# Long-term outcomes of Mohs micrographic surgery for invasive melanoma of the trunk and proximal portion of the extremities

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***Background:*** Microscopic evaluation of the entire surgical margin during excision of cutaneous malignancies results in the highest rates of complete excision and lowest rates of true local scar recurrence. Few studies demonstrate the outcomes of Mohs micrographic surgery specifically for invasive melanoma of the trunk and proximal portion of the extremities.

***Objective:*** To evaluate the long-term efficacy of Mohs micrographic surgery for invasive melanoma of the trunk and proximal portion of the extremities, including true local scar recurrence rate, distant recurrence-free survival, and disease-specific survival.

***Methods:*** Prospectively collected study of 1416 cases of invasive melanoma of the trunk and proximal portion of the extremities was performed to evaluate long-term outcomes.

***Results:*** True local scar recurrences occurred in our cohort at a rate of 0.14% (2/1416), after a mean follow-up period of 75 months and were not associated with tumor depth. The rate of satellite/in-transit recurrences and the disease-specific survival stratified by tumor thickness were superior to historical control values.

***Limitations:*** We used a nonrandomized, single institution, retrospective design.

***Conclusions:*** Mohs micrographic surgery of primary cutaneous invasive melanoma on the trunk and proximal portion of the extremities resulted in local control of 99.86% of tumors and an overall disease-specific death rate superior to that of wide local excision. (J Am Acad Dermatol 2021;84:661-8.)

***Key words:*** excision margins; guidelines; invasive melanoma; malignant melanoma; melanoma; Mohs micrographic surgery; recurrence; surgery; surgical margins; wide local excision.

Clinical practice guidelines for the treatment of primary cutaneous melanoma (CM) recommend surgical excision as the principal treatment method, with the goal to confirm histologically clear margins.[1,2] These guidelines specifically recommend the use of wide local excision (WLE) as the treatment method of choice for invasive melanoma on the trunk and extremities. The WLE method is performed by using a predetermined surgical margin comprising normal-appearing skin, as assessed with only visual inspection by the surgeon. The surgical margin drawn circumferentially around the visible tumor is of a width that is based on the depth of tumor invasion.[1] Tissue specimens surgically excised by WLE are subsequently processed and evaluated for margin involvement by a pathologist by using the standard vertical sectioning technique.

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Local recurrences after this method of surgical excision occur because of the persistence of tumor cells at the surgical margin, allowing for the disease to recur.[3,4] Persistent tumor cells may go undetected if a pathologist cannot histologically examine the entirety of the margin. This may occur because vertical sectioning of surgical specimens, also known as bread-loafing or step-sectioning, results in microscopic evaluation of less than 1% of the tissue margin,[5] leading to the possibility of undetected residual tumor, resulting in a true local scar recurrence. Importantly, the ability of vertical sectioning to detect residual tumor is inversely proportional to the sectioning interval. For example, the chance of detecting positive margins with conventional vertical sectioning is only 19% when specimens are sectioned at 4-mm intervals.[6] Such limitations in margin evaluation may underpin local recurrence rates after conventional WLE, which have been reported to be approximately 3% for invasive melanoma of the trunk or proximal portion of the extremities (Table I[7-11]). Currently, vertical sectioning is the most commonly used method for histologic evaluation of melanoma excision specimens after removal with WLE. Furthermore, there are no universally applied standards or guidelines that outline the manner or extent to which vertical sectioning of tissue specimens is performed.

