Surgical Margins for Lentigo Maligna and Lentigo Maligna Melanoma

The Technique of Mapped Serial Excision

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Objectives: To assess the margins required for excision of lentigo maligna (LM) and lentigo maligna melanoma (LMM) by the technique of mapped serial excision (MSE), and to assess the efficacy of MSE.

Design: An interventional, prospective, noncontrolled case series.

Setting: Tertiary referral, dermatologic surgery unit.

Patients: Consecutive patients with head and neck LM or LMM who underwent MSE between March 1, 1993, and October 31, 2002.

Intervention: The MSE of LM or LMM.

Main Outcome Measures: The number of 5-mm levels for excision of LM and LMM and recurrence.

Results: One hundred sixty-one LMs or LMMs in 155 patients were treated. Thirty percent (37 of 125) of LMs required more than 5-mm margins. For LMMs less than 1 mm in Breslow thickness, 12% (4/32) required more than 10-mm margins. For primary tumors, 20% of LMs (18 of 91) required more than 5-mm margins, while 10% of LMMs less than 1 mm in Breslow thickness (2 of 21) required more than a 10-mm margin. For recurrent tumors, 56% of LMs (19/34) required more than a 5-mm margin. Mean follow-up of 38 months (range, 5-100 months) showed 4 recurrences (2%) after MSE. The extrapolated recurrence at 5 years was 5.0%.

Conclusions: The current recommendations of 5-mm margins for LM and 10-mm margins for LMM less than 1 mm in Breslow thickness are often insufficient. Our results demonstrate the importance of margin-controlled excision, particularly in recurrent lesions. The use of MSE offers a high cure rate, in conjunction with tissue conservation.

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Lentigo Maligna (LM) is a form of melanoma in situ and most commonly presents as a very slowly progressive, irregularly pigmented macule on the face of elderly individuals with sun-damaged skin. In Australia, the annual incidence of LM is the highest in the world and has been estimated at 1.3:100,000, with the most significant risk factor being UV radiation exposure. Lentigo maligna has a risk of progression to lentigo maligna melanoma (LMM), a subtype of invasive melanoma. Estimates of this risk have ranged as high as 30% to 50%, but the true risk is likely to be lower than this. In the United States, Newell et al reported an estimated annual incidence of LMM of 0.8:100,000 in men and 0.6:100,000 in women.

The treatment options for LM include surgical excision and destructive modalities, while LMM is preferably treated surgically. In LM, destructive modalities such as cryotherapy, electrodessication and curettage, laser surgery, radiotherapy, and fluorouracil have high recurrence rates of 20% to 100%. Surgical excision of LM has the advantage of treating deep periadnexal melanocytes, detecting unsuspected invasive LMM, and permitting histologic assessment of the margins for atypical melanocytes, which commonly extend beyond the clinically apparent border. However, the clinical margins of LM and LMM are often poorly defined and may also be masked by ephelides, pigmented actinic keratoses, lentigines, nevi, and seborrheic keratoses. Confirming the difficulties with both clinical and histologic margin control is a study of 92 patients with LM showing that standard surgical excision with “bread-loaf” histologic assessment of margins of LM had incomplete excision rates of 9%, with extrapolated 5-year recurrence rates of lesions thought to be completely excised of 31%.
The current Australian guidelines from the National Health and Medical Research Council for primary cutaneous melanoma recommend surgical margins of 5 mm for in situ lesions, 10 mm for invasive tumors less than 1 mm in Breslow depth, and 20 mm for invasive tumors with 1- to 4-mm Breslow depth. These recommendations are based on the National Institutes of Health consensus guidelines and 2 prospective multicenter trials and provide an acceptable compromise between achieving local control and tissue conservation. However, these recommended margins are based on trials for melanoma on the trunk and proximal extremities and have not specifically addressed tumors on the head, neck, hands, and feet. Excision margins on the head and neck are often reduced to preserve important anatomic structures and for cosmetic reasons. Therefore, LM and LMM present a unique problem because of the characteristic unpredictability of subclinical extension in head and neck locations where tissue preservation is imperative.

