The Role of Mohs Surgery in Cutaneous Head and Neck Cancer

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KEYWORDS

• Mohs micrographic surgery • Cutaneous cancer • Head and neck
• Basal cell carcinoma • Squamous cell carcinoma • Melanoma
• Merkel cell carcinoma

KEY POINTS

- MMS is most comonly used in treating basal cell and squamous cell cutaneous cancers.
- MMS allows the dermatologic surgeon to analyze 100% of the peripheral and deep margins by horizontal saucering technique.
- Certain, high-risk cSCC, and melanomas require consideration of alternative surgical interventions from MMS and additional therapies.

INTRODUCTION

In the 1930s, Frederic E. Mohs, while studying the effect of various substances injected into different neoplasms, encountered a 20% solution of zinc chloride that resulted in tissue necrosis without altering the microscopic structure of the tissue. Mohs conceptualized surgical excision of neoplasms after in situ fixation with zinc chloride to serially excise the neoplasm in total under the microscope. Furthermore, he developed a horizontal frozen section technique to evaluate 100% of the specimen margins, both deep and peripheral, in contrast to the traditional vertical section technique.[1,2] Mohs microsurgery has become the gold standard for treating a variety of cutaneous tumors.[3]

Evolution of Mohs Micrographic Surgery

The technique of Mohs micrographic surgery (MMS) was initially described as chemosurgery by Mohs. Chemosurgery references the application of dichloroacetic acid as a keratolytic followed by application of a zinc chloride paste combination with stibnite and bloodroot to a desired thickness in order to produce a predictable and

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Otolaryngol Clin N Am 54 (2021) 439–447
https://doi.org/10.1016/j.otc.2020.11.015
oto.theclinics.com

controllable depth of penetration. These chemicals permitted in situ tissue fixation while preserving microscopic features necessary for evaluation of residual cancer cells. After tissue application, the patient's wound was dressed, and the patient returned the next day for surgical excision of the fixed tissue followed by excision of the first Mohs micrographic layer. The first micrographic layer is accomplished by incising around the tumor with a 1 mm to 5 mm margin with a scalpel beveled at a 30° to 45°angle to the desired depth. This permits excision of a saucer-shaped specimen that once flattened lends itself to deep and peripheral margin assessment. A surgeon may opt to perform debulking of the visible tumor first to submit for vertical histopathologic sections if warranted clinically. Both the resected tumor and the first micrographic layer were analyzed histologically with hematoxylin and eosin. The micrographic layer was inked, mapped, and examined under the microscope encompassing the entire peripheral and deep surface margins. If a tumor was seen, more fixative was applied to the resection site, and the process was repeated the following day until the cancer was completely resected.[1,3,4]

There were disadvantages to the originally described chemosurgery. Each stage of chemosurgery lasted an entire day, necessitating numerous consecutive days of treatment for patients requiring multiple stages for complete excision. The paste itself was painful, and some patients reportedly required hospitalization for pain management. Residual surgical defects required delayed reconstruction, given the additional 7 to 10 days typically required for the fixed tissue site to slough off, leaving the healthy bed of granulation tissue.[3]

In 1953, Mohs wanted to speed the procedure time for a patient with pigmented basal cell carcinoma (BCC) of the lower eyelid. He removed 2 additional layers after the excision of the tumor using local anesthetic without any fixation. Dr. Mohs published the technique in 1956 and presented the technique at a national meeting in 1969. Tromovitch and Stegman reported in 1974 a series of 102 head and neck BCCs treated by the fresh-tissue technique, demonstrating equivalent outcomes to the chemosurgery technique and thereby launching this fresh-tissue technique as the method utilized today.[1,3,5] In 1976, Mohs reported impressive results for patients he treated with either the fixed-tissue technique or the fresh-tissue technique. For a total of 9351 treated cancers, Mohs reported a 99.3% cure rate using the zinc chloride fixed tissue method, and 97% cure rate for the 127 patients treated by the fresh-tissue technique.[2,6]

