SKIN

ORIGINAL ARTICLE

Review of Tumor Margins for Lentigo Maligna with Staged Surgical Excision and Permanent Section en face Processing

Michael Adkison, BS[1], Andrew Armenta, MD[2], Frank Winsett, MD[2], Richard F. Wagner Jr., MD[2]

[1] John Sealy School of Medicine, The University of Texas Medical Branch, Galveston, TX
[2] Department of Dermatology, The University of Texas Medical Branch, Galveston, TX

ABSTRACT

Background: The optimal surgical margins required for the excision of lentigo maligna remains a topic of debate. Recent literature suggests that wider margins are warranted.
Objective: Comparison of lentigo maligna margin sizes and clearance rates from a single center to existing literature.
Methods: A retrospective analysis of primary and recurrent lentigo maligna treated by staged excision with complete circumferential and deep margin assessment between 2011 and 2023 at a single institution was conducted. The percentage of tumors with clear margins after the initial excision with 5 mm margins was determined.
Results: A total of 65 tumors were identified. Fifty-eight patients (89.2%) had clear margins after initial excision with 5 mm margins.
Conclusions: This study reports a higher percentage of lentigo maligna clearance following the initial staged excision with 5 mm margins than reports in the literature. These differences may be attributed to variations in section processing, staining techniques, and factors associated with differences in subclinical spread.

INTRODUCTION

Lentigo maligna (LM), a subtype of Melanoma in situ (MIS), is characterized by the lentiginous growth of atypical melanocytes on sun-damaged skin such as the face, scalp, and neck.[1] LM merges with cutaneous changes sustained from sun damage, making its clinical and histological boundaries challenging to define.

Mohs micrographic surgery (MMS), a surgical technique involving frozen section assessment, has gained acceptance for treating LM and other melanoma subtypes because of its ability to detect subclinical spread while sparing excision of uninvolved tissue.[5] Another conservative technique for treating LM is staged excision (SE) with en face permanent sections. Despite the growing prevalence of MMS and SE techniques, an ongoing debate persists regarding optimal margin sizes due to challenges in identifying the boundaries of LM.[1–4] Our study compared margin sizes following SE for tumor clearance of LMs from a single-center with existing literature.

METHODS

Biopsy reports from the Electronic Medical Record from 2011 to 2023 were compiled to

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identify biopsy-proven primary or recurrent LM. Inclusion criteria consisted of pathology reports with a diagnosis of LM, while exclusion criteria eliminated cases of MIS subtypes or invasive melanoma.

All staged excisions were performed with an initial 5 mm margin. Excised tumor was examined by dermatopathologists using permanent section en face processing with hematoxylin and eosin (H&E) staining. In cases where margins showed residual LM, re-excision with 5 mm margins of tumor-affected areas and the same section processing was performed until a negative margin was achieved. If requested by the dermatopathology team, immunostaining with Microphthalmia transcription factor (MITF) was performed. Wounds were mapped with hatch marks and corresponding 5-0 Polypropylene sutures, and a xenograft was secured with 5-0 Poliglecaprone 25 while awaiting dermatopathology results. Data on age, sex, tumor site, preoperative size, the number of excisions, and the total margin required for clearance were collected.

A linear regression model was applied. The outcome variable, Total Margin Before Clearance (TMBC), was log-transformed for analysis. Correlation coefficients were calculated to assess the relationship between TMBC, preoperative size, and age. This study was conducted with the approval of the University of Texas Medical Branch Institutional Review Board.

RESULTS

A total of 65 patients meeting our inclusion criteria were identified, with 54 (83.1%) males and 11 (19.9%) females. The patients' mean age was 71.4 ± 9.1 years. The mean preoperative tumor size was 2.2 ± 0.9 cm. Sixty patients (92.3%) presented with primary tumors, while five patients (7.7%) had recurrent tumors at sites where a previous LM was excised. Thirty-seven tumors (56.9%) were located on the face, eleven (16.9%) on the scalp, seven (10.8%) on the ear, three (4.6%) on the upper extremity, two (3.1%) on the trunk, two (3.1%) on the nose, one (1.5%) of the neck, one (1.5%) on the lip, and one (1.5%) on the lower extremity **(Table 1)**.

Fifty-eight patients (89.2%) had clear margins after the initial excision. Of the seven patients requiring more than one excision, three patients needed two, two required three, one required four, and one underwent five. The mean preoperative tumor size of cases requiring multiple staged excisions was 2.4 ± 1.2 cm, with four located on the face, one on the scalp, one on the ear, and one on the trunk; One of these tumors was a recurrent LM, while the remaining six were primary tumors.