The aim of this study was to assess the required surgical margins for excision of LM and LMM, using the technique of mapped serial excision (MSE). We compare the results with recommended margins for these tumors and assess the incidence of recurrence after MSE.

STUDY DESIGN AND PATIENT SELECTION
A single-center, prospective study of consecutive patients with head and neck LM or LMM undergoing MSE between March 1, 1993, and October 31, 2002, was conducted.

INCLUSION CRITERIA
Inclusion criteria were histologically confirmed LM or LMM, larger than 1 cm, occurring on the head and neck. All patients gave informed consent before MSE, and all surgical excisions were carried out in a tertiary-referral, private dermatologic day surgery facility by 2 of us (C.L.J. and A.G.). Histopathological examination was performed by 2 of us (C.L.J. and A.G.).

Lentigo maligna was defined as a form of melanoma in situ with continuous proliferation of atypical melanocytes, singly and in nests, along the basal layer of the epidermis and adnexae; arising in sun-damaged skin with an atrophic epidermis; and with minimal pagetoid invasion into the upper dermis. Lentigo maligna melanoma was defined as LM with a component of dermal invasion.

INTERVENTIONS
The methods used were previously described by Hill and Gramp. The diagnosis of LM or LMM was histologically confirmed by previous shave, punch, or incisional biopsy. A Wood’s light was used to assist in marking the tumor borders and a 5-mm margin was added (Figure 1). In rare cases, such as adjacent to the nostril rim, 5-mm margins could not be achieved around the entire tumor circumference, and the largest possible margin was taken. Excision to the level of the middle to deep subcutaneous fat layer (to include adnexal structures) was performed with the patient under local anesthetic. The excised specimen was mapped, dyed, and sent to the pathology laboratory in formalin. A simple dressing was applied to the wound with an antibiotic ointment, and the patient was examined within 24 hours together with the histology report.

The histopathologic examination consisted of orienting a formalin-fixed specimen according to marker dyed, nicked, and sutures and the accompanying color-coded diagram (Figure 2). Vertically cut paraffin-embedded sections cut at 1- to 2-mm intervals (ie, bread-loaf sections) with block identification were stained with hematoxylin-eosin (Figure 3 and Figure 4). The sections were examined by 2 experienced dermatopathologists (C.L.J. and A.G.). The report, including a diagram with the oriented site(s) of any incomplete excision and the distance between the tumor and surgical margins, was faxed to the dermatologist within 24 hours (Figure 5).

Where excision was incomplete, as defined earlier, a further targeted 5-mm excision was taken from the involved margin and sent for histopathologic assessment. This was repeated until histologic confirmation of clear margins was achieved. The final defect was repaired either by the dermatologist or by oculoplastic or plastic surgeons. Where excision was complete but margins were noted to be less than 3 mm, one dermatologist (S.C.H.) reexcised the relevant margin to give a total margin of 5 mm.

All patients were contacted by telephone and invited to return for clinical review to detect recurrence. The site of previous MSE was examined with magnification, and photographs were compared with previous clinical photographs to detect any signs of recurrence. For those unable to attend, a telephone interview with a set of questions aimed at determining recurrence was conducted. The patients were asked whether there was a new lesion at the site of previous MSE, whether there had been any change in pigmentation or appearance of the scar, and whether any further procedure had been carried out; if so, the reasons for this were noted and the histopathology report was retrieved.

OUTCOME MEASURES
Each 5-mm surgical excision was defined as a “level of excision.” The margin of complete excision was defined by the number of 5-mm levels required. The outcome measures were the number...
of 5-mm margin levels required for complete excision of LM and LMM less than 1 mm thick and the incidence of recurrence.

STATISTICAL ANALYSIS

Continuous data were analyzed by a t test and described as mean and standard deviation. The Wilcoxon rank-sum test was used for nonnormally distributed data. Where appropriate, 95% confidence intervals were stated. Regression with robust standard errors was used to allow for analysis of 2 sites on the same person. A P value of less than .05 was considered statistically significant. Statistical analysis was performed with Stata Statistical Software version 7.0 (Stata Corp, College Station, Tex).

