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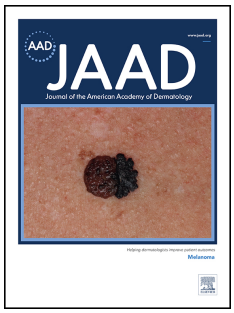

Clinical size is a poor predictor of invasion in melanoma of the lentigo maligna type

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Title:

Clinical size is a poor predictor of invasion in melanoma of the lentigo maligna type.

Running head: Predictors of invasion in lentigo maligna melanoma

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(1) Acquisition, analysis and interpretation of data.

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Keywords: lentigo maligna; melanoma; head and neck; invasion; Breslow; lentigo maligna melanoma; prognosis.

Abstract:

Background: There are no well-defined clinical factors to predict the risk of occult invasion in melanoma of the lentigo maligna type (LM) prior to complete histopathologic analysis.

Objective: To evaluate whether clinical size was a predictor of invasion in LM and subclinical extension.

Methods: Consecutive cases of LM were recorded in a prospectively maintained database from 2006 to 2019. Patient and tumor data were recorded during initial evaluation. 'LM clinical area' was calculated in square millimeters (length x width). All patients were treated with staged excision.

Results: We included 600 patients. Mean age was 65.9 years (SD 12.3; range 27 – 95 years); 62.8% (n=377) were males. The mean LM clinical area was 128.32 mm^2 for in situ lesions vs 200.14 mm for invasive lesions (p=0.1). Based on quantile regression, the median margin required for complete removal increased with LM clinical area.

Limitations: study performed in a tertiary cancer center with possible referral bias and more complex cases.

Conclusions: LM can present with variable clinical size which may correlate with subclinical extension; however, the presence of invasion is not well estimated by LM clinical area.

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Capsule summary:

- In this study of 600 patients with LM treated with staged excision, lesion diameter and area were poorly associated with the presence of invasion; however, larger lesions required wider surgical margins.
- Since LM lesions are unpredictable and clinical assessment is challenging; careful pre-surgical planning and margin controlled techniques are necessary.

Word count: 50/50

Introduction:

Melanomas arising on chronically sun-damaged skin are commonly classified as the lentigo maligna (LM) subtype. These melanomas have a distinct clinical and genetic profile when compared to those arising in intermittently-exposed skin.[1-3] They account for 5 – 15% of all melanomas but are the most common melanomas on the head and neck region.[4-7] Melanomas of the LM type typically present as large, ill-defined, solitary pigmented lesions. Since they occur in highly functional and cosmetically sensitive areas, biopsies are often partial and may not demonstrate the true extent of disease including occult invasion.[8-11]

There are no well-defined clinical features to predict the risk of invasion in LM. A recent study showed that the sensitivity of a partial biopsy for diagnosing an invasive component was only 47%.[9] Defining clinical predictors of invasion, may improve LM management. This becomes particularly relevant when selecting patients for surgical vs non-surgical management based on a partial biopsy.[12] The presence of invasive disease in LM may also have an impact on surgical margins needed to clear.[13,14] In addition, predicting margins needed for tumor clearance can help counsel patients on anticipated surgical defect size and repair options.[15]

Given the frequent lack of complete clinical and histological information available when deciding complex LM management, improved clinical predictors of invasion and subclinical extension are needed. In the present study, we sought to evaluate if LM clinical size was associated with invasion. Our secondary outcome was to the determine the association between clinical size and surgical margins needed to clear LM on staged excision.

Patients and Methods:

This study was approved by the institutional review board of the study site. Consecutive cases of LM referred for evaluation to the dermatologic surgery service at a tertiary cancer center were prospectively recorded in a database from November 1st, 2006 to April 1st, 2019. We included patients with (1) biopsy-proven diagnosis of a primary melanoma <1 mm depth, (2) histopathologic subtype of LM, and (3) treated with staged excision. We excluded patients that were (1) treated with non-surgical treatment modalities (i.e. imiquimod, radiation therapy) given the lack of definitive histopathological evaluation; (2) treated with wide local excision due to the absence of margin mapping; (3) patients presenting with incompletely excised or recurrent LM; and (4) treated at another institution after initial evaluation.

Patient's demographics:

Patient data (age, gender, skin type, hair color, eye color, personal and family history of skin cancer) were recorded during initial evaluation.