The procedure was officially renamed Mohs micrographic surgery in 1985 to emphasize the microscopic evaluation and tumor mapping characteristic while permitting same-day resection and reconstruction. The MMS technique advantages include high rates of cure given the complete evaluation of the deep and peripheral tumor margin in contrast to the traditional vertical sectioning of tissue (**Fig. 1**). The vertical section method of pathologic assessment of margins permits sampling error while only evaluating 1% of the surface area for residual tumor. Another advantage is the conservation of normal, uninvolved tissue, resulting in the smallest possible defect. Because the dermatologic surgeon serves also as the pathologist, room for errors by tissue handoffs is minimized. Reconstruction is undertaken only after 100% margin evaluation confirms a completely free margin status.[1,3]

APPLICATION OF MOHS MICROGRAPHIC SURGERY IN THE HEAD AND NECK

Nonmelanoma skin cancer (NMSC) is the most common malignancy in the United States. Cutaneous BCC and squamous cell carcinoma (cSCC) are the most commonly diagnosed NMSCs, comprising over 1 million new cancer diagnoses annually. BCCs constitute 70% to 80% of all skin cancers, and 15% are cSCC. Melanoma makes up

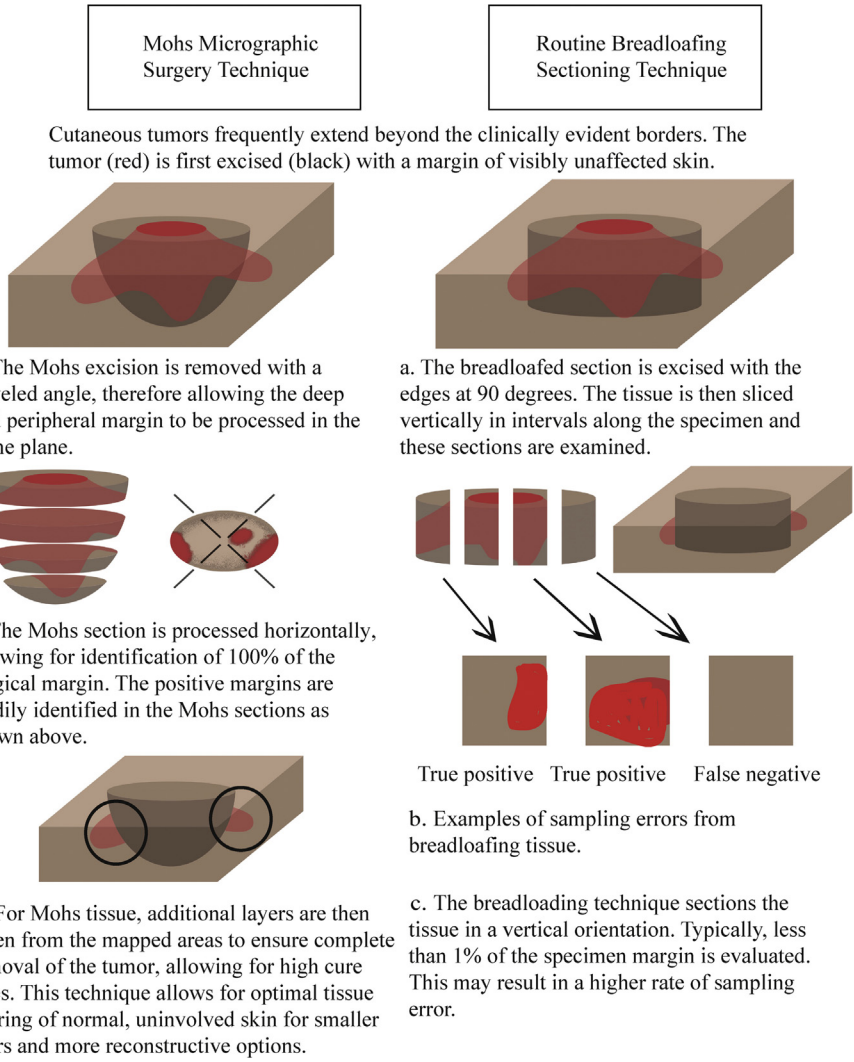

Fig. 1. Comparison of Mohs micrographic pathology technique compared with traditional vertical pathology sectioning. *From* Tolkachjov SN, Brodland DG, Coldiron BM, et al. Understanding Mohs Micrographic Surgery: A Review and Practical Guide for the Nondermatologist, Mayo Clin Proc 2017; 92(8):1261-71; with permission