RESULTS

One hundred fifty-five patients (mean age, 68.2±11.8 years; range, 30-94 years), of whom 73 (47%) were female and 82 (53%) were male, underwent 161 MSE procedures for head and neck LM and LMM. Six patients had 2 LMs or LMMs at separate sites and underwent more than 1 MSE. Of these cases, 141 with shorter follow-up were previously reported in a study comparing periorcular and nonperiorcular LMs and LMMs, but in this report we include an additional 20 cases and report on all patients with a longer follow-up.

NUMBER OF 5-mm LEVELS REQUIRED FOR COMPLETE EXCISION

One hundred twenty-five patients had LM; of these lesions, 30% (37/125) required more than 1 level (>5-mm margins) for complete excision. Thirty-six patients had LMM; 32 (89%) of 36 LMMs were less than 1 mm thick and 12% (4/32) of these lesions required more than 2 levels (>10-mm margins) for complete excision. The remaining 4 (11%) of 36 LMMs were 1.4 mm, 1.4 mm, 2.9 mm, and 4.0 mm thick. All additional levels for LM and LMM were for marginal in situ disease (Table). There was no significant relationship between preoperative clinical lesion size (both maximum diameter and estimated area were assessed) and the number of 5-mm levels required for complete histologic excision (data not shown).
Forty-six (29%) of the 161 cases had recurred before MSE; of these, 34 (74%) were LM and 12 (26%) were LMM. Previous treatment modalities included surgical excision (32 cases), cryotherapy (12), and argon or carbon dioxide laser therapy (2). Review of previous histology and post-MSE histology reports showed that only 1 LM lesion (previously treated by excision without margin control) recurred as LMM. None of these 46 lesions had previously been treated by MSE.

Recurrent LM was more likely than primary LM to require more than 1 level for complete clear margin excision ($P=.01$) (Table).

**PRIMARY LM AND LMM**

Twenty percent of cases of primary LM required greater than 5-mm margins for complete excision, and 10% of primary LMMs less than 1 mm in Breslow thickness required more than 10-mm margins for complete excision (Table).

**UNSUSPECTED LMM**

Thirty-six lesions (22%), all of which were referred by other dermatologists, were invasive melanoma (LMM). At least 28 of these (78%) were not considered to be invasive LMM before biopsy and/or MSE. Twenty-four (67%) were referred with a biopsy result of LM but were found to be LMM after MSE.

**FOLLOW-UP AND RECURRENCE**

One hundred fifty-five cases (96%) were available for follow-up at a mean period of 38±25 months (range, 3-100 months; median, 18 months). Four patients (2%) could not be contacted for final follow-up, and 2 patients (1%) died during the follow-up period, both as a result of known cardiac disease.

Four cases (2%) recurred after MSE at intervals of 12, 31, 39, and 40 months. All 4 were initially primary LM. They all underwent repeat MSE procedures, at which time 2 were histologically confirmed to be LMM (thickness, 1.1 mm and 0.25 mm). To date, no further recurrence has occurred. Kaplan-Meier statistical analysis to extrapolate recurrence rates gave the probability of recurrence at 5 years as 0.05 (95% confidence interval, 0.013-0.186).

**COMMENT**

The technique of MSE demonstrates that the current recommendations of 5-mm margins for in situ melanoma and 10-mm margins for invasive melanoma less than 1 mm in Breslow thickness are often insufficient for head and neck LM and LMM. Only 80% of primary LM larger than 10 mm and 90% of primary LMM larger than 10 mm and less than 1 mm in Breslow thickness would be managed effectively with the current recommended margins. In recurrent LM, 56% required more than one 5-mm level of excision, compared with 20% of primary LM. These figures show the tendency toward subclinical extension of LM and LMM, particularly in recurrent lesions, and the usefulness of margin-controlled excision in achieving complete tumor eradication.

