



Michele R. Sassi. *The Desert of Rajasthan, India*. Photograph, 2007.

Standard surgical margins are often insufficient for lentigo maligna due to its indistinct borders.

Surgical Management of Melanoma In Situ on Chronically Sun-Damaged Skin

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Background: *Lentigo maligna (LM) commonly presents as a slow-growing pigmented macular lesion in chronically sun-damaged skin and may progress to invasive melanoma. Many regard it as a subtype of melanoma in situ (MIS), and surgical excision remains the preferred treatment, but standard 5-mm surgical margins recommended for typical MIS are often insufficient for LM due to its indistinct borders both clinically and histologically.*

Methods: *A search of the literature was conducted to review specialized surgical techniques for the treatment of LM, focusing on methods that employ total peripheral margin assessment prior to definitive closure, using either frozen or permanent histologic sections.*

Results: *Many investigators have reported surgical modalities utilizing permanent sections for margin control, including variations of the "square" procedure and "perimeter" technique. Recurrence rates are low with these methods, but only short-term data have been reported. Similarly, several studies have demonstrated the efficacy of Mobs micrographic surgery (MMS) for treatment of MIS, with recurrence rates generally less than 1% over 3 to 5 years of follow-up. Many investigators have had success with immunohistochemical stains to identify melanocytes on frozen sections, aiding margin assessment in MMS.*

Conclusions: *Compared to standard excision, methods that employ surgical margin control offer superior cure rates for LM and should be utilized when available. Total peripheral margin assessment using staged excisions and permanent sections is a simple and effective alternative to MMS for institutions that lack the resources for intraoperative frozen section analysis.*

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Abbreviations used in this paper: LM = lentigo maligna, MIS = melanoma in situ, MMS = Mobs micrographic surgery, LMM = lentigo maligna melanoma.

Introduction

Lentigo maligna (LM) is a melanocytic dysplasia that usually presents as a slow-growing pigmented macule or patch on chronically sun-damaged skin of the head and neck, especially on the face of elderly patients. Its first description by Hutchinson¹ in 1894 led to the eponymous designation “Hutchinson’s melanotic macule.” Most authors now consider LM to be a subtype of melanoma in situ (MIS), although some still classify it as a precancerous lesion. Regardless of terminology, it can eventually extend into the dermis or subcutaneous fat; similar to other subtypes of melanoma described by Clark et al,² and its progression beyond MIS is termed *lentigo maligna melanoma* (LMM). LMM represents 4% to 15% of all melanomas^{2,3} and has the same behavior as other forms of melanoma after accounting for Breslow depth.⁴ The true risk of progression from LM to LMM is unknown but has been extensively reviewed by Cohen⁴; it has been estimated to be as high as 30% to 50% or as low as 5% based on epidemiologic data.

Surgical excision with 5-mm margins remains the standard of care for MIS, as established by the National Institutes of Health (NIH) consensus conference in 1992,⁵ and subsequently incorporated into the official melanoma treatment guidelines published by the American Academy of Dermatology⁶ and the National Comprehensive Cancer Network.⁷ However, mounting literature suggests that margins of 5 mm are inadequate for the treatment of LM, as clearance rates as low as 24% have been reported (Table 1).⁸⁻¹² In fact, for acceptable clearance rates of greater than 94%, margins as large as 9 mm,⁸ 10 mm,⁹ and 15 mm¹¹ have been required.

Recognition of the need for larger margins prompted the endeavor to perfect a system for margin control. Many techniques have been employed, including the “square” method,¹³⁻¹⁵ “perimeter” technique,^{12,16} “slow Mohs,”¹⁷ staged radial sections,¹⁸ staged

“mapped” excisions,^{9,19-21} and Mohs micrographic surgery (MMS).^{8,10,11,19,22-26} This review focuses on those modalities that employ en face histologic sectioning, which analyzes 100% of surgical margins. To avoid confusion with terminology discussed above, the term MIS is used instead of LM, with the understanding that this review specifically focuses on MIS in chronically sun-damaged skin.

