OPEN

Retro- and prospective histologic and immunohistochemical analysis of safety margins following complete excision of less than 1 mm melanomas

Amandine Bouillenne[a], Pascale Quatresooz[b], Patrick Collins[b] and Arjen F. Nikkels[a]

Reexcisions for melanoma do rarely present residual melanoma. To analyze the number of positive margins in reexcisions of in situ and <1 mm melanomas. To see whether the immunohistochemical (IHC) panel (Preferentially expressed antigen of melanoma (PRAME), Sry-related HMg-Box gene 10 (SOX 10), Human melanoma black 45 (HMB45), and Melan A) detected additional cases of melanoma. Three pilot cohorts (retrospective, prospective, and direct safety margins) were analyzed on the persistence of melanoma in reexcisions. Among the 97 cases of the retrospective cohort (27 in situ and 69 invasive melanomas), one residual in situ melanoma was detected in the reexcisions. In the second cohort, among 81 cases (18 in situ and 63 invasive melanomas), two cases (2.5%) presented in situ melanoma. In the group where direct margins were taken (*n* = 21) 2 (9.5%) in situ melanoma were evidenced in the margins. The IHC panel was needed to confirm three additional in situ melanomas in cohort 2. In a total of 178 cases (97 + 81) of reexcision, three and five cases (1.7 and 3.4%) of in situ melanoma were evidenced after H/E and IHC, respectively. These pilot data could question the usefulness of reexcision in <1 mm melanomas, particularly as only cases of in situ melanoma were detected. Larges prospective series would be required to answer this issue. *Melanoma Res* 36: 54–57 Copyright © 2025 The Author(s). Published by Wolters Kluwer Health, Inc.

Melanoma Research 2026, **36**:54–57

Keywords: histology, immunohistology, melanocytic hyperplasia, melanoma, surgical margin

Departments of [a]Dermatology and [b]Dermatopathology, CHU du Sart Tilman, University of Liège, Liège, Belgium

Correspondence to Prof Dr Arjen F. Nikkels, MD, PhD, Department of Dermatology, Skin Cancer Center, CHU of Sart Tilman, University of Liège, B-4000 Liège, Belgium
Tel: +32 43667232; fax: +32 43667234; e-mail: af.nikkels@uliege.be

Received 23 June 2025 **Accepted** 23 October 2025.

Introduction

The reexcision with wide margins [wide local excision (WLE)] after an initial surgical in toto excision of melanoma was formerly justified by the concept of the superficial spreading growth pattern of melanoma, with the final goal of minimizing the risk of leaving microsatellite metastases in the adjacent skin hence reducing the risk of a loco-regional recurrence. After the initial recommendations of a 2-in. (5 cm) margin, the importance of the safety margins became progressively less, especially after the introduction of the Breslow depth in millimeters, which directs the management and the follow-up [1]. Currently, the recommended safety margins are the following: in situ (0 mm): 5 mm [2], ≤1 mm: 1 cm, >1–2 mm: 1–2 cm, and >2 mm: 2 cm, all if surgically reasonable and responsible. Margins exceeding 2 cm are not recommended anymore [1,3–6].

The usefulness of WLE is currently increasingly questioned, especially considering the efficacy and safety data of adjuvant systemic therapy [1,4–8].

Clinical experience reveals that in most reexcisions of in situ and small invasive melanomas (<1 mm), no residual melanoma is detected on histological examination. Literature data report the presence of residual melanoma in WLE specimens after prior complete excision-biopsy in 0–6.3% of cases. A recent study including 640 patients (79.7% invasive melanomas and 20.3% in situ melanomas) identified residual disease in 20 cases (3.1%), of which 3 (15%) were in situ melanoma on complete excision and 17 (85%) were invasive melanomas [9]. Furthermore, WLE can be associated with esthetic/cosmetic issues, increased morbidity (infection, dehiscence) as well as increased costs. In addition, the recommended safety margins are not always achievable from a surgical point of view due to functional difficulties or lesions in at-risk zones.

