiotherapy, application of imiquimod, or observation) were evaluated. For patients who underwent surgery, we assessed whether or not they had a wide excision after the first biopsy or excision. We also recorded whether the surgical margins were reported on pathology to be clear or involved, the type of reconstruction that was used (direct closure, flap, graft), and whether patients had adjuvant local treatment (imiquimod or radiotherapy) after their wide excision. Finally, the data related to follow-up were evaluated, and for those patients who had LR, the number of recurrences, the time interval between treatment and recurrence, and how they were treated were recorded.

Statistical Analysis

Continuous variables were described using means and standard deviations or by medians and interquartile ranges according to data distribution, while categorical variables were reported as numbers and percentages. Analysis of categorical variables was performed using either the Mann-Whitney U test or χ^2 test, as appropriate.

All analyses were performed using SPSS version 15.0 (IBM) and R version 3.6.1. A two-sided *P*-value of <.05 was considered statistically significant.

RESULTS

From 2008 to 2012, details of 1407 patients with MIS were recorded in the MIA database.

From this unmatched cohort, we identified 34 patients (2.5%) with LR, while 1373 (97.5%) did not develop LR and formed the control group. There were no significant differences in age or gender between the patients who developed LR and those who did not. Comparing the location of the tumors, patients with LR were more likely to have had MIS in the head and neck region (61.8%), (*P* < .001). There was also a statistically significant difference for excision margins; pathological margins <4 mm were recorded for 67.6% of patients with LR, compared with 27.7% of the controls (*P* < .001). The 34 patients with LR comprised 16 patients who had an initial diagnosis of MIS (not otherwise specified) and 18 with LM. Eight of the 34 patients who developed LR had a history of a previous melanoma (5 invasive [4 superficial spreading melanomas and 1 lentigo maligna melanoma] and 3 in situ) and one had been treated with immunosuppressive agents. Initially, 16 of the 34 patients did not have a formal wider excision of their MIS because of anatomic limitations (14 patients) or patient refusal (2 patients); of these, 3 received imiquimod, 4 had radiotherapy, and 9 declined further treatment. Of the 34 primary tumors 18 were treated with a wider excision after an initial biopsy; the median time to wider excision was 36 days (range = 32-109 days). For these patients who developed LR, the median time to LR was 20 months. Median follow-up was for the whole cohort 5.7 years (95% CI = 5.2-6.2 years), and that for the matched cases and control cases was 4.4 years (95% CI = 0.4-9.7) and 6.2 years (95% CI = 2.0-10.3), respectively (Table I). The median time to the wider excision was not significantly different for patients with LR and controls. The LR was treated surgically in

Table I. Characteristics of patients with and without local recurrence before and after matching

	Before matching			After matching		
Characteristics	Cases with LR (N = 34)	Control (N = 1373)	P value	Cases with LR (N = 34)	Matched control (N = 34)	P value
Sex*						
Female	16/34 (47.1%)	623/1373 (45.4%)	.8456	16/34 (47.1%)	15/34 (44.1%)	.8076
Male	18/34 (52.9%)	750/1373 (54.6%)		18/34 (52.9%)	19/34 (55.9%)	
Age (categorized)*						
≤60	14/34 (41.2%)	695/1373 (50.6%)	.2767	14/34 (41.2%)	13/34 (38.2%)	.8043
>60	20/34 (58.8%)	678/1373 (49.4%)		20/34 (58.8%)	21/34 (61.8%)	
Margin group						
<4 mm (group 1)	23/34 (67.6%)	381/1373 (27.7%)	<.0001	23/34 (67.6%)	15/34 (44.1%)	.0507
≥4 mm (group2)	11/34 (32.4%)	992/1373 (72.3%)		11/34 (32.4%)	19/34 (55.9%)	
Primary site*						
Head & neck	21/34 (61.8%)	295/1373 (21.5%)	<.0001	21/34 (61.8%)	20/34 (58.8%)	.5499
Lower limb	5/34 (14.7%)	257/1373 (18.7%)		5/34 (14.7%)	2/34 (5.9%)	
Trunk	3/34 (8.8%)	456/1373 (33.2%)		4/34 (11.8%)	6/34 (17.6%)	
Upper limb	5/34 (14.7%)	365/1373 (26.6%)		4/34 (11.8%)	6/34 (17.6%)	
Follow-up time*						
N	34	1117	.0233	34	34	.0002
Median (range)	4.4 (0.4, 9.7)	2.2 (0.6, 10.3)		4.4 (0.4, 9.7)	6.2 (2.0, 10.3)	
Presence of associated nevus[†]						
No	26/32 (81.3%)	37/37 (100%)	.631			
Yes	6/32 (18.8%)	0/37 (0.0%)				
Histogenesis						
In situ with dysplastic nevus	0/34 (0.0%)	23/1373 (1.7%)				
Regression						
Absent	0/34 (0.0%)	4/1373 (0.3%)	.0657	3/34 (8.8%)	1/34 (2.9%)	.3559
Early (mild or focal)	2/34 (5.9%)	13/1373 (0.9%)		1/34 (2.9%)	0/34 (0.0%)	
Intermediate (med fibrosis)	0/34 (0.0%)	2/1373 (0.1%)		30/34 (88.2%)	33/34 (97.1%)	
Late (ext fibrosis)	1/34 (2.9%)	15/1373 (1.1%)				
Not reported	31/34 (91.2%)	1339/1373 (97.5%)				

*Indicates variable is included in the matching process.
[†]Presence of associated nevus had more than 95% missing data.

