Surgical Treatments for Lentigo Maligna: A Review

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BACKGROUND Since its initial description by Jonathan Hutchinson 120 years ago, a substantial amount of research has occurred to determine the optimum surgical therapy for lentigo maligna (LM).

OBJECTIVE To summarize the literature regarding the surgical treatment of LM.

METHODS We searched the National Library of Medicine using Pubmed Central and MEDLINE and included as many investigational reports regarding LM therapy that were available in an attempt to form a comprehensive review of surgical modalities. The key words ''lentigo maligna,'' ''lentigo maligna treatment,'' ''lentigo maligna therapy,'' and ''lentigo maligna therapeutic modalities'' were used.

RESULTS We included 12 studies examining staged surgical excision (SSE), nine using Mohs micrographic surgery (MMS), six investigating cryosurgery, 22 investigating imiquimod, seven using lasers, nine investigating radiation therapy, and two investigating electrosurgery and curettage.

CONCLUSIONS SSE and MMS are associated with the lowest recurrence rates for LM. Cryotherapy and radiation therapy may be considered the options for treatment of LM in patients who cannot tolerate surgery. Imiquimod, although not currently approved by the FDA, has shown some efficacy in limited experimental studies and may play a future role in the treatment of LM.

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In 1890, Jonathan Hutchinson first described lentigo maligna (LM).[1,2] As a result of Hutchinson's description, LM became known as "Hutchinson's melanotic freckle" in 1896.[2–6] Four years after Hutchinson's description, Dubreuilh used the French phrase "lentigo malin des viellards," which translates to "malignant lentigo of the elderly."[7] Hutchinson originally thought the lesion was infectious in nature, using the terminology "infective senile freckles;" however, it was Dubreuilh, in 1912, who classified it as precancerous, using the phrase "de la mélanose circonscrite precancereuse," which translates to "circumscribed precancerous melanosis."[2,8–11] The current concept of LM encompasses what are probably two entities.[12] In 1999, Flotte and Mihm proposed that there exist two histologic subtypes of LM with distinct biological behaviors.[12] Under their definition, LM is defined as atypical melanocytic hyperplasia, whereas malignant melanoma in situ (MIS), LM type is characterized by confluence and nesting of atypical melanocytes at various layers of the epidermis (Figure 1).[12] This distinction was later found to be clinically relevant in a study by Tannous and colleagues, where all of the cases of invasive melanoma, LM type were associated with MIS, LM type.[13] Despite this distinction, most therapeutic studies have not made this distinction, so LM cases discussed in this review largely contain LM and malignant MIS, LM type as defined above. Future studies should clearly make this distinction because the biologic behavior of LM or malignant MIS, LM type is different.[13] Thorough sampling of lesions without this distinction made may reveal areas of LM; MIS, LM type; and invasive melanoma.[2,14] Several histologic studies have suggested that 16% to 50% of LM lesions have an invasive

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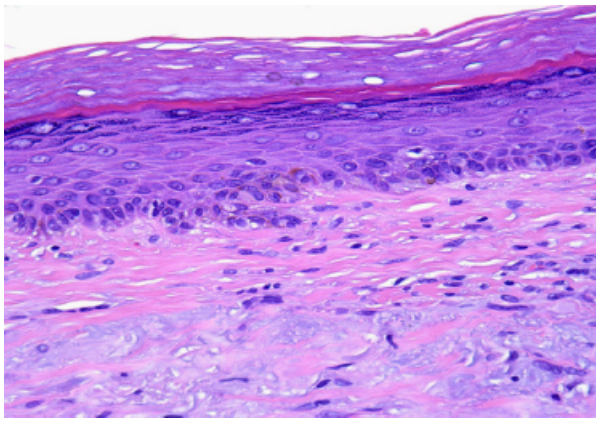

Figure 1. Hematoxylin and eosin permanent section of lentigo maligna at ×40 magnification. Courtesy of Basil Cherpelis, MD, and Frank Glass, MD.

component.[15–17] This review focuses on current surgical therapies for LM (which is defined as two separate entities as outlined above, but largely without this distinction made in the studies reviewed) and briefly touches on clinical presentation.

Clinical Presentation and Diagnosis

LM is a slowly growing pigmented lesion most commonly located on the head and neck of elderly individuals—areas of the body that have been chronically exposed to sunlight (Figure 2).[18] It presents as a macule that can range in size from 0.5 cm to 20 cm, with "haphazard" hues of black on

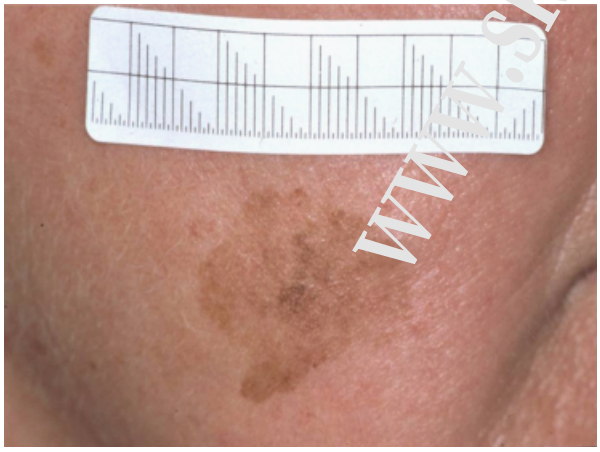

Figure 2. Clinical image of lentigo maligna. Image courtesy of Robert Johr, MD, and Wilhelm Stolz, MD.

a brown background.[19] The addition of red, white, and blue colors, as well as papules and nodules, tends to signify areas where LM may have advanced into the dermis.[19,20] The exact percentage and the time frame in which LM and MIS, LM type progress to lentigo maligna melanoma (LMM) are unknown.[18] LM progresses to LMM slowly, although rapid progression has been noted.[21] The rapid progression to LMM may be associated with lesions that consist of MIS, LM type or lesions with microinvasion present but not detected on biopsy. Weinstock and Sober suggested that 4.7% of LM progresses to LMM when diagnosed at the age of 45 and 2.2% when diagnosed at 65.[22] The risk of LM progressing to LMM may be related to the size of the lesion.[2]

