Management of Lentigo Maligna and Lentigo Maligna Melanoma With Staged Excision

A 5-Year Follow-up

Jennifer L. Bub, MD; Daniel Berg, MD; April Slee, BA; Peter B. Odland, MD

Objective: To assess the long-term cure rate for treatment of lentigo maligna (LM) and lentigo maligna melanoma (LMM) by means of a staged, margin-controlled, vertical-edged excision with rush permanent specimens and a radial sectioning technique.

Design: Retrospective follow-up study.

Setting: University-affiliated and private-practice dermatologic surgery clinics.


Interventions: The technique included vertical excision with initial 2- to 3-mm margins examined by rush permanent sections (prepared and read within 24 hours). Further excision took place as guided by histologic findings. Data on patient and lesion characteristics were obtained via a medical chart review. Patients were then contacted and examined for local recurrence. Biopsies were performed on all patients with possible recurrence on clinical examination.

Main Outcome Measures: Local recurrence of LM or LMM.

Results: After a mean follow-up of 57 months (median, 54 months; 293.8 person-years), 95% of patients were free of recurrence. Three patients had local recurrence and no patients had evidence of metastasis. Two of the 3 local recurrences were of previously excised LM, and 1 was of an LMM. Half (32) of all lesions required 2 or more stages. One required more than 4 stages. The average margin of excision was 0.55 cm. Three of the 58 lesions read as LM on biopsy were found to have invasive disease (LMM) at the time of definitive excision.

Conclusions: The technique described herein for the treatment of LM and LMM provides a long-term disease-free survival of 95%. The cure rate is greater than that reported for standard excision and is similar to that for other margin-control techniques. To our knowledge, this is the largest reported study and has the longest follow-up for this excision method for LM and LMM.

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First described by Hutchinson in 1890 as “infective senile freckles,”1 lentigo maligna (LM) is a pigmented melanocytic neoplasm found mainly on the sun-exposed skin of the head and neck2,3 in elderly patients. In Australia, the annual incidence of LM has been estimated to be 1.3 per 100,000.4 In the United States, analysis of the Surveillance, Epidemiology, and End Results data estimated the incidence of LM melanoma (LMM) to be 0.8 and 0.6 per 100,000 for males and females, respectively.5 Overall, the incidence of LM appears to be increasing.6-8 The number of cases of LM and LMM also increases with age,5,7 with a peak in the seventh and eighth decades of life.9-10 The incidence ratio of LMM is consistently higher in the central and southern United States compared with the north,9 and in Australia, LM had a strong association with indicators of sunlight exposure, such as a history of nonmelanoma skin cancer, actinic damage, and number of years in Australia.11

For editorial comment see page 607

From the Division of Dermatology, School of Medicine (Drs Bub and Berg), and Department of Biostatistics (Ms Slee), University of Washington; and Skin Surgery Center (Dr Odland), Seattle, Wash. The authors have no relevant financial interest in this article.

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Although no longitudinal studies have been done on the natural course of LM, an epidemiologic analysis estimated that at age 65 years, a patient with an untreated LM would have a 1.2% risk of developing LMM by age 75 years and a
lifetime risk of 2.2%. At age 45 years, the risk of developing LMM by age 75 years would be 3.3%, and the lifetime risk, 4.7%. After controlling for depth of invasion, the prognosis for LMM has been shown to be equal to that of other types of melanoma.

Many different treatment modalities have been recommended for LM. Destructive methods include cryosurgery, electrosiccation and curettage, laser surgery, radiotherapy, and topical treatments. A recent retrospective study on radiotherapy reported recurrence rates of only 7%. Previous studies on other superficial destructive methods have found recurrence rates of 10% to 50% for cryosurgery and up to 100% for laser and topical modalities. These high recurrence rates are thought to result from failure to treat the subclinical peripherally spread and atypical junctional melanocytes in the deep adnexal epithelium.

