

# Mohs Micrographic Surgery



Nicholas Golda, MD<sup>a,\*</sup>, George Hruza, MD, MBA<sup>b</sup>

## KEYWORDS

- Mohs surgery • Micrographic surgery • Skin cancer treatment
- Complete circumferential peripheral and deep margin assessment

## KEY POINTS

- Mohs surgery is the most effective treatment of skin cancer and offers maximum tissue conservation.
- The procedure requires refined surgical technique and careful laboratory processes in order to achieve the best possible patient outcomes.
- The treatment of melanoma and melanoma in situ by Mohs micrographic surgery has undergone significant refinement and wider acceptance, with cure rates equal to or superior to conventional excision.

## INTRODUCTION

Mohs micrographic surgery (MMS) is a specialized technique for the surgical management of skin cancer. Since the first patient was treated by Dr Mohs in 1936, Mohs surgeons have established themselves as leading contributors to the science of cutaneous oncology, innovators in laboratory techniques for the microscopic assessment of skin cancer specimens, and expert providers of reconstruction following the surgical removal of skin cancer. MMS, nearly 90 years following its first use, remains the gold standard for skin cancer cure and is one of the most tissue-conserving and cost-effective options for skin cancer care when used appropriately and when recurrences and prevention of advanced disease are accounted for.

## INITIAL PATIENT EVALUATION

Although MMS is the most effective and often the most conservative treatment of skin cancer, there are many situations where less technically demanding and lower cost treatment options may be a superior option for a given clinical scenario. To this end, the American Academy of

Dermatology (AAD) developed the appropriate use criteria (AUC) for Mohs surgery.<sup>1</sup> This tool can assist physicians in determining whether MMS is appropriate for a given skin cancer. As a decision aid, the AUC does not serve to mandate a particular treatment over another. Tumors that are deemed appropriate for MMS by the AUC may still be treated with other techniques based on specific patient factors, and tumors that are uncertain or inappropriate may occasionally be treated with MMS if there are patient factors unaccounted for by the AUC that compel this decision. In general, however, MMS is considered appropriate in the following scenarios<sup>2</sup>:

- Where there is risk of disfigurement or functional impairment
- Recurrence
- Most cancers in immunosuppressed patients
- Large malignancies
- Poorly defined clinical borders
- Aggressive histologic features
- Sites where healing is difficult and tissue conservation will facilitate wound healing
- Patients with genetic skin cancer predisposition syndromes

<sup>a</sup> US Dermatology Partners, 3265 NE Ralph Powell Rd, Lee's Summit, MO 64064, USA; <sup>b</sup> Saint Louis University, Laser and Dermatologic Surgery Center, 1001 Chesterfield Pkwy E #101, Chesterfield, MO 6301, USA

\* Corresponding author.

E-mail address: nicholas.golda@gmail.com

- Cancers in previously irradiated skin, traumatic scars, sites of osteomyelitis, and chronically inflamed skin.

In order for MMS to be successful, the tumor being treated must grow in a contiguous manner. This includes most cutaneous malignancies such as basal cell carcinoma, squamous cell carcinoma, cutaneous adnexal malignancies, melanoma and melanoma in situ/lentigo maligna, dermatofibrosarcoma protuberans, cutaneous leiomyosarcoma, extramammary Paget disease, atypical fibroxanthoma/pleomorphic dermal sarcoma, Merkel cell carcinoma, and other less common cutaneous malignancies.<sup>3</sup> Cutaneous malignancies typically not amenable to treatment with MMS include angiosarcoma and Kaposi sarcoma. A patient must also be able to tolerate the procedure with the use of local anesthesia and possibly oral anxiolysis only.