The linear regression analysis yielded an R^2 of 35.8% ($p<0.01$). A positive correlation between preoperative size and TMBC ($r(63)=0.21$, $p=0.09$) and a negative correlation between age and TMBC ($r(63)= -0.02$, $p=0.9$) were observed, although the findings were not significant.

MITF immunostaining was requested for four tumors (6.2%). Of these four, three were primary tumors, and one was recurrent. Additionally, two of the four had clear margins after the initial excision, while the remaining two required three excisions. MITF was utilized by dermatopathology to diagnose the initial biopsy in eight (12.3%) patients but not on their SE. Findings are summarized in **Table 2**.

DISCUSSION

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Table 1. Patient and Tumor Characteristics.

Characteristics	All Patients (n=65)	One Stage (n=58)	Two or More Stages (n=7)
Male, (%)	54 (83.1)	50 (86.2)	4 (57.1)
Female, (%)	11 (16.9)	8 (13.8)	3 (42.9)
Average age, mean ± sd	71.4 ± 9.1	71.7 ± 9.3	69.3 ± 7.6
Pre-op lesion size, mean ± sd (cm)	2.2 ± 0.9	2.1 ± 0.9	2.4 ± 1.2
Tumor location, (%)			
Face	37 (56.9)	33 (56.9)	4 (57.1)
Scalp	11 (16.9)	10 (17.2)	1 (14.3)
Ear	7 (10.8)	6 (10.3)	1 (14.3)
Upper extremity	3 (4.6)	3 (5.2)	0
Trunk	2 (3.1)	1 (1.7)	1 (14.3)
Nose	2 (3.1)	2 (3.5)	0
Neck	1 (1.5)	1 (1.7)	0
Lip	1 (1.5)	1 (1.7)	0
Lower extremity	1 (1.5)	1 (1.7)	0
Primary, (%)	60 (92.3)	54 (93.1)	6 (85.7)
Recurrent, (%)	5 (7.7)	4 (6.9)	1 (14.3)
No. of stages, (%)			
One	58 (89.2)	58 (100)	0
Two	3 (4.6)	0	3 (42.9)
Three	2 (3.1)	0	2 (28.6)
Four	1 (1.5)	0	1 (14.3)
Five	1 (1.5)	0	1 (14.3)

Tumor location, “face” includes cheeks, forehead, or temples. Abbreviations: sd, standard deviation

The American Academy of Dermatology and the National Comprehensive Cancer Network recommend surgical margins between 5 and 10 mm for the excision of MIS.[1] However, recent literature has raised questions about the necessity of wider margins, especially in the LM subtype, to achieve histologic clearance.[1–4] This ongoing debate extends to determining the efficacy of SE and MMS techniques and their associated section specimens in accurately identifying margin positivity for LM.

In studies assessing margin requirements for the resection of LM by SE and permanent section processing, clearance rates with 5 mm margins or less exhibit notable variability, ranging from 15% to 73.8%.[5–12] Among these studies, the mean margin size required for clearance ranges from 6.6 mm to 13 mm, and the margins necessary to achieve a 97% clearance vary from 11 mm to 25 mm. In comparison, two studies evaluating margin requirements for the resection of LM by MMS and frozen section processing reveal clearance rates of 79% with 6 mm margins and 69% with 6-10 mm margins, with the

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Table 2. Immunoperoxidase Staining in Lentigo Maligna Series.