LM lesion characteristics:

LM lesion anatomic location was recorded. Clinical lesion size was determined by an expert dermatologic surgeon using physical examination, Wood's lamp, and dermoscopy,[16] and recorded as longest length and width (millimeters). The longest length of the lesion in any axis was termed 'LM clinical diameter'. 'LM clinical area' was calculated in square millimeters (length x width) and as an ellipse (0.5*length x 0.5*width x π), to account for lesion variability.

Surgery and Histopathological analysis:

Initial biopsies and subsequent excision specimens were reviewed by a board-certified dermatopathologist and Breslow depth (millimeters [mm]) was recorded. Biopsies were formalin-fixed, paraffin-embedded and routinely stained with hematoxylin and eosin (H&E). Special stains were used only if deemed necessary by the dermatopathologist. Staged excision was performed by a dermatologic surgeon, as described by Hazan et al.[14] Initial surgical margins were based on National Comprehensive Cancer Network (NCCN) guidelines starting with 5 - 7 mm margins.[17] Briefly, the center (debulking) of the lesion was processed with serial-sections to determine the final Breslow depth and the four clockwise-quadrants were processed radially to evaluate the surgical margins. If residual melanoma was observed in any surgical margin quadrant, a subsequent excision was performed until margins were clear.[14] Final Breslow depth used for analysis was the deepest measurement, whether it was in the initial biopsy or in the final excision. The 'total surgical margin' required to clear LM was the maximum radial margin excised (in any quadrant, on each side) in millimeters.

Statistical analysis:

Descriptive statistics including means, medians, interquartile range, standard deviation and relative frequencies were used to describe the study participants, and the characteristics of the procedures. Logistic regression was used to assess the relationship between invasion status with patient and surgical characteristics. Odds ratios along with 95% confidence intervals are included to express the strength and precision of the estimates. Due to the skewed nature of the lesional area, lesion area was explored as both a continuous and a categorical variable in the analysis. When categorized, lesion area was recoded into quartiles of the distribution. Linear and

quantile regression were used to explore the association between surgical margins required to completely remove the lesion and lesion area size (mm^2) while adjusting the estimates for in-situ/ invasive lesion classification. Predictive marginal mean estimates were calculated and plotted to depict the relationship between surgical margins and lesion area for in-situ and invasive lesions. Alpha-level was 5% for all comparisons, and all tests were two-sided. Analyses were performed using Stata v.16.1 (Stata Corporation, College Station, TX).

Results:

A database search yielded 781 patients with biopsy-proven diagnosis of melanomas arising in chronic sun-damaged skin during the study period. Eighty-four patients were excluded; 28 had no surgery, 28 were non-LM subtype, 14 were treated with WLE, 8 had missing data, 2 were treated with imiquimod, 2 were duplicates, 1 had radiation therapy, and 1 patient was lost to follow-up. A total of 697 LM patients underwent staged excision; 44 recurrent and 53 incompletely excised cases were further excluded. Six hundred patients with primary LM were included in the final analysis.

Patients' demographics:

Mean age was 65.9 years (SD 12.3; range 27 – 95 years); 62.8% (n=377) were males. The most common characteristics were skin type II (59.1%; n=317), blue eyes (44.3%, n=252), and brown hair (64.9%, n=366). Overall, 47.9% (n=284) had history of non-melanoma skin cancer, 31.4% (n=187) had personal history of melanoma, and 24.8% (n=144) had family history of melanoma (**Table 1**).

LM lesion characteristics:

Most LM were located on the head and neck (87.6%; n=526). The most common location was the central face (55.3%, n=332), including cheeks (34.5%, n=207), nose (12.7%, n=76), and forehead (8.2%, n=49). Two-hundred seventy lesions (45.0%) were on the left side and 284 on the right side (47.3%); 46 were on the midline (7.6%). Overall, 438 (73.0%) melanomas were in

situ and 162 (27.0%) were invasive, with a median final Breslow of depth of 0.3mm (IQR: 0.3; mean 0.44 mm; SD 0.47 mm; range 0.1-3.9 mm).

Primary outcome: clinical lesion size vs invasion

The mean overall 'LM clinical diameter' was 11.4 mm (SD 8.3; range 2 – 56 mm) (**Table 2**). Mean 'LM clinical diameter' was 10.76 mm for in situ vs 13.17 mm for invasive LM (p=0.01). **Figure 1** shows the average LM clinical diameter for in situ and invasive LM. In contrast, the difference in 'LM clinical area' (length x width) for in situ and invasive LM was not statistically significant (128.32 mm^2 for in situ vs 200.14 mm^2 for invasive cases; p=0.1). Additionally, no differences were found when calculating LM clinical area as an ellipse (**Table 1**). No association was seen between other clinical features (age, gender, anatomic location, and laterality) and the presence of in situ or invasive LM.