## PROCEDURE OVERVIEW

### *Preoperative Considerations*

Identifying the correct site for surgery is important because wrong site surgery is a common cause of legal action against dermatologic surgeons.<sup>4</sup> Patients are often unable to accurately recall the correct site of a biopsy. Utilizing photographs taken at the time of biopsy is a best practice for avoiding wrong site surgery.<sup>5</sup> When no photograph of the biopsy site is available, Mohs surgeons can often identify the biopsy site clinically but may also confirm their site selection with the patient and any family that are present who may have assisted the patient with wound care for the biopsy site.

Photography and clinical documentation of the patient's state before initiating surgery can be helpful in both illustrating for the patient and documenting for medicolegal purposes any existing asymmetries, scars, palsies, or other anatomic irregularities that the patient may not be aware of to avoid attribution of these to the surgical procedure. Before injecting local anesthetic, mark relevant anatomic boundaries or features that may be helpful in reconstruction planning because the edema from injected anesthesia can make landmarks more challenging to identify.

### *Initiating the Procedure*

Mohs surgery, in most cases, is carried out as a clean (nonsterile) procedure utilizing sterile instruments in a nonsterile clinical setting, nonsterile gloves, and clean drapes. Surgeons generally prepare for surgery using handwashing or alcohol hand sanitizers, and the surgical site is made

antiseptic by the use of chlorhexidine gluconate or povidone iodine.

Some surgeons will then proceed to take the first Mohs stage, whereas others will first debulk the tumor by either curettage or scalpel. Curettage can grossly define the size of the skin cancer because tumors with noninfiltrative diagnoses can shell out easily providing firmer tactile feedback to the surgeon when tissue uninvolved by frank tumor is encountered. Benefits of curettage before the first layer of MMS include the following:

- Confirmation of the gross size and depth of a malignancy thereby avoiding unnecessary subsequent layers or allowing for a more conservative excision.
- Possible reduction in the presence of tumor floaters that may confound histologic analysis or result in false-positive interpretations.
- Tissue relaxation that may facilitate tissue processing.

Potential drawbacks include the chance of inducing skin tears or damaging adjacent epidermis, thereby rendering a Mohs layer taken through the damaged zone uninterpretable.

Scalpel-based sharp debulking may also be used. Sharp debulking is most often used to remove an exophytic tumor to facilitate taking a first Mohs stage or to debulk a tumor for histologic staging purposes. The primary pitfall of taking a debulking specimen is inadvertently taking too wide or too deep a debulk, thereby making the final Mohs excision larger than necessary. This risk can be minimized through careful technique.

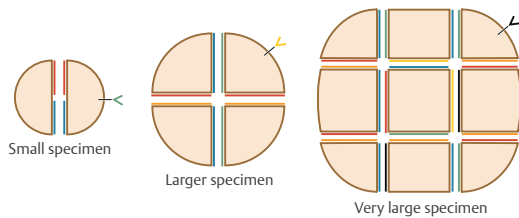
### *Excising Mohs Tissue Specimens*

The goal with each stage of MMS is to conservatively remove the malignancy in its entirety. The first stage consists of complete removal of the gross tumor as well as a narrow margin of clinically normal skin immediately around and deep to the tumor to allow for histologic processing and quality control. The specimen is removed with convex rounded contours whenever possible, and a bevel is placed around the periphery of the specimen such that the specimen is narrower at the base than it is at the surface. These actions facilitate tissue processing. If the surgeon provides a specimen that is challenging to process, then the specimen may not yield completely interpretable results even with skilled laboratory staff. This may lead to unnecessary additional stages of surgery or a greater chance of tumor recurrence for the patient.