Patient No.	Age	Sex	Location	Primary or Recurrent	Pre-op Size (cm)	No. of Stages	Immunostaining
1	61	M	Ear	Primary	0.9	1	
2	61	M	Face	Recurrent	1.9	1	
3	71	M	Face	Recurrent	1.2	1	MITF used at first stage
4	76	F	Face	Primary	3.4	1	
5	80	M	Face	Primary	3	1	
6	59	M	Ear	Primary	2.5	1	
7	86	M	Nose	Primary	2.7	1	
8	64	M	Face	Primary	3.8	1	MITF used at initial diagnostic biopsy
9	68	M	Nose	Primary	1.8	1	MITF used at initial diagnostic biopsy
10	73	M	Face	Primary	2.2	1	
11	57	M	Scalp	Primary	1.3	1	
12	60	M	Face	Primary	2.2	1	
13	60	M	Face	Primary	2.2	1	
14	88	M	Scalp	Primary	2.7	1	
15	62	M	Face	Primary	1.9	1	
16	66	M	Face	Primary	2.5	1	
17	92	M	Lip	Primary	2.4	1	
18	62	M	Scalp	Primary	2.3	1	HMB45 and SOX-10 used at initial diagnostic biopsy
19	79	M	Face	Primary	1.2	1	
20	79	M	Ear	Primary	3.3	1	
21	81	M	Face	Primary	2.4	1	MITF used at initial diagnostic biopsy
22	63	M	Face	Recurrent	2	1	
23	71	M	Scalp	Primary	2.5	1	
24	65	M	Scalp	Primary	2.7	1	
25	75	F	Face	Primary	3.6	1	
26	71	M	Scalp	Primary	2	1	MITF used at initial diagnostic biopsy
27	85	M	Face	Primary	1.2	1	MITF used at initial diagnostic biopsy
28	74	M	Face	Primary	2.1	1	
29	76	M	Face	Primary	2.2	1	SOX-10 used at initial diagnostic biopsy

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30	59	M	Face	Primary	1.2	1	MITF used at initial diagnostic biopsy
31	70	F	Face	Primary	2.2	1	MITF used at initial diagnostic biopsy
32	70	F	Face	Primary	2.9	1	
33	64	F	Face	Primary	2.5	1	
34	75	M	Scalp	Primary	4	1	
35	75	M	Face	Primary	1.5	1	AE1/AE3 and Ber-EP4 used at initial diagnostic biopsy
36	93	F	Face	Primary	2.5	1	
37	80	M	Face	Primary	1.8	1	HMB45 and SOX-10 used at initial diagnostic biopsy
38	68	M	Scalp	Primary	1	1	MITF used at initial diagnostic biopsy
39	66	M	Face	Recurrent	1.5	1	
40	74	M	Face	Primary	1	1	
41	85	M	Ear	Primary	1	1	
42	63	M	Scalp	Primary	2.4	1	
43	70	M	Face	Primary	2.2	1	SOX-10 used at initial diagnostic biopsy
44	67	M	Neck	Primary	2	1	MITF used at first stage
45	77	M	Scalp	Primary	2.1	1	
46	78	M	Ear	Primary	2	1	
47	77	M	Face	Primary	0.7	1	
48	86	M	Face	Primary	2.2	1	
49	81	M	Face	Primary	1.5	1	
50	75	M	Face	Primary	0.6	1	
51	56	F	Ear	Primary	0.8	1	
52	84	M	Face	Primary	1.6	1	
53	67	F	Face	Primary	2	1	
54	65	M	Upper Extremity	Primary	5.5	1	
55	60	M	Upper Extremity	Primary	3.2	1	
56	79	M	Upper Extremity	Primary	2.2	1	
57	63	M	Trunk	Primary	2.4	1	
58	65	M	Lower Extremity	Primary	0.9	1	

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59	58	M	Ear	Primary	3.6	2	
60	70	F	Face	Recurrent	1.9	2	
61	68	M	Scalp	Primary	0.5	2	
62	73	M	Face	Primary	2.5	3	MITF used at first stage
63	71	M	Trunk	Primary	3.9	3	MITF used at first stage
64	63	F	Face	Primary	1.8	4	
65	82	F	Face	Primary	2.9	5	

former reporting a minimum margin size of 12 mm to achieve a 97% clearance rate.[2,13] Additionally, studies that do not distinguish LM from MIS subtypes in their analysis and utilize MMS report clearance rates with 6 mm margins ranging from 41% to 65%, along with a 97% clearance rate range of 15 to 19 mm.[14–16] In the present study, 58 patients (89.2%) had clear margins after initial excision with a 5 mm margin. This clearance percentage deviates from margin sizes reported in previous literature. The authors speculate that these differences could be attributed to variations in section processing, staining techniques, and elements associated with greater subclinical spread.