30 cases, and in 4 cases with radiotherapy. Once the LR was treated, the patients underwent close follow-up: 10 patients had a second recurrence, of which 5 were treated surgically (3 by topical application of imiquimod and 2 using radiotherapy). LR was associated with further spread (metastasis) in 4 cases, and all 4 patients ultimately died of metastatic melanoma following locoregional recurrence, with no other primary melanoma to explain the distant metastasis. Pathology was available for review in 3 of these cases. Evidence of early dermal regression was seen in 2 cases, while the third case developed invasive disease at the MIS scar site within 6 months of excision.

Matching cases by age, sex, and site of the lesion (the body site was matched as closely as possible) to assess the impact of resection margins, we selected 38 cases with margins <4 mm and 30 cases with margins ≥4 mm. In the matched cohort, there were apparent differences in the overall mortality and LR

rates associated with<4 mm and ≥4 mm margins: with pathological margins <4 mm more frequently recorded for subjects with LR (67.6%) compared to the matched controls without LR (44.1%), but these differences did not reach statistical significance (P values .093 and .051, respectively—Table I).

Based on the differences between the margins, to assess the impact on recurrence, we divided the entire cohort of 1407 patients into 2 groups: 404 patients (group 1) with excision margins <4 mm and 1003 patients (group 2) with margins ≥4 mm.

There was a significant difference with respect to age: in patients>60 years of age, the excision margins were <4 mm more frequently (61.1% vs 45%, $P < .001$). Significant differences were also observed for the site of MIS, with margins <4 mm more frequent for the head and neck in group 1 (41.8% vs 14.7%, $P < .001$). No differences were observed in the duration of follow-up. In patients with margins <4 mm, there was a higher mortality

Table II. Baseline patient characteristics and clinical outcome for <4 and ≥4 mm margin groups before and after matching

	Before matching			After matching		
Characteristics	<4 mm (N = 404)	≥4 mm (N = 1003)	P value	<4 mm (N = 38)	≥4 mm (N = 30)	P value
Patient characteristics						
Gender						
Female	174/404 (43.1%)	465/1003 (46.4%)	.2619	19/38 (50.0%)	12/30 (40.0%)	.4110
Male	230/404 (56.9%)	538/1003 (53.6%)		19/38 (50.0%)	18/30 (60.0%)	
Age (categorized)						
≤60	157/404 (38.9%)	552/1003 (55.0%)	<.0001	13/38 (34.2%)	14/30 (46.7%)	.2972
>60	247/404 (61.1%)	451/1003 (45.0%)		25/38 (65.8%)	16/30 (53.3%)	
Primary site						
Head & neck	169/404 (41.8%)	147/1003 (14.7%)	<.0001	28/38 (73.7%)	13/30 (43.3%)	.0319
Lower limb	43/404 (10.6%)	219/1003 (21.8%)		4/38 (10.5%)	3/30 (10.0%)	
Trunk	101/404 (25.0%)	358/1003 (35.7%)		2/38 (5.3%)	8/30 (26.7%)	
Upper limb	91/404 (22.5%)	279/1003 (27.8%)		4/38 (10.5%)	6/30 (20.0%)	
Follow-up time						
N	357	794	.1019	38	30	.0393
Median (range)	2.0 (-3.0, 10.3)	2.4 (-3.6, 10.3)		5.1 (0.4, 10.3)	5.9 (1.0, 10.3)	
Clinical outcome						
Number of deaths						
Alive	323/357 (90.5%)	756/793 (95.3%)	.0015	32/38 (84.2%)	29/30 (96.7%)	.0933
Death	34/357 (9.5%)	37/793 (4.7%)		6/38 (15.8%)	1/30 (3.3%)	
Locoregional recurrence						
No	381/404 (94.3%)	992/1003 (98.9%)	<.0001	15/38 (39.5%)	19/30 (63.3%)	.0507
Yes	23/404 (5.7%)	11/1003 (1.1%)		23/38 (60.5%)	11/30 (36.7%)	
Head & neck	15/169 (9%)	6/147 (4%)		15/28 (54%)	6/13 (46%)	
Lower limb	4/43 (9%)	1/219 (0.5%)		4/4 (100%)	1/3 (33%)	
Trunk	2/101 (2%)	2/358 (0.6%)		2/2 (100%)	2/8 (25%)	
Upper limb	2/91 (2%)	2/279 (0.7%)		2/4 (50%)	2/6 (33%)	

from all causes (9.5% vs 4.7%, $P < .001$) and LR was more frequent (5.7% vs 1.1 %, $P < .001$—Table II).