Mohs surgeons place orienting marks on the patient's skin surrounding the specimen being

excised that coordinate with marks placed on the specimen itself. This is most commonly carried out by the placement of small tissue nicks or scores with the scalpel, and the patterns of these scores can be variable based on surgeon preference. Placement of the scores in a systematized manner is important so that when the tissue is processed and interpreted, the surgeon can correlate the histologic findings with the correct location on the patient for a focused reexcision of any residual malignancy if necessary. To this end, most surgeons place tissue scores in an asymmetric manner so that the surgeon can reorient the specimen to the patient if any tissue handling error occurs during tissue processing because the specimen will only “fit” on the patient’s defect one way. The most commonly deployed patterns for uncomplicated specimens include a single score in 1 location or 3 scores in a 12:00, 3:00, and 6:00 or similar asymmetric orientation (Fig. 1). Larger tumors are best scored with a grid or “graph paper” technique because this allows the highest possible resolution for residual tumor in the deep margin within the larger field of these tumors (see Fig. 1; Fig. 2). In this technique, scores are placed on each side of the tumor in strict 90° relation to one another such that the tissue can be divided into graph paper-like squares during tissue processing. Tissue scores, although necessary, also introduce potential error into the MMS process because each score produces an area where epidermis may be incompletely laid down into the sectioning plane. If the score results in failure to visualize focal residual tumor on a margin because of incomplete epidermal visualization, then a false negative may result.

Once the beveled incision at the periphery of the specimen is complete and scores are placed, the specimen is removed from the patient by making a flat incision across the deep margin of the specimen just below the deepest extent of the tumor. Pitfalls with incision through the deep margin of the Mohs specimen include making a jagged deep marginal incision that will create “drop out” areas on the specimen, taking an incomplete or buttonholed deep margin, grasping the tissue too firmly with toothed forceps causing triangular impressions in the deep margin that interfere with the assessment of the deep margin, and accidentally transplanting the tumor from the superficial part of the specimen to the deep part of the specimen by toothed forceps thus creating a false positive or tumor floater in the deep margin of the specimen. Fig. 3 demonstrates proper basic technique as well as several possible pitfalls with taking of initial layers.



**Fig. 1.** Possible scoring, division, and inking patterns for various sized tissue specimens. (From Golda NJ, Hruza GJ. *Mohs Micrographic Surgery From Layers to Reconstruction*. 1st ed. (Harmon CB, Tolkachjov SN, eds.). © Thieme 2022.)

### **Taking an Initial Layer from a Recurrent or Incompletely Excised Site**

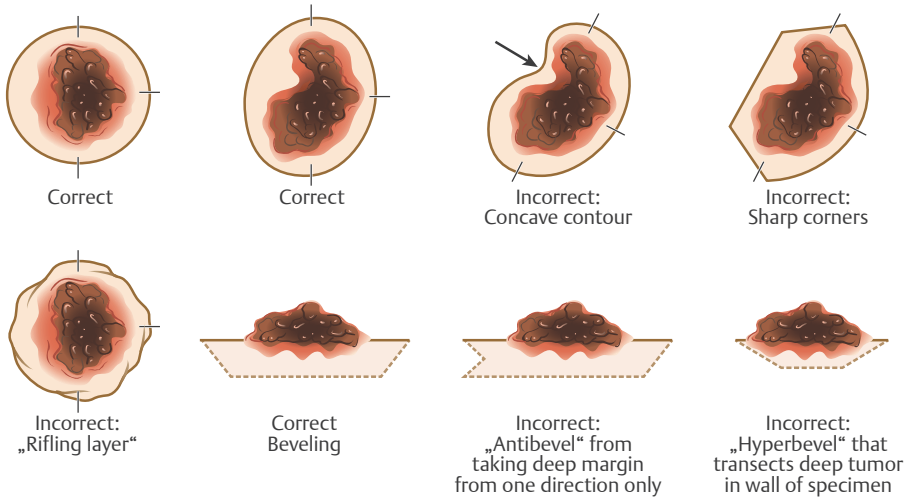
Recurrent or incompletely excised sites present unique challenges because the normal anatomy has been modified by a previous closure and the tumor may now be discontinuous. This is why cure rates for tumors in these categories are lower than those for tumors treated primarily with Mohs surgery.<sup>6–8</sup> For incompletely excised sites, having information about whether the residual tumor is present at lateral or deep margins, or having the slides from the original excisional specimen available for review, can be helpful when planning for subsequent MMS.

