Comparison of surgical margins for lentigo maligna versus melanoma in situ

Joy H. Kunishige, MD, Linda Doan, MD, David G. Brodland, MD, and John A. Zitelli, MD

Pittsburgh, Pennsylvania

Background: Multiple studies have shown a 5-mm surgical margin to be inadequate for excision of melanoma in situ. Some have suggested that a wider margin is needed only for the lentigo maligna subtype.

Objective: To compare subclinical extension of lentigo maligna with that of melanoma in situ. The secondary objective was to investigate the effect of other factors on extent of subclinical extension.

Methods: A prospectively collected series of noninvasive melanomas was studied. Original pathology reports were used to identify lentigo maligna and compare data for that subtype with data for the remaining melanomas in situ.

Results: A total of 1506 lentigo maligna cases and 829 melanomas in situ were included. To obtain a 97% clearance rate, both lentigo maligna and melanoma in situ required a 12-mm margin on the head and neck and a 9-mm margin on the trunk and extremities. Only 79% of lentigo maligna and 83% of melanoma in situ were successfully excised with a 6-mm margin ($P = .12$). Local recurrence was identified in 0.26% (5 facial, 1 scalp, and 1 acral), with a mean follow-up time of 5.7 years.

Limitations: Margins less than 6 mm were not studied. The use of lentigo maligna diagnosis was not used by all dermatopathologists consistently. The degree of surrounding photodamage was not assessed.

Conclusion: Subclinical extension of lentigo maligna and melanoma in situ are similar. Standard surgical excision of all melanoma in situ subtypes, including lentigo maligna, should include at least 9 mm of normal-appearing skin, which is similar to the amount recommended for early invasive melanoma. Lesions on the head and neck or those with a diameter greater than 1 cm may require even wider margins and are best treated with Mohs micrographic surgery. The perception that lentigo maligna has wider subclinical extension may be related to its frequent location on the head and neck, where photodamage can camouflage the clinical border. (J Am Acad Dermatol 2019;81:204-12.)

Key words: excision; guidelines; lentigo maligna; melanoma; melanoma in situ; Mohs micrographic surgery.

Numerous studies have shown 5 mm to be inadequate for half of melanoma in situ (MIS).[1-19] The American Academy of Dermatology (AAD) and National Comprehensive Cancer Network recommend 5-mm to 1-cm surgical margins for MISs. Some have questioned the need for 1-cm margins for all types of MIS, suggesting that only the lentigo maligna (LM) subtype requires this wider margin.[20,21] Note that LM is a pathologic distinction and will be referred to as pathologic LM (pLM); all other subtypes of melanoma in situ will be referred to as pathologic MIS (pMIS).

This study offers guidelines for the standard excision of all noninvasive melanomas, with a focus

on whether pLM has different margin requirements than pMIS. Secondary objectives were to determine which features make wider subclinical involvement more likely. Recommendations are validated by the determination of recurrence rate, which is directly related to inadequate excision.

METHODS

A prospective database of all patients referred for Mohs excision of melanoma was begun in 1982, recording various patient and tumor characteristics. All patients with biopsy-proven primary noninvasive melanoma from March 1982 through March 2016 were considered for this study. Patients without original pathology reports were excluded.

For all patients, original pathology reports were reviewed to determine whether the diagnosis or microscopic description contained the words *lentigo maligna*. All patients were treated with Mohs micrographic surgery. Mohs micrographic surgery was initiated by excising the biopsy site or remaining visible tumor with a 3-mm margin of normal-appearing skin to adipose tissue (debulking procedure). Immediately after debulking, an additional 3-mm margin was taken laterally and excised as a single piece down to deeper adipose tissue for frozen section examination by Mohs technique. Therefore, except in occasional cases near the eye or nasal tip, the smallest margin attempted was 6 mm. Four-micron-thick sections were stained with hematoxylin and eosin. HMB-45 immunostain was used in the early 1990s but discontinued after having been determined to be unreliable, and MART-1 immunostain has been used since 2003.[22] Frozen sections were examined, and any remaining tumor was marked on a map representing the surgical wound. When necessary, another stage was performed (ie, another 3-mm margin of skin was excised from areas of the wound containing tumor until a tumor-free plane was reached). The total number of millimeters needed to achieve tumor clearance was recorded by the physician at the conclusion of surgery. The wound was then repaired or allowed to heal by secondary intention.