Variations in processing techniques may partly explain the discrepancies in margin sizes for clearance between existing literature and the present study. Permanent sections have historically been favored for evaluating melanocytic lesions due to their preservation of pericytoplasmic vacuolization, which enhances melanocyte identification.[3] However, the increased processing time required for permanent sections may offset this advantage. In contrast, frozen sections permit immediate microscopic examination of excision margins. Critics of frozen sections, however, highlight the potential for false positives due to freeze artifacts, tissue folding, and keratinocyte vacuolization resembling melanocytes.[1,3]

Immunohistochemical stains like MITF, melanoma antigen recognized by T cells (MART-1, melan-A), human melanoma black-45 (HMB-45), S-100, and Mel-5 have been developed to address the challenges associated with frozen sections and better differentiate melanocytes from surrounding keratinocytes.[17] While studies have shown immunostained frozen sections and permanent sections to be comparable, skepticism remains due to reports of false positives in the setting of actinic damage, as sun-damaged skin makes distinguishing benign melanocytes from malignant melanocytes challenging.[3,18,19] This may inadvertently result in more extensive margin requirements and overtreatment of tumors. Notably, studies comparing the accuracy of frozen and permanent sections have shown conflicting outcomes. One study showed a diagnostic discrepancy as high as 40% for melanocytic lesions when comparing these two techniques.[20]

Conversely, another study indicated an 86% agreement between immunostained frozen sections and permanent paraffin sections assessing margins of LM.[4] In reviewing variations in margin requirements for tumor clearance across studies utilizing different tissue sectioning and immunostaining methods, the authors suspect that the present study's utilization of permanent sections with en face processing and occasional immunostaining, as opposed to

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frozen section processing with immunostaining for each section, may have minimized events of overstaining or sections affected by artifacts, thereby reducing the number of false positives.

The degree of subclinical spread may further explain discrepancies in margin sizes. Areas that have been associated with subclinical spread include tumors of the head, neck, acral sites, and pretibial leg.[21,22] In the present study, approximately 86% (six of seven) of our patients requiring additional excisions had tumors located on the head or neck, a consistency observed in earlier studies.[21,22] Additional factors that have been reported to be associated with subclinical spread are tumors exceeding 1 cm in diameter and patients being aged 60 years or older, although another study found that neither the patient's age nor preoperative tumor size was predictive of surgical margins.[16] In the present study, no significant relationship between margin requirements, age, and preoperative tumor size was observed, indicating the need for further investigation.

Part of the discussion concerning permanent and frozen sections involves considering whether subclinical spread might be overlooked when assessing permanent H&E stains. In a study evaluating 37 cases, discrepancies emerged in seven cases where the dermatopathologists initially deemed the margins clear while the Mohs surgeons identified positive margins after the first stage.[4] Following an external pathologist review, one case was reclassified as concordant, and another was excluded due to incomplete slides, leaving five cases with an undetermined status. While recognizing the need for further investigation on this topic, the present study's authors acknowledge this limitation, as exemplified by cases where our dermatopathologists obtained MITF immunostain in instances where the first excision had ill-defined margins on H&E examination.

Our findings may offer insights for dermatology clinics without an on-site Mohs surgeon. When comparing studies assessing the geographical distribution of Mohs surgeons to those of general practicing dermatologists, it becomes evident that the former have less geographic coverage across the United States than their general dermatology counterparts.[23,24] Given their broader geographic distribution, staged excision with 5 mm margins and permanent section en face processing is a viable treatment option for general dermatologists to consider, especially for patients in regions where Mohs surgeons are not readily available. Practicing dermatologists can employ a tissue-sparing technique to achieve clearance of LM without an immediate need for a Mohs surgeon. In doing so, this can help minimize the need for extensive reconstruction that may follow treatment by a conventional approach of wide local excision. Notably, while the findings in the present study provide evidence for the utilization of SE with 5 mm margins and permanent section en face processing, the authors acknowledge the ongoing inconsistencies within existing literature and the need for further research before a clear margin guideline can be established.

In conclusion, our study demonstrates a slightly higher percentage of tumors cleared with 5 mm margins than reported in existing literature. We suspect that this may be due to a reduced number of false positives resulting from the primary use of permanent section en face processing of tissue and the selective utilization of immunostaining in cases with unclear margins. Strengths of the present study include the focused analysis distinguishing LM from MIS and invasive

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melanoma and consistency in our analysis of resections performed. The single-center approach may limit the generalizability of our findings. Additional limitations include the retrospective design and small sample size, which pose challenges in drawing definitive conclusions. As such, future studies should further investigate the concordance between SE utilizing en face permanent paraffin sections and MMS utilizing immunostained frozen sections and disparities in accurately identifying the subclinical spread of LM.

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Corresponding Author:
Michael Adkison
301 University Blvd, Galveston, TX 77555
Phone: 713-829-4755
Email: mdadkiso@utmb.edu

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