LM is distinguished from other melanoma subtypes such as nodular melanoma and superficial spreading malignant melanomas by having more-numerous dendritic processes and abundant ellipsoidal and normal-appearing melanosomes (vs spheroidal, granular, and abortive forms) that are better differentiated.[23]

Excisional biopsy remains the most accurate technique to diagnose LM, because incisional biopsies may not detect focal areas of invasion.[18] Shave biopsies are also not recommended because the tumor may be transected, thereby not allowing an accurate Breslow measurement.[18] In areas where the LM lesion is clinically large, biopsying the darkest, most-palpable portion with deep saucerization may reveal areas of invasion and rarely transects the invasive portion.[18]

Surgical Excision

There have been numerous technical variations in the surgical excision of LM. To categorize each technique for evaluation purposes, we used three broad categories: wide local excision (WLE), staged surgical excision (SSE), and Mohs micrographic surgery (MMS). WLE is the standard, one-stage surgical excision, using margins of 0.5 cm. SSE is any

surgical procedure for LM incorporating more than one stage of excision, usually with the next stage defined by the histologic findings of the previous stage. MMS is a subset of SSE using the appropriate technique defined in the MMS section of this review.

LM presents an interesting dilemma for surgical excision because subclinical extension can be unpredictable, and histopathologic evaluation poses certain challenges discussed later.[18,24] In an effort to overcome these two therapeutic obstacles, surgical approaches using multiple stages, including the square, perimeter, contoured, and total circumferential margin control (TCMC) techniques, have been developed. This is in addition to conventional MMS and slow Mohs. These techniques use different methods of histologic analysis, including frozen sections, permanent sections, combined frozen and permanent sections, and immunohistochemistry, along with different types of section cuts, such as radial,[25] en face as in MMS, and vertical or "bread loafing" that commonly occurs in WLE and SSE.

The current recommendation for MIS is a border margin of 5 mm, suggested by the National Institute of Health Consensus Conference in 1992 and subsequently published in the cutaneous melanoma treatment guidelines by the National Comprehensive Cancer Network (NCCN).[26] Despite this recommendation, using 5-mm margins as in WLE is inadequate for many cases of LM, because clearance rates using those margins range from 24% to 70%,[26] with recurrence rates ranging from 7% to 20%.[27–30] Some reports suggest that 5-mm margins are sufficient in less than 50% of cases.[16] More appropriate margins such as 9 to 15 mm result in greater than 94% clearance rates.[31–33] Some investigators have attributed the high recurrence rate of WLE using 5-mm margins to a failure to treat subclinical peripheral disease.[18,27] This subclinical disease often consists of atypical junctional melanocytes located in the deep adnexal structures along with striking horizontal growth.[18,27] The high recurrence rate when using 5-mm margins led the NCCN to issue a new statement in 2008. Their conclusion suggested that the surgical margins of larger LM lesions may need to be greater than 5 mm, along with a more thorough histologic analysis.[34]

Staged Surgical Excision

Johnson and colleagues developed the square procedure in an effort to achieve sufficient marginal excision and adequate histologic analysis (Table 1).[35] Using this technique, the lesion is initially delineated using a Wood's lamp. Then it is outlined using a double-lined square separated by a 5- to 10-mm margin from the lesion with 2 to 4 mm between the double lines of the square. The outer perimeter of the square is excised using a two-bladed knife. The perimeter square tissue obtained is sectioned from the outside edge inward and evaluated using horizontal permanent sections. At the surgical site, the resulting 2- to 4-mm circumferential band of exposed adipose tissue surrounding the tumor is closed. Positive areas are marked on a map, and the patient returns for subsequent excision stages until negative margins are achieved. The central portion of the tumor is excised during the last step. Vertical sectioning of the tumor is performed, and the wound is repaired. This technique offers dual advantages of open wound avoidance between stages and the production of high-quality permanent sections. It suffers from requiring multiple office visits for the patient and late tumor staging because the central lesion is excised last.

In 2008, Clark and colleagues modified the square technique. They termed their new approach "contoured"[36] (Table 1). This technique has only been applied to MIS and not specifically to LM. The contoured technique does not rely on sharp lines and edges, like the square procedure, so better preservation of cosmetic units is achieved. Despite the change in the shape of the strips, Clark and colleagues did not have any difficulty in processing them as full horizontal sections. Similar to the square procedure, the patient undergoes weekly visits for subsequent

TABLE 1. Studies Using Staged Surgical Excision for Lentigo Maligna (LM)