Secondary outcome: clinical lesion size vs total surgical margin

Overall, LM cases required a median of 8 mm in longest radial surgical margin (on each side) for clearance (SD=3.5mm, range 2-29mm); 7.0 mm for in situ and 10.0 mm for invasive lesions. Forty-six percent (n=279) of cases required a single stage for complete clearance, 43.5% required 2 stages, and 10% (n=60) required 3 or 4 stages. Based on quartile regression, the median margin required for complete removal for in situ lesions on the 1^{st} quartile of LM clinical area (smallest lesions) was 5mm (95% CI: 4.4 – 5.6 mm). For the 2^{nd} to the 4^{th} quartiles of LM clinical area, the median margin for complete removal for in situ lesions was 7mm (95% CI: 5.5 – 8.8 mm). These analyses also showed that invasive lesions required on average 3mm (95% CI: 2.3 – 3.7; p<0.001) more in overall margins for complete removal for each lesion quartile

category. **Figure 2** presents graphical representation of adjusted marginal means of the difference in surgical margins between in situ and invasive LM/LMM by overall lesion area.

Discussion

In this study including 600 primary LM patients treated with staged excision over a 13-year period, clinical lesion size was a poor predictor of invasion. The mean clinical lesion diameter of invasive LM was 2.41mm greater than in situ LM (13.17 vs 10.76 mm), which achieved statistical significance. However, this relatively small difference when using lesion diameter does not appear to be clinically meaningful, as LM lesion area did not predict invasion. Furthermore, no other clinical variables (age, gender, anatomic location, laterality) predicted invasion. Thus, LM clinical size alone cannot be used as a clinical factor predicting invasive disease.

Two recent studies have examined histopathologic factors associated with occult invasion in LM.[9,12] Moreno et al. demonstrated that the presence of melanocytes forming rows, >25% melanocytes forming nests, subepidermal clefts, and lesser degree of solar elastosis on a LM biopsy were associated with the finding of LM invasion on complete excision.[12] Aouidad et al. found that a pagetoid spread of tumor cells and moderate-to-strong dermal inflammation on initial biopsies were interpedently associated with invasion on subsequent excision.[9] Interestingly, in their study (n=100) they also found no association between clinical criteria (age, sex, size, and LM type [primary/recurrent]), although data was not shown.[9] Our study similarly found no clinical variables to portend invasion in LM.

While LM clinical lesion size did not reliably predict invasion, it was associated with subclinical extension. We found that the larger the LM lesion area, the greater the total surgical margins needed for clearance when evaluating LM lesion area by quartiles. The margins needed to clear LM increased logarithmically in larger lesions. According to previous studies, smaller lesions have been associated with fewer stages.[13,14,18,19] For lesions 3.0 cm^2 or larger, 29% required a margin of more than 6 mm compared with those smaller than 3.0 cm^2 in which 7% required margins larger than 6 mm.[18] Hazan et al. showed that lesions >2 cm had an average margin of 13.1 mm vs lesions <1 cm had margins of 8.6 mm.[14] Shin et al. showed that preoperative size >1.0 cm was associated with subclinical spread defined as >1 stage on Mohs surgery to achieve tumor-free margins. In the same study, location on the head and neck was also associated with a higher risk of subclinical spread (OR 2.13 [1.37 – 3.34]).[19] Moyer et al. showed similar results regarding clinically-calculated area and margins needed to clear a melanoma with the square technique. They also showed in a multivariate analysis that size was associated with a 9% increase in rate of local recurrence per each 50 mm^2 increase in area of the primary lesion.[13] Our results were similar to the previous studies, and margins were 3 mm larger for invasive lesions.

This study demonstrates no clinical features can reliably predict the presence of invasive disease in LM. Yet, we often make management decisions based on partial biopsies. It becomes challenging to decide when non-surgical options (e.g. imiquimod, radiation therapy) can be considered safely in specific patients who might not be good surgical candidates.[6,17] The advent of novel non-invasive tools such as dermoscopy and reflectance confocal microscopy (RCM) may improve the pre-surgical prediction of invasive disease and surgical margin planning.

