Mohs micrographic surgery for melanoma: A prospective multicenter study

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Background: Single-institution studies show that frozen section Mohs micrographic surgery (MMS) is an effective treatment modality for cutaneous melanoma, but no multi-institutional studies have been published.

Objective: To characterize the use of MMS in the treatment of melanoma at 3 academic and 8 private practices throughout the United States, to recommend excision margins when 100% histologic margin evaluation is not used, and to compare actual costs of tumor removal with MMS vs standard surgical excision.

Methods: Prospective, multicenter, cohort study of 562 melanomas treated with MMS with melanoma antigen recognized by T cells 1 immunostaining.

Results: Primary trunk and extremity melanomas (noninvasive and invasive melanoma) achieved histologically negative margins in 97% of tumors with 10-mm margins, whereas 12-mm margins were necessary to achieve histologically negative margins in 97% of head and neck melanomas. Overall average cost per tumor treated was $1328.46.

Limitations: Nonrandomized and noncontrolled study.

Conclusions: MMS with melanoma antigen recognized by T cells 1 immunostaining safely provides tissue conservation and same-day reconstruction of histologically verified tumor-free margins in a convenient, single-day procedure. When comprehensive margin evaluation is not used, initial surgical margins of at least 10 mm for primary trunk/extremity and 12 mm for head/neck melanomas should be used to achieve histologically negative margins 97% of the time. (J Am Acad Dermatol 2019;81:767-74.)

Key words: excision margins; guidelines; lentigo maligna; MART-1; melanoma in situ; melanoma; Mohs micrographic surgery; prospective multicenter; surgery; surgical.

The incidence of invasive melanoma (IM) continues to increase, with the American Cancer Society estimating greater than 96,480 new cases in the United States in 2019,[1] highlighting the need for reliable, safe, and cost-effective therapy.[2]

Historically, most melanomas are excised with standard surgical excision (SSE), a technique that excises the tumor and a margin of normal-appearing skin. Tissue is then processed as paraffin-embedded permanent sections with serial cross-sectioning

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(bread loafing) to evaluate the histologic margin. The total margin evaluation in SSE is incomplete (<0.1%) and may only identify a proportion of all positive margins, with false-negative rates of 81% when processing using 4-mm intervals between sections.[3] Many single-institution studies have demonstrated the effectiveness of Mohs micrographic surgery (MMS) in the treatment of melanoma, with very low marginal recurrence rates and metastasis rates along with as disease-specific survival rates comparable to or better than historical controls using SSE (Table I).[4-11]

This prospective, multiinstitutional study of 562 melanomas characterizes the treatment of melanoma with MMS. The cohort included 377 noninvasive (NIMs) and 185 IMs removed using MMS using melanoma antigen recognized by T cells 1 (MART-1) immunostains with frozen section processing.

CAPSULE SUMMARY

- This prospective, 13-surgeon, multicenter study of Mohs micrographic surgery for melanoma further affirms and refines findings of single institutional studies that Mohs micrographic surgery is effective and affordable, averaging $1328.46 per tumor treated.
- With the goal of achieving negative margins 97% of the time, surgical margins of 10 mm for trunk/extremity and 12 mm for head/neck are recommended for primary noninvasive melanoma and invasive melanoma when 100% histologic margin evaluation is not used.

METHODS

Patients

This study was initiated after Western Institutional Review Board review and approval (approval #20122132). The study consisted of 518 patients with 562 melanomas treated with MMS with MART-1 immunostaining prospectively recruited between April 8, 2013, and August 28, 2014. Inclusion criteria for our study were primary or recurrent melanoma confirmed by biopsy specimen, age 18 years or older, no clinical signs of regional or systemic disease, and treatment with MMS. All MMS procedures discussed in this report were done with MART-1 immunostaining using frozen section processing. Before surgery, a full-body skin examination, review of systems, and lymph node examination was performed on all patients. Informed consent was obtained on the day of surgery. Thirteen fellowship-trained MMS surgeons treated all patients and recorded demographic, clinical, histologic, and therapeutic data.

Procedure

Margins were measured by each surgeon at each stage of the surgical process. Preoperatively, clinical borders of the remaining visible tumor or biopsy scar were identified by visual inspection under bright operative lighting. The use of a Wood's light examination was not required for this study. A variable margin of not less than 2 mm and most typically 6 mm of normal appearing skin representing the first-stage margin was scored and recorded, followed by debulking of tissue inside of the scored margins for further pathologic examination as indicated.[6] The originally scored margins were then incised to the deep subcutaneous fat to assure removal all adnexal structures.

