# Clinical and pathologic factors associated with subclinical spread of invasive melanoma

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***Background:*** Indications to treat invasive melanoma with Mohs micrographic surgery (MMS) or analogous techniques with exhaustive microscopic margin assessment have not been defined.

***Objective:*** Identify clinical and histologic factors associated with subclinical spread of invasive melanoma.

***Methods:*** This retrospective, cross-sectional study evaluated 216 invasive melanomas treated with MMS and melanoma antigen recognized by T cells 1 immunostaining. Logistic regression models were used to correlate clinicopathologic risk factors with subclinical spread and construct a count prediction model.

***Results:*** Risk factors associated with subclinical spread by multivariate analysis included tumor localization on the head and neck (OR 3.28, 95% confidence interval [CI] 1.16-9.32), history of previous treatment (OR 4.18, 95% CI 1.42-12.32), age ≥65 (OR 4.45, 95% CI 1.29-15.39), and ≥1 mitoses/mm$^2$ (OR 2.63, 95% CI 1.01-6.83). Tumor thickness and histologic subtype were not associated with subclinical spread. The probability of subclinical spread increased per number of risk factors, ranging from 9.22% (95% CI 2.57%-15.86%) with 1 factor to 80.32% (95% CI 68.13%-92.51%) with 5 factors.

***Limitations:*** This study was conducted at a single academic institution with a small study population using a retrospective study design that was subject to potential referral bias.

***Conclusion:*** Clinical and histologic factors identify invasive melanomas that are at increased risk for subclinical spread and might benefit from MMS or analogous techniques prior to reconstruction. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.11.048.)

***Key words:*** appropriate use criteria; excision; invasive melanoma; Mohs micrographic surgery; subclinical spread.

## INTRODUCTION

Subclinical spread,[1-4] a term describing microscopic tumor extension beyond the visible margin, increases the likelihood that conventional wide local excision (WLE) will result in positive margins or local recurrence. The rates of positive margins after conventional WLE of melanomas vary widely from 2% on the trunk and upper extremities[5] to 21% on the upper face.[3] Likewise, the rates of local recurrence vary widely from 1%-2% for melanomas on the trunk and extremities[6-8] to 2.8%-28% for melanomas of the head and neck.[3,6-18] Both positive margins and local

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recurrence complicate surgical management of melanoma with repeat excisions and an increased likelihood for more complex reconstruction.[2]

In contrast to conventional WLE, more rigorous margin assessment techniques, such as Mohs micrographic surgery (MMS), slow-Mohs, the square technique, and others,[1,19-30] can be used to identify and remove subclinical tumor prior to reconstruction. However, indications to use these techniques have not been defined for invasive melanoma. Consensus guidelines from the National Comprehensive Cancer Network (NCCN) restrict consideration of exhaustive histologic assessment of margins to large in situ melanoma of the lentigo maligna type.[31] Similarly, the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery have proposed guidelines for the use of MMS to treat in situ melanoma, but they omitted commentary on invasive melanoma.

**CAPSULE SUMMARY**

- Risk factors have not been defined for subclinical spread of invasive melanoma.
- Location on the head and neck, history of previous treatment, age ≥65 years, and ≥1 mitosis/mm$^2$ correlate with increased odds of subclinical spread.
- Invasive melanomas with these risk factors may benefit from rigorous microscopic margin control before reconstruction.

This single academic center, retrospective, cross-sectional study evaluates clinicopathologic factors associated with subclinical spread of invasive melanomas treated with MMS with melanoma antigen recognized by T cells 1 (MART-1) immunostaining. These data might identify indications for the treatment of invasive melanomas with MMS or similar techniques with more rigorous margin control prior to reconstruction.

## METHODS

### Study design

This retrospective, cross-sectional study was approved by the University of Pennsylvania institutional review board. A total of 216 invasive melanoma cases in 212 patients with localized, cutaneous melanoma were treated at the University of Pennsylvania with MMS using hematoxylin-eosin and MART-1 staining from March 2006 to September 2013. Only cases with a preoperative biopsy report indicating invasive melanoma were included. Metastatic melanoma lesions were excluded. Data for all tumors had been prospectively entered at the time of MMS in an electronic database. All data were verified by a search through the electronic or physical medical records. All diagnoses were verified by examination of the biopsy reports from both the preoperative diagnostic biopsy and from the formalin-fixed paraffin-embedded sections of the debulking excision.

### Surgical procedure

All patients were treated under local anesthesia with a similar protocol, which has been previously described and illustrated.[1] Briefly, MMS was performed by combining frozen-section bread-loaf processing of the debulking excision with complete peripheral and deep microscopic margin assessment of the Mohs layer by using both hematoxylin-eosin and MART-1 staining. For American Joint Committee on Cancer (AJCC) stage T1a tumors, a minimum surgical margin of 5-6 mm was excised. For AJCC stage T1b and above, a minimum surgical margin of 1 cm was excised. Margins <5-6 mm were rare.

Criteria for positive margins on the Mohs layer included nesting of ≥3 melanocytes; confluence of ≥10 melanocytes in direct contact with the basement membrane; pagetoid spread of melanocytes at or above the level of the mid-epidermis and in the presence of increased melanocyte density; confluent extension of melanocytes deep to the follicular infundibulum; and severe melanocytic atypia, defined by large atypical nuclei or significant pleomorphism.[1,30,32-34]

Sentinel lymph node biopsy (SLNB) was discussed and offered to patients with stage T1a and T1b tumors >0.75 mm in thickness and for any melanoma with a Breslow depth ≥1.0 mm. For patients with T1b tumors ≤0.75 mm, SLNB was considered on an individual basis (such as the presence of ulceration, high mitotic rate, lymphovascular invasion, transected deep margin of biopsy, or Clark level IV or V). If the diagnostic biopsy met criteria for SLNB, patients underwent the procedure before MMS. If a T1a melanoma was upstaged to SLNB eligibility during frozen-section evaluation of the residual tumor in the debulking excision, patients were offered SLNB prior to reconstruction. If patients elected to undergo SLNB, margins were cleared of the primary tumor, but reconstruction was delayed until after the SLNB was completed. After MMS, the debulking excision was always sent for formalin-fixed paraffin-embedded sectioning to confirm tumor staging and to archive the primary tumor.