Staged Margin Excisions Utilizing En Face Permanent Sections

The prototype for staged excisions utilizing permanent en face sections is the “square” procedure, described in 1997 by Johnson et al¹⁵ and employed subsequently by their group and others.^{13,16} In this method, a biopsy-proven MIS is identified and clinical margins are drawn with the aid of a Wood’s lamp to delineate subclinical spread of pigment. Next, 5-mm margins are drawn around the lesion in the shape of a square. An additional square is then drawn 2 to 3 mm around the first, and these 2- to 3-mm strips are excised, tagged for orientation, fixed in formalin, and submitted for vertical en face permanent-section histologic analysis. The excised strips leave a thin defect around the LM in the shape of a picture frame; these are simply sutured closed. In doing this, the patient has no open wound to care for while awaiting margin assessment. The patient returns in approximately 1 week. If margins are positive, another strip of tissue is taken in the appropriate area and the defect is again sutured closed. This cycle is repeated until negative margins are obtained, and the patient returns for excision of the central tumor portion as well as definitive reconstruction.

The key advantages of the “square” method are that it allows the use of high-quality permanent sections for total peripheral margin assessment and it avoids creating an open wound for the patient to care for while awaiting closure. The main disadvantage is that the

Table 1. — Margins for MIS

Study	Method	Clearance at 5 mm	Margin for High Clearance Rate	Immunohistochemistry
Bricca et al ⁸	MMS; first layer was 6 mm, subsequent were automatically 3 mm	Not studied; 89.1% clearance at 6 mm	9 mm: 98.5% clear	HMB45 used sporadically; not deemed helpful and did not extend margins anecdotally
Huilgol et al ⁹	Mapped excisions at 5-mm increments - en face 24-hr permanent standard vertical sectioning	70%	1 cm (next cut-off): 94% clear	None reported
Albertini et al ¹⁰	MMS	24%	Not explicitly reported	MART-1; also tried S-100, HMB45
Zalla et al ¹¹	MMS	50% at ≤6 mm	15 mm: 96% clear	MART-1; also tried S-100, HMB45, MEL-5
Agarwal-Antal et al ¹²	Staged excisions (en face)	42%	Reported only in number of layers	None reported

patient must wait a week for pathology results. In extensive cases, this may lead to a significant delay in final excision and repair. In fact, 1 patient in a series by Mahoney et al¹⁶ had to wait 31 weeks for clear margins and repair. Another disadvantage is that the central tumor is not excised until the time of closure, so an unsuspected invasive melanoma would not be identified until after closure is complete. Dawn et al²⁷ summarized the evidence that many histologically proven MIS cases have an invasive component. Examining 10 studies with a total of 570 lesions between 1968 and 2005, they determined that almost 25% have an invasive melanoma upon reexcision (range 5% to 67%). Interestingly, this number was not affected by surgical technique or use of immunohistochemical stains.

These important disadvantages of the “square” method have led to many modifications of the surgical technique. Most commonly, the central portion of the

tumor is excised at the first surgical visit.^{12,17} This modification allows for more accurate staging prior to reconstruction but creates an open wound. Another common modification is the use of specific polygons instead of a true square.^{12,16} This allows the surgeon to match the surgical defect with the shape of the MIS as well as the surrounding cosmetic units and structures. Straight lines are maintained to preserve the ease of histologic processing. Finally, another common modification is the use of 24-hour rush permanent sections instead of routine processing.^{12,14,17,19} This modification allows the reconstruction to be initiated much sooner than the 1-week waiting period needed for each margin assessment, but it relies on the availability of a dermatopathologist willing to do multiple rush sections.

Worthy of mention is the “mapped excision” described by Hill and Gramp²¹ in 1999, with additional cases described by their group and others^{9,19,20,28} as well

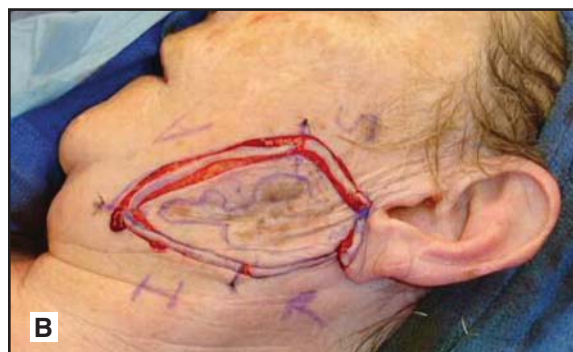


Fig 1A-E. — MIS excised with contoured excisions. The extent of the tumor is delineated with a Wood's lamp (A), and 5-mm margins are drawn (B). Strips of 2 to 3 mm are excised around these margins (B-C) and sent for permanent histologic analysis. The defect is sutured closed, leaving the central portion intact (D). This patient had clear margins at 1 week of follow-up, at which time the central tumor was excised and reconstruction performed (E).