### **Tissue Grossing**

To execute the Mohs technique, the 3-dimensional tissue specimen must be converted to a 2-dimensional plane such that the epidermal, dermal, and deep margins can all be visualized in a single plane. This is accomplished during grossing by a series of relaxing cuts that allow the superficial



**Fig. 2.** Representative “grid style” scoring pattern for a larger tumor (DFSP pictured). (From Golda NJ, Hruza GJ. *Mohs Micrographic Surgery From Layers to Reconstruction*. 1st ed. (Harmon CB, Tolkachjov SN, eds.). © Thieme 2022.)



**Fig. 3.** Representative correct techniques and pitfalls for excision of the first layer of MMS. (From Golda NJ, Hruza GJ. *Mohs Micrographic Surgery From Layers to Reconstruction*. 1st ed. (Harmon CB, Tolkachjov SN, eds.). © Thieme 2022.)

part of the tissue to open like an accordion, thereby permitting the epidermal edge to lay down into the same plane as the deep margin. Tissue relaxation is facilitated as well by debulking as described previously.

Based on surgeon preference, MMS specimens can be divided before freezing and sectioning or can be processed as a single piece.<sup>9</sup> There are merits and drawbacks to both approaches. There may be time saved in the laboratory when a specimen is processed as a single piece but obtaining sufficient tissue relaxation to achieve full lay-down of the epidermis into the processing plane is more challenging and may result in lost time or the need for specimen recuts. A divided specimen is always required if the excised tumor is too large to fit on a microscope slide. The tissue grossing process is a source of several potential causes of false-positive findings on Mohs histologic specimens that the surgeon must be aware of:

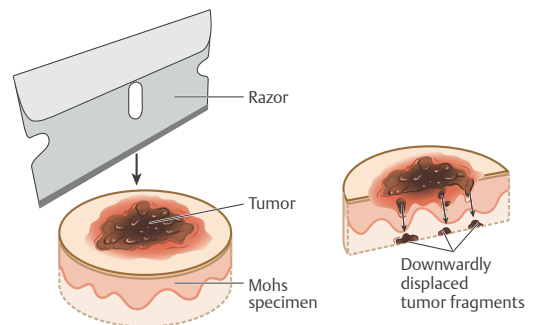
- Dividing specimens can result in superficial tumor being pushed through to the deep margin of the specimen (Fig. 4).
- Following specimen division, superficial tumoral tissue in the center of the specimen may fall into continuity with the deep margin (Fig. 5).
- Excessive downward pressure on the specimen while freezing the tissue into the planar orientation for tangential sectioning may press tumoral tissue closer to the deep margin and predispose to false positives.
- Excessive facing into the frozen tissue block due to suboptimal epidermal relaxation and epidermal lay-down can cut into the gross

tumor when it may not have been present in the true margin if the specimen had been sectioned more conservatively.

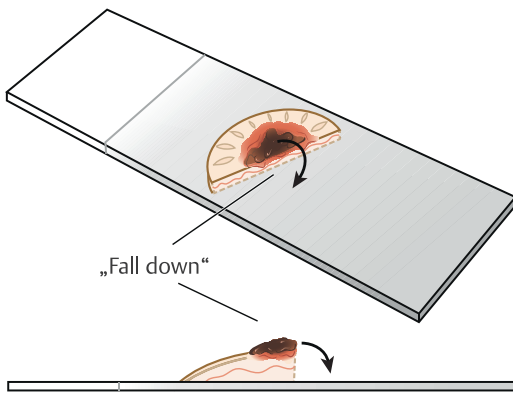
Once the tissue is relaxed, it is marked with tissue dyes to further allow the surgeon to orient the histologic findings to the tumor site on the patient, and a map is created illustrating the tissue divisions, the tissue-inking pattern, and often the anatomic position and orientation of the tumor on the patient.