Surgical Excision	*Follow-Up Duration*	*Time to Recurrence*	*Recurrence*	*Limitations*
Walling et al.[51] with bread loaf sections	96 ± 43.6 months (range 60–240 months)	24 ± 13 months	3/41 (7.3%)	Single practice site, fewer patients underwent Mohs micrographic surgery than staged surgical excision, nonrandomized, nonblinded retrospective chart review
Bub et al.[37] (radial sections)	57 months (range 9–139 months)	Not reported	2/55 (3.6%) 55 LM, 7 LMM	Nonrandomized, noncontrolled, nonblinded, Follow-up by direct examination, by contacting the referring physician, or by telephone interview with the patient or nearest relative if the patient was debilitated or deceased
Huilgol et al.[32] mapped method similar to Hill and Gramp (bread loaf sections)	38 ± 25 months	Between 2 cases of LM and LMM: 12, 31, 39, and 40 months, it was not specified which time period was LM vs LMM	2/125 (1.6%) LM 125, LMM 36	Follow-up was conducted over the telephone or at a clinic visit, noncontrolled, nonblinded
Johnson et al.[35] square technique	None	N/.	0%, 0/35 35 LM + LMM	Described novel surgical technique that had been applied to 35 patients, with no follow-up reported; nonrandomized, noncontrolled, nonblinded
Hill and Gramp[138]	25 months (range 10–48 months)	10 months	.6% (1/38) LM + LMM = 66, LM = 38	Nonrandomized, noncontrolled, nonblinded; short follow-up
Anderson et al.[39] square technique similar to Johnson et al.	Not defined	"Less than 5 years"	1/150 (0.67%) 150 LM + LMM	Nonrandomized, noncontrolled, nonblinded, Did not segregate results into LM vs LMM, ill-defined follow-up
Agarwal-Antal et al.[16] Polygonal, similar to square technique Perimeter margins were longitudinal sections, central portion was "bread loaf" sections	NR, "4 years after first patient"	Not reported	0/93 (0%) 93 LM	Nonrandomized, noncontrolled, nonblinded, ill-defined follow-up
Malhotra et al.[139] Mapped method similar to Hill and Gramp	32 ± 26 months	Recurrences of 12, 40, 39, and 31 months after mapped serial excision (MSE)	LM 4/109 (3.7%), LMM 0/32	Nonrandomized, noncontrolled, nonblinded, short follow-up

TABLE 1. Continued

Surgical Excision	*Follow-Up Duration*	*Time to Recurrence*	*Recurrence*	*Limitations*
Mahoney et al.[38] Described a Perimeter technique similar to square technique by Johnson et al. in 1997[35] using triangles, rectangles, and pentagons	4.7 months (range 1–13 months)	NA	0/11 (0%) LM-11	Nonrandomized, noncontrolled, nonblinded, short follow-up
Jejurikar et al.[140] "Square" as described by Johnson et al. 1997	31 months (range 15–45 months)	NA	0/48 (0%) 42 LM, 9 LMM	Nonrandomized, noncontrolled, nonblinded, short follow-up
Bosbous et al.[40] Mapped permanent sections, central lesion was bread loafed, peripheral margin used en face sections	2.2 years (range 0–10.2 years)	Not reported	1/59 (1.7%) 49 (83.1%) LM, 10 (16.9%) LMM	Institutional chart review board, nonrandomized, short follow-up
Lee and Ryman[56] Total circumferential margin control using vertical and horizontal permanent sections	42 months	Mean 4 years	3/31 (9.7%) LM	Medical chart review, nonrandomized, noncontrolled, nonblinded; follow-up via direct examination, telephone with general practitioner, patient, or relative

LMM, lentigo maligna melanoma.

stages until the central tumor is excised and cleared in the last stage.

In 2004, Bub and colleagues documented a recurrence rate of 5% using another method of SSE. They used radially cut rush permanent sections with a mean follow-up of 57 months and an average margin of 5.5 mm[37] (Table 1). Briefly, the lesion is delineated with a margin of 2 to 3 mm using a Wood's lamp, excised using a vertical incision to the subcutaneous tissue, and mapped for orientation. The pathologist processes the specimen and reads it within 24 hours. It is bisected or divided into quadrants and sectioned radially. The following morning, the patient returns for the next stage of surgery, be it closure or further excisions. If the next surgical stage is required, a 2- to 3-mm rim of tissue is excised according to the mapped findings from the previous stage. It was during this study that Bub and colleagues made the astute recommendation that a minimum of 3 to 5 years of follow-up after SSE should occur, because LM is known to be a slow-growing lesion.

Huilgol and colleagues used a method of mapped serial excision similar to that of Bub and colleagues in 2004 and documented a recurrence rate of 2% out of 155 cases, albeit with a shorter mean follow-up time of 38 months[32] (Table 1).

Mahoney and colleagues reported no recurrences in 11 patients with an average follow-up of 4.7 months using the perimeter technique to obtain permanent sections.[38] This technique is similar to the square procedure used by Johnson and colleagues, Anderson and colleagues, and Agarwal-Antal and colleagues (Table 1).[16,35,38,39] The first step in the perimeter technique involves outlining a 2- to 3-mm margin around the lesion using a Wood's lamp. A margin of 5 mm is delineated using a geometric shape, which could be a triangle, rectangle, or pentagon. Angled corners and flat edges assist in orientation and processing. Two-mm vertical tissue strips are taken around the margin, leaving the central area of tissue containing tumor until the last step. The tissue is sutured so that it is "closed" between each

subsequent stage. The excised tissue is processed using permanent sections. A map is generated to facilitate where the next excisional stage is to be performed. Each stage occurs at intervals of 1 to 2 weeks. When an area is deemed "positive," an additional 1- to 2-mm strip is excised.

A significant disadvantage of this method is the large amount of time that can be required to complete the treatment, with one patient in the series waiting 31 weeks before free margins were detected for the final repair.[38] Despite Mahoney and colleagues' excellent results, an average follow up time of 4.7 months is an insufficient time period to monitor for LM recurrences (Table 1).

A recently reported study by Bosbous and colleagues detailed their 10-year experience with staged excision using rush permanent sections of LM and LMM[40] (Table 1). The first step in this technique involves delineating an initial surgical margin of 5 to 10 mm around the clinical lesion. Bosbous and colleagues used the wider margin for larger lesions, those known to harbor invasive sites, and recurrent tumors. After delineation, the lesion and its margins were fully excised en bloc. They used a marking suture on the specimen and the patient to demarcate the 12 o'clock position. The specimen was processed using rush permanent sections. If it had positive margins on histology, an additional specimen was taken with 5-mm margins. If further stages were required, they occurred at 24-hour intervals. Once the tumor had been cleared in its entirety, the surgical wound was repaired in approximately 24 to 48 hours.