In addition, in terms of overall survival or increased local recurrence compared to 10 mm margins, the 5 mm excision margins for T1 radial growth phase melanoma were not associated with worse results and may probably be safely applied to such lesions, with caution for lentigo maligna melanoma types [10,11].

In sum, WLE is seriously questioned, and it is recommended to initiate prospective studies to evaluate whether WLE can be avoided in the future [1].

1473-5636 Copyright © 2025 The Author(s). Published by Wolters Kluwer Health, Inc. DOI: 10.1097/CMR.0000000000001070

As no specific data are available for small melanomas, the aim of this study was to verify histologic clearance in the WLE specimens after a diagnosis of <1 mm melanomas, totally excised, in a retro- and prospective cohort.

Immunohistochemistry (IHC) has become an added value and is currently standard practice for the diagnosis of cutaneous melanoma [12], but is not systematically used for the examination of WLE specimens. Whether the use of an IHC melanoma panel, including PRAME, SOX 10, HMB45, and Melan A, presents an additional diagnostic value for the examination of WLE specimens is evaluated prospectively in this study (cohort 2).

Materials and methods

The local university hospital ethical committee approved the study design (EudraCT B7072023000020, ref 2023/73). The patients in the prospective cohorts (2 and 3) were informed of the procedures.

WLE cases were retrieved from charts of the dermatopathology department (PQ and PC) over a period from January 2017 to September 2022. Only cases with an initial diagnosis of 'completely excised' melanoma <1 mm and of 'completely excised' in situ melanoma cases at the initial surgery were included (cohort 1).

Furthermore, a prospective study included patients with in situ and invasive <1 mm melanomas, again completely excised at the initial surgery, from January 2023 to December 2024 (cohort 2). Following current guidelines, in situ melanomas were reexcised to obtain a total clinical margin of 0, 5 cm, and <1 mm melanomas with a total clinical margin of 1 cm [3].

A third study examined the margins of a series of excisions of melanoma where the recommended margins were directedly taken after the evaluation of the depth of the suspected lesion using 20 MHz ultrasound examination or optical coherence tomography. Only in situ and <1 mm lesions were included (cohort 3).

Two experienced dermatopathologists (PQ and PC) independently reexamined the H/E specimens for histological evidence of persistence of melanoma in the WLE specimens of the cohorts 1 and 2. In addition, the IHC panel using antibodies against PRAME, SOX 10, HMB45, and Melan A was performed on all the specimens of cohort 2, to evaluate whether IHC presents an added value in diagnostic terms compared to H/E examination of the reexcisions. The IHC evaluation was not performed on cohort 1 due to incomplete or unavailable clinical material.

Melanocytic hyperplasia (MH), defined as an increased melanocytic density with confluence, mild atypia, suprabasal scatter, and a superficial follicular extension [11], should be distinguished from in situ melanoma. MH was searched for in the WLE specimens of all three cohorts.

Table 1 summarizes the study demographics.

Results

The demographics and results are summarized in Table 1. There were no differences between the number of persistant in situ melanomas between cohorts 1 and 2. No cases of invasive melanoma were detected in both cohorts.

IHC confirmed three additional cases of in situ melanoma after H/E examination detected a suspicion of in situ melanoma in the WLE specimens (Table 2).

MH was detected in around 7% of the WLE specimens but never in cases of one-step surgery.

Discussion

The retrospective and prospective parts of this study demonstrate the rarity of persistent melanoma on WLE specimen for a series of 178 cases of in toto excised in situ and <1 mm cutaneous melanomas. On H/E examination, 1.7% presented persistent melanoma and 3.4% after H/E combined with IHC analysis. These figures are consistent with those previously published

