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Introduction

Mohs chemosurgery, using the fixed-tissue technique, was proposed for the treatment of melanoma by Frederic Mohs in 1950.[1] In numerous publications since, Mohs reported cure rates at least comparable to those obtained with the conventional surgical therapies of the time. Initially, Mohs believed that the in situ tissue fixation with zinc chloride paste inherent in the fixed-tissue technique was an important element in limiting the possibility of tumor spread during the procedure. He later advocated the use of the fresh-tissue technique for periorbital melanomas involving the lid margins or conjunctiva to avoid the local destruction associated with the use of the chemical fixative.[2] As evidence mounted that incising a melanoma did not contribute to its spread, and as the fresh-tissue technique became widely accepted for nonmelanoma skin cancer, the use of the fresh-tissue technique of Mohs Micrographic Surgery (MMS) began to be reported.[3]

In a morning mini-session entitled "Mohs for Melanoma: How You Can and Should Do It With the New Immunoperoxidase Technique," John Zitelli, MD,[4] of Pittsburgh, Pennsylvania, presented the case for MMS in the treatment of melanoma. Although MMS is not accepted by all physicians as appropriate treatment for primary cutaneous melanoma, Dr. Zitelli provided compelling answers to 2 basic questions about MMS for melanoma: "Does MMS for melanoma work?" and "How do you do MMS for melanoma?"

"Does MMS for Melanoma Work?"

Dr. Zitelli reviewed his personal experience and the published evidence for the efficacy of MMS in the treatment of melanoma. First, he demonstrated with clinical examples and scientific studies that melanoma can be detected histologically in Mohs-style frozen sections. In 1991, Dr. Zitelli published a study in which he compared the interpretation of frozen and paraffin-embedded sections from the same block in 221 specimens from 59 patients.[5] In every case in which melanoma was detected in the paraffin sections, it was also found in the frozen sections, yielding a sensitivity of 100%. In situations in which the paraffin sections were negative for melanoma, 10% of the frozen sections were interpreted as positive for tumor, resulting in a 90% specificity for the test. In this study, no melanoma at the margin was missed, but in a small number of cases extra tissue was removed.

Dr. Zitelli also directly addressed studies with findings that conflict with his views. Barlow and colleagues[6] have questioned the reliability of using frozen sections to detect single atypical melanocytes at the margins of melanoma in situ. In their study, 50 out of 154 frozen section specimens of melanoma in situ were considered difficult to interpret and were subsequently processed for conventional paraffin-embedded sections. Using the pathologist's report of the permanent sections as the standard, the sensitivity of the frozen sections was 59% and the specificity was 81%.

Dr. Zitelli addressed 2 issues that may explain the conflict with his findings. First, the Barlow study did not examine the remaining 104 specimens, which were diagnosed with certainty on frozen section examination. If these

specimens had been included, the sensitivity and specificity would have been much higher. Second, this study defined a positive margin as a single atypical melanocyte, whereas Dr. Zitelli included only nests of cells in the epidermis or dermis or contiguous atypical melanocytes in the basal layer as positive for melanoma. The significance of single atypical melanocytes at the periphery of melanoma in situ is unclear. The problem of differentiating atypical melanocytes from keratinocytes altered by freezing and processing can also be significant. The addition of immunohistochemical staining with melanoma antigen recognized by T cells (MART-1) eases that identification by labeling melanocytes in the histologic sections.

Prieto and colleagues[7] also found poor agreement between frozen sections and permanent sections in specimens from 13 melanomas and 10 nonmelanocytic lesions. However, Dr. Zitelli pointed out, the study did not specify diagnostic criteria for melanoma, and there was often disagreement between pathologists about the diagnosis on the permanent sections.

From his own experience and review of the available data, Dr. Zitelli believes that melanoma can be detected in MMS sections and the tumor can be removed completely. Because most current therapeutic guidelines focus on margins of excision, how do the margins required to clear melanomas by MMS compare with recommended margins, and are the recurrence and survival rates comparable?