Bosbous and colleagues reported that there was a 1.7% recurrence rate in 59 patients during a median follow-up period of 2.25 years.[40] Additionally, 62.7% of the lesions demanded 1.0-cm or greater margin borders for tumor clearance, and 10.2% of patients thought to have MIS, LM type had invasive LMM, placing even greater importance on histologic analysis.[40]

Mohs Micrographic Surgery

An alternative to WLE and SSE is MMS, a specialized form of staged surgical excision (SSE) using frozen sections (some groups use permanent sections and call the technique slow Mohs) for histologic analysis.[2,41–44] Subsequent stages are undertaken pending the findings from the histologic evaluation. It has been noted to be effective in melanoma[45–50] and offers the distinct advantage over methods that use vertical sections or "bread loafing" of analyzing virtually 100% of the tumor borders.[51]

MMS uses smaller initial margins than WLE and SSE and therefore, in general, may possess a functional and cosmetic advantage over the other two forms of surgical excision. Zitelli and colleagues demonstrated that, on average, MMS when used for melanoma spared 1.8 cm more tissue than SSE[49] (Table 2). Despite this, Waller and colleagues reported that there was no significant difference in lesion size postsurgically between SSE and MMS for LM and LMM.[51] Recurrence rates for LM treated with MMS have ranged from 0% to 33% (0% to 6.25% if the Walling and colleagues[51] study is excluded) with false-positive and false-negative rates of frozen sections of 20% and 50%, respectively, and a sensitivity range from 59% to 100% and a specificity range from 68% to 100%.[52–55]

A variation of MMS that Lee and Ryman have explored is total circumferential margin control (TCMC)[56] (Table 2). Briefly, the lesion is delineated using a Wood's lamp along with 5-mm margins. Blocks are demarcated on the patient's skin before excision to facilitate specimen preparation for histologic analysis. The area is also photographed and mapped before excision. As in traditional MMS, the area is excised using a surgical blade angled at 45° to the level of the subcutaneous tissue. Each block is marked with a different dye to facilitate mapping. Horizontal sections are made from the periphery of the blocks, similar to traditional MMS, but vertical sections are taken from the inner parts of the blocks. For histologic analysis, each block is

TABLE 2. Studies Using Mohs Micrographic Surgery (MMS) for Lentigo Maligna (LM)

MMS	*Follow-Up Duration*	*Time to Recurrence*	*Recurrence Rate*	*Limitations*
Walling et al.[51]	117.5 ± 36.4 months (range 61–157 months)	53.5 ± 24 months	6/18 (33%)	Single practice site, fewer patients underwent MMS than SSE, nonrandomized, retrospective chart review
Cohen et al.[43] with rush permanent sections	58.0 months	1 recurrence in a patient with LMM, time to recurrence was not reported	0/26 (0%) LM 1/19 (5.35) LMM 0/26 LM 1/19 (5.3%) LMM	Nonrandomized, noncontrolled, nonblinded
Clayton et al.[141] with rush permanent sections	22 months	31 months	1/81 (1.2%) 77 patents were placed in the MIS/LM group but 81 total MIS + LM lesions, 24 LMM	Medical record review, nonrandomized, noncontrolled, nonblinded, distinction between LM and MIS was not clear, short follow-up
Temple and Arlette [142]	29.8 months	NA	0/119	Medical record review, not blinded, nonrandomized, noncontrolled, short follow-up
Bhardwaj et al.[143] (Frozen section with Mel-5 immunostain)	38.4 months (range 6–58 months)	Not reported	1/158 (0.63%)	Nonrandomized, noncontrolled, nonblinded
Bienert et al.[144]	33 months	NA	0/67	Nonrandomized, noncontrolled, nonblinded
Robinson[42] used conventional MMS with frozen and permanent sections Immunohistochemistry: S-100, human melanoma black-45 for LM	5–9 years	8 years	(6.3%) 1/16	Nonrandomized, noncontrolled, nonblinded
Dhawan et al.[41] Mohs with rush permanent sections with horizontal sections (case report)	1 year	NA	0/1	Case report, short follow-up
Bene et al.[145] Frozen + permanent sections No immunohistochemistry	Mean 63 months	4 years	1/116 (0.87%)	Follow-up by telephone or direct examination; nonrandomized, noncontrolled, nonblinded

LM, lentigo maligna; LMM, lentigo maligna melanoma; MIS, melanoma in situ.

sectioned at 50 to 100 μm and stained with hematoxylin and eosin (H&E). Positive areas are mapped within 48 hours of the excision, and the patient returns for a subsequent stage consisting of a 5-mm marginal excision. If the margins reveal no evidence of LM, the patient returns for closure.

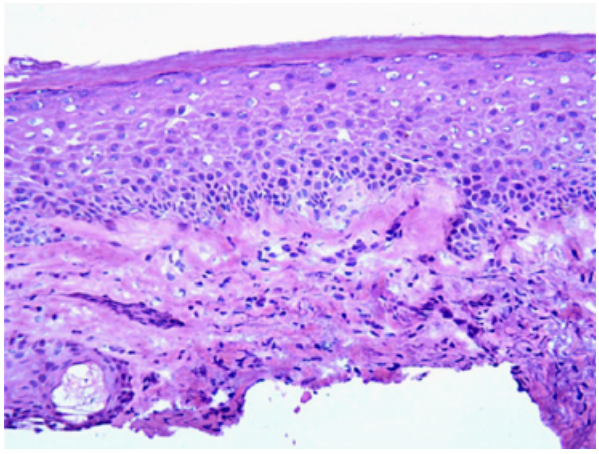

Figure 3. Hematoxylin and eosin frozen section of lentigo maligna at ×40 magnification. Courtesy of Basil Cherpelis, MD, and Frank Glass, MD.

Histologic analysis drives MMS and SSE (excluding WLE) and their variations (i.e., the next stage of surgical therapy rests upon the previous stage's histologic evaluation). There are a number of histologic techniques that have been explored and can be combined with specific surgical techniques.