Our finding that complete excision of LM and LMM often requires wider margins than are currently recommended in the National Institutes of Health and National Health and Medical Research Council guidelines supports the results of previous studies. Zitelli et al used a modified form of Mohs surgery to excise 231 head and neck tumors in a series of 553 primary cutaneous melanomas. It is not clear how many of these head and neck tumors were of LM-LMM subtype, although it is likely, given...
been described. In 1990, Dhawan et al described the first frozen-section interpretation have difficulty with frozen-section interpretation have activity and specificity of 100% and 90%, respectively, in the surgery frozen sections of margins in combination with gin, staged excision with rushed paraffin en face sections, and this approach has been subsequently used with margins of 10 mm or less. Cohen et al performed Mohs surgery in a series of patients with LM and LMM and found that a mean margin of 13 mm was required for complete excision. Agarwal-Antal et al, using the “square” technique (staged excision with rushed paraffin-embedded en face sections of margins and rushed vertical sections of a central debulking specimen) described by Johnson et al, found that 58% of 92 LM lesions required margins greater than 5 mm.

The knowledge that LM and LMM often extend beyond clinically apparent margins has prompted various methods of margin control. Mohs micrographic surgery is the best known technique of margin control; however, visualization of atypical melanocytes on frozen sections can be extremely challenging for the Mohs surgeon and/or pathologist. Cohen et al and Barlow et al reported sensitivities of only 73% and 59%, respectively, combined with specificities of only 68% and 81%, respectively, in frozen sections of LM and LMM. In contrast, Zitelli et al reported sensitivity and specificity of 100% and 90%, respectively, in the diagnosis of melanoma on frozen sections.

A variety of modified Mohs surgery techniques to overcome the difficulty with frozen-section interpretation have been described. In 1990, Dhawan et al described the first case of LM treated with a modified form of Mohs micrographic surgery, using rushed paraffin-embedded en face sections, and this approach has been subsequently used with success. Other approaches have included a combination of vertical paraffin sections for central tumor staging and Mohs surgery frozen-section analysis of margins, and Mohs surgery frozen sections of margins in combination with rushed paraffin-section confirmation of tumor-free margins, staged excision with rushed paraffin en face sections of margins and rushed vertical sections of a central debulking specimen, vertical central paraffin sections and rushed paraffin tangential sections of margins in combination with immunohistochemistry, and immunohistochemistry to assess both frozen and paraffin sections. Recurrence rates for these techniques with follow-up ranging from 2 to 9 years have ranged from 0.3% to 3%. The best results were obtained by Zitelli et al, using a modified form of Mohs surgery with frozen-section margin control and vertical paraffin sections of the central tumor, with a recurrence rate of 0.5% at 5 years for 184 in situ melanomas, of which 106 were on the head and neck.

Our technique of MSE differs from standard Mohs surgery in certain key aspects. Although the tumor was excised, mapped, and dyed by a Mohs surgeon, numerous vertical bread-loaf paraffin, rather than en face frozen, sections were taken (Figures 1-5). Furthermore, these were assessed by a dermatopathologist rather than the Mohs surgeon. The main disadvantage of our technique when compared with Mohs surgery and modified Mohs techniques with paraffin en face sections is that only a percentage of the peripheral margins rather than close to 100% of margins is examined, and this may well account for our small number of recurrences.

However, there are advantages of MSE in comparison with Mohs surgery and some of the modified Mohs surgery techniques, including no requirement for a laboratory technician, cryostat, and staining machine for making frozen sections. In addition, other than the greater number of sections required, processing by the pathology service may be carried out in a standard fashion. Furthermore, sections through the tumor permit assessment of marginal melanocytic atypia and hyperplasia in comparison with the central portion of the tumor; the tumor often exists as an island in a sea of sun- and age-related melanocyte abnormality, which must be differentiated, sometimes with difficulty, from the tumor. Sectioning through the tumor out to the surgical margins also allows accurate measurement of the distance between the tumor and the surgical margins. In common with MSE, many of the modified Mohs surgery techniques also describe vertical central sections to permit adequate assessment of adnexal involvement and also the diagnosis and assessment of the depth of invasion in LMM. The use of paraffin sections with dermatopathologist interpretation generates a pathology report with melanoma prognostic indicators; this can be circulated to other medical personnel and sent to central cancer-reporting agencies. Finally, although a few centers of excellence have reported good results with frozen sections, we believe that paraffin sections are to be preferred to frozen tissue sections in the interpretation of melanoma.