The Mohs layer specimen was then processed using frozen sectioned tissue stained with hematoxylin and eosin and MART-1.[12] Positive margins were defined as previously described[13-15] and marked on the map. The involved margin was excised with an additional margin of not less than 2 mm and most typically 3 mm of normal-appearing skin. The steps described were repeated until histologically tumor-free margins were achieved. Each millimeter of margin taken on the initial and subsequent layers was measured and contemporaneously recorded by the surgeon at each stage of the process. The total number of millimeters to achieve tumor clearance was added and then recorded at the conclusion of surgery.

Analysis

Data were used to analyze the minimum margins necessary to achieve histologic clearance for 97% of each study cohort stratified by Breslow depth, tumor type, location, size, and history of prior treatment. Statistical calculations were performed using R 3.0.3 software (https://www.r-project.org). Wilcoxon, *t*, Pearson χ^2, and Fisher exact tests, as appropriate, were performed.

Actual costs for MMS and reconstructions were calculated based on Current Procedural Terminology 2016 for non-Philadelphia, Pennsylvania (American Medical Association, Chicago, IL). The cost of treatment included MMS codes (17311-17315), immunopathology code (88342), and reconstruction codes. Multiple surgery reimbursement reduction was factored into all calculations.

RESULTS

Patient and tumor characteristics

Demographics, clinical, and histopathologic characteristics of the 562 melanomas are outlined in

Abbreviations used:

IM: invasive melanoma
LM: lentigo maligna
MART-1: melanoma antigen recognized by T cells 1
MIS: melanoma in situ
MMS: Mohs micrographic surgery
NIM: noninvasive melanoma
SSE: standard surgical excision

Table II. When performing MMS, we consider "melanoma in situ"(MIS) and "lentigo maligna"(LM) the same for surgical margin purposes because they have been shown to be identical in prior studies.[6,9,16] To avoid confusion, all in situ melanomas, regardless of histologic subtype, are referred to as NIM (noninvasive melanoma). Quantitatively, histologically characterized LM tumors (primary and recurrent) were more often associated with tumors of the head and neck (223 head/266 neck vs 60 trunk/107 extremity, $P < .0001$) and were seen in older patients (mean age, 68 years for LM vs 64 years for MIS, $P = .004$). Of the primary NIM tumors, there were no statistically significant differences in the proportions of MIS and LM tumors for excision margins of ≤6 mm, ≤9 mm, ≤12 mm, and ≤15 mm ($P = .144$) (Fig 1). Head and neck location was associated with a wider margin requirement for both primary MIS and LM tumors. For head and neck tumors, 12 mm and 10 mm margins achieved 97% histologic clearance for LM and MIS, respectively ($P = .133$). Smaller margins of 10 mm and 9 mm achieved similar results for LM and MIS of the trunk/extremity, respectively ($P = .365$).

Surgical margins

We measured the minimum surgical margin needed to obtain histologically negative margins after we examined 100% of the margin. Then we used those measurements to develop recommendations for surgical margins when routine margin examination techniques are used that incompletely examine the margin. We chose a goal of achieving true histologic negative margins in 97% of cases to develop guidelines for routine excision that use routine pathology methods for margin examination. This goal accepts the possibility of a 3% local recurrence rate. If a 100% clearance rate was used, those rare outlier melanomas with wide invisible extensions may result in impracticably wide margin guidelines.

Primary NIM. For all NIMs, 6-mm margins achieved histologic tumor clearance in 77.4% of tumors, 9-mm margins cleared 92.1%, and 12-mm margins were adequate for complete clearance in 97.1%. There was a difference in margins based on location, with trunk/extremity requiring 10 mm and head/neck necessitating 12 mm to achieve 97% clearance ($P < .01$).

Primary IM. Most of primary the IMs, 88.4% (137 of 155), were <1-mm Breslow depth. For this subset, margins of 6 mm, 9 mm, and 12 mm completely excised 69%, 88%, and 98% of these tumors, respectively. Thicker melanomas also required a 12-mm margin to achieve 97% clearance for each subset

Table I. Mohs micrographic surgery local recurrence rates, margin for 97% clearance

Study	Location	Diagnosis	LR/total patients, No.	LR rate, %	LR definition	Follow-up, y	MR, %	DSS rate, %	Margin, mm
Zitelli et al,[4] 1997	All locations	MIS/IM combined	3/553	0.5	Within scar	>5	0.5	NS	15
Bricca et al,[5] 2005	Head/neck	MIS	1/331	0.2	Within scar	4.8 mean	0.3	99.7	9 (MIS)
		IM	1/294	0.3			6	96.1	12 (IM)
Kunishige et al,[6] 2012	All locations	MIS	3/1120	0.3	Within scar	4.7 mean	0.3	99.2	9
Etzkorn et al,[7] 2015	All locations	MIS	2/436	0.46	Within scar	2.8 mean	NS	NS	NS
		IM	0/161	0					
Felton et al,[8] 2016	Face	MIS	1/343	0.3	NS	2.4 mean	0	100	15
Stigall et al,[9] 2016	Trunk/Ext	MIS	1/882	0.1	Within scar	5 mean	0.1	NS	9
Valentin et al,[10] 2016	All locations	MIS	3/863	0.35	Within scar	3.73 mean		100	15 Head/neck
		IM	4/556	0.72				96.42	9 Trunk/Ext
									12 MIS

DSS, Disease-specific survival; *Ext*, extremities; *IM*, invasive melanoma; *LR*, local recurrence; *MIS*, melanoma in situ; *MR*, metastatic rate; *No.*, number; *NS*, not stated.