Horizontal frozen sections used with MMS offer the distinct advantage of completing the surgical therapy in the same day (Figure 3). Despite being convenient from a time-conserving perspective, frozen sections of LM lesions are associated with certain artifactual changes such as lack of melanocyte cytoplasmic vacuolization and fixation artifacts including tissue folding, bubbles, and chatter.[16,57] On permanent sections, atypical melanocytes appear as clear cells with hyperchromatic nuclei and fewer artifactual as well as fixational changes compared to frozen sections (Figure 2).[57] Cohen and colleagues reported a sensitivity of 73% and specificity of 68% using H&E frozen sections for melanoma, whereas Zitelli and colleagues reported 100% sensitivity and 90% specificity for surgical margin evaluation of LM using H&E frozen sections.[55,58]

In an effort to circumvent the disadvantages associated with histologic analysis of frozen sections for LM,[16,57] Dhawan and colleagues developed slow Mohs in 1990, and several other groups have since investigated using permanent sections during MMS and SSE[16,41] (Table 2). Slow Mohs uses the same surgical technique as conventional MMS, but instead of frozen en face sections, permanent en face sections are used. These permanent sections are in a rushed format so that the patient can undergo surgical wound closure or the next surgical stage the following day. Some groups have examined rush permanent sections in which paraffin-embedded slides are processed overnight, whereas others[38] have used non-rushed permanent sections, waiting 1 week for the subsequent surgical stage pending permanent section processing.

Immunohistochemistry

Immunohistochemistry has also been investigated as a histologic technique to closely delineate the surgical borders of LM on frozen sections in a timelier manner than that associated with permanent sections or rush permanent sections. A number of immunohistochemical stains have been explored to identify melanoma cells and may also be useful in delineating the surgical borders of an LM lesion.

Human melanoma black (HMB)-45 is a murine monoclonal antibody that binds to a melanosome-associated sialated glycoprotein known as gp100. It is found in neoplastic melanocytes, fetal melanocytes, and immature melanosomes[59] and is approximately 30 to 35 kDa in size.[60] HMB-45 has demonstrated a sensitivity of 86% to 97% for permanent sections involving melanocytes in melanoma.[33,61–68] Although its sensitivity and specificity for LM with frozen sections remains unknown, in one study, HMB-45 stained positive in 79% and was negative in 29% of the LM cases when distinguishing between pigmented actinic keratosis and LM.[69] It has not been used recently for melanoma because other stains are more sensitive and less variable.[59]

Melanoma antigen recognized by T cells (MART-1) is a 22-kDa cytoplasmic melanosome-associated glycoprotein found in adult melanocytes, skin melanomas, and dermal and epidermal constituents of

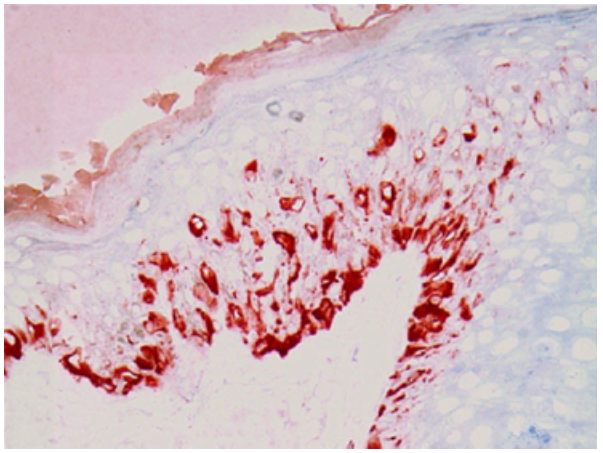

Figure 4. Frozen section of lentigo maligna at × 40 magnification using melanoma antigen recognized by T cells-1 (MART-1) immunostain. Courtesy of Basil Cherpelis, MD, and Frank Glass, MD.

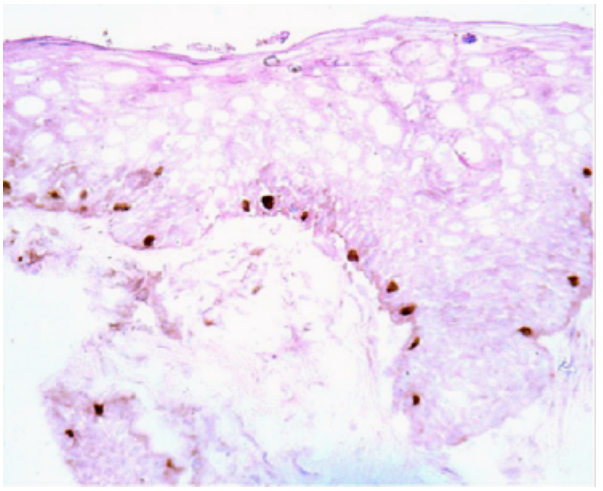

Figure 5. Frozen section of lentigo maligna at × 40 magnification using microphthalmic transcription factor (MITF) immunostain. Courtesy of Basil Cherpelis, MD, and Frank Glass, MD.

nevus cells (Figure 4).[60] It is also known as Melan A. El Shabrawi-Caelen and colleagues demonstrated that MART-1 was not a useful stain to distinguish between MIS with sun damage and pigmented actinic keratoses. They suggested that additional HMB-45 or S-100 staining in these situations is required.[70] Zalla and colleagues came to the conclusion that MART-1 is a better stain than HMB-45, Mel-5, and S-100 for determining surgical borders of malignant melanoma using MMS.[33] Albertini and colleagues also concluded that MART-1 is a better marker available for malignant melanoma and MIS than HMB-45, S-100, and MART-1.[71] Further studies will be needed to determine whether this holds true specifically for LM as well.