For both LM and LMM, complete surgical excision results in the highest cure rate and is considered the treatment of choice. In 1992, the National Institutes of Health Consensus Development Conference recommended a margin of 0.5 cm for melanoma in situ and 1.0 cm for thin melanomas (<1.0 mm). However, studies have demonstrated that more than 50% of LMs require margins greater than 3 mm, and that necessary margins are greater for larger lesions. In addition, recurrence rates for standard excision of LM range from 8% to 20%. More recently, the use of margin control surgical techniques has been advocated. These include Mohs micrographic surgery (MMS), MMS aided by rush permanent sections, “slow Mohs,” the “square technique” (Table 1), and others.

Since 1990, we have treated LM and LMM with a staged technique using perpendicular excision and rush permanent, radically cut sections. With good communication between the clinician and pathologist, this technique is easy to use. We report our observations with 62 cases during a mean follow-up of 57 months. To our knowledge, this is the largest retrospective follow-up study looking at staged excision with permanent sectioning for LM to date.

| Table 1. Comparative Analysis of Different Surgical Techniques for Treatment of Lentigo Maligna and Lentigo Maligna Melanoma |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| **Standard Excision** | **MMS** | **MMS Followed by Rush Permanent Sections** | **“Slow MMS”** | **“Square” Procedure** |
| **Angle of excision** | ° | ° | ° | ° |
| **Margin size** | 2-10 mm | 2-3 mm (plus 3-mm initial margin excised with central tumor) | 4-6 mm | 5-10 mm |
| **Tissue-mapping technique** | Varies; none to orientation to face of clock | Standard MMS mapping | Standard MMS mapping | Tissue “strips” oriented and mapped |
| **Tissue fixation method** | Permanent | Frozen | Permanent and frozen | Oriented and mapped to face of clock |
| **Reader of margin histologic findings** | Pathologist | MMS surgeon | Pathologist | Pathologist |
| **Sectioning orientation** | Bread loaf | En face (horizontal or vertical) | En face (horizontal) | En face (vertical) |
| **Duration of follow-up** | 3-3½ y | 2-5 y | 2-5 y | Radial |
| **Recurrence rate** | 6/68 (8.8%) | 18/20; 4 2mo | 3/62 (4.8%) | 22 mo |

**Abbreviation:** MMS, Mohs micrographic surgery.

*Technique in current study; similar to technique described by Hill and Gramp, except the latter uses a 5-mm initial margin.
†Per stage.
‡Includes 2- to 3-mm rim for both frozen and permanent sections used in study cited. In clinical practice, margins are 2 to 3 mm.
§Includes local and distant recurrences; data are aggregated on the basis of literature review.
\*Study based on all melanomas with 184 melanomas in situ.

DATA COLLECTION

We reviewed the medical records of 62 patients treated at the University of Washington Dermatologic Surgery Unit or the Skin Surgery Center in Seattle, Wash, for LM or LMM by means of staged excision (as described in the following subsection) between January 1, 1990, and December 31, 2001. Approval was obtained from the University of Washington Human Subjects Review Committee before data collection. The following information was obtained from each medical chart: age at diagnosis, sex, tumor type, location and depth of invasion if LMM, history of previous treatment, size of preoperative tumor and postoperative surgical defect, number of stages required, type of reconstruction, complications, recurrences, and duration of follow-up.

Follow-up was obtained by direct examination, by contact with the referring physician, or by telephone interview with the patient or nearest relative if the patient was debilitated or deceased. Three patients were unable to be located (lost to follow-up). Before inclusion in the study, all patients signed a written consent form. A free clinical examination was then performed by one of us (J.L.B.) on all able patients re-
obtained.

**Table 2. Method by Which Follow-up Was Obtained**

<table>
<thead>
<tr>
<th>Person Performing Clinical Examination, No.</th>
<th>Study Personnel</th>
<th>Outside Dermatologist*</th>
<th>Outside Primary Care Physician*</th>
<th>Per Patient/Next of Kin Report</th>
</tr>
</thead>
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<td>Total†</td>
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<td>10</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Reason not seen by study personnel</td>
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<td>Recent dermatologic examination*</td>
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<td>0</td>
</tr>
<tr>
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<td>3</td>
</tr>
<tr>
<td>Debilitated</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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<td>Moved</td>
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<td>2</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Other‡</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
*All examinations were done within 3 months of onset of study, excluding patients who died.
†Excluding the 3 patients with local recurrence.
‡Declined examination because of death in the family.