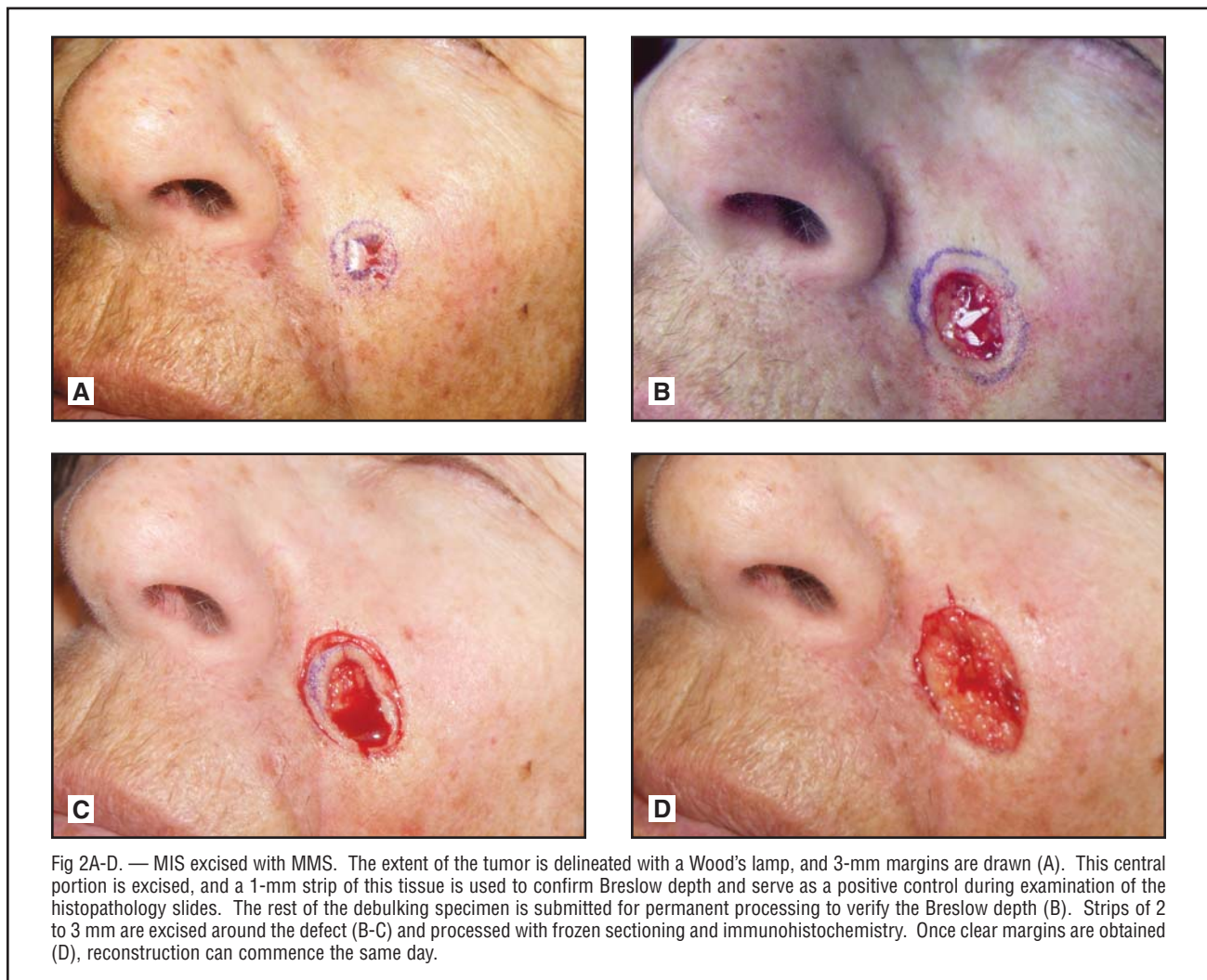
as the radial processing described by Bub et al.¹⁸ While often included in review articles of MIS treatment for completeness, these forms of staged excisions do not employ en face histologic processing and represent fundamentally different modalities than either the “square” method and its modifications or MMS.