Thirty-four patients developed LR, of whom 23 (67.6%) were in group 1 (margins <4 mm) and 11 in group 2 (margins ≥4 mm) (32.4%) ($P < .001$). The difference in LR rates between groups 1 and 2 when matching was performed for age, sex, and localization (LR rates 60.5% and 36.7%, respectively) was of borderline significance ($P = .051$) (Table II). There were differences in the proportions of deaths from any cause for MIS treated with margins <4 mm or ≥4 mm, with 9.5% dying in group 1 and 4.7% in group 2 ($P = .0015$). After matching the 2 groups with respect to age, sex, and localization, the difference in terms of deaths was apparently even greater (15.8% vs 3.3%), but with reduced absolute numbers, the difference was no longer statistically significant ($P = .093$).

DISCUSSION

The management of MIS is often complicated by difficulty in identifying the clinical extent of the lesion or by its location in sites that make obtaining adequate clearance margins challenging, and sometimes by the age or comorbidities of the patient that make further surgery inappropriate.[3,15]

The best way to evaluate the adequacy of management of MIS is to document long-term local recurrence rates, but many studies report only short-term data. Some argue that the wide variation of outcomes reported in the literature is due to different surgical techniques and methods of pathological assessment of margins (standard excision vs Mohs surgery or CCPDMA) or the failure to differentiate between clinical and pathological margins. It could also be due to a "field defect," with development of another melanoma not directly related to the initial lesion.

Many studies have confirmed that complete excision of MIS, with clinically determined excision margins of ≥5 mm and if possible ≥10 mm, reduces the risk of LR, in particular for the LM subtype on the head and neck.[6,16,17] Others have argued that it is not a question of subtype being LM but rather a question of location on the head or neck. Kunishige et al[6] published a large series of LM and MIS showing that

subtype was not an independent risk factor but that margins mattered and depended on location: 12 mm margins for the head and neck versus 9 mm for the trunk and extremities resulted in negligible LR rates after long-term follow-up.[18]

Most guidelines indicate that an involved margin[19] is not acceptable, and the results of our study support this, further showing that <4 mm pathological margins carried a higher risk of recurrence than ≥4 mm margins (5.7% vs 1.1%, $P < .01$) after 2 years of follow-up. Our finding that 4 patients died of metastatic melanoma following recurrence in the field of the operated MIS, with no other primary melanoma to explain distant metastasis, suggests that they died of invasive melanoma that had arisen from MIS. That the site of MIS was the source of the ultimately progressive disease is supported by the pathology review process, which identified local recurrence of invasive melanoma adjacent to the site of previous MIS excision in 1 case. A further 2 cases demonstrated early regressive changes within the dermis, likely reflecting a prior invasive component in otherwise residual MIS. It is important to note that most guidelines recommend surgical margins but do not specify desirable pathological margins for the management of MIS. While obtaining large margins on the head and neck is often difficult,[20] surgical excision margins >8 mm are now generally advised for LM.[13,14] While it is often possible for experienced practitioners to identify single junctional melanocytes on frozen sections with standard H&E staining or with rapid immunostains during Mohs surgery or CCPDMA, it can be challenging to determine the nature and significance of single melanocytes without interpreting them in the context of the main part of the lesion or the sun damaged background and its associated solar melanocytosis.[7,21-23] Some have argued that the type of surgery is not important but that complete pathological clearance is what must be achieved.[24] Surgical margins are not reliably predictive of pathological margins,[10] but it seems likely that ≥7.5 mm surgical margins are necessary to obtain ≥4 mm pathological margins since it has previously been reported that ≥6.5 mm clinically determined surgical excision margins were necessary to obtain ≥3 mm pathological margins.[8]

Limitations

The limitations of our study are those inherent in any retrospective study, with some patients lost to follow-up, as well as the incompleteness of pathology reports differentiating LM from other forms of MIS. The survival differences between the groups with <4 mm and ≥4 mm pathological margins were not statistically significant in the matched cohort, possibly because the numbers were too small, so further studies are needed to examine this matter.

CONCLUSIONS

Analysis of 1407 patients with MIS/LM, of whom 404 had pathological clearance margins <4 mm, showed that location was an important prognostic factor and that <4 mm margins were associated with a substantially higher rate of LR (60.5% vs 36.7%) in matched patients. Our results suggest that clinicians should discuss with their patients the risks and benefits of more extensive surgery and should consider achieving pathological clearance margins of ≥4 mm whenever possible.