Mel-5 is a murine monoclonal antibody that attaches to the gp75 in stage III and IV melanocytes.[59] It stains epidermal melanocytes, the epidermal components of benign nevi, basal epithelial cells, and most melanomas. It may not stain amelanotic melanomas or melanomas that have extended into the dermis.[60] Bhardwaj and colleagues demonstrated that, when using MMS with frozen sections using the Mel-5 immunostain for 200 cases of LM/LMM, Mel-5 apparently detected all cases of LM and LMM.[60] It is useful for known LM cases with no dermal invasion because it stains the basal layer cells.

S-100 is thought to be involved in intracellular calcium trafficking and is known to have a low specificity staining ependymomas, astrogliomas, schwannomas, Langerhans cells, and nearly all benign and malignant melanocytic lesions.[60] It has been used extensively for staining malignant melanomas, but less is known about its properties regarding LM. S-100 seems to have difficulty staining frozen sections but may be appropriate for permanent sections.[59]

Microphthalmic transcription factor is a nuclear stain used for MMS with MIS. Its use may be particularly advantageous for LM because it does not stain the cytoplasm of highly dendritic melanocytes that are often observed in chronically sun-damaged skin (Figure 5).[72] Previous studies have shown a sensitivity ranging from 81% to 100% and a specificity of 100% for certain melanoma subtypes.[73–78] Its application to surgical margin detection has not been formally studied.

When using immunohistochemical staining protocols, approximately 1 hour used to be required, however, a new 20-minute protocol for frozen section immunostaining with MART-1 has been introduced.[79] Cherpelis and colleagues recently

demonstrated that this new protocol provides nearly equivalent information with permanent sections using MART-1 immunohistochemistry.[80] Before that study, another group produced an ultrarapid 11-minute protocol using MART-1 immunohistochemistry, but no data exist as to the sensitivity and specificity of this protocol.[81]

Cryotherapy

Cryotherapy involves applying a cold or cryogenic agent, such as liquid nitrogen, to the cutaneous surface, which acts to remove heat from the skin.[82] Melanocytes are known to be destroyed by temperatures ranging from −4°C to −7°C,[83] whereas keratinocytes and fibroblasts are destroyed by temperatures ranging from −20°C to −30°C and −30°C to −35°C, respectively.[82] It is unknown whether the atypical melanocytes associated with LM are more or less sensitive to this temperature range. Similar to MMS, the evidence behind the majority of studies involving cryosurgery is limited to case series and reports (Table 3).

Cryotherapy has been used with varying degrees of success (Table 3). In 1994, Kuflick and colleagues[84] reported that their 3-year recurrence rate was two of 30 (6.6%) patients treated with cryosurgery with an average follow-up of 3 years. Their method involved temperatures from −40°C to −50°C to the lesion base, with double freeze and thaw cycles, extending at least 1.0 cm beyond the lesion. They believed that in order, for cryotherapy to be successful, it must be performed in an aggressive fashion (Table 3).

In 1979, Dawber and Wilkinson reported 14 patients with LM who underwent cryotherapy, with six patients treated using a liquid nitrogen cotton wool swab and eight with liquid nitrogen spray.[85] After a follow-up period ranging from 7 months to 2.5 years, only one patient recurred. That patient underwent another cryotherapy session, with no further observed recurrences. Side effects included two patients with hyperpigmentation for 3 months after treatment and one patient with hypopigmentation. The fact that the investigators did not measure the temperature during the freezing process limited this study (Table 3).

In 1982, Zacarin used a double freeze–thaw cycle with liquid nitrogen spray, attaining a temperature of approximately −50°C, and 5-mm margins around the tumor.[86] The study involved 20 patients with biopsy-proven LM treated with cryosurgery. There were recurrences in two of 20 patients (10%) during a mean follow-up of 42.6 months (Table 3).

In 1992, Böhler-Sommeregger and colleagues reported a case series involving 12 patients treated with cryotherapy with two freeze–thaw cycles and 5–mm lesion margins. Only one patient experienced a recurrence over a mean follow-up of 51.4 months.[87] The one patient who developed recurrent LM underwent further cryotherapy and was free of recurrence 18 months later. Additionally, four post-treatment biopsies revealed no atypical melanocytes (Table 3). All patients in this series developed hypopigmented areas and atrophy. One month later, Böhler-Sommeregger and colleagues reported another 20 patients who developed reactive lentiginous hyperpigmentation after cryosurgery for LM.[88] A similar protocol was used, with a double freeze–thaw cycle and a temperature of −30°C to −40°C with 5-mm margins. Follow-up ranged from 7 to 80 months. Eight of the 20 patients developed lentiginous hyperpigmentation with recurrent LM, developing in three patients diagnosed by biopsy (Table 3). The remaining five patients were found to have solar lentigo on biopsy. A 15% recurrence rate occurred in this series.

In 1991, Collins and colleagues documented 10 patients with LM treated with cryotherapy.[89] Four developed recurrences (40% recurrence rate), with two of those patients having more than one recurrence. The authors explained that their high recurrence rate could be because of their short triple freeze–thaw cycle technique. The recurrences occurred a number of years after the initial cryotherapy treatment, with a range from 1 to 5 years (Table 3), emphasizing the need for studies involving LM to have long-term follow-up.