Dermoscopy has facilitated the diagnosis of LM and also detected areas of potential invasion by showing suspicious features such as 'obliteration of hair follicles'.[20-23] RCM has been shown to aid in the diagnosis of both primary[20,24] and recurrent[25] LM as well as to help estimate the subclinical extension and evaluate incompletely excised LM.[26-30] More widespread use of these non-invasive technologies is expected with the growing body of knowledge and experience worldwide.[31,32]

Limitations:

This study was performed in a tertiary cancer center with possible referral bias and more complex cases than those seen in the general population. Further, correlation of LM lesion size to invasion was limited to lesions presenting with a Breslow thickness <1 mm.

Conclusion:

LM can present with variable clinical size; however, the presence of invasion is not reliably predicted by clinical size or other clinical characteristics. Larger lesions tend to have more subclinical extension and therefore, may need additional surgical margins for clearance. Given that margins can be larger than those required for clearance of other melanoma subtypes of equivalent Breslow depth, utilization of surgical techniques that use complete margin assessment prior to surgical reconstruction is recommended.[33] This information should be integrated into clinical shared decision-making tools.[34]

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297 **References**

298 1. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. *N Engl J*
299 *Med.* 2005;353(20):2135-2147.
300 2. Freedman JA, Tyler DS, Nevins JR, Augustine CK. Use of gene expression and pathway signatures
301 to characterize the complexity of human melanoma. *Am J Pathol.* 2011;178(6):2513-2522.
302 3. DeWane ME, Kelsey A, Oliviero M, Rabinovitz H, Grant-Kels JM. Melanoma on chronically sun-
303 damaged skin: Lentigo maligna and desmoplastic melanoma. *J Am Acad Dermatol.*
304 2019;81(3):823-833.
305 4. Cox NH, Aitchison TC, Sirel JM, MacKie RM. Comparison between lentigo maligna melanoma and
306 other histogenetic types of malignant melanoma of the head and neck. Scottish Melanoma
307 Group. *Br J Cancer.* 1996;73(7):940-944.
308 5. Swetter SM, Boldrick JC, Jung SY, Egbert BM, Harvell JD. Increasing incidence of lentigo maligna
309 melanoma subtypes: northern California and national trends 1990-2000. *J Invest Dermatol.*
310 2005;125(4):685-691.
311 6. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary
312 cutaneous melanoma. *J Am Acad Dermatol.* 2019;80(1):208-250.
313 7. Koh HK, Michalik E, Sober AJ, et al. Lentigo maligna melanoma has no better prognosis than
314 other types of melanoma. *J Clin Oncol.* 1984;2(9):994-1001.
315 8. Rzepecki AK, Hwang CD, Etzkorn JR, et al. The "Rule of 10s" versus the "Rule of 2s": High
316 complication rates after conventional excision with postoperative margin assessment of
317 specialty site versus trunk and proximal extremity melanomas. *J Am Acad Dermatol.* 2018.
318 9. Aouidad I, Fargeas C, Romero P, et al. Histologic predictors of invasion in partially biopsied
319 lentigo maligna melanoma. *J Am Acad Dermatol.* 2019;80(4):1150-1152.
320 10. Agarwal-Antal N, Bowen GM, Gerwels JW. Histologic evaluation of lentigo maligna with
321 permanent sections: implications regarding current guidelines. *J Am Acad Dermatol.*
322 2002;47(5):743-748.
323 11. Bax MJ, Johnson TM, Harms PW, et al. Detection of Occult Invasion in Melanoma In Situ. *JAMA*
324 *Dermatol.* 2016;152(11):1201-1208.
325 12. Moreno A, Manrique-Silva E, Viros A, et al. Histologic Features Associated With an Invasive
326 Component in Lentigo Maligna Lesions. *JAMA Dermatol.* 2019;155(7):782-788.
327 13. Moyer JS, Rudy S, Boonstra PS, et al. Efficacy of Staged Excision With Permanent Section Margin
328 Control for Cutaneous Head and Neck Melanoma. *JAMA Dermatol.* 2017;153(3):282-288.
329 14. Hazan C, Dusza SW, Delgado R, Busam KJ, Halpern AC, Nehal KS. Staged excision for lentigo
330 maligna and lentigo maligna melanoma: A retrospective analysis of 117 cases. *J Am Acad*
331 *Dermatol.* 2008;58(1):142-148.
332 15. Mori S, Blank NR, Connolly KL, et al. Association of Quality of Life With Surgical Excision of Early-
333 Stage Melanoma of the Head and Neck. *JAMA Dermatol.* 2019;155(1):85-89.
334 16. Paraskevas LR, Halpern AC, Marghoob AA. Utility of the Wood's light: five cases from a
335 pigmented lesion clinic. *Br J Dermatol.* 2005;152(5):1039-1044.
336 17. National Comprehensive Cancer Network. Melanoma (Version 2.2018).
337 https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf. Accessed April 4, 2018.