### Tissue Processing

There are several techniques used to obtain a flat specimen following grossing in preparation for tissue freezing. One commonly deployed technique



**Fig. 4.** The creation of "push-through" artifact during specimen division where tumor is displaced from friable tissue at the surface to create a false-positive deep margin. (From Golda NJ, Hruza GJ. *Mohs Micrographic Surgery From Layers to Reconstruction*. 1st ed. (Harmon CB, Tolkachjov SN, eds.). © Thieme 2022.)



**Fig. 5.** The mechanism for “fall over” artifact where superficial tissue from the center of a divided specimen can relax into the deep plane and create false-positive findings. (From Golda NJ, Hruza GJ. *Mohs Micrographic Surgery From Layers to Reconstruction*. 1st ed. (Harmon CB, Tolkachjov SN, eds.) © Thieme 2022.)

is to lay the specimen flat on a microscope slide such that the complete epidermal margin and deep margin are in full contact with the slide. The slide is then placed on a heat sink in the cryostat, covered with optimal cutting temperature medium, and a prepared cryostat chuck is placed on top of it. This is allowed to freeze, and the tissue is subsequently sectioned into thicknesses ranging from very thin 4- $\mu\text{m}$  sections for immunohistochemical (IHC) staining up to 8- $\mu\text{m}$  sections for traditional hematoxylin and eosin or toluidine blue staining. In certain scenarios, longer freezing times or thicker specimens may be needed to obtain excellent sections, particularly for sections with considerable fat; thus, the surgeon and laboratory staff must be able to make adjustments as necessary when certain scenarios requiring nuance arise. The tissue is then stained.

### **Histologic Interpretation and Mapping**

A significant part of MMS fellowship training includes the proper interpretation of tangentially processed frozen section histology. Histologic interpretation requires the ability to recognize subtle changes consistent with the trailing edge of skin cancer at the margins of a Mohs excision and the ability to assess tissue specimens for quality.

An important first step in interpretation is awareness of the tumor that is being excised. Although common malignancies are easily recognized with experience, less common variants can be more challenging, and it is often helpful to review the original diagnostic biopsy slides or to take a frozen section biopsy or debulk specimen for vertical

sectioning from the center of the malignancy on the day of surgery in these cases.

Errors in slide preparation and interpretation have been shown to account for a large proportion of recurrences following MMS.<sup>10–12</sup> Therefore, attention to careful processes that avoid errors as well as expert interpretation of histologic specimens is important in the success of the technique.

Accuracy begins with confirming that maps and tissue specimens are correctly coordinated and identified. Next, the surgeon may inspect the specimen to confirm that there are no obvious features that indicate the specimen is incorrect such as gross size differences from what is expected, scoring patterns that do not coordinate with the map, and histologic features on the specimen that suggest an anatomic location different than that being treated. The specimen is then assessed for laboratory process and staining quality. Common issues include but are not limited to air bubbles from improper coverslipping, brown discoloration from insufficient clearing, missing stains or stain darkness issues, folded, chattered, or otherwise poorly flattened or sectioned specimens, and specimens cut too thick. A complete representation of the epidermis around the total circumference of the specimen as well as a complete deep margin with no zones of missing tissue are ideal for Mohs histologic interpretation.

### **Histologic Interpretation**

The surgeon and pathologist being the same physician is a required element of MMS. Mohs surgeons are well-trained in the assessment and histologic mapping of frozen section tissue processed by tangential sectioning for both common and rare malignancies of the skin and are able to recognize even subtle residual malignancy in a specimen margin. A thorough description of these tumors and their features is beyond the scope of this article but common pearls and pitfalls are described herein.