Our follow-up data confirm that MSE has a low recurrence rate and compares favorably with Mohs surgery and modified forms of Mohs surgery; with a mean follow-up of 38 months, only 4 cases (2%) recurred. Kaplan-Meier statistical analysis to extrapolate recurrence rates gave the probability of recurrence at 5 years as 0.05. Like Mohs surgery, MSE permits tissue conservation, of particular importance on the head and neck.

The lesions that we excised with MSE are likely to represent a more difficult group of lesions than untreated cases, as all were treated in a tertiary referral practice. A high proportion (29%) were recurrent after previous treatment. Many had at least a component of lightly pigmented to amelanotic tumor, making margin assessment more difficult.

In clinical examination of LM and LMM, there are no reliable predictors for the presence of invasive disease other than the presence of an obvious nodule. In a series of 85 patients diagnosed clinically as having LM, more than 50% had invasive LMM. Our study confirms the difficulty in clinically distinguishing LM from LMM; none of the 36 patients with LMM had a tumor nodule and more than 75% were not suspected to be invasive LMM by dermatologists before biopsy and/or MSE. Furthermore, the sampling problems associated with biopsies are highlighted by our finding that 24 (67%) of 36 patients with LMM were referred with a biopsy result of LM that was subsequently found to be LMM after MSE.

A lack of prospective longitudinal data makes it difficult to estimate the risk of LM progression to LMM. Wayte and Helwig proposed that 30% to 50% of LM may progress to LMM if untreated. However, Weinstock and
Sober estimated, on the basis of statistical analysis, that a patient with LM at 45 years of age has a 4.7% lifetime risk of developing LMM, while a 65-year-old patient has a 2.2% lifetime risk. This decreasing lifetime risk of LM transforming to LMM with increasing age at onset most likely reflects patient mortality from unrelated causes before the LM lesion becomes invasive. Thus, we suggest that factors such as age and general health be taken into consideration before undertaking surgical management. In our study, the mean age of patients was 68 years, and all patients were considered fit for surgery.

The unknown natural course, lack of reliable clinical predictors of LM and LMM, and the unpredictable subclinical atypical melanocyte extension make a strong argument for complete obliteration of the lesion as the aim of treatment. A wide variety of destructive and surgical therapies have been used. We believe that surgical excision has several advantages. First, it allows assessment of tumor thickness, which is the single most significant prognostic indicator in the management of melanoma. Second, it allows treatment of deep periaxial melanocytes and detection of both invasive melanoma and atypical melanocytes beyond the clinically apparent margins. Third, surgical excision does not result in the pigmentary changes sometimes seen in destructive modalities such as radiotherapy and cryotherapy; these pigmentary changes may also make subsequent recurrence difficult to detect.6,36

In conclusion, the current recommendations of 5-mm margins for in situ melanoma (LM) and 10-mm margins for melanoma less than 1 mm in Breslow thickness are sufficient for only 80% of primary LMs larger than 10 mm and 90% of primary LMMs larger than 10 mm and less than 1 mm in Breslow thickness. These guidelines may, however, be useful initial margins for the technique of MSE. As the natural course of LM is essentially unknown and there are difficulties in clinical differentiation of LM and LMM, we suggest that complete excision is the treatment of choice. The findings of this series of head and neck LM and LMM show that MSE appears to be an effective means of attaining a high cure rate in these tumors with characteristic subclinical extension, while also conserving facial and neck tissue.

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REFERENCES