Criteria for determining positive margins have been published previously.[22,23] Positive margins were defined as those containing at least 1 of the following: (1) nests of at least 3 atypical melanocytes,

CAPSULE SUMMARY

- A 5-mm margin will clear only 81% of melanomas in situ.

- Subclinical extension is similar for lentigo maligna, melanoma in situ, and invasive melanoma. Wide local excision of all noninvasive melanomas on the trunk and extremities should include a 9-mm surgical margin. Head and neck lesions may require wider margins.

(2) melanocytes above the dermoepidermal junction, and (3) "nonuniform" crowding of cells along the basement membrane. Other histologic findings raising suspicion include (1) extension of atypical, crowded melanocytes far down adnexal structures, especially into sebaceous glands, (2) nonuniform distribution of pigment, (3) excessive number of melanophages, and (4) brisk inflammatory response. Increased melanocyte density and mild-to-moderate confluence alone is typical of melanocytic hyperplasia in sun-damaged skin and was not interpreted as melanoma.[23] Using these criteria, our center has previously compared the interpretations of frozen sections with paraffin sections by a blinded dermatopathologist: frozen sections had a sensitivity of 100% in detecting melanoma when present and a specificity of 90%.[24]

The minimum surgical margins that would successfully remove 97% of pLM, pMIS, and all MIS were calculated for the entire cohort, as well as for subgroups based on location, diameter, use of MART-1 immunostain, and sex. Location was analyzed in terms of 2 groups: head and neck versus trunk and extremities (including acral and genital areas). This figure of 97% allowed a 3% chance of inadequate excision, which is consistent with the historical tolerance of local recurrence and previous studies.[25-27]

Local recurrence rate was tabulated. Local recurrence was defined as reappearance of tumor within or adjacent to the scar, with an intraepidermal component, and it represents inadequate initial excision. All patients who had not been examined within the past year were called to determine whether there was any color or concern regarding the old surgical site.

RESULTS
Patient and lesion characteristics

From 1982 to 2016, a total of 2734 cases were treated by Mohs micrographic surgery for primary MIS. The original pathology report could not be found or deciphered for 64 cases and adequate follow-up could not be established in 335 cases; thus, these cases were excluded. The final cohort comprised 2226 patients with 2335 cases, of which 1506 were pLM and 829 were pMIS. Of the patients, 61% were men. The mean patient age was 66 years (standard deviation, 14), with patients with pLM 9

Abbreviations used:

LM: lentigo maligna
MIS: melanoma in situ
NOS: not otherwise specified
MART-1:   melanoma antigen recognized by T-cells
RR: recurrence rate
MSS: melanoma-specific survival
OS: overall survival

years older than those with pMIS on average. The mean follow-up time was 5.7 years (range, 0.2-23.5 years; median, 4.5 years), with 76% of patients having follow-up longer than 2 years.

Margins and percent clearance for various categories

For the entire cohort, 6-mm margins were adequate for complete clearance in only 79% of