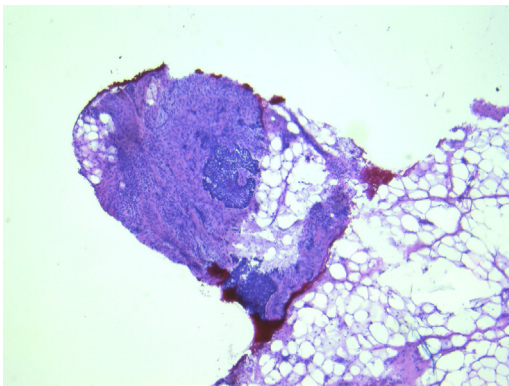
Inflammation, typically manifesting as dense lymphocytic aggregates in the specimen, can occur for a variety of reasons including unrelated inflammation in the skin, inflammation related to the biopsy that was recently performed in the treatment zone, incidental chronic lymphocytic leukemia (CLL), or inflammation related to the tumor being treated. The latter cause is important to recognize because such peritumoral inflammation may alert the surgeon to small foci of invasive malignancy or may obscure tumor, thereby making it more difficult for the surgeon to diagnose.<sup>13</sup>

Tumoral tissue may also be artifactually present on the MMS histologic slides due to process errors

during excision and tissue processing. The surgeon must be able to recognize these scenarios and work to correct the errors that underlie them. A commonly encountered artifact is a tumor floater (Fig. 6), which is an artifactual segment of tumor that has been dislodged and has come to rest on some portion of the margin being assessed on the histologic slide. Common causes of tumor floaters include tumor fragments that are displaced during tissue grossing, fragments transferred from the superficial to the deep margin during excision by a toothed forcep, and “fall-down artifact” that may occur in divided specimens as discussed earlier. When there is doubt, the surgeon should err on the side of excising a thin layer of additional tissue to confirm that the margins are free of tumor as oncologic cure is the most important motivating factor for performing MMS.

Proper histologic interpretation also demands that the surgeon be able to recognize benign neoplasms and normal structures in the tissue and not confuse these with malignant tissue that requires excision. Structures in the skin that may mimic malignancy include the following:

- Salivary glands can be encountered particularly on the lip or in the area immediately anterior and inferior to the ear (parotid gland)
- Hair follicles and sebaceous glands
- Goblet cells in conjunctival epithelium or urethral transitional epithelium can be confused with pagetoid cells associated with sebaceous carcinoma or extramammary Paget disease
- Follicular basaloid proliferation (benign follicular proliferation or benign follicular hamartoma)<sup>14</sup>



**Fig. 6.** An example of a tumoral tissue floater creating a false-positive deep margin. (From Golda NJ, Hruza GJ. *Mohs Micrographic Surgery From Layers to Reconstruction*. 1st ed. (Harmon CB, Tolkachjov SN, eds.). © Thieme 2022.)

- Benign adnexal neoplasms<sup>14</sup>
- Calcinosis cutis

Ideally, the Mohs surgeon will examine the tissue specimens not only for the presence or absence of malignancy but also for the presence of factors that may contribute to the patient's care such as finding and documenting features that may upstage a patient's SCC<sup>15</sup> and documenting the presence of lymphocytic infiltration consistent with lymphoproliferative disease, such as CLL, and initiating a workup if these features are identified.<sup>16</sup>

### Tissue Mapping

MMS is effective because the surgeon is able to accurately pinpoint the exact location of any residual malignancy on the patient and selectively reexcise it. Histologic mapping is the tool that allows documentation of residual malignancy in relation to the patient's anatomy and the orienting marks the surgeon has placed on the patient and specimen.

Imprecise mapping may lead to selective reexcision of an incorrect site or reexcision of an inadequate breadth or depth of the correct site. Selective reexcision of the incorrect site is particularly challenging because the result will be a histologically tumor-free margin on the subsequent layer and false reassurance that the tumor was properly treated.

When mapping a tumor, the surgeon is aware that the tumor being mapped is a 3-dimensional figure with an edge, a wall, a hinge where the wall transitions to the base, and a deep margin. Often there is histologic evidence that aids the surgeon in accounting for tumor in the wall of a specimen and tumor in the hinge point or base. The most obvious form of this evidence comes from hair follicles, which are sectioned vertically in the wall and horizontally in the base. Careful attention to the precise 3-dimensional location of the residual tumor when mapping is important. Proper tumoral mapping should include the tumor type and subtype and anatomic depth. The notation of scar tissue, when observed, may aid the surgeon in resolving if the true deep or lateral margin has been reached and histologically assessed in a recurrent or incompletely excised tumor.