For 100% of the peripheral and deep margin to be examined, the tumor must be treated by using Mohs micrographic surgery (MMS) or excision specimens must be paraffin embedded as permanent sections and processed en face, in a staged manner, including deep margins for equivalent margin control. Head and neck melanoma tumors of any thickness treated in stages with en face processing of paraffin-embedded specimens have resulted in published local recurrence rates ranging from 0% to 7.3%.[12-21] In comparison, complete margin evaluation using MMS to treat primary cutaneous melanoma of any thickness or anatomic site has resulted in published local recurrence rates ranging from 0.1% to 0.5%.[22-29] These data likely underpin both the observed increase of 304% in the use of MMS to treat cutaneous melanoma over the last 15 years,[30] as well as the current Mohs Appropriate Use Criteria recommendations advising the use of MMS for melanoma in situ of the head and neck or any anatomic site when WLE has failed.[31]

Recent work has shown the superiority of MMS in the treatment of melanoma in situ of the trunk and proximal portion of the extremities when compared to historical control patients treated with WLE.[28] To date, however, the cumulative body of evidence surrounding the use of MMS for invasive melanoma on the trunk and extremities has continued to be labeled as insufficient to be deemed appropriate.[2,31] Our study addresses this evidence gap by reporting true local scar recurrence rates, metastatic rates, and disease-specific survival rates over the longest mean follow-up period and from the largest prospectively collected cohort of invasive melanomas treated with MMS reported to date, to our knowledge.

**CAPSULE SUMMARY**

- Long-term outcomes from Mohs micrographic surgery for invasive melanoma are unreported on the trunk and proximal portion of the extremities.
- Mohs surgery demonstrated a true local scar recurrence rate of 0.14% after a mean follow-up period of 6.25 years and disease-specific survival superior to historical control values.

## METHODS

Beginning in 1982, a prospectively maintained database was created and comprised all biopsy-proven melanomas treated by MMS. In keeping with historically defined anatomic subdivisions,[32-36] all cases of invasive melanoma on the trunk and proximal portion of the extremities (excluding wrists, hands, ankles, and feet) were identified from 1982 to mid-2017. Written consent was obtained from all participants. The use of deidentified patient information exempted the study from institutional review board approval. To ensure the integrity of the study data, all 1416 patients meeting study criteria were audited for accuracy and compared with the database. No patients meeting study criteria were otherwise excluded. Clinical examination of all patients in the study took place at least once per year at either the study site or by the patient's referring physician.

Follow-up data were collected at the study site by the senior authors at least once yearly. Data regarding patients who were no longer living in the region were obtained from clinical records provided by either the patient's referring dermatologist or primary care physician. Patient self-reports were not used to update the database unless confirmation of at least 1 clinical examination within the past year was obtained. A total of 24 patients (1.7%) were unable to provide clinical documentation confirming

*Abbreviations used:*

| | |
|---|---|
| CM: | cutaneous melanoma |
| MMS: | Mohs micrographic surgery |
| NCCN: | National Comprehensive Cancer Network |
| RCT: | randomized controlled trial |
| WLE: | wide local excision |

that they had obtained follow-up and were therefore considered lost to follow-up.

All melanomas were excised by MMS with frozen-section examination of the deep and peripheral margins. The MMS technique for melanoma excision and the histologic criteria used for frozen section analysis have been previously published.[22-24,37] Any visible tumor present before surgery was removed along with the central tumor as a debulking step and sent for permanent section processing to obtain more comprehensive pathologic staging. A positive margin was defined as follows: (1) nesting of 3 or more atypical melanocytes, (2) melanocytes above the dermoepidermal junction (ie, showing pagetoid spread), (3) nonuniform crowding of atypical melanocytes at the basement membrane or a confluence of more than 9 adjacent melanocytes, or (4) invasion of atypical melanocytes into the dermis. The presence of superficial follicular extension, isolated pagetoid cells alone, isolated increased melanocytic density, or only a mild to moderate confluence of melanocytes was not adequate to make the diagnosis of margin positivity. Programs to maintain quality control and diagnostic accuracy are maintained at the study sites on an ongoing basis and have been previously published.[38] Between 1982 and 1992, tissue specimens were stained with hematoxylin-eosin alone (n = 177). After 1992, immunohistochemical stains were used for all specimens alongside hematoxylin-eosin. Specifically, HMB-45 was used from 1993 to 2002 (n = 347), and MART-1 (Melan-A) was used exclusively from August 2002 (n = 892).