REFERENCES

1. Fitzsimmons GJ, Sadkowsky KR. The Australian Institute of Health and Welfare. *Commun Dis Intell Q Rep.* 2002;26:605-607.
2. Linos E, Li WQ, Han J, Li T, Cho E, Qureshi AA. Lifetime ultraviolet radiation exposure and lentigo maligna melanoma. *Br J Dermatol.* 2017;176:1666-1668.
3. Aitken JF, Youlden DR, Baade PD, Soyer HP, Green AC, Smithers BM. Generational shift in melanoma incidence and mortality in Queensland, Australia, 1995-2014. *Int J Cancer.* 2018;142:1528-1535.
4. Wolner ZJ, Yelamos O, Liopyris K, Rogers T, Marchetti MA, Marghoob AA. Enhancing skin cancer diagnosis with dermoscopy. *Dermatol Clin.* 2017;35:417-437.
5. Robinson M, Primiero C, Guitera P, et al. Evidence-based clinical practice guidelines for the management of patients with lentigo maligna. *Dermatology.* 2020;236:111-116.
6. Kunishige JH, Doan L, Brodland DG, Zitelli JA. Comparison of surgical margins for lentigo maligna versus melanoma in situ. *J Am Acad Dermatol.* 2019;81:204-212.
7. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol.* 2019;80:208-250.
8. Crouch G, Sinha S, Lo S, et al. Clinical outcomes following surgical treatment of lentigo maligna of the head and neck. *Eur J Surg Oncol.* 2021;47:1145-1151.
9. Tababa E, Teulings HE, Bhawan J. Differences between recommended surgical margins and measured histological margins in malignant melanoma in situ and malignant melanomas. *Am J Dermatopathol.* 2021;43:881-886.

10. Friedman EB, Dodds TJ, Lo S, et al. Correlation between surgical and histologic margins in melanoma wide excision specimens. *Ann Surg Oncol*. 2019;26:25-32.

11. Wehkamp U, Schwarz T. Topical imiquimod for melanoma in situ? A word of caveat. *Dermatol Surg*. 2018;44:582-583.

12. Tio D, van Montfrans C, Ruijter CGH, Hoekzema R, Bekkenk MW. Effectiveness of 5% topical imiquimod for lentigo maligna treatment. *Acta Derm Venereol*. 2019;99:884-888.

13. Shi W. Role for radiation therapy in melanoma. *Surg Oncol Clin N Am*. 2015;24:323-335.

14. MacKenzie Ross AD, Haydu LE, Quinn MJ, et al. The association between excision margins and local recurrence in 11,290 thin (T1) primary cutaneous melanomas: a case-control study. *Ann Surg Oncol*. 2016;23:1082-1089.

15. Mar VJ, Chamberlain AJ, Kelly JW, Murray WK, Thompson JF. Clinical practice guidelines for the diagnosis and management of melanoma: melanomas that lack classical clinical features. *Med J Aust*. 2017;207:348-350.

16. Nosrati A, Berliner JG, Goel S, et al. Outcomes of melanoma in situ treated with Mohs micrographic surgery compared with wide local excision. *JAMA Dermatol*. 2017; 153:436-441.

17. Menzies SW, Liyanarachchi S, Coates E, et al. Estimated risk of progression of lentigo maligna to lentigo maligna melanoma. *Melanoma Res*. 2020;30:193-197.

18. Michielin O, van Akkooi A, Lorigan P, et al. ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee. *Ann Oncol*. 2020;31:1449-1461.

19. Coit DG, Thompson JA, Albertini MR, et al. Cutaneous melanoma, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2019;17:367-402.

20. Glazer ES, Porubsky CF, Francis JD, et al. Treatment of head and neck melanoma in situ with staged contoured marginal excisions. *Ann Plast Surg*. 2017;78:663-667.

21. Erickson C, Miller SJ. Treatment options in melanoma in situ: topical and radiation therapy, excision and Mohs surgery. *Int J Dermatol*. 2010;49:482-491.

22. Kimyai-Asadi A, Katz T, Goldberg LH, et al. Margin involvement after the excision of melanoma in situ: the need for complete en face examination of the surgical margins. *Dermatol Surg*. 2007;33:1434-1439; discussion 9-41.

23. Welch A, Reid T, Knox J, Wilson ML. Excision of melanoma in situ on nonchronically sun-exposed skin using 5-mm surgical margins. *J Am Acad Dermatol*. 2014;71:834-835.

24. Sladden MJ, Nieweg OE, Howle J, Coventry BJ, Thompson JF. Updated evidence-based clinical practice guidelines for the diagnosis and management of melanoma: definitive excision margins for primary cutaneous melanoma. *Med J Aust*. 2018; 208:137-142.