The surgeon may also wish to note histologic abnormalities that are not malignancies to document that these were observed and deemed to not be a positive margin. Noting actinic keratoses on the Mohs map may be helpful in that the surgeon has noted in the medical record the presence of actinic damage that did not require

excision but will require subsequent superficial treatment.

The MMS map is an important part of the medical record that illustrates the observations the surgeon makes histologically and the decision-making regarding structures that will require reexcision because they were determined to be malignant and those that will be left behind because they were determined to be benign or more appropriately treated by other means such as in the case of actinic keratoses. A surgeon may wish to make written comments on the map as well to add clarity to decisions that are made based on histology and to guide selective reexcision of residual tumor.

### Subsequent Layers

The rate of recurrence increases when numerous stages are required to obtain clear margins for a skin cancer being treated by MMS.<sup>11</sup> Tumors requiring multiple stages may be more biologically aggressive, and when multiple stages are required, there are more opportunities for a surgeon or processing error such as inaccurate mapping. Being purposeful in the planning and execution of subsequent layers is important. Although the surgeon should attempt to completely remove all residual tumor with each subsequent layer, the goal remains to also be tissue-sparing, so the surgeon should excise subsequent layers in a manner that will allow easy reorientation to the site if yet another stage is required.

The most common mechanism for indicating the extent of a subsequent layer on the patient is to place tissue scores in the skin at either side of a selective reexcision where the curvature of the edges fades back into the rounded contour of the original MMS stage although other acceptable techniques exist. The surgeon should ensure that these terminal scores on either side of a subsequent stage are discernible from those in place from earlier layers so reorientation is possible if another stage is required. Additional scores can also be placed in the span of subsequent layers to provide better resolution of the location of residual tumor if a subsequent layer persists in having tumor at the margins. Additionally, if a surgeon determines that more than one distinct tissue specimen should be excised during a single subsequent layer, these specimens can be differentiated from one another by the placement of a midpoint score in one specimen and no score in the other. Attention must be paid to inking of multiple distinct tissue specimens in one layer so they may be distinguished from one another.

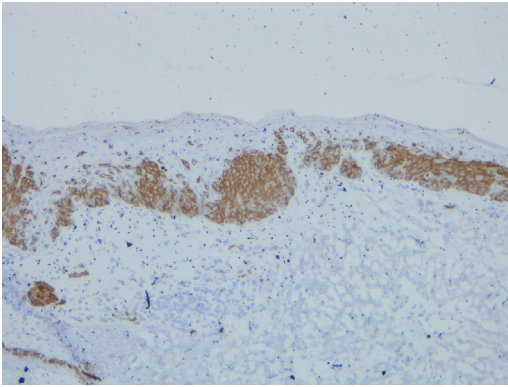
At times, the surgeon may need to reexcise residual tumor that is present only in the deep margin of the specimen. Maintaining tissue orientation can be challenging when the more fragile deep tissue, consisting often of fat and possibly muscle, requires reexcision and there is no adjacent dermis, thus making orientation utilizing dermal scores or marks not possible. Below are some techniques that facilitate orientation in this scenario:

1. The necessary deep tissue can be removed as well as a nearby thin margin of dermis. The location of this dermal tag is marked by a tissue score. When tissue processing is done, the dermis is laid down as per normal Mohs tissue processing and any residual tumor in the deep margin can be mapped using this dermal tag as a reference point.
2. In large tumors where there is an extensive field of deep tissue, the surgeon uses the previously described gridding technique to accurately locate residual tumor on a deep margin. Once the appropriate zone in the grid that requires reexcision is identified, the surgeon excises the entirety of that polygon of involved tissue and inks the flat sides with different colors to correspond with the map. This allows precise location of any residual deep tumor relative to the uniquely inked margins.