Table 1 **Demographics and results of the study population**

Cohort	*n*	M	F	Mean age range	Localization	Melanoma type	Mean Breslow (mm)	Number of persistant melanoma (H/E)	Number of persistant melanoma (IHC)	Type of persistance	Melanocytic hyperplasia
Cohort 1	97	34	63	55.5 (25–87)	Trunk: 35 (36%) Member: 56 (58%) Cephalic: 6 (6%)	In situ: 27 (28%) Invasive: 69 (71%)	0.45	1 (1%)	Not done	In situ (H/E) In situ (IHC)	7 (7%)
Cohort 2 (two-step-excision)	81	36	45	55.4 (24–86)	Trunk: 29 (36%) Member: 46 (57%) Cephalic: 6 (7%)	In situ: 18 (22%) Invasive: 63 (78%)	0.53	2 (2.5%)	5 (6%)	In situ (H/E) In situ (IHC)	6 (7%)
Cohort 3 (one-step-excision)	21	10	11	79.6 (32–100)	Trunk: 6 (29%) Member: 9 (42%) Cephalic: 6 (29%)	In situ: 11 (53%) Invasive: 10 (47%)	0.57	2 (10%)	2 (10%)	In situ (H/E) In situ (IHC)	0
Total cohorts 1 + 2	178			55.4 (24–87)				3 (1.7%)	6 (3.4%)		13 (7.3%)

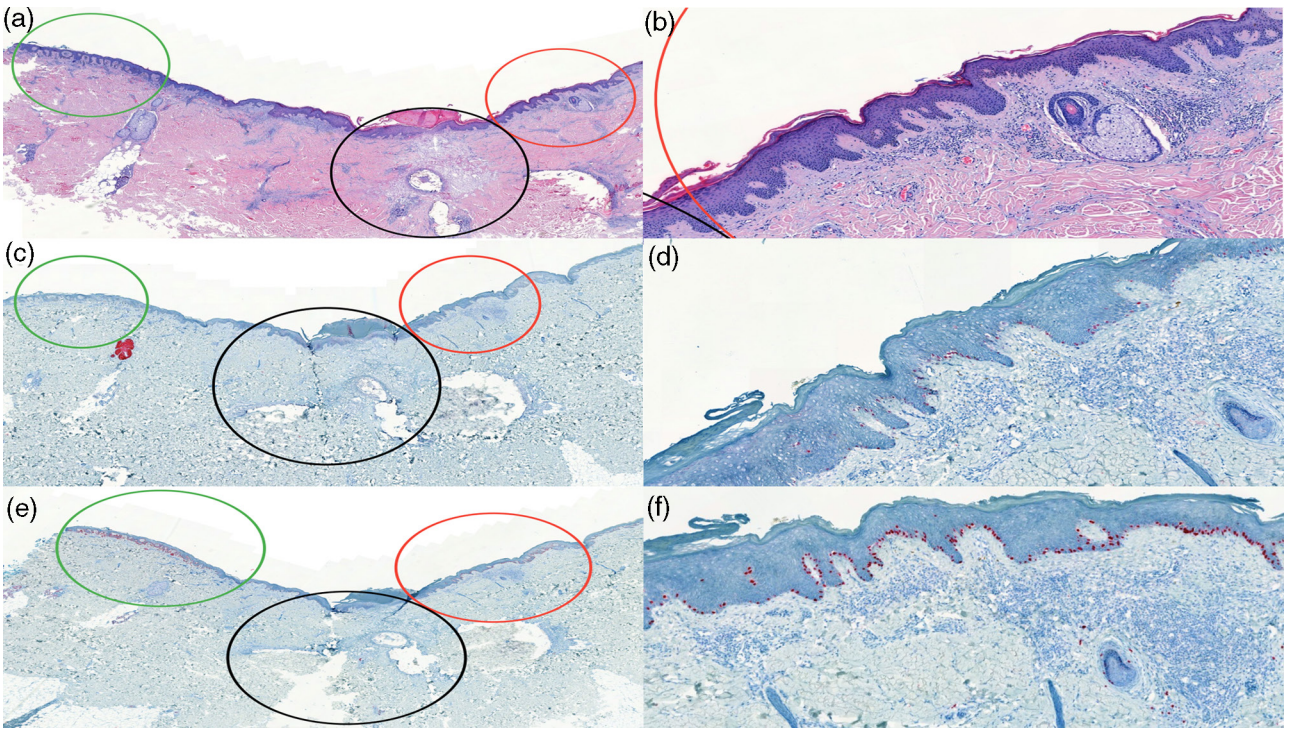
IHC, immunohistochemical.