Local, regional, and distant events were recorded for each patient and used to calculate local recurrence rates as well as distant recurrence-free and disease-specific survival rates. The term *local recurrence* has been previously defined in 2 ways: the first definition, from the National Comprehensive Cancer Network (NCCN),[1] is "true scar recurrence" or "persistent disease" and includes tumor with an in situ and/or radial growth phase. This is now the preferred definition for local recurrence. However, the second definition of local recurrence is historical in nature and is defined as tumor recurrence occurring 2 cm or less from a previous excision scar site.[39-44] The latter definition includes satellite metastases occurring within 2 cm of a surgical scar and was used only to compare our true local scar recurrence rate to rates from historical data, which applied this definition. As reflected in the American Joint Committee on Cancer staging system,[45] there is a lack of biologic distinction or significance between the terms *in transit* and *satellite* metastasis. Therefore, these 2 terms were defined together to include tumor recurrence occurring between, but not contiguous with, the surgical scar and the nearest nodal basin.

Statistical analysis was performed by an independent firm specializing in biostatistics (Adolos Strategic, San Antonio, TX) using R, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Patient characteristics, tumor variables, and outcome metrics were assessed with the chi-square test, Fisher's exact test, Cramér's *V*, and the log-rank test, along with Kaplan-Meier estimations.

## RESULTS

### Patient and tumor characteristics

A total of 1416 cases met criteria (primary or recurrent invasive melanoma on the trunk or proximal portion of an extremity) and were selected for study analysis (Table II). Of note, 474 cases fitting study criteria from this data set were previously included in a separate study with distinctly different objectives.[27] The mean Breslow thickness was 1.0 mm (range, 0.03-17 mm), reflecting a normal thickness distribution expected in the general population.

### Margins and tumor clearance

**Margins.** The margin required to remove at least 97% of primary tumors on the trunk and extremity was 1 cm. Recurrent tumors required wider margins than primary tumors to reach histologic clearance (Supplemental Table I; available via Mendeley at https://doi.org/10.17632/mpr2cy4ktr.1).

**Local recurrence rates.** Of the 1416 cases of invasive melanoma treated with MMS, there were a total of 2 local recurrences over the entire study period, resulting in a true local scar recurrence rate of 0.14%. Both of these recurrences occurred before the use of MART-1 immunohistochemistry became standard in our practice (Supplemental Table II; available via Mendeley at https://doi.org/10.17632/mpr2cy4ktr.1). These recurrences reflected the true local scar recurrence definition of tumor recurring with an in situ and/or radial growth phase. One of

**Table I.** Local recurrence rates after standard wide local excision from studies in which the published data allow for determination of invasive melanoma tumors limited to the trunk and extremities

| Study | n/N | Local recurrence, % | Margin, cm | Median follow-up, y |
|---|---|---|---|---|
| Urist et al, 1985[7] | 70/2738 | 2.7 | 2.5, median | 8 |
| Griffiths et al, 1986[10] | 44/499 | 8.8 | 5-10 | 11 |
| Neades et al, 1993[47] | 5/356 | 1.4 | 1, 2, and 3-5 | 10 |
| Karakousis et al, 1996[48] | 22/678 | 3.3 | 2 or 4 | 7.6 |
| Cohn-Cedermark et al, 1997[8] | 26/3143 | 0.8 | 2 or 5 | 8 |
| Heaton et al, 1998[9] | 29/233 | 12.5 | ≤2 or >2 | 2.3 |
| Balch et al, 2001[32] | 22/676 | 3.3 | 2 or 4 | 10 |
| Moehrle et al, 2004[4] | 25/3068 | 0.8 | 1, 2, or 5 | 5 |
| Agnese et al, 2007[11] | 21/624 | 3.4 | Not specified | 2.8 |