Table I. Clearance rates for various tumor characteristics

| Tumor characteristic | Surgical margin | | | |
	6 mm	9 mm	12 mm	15 mm
Pathologic subtype				
Overall, n (N = 2335)	1886	2213	2288	2313
% (95% CI)	80.8 (79.0, 82.0)	94.8 (93.7, 95.6)	**98.0** (97.3, 98.5)	99.1 (98.6, 99.4)
LM, n (n = 1506)	1196	1421	1467	1486
% (95% CI)	79.4 (77.3, 81.4)	94.4 (93.0, 95.4)	**97.4** (96.4, 98.1)	98.7 (97.9, 99.2)
MIS other, n (n = 829)	690	792	821	827
% (95% CI)	83.2 (80.5, 85.7)	95.5 (93.8, 96.8)	**99.0** (98.0, 99.6)	99.8 (99.0, 100.0)
Pathologic subtype by location				
H&N LM, n (n = 1101)	870	1033	1068	1084
% (95% CI)	79.0 (76.5, 81.4)	93.8 (92.2, 95.1)	**97.0** (95.8, 97.9)	98.5 (97.5, 99.1)
H&N MIS, n (n = 261)	202	240	256	259
% (95% CI)	77.4 (71.8, 82.2)	92.0 (87.8, 94.8)	**98.1** (95.3, 99.2)	99.2 (99.2, 99.9)
T&E LM, n (n = 405)	326	388	399	402
% (95% CI)	80.5 (76.2, 84.1)	95.8 (93.2, 97.5)	**98.5** (96.6, 99.4)	99.3 (97.0, 99.9)
T&E MIS, n (n = 568)	488	522	565	568
% (95% CI)	85.9 (82.7, 88.6)	**97.2** (95.4, 98.3)	99.5 (98.3, 99.9)	100 (97.7, 99.8)
Location				
H&N all, n (n = 1362)	1072	1273	1324	1343
% (95% CI)	78.7 (76.4, 80.8)	93.5 (92.0, 94.7)	**97.2** (96.2, 98.0)	98.6 (97.8, 99.1)
T&E all, n (n = 973)	814	940	964	970
% (95% CI)	83.7 (81.5, 85.9)	**96.6** (95.2, 97.6)	99.1 (98.1, 99.6)	99.7 (99.0, 99.9)
Diameter				
Diameter <1 cm, n (n = 340)	300	331	336	339
% (95% CI)	88.2 (84.2, 91.4)	**97.4** (94.9, 98.7)	98.8 (96.8, 99.6)	99.7 (98.1, 100.0)
Diameter 1-2 cm, n (n = 1254)	1031	1197	1235	1244
% (95% CI)	82.2 (80.0, 84.3)	95.5 (94.1, 96.5)	**98.5** (97.6, 99.1)	98.0 (98.5, 99.6)
Diameter 2-3 cm, n (n = 396)	293	364	388	392
% (95% CI)	74.0 (693, 78.2)	91.9 (88.7, 94.3)	**98.0** (95.9, 99.1)	99.0 (97.3, 99.7)
Diameter >3 cm, n (n = 345)	262	321	329	338
% (95% CI)	75.9 (71.0, 80.3)	93.0 (89.7, 95.4)	95.4 (92.4, 97.2)	**98.0** (95.7, 99.1)
Immunostain				
MART-1 not used, n (n = 516)	447	504	508	513
% (95% CI)	86.6 (83.3, 89.4)	**97.7** (95.9, 98.7)	98.4 (96.8, 99.3)	99.4 (98.2, 99.9)
MART-1 used, n (n = 1819)%	1439	1709	1780	1800
(95% CI)	79.1 (77.2, 80.9)	94.0 (92.7, 95.0)	**97.9** (97.1, 98.5)	99.0 (98.3, 99.4)
Sex				
Female, n (n = 909)	751	853	882	896
% (95% CI)	82.6 (80.0, 85.0)	93.8 (92.0, 95.3)	**97.0** (95.7, 98.0)	98.6 (97.5, 99.2)
Male, n (n = 1426)	1135	1360	1406	1417
% (95% CI)	79.6 (77.4, 81.6)	95.4 (94.1, 96.4)	**98.6** (97.8, 99.1)	99.4 (98.8, 99.7)