Table II. Demographics, clinical, and histologic characteristics of the participants and tumors

Variables	Noninvasive (n = 352 pts/377 melanomas)	Invasive (n = 166 pts/185 melanomas)
Patients		
Age, mean (range) y	67 (20-98)	64 (21-92)
Sex, No. (%)		
Male	223 (63)	104 (63)
Female	129 (37)	62 (37)
Location, No. (%)		
Head/neck	266 (71)	79 (43)
Trunk	64 (17)	50 (27)
Extremities	42 (11)	48 (26)
Hands/feet/genitalia	5 (1)	8 (4)
Tumor size, mean cm	1.7	1.6
Thickness, mm (%)		
In situ	378	
Melanoma in situ	93 (25)	
Lentigo maligna	284 (75)	
≤1 mm		162 (88)
1.01-2 mm		12 (6)
2.01-3.99 mm		6 (3)
>4.0 mm		5 (3)
Primary/recurrent, No. (%)		
Primary	340 (90)	174 (94)
Recurrent	37 (10)	11 (6)
Research sites, No.		
Chapel Hill, NC	14	4
Charleston, SC	87	49
Chevy Chase, MD	18	14
Dallas, TX	25	11
Mesa, AZ	28	15
Mobile, AL	13	6
Overland Park, KS	34	12
Pittsburgh, PA	77	46
Sacramento, CA	70	27
Sarasota, FL	9	0
Tucson, AZ	2	1
Initial excision margin, No.		
2 mm	7	0
3 mm	7	3
4 mm	15	2
5 mm	74	24
6 mm	271	142
7 mm	1	2
8 mm	0	3
9 mm	0	1
10 mm	2	8

No., Number; *pts*, patients.

(Fig 2). Location did affect clearance margins, with trunk/extremity reaching 97% clearance at 10 mm, whereas head/neck required 12 mm ($P < .01$). For primary invasive tumors with a positive Mohs layer, the positive margin was the lateral cutaneous margin and not the deep margin in nearly all cases.

Effects of preoperative size. Preoperative tumor size was positively associated with larger surgical margins. For primary NIMs, a 6-mm margin excised 87% of tumors <1 cm, 82% between 1 and 2 cm, and 48% >2 cm. The same initial 6-mm margin cleared 76% of primary IM tumors <1 cm, 61% between 1 and 2 cm, and 70% of tumors >2 cm. Standard excision margins of 9 mm, 12 mm, and 15 mm were required to achieve tumor free margins for at least 97% histologically confirmed clearance for primary tumors <1 cm, 1 to 2 cm, and >2 cm diameter, respectively. A similar trend was observed for recurrent tumors, with larger preoperative sizes necessitating larger surgical margins (Table III).

Recurrent tumors. Recurrent tumors presented as local marginal recurrences confirmed on a biopsy specimen and represented a smaller cohort composed of 37 NIMs and 11 IMs. The tumor characteristics of the primary tumor were not recorded. For all recurrent NIMs, 6-mm margins achieved histologic clearance in 48.6%, whereas 9 mm, 12 mm, and 21 mm cleared 72.9%, 86.4%, and 97.3%, respectively. There was a difference in margins on location, with trunk/extremity requiring 9 mm for clearance of these 3 tumors, whereas the 34 recurrent head/neck NIMs necessitated 20 mm to achieve 97% clearance. Within the invasive subset, 72.8% (8 of 11) were <1-mm Breslow depth. For all IMs 12-mm margins achieved histologic clearance in 45.5% of tumors and increased to 63.6% for 15 mm, 72.7% for 18 mm, 90.9% for 21 mm, and 100% for 30 mm. Location did affect clearance margins for IMs, with the 6 head/neck tumors reaching >97% clearance at 20 mm, whereas the 5 trunk/extremity required 30 mm. As a group, compared with primary tumors, margins to clear recurrent tumors were measurably larger ($P = .01$). If routine margin examination techniques are used, a margin of 9 mm for recurrent NIM trunk/extremity and 20 mm for recurrent NIM and IM head/neck tumors are required to achieve histologically clear margins in 97% of cases. Because of