most of the remaining cutaneous malignancies. BCC is locally aggressive but exhibits low likelihood for development of metastasis, while cSCC is biologically more aggressive, demonstrating perineural invasion (PNI) and regional cervical metastasis.[7] Surgical resection is the mainstay of treatment for these malignancies. Both wide local excision and MMS play a role in the management of these NMSCs.

Basal Cell Carcinoma

For primary BCC, MMS achieves high cure rates on the order of 98% to 99% compared with 91% to 95% for non-MMS treatment modalities.[8,9] Although the gold standard for primary treatment of BCC of the face is surgical excision, MMS is regarded as the

treatment of choice for high-risk BCC. High-risk BCC is described as tumor location around the eyes, nose, lips and ears, also known as the H-zone; aggressive histopathologic types of morpheaform, infiltrative, micronodular and basosquamous; recurrent or incompletely excised lesions; lesions demonstrating perineural or perivascular involvement; and lesions excised with ill-defined margins.[8,10]

A randomized trial of 599 BCCs prospectively compared standard surgical excision to MMS for primary (n = 397) and recurrent (n = 202) BCC of the face where the primary outcome measure was clinical and biopsy-proven tumor recurrence after 5 years. The 5-year Kaplan-Meier estimated recurrence rate for primary BCCs treated by surgical excision was 4.1%, and for MMS, it was 2.5%, a nonsignificant difference (P=.397); all recurrences occurred in the H-zone. The authors surmised that the seemingly high recurrence rate after MMS was because all BCCs included in this study exhibited high-risk features. Regarding recurrent BCCs, the estimated Kaplan-Meier recurrence rate for tumors treated by surgical excision was 12.1% versus 2.4% for MMS, a difference in recurrence rate that was significant (P=.015).[8] This advantage in recurrence rate for recurrent BCCs treated by MMS may derive from the often infiltrative nature of recurrent tumor within scar tissue, whereby complete peripheral and deep margin assessment provides 100% excision capability.

Another prospectively performed randomized controlled trial inclusive of 408 primary BCCs and 202 recurrent BCCs assessed over a 10-year period for clinically evident and biopsy-proven tumor recurrence. The authors observed an estimated Kaplan-Meier recurrence rate of 12.2% for primary BCCs surgically excised and 4.4% for lesions treated by MMS, P=.10. For recurrent BCC lesions treated by surgical excision, the estimated recurrence rate was 13.5% and 3.9% for those lesions treated by MMS, significant with P=.023.[11]

There was not a statistically significant difference in recurrence between surgical excision and MMS for primary BCCs in either study. Surgical excision of most BCCs remains an efficacious and efficient means of management. MMS may provide added benefit for high-risk BCCs given this method's ability to assess 100% of the resection margin, particularly when the primary site occurs near vital structures in the head and neck.[8,11,12] Evidence that further supports this conclusion includes several studies demonstrating low recurrence rates of head and neck BCC after treatment via MMS of 1.4% to 4%.[9–11]

There is an apparent advantage when technically feasible to treat recurrent BCCs with MMS based on these 2 prospective studies. High-risk features such as perineural invasion or deep subcutaneous tumor extension that render BCC more likely to recur are features that MMS may more readily identify intraoperatively.[13] By virtue of MMS comprehensive intraoperative assessment of 100% of the peripheral and deep margins, another Mohs resection layer is possible in real time, thereby increasing the likelihood of margin clearance.