Bold indicates minimum surgical margin yielding 97% tumor clearance.
CI, Confidence interval; *H&N,* head and neck; *LM,* lentigo maligna; *MIS,* melanoma in situ; *T&E,* trunk and extremities.
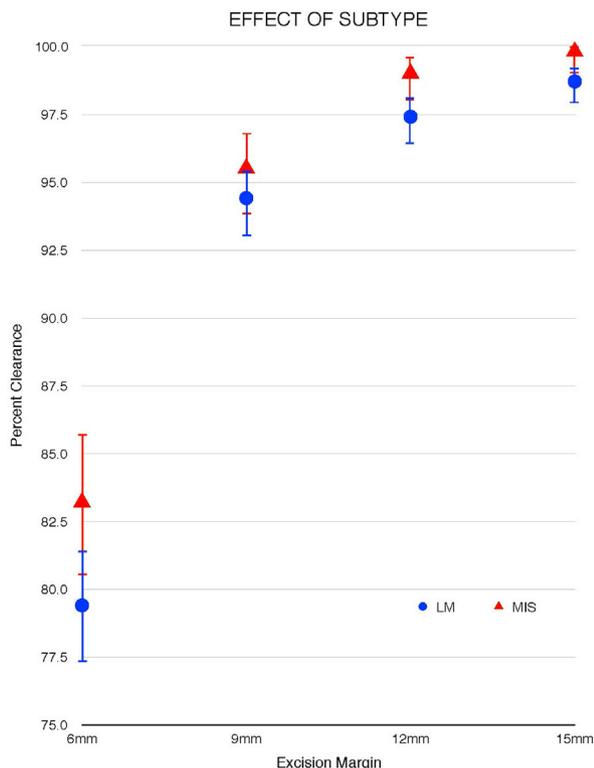
EFFECT OF SUBTYPE

EFFECT OF LOCATION

Fig 1. The clearance rates for melanoma in situ (MIS) and those for lentigo maligna (LM) are similar. Note that the confidence intervals overlap.

Fig 2. The clearance rates for the head and neck (H&N) are significantly lower than those for the trunk and extremities (T&E) for each margin. Note that confidence intervals do not overlap.

pLMs and 83% of pMISs. When all lesions were considered regardless of location, a 12-mm margin was necessary to achieve 97% clearance for both pLM and pMIS (Table I).

When only lesions on the head and neck were considered, both pLM and pMIS still required 12 mm for 97% clearance. However, when only lesions on the trunk and extremities were considered, both pLM and pMIS required only 9 mm for 97% clearance (Table I). Even small pLMs and pMISs (diameter <1 cm) on the trunk and extremities required 9 mm for 97% clearance.

Larger-diameter lesions had wider subclinical extension. The use of MART-1 immunostains made it more likely to perform a second stage of Mohs, but not additional stages. Sex did not have an effect on margin requirement. Classifying the neck as part of head and neck versus as part of the trunk and extremities did not change the results.