At our institute a modification of the “square” procedure is utilized that involves a marginal contoured excision initially, then a central tumor excision if the permanent sections reveal clear margins (Fig 1). These contoured excisions do not rely on sharp angles, so particular attention can be paid to preserving cosmetic units in anticipation of the reconstruction. Despite the lack of true straight lines, our group has had no difficulty in processing the strips as full en face sections. As with the original “square” procedure, the patient is seen at weekly intervals for additional stages as necessary, and the central tumor is not excised until the time of repair. The initial marginal contoured excision can be accomplished under local anesthesia. This method minimizes the use of resources and is therefore particularly useful at busy tertiary-care cancer referral centers.

Staged Margin Excisions Utilizing En Face Frozen Sections: Mohs Micrographic Surgery

MMS is a specialized surgical and pathologic technique used to treat a variety of cutaneous neoplasms, first described in 1941 by Mohs.²⁹ Its design integrates the role of surgeon and pathologist and is unique in providing assessment of 100% of surgical margins intraoperatively, in contrast to a significantly lower percentage of assessed margins, typically 0.1%²⁵ to 5%, by standard specimen analysis.

In MMS for MIS, excision generally occurs under local anesthesia. The surgical site is prepped and draped in the usual manner. The surgeon marks the tumor’s clinical margin (Fig 2). Appropriate margins are drawn around the tumor. Margins vary from 1 to 3 mm depending on the surgeon performing the technique and the clinical scenario. Reference marks are placed by making small nicks overlapping the tumor and perilesional skin at 12, 3, 6, and 9 o’clock. A debulking layer is performed that removes the clinically visible tumor. A small 1-mm strip of tissue is taken from this debulking layer to con-



firm Breslow depth and to serve as a positive control during examination of the histopathology slides. The rest of the debulking specimen is submitted for permanent processing to confirm the Breslow depth. The first Mohs layer is then ready to be taken. The initial peripheral incision of each Mohs layer is beveled inward at approximately 45 degrees, until reaching the level at which the specimen will be undercut. The remainder of the deep portion of the specimen is then excised horizontally or parallel to the tissue surface. The purpose of the angled incision is to create a bevel that allows the peripheral and deep margins to be on the same plane for processing. A detailed map of the excised tissue and reference marks is made and care is taken to preserve the orientation of the tissue. The edges are inked and the specimen is embedded top-down on the cryostat chuck. In this manner, a horizontal tissue layer will contain all of the true surgical margins, including the entire circumference of epidermis and deep tissue. Tissue staining with hematoxylin-eosin (H&E) is performed, as well as immunostains. The surgeon analyzes the prepared histopathology specimens and marks any areas positive for tumor on the map. Additional stages of excision are performed as necessary with processing in the same manner as above. When all margins are free of tumor, the defect is repaired. Shriner et al³⁰ has provided a detailed description of the micrographic technique.

MMS surgery has the advantage of offering intra-operative margin control with assessment of 100% of margins, and it does not require a separate dermatopathologist to be available for rush specimen analysis. While the actual procedure may take several hours, MMS has an advantage in that definitive excision and closure can be achieved on the same day. It also offers excellent cure rates and can achieve the most accurate margins, especially on the head, neck, hands, and other areas with a high risk of recurrence.^{8,22,24,25} A disadvantage of MMS is the difficulty associated with adequately preparing frozen sections for visualization of melanocytes, including the need for immunohistochemical stains. Because of this, some still regard MMS as an unreliable method of resection for MIS. This is discussed in greater detail below. This disadvantage of MMS has led to a modification — “slow Mohs,” in which frozen sections are utilized as long as tumor is obvious, but when frozen layers become equivocal, the specimen is sent for permanent processing.¹⁷ The patient is then seen the following day for additional stages or closure, as dictated by the permanent histology. This surgical technique minimizes the number of return visits for the patient but sacrifices the option of same-day closure available for true MMS. However, as experience with the use of

immunostains increases, true MMS is becoming more commonly employed.