**Table II.** Patient and tumor characteristics

| Characteristics | Value |
|---|---|
| Invasive melanomas (N = 1416) | |
| Age, y | |
| Mean | 61 |
| Range | 15-97 |
| Follow-up, mo | |
| Average | 75 |
| Range | 0-380 |
| Sex, n (%) | |
| Male | 780 (55.1) |
| Female | 636 (44.9) |
| Location, n (%) | |
| Trunk | 721 (51) |
| Proximal portion of an extremity | 695 (49) |
| Tumor thickness, mm | |
| Mean (range) | 1.0 (0.03-17) |
| Tumor thickness by categories, mm, n | |
| 0.01-1.00 | 1053 |
| 1.00-2.00 | 214 |
| 2.01-4.00 | 91 |
| >4.00 | 54 |
| Unspecified | 4 |
| Primary/recurrent (%) | |
| Primary | 97 |
| Recurrent | 3 |

the 2 patients died more than 5 years after MMS of causes unrelated to melanoma. The other patient is alive and remains free of disease at last follow-up.

### Long-term outcomes and survival

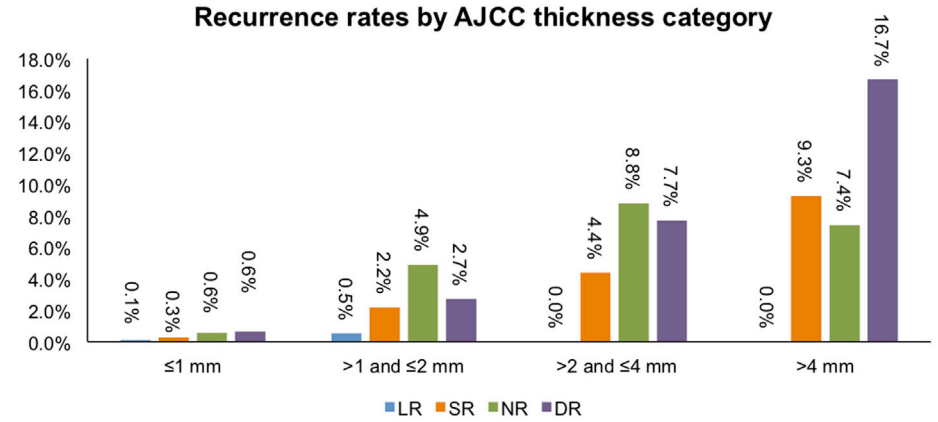
**Recurrences.** The incidences of true local scar, satellite/in-transit, nodal, and distant recurrences are stratified by tumor depth and presented in Fig 1.[46] Notably, tumor thickness was not associated with true local scar recurrence. The overall incidence of satellite/in transit recurrences was 1.1% (n = 16 (Supplemental Table III; available via Mendeley at https://doi.org/10.17632/mpr2cy4ktr.1) over the entire study period, a rate lower than historical data, which has ranged from 1.5% to 7.7%.[47-51]

**Survival.** Our study group had a total of 52 (3.7%) disease-specific deaths over the entire study period of 31.7 years, all of which occurred in patients with primary tumors (31 trunk, 21 extremity). No disease-specific deaths occurred among patients with recurrences subsequently treated with MMS. The incidence of distant recurrence-free survival was 98% (Supplemental Table III). Distant recurrence-free survival was not statistically associated with either tumor type (ie, primary or recurrent) or anatomic location.

Cox proportional hazard models were calculated for death by melanoma for tumor thickness and tumor thickness categories (Supplemental Table IV; available via Mendeley at https://doi.org/10.17632/mpr2cy4ktr.1). Kaplan-Meier survival curves were calculated for patients with invasive melanoma treated with MMS (Supplemental Figs 1 and 2; available via Mendeley at https://doi.org/10.17632/mpr2cy4ktr.1). No difference was seen in disease-specific survival probability by anatomic location.