Head and neck surgeons may encounter patients who have recently undergone an attempt at surgical resection or MMS, where final pathologic evaluation reveals incomplete resection. A retrospective study of 1021 MMS performed on primary, residual, and recurrent BCCs showed a 2.6% 5-year recurrence rate for primary, 5.4% recurrence rate for residual, and 2.9% recurrence rate for recurrent BCCs. The higher rate of recurrence for residual tumors is likely because of repeat resection of a scar rather than the gross tumor itself. Gross tumor when present provides a visible periphery to guide margins. The authors also noted that there was a higher incidence of residual BCCs located in high-risk locations.[10] This study is demonstrative of the importance of a multidisciplinary tumor board for high-risk cutaneous cancer, where head and neck and Mohs micrographic surgeons, neuroradiologists,

pathologists, and radiation and medical oncologists participate to provide the best treatment recommendations aimed at local disease control. High-risk regions, depth of tumor assessment with respect to underlying bone/cartilage, and surgical planning improve outcomes for complex head and neck cancer resection that is facilitated by tumor conference. Multidisciplinary discussion of complex head and neck tumors may result in almost 33% modification of the original treatment plan.[14]

Squamous Cell Carcinoma

Similar to BCC, MMS is regarded as the gold standard method of care for cSCC. For cSCC of the head and neck, there is a reported local recurrence rate of 3% to 5.2% for standard wide local excision compared with 1.2% to 3.9% for cSCCs treated by MMS.[15] However, there is a subset of high-risk cSCCs that warrant even greater attention when making treatment recommendations given greater risk for poor outcomes of local recurrence, metastasis, and even death.[16] The rate of nodal metastasis of cSCC ranges from 1.5% to 4%, and the disease-specific death rate is between 1.5% and 2.8%.[17]

High-risk cSCC is inconsistently defined in the literature.[16,18] An early study by Rowe and colleagues identified treatment modality, prior treatment history, location of tumor, size and depth of tumor, histologic differentiation, PNI, and immunosuppressed state as high-risk features for disease recurrence and metastasis. Other studies define high risk for recurrence and metastasis as location on the ear or lip, poor differentiation, desmoplastic or acantholytic histologic grades, and presence of lymphovascular involvement (LVI). There is also variability among studies with respect to the definition of tumor depth, with some using anatomic depth and others using Breslow thickness, differing definitions of PNI, and lack of control for confounding variables that commonly occur together such as tumor depth and PNI.[16]

A 5-year prospective, multicenter analysis of 745 cSCCs treated with MMS showed a local recurrence-free survival rate of 99.3%, nodal metastasis-free survival rate of 99.2%, and disease-specific survival rate of 99.4%. The authors identified Breslow depth as the only factor with associated increased hazard for local recurrence. For each 1 mm increase in Breslow depth, the hazard of nodal metastasis increased by almost 30%. Furthermore, no patient with incidental PNI received adjuvant treatment, and these tumors demonstrated no increased association with local recurrence, nodal metastasis, or disease-specific death when other variables were controlled. However, a separate analysis of tumors exhibiting perineural invasion showed a significant correlation of PNI greater than 0.1 mm with Breslow thickness, tumor invasion beyond subcutaneous fat, and poorly differentiated histology.[15]

Another retrospective study of 531 tumors demonstrated a 2.9% local recurrence rate, 4.8% nodal metastasis rate, 1.1% distant metastasis rate, and 1.1% disease-specific death rate after at least 1 year follow-up of MMS for cSCC. On multivariate analysis, poor tumor differentiation and tumor invasion beyond the subcutaneous fat were significantly associated with local recurrence and nodal metastasis.[18]

These 2 studies highlight the low incidence of poor outcomes for cSCC treated with MMS. In addition, a meta-analysis that compared standard wide local excision with MMS showed lower recurrence rates with MMS of 3.1% versus 8.1% for primary tumors. The improved cure rates were significant for higher-risk tumors with PNI. Local recurrence after MMS was 0% for tumors with PNI in comparison to 47.2% for those with PNI treated by standard wide local excision.[19] This is likely attributed to the enhanced examination of 100% of the tumor margins provided by MMS.