Dhawan et al³¹ are credited with the first report of treating MIS with MMS, though they used permanent sections akin to what is now considered “slow Mohs.” Subsequently, many groups have published data on the treatment of MIS with MMS. A recent article by Dawn et al²⁷ reviews the current literature regarding MMS for treatment of patients with MIS.

It is worth acknowledging that due to the indistinct clinical and histologic borders of MIS in sun-damaged skin, large surgical defects are routinely encountered that almost invariably jeopardize major cosmetic units or free-margins on the face. Therefore, interdepartmental consultation with appropriate colleagues such as plastic, head and neck, or oculoplastic surgeons may be necessary in anticipation of reconstruction.

Efficacy of Staged Margin Control Techniques for MIS

While a number of groups have treated MIS with staged margin excision utilizing permanent sections, the published reports focus on technique description, and none have adequately reported long-term follow-up data (Table 2).^{12-17,32,33} Cohen et al^{17,33} reported the most extensive series to date, with 1 recurrence out of 38 patients with LM or LMM with almost 5 years of follow-up. While they reported their technique as MMS, they used permanent sections and thus avoided the benefits and difficulties associated with true MMS. A limitation of this and other studies^{8,9,11,22,24,32} is that follow-up in many instances was obtained by telephone conversation with the patient, which cannot reliably assess for recurrences. Also, some studies of both the permanent-section group³² and MMS^{8,11,25,26} did not delineate between

Table 2. — Recurrence of MIS Treated With Staged Margin Excisions and Permanent Sections

Study	No. of MIS Lesions	Follow-up (mos)	Recurrence Rate
Jejurikar et al ¹³	42 LM 9 LMM	31	0
Mahoney et al ¹⁶	11 LM	4.7	0
Agarwal-Antal et al ¹²	93 LM	Not reported; “4 yrs after first patient”	0
Anderson et al ¹⁴	~150 LM + LMM	“Less than 5 yrs”	0.67% (1/150)
Clayton et al ³²	77 MIS/LM 23 LMM	Not reported	1% (1/100)
Cohen et al ^{17,33}	26 LM 19 LMM	58	2.6% (1/38)
Johnson et al ¹⁵	35 LM + LMM	Not reported	N/A

LM and other subtypes of MIS, which has the potential for inflating cure rates. At our institute, 61 lesions of MIS have been treated with the staged “contoured” excisions described above, with no recurrences in a mean of 7 months of follow-up (C.W.C., unpublished data, 2007).

The data for MMS as a treatment for MIS are more robust, as most studies have reported 3 to 5 years of follow-up data with generally less than 1% recurrence rates (Table 3).^{8,22-25} In the most extensive study to date, Bricca et al⁸ used MMS to treat 331 patients with MIS and reported a cure rate of 99.7% at almost 5 years of follow-up. Of note, Bhardwaj et al²³ reported a cure rate of 99.4% in their study of 158 LM lesions, 38% of which were either recurrent or incompletely excised at presentation.

A recent report by Walling et al¹⁹ sought to compare MMS and permanent-section staged excisions in the treatment of LM. They reported 6 (33%) of 18 LM lesions excised by MMS recurred in 10 years of follow-up. Even at 5 years of follow-up, the recurrence rate (17%) was much higher than that reported in other studies. This study was limited by a small sample size, and the surgeons performed MMS in the early 1990s prior to the routine use of immunohistochemical stains in frozen sections.

Immunohistochemical Stains

One of the obstacles in using MMS for excision of MIS has been the difficulty in accurate identification of melanocytes on frozen sections (Fig 3). In a landmark paper in 1991, Zitelli et al³⁴ reported 100% sensitivity and 90% specificity in detecting atypical melanocytes at the margins of melanoma with frozen sections, using permanent sections as a gold standard. However, subsequent investigators have reported lower accuracy; Barlow et al³⁵ report a sensitivity of 59% and specificity of 81%. Their study examined only equivocal cases of frozen sections and contributed to the lower accuracy, but controversy still exists as to the appropriateness of using frozen sections to assess margins in melanoma.