Table 2 Summary of cases where residual in situ melanoma was detected

Cases gender age site	Initial melanoma Type and Breslow	WLE margins	Histological diagnosis WLE H/E	Melanoma IHC panel
Cohort 1				
Male 64 years Forearm	SSM Breslow 0.6 mm	1 cm	In situ melanoma	ND
Cohort 2				
Male 76 years Upperarm	In situ melanoma	0.5 cm	In situ melanoma	Confirms in situ melanoma
Female 84 years Head	In situ melanoma	0.5 cm	In situ melanoma	Confirms in situ melanoma
Male 65 years Back	SSM Breslow 0.9 mm	1 cm	Free margins	Detects in situ melanoma
Female 46 years Arm (three previous melanomas)	In situ melanoma	0.5 cm	Free margins	Detects in situ melanoma
Male 71 years Right scapula	SSM Breslow 0.3 mm	1 cm	Free margins	Detects in situ melanoma

IHC, immunohistochemical; ND, not done; SSM, superficial spreading melanoma; WLE, wide local excision.

Fig. 1



(a) H/E of a wide local excision illustrating the interest of IHC to confirm a suspicion of in situ melanoma (green circle: regular melanocytic naevus, black circle: scar tissue, red circle: potential in situ melanoma) (H/E × 10), (b) H/E × 20, (c) PRAME immunostaining (×10), (d) ×20, (e) SOX 10 immunostaining (×10), and (f) ×20. IHC, immunohistochemical.

(positive margins: 3.1–5%) [9,13,14]. Furthermore, no single case of invasive melanoma was evidenced on H/E and IHC examination. Only in situ melanomas were observed. Contrary to this study, where in situ melanomas represented 15% of the total specimens with invaded margins [9], in our study, there were 100% in situ melanomas. This difference could be linked to the fact that only small melanomas were included (in situ and <1 mm).

These results suggest that WLE after small melanomas is probably not useful. When persistent in situ melanoma appears adjacent to the surgical scar, an additional surgical treatment remains the gold standard, although other options such as topical imiquimod, cryotherapy, radiotherapy, or a 'wait and see' attitude could be proposed [15]. This nonsurgical attitude could be justified as the newest 5-year net-survival rates in England between 2013 and 2015 are 100% for in situ melanoma.

Caution should be given to elderly patients presenting in situ melanoma on areas with severe photodamage on photo-exposed areas.

MH is defined as an augmented number of melanocytes and is usually observed in skin with severe photodamage. It has also been described in recurrent nevi as well as in the epidermis overlying a series of benign and malignant skin tumors [16].

This study evidenced MH in around 7% of the WLE specimens. As MH was never observed in cases of one-step surgery, it could be assumed that this phenomenon is triggered by the healing process following surgery. Given that MH may mimic early melanoma in heavily sun-damaged skin, its recognition is essential to avoid overdiagnosis of residual melanoma.

The histopathologic examination of reexcision specimens does not routinely include a melanoma IHC panel. In this study, three additional cases, highly equivocal on haematoxylin eosin (H/E) examination, of in situ melanoma were confirmed after using the PRAME, SOX 10, HMB45, and Melan A panel, demonstrating an additional value in terms of histopathologic diagnosis (Fig. 1). However, whether a complementary IHC melanoma panel should be routinely recommended remains to be evidenced. However, IHC could be recommended as a useful tool in selected equivocal cases, but not routinely indicated.

Whether a complementary therapy with topical imiquimod [15,17] could be recommended systematically in the event of peripheral presence of in situ melanoma at complete excision remains to be evaluated prospectively.