TABLE 3. Studies Using Cryosurgery for Lentigo Maligna (LM)

Study	*Method of Cryosurgery*	*Complete Clearance rate*	*Recurrence Rate*	*Follow-Up*	*Time to Recurrence*	*Limitations*
Dawber and Wilkinson[85]	6 patients treated with cotton wool swab, 8 treated with liquid nitrogen spray	13/14 14 total LM, the remaining patient was re-treated and the lesion cleared	0/14	7.5–30 months	NA	Small patient population, short follow-up duration, nonrandomized, noncontrolled, nonblinded
Zacarin[86]	Double freeze-thaw cycle with closed probe or intermittent spray with temperature brought to −50°C	Not reported	2/20 (10%)	42.6 months	Not reported	Small patient population, short follow-up duration, nonrandomized, noncontrolled, nonblinded
Böhler-Sommeregger et al.[87]	Double freeze–thaw cycle intermittent open spray, Temperature = −30°C to −40°C	Not defined	(1/12) 8.3%	51.4 months	5 months	Small patient population, short follow-up duration, nonrandomized, noncontrolled, nonblinded
Böhler-Sommeregger et al.[88]	Intermittent open spray technique, double freeze–thaw cycle with 0.5-mm margins, Temperature = −30°C to −40°C	Not reported	3/20 (15%)	7–80 months	Not reported	Small patient population, short follow-up duration, nonrandomized, noncontrolled, nonblinded, lentiginous hyperpigmentation in 8/20 patients
Collins et al.[89]	First 3 patients treated using double freeze–thaw cycles of cotton wool swab with 5-mm lesion margins; 8 patients treated with liquid nitrogen spray, treated until clearance or once per 6 weeks for 6 times	9/10 patients with LM cleared in 2–4 treatments	4/10 (40%)	Mean 4 years	1–9 years	Retrospective case review
Kuflick and Gage[84]	Liquid nitrogen spray double freeze–thaw at a temperature of −40°C to −50°C, spray was "well beyond the outline of border of the lesion"	Not reported	2/30 (6.7%)	Mean 3 years	17 months, and 12 months after treatment	Nonrandomized, noncontrolled, nonblinded

The major limitation with this technique is that no sample is available for histologic analysis.[90] Treating a lesion using this modality without biopsy to exclude invasion could be a risky undertaking, and as previously cited, 16% to 50% of LM lesions already have an invasional component when only malignant MIS, LM type is suspected,[15–17] although only 4.7% of LM diagnosed at age 45 and 2.2% when diagnosed at 65 progress to LMM,[22] and given the likely differences in the biologic behavior between LM and malignant MIS, LM type, cryosurgery may be an appropriate treatment for LM.

Imiquimod

A topical immune response modifier known as imiquimod has been FDA approved for the treatment of superficial basal cell carcinomas, actinic keratoses, and genital–perianal warts. Its use for treating LM has been examined in numerous case reports and studies.[14,91–110] Although studies have demonstrated clearance rates ranging from 66% to 100%, a number of side effects including influenza-like symptoms,[111] pruritus,[112] transient decreases in vision,[113] chemosis,[113] keratitis,[114] conjunctivitis[114] (when used in the periocular region), and marked erythema[114] have been reported.

Imiquimod has also been combined with surgical therapy. A study by Cotter and colleagues used imiquimod 5 times per week for 3 months before SSE, with zero of 40 patients experiencing a recurrence after only 18 months.[110] Thirty of forty patients had histologic evidence of residual LM. Cotter and colleagues also used tazarotene 0.1% gel in 10 individuals who did not mount an inflammatory response to the imiquimod.[110]

At least one other clinical trial is underway comparing imiquimod 5% cream with tazarotene 0.1% gel imiquimod 5% cream alone.[115] Tazarotene 0.1% gel causes the thickness of the stratum corneum to decrease, allowing for better imiquimod penetration. In addition, further investigation is occuring using imiquimod 0.1% cream applied to postsurgical excision sites of LM and LMM to determine whether it can prevent or decrease recurrence.[116]

Laser Therapy

Argon, carbon dioxide, Q-switched ruby, Q-switched neodymium-doped yttrium aluminum garnet, and alexandrite lasers and laser combinations have been used in the treatment of LM, with high recurrence rates of 22.7% to 37.8% (Table 4). In addition, three of eight patients in one study did not respond to laser therapy.[117–121] Current laser technology may not reach a sufficient depth to destroy the atypical melanocytes that extend down the deep periappendageal structures.[121,122] Madan suggests that the atypical melanocytes may be resistant to laser destruction.[121] Previous laser studies have primarily lasered margins of normal surrounding tissue up to 5 mm. Perhaps margins approaching 1 cm might be more appropriate when using lasers, similar to margins that may be required for WLE.

Madan and colleagues further suggested a number of advantages of laser therapy for treating LM, including less pain; better cosmesis than traditional surgical excision; speed of therapy, with each session requiring only 2 to 5 minutes; and less post-treatment care.[121] However, at this time the disadvantages (high recurrence rates) outweigh the advantages of laser therapy.

Radiation Therapy

Another modality that has been investigated for its possible role in treating LM is radiation therapy. One of the first studies conducted in this area was by Miescher in 1954.[123] Since that time, numerous case reports and studies throughout Europe using Miescher's technique have been reported.[123–130] Orthogonal X-rays have also been investigated, yielding somewhat better results than those achieved by Miescher's technique, with recurrence rates ranging from 0% to 12.5% and 0% to 20%, respectively.[30,131–134] Another variation that has been explored is lead metal shaped so that margins from 0.5 to 2.0 cm surrounding the clinical tumor

TABLE 4. Laser Studies for Lentigo Maligna (LM)