## DISCUSSION

Current guidelines for the use of standardized surgical margins for melanoma of any anatomic site are based on data derived from randomized controlled trials (RCTs) comprised almost entirely of tumors on the trunk and proximal portion of the extremities, using strict margin measurements.[32-36] In practice, however, published local recurrence rates are higher than the expected recurrence rates using margins established by RCTs (Table I). This is likely because the current guidelines for standardized margins using WLE state that a narrower surgical




| Tumor thickness | True local scar recurrence | Satellite/In-transit recurrence | Nodal recurrence | Distant recurrence |
|---|---|---|---|---|
| ≤ 1 mm | 0.1% | 0.3% | 0.6% | 0.6% |
| >1.01 and ≤2 mm | 0.5% | 2.2% | 4.9% | 2.7% |
| >2.01 and ≤4 mm | 0.0% | 4.4% | 8.8% | 7.7% |
| >4 mm | 0.0% | 9.3% | 7.4% | 16.7% |

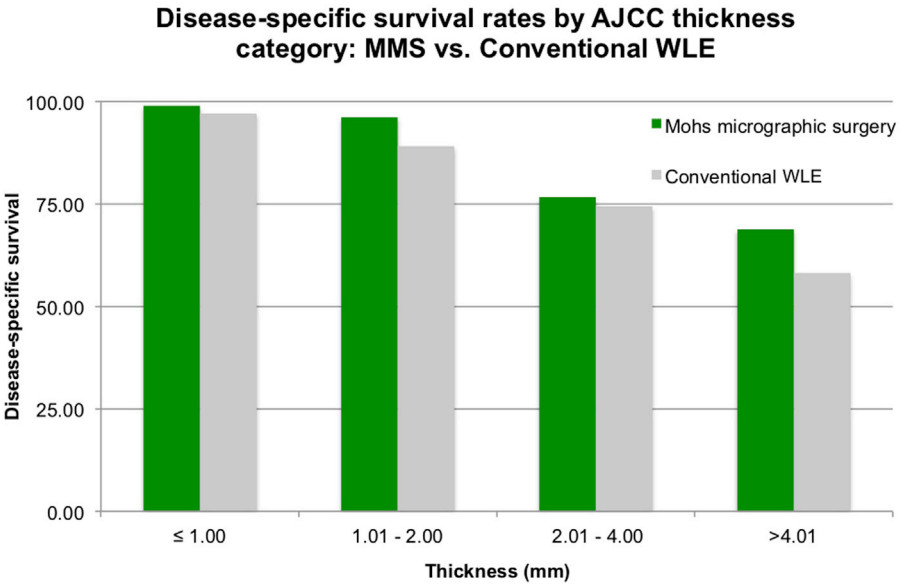
**Fig 1.** Rates of recurrence of invasive melanomas treated with MMS stratified by American Joint Committee on Cancer tumor thickness categories. *DR*, Distant recurrence; *LR*, true local scar recurrence; *NR*, nodal recurrence; *SR,* satellite/in-transit recurrence.

margin may be used "to accommodate individual anatomic or cosmetic considerations."[1] Instances in which a more narrow standardized margin is applied may be more frequent in practice than expected, because up to 59% of melanomas on the trunk and extremities may be treated with surgical margins more narrow than those outlined by the NCCN guidelines.[52]

Complete removal of primary melanoma is critical, because up to 33.3% of incompletely excised invasive melanomas recur as more deeply invasive disease.[53] Given the potential impact of local recurrences on patient outcomes, this and other studies provide strong evidence for the role of MMS or similar methods for complete margin examination as a safe and effective surgical treatment method for invasive melanoma. However, current guidelines suggest that "techniques for more exhaustive histologic assessment of margins should be considered" only for certain subtypes of melanoma. Specifically, guidelines from the NCCN recommend MMS only for large melanoma in situ, lentigo maligna subtype.[1] Similarly, the melanoma management guidelines provided by the American Academy of Dermatology suggest that MMS should be considered only for melanoma in situ, lentigo maligna subtype, "on anatomically constrained sites (e.g., face, ears, or scalp)."[2] To date, however, each of the prospective cohort studies evaluating the use of MMS to treat melanoma, of any anatomic site or tumor thickness, have reported a local recurrence rate that is a fraction of the lowest local recurrence rate reported for WLE.[22-24]

Perhaps even more importantly, MMS for melanoma may improve disease-specific survival. Patients in our cohort treated with MMS showed superior 5-year disease-specific survival probability when compared with historical control patients treated with WLE (Fig 2). To date, to our knowledge, no published study has shown that patients with melanoma treated with MMS have disease-specific survival rates that are inferior to WLE. In fact, every published clinical study evaluating disease-specific survival after MMS has shown a survival advantage when compared to historical control patients.[22,23,27,54-57] This may be due to the reduction in true local scar recurrences occurring as thicker tumors with worse survival rates.