18. Bub JL, Berg D, Slee A, Odland PB. Management of lentigo maligna and lentigo maligna melanoma with staged excision: a 5-year follow-up. *Arch Dermatol.* 2004;140(5):552-558.
19. Shin TM, Etzkorn JR, Sobanko JF, et al. Clinical factors associated with subclinical spread of in situ melanoma. *J Am Acad Dermatol.* 2017;76(4):707-713.
20. Cinotti E, Labeille B, Debarbieux S, et al. Dermoscopy vs. reflectance confocal microscopy for the diagnosis of lentigo maligna. *J Eur Acad Dermatol Venereol.* 2018.
21. Schiffner R, Schiffner-Rohe J, Vogt T, et al. Improvement of early recognition of lentigo maligna using dermatoscopy. *J Am Acad Dermatol.* 2000;42(1 Pt 1):25-32.
22. Tiodorovic-Zivkovic D, Argenziano G, Lallas A, et al. Age, gender, and topography influence the clinical and dermoscopic appearance of lentigo maligna. *J Am Acad Dermatol.* 2015;72(5):801-808.
23. Pralong P, Bathelier E, Dalle S, Poulalhon N, Debarbieux S, Thomas L. Dermoscopy of lentigo maligna melanoma: report of 125 cases. *Br J Dermatol.* 2012;167(2):280-287.
24. Guitera P, Pellacani G, Crotty KA, et al. The impact of in vivo reflectance confocal microscopy on the diagnostic accuracy of lentigo maligna and equivocal pigmented and nonpigmented macules of the face. *J Invest Dermatol.* 2010;130(8):2080-2091.
25. Navarrete-Dechent C, Cordova M, Liopyris K, et al. Reflectance confocal microscopy and dermoscopy aid in evaluating repigmentation within or adjacent to lentigo maligna melanoma surgical scars. *J Eur Acad Dermatol Venereol.* 2020;34(1):74-81.
26. Yelamos O, Cordova M, Blank N, et al. Correlation of Handheld Reflectance Confocal Microscopy With Radial Video Mosaicing for Margin Mapping of Lentigo Maligna and Lentigo Maligna Melanoma. *JAMA Dermatol.* 2017;153(12):1278-1284.
27. Pellacani G, De Carvalho N, Ciardo S, et al. The smart approach: feasibility of lentigo maligna superficial margin assessment with hand-held reflectance confocal microscopy technology. *J Eur Acad Dermatol Venereol.* 2018.
28. Navarrete-Dechent C, Hibler BP, Cordova F, Cordova M, A MR. Lentigo Maligna Margin Template for Surgical Excision Using Reflectance Confocal Microscopy and a Transparent Adhesive Dressing. *Dermatol Surg.* 2019;In press.
29. Navarrete-Dechent C, Aleissa S, Cordova M, et al. Incompletely excised lentigo maligna melanoma is associated with unpredictable residual disease: clinical features and the emerging role of reflectance confocal microscopy. *J Eur Acad Dermatol Venereol.* 2020.
30. Navarrete-Dechent C, Cordova M, Aleissa S, et al. Lentigo maligna melanoma mapping using reflectance confocal microscopy correlates with staged excision: A prospective study. *J Am Acad Dermatol.* 2019.
31. Navarrete-Dechent C, DeRosa AP, Longo C, et al. Reflectance confocal microscopy terminology glossary for nonmelanocytic skin lesions: A systematic review. *J Am Acad Dermatol.* 2019;80(5):1414-1427 e1413.
32. Navarrete-Dechent C, Liopyris K, Monnier J, et al. Reflectance confocal microscopy terminology glossary for melanocytic skin lesions: A systematic review. *J Am Acad Dermatol.* 2020.
33. Navarrete-Dechent C, Aleissa S, Ariyan C, Busam KJ, Nehal KS. Comment on "Comparison of surgical margins for lentigo maligna versus melanoma in situ". *J Am Acad Dermatol.* 2019;81(4):e115-e116.
34. Fosko SW, Navarrete-Dechent CP, Nehal KS. Lentigo Maligna-Challenges, Observations, Imiquimod, Confocal Microscopy, and Personalized Treatment. *JAMA Dermatol.* 2018;154(8):879-881.

384 **Number of references:** 33.