**Surgical Technique**

Since 1990, we have treated LM and LMM with serial excisions in a staged fashion (Figure 1). Before treatment, a positive histologic diagnosis is made by biopsy. The procedure is performed in an outpatient setting with the patient under local anesthesia, with additional oral sedation as needed. The lesion is demarcated with a Wood lamp and a 2- to 3-mm rim is outlined before anesthesia. Scalpel excision is made with a vertical (90°) incision into subcutaneous tissue deep to the hair follicles (when present). Precise mapping of the specimen and excision site (defect) is performed with orientation to the face of a clock. The specimen is placed in formalin, and sent with a line drawing to the pathologist. The pathologist is notified before the surgery so that the specimen can be processed, sectioned, and read within 24 hours. Good communication with the pathologist concerning methods for proper specimen orientation, sectioning technique, and positive margin mapping is necessary.

In the histopathology laboratory, the accompanying drawing is reviewed and the margins of the specimen are inked to maintain orientation. Depending on size, the specimen may be bisected or divided into quadrants. It is then divided radially (like pieces of a pie) according to the numbers on a clock face, and each pie wedge is placed in a cassette, embedded in paraffin, and then sectioned radially (Figure 2). Sections are taken at approximately 1-mm intervals. The following morning, the dermatopathologist reviews the slides, and a telephone report and faxed diagram are relayed to the surgeon. The diagram indicates precisely the status of the margin (Figure 3). On that morning, the patient returns. A second stage is performed if LM (nested or confluent single melanocytes with significant cytological atypia) is present at, or within 1 to 2 mm of, the margin in any section.

In stage 2 (Figure 1), a second “layer” of normal-appearing tissue is taken only from the region marked positive. This is again done with a 2- to 3-mm rim (and to a similar depth as in stage 1) and produces a 2- to 3-mm tissue “strip” of varied length depending on the extent of the positive margin. This specimen is oriented with color-coded inked margins or suture, placed in formalin, and again sent with a line drawing to the pathologist. During histopathologic processing, the outside margin is inked, and the specimen is divided into smaller numbered strips (if needed), placed in cassettes, and embedded in paraffin. Maintaining meticulous orientation, the strips are then vertically sectioned (rather than en face), and the slides are examined by the pathologist. The entire process is repeated until the margins are histologically free of tumor (as with stage 1, if tumor cells approach to within 1 to 2
mm of the margin, an additional 2- to 3-mm specimen is obtained. On clearance of the tumor, the patient returns for surgical wound repair.

HISTOPATHOLOGIC DEFINITION

The following criteria were used to make the diagnosis of LM:
(1) solitary units and small nests of atypical melanocytes along the basal layer; (2) extension of atypical melanocytes along adnexal structures; (3) solar elastosis; (4) epidermal atrophy and effacement of the rete ridges; and (5) a predominantly lymphocytic dermal infiltrate. In some cases, not all criteria were required for diagnosis. The diagnosis of LMM was made on the basis of invasion of atypical melanocytes into the dermis.

STATISTICAL ANALYSIS

The primary outcome of interest was recurrence. Data for subjects lost to follow-up were treated as missing at random. A secondary question of interest was the relationship between lesion size and the number of stages required to clear the margins. We calculated lesion size by averaging lesion width and length, and then approximating the area by calculating the area of a circle.

Sixty-two patients underwent staged surgical excision for LM between 1990 and 2001. Fifty-nine patients with a total of 62 lesions (55 LM and 7 LMM) were included in the study. Table 3 contains lesion and patient characteristics. The age range at initial presentation was 34 to 93 years, with an average of 67 years. Fifty-nine percent of subjects were men and 41% were women. Lesions were located on the head and neck in 92% of cases. The most common location was the cheek (39%), followed by the nose (10%) (Figure 4).