Consistent with previous studies, primary tumor thickness was not associated with true local scar recurrence after treatment with MMS. This suggests that true local scar recurrences occurring after WLE are caused by primary tumor persistence after surgery and not satellite metastases that could have been excised with increasingly wider margins. As a corollary, these and other data suggest that the theory that wide margins beneficially include microsatellites near a primary tumor do not, in practice, provide survival benefit. This notion is further supported by the fact that in each of the RCTs comparing surgical margins for WLE, the group of patients randomized to the narrower margin width




| Tumor thickness | Mohs Micrographic Surgery (95 % CI) | Conventional WLE (95 % CI) |
|---|---|---|
| ≤ 1 mm | 99.2 (98.5 – 99.8) | 97.1 (96.9 – 97.4) |
| >1.01 and ≤2 mm | 96.2 (93.5 – 99.0) | 89.1 (88.2 – 89.9) |
| >2.01 and ≤4 mm | 76.6 (66.6 – 88.1) | 74.4 (72.8 – 76.0) |
| >4 mm | 68.8 (55.3 – 85.6) | 58.1 (55.5 – 60.5) |

**Fig 2.** Five-year Kaplan-Meier melanoma-specific survival rates for invasive melanoma of the trunk and proximal portion of an extremity treated with MMS in this cohort (N = 1416) compared with historical control values (n = 9129) treated with WLE.[46] *AJCC,* American Joint Committee on Cancer; *CI,* confidence interval; *MMS,* Mohs micrographic surgery; *WLE,* wide local excision.

had equivalent survival rates compared to the group of patients with wider margins. To that end, the data here are evidential that excisions of less than 1 cm, and in which complete surgical margin examination is performed, have no adverse impact on outcomes for patients with invasive melanoma, as has been suggested by some guidelines.[2]

These data also allow for the extrapolation of histologic clearance rates with standardized margins (Table III). In this cohort, the application of a 1-cm clinical margin circumferentially around each tumor may have allowed for histologically positive margins in up to 3.3% of tumors of 1.0 mm or less in thickness. For tumors of 1.01 to 2 mm in thickness, the application of a 1-cm margin may have allowed up to a 4.2% histologically positive margin rate. In both of these instances, a margin-controlled technique allowed for these outliers to be detected and for potential true local scar recurrences to be averted. In contrast to the traditional tissue-sparing properties of MMS, the primary value of MMS for invasive melanomas on the trunk and extremities is to identify outlier melanomas requiring a margin of greater than 1 cm, with the effect of reducing local recurrence and improving survival. As such, and despite evidence to the contrary, concerns about using a margin of less than 1 cm may be allayed by initiating MMS with a 1-cm margin for invasive melanomas on the trunk and extremities.

**Table III.** Percent clearance by tumor thickness if 1- or 2-cm standardized margins were applied

| Tumor thickness, mm | Standard margin | |
|---|---|---|
| | 1 cm | 2 cm |
| <1 | 96.7% (95% CI: 95.4-97.6) | N/A |
| 1-2 | 95.8 (95% CI: 91.9-97.9) | 100.0 (95% CI: 97.8-100.0) |
| >2 | N/A | 99.3 (95% CI: 95.6-100.0) |

*CI,* Confidence interval; *N/A,* not applicable.

Among studies evaluating MMS for the treatment of invasive melanoma published to date, to our knowledge, this study is of the largest cohort and of the longest mean follow-up period. The extended follow-up period provides greater power to detect recurrences of any kind, further supporting the value of this technique as a viable and valuable method for

melanoma removal. This information may be useful for future guidelines and for future iterations of the Mohs Appropriate Use Criteria.[31]

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