These studies also demonstrate that poor outcomes extend beyond local recurrence to include nodal and distant metastasis, and even death. The Brigham and

Women's Hospital (BWH) staging system for cSCC and eighth edition of the American Joint Committee on Cancer (AJCC) Staging both attempt to account for higher-risk tumors. These staging systems rely upon reporting of various pathologic and clinical features that are inconsistently reported. Regular reporting of tumor location, size, treatment history, rapid growth, neurologic symptoms, immune status of the patient, histologic differentiation, depth of invasion, presence of LVI or PNI would aid in identifying high-risk cSCC in need of further evaluation and aggressive treatment.[16] Reporting of these high-risk features would prompt appropriate imaging studies to evaluate for nodal metastasis. Imaging could change treatment 33% of the time through early detection and management of regional disease, thereby improving disease-free survival.[20] Discussion of high-risk cSCC patients with a multidisciplinary cutaneous malignancy tumor board is also recommended for discussion of adjuvant treatment modalities.

Melanoma

Cutaneous melanoma accounts for less than 5% of all skin cancers but contributes up to 60% of all skin cancer-related mortality. There is a well-documented role for MMS in the management of BCC and cSCC cancers, but as of yet there is no clearly defined role for MMS in the management of cutaneous melanoma.[21]

A prospective multicenter study evaluated 562 melanomas (377 noninvasive in situ and 185 invasive melanomas) treated with MMS. Melanoma antigen recognized by T cells-1 (MART-1) antigen immunostain was utilized on frozen section processing. The study objective was to recommend excision margins and to compare actual costs of tumor removal with MMS versus standard surgical excision. Recognizing that outlier melanomas characterized by wide subclinical extensions would create an unreasonable recommendation for margin guidelines to accomplish 100% complete excision rates, the authors chose a predetermined goal for 97% complete excision rate. They derived this 97% complete excision rate based on a historically known recurrence rate of 3% for standard wide local excision of melanoma. This resulted in recommendation for 12 mm margins for invasive and noninvasive melanoma of the head and neck region. With respect to cost, the authors found the use of MMS with MART-1 staining and immediate reconstruction resulted in a median cost of $1336.60 per tumor in a cohort inclusive of the head and neck (n = 345), hands/feet/genitalia (n = 13), extremities (n = 90), and trunk (n = 114). Tumors located on the head and neck average cost was $1459.22. Although the authors of this study mentioned other single institution retrospective reports of improved disease-specific survival rates and low marginal recurrence rates in treating melanoma with MMS, their own study did not report on disease-related outcomes. The authors did argue that the tendency of melanoma to extend beyond clinically visible tumor margin with amelanotic and subclinical invasion "reinforces the benefit of comprehensive margin evaluation."[22]

A summary of histopathologic pitfalls associated with MMS was recently reported, however, in which the authors highlighted the limitations of MMS assessment for melanoma. The accuracy of MMS for melanoma may improve by the use of IHC staining such as MART-1. Standard wide local excision is typically a 2-stage procedure because of the difficulty in interpretation of frozen sections with typical H&E stains. It is difficult to distinguish freeze artifact and actinic keratoses from junctional melanocytic proliferations on routine frozen sections stained with H&E.[23] Melanocytes are more readily identified in specimens that are formalin-fixed paraffin-embedded due to production of a clear halo artifact that differentiates the melanocyte from keratinocytes.[24]

To address concern regarding frozen section identification of melanocytes, and in particular subclinical extensions of disease, several Mohs surgeons have reported

success of using immunostains for each Mohs layer including S100, HMB-45 and MART-1. One study directly compared the 3 aforementioned immunostains and noted that S100 failed in all cases because of inability to establish adequate controls for each case. HMB-45 was noted to fail at demonstrating the melanocyte proliferation at tumor edge that was visible with MART-1.