Regardless of which technique is used, the critical element of deep-only layers is the same as that for all subsequent layers: complete removal of the malignancy and the ability to reorient for another selective reexcision if the margins remain involved by malignancy.

### New Developments

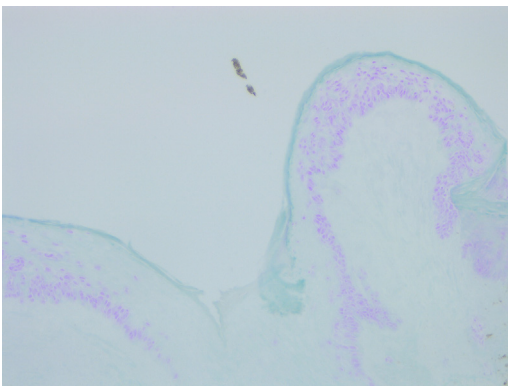
An area of profound development in recent years is the use and acceptance of MMS for the treatment of melanoma. Although dermatologic surgeons have treated melanoma in situ as well as invasive melanoma for years using MMS,<sup>17,18</sup> the development of rapid protocols for melanocyte-specific IHC staining on frozen section specimens and increasing evidence supporting MMS as noninferior or superior to wide local excision, particularly on special sites,<sup>19–21</sup> has led to an expansion of the use of MMS for melanoma, and the most recent iteration of the Mohs AUC published by the AAD recognizes the treatment of lentigo maligna and melanoma in situ as appropriate in most scenarios.<sup>1</sup> An update to the AUC is expected this year that will likely further clarify the appropriateness of MMS for melanoma. The most commonly used IHC stain



**Fig. 7.** Melanoma in situ MMS frozen section stained with MART-1 IHC (100 $\times$ ).

is the melanoma antigen recognized by T cells (MART-1) stain (**Fig. 7**), although effective protocols for SRY-related HMG-box 10 (SOX-10) and others are becoming available (**Fig. 8**). The execution of these laboratory techniques is painstaking, time-consuming, and requires well-trained laboratory staff to produce consistent results, but consensus is emerging that the use of IHC while doing Mohs surgery for melanoma is a best practice.<sup>22,23</sup>

The execution of the MMS procedure for melanoma is much the same as it is for conventional MMS although a few key differences exist.<sup>24</sup> Mohs surgeons will more commonly take sharp debulking specimens for staging purposes, which are processed with vertical sections by frozen section, permanent sections, or both. Surgeons will also start with wider margins than typically used in nonmelanoma skin cancer, often 5 mm from the visible tumor border, and will excise to a depth appropriate for melanoma treatment where anatomically appropriate.



**Fig. 8.** Melanoma in situ MMS frozen section stained with SOX-10 IHC (40 $\times$ ).

## SUMMARY

MMS is widely accepted as the gold standard for skin cancer care, and the surgeons who carry out this procedure are experts in the management of skin cancer. There are many potential pitfalls and challenges that a surgeon may encounter while carrying out MMS, which can increase the likelihood of tumor recurrence and increased patient morbidity. With proper training and careful processes that safeguard against errors, this procedure can provide excellent cure rates for most skin cancers, including melanoma, while maximizing tissue conservation in a low-cost outpatient clinical setting.

## CLINICS CARE POINTS

- Mohs micrographic surgery (MMS) is the most effective treatment available for skin cancer but its use should be limited to only those malignancies for which it has been deemed appropriate.
- Careful processes are required at every step in the procedure (surgical, laboratory and pathologic interpretation) to achieve the dual goals of MMS: highest possible cure and maximal tissue conservation.
- Evidence and consensus support the expanding use of MMS for the treatment of melanoma, and research is underway to establish best practices.

## DISCLOSURE

The authors have no relevant conflicts of interest to disclose.

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