Of the 62 lesions, 58 were initially read as LM. Three (5%) of these 58 were found to be invasive LMM at the time of definitive excision. Of the 7 lesions of LMM, Breslow thickness ranged from 0.3 mm to 1.1 mm with a mean of 0.52 mm. For all lesions, the average number of stages needed to histologically clear the tumor was 1.68. While half of all lesions (32) required 2 or more stages, only 1 required 4 stages. Using the previously reported cutoff of 3.0 cm², we found that smaller lesions tended to require fewer stages (Table 4). The mean number of stages for lesions measuring 3.0 cm² or more was 1.95 compared with 1.54 for lesions smaller than 3.0 cm² (t test, \( P = .04 \)). The mean lesion size before staged excision was 2.1 cm (3.5 cm²), and the mean postoperative depth was 2.5 cm (7.7 cm²). Thus, the average margin of skin excised (and rough estimate of subclinical tumor spread) was 0.55 cm. For lesions of 3.0 cm² or more, 29% would have required a standard surgical margin of more than 6 mm compared with 7% of those smaller than 3.0 cm². Fifty-two percent of all lesions would have required a standard surgical margin of 4 to 6 mm, and 15% would have required a margin greater than 6 mm.

Follow-up was obtained by personal clinical examination at the time of the study for the majority of the pa-
lems that recurred after staged excision, 1 was a primary tumor and 2 had been previously excised. The recurrence rate after staged excision for primary tumors was 2% (1/50) compared with 17% (2/12) for previously treated tumors. These differences do not reach statistical significance.

Figure 4. Number of lentigo maligna and lentigo maligna melanoma lesions by location.

Mohs first described margin-controlled surgery for the treatment of LMM in 1978. In 1990, Dhawan et al described a modified staged surgery for LM treatment. Later called “slow Mohs,” their technique called for excising and mapping the tumor by Mohs technique with beveled edges, and then fixing the tissue in formaldehyde and sending it for “rush” permanent sections to be examined by a dermatopathologist. Since then, several margin control techniques have been described. However, since most recurrences of LM do not occur until 3 to 5 years after initial excision, long-term follow-up is needed to determine the success rate of any treatment modality. Although many authors have reported on recurrence rates, only a few have obtained long-term (5-year) follow-up. Additionally, results may not be comparable because follow-up methods are not always adequately described.

In 1994, Cohen et al described the use of frozen-section MMS followed by rush permanent sections in 45 patients. They subsequently reported follow-up on 38 of the 45 patients and found a recurrence rate of 3% after a mean of 57 months. Using a similar technique with the addition of immunohistochemical stains, which resulted in increased sensitivity, Robinson et al found 1 recurrence in 16 patients (6%) after 8 years. Zitelli et al treated 553 melanomas with MMS (frozen section only). Of these, 184 were melanoma in situ, for which they reported a local recurrence rate of 0.5% at 5 years. They did not differentiate between LM and other types of melanoma in situ and did not report on methods of follow-up. We followed up 59 patients with a total of 62 lesions of LM or LMM and found a recurrence rate of 5% at 5 years. We use a staged, margin-controlled, vertical-edged excision with rush permanent, paraffin-embedded specimens and radial histologic sectioning technique.

The rationale for using vertical rather than horizontal or tangential edges and radial rather than en face sectioning is ease of tissue processing in pathology laboratories not accustomed to MMS technique, and improved margin interpretation. As suggested previously, we also have had great difficulty obtaining properly oriented specimens when the tumor is excised by means of traditional
MMs bevel-cut margins, fixed in formalin, and then sent to the histopathology laboratory for paraffin embedding and en face sectioning. In addition, there is another potential benefit of using radial rather than en face sectioning. It is well documented that the peripheral margins of LM found in areas of chronic sun damage are difficult to interpret (true LM vs “background” sun-induced melanocyte atypia).31,32 The dermatopathologist who reads the slides for this study believed that it is easier to evaluate the margins by following the tumor’s “evolving” architecture from the center in a centrifugal fashion rather than examining only the peripheral edge, as is done with traditional MMs en face sectioning. When only an en face margin is examined, it can be difficult to tell the difference between scattered baseline atypical melanocytes and the single melanoma cells that taper out toward the periphery of a lesion of LM. Other experts may feel that evaluation of the complete margin is preferable.