Recommended excision margins for melanoma are at least partially based on consensus and have generally decreased in size over recent years. Current recommendations from the National Comprehensive Cancer Network[8] based on Breslow thickness include:

In situ	0.5 cm margin
< 1 mm thickness	1.0 cm margin
1-2 mm thickness	1-2 cm margin
2-4 mm thickness	2 cm margin
> 4 mm thickness	2 cm margin

In a study of 535 primary cutaneous melanomas treated with MMS,[9] Dr. Zitelli found that 83% of melanomas were excised with a 0.6-cm margin, 95% with a 0.9-mm margin, and 97% with a 1.2-cm margin. Margins required were greater on the head/neck (1.5 cm to remove 97%) and hands/feet (1.5 cm to remove 96%) than on the trunk (0.9 cm to remove 98%). The size of the margin required was related to the diameter of the clinical melanoma, with larger margins needed for tumors of greater diameter. There was no significant relationship between required surgical margins and Breslow thickness. An important finding in this study, confirmed by other authors,[10,11] is that lentigo maligna (melanoma in situ), with its often large clinical diameter, usually requires greater than the recommended 0.5-cm margins for complete removal.

Because the margins of resection for melanoma have narrowed over recent years, most evidence has pointed to no decline in overall survival rates. However, in 2001, Ng and coworkers[12] found in a retrospective study of 1155 patients with melanoma in New Zealand that narrower margins for tumors < 4 mm in thickness resulted in increased local recurrences and a higher mortality rate. Although all lesions were believed to have been completely excised, histopathologic examination was done with conventional cross-sections, not with complete margin control. Many of the recurrences occurred with surgical margins ≤ 5 mm, a margin previously noted to have considerable risk of incomplete tumor resection.

In a randomized, prospective study, Thomas and colleagues[13] compared 1-cm margins with 3-cm margins in 900 patients with melanoma of the trunk and extremities. This was a group of melanomas at relatively high risk for

recurrence and metastasis, with inclusion criteria of tumors with a thickness of 2 mm or greater. They found an increased risk of locoregional recurrence in the 1-cm group compared with the 3-cm group. There was no statistically significant effect on melanoma-specific survival. Unfortunately, tumor diameter was not reported in this study. Tumors of greater risk also tend to be of greater diameter and therefore require greater margins for complete removal. Because MMS postulates the complete removal of the tumor regardless of margins, the findings of these studies may not apply to MMS.

If removal of the tumor to clear histologic margins were the only goal of treatment, then MMS would seem to offer the advantages of more certain complete tumor removal with possible tissue sparing. However, the prevention of local recurrence and the avoidance of melanoma-related death are perhaps better measures of therapeutic success. Dr. Zitelli related several studies in which MMS compared favorably to historic controls in this regard. In his own group of 535 patients with 553 primary cutaneous melanomas, with a 5-year follow-up, the survival rates were equivalent or better than historical controls treated with wide local excision.[14] He related that his practice will soon publish a report of 625 head and neck melanoma cases, again with rates of recurrence and survival as good as those provided by wide local excision. Of note, in both groups, 83% of melanomas were cleared with 0.6-cm margins, indicating that tissue can be conserved in many patients with ultimate resection margins less than those typically recommended. Several smaller studies with somewhat different methods of tissue processing have produced similar survival and recurrence results.[15-17]

Dr. Zitelli believes strongly that MMS is simply a better way of excising melanoma. With MMS, you know that the tumor is completely excised at completion of the procedure, whereas with conventional excision you must rely on predefined margins that, by necessity, will be larger but still will clear the tumor in less than 100% of the cases.

"How Do You Do MMS for Melanoma?"

Dr. Zitelli detailed his process for performing MMS on melanoma. He first marks the visible tumor and 3-mm margins of normal-appearing surrounding tissue. This area is then excised, with the depth being taken into the subcutaneous fat. This initial excision is submitted for permanent paraffin sections to further evaluate the tumor and its depth of invasion. The first specimen processed for MMS consists of another 3-mm margin of surrounding tissue and completely encompassing the base of the debulking wound. With these two 3-mm resections, the minimum margin taken on any lesion is 6 mm.