MART-1 was successful in all cases in this study, where only 10 cases were assessed by all 3 immunostains.[23] Sensitivity for MART-1 is reportedly 75% to 100%, with most reports in the 85% to 100% range, while sensitivity reported for HMB-45 ranges also from 75% to 100%, with most in the 70% to 80% range.[23] There is also potential difficulty with the MART-1 stain resulting in larger margins than typical for MMS of 5 mm. MART-1 staining of melanocytic hyperplasia due to solar damage may extend tumor margins artificially. MART-1 may also create false-positive interpretation with overstaining of certain inflammatory conditions, pigmented solar keratosis, and solar lentigo.[25] Furthermore, the horizontal sectioning by MMS technique does not permit assessment of maximal Breslow depth or evaluation of the melanoma growth characteristics. Breslow depth in particular is critical to the staging and prognostication of melanoma.[24]

A recent study derived from the National Cancer Database (NCDB) for head and neck melanoma inclusive of 50,397 cases reports a survival advantage for patients treated with MMS in comparison to WLE after controlling for potentially confounding variables. Patients treated with MMS were more likely than patients treated by standard WLE to survive 5 years (hazard ratio 1.181, 95% confidence interval 1.083–1.288, $P<.001$).[26] This overall conclusion requires cautious interpretation. On multivariate analysis, the survival benefit was only significant for melanomas less than 0.74 mm. Lentigo maligna was the only subtype on multivariate analysis to demonstrate survival advantage. Furthermore, there was a significantly disproportionate representation of melanomas treated by wide local excision (93% vs 7%), and most treated by MMS were thinner (mean Breslow depth of 0.8 mm) than those treated with wide local excision (mean Breslow depth of 1.7 mm).[26] The potential survival advantage of MMS may disappear with additional melanomas treated by MMS for comparison. Finally, a limitation of the NCDB database analysis is the lack of description of histologic examination of the MMS specimens. This is important in order to replicate outcomes because of the variety of methods described in the literature regarding histologic assessment.

Adoption of MMS for the treatment of cutaneous melanoma requires further investigation regarding margin assessment and outcomes compared with the standard technique of wide local excision. Furthermore, cutaneous melanoma requires evaluation of lymph node basins as per the National Comprehensive Cancer Network (NCCN) guidelines.[27] For this reason, wide local excision at the same time as sentinel node biopsy is often preferred over separate MMS.

Other Cutaneous Diseases

Merkel cell carcinoma (MCC), dermatofibrosarcoma protuberans (DFSP), and sebaceous and other adnexal carcinomas are rare and have propensity to recur locally. The technique of MMS has shown equal efficacy in the treatment of MCC and perhaps improved local control for DFSP and adnexal tumors all in retrospective reviews.[28,29] Although MMS appears efficacious in treating some rare cutaneous neoplasms, it is imperative to assess potential for regional disease with certain pathologies and to carefully surveil all patients undergoing either standard excision or MMS for treatment of these rare conditions.

SUMMARY

MMS represents an excellent means to address BCC and some cSCCs of the head and neck region, achieving excellent outcomes with respect to local recurrence rates and disease-specific survival. MMS by virtue of its technique maximally preserves uninvolved tissues of the head and neck, thereby maintaining form, cosmesis, and function to the greatest extent as dictated by the disease. However, the application of MMS for managing high-risk cSCC and melanoma requires additional investigation, and patients harboring these diseases should have case discussion with a cutaneous malignancy tumor board. MMS may also prove beneficial in treating rare cutaneous diseases such as MCC and DFSP while remembering to assess for regional spread of disease where applicable.

CLINICS CARE POINTS

- It is efficacious to utilize MMS for most head and neck BCCs and many cSCCs.
- There is not adequate evidence to suggest MMS allows for adequate margin assessment when treating melanoma.
- The use of MMS for melanoma does not permit appropriate staging of the cancer.

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