Use of a 90° incision angle and permanent sectioning technique may avoid some of the potential pitfalls associated with interpreting the margin of LM on bevel-cut, frozen sections.35,31,32 With beveled sectioning, normal melanocytes may appear enlarged, and frozen-tissue processing causes keratinocyte vacuolization and loss of the melanocyte retraction artifact used to distinguish the 2 cell types. Because of different comparison techniques, studies addressing the sensitivity and specificity of frozen sections for LM are difficult to compare. Zitelli34 found the sensitivity and specificity of frozen sections for melanoma (not just melanoma in situ) to be 100% and 90%, respectively. Other studies looking at LM and LMM have found sensitivities of 59% to 73% and specificities of 68% to 81%,3,21

We understand that the major advantage of MMs surgery over our described method is that Mohs surgery ideally allows for examination of 100% of the margin. For margin interpretation, our described method might thus be expected to have a lower sensitivity (ability to pick up tumor cells when they are truly present), but not specificity, compared with MMs. Proponents of MMs for LM and LMM believe that it offers rapid treatment while sparing unnecessary tissue removal in cosmetically sensitive areas, and allows for identification of subclinical spread and examination of 100% of the margin. The most important criterion as to the usefulness of a margin control method is the long-term cure rate. As demonstrated by the long average time to first recurrence in our study (4.7 years; range, 2-7 years), evaluation of the efficacy of any treatment method for LM requires long-term follow-up.

Many margin-controlled techniques for treatment of LM use initial excision margins equal to or greater than the 5-mm recommended standard excision margin (Table 1). With our technique, we take an initial margin of only 2 to 3 mm around the visible tumor. Our average number of stages to tumor clearance was 1.7, which is comparable to other reports of 1.9,27 2.1,23 and 2.3.26 In contrast, our mean postoperative defect sizes tended to be smaller than those reported previously (2.5 x 3.3 cm vs 4.2 x 4.5 cm, respectively26), while the mean initial lesion sizes were similar (1.5 x 2.1 cm vs 1.7 x 1.7 cm, respectively26). Thus, while lesion size and number of stages were similar, our final defect sizes were, on average, smaller, which may be due to the narrower margins excised with each stage. If smaller defect size can be attained with similar margin control, this is beneficial in cosmetically sensitive locations on the face.

Our data suggest, as has been previously shown,3,9,21 that larger lesions tend to have greater subclinical spread and that a 5-mm margin may not be adequate in all cases. Fifty-four percent of lesions smaller than 3.0 cm² were cleared in one stage compared with 38% of lesions 3.0 cm² or larger. For lesions 3.0 cm² or larger, 62% required margins of 4 to 6 mm or greater, and 29% required margins greater than 6 mm. Of all lesions, 15% required margins greater than 6 mm. Previous studies have shown that approximately 5% to 10% of biopsy-proved LMs have an invasive component on histologic examination of the entire lesion. We found that 3 (5%) of the 58 lesions initially read as LM on biopsy had invasive disease at the time of definitive excision. This supports the need for complete resection of LM when possible.

In summary, we present long-term follow-up on a staged, margin-control surgical technique for the treatment of LM and LMM. From 1990 to 2001, we treated 59 patients with 62 lesions and achieved a 95% cure rate during an average follow-up of 57 months. This is one of the largest studies with an adequate duration and explanation of follow-up looking at surgical treatment for melanoma in situ. Since the average time to recurrence was 4.7 years, even longer follow-up (≥10 years) would be useful. Our intent has been to describe our technique with a thorough “Methods” section and figures allowing for easy reproduction for practitioners treating these lesions. With good communication between the surgeon and the pathologist, this technique is relatively simple to execute, has a cure rate that exceeds that of conventional surgery,16,18,23 and is comparable to other margin-controlled techniques.20,27

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Corresponding author: Jennifer L. Bub, MD, Division of Dermatology, University of Washington, Campus Box 356524, 1959 NE Pacific, Seattle, WA 98195.

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