Recurrence

Five head and neck pLMs and 1 acral lentiginous pMIS reappeared within or adjacent to the scar, reflecting incomplete removal. The probability of recurrence for pLM versus for pMIS was not significantly different ($P = .492$). Notably, 3 of the 6
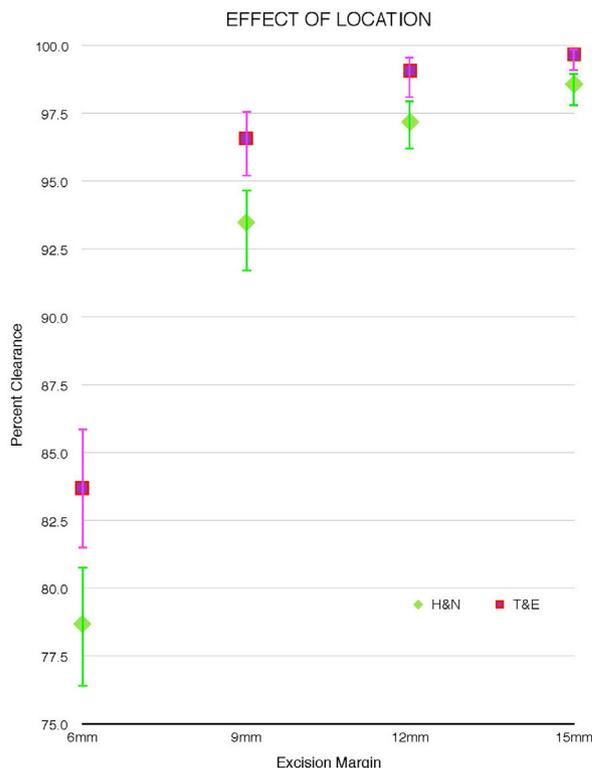
recurrences presented as lesions larger than 3 cm in diameter. The 5- and 10-year recurrence rates for pLM were 0.27% and 0.33%, respectively. The 5- and 10-year recurrence rates for pMIS were 0.00% and 0.12%, respectively. The average time to recurrence was 63 months (range, 37-105 months). All patients underwent Mohs micrographic surgery to remove the recurrent tumor, and none died of disease.

DISCUSSION

Subclinical extension occurs equally in both LM and MIS

The term *lentigo maligna* has a confusing history. First reported as Hutchinson's melanotic freckle in 1892, it was thought to be an infectious process. Some have postulated that there are 2 types of LM, 1 that is benign and 1 that is malignant.[28] LM is now well recognized to be malignant and a histologic subtype of MIS.[29] All definitions of LM describe it as occurring within photodamaged skin, with evidence of photodamage as a histologic sine qua non of LM.

Melanomas may grow with invisible subclinical extensions analogous to basal cell carcinoma, squamous cell carcinoma, and other cutaneous malignancies. In particular, LM is infamous for surprisingly

Table II. Clearance rates for primary MIS on the head and neck

Study	MIS cases, n	Treatment	Clearance rate with a 5- to 6-mm margin	Clearance rate with a 1-cm margin	Margin for 97% clearance	Comments
Jejurikar et al[2]	42	SE	35% at 7 mm	84% at 9 mm	11 mm	
Current study	1362	Mohs	79%	94%	12 mm	
Garcia et al[3]	27	Modified SE	55%	<93%	12 mm	
Mahoney et al[4]	10	SE	50% at 7 mm	70% at 9 mm 80% at 11 mm	13 mm	Analysis included 9 recurrent MISs
de Vries et al[5]	100	SE	49% at 3 mm	88% at 8 mm	13 mm	Analysis included 3 MISs son trunk and extremities
Abdelmalek et al[6]	225	SE	72%	94%	13 mm	Analysis included few MISs on trunk and extremities
Walling et al[7]	51	Modified SE	46%	83%	14 mm	Analysis included 10 invasive melanomas
Moller et al[8] and Glazer et al[19]	127	SE	76%	94%	14 mm	
Moyer et al[9]	564	SE	41%	75%	15 mm	
Felton et al[10]	343	Mohs	65%	92%	15 mm	
Huilgol et al[11]	91	Modified SE	80%	95%	15 mm	
Albertini et al[12]	42	Mohs	41%	57%	18 mm	Analysis included 3 recurrent MISs
Zalla et al[13]	46	Mohs	50%	83%	19 mm	Analysis included 2 MISs on trunk and extremities and 2 recurrent MISs
Demirci et al[14]	26	SE	15%	50%	25 mm	
Agarwal-Antal et al[15]	92	SE	42%	69%	25 mm	Analysis included 23 MISs on trunk and extremities and 3 recurrent MISs
Shumaker et al[16]	18	SE	33%	83%	NR	
Shin et al[17]	586	Mohs	66%	NR	NR	Analysis included 51 MISs on trunk and extremities and 83 recurrent MISs
Malhotra et al[18]	109	Modified SE	69%	NR	NR	Analysis included 34 recurrent MISs
Total	3883		49% (mean)	82% (mean)	19 mm (mean)	