Table 3. — Recurrence of MIS Treated With MMS

Study	No. of MIS Lesions	Follow-up (mos)	Recurrence Rate
Temple et al ²²	LM = 119 LMM = 34	29	2% (4/196)
Bhardwaj et al ²³	LM = 158 LMM = 42	38	0.6% (1/200)
Bricca et al ⁸	MIS = 331	58	0.6% (2/331)
Bienert et al ²⁴	LM = 67 LMM = 8	33	0
Zitelli et al ²⁵	MIS = 184	60	0.5% (1/184)

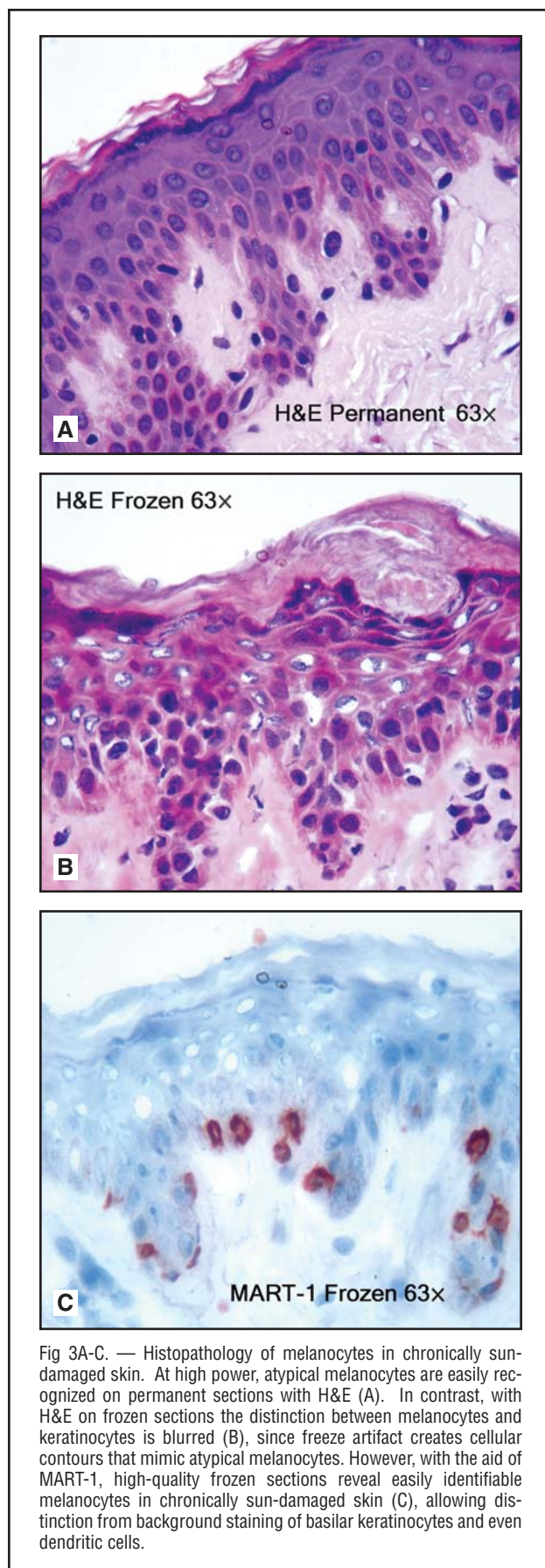


Fig 3A-C. — Histopathology of melanocytes in chronically sun-damaged skin. At high power, atypical melanocytes are easily recognized on permanent sections with H&E (A). In contrast, with H&E on frozen sections the distinction between melanocytes and keratinocytes is blurred (B), since freeze artifact creates cellular contours that mimic atypical melanocytes. However, with the aid of MART-1, high-quality frozen sections reveal easily identifiable melanocytes in chronically sun-damaged skin (C), allowing distinction from background staining of basilar keratinocytes and even dendritic cells.