The deep margin is rarely involved with residual tumor, and the excess fat usually present in the central portion of the specimen can make cutting and staining thin sections of the peripheral epidermis difficult. To ease this problem, with larger tumors the periphery is sectioned away and processed separately from the central portion (Figure 1). After typical tissue marking and mapping, embedding and freezing, thin (2-4 micron) sections are cut for hematoxylin and eosin (H&E) staining, and additional sections are prepared for immunohistochemistry (IHC) with MART-1. The MART-1 process will reliably stain normal melanocytes, nevi, and melanoma. By using a polymer-based IHC protocol, the processing time can be reduced to approximately 1 hour.[18]

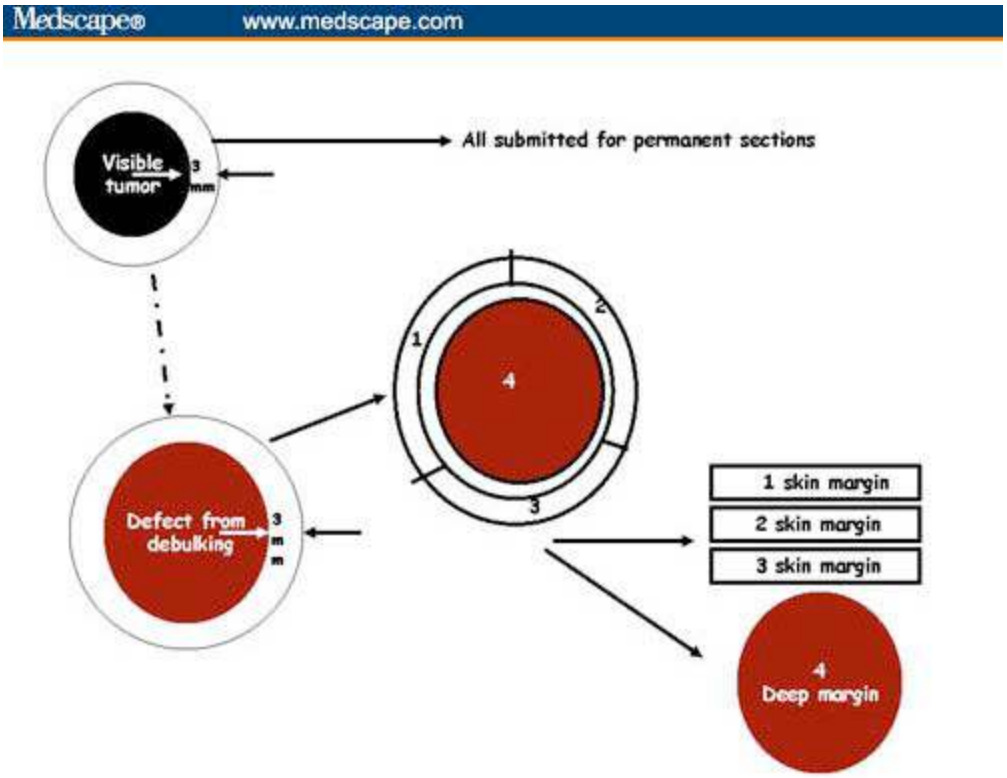

Figure 1. Scheme for removing and processing specimens during MMS for melanoma. First the tumor is removed with 3-mm margins and submitted for permanent sections. A Mohs layer is then taken with an additional 3-mm margin. In sectioning, the epidermal margins are separated from the deep margin to aid in processing.

If the frozen sections stained with H&E unequivocally demonstrate melanoma, another layer is taken and IHC with MART-1 is not done. If the H&E frozen sections are obviously negative for melanoma, no further action is taken. Otherwise, the MART-1-stained sections are processed and evaluated for the presence of tumor. A positive margin is defined as:

1. Nests of atypical melanocytes
2. Pagetoid spread or vertical stacking of atypical melanocytes
3. Confluent hyperplasia or nonuniform crowding of melanocytes along the basement membrane

When evaluating for this criteria, areas of possible involvement can be compared with "control" areas of normal-appearing margin. Findings that are not definitive but raise suspicion for tumor include extension of atypical melanocytes deeply down hair follicles and other adnexal structures, the presence of excessive pigment, excessive numbers of melanophages, and dermal scarring. Dr. Zitelli has found that not all MART-1-positive cells in the dermis are melanocytes and therefore troublesome. Some staining of dermal cells is nonspecific. When the MART-1 antibody is omitted from the procedure, the chromogen is still taken up by some dermal cells. Figures 2a and 2b are examples of H&E and MART-1 staining of lentigo maligna.