MIS, Melanoma in situ; *Modified SE,* margins evaluated by a method other than en face (ie, bread-loafing, vertical or radial sections); *NR,* not reported; *SE,* staged excision (en face sections used to evaluate margins on permanent sections).

wide invisible extensions,[30-34] resulting in frequent re-excisions.[31,32] The AAD guidelines specifically state that "wider margins may be necessary for the lentigo maligna subtype."[34] In contrast to this historically purported belief, data suggest that subclinical extension occurs equally in all subtypes of MIS. In this study of 2335 tumors, margin requirements were equal for pLM and pMIS subtypes (Fig 1).

Head and neck location and diameter are associated with a wider margin requirement

Significant subclinical extension appears to be related to location more than to subtype (Fig 2).

The University of Pennsylvania has reported that lesions on the head and neck are 2 times more likely than other sites to have subclinical spread beyond 5 mm.[17] Multiple studies have found head and neck location to be associated with subclinical extension, sometimes more than 1 cm (Table II).[1-19,35-38]

The possibility of subclinical extension beyond 1 cm is not new. This occurs in invasive melanoma on the head and neck as well. The 6 prospective randomized controlled trials behind the AAD and National Comprehensive Cancer Network guidelines that recommend 1-cm margins for early

Table III. Low recurrence rates associated with the Mohs technique

Study	MIS cases, n	Treatment	Follow-up, mo	Recurrence
Bienert et al[64]	76	Mohs	33	0%
Agarwal-Antal et al[15]	92	Mohs	48	0%
Zalla et al[13]	46	Mohs	16	0%
Johnson et al[65]	35	SE	NR	0%
Jejurikar et al[2]	42	SE	31	0%
Mahoney et al[4]	11	SE	4.7	0%
Moller et al[8]	49	SE	14	0%
Shumaker et al[16]	18	SE	94	0%
Gaudy-Marquest et al[66]	16	SE	25	0%
Current study	2335	Mohs	56	0.3%
Felton et al[10]	343	Mohs	29	0.3%
Etzkorn et al[67]	436	Mohs	34	0.5%
Bhardwaj et al[68]	158	Mohs	38	0.6%
Anderson et al[69]	150	SE	<60	0.7%
Clayton et al[70]	77	Mohs	22	1%
Moyer et al[9]	564	SE	101	1.4%
Abdelmalek et al[6]	225	SE	32	1.7%
Bosbous et al[71]	49	SE	26	1.7%
Bene et al[72]	116	Mohs	63	1.8%
Nosrati et al[73]	277	Mohs	103	1.8%
Hou et al[74]	407	Mohs	95	1.9%
Huilgol et al[11]	125	Modified SE	38	2%
Cohen et al[33]	26	SE	58	2.2%
Glazer et al[19]	127	SE	10	2.4%
Hill and Gramp et al[75]	38	Modified SE	25	2.6%
Bub et al[76]	55	Modified SE	57	3.6%
Malhotra et al[18]	109	Modified SE	32	3.7%
deVries et al[5]	100	SE	60	4%
Walling et al[7]	50	Modified SE	95	6.2%
Lee and Ryan et al[77]	31	Modified SE	42	9.6%
Total	6183	Mohs or SE	46 (mean)	1.7% (mean)

Note many of the studies in this table included recurrent MIS.
MIS, Melanoma in situ; *Modified SE*, margins evaluated by a method other than en face (ie, bread-loafing, vertical, or radial sections); *NR*, not reported; *SE*, staged excision (en face sections used to evaluate margins on permanent sections).