Compounding the difficulty in assessing margins for MIS is determining the cut-off between melanoma and the lentiginous melanocytic hyperplasia that is normally found in sun-damaged skin. This difficulty is not unique to MMS as it exists in permanent sections also, though it is accentuated in frozen section analysis without the aid of immunostains. Several studies have attempted to quantify melanocyte characteristics that favor a diagnosis of melanoma.³⁶⁻³⁹ Hendi et al³⁸ determined that single atypical melanocytes and even confluence of up to 6 melanocytes can be normal in sun-damaged skin. However, blinded inter- and intraobserver studies are lacking. Florell et al⁴⁰ assessed interobserver concordance in assessing negative margins for LM and determined that a skin sample from the face ipsilateral to the MIS lesion

would aid in the diagnosis, though a punch biopsy is not sufficient; a thin elliptical excision is required. Even so, interobserver concordance was deemed to be only moderate and underscores the difficulty in assessing margins of MIS.

To aid in the diagnosis of melanoma on frozen sections, a variety of immunohistochemical stains have been studied that highlight melanocytes, including S-100, HMB-45, MART-1/Melan-A, and Mel-5. Multiple groups have found MART-1/Melan-A to be helpful in identifying atypical melanocytes in frozen sections,^{10,11,38,41-43} and it is currently regarded as the most accurate (Fig 4).²⁷ A number of investigators have extrapolated these results to MMS, reporting good results using immunohistochemistry on frozen sections during MMS for MIS.^{8,10,11,44}