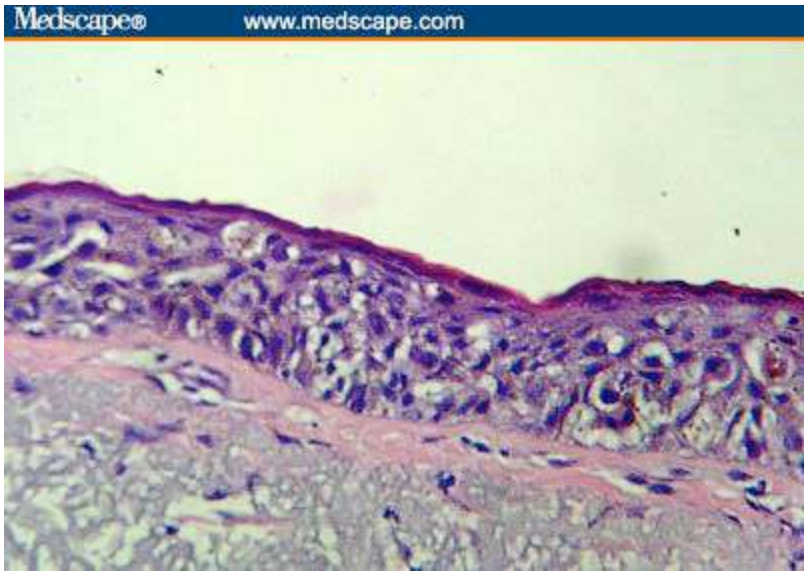

Figure 2a. H&E staining of permanent sections of lentigo maligna. Note the large atypical clear cells in clusters and individually.

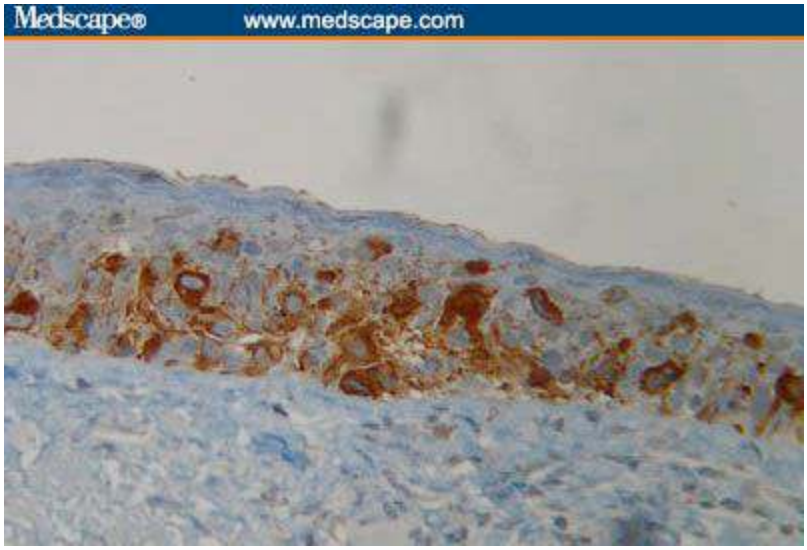

Figure 2b. MART-1 staining of permanent sections of lentigo maligna. The atypical cells are stained brown in the IHC MART-1 process, indicating that they are melanocytes. These atypical cells with pagetoid spread and vertical stacking indicate the presence of lentigo maligna.

Because MART-1 stains normal melanocytes as well as atypical melanocytes, it is important to recognize the density of melanocytes in normal sun-exposed skin. Dr. Zitelli discussed a study from his group, which was also presented by Dr. Ali Hendi[19] at an abstract session. MART-1 staining of frozen sections of the normal skin, removed with the excision of Burrows triangles during reconstruction after MMS of nonmelanoma skin cancer, showed side-by-side confluence of melanocytes to be common. Three to 6 such cells were noted in the majority of specimens. Melanocytes were also seen extending along the superficial portions of the hair follicle. In at least 25% of normal sun-exposed skin specimens, areas of increased melanocyte density were found. Pagetoid spread or nesting of melanocytes was not seen in normal skin. Recognizing the melanocyte patterns of normal skin makes the evaluation of the margins of melanoma specimens much easier (Figures 3a and 3b).