invasive melanoma virtually excluded melanomas on the head and neck: only 16 of 4231 melanomas were on the head and neck.[39-44] The adequacy of 1-cm margins on the head and neck has never been validated by high-level studies. In fact, the studies available suggest that only 52% to 91% of invasive melanomas on the head and neck will clear with a 1-cm margin.[9,45-47] In a long-term prospective study of 272 head and neck melanomas excised *with a 2-cm margin*, 9.4% of patients had local recurrence.[41] Not surprisingly, local recurrence rates for wide local excision of melanoma on the head and neck (9%-15%)[41,48-51] surpass those for melanoma on the trunk and extremities (1%-4%).[39-43,52]

The perception that LM has more subclinical extension may be related to its propensity to be located on the face within photodamaged skin. Lentigines, pigmented actinic keratoses, macular seborrheic keratosis, rosacea, scars, and stigmata common on the face make it more difficult or impossible for the clinician to identify the lesion border.

It makes sense that larger-diameter lesions, with increased circumference, would be more likely to have an area with subclinical extension. Our finding of increased margin requirements with increased lesion diameter corroborates the findings of multiple previous studies.[8,9,17,53]

Low recurrence validates recommended margin and Mohs micrographic surgery

The AAD guidelines state that the goal is to obtain histologic clearance.[34] It is unacceptable to leave tumor because a proportion will recur and become invasive.[54,55] Also, many lesions diagnosed as MIS are later found to contain invasive melanoma.[6,15,56-59] Surprisingly, the invasive area may be 1 cm away

from the edge of the visible lesion.[60] A good measure of how surgical standards match up to biologically important tumor is the recurrence rate. In this study, only 0.26% of patients had a recurrence. When compared with the recurrence rate of 8% to 20% reported with 5-mm surgical margins,[61-63] it is clear that the margins used in this study removed biologically important tumor. The margin requirements and recurrence rates found in this study are corroborated by numerous studies (Tables II and III).[64-77]

Mayo Clinic published its experience with wide excision using 5-mm margins versus Mohs technique for lentigo maligna.[74] They reported a recurrence rate of 5.9% with wide excision and a rate of 1.9% with Mohs technique. The authors concluded that both treatments were satisfactory. It is important to recognize that the 2 treatment arms were not randomized: "The treatment choice was not randomized and was influenced by a number of factors, including lesion size, location, and clinical definition of tumor margins, anticipated closure options, surgeon preference, patient preference, and year of study. The tumors treated by Mohs micrographic surgery in this cohort were statistically more likely to have a larger preoperative and postoperative diameter, to be located on a head or neck site, and to be repaired by a more complicated closure." The University of California San Francisco recently published similar results, reporting a 5-year recurrence rate of 4.1% in the wide excision group versus 1.1% in the Mohs group.[73] Again, this was a nonrandomized study, with larger lesions and those on the head and neck being referred for Mohs micrographic surgery.

A major limitation of this study is dermatopathologists not using the diagnosis of LM equally or at all. But this limitation exists within real clinical practice. The University of Texas Southwestern specifically notes that "it is the practice of the dermatopathology department to designate all in situ lesions as MIS, rather than to separately subclassify lentigo maligna."[10] The findings of this study provide real-world recommendations on how to approach MIS.

CONCLUSION

Margin guidelines for pLM and pMIS should be the same for 2 reasons. First, the diagnosis of pLM is not reliably indicated on pathology reports. Second and most important, the subclinical extension associated with each entity is the same. Even if there are clinical, histologic, and genetic differences between the 2 melanoma types, this study shows that their margin requirements are similar.

Furthermore, the margin requirements for both are similar to that for early invasive melanoma. This is fortunate because both can harbor invasive components.[15,56-59] A wider margin or use of the Mohs technique ensure complete extirpation of any occult invasive melanoma.

Both pLM and pMIS on the trunk and extremities can be safely removed with a 9-mm margin, which is similar to the findings for invasive melanoma on the trunk and extremities. Both pLM and pMIS on the head and neck, or those with a diameter greater than 1 cm, may require margins greater than 1 cm, which is similar to the findings for invasive melanoma on the head and neck. When these margins cannot be used, Mohs technique should be considered and is associated with low recurrence rates.

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