Study	*Laser type and settings*	*Follow-Up Duration*	*Time to Recurrence*	*Recurrence Rate*	*Limitations*
Arndt et al.[117]	Argon laser, 0.1-cm aperture, 5-cm distance, 3.8 W, 50-ms pulse duration, 582 impulses	8 months	No recurrence	NA	Single case
Arndt[146]	Argon laser, 0.1-cm aperture, 5-cm distance, 3.8 W, 50-ms pulse duration, 582 impulses	Mean 75 weeks	4 years	33% (1/3)	Single case
Kopera[118]	10,600-nm carbon dioxide laser, 12 W, 1 mm, defocussed beam, 2 passes	Mean 15 months	NA	0% (0/4)	Case series, not randomized, not controlled, not blinded
Orten et al.[147]	Q-switched Nd:YAG laser at 4 to 11 J/cm², wavelength 532 and/or 1,064 nm, pulse duration 10–20 ns, spot size 2–3 mm, and pulse repetition rate 10 Hz.	8 months–3.5years	13.6 months	37.8% (3/8) 3/8 patients had no/partial response	Nonrandomized, noncontrolled, nonblinded
Iyer and Goldman[120]	5 total treatments: treatment 1 and 2 separated by 1 month, treatments 2 and 3 separated by 3 months, treatments 3 and 4 separated by 8 months, treatments 4 and 5 separation interval not defined. Treatment 1: Q-switched alexandrite laser, 3.0-mm spot size, fluence of 8.0 J/cm², 5-mm margin of normal skin Treatment 2: same as treatment 1 but with 8.2 J/cm² Treatment 3: same as 1 but with 4.0-mm spot size Treatment 4: long-pulse alexandrite laser, pulse width 5 ms, 7-mm spot size, 2 passes, pass 1 35.0 J/cm², pass 2 50 J/cm² Treatment 5: long-pulse alexandrite laser with 48.5 J/cm², 5-ms pulse duration, and 7-mm spot size	3.5 years	The lesion did not completely respond, but 3 years after treatment, it had not clinically progressed. 3.5 years later, developed an amelanotic superficial spreading melanoma where the LM was treated.	1/1, likely became invasive superficial spreading melanoma	Case report, nonrandomized, nonblinded, noncontrolled

Madan and August[121]	Q-switched Nd:YAG laser, 532 nm, 6 J/cm^2, 2-mm spot size, 5 ns and Alexandrite laser 755 nm, 12 J/cm^2, 2-mm spot size, 50 ns	2–5 years	2.74 months	23% (5/22)	Nonrandomized, noncontrolled
Niiyama et al.[148]	Q-switched ruby laser, 5 J/cm^2, 4-mm spot size, no overlap	2 years	2 years, the lesion developed into invasive lentigo maligna melanoma	1/1	Case report Nonrandomized, noncontrolled, nonblinded

Nd:YAG, neodymium-doped yttrium aluminum garnet.

are irradiated; with wider margins associated with lower recurrence rates.[127,130] A number of side effects have been observed or are of concern when using radiation therapy, including telangiectasias,[133] pigmentary changes,[133] radiation necrosis,[30,130] squamous cell carcinoma,[130] and erythema.[130] Radiation therapy may be beneficial, especially in patients who cannot tolerate or do not develop an inflammatory reaction to imiquimod.

Curettage and Electrosurgery

Curettage uses a looped metal instrument with one side sharpened to "scrape" the surface of a lesion, usually in an attempt to remove part or, sometimes, a whole lesion. Electrosurgery uses an electric current to cut, cauterize, or destroy a targeted area of a lesion.

Only two studies exist in the literature detailing treatment results with curettage and electrosurgery.[28,29] The first study was by Pitman and colleagues in 1979, who treated eight cases of LM using this method and had two recurrences (25%). In 1980, Coleman and colleagues treated three patients who experienced recurrences. Unfortunately, the time frame involved in the follow-up was not reported for either study. Even though these studies treated only a small number of patients, it is not advisable to continue further investigations because of the lack of histologic analysis with this technique and the high recurrence rate. In addition, in 1997, Gaspar and Dawber found that atypical melanocytes in the hair follicle are not likely to be destroyed using this technique.[90]

Conclusion

A considerable amount of investigation involving these surgical techniques has been conducted. Unfortunately, high levels of evidence do not yet exist. As a result, it is nearly impossible to conclude with confidence which surgical technique is best suited for or is truly associated with the lowest level of long-term recurrence for LM. The heaviest weight of evidence exists for WLE, with a lower level ev-

idence for SSE and MMS. SSE and MMS seem to have similar recurrence rates (0–9.7% and 0–33%, respectively, or 0–6.25% for MMS if the Walling and colleagues[51] study is excluded). If the healthcare team is going to use WLE with vertical sections, we agree with the NCCN that greater than 0.5-cm margins are required. Margins close to 1.0 cm or greater should be taken, especially for large lesions.

The immunohistochemistry staining protocols will continue to become shorter in time duration, more accurate, and have the potential to assist in MMS for LM. A number of studies have reported low recurrence using MMS with immunostains and frozen sections, but short follow-up times and small patient populations also limit these studies. In addition, fewer than 15% of Mohs laboratories use immunostaining,[135] so it may be some time before immunohistochemistry for MMS becomes well accepted. MART-1 and microphthalmic transcription factor (MITF) are promising immunostains and will likely play an important role, alone or in combination, in the future of surgical margin definition when using MMS for LM.

Future studies examining cryotherapy for LM should be conducted in an aggressive fashion to make certain that the entire lesion is below −4°C to −7°C. It is particularly worrisome that the entire lesion cannot be measured histologically using this technique. Microscopic areas of invasion may lead to metastasis, so cryosurgery may be best suited for LM and not malignant MIS, LM type.

No large series or studies with long-term follow-up have been published regarding the efficacy of laser treatment for LM. Only low-lying levels of evidence exist.[136] Future laser studies should investigate the photoactivating agent indocyanine green in combination with the low-power titanium sapphire laser. It has recently been shown to induce apoptosis via caspases 3 and 9 in an in vitro setting.[137]

Novel approaches using imiquimod as a presurgical adjuvant to SSE have yielded a low recurrence rate. Studies using imiquimod after surgery to prevent recurrences are also underway. In patients who cannot tolerate surgery, imiquimod is a viable option for treating LM. If no inflammatory response is generated, tazarotene can be added to encourage imiquimod's penetration.

Similar to imiquimod's use in patients who cannot undergo surgery, radiation therapy may be beneficial, especially in patients who cannot tolerate or do not develop an inflammatory reaction to imiquimod.

Curettage and electrosurgery probably does not require further exploration because of the high recurrence rate noted in the studies cited and lack of histologic analysis.

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