In conclusion, this pilot study reveals that in situ melanoma was evidenced in 1–3% of reexcision specimens, but no case of invasive melanoma was found. Although the reexcision of invasive melanoma is important to be performed according to current guidelines, these pilot findings could question the utility of WLE after a diagnosis of an in situ or a <1 mm melanoma. This attitude could reduce unnecessary esthetic prejudices, avoid morbidity, and reduce costs. Overall survival will probably not change in this group. Validation of these pilot findings would require larger prospective cohorts.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Zijlkera LP, Eggermont AMM, van Akkooie ACJ. The end of wide local excision (WLE) margins for melanoma? *Eur J Cancer* 2023; **178**:82–87.
2 Friedman EB, Scolyer RA, Williams GJ, Thompson JF. Melanoma in situ: a critical review and re-evaluation of current excision margin recommendations. *Adv Ther* 2021; **38**:3506–3530.
3 Joyce KM. Chapter 7 Surgical management of melanoma. In *Cutaneous melanoma. Etiology and Therapy*; 2017. https://www.ncbi.nlm.nih.gov/books/NBK481850/.
4 Hanna S, Lo SN, Saw RP. Surgical excision margins in primary cutaneous melanoma: a systematic review and meta-analysis. *Eur J Surg Oncol* 2021; **47**:1558–1574.
5 Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, *et al*; European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC). European consensus-based interdisciplinary guideline for melanoma. Part 1: diagnostics: update 2022. *Eur J Cancer* 2022; **170**:236–255.
6 Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, *et al*; European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC). European consensus-based interdisciplinary guideline for melanoma. Part 2: treatment - Update 2022. *Eur J Cancer* 2022; **170**:256–284.
7 Bell KJL, Soyer HP, Ferguson PM. Is wide local excision after primary excision of melanoma in situ unnecessary? *JAMA Dermatol* 2025; **161**:999–1001. doi: 10.1001/jamadermatol.2025.3077.
8 Dessinioti C, Befon A, Plaka M, Niforou A, Kypreou K, Geller AC, Stratigos AJ. Local recurrence and survival in patients with melanoma in situ. *JAMA Dermatol* 2025; **161**:1002–1006.
9 Jackett LA, Satgunaseelan L, Roper E, Lo SN, Thompson JF, Scolyer RA. Residual melanoma in wide local excision specimens after 'complete' excision of primary cutaneous in situ and invasive melanomas. *Pathology (Phila)* 2022; **54**:71–78.
10 Maurichi A, Barretta F, Patuzzo R, Miceli R, Gallino G, Mattavelli I, *et al*. Similar local recurrence and survival in patients with T1 radial growth phase melanoma on head and neck treated with 5 or 10 mm margins: A retrospective study. *J Eur Acad Dermatol Venereol* 2023; **37**:1318–1326.
11 Maurichi A, Barretta F, Patuzzo R, Sala L, Miceli R, Gallino G, *et al*. Association of excision margin size with local recurrence and survival in patients with T1a melanoma at critical structures. *JAMA Dermatol* 2023; **159**:587–595.
12 Ojukwu K, Eguchi MM, Adamson AS, Kerr KF, Piepkorn MW, Murdoch S, *et al*. Immunohistochemistry for diagnosing melanoma in older adults. *JAMA Dermatol* 2024; **160**:434–440.
13 Miller CJ, Shin TM, Sobanko JF, Sharkey JM, Grunyk JW, Elenitsas R, *et al*. Risk factors for positive or equivocal margins after wide local excision of 1345 cutaneous melanomas. *J Am Acad Dermatol* 2017; **77**:333–340.e1.
14 Namin AW, Welby L, Baker AT, Dooley LM. Positive margins in cutaneous melanoma of the head and neck: implications for timing of reconstruction. *Otolaryngol Head Neck Surg* 2021; **164**:1052–1057.
15 Karponis D, Joshy J, Stratigos IA, Craig PJ, Mistry K, van Bodegraven B, *et al*. Cutaneous melanoma in situ: a review. *Clin Exp Dermatol* 2025; **50**:529–536.
16 Farah M, Suzuki S, Bhawan J. Melanocytic hyperplasia associated with surgical scars in basal cell carcinoma re-excision specimens: a single-center retrospective study. *J Cutan Pathol* 2022; **49**:7–16.
17 Martínez-Fernández S, González-Sixto B, Espasandín-Arias M, Soto-García D, Flórez A. Topical and intralesional immunotherapy for melanoma in situ: a review. *Cancers (Basel)* 2023; **15**:4468.