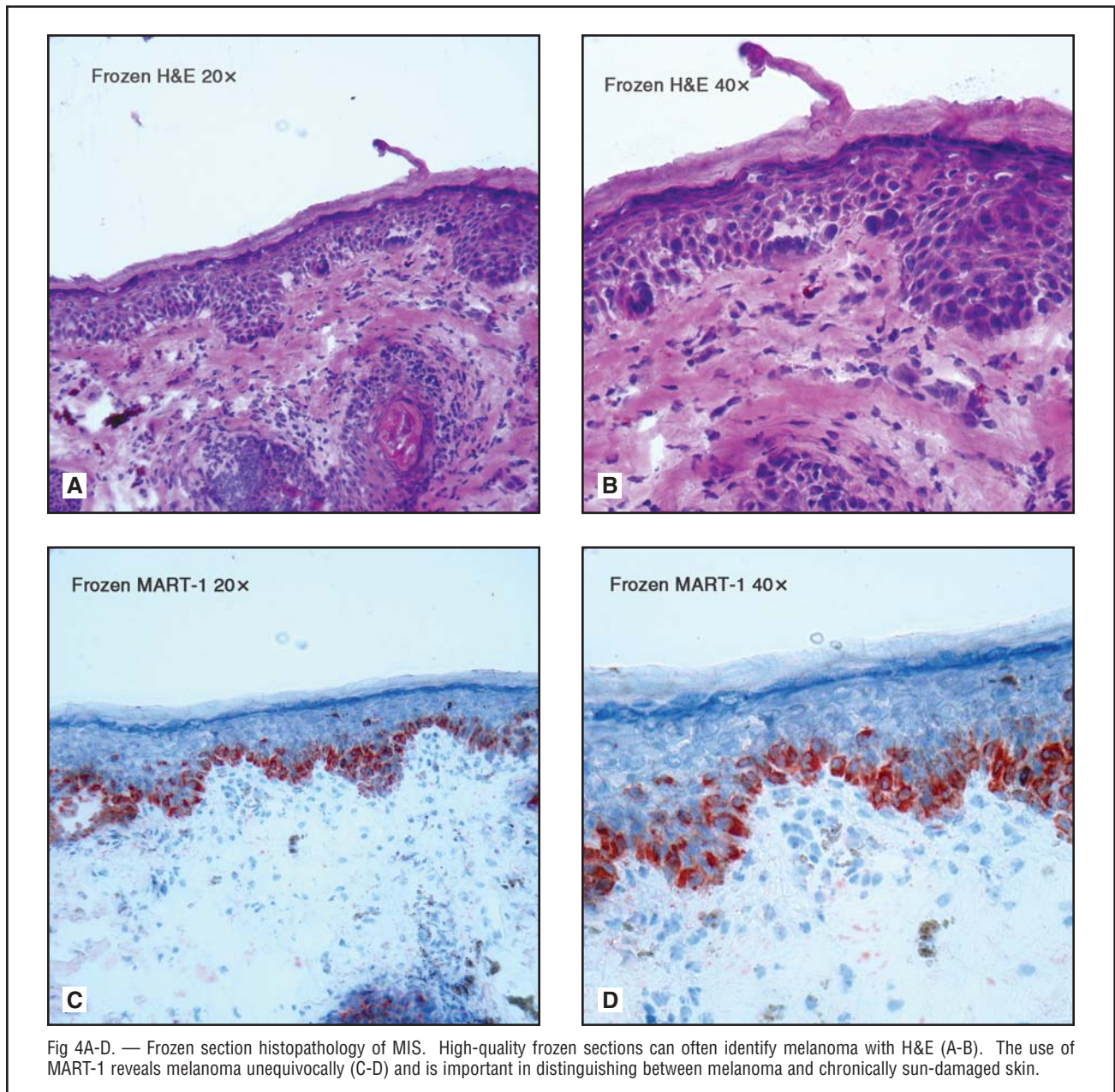


Fig 4A-D. — Frozen section histopathology of MIS. High-quality frozen sections can often identify melanoma with H&E (A-B). The use of MART-1 reveals melanoma unequivocally (C-D) and is important in distinguishing between melanoma and chronically sun-damaged skin.

However, while MART-1 has superb sensitivity, its lack of specificity has led some investigators to determine that it falsely extends surgical margins into normal tissue. For example, El Shabrawi-Caelen et al⁴⁵ showed that MART-1 stained 10 of 10 pigmented actinic keratoses, with 4 lesions showing focal nested staining easily misinterpreted as melanoma. However, a recent study by Wiltz et al⁴⁶ failed to confirm this, as MART-1 was deemed helpful in delineating 66 of 68 pigmented actinic keratoses from MIS. Both studies relied on the subjective interpretation of pathologists without true blinding.

Barlow et al³⁵ found high densities of melanocytes adjacent to both melanoma and nonmelanoma skin cancers employing MART-1 immunohistochemistry on permanent sections as well as features usually attributed to MIS, such as contiguous melanocytes, melanocyte atypia, and follicular involvement. These findings, common in chronically photodamaged skin, should not be misinterpreted as a positive margin when using MART-1 on frozen or permanent sections. Consultation with colleagues in dermatopathology may be useful in these difficult cases. Whether immunohistochemistry with MART-1 will ultimately provide reliable distinction between MIS and melanocytic hyperplasia on photodamaged skin is uncertain. Additional studies with blinded inter- and intraobserver confirmation would be helpful.

A second impediment to the use of immunohistochemistry on frozen sections has been the time constraints. The time needed to perform protocols has improved over the past decade from over 2 hours to under 1 hour.⁴¹ Even with this protocol, each MMS layer may take more than 90 minutes total. Few rapid protocols are available⁴³; our group is currently investigating a 12-minute protocol that would allow a complete MMS to be performed in under 45 minutes. Nevertheless, the development of immunostains and protocols that rapidly and accurately identify melanocytes and aid in the determination of MIS margins is an area of intense interest and research.

Conclusions

Surgical excision with a 5-mm margin is often inadequate for MIS on sun-damaged skin, where a background of melanocytic hyperplasia obscures the true borders of the lesion both clinically and histologically. While standard excision with 5-mm margins offers variable cure rates between 80% and 94%,²⁷ staged margin excisions utilizing frozen or permanent sections consistently provide much higher cure rates, though no studies have reported 10-year outcomes, a typical standard for melanoma research. Total peripheral margin assessment using staged excisions and permanent sections is a simple and effective alternative to MMS for institutions that lack the resources for intraoperative frozen section analysis. While the optimal method for surgical resection of MIS is unknown, it is hoped that

results from future randomized trials will guide the application of new technology for more accurate margins of resection of MIS.

Disclosures

No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

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