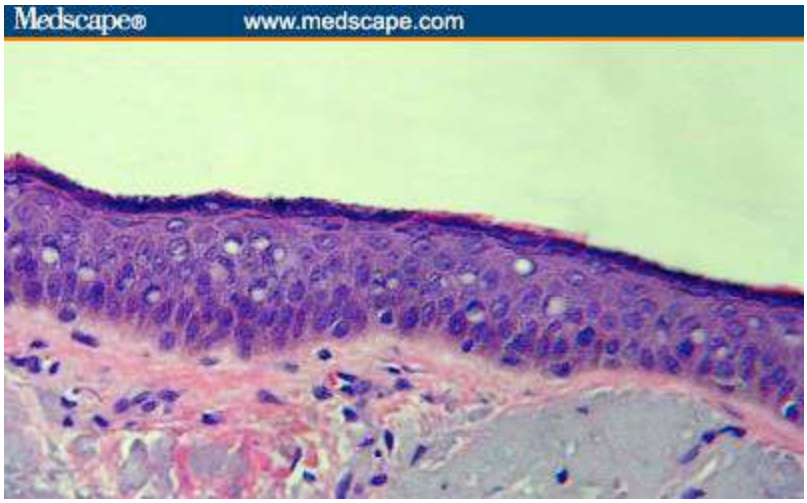

Figure 3a. H&E staining of permanent sections of sun-damaged skin. Note scattered clear cells in the mid- and upper dermis.

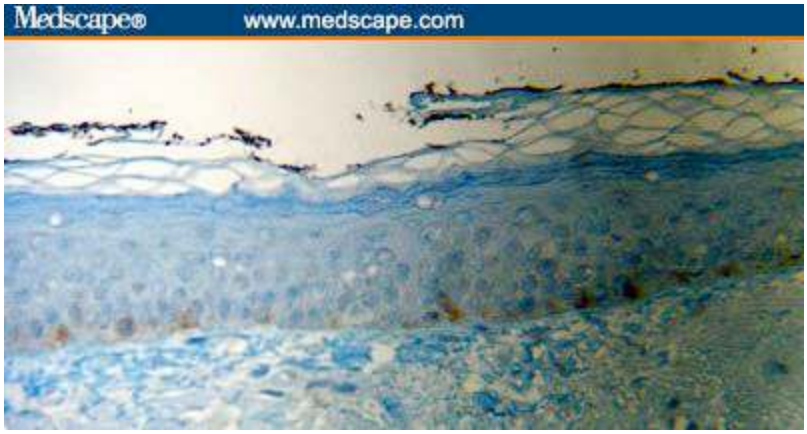

Figure 3b. MART-1 staining of permanent sections of sun-damaged skin. The clear cells in the mid- and upper epidermis do not stain with MART-1, indicating that they are not melanocytes. Individual melanocytes are noted at the basal cell layer. Side-by-side confluence is not prominent.

Pitfalls in MART-1 staining include:

1. Cutting sections too thick. Individual cells staining with MART-1 are difficult to visualize if sections are cut thicker than 4 microns.
2. Tangential cuts of the epidermis may resemble pagetoid spread of melanocytes. In this circumstance, the melanocytes will be in the basal cell layer. Comparison to adjacent tissue may provide evidence of the tangential cut.

Dr. Zitelli relates that MMS for melanoma is generally simple from a surgical standpoint. Ninety percent of trunk lesions clear after the first stage, and even 75% of head and neck melanomas require only 1 layer. These patients benefit from the tissue sparing that is inherent when complete tumor removal is assured with narrower margins. However, it is the patient who requires multiple stages who truly benefits by avoiding incomplete resection of the melanoma and its attendant risk of recurrence and spread.

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Authors and Disclosures

Author(s)

Thomas Stasko, MD

Associate Professor, Dermatology, Vanderbilt University School of Medicine, Nashville, Tennessee; Director of Dermatologic Surgery, Vanderbilt University Medical Center, Nashville, Tennessee

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