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Variable	Coding	Melanoma, In-situ N=438	Melanoma, Invasive N=162	Melanoma, Total N=600		OR (95 % CI)	p-value
Age at surgery	Continuous: mean (SD)	65.7 (12.1)	66.4 (12.7)	65.9 (12.3)		1.0 (1.0 – 1.0)	0.303
		N (%)	N (%)	N (%)			
Sex	female	162 (37)	61 (37.7)	223 (37.2)		1.0 (referent)	--
	male	276 (63)	101 (62.4)	377 (62.8)		1.0 (0.7 - 1.4)	0.881
Eye color	green	41 (9.8)	13 (8.7)	54 (9.5)		1.4 (0.7 - 2.9)	0.388
	blue	182 (43.4)	70 (46.7)	252 (44.3)		1.0 (1.0 - 2.7)	0.035
	brown	131 (31.3)	30 (20)	161 (28.3)		1.0 (referent)	--
	hazel	65 (15.5)	37 (24.7)	102 (17.9)		2.5 (1.4 – 4.4)	0.002
Hair color	red	27 (6.5)	19 (12.6)	46 (8.2)		2.1 (1.1 – 3.9)	0.025
	blonde	99 (24)	36 (23.8)	135 (23.9)		1.1 (0.7 – 1.7)	0.775
	brown	273 (66.1)	93 (61.6)	366 (64.9)		1.0 (referent)	--
	black	14 (3.4)	3 (2)	17 (3)		0.6 (0.2 – 2.2)	0.474
Skin type	I	25 (6.4)	14 (9.7)	39 (7.3)		1.0 (referent)	--
	II	235 (60)	82 (56.9)	317 (59.1)		0.6 (0.3 - 1.3)	0.186
	III	130 (33.2)	47 (32.6)	177 (33)		0.6 (0.3 - 1.3)	0.243
	IV	2 (0.5)	1 (0.7)	3 (0.6)		0.9 (0.1 - 10.7)	0.929
Personal history of NMSC	No	223 (51.4)	86 (54.1)	309 (52.1)		1.0 (referent)	--
	Yes	211 (48.6)	73 (45.9)	284 (47.9)		0.9 (0.6 - 1.3)	0.559
Personal history	No	287 (66.1)	121 (75.2)	408 (68.6)		1.0 (referent)	--

of melanoma	Yes	147 (33.9)	40 (24.8)	187 (31.4)		0.6 (0.4 – 1.0)	0.036
Family history of melanoma	No	324 (76.4)	113 (72)	437 (75.2)		1.0 (referent)	--
	Yes	100 (23.6)	44 (28)	144 (24.8)		1.3 (0.8 - 1.9)	0.272
Anatomic site	cheek	159 (36.3)	48 (29.6)	207 (34.5)		1.0 (referent)	--
	nose	60 (13.7)	16 (9.9)	76 (12.7)		0.9 (0.5 - 1.7)	0.704
	periorbital	12 (2.7)	6 (3.7)	18 (3)		1.7 (0.6 - 4.6)	0.338
	Temple	19 (4.3)	8 (4.9)	27 (4.5)		1.4 (0.6 - 3.4)	0.462
	chin	13 (3)	2 (1.2)	15 (2.5)		0.5 (0.1 – 2.3)	0.386
	lips	9 (2.1)	0 (0)	9 (1.5)		--	--
	forehead	34 (7.8)	15 (9.3)	49 (8.2)		1.5 (0.7 - 2.9)	0.280
	jawline	3 (0.7)	0 (0)	3 (0.5)		--	--
	extremity	28 (6.4)	19 (11.7)	47 (7.8)		2.2 (1.2 - 4.4)	0.017
	neck	19 (4.3)	10 (6.2)	29 (4.8)		1.7 (0.8 – 4.0)	0.190
	periauricular	28 (6.4)	16 (9.9)	44 (7.3)		1.9 (0.9 – 3.8)	0.071
	scalp	33 (7.5)	16 (9.9)	49 (8.2)		1.6 (0.8 - 3.2)	0.171
	trunk	21 (4.8)	6 (3.7)	27 (4.5)		0.9 (0.4 - 2.5)	0.911

389 **Table 1.** Distribution of patient characteristics by final status of in situ vs invasive melanoma, lentigo maligna type. Odds ratios along with 95%
390 confidence intervals are included to show the association between lesion status and patient characteristics.

391 Abbreviations: OR=odds ratio

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Variable	Categorized	N	Mean	SD	Median	IQR	Min.	Max.	p-value

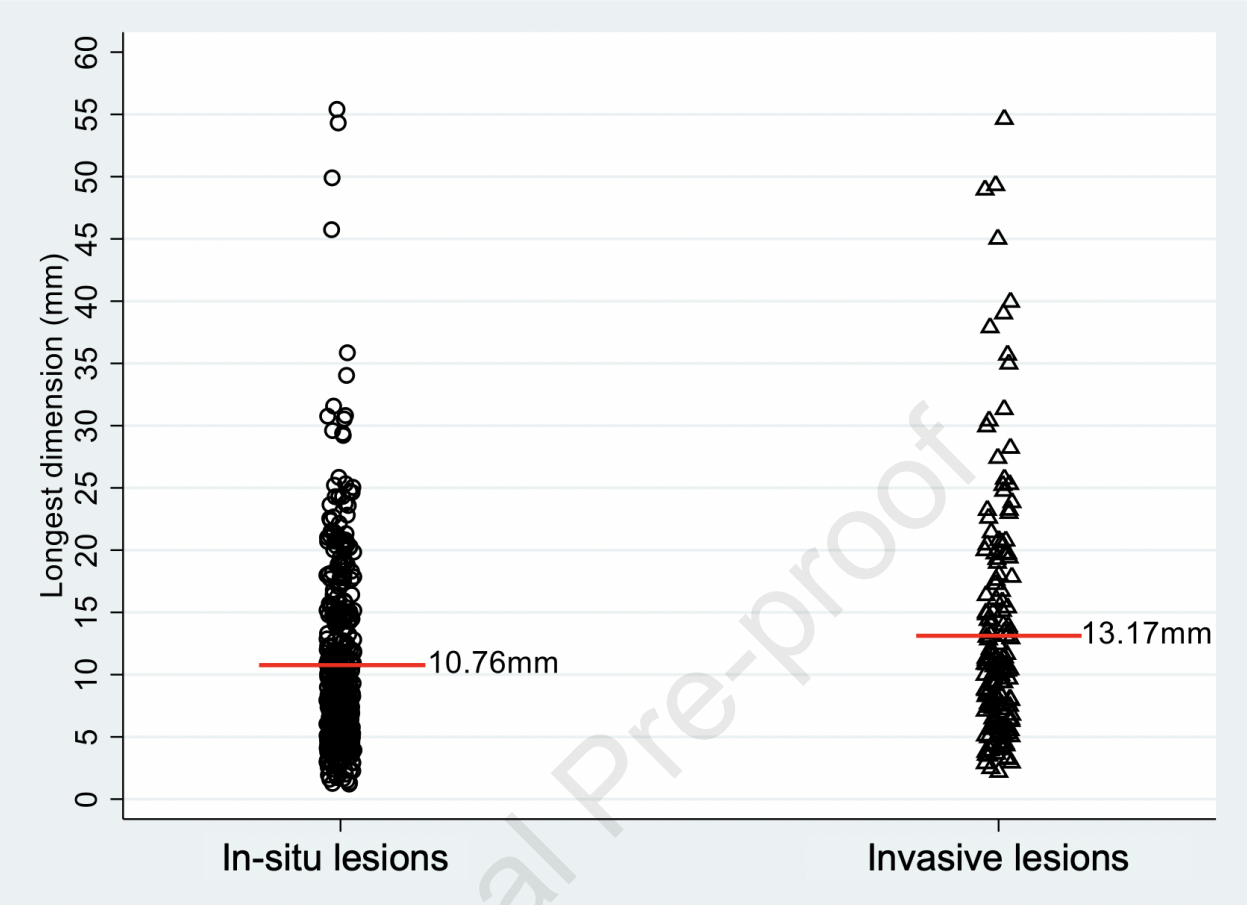
Longest LM diameter	In-situ	438	10.76	7.53	8	9	2	56	
	Invasive	162	13.17	9.87	11	10	2	55	0.010
	Overall	600	11.41	8.29	9	9	2	56	
LM lesion area (Length x width)	In-situ	438	128.32	220.92	64	119	4	2240	
	Invasive	162	200.14	394.92	66	138	4	2750	0.113
	Overall	600	147.72	280.28	64	123.5	4	2750	
LM lesion area (0.5*length x 0.5*width x π)	In-situ	438	100.78	173.50	64	50.3	4	2240	
	Invasive	162	157.18	310.16	66	51.8	4	2750	0.113
	Overall	600	116.02	220.12	64	50.3	3.1	2159.8	

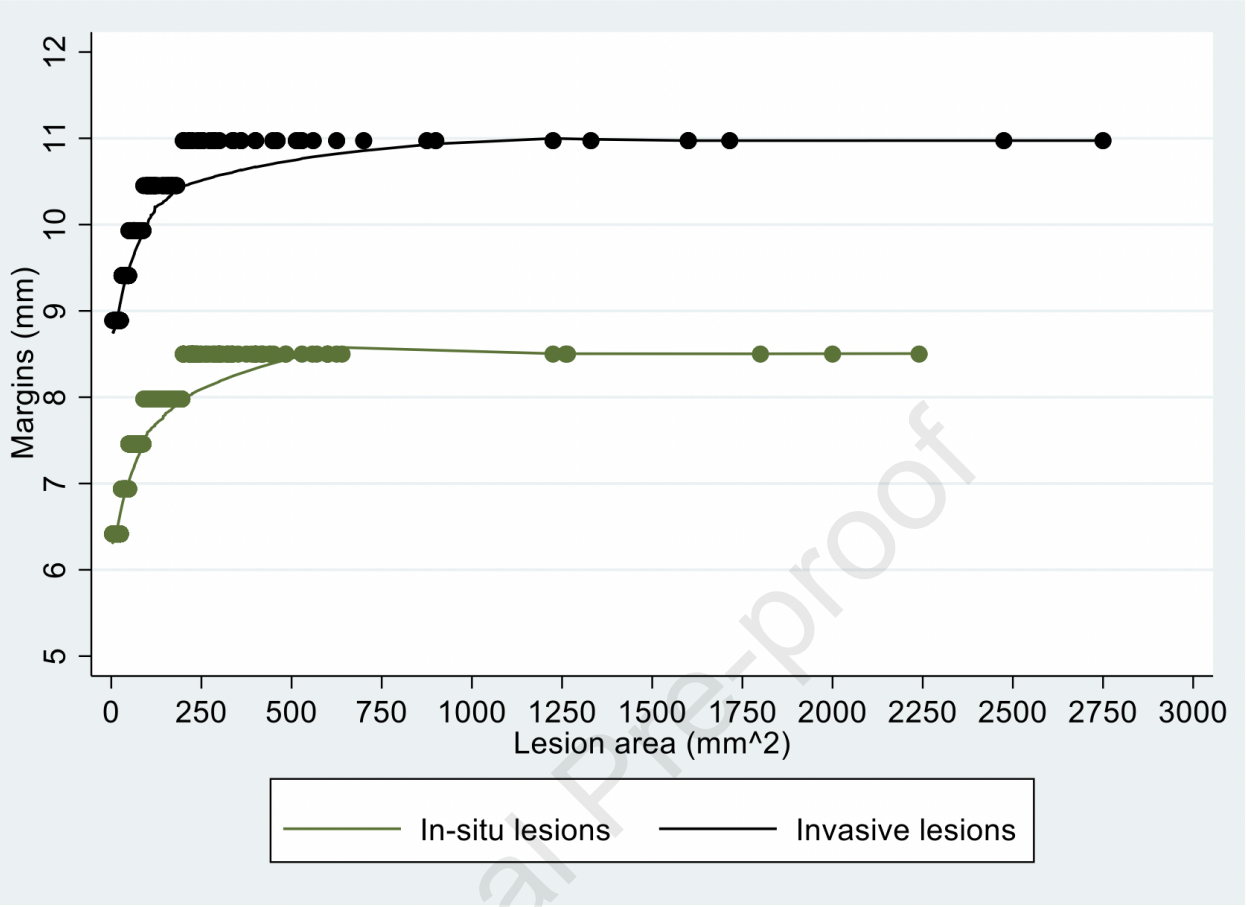
Table 2. Summary measures of longest diameter of lesion and lesion area, by lesion status (in-situ and invasive).

Figure legends:

Figure 1. Scatterplot of lentigo maligna clinical diameter (in mm) and invasion stratified by status of lesion (in-situ vs invasive).

Figure 2: Relation between primary lesion area (in mm^2) and the margins needed for histopathological clearance for lentigo maligna.





Capsule summary:

- In this study of 600 patients with LM treated with staged excision, lesion diameter and area were poorly associated with the presence of invasion; however, larger lesions required wider surgical margins.
- Since LM lesions are unpredictable and clinical assessment is challenging; careful pre-surgical planning and margin controlled techniques are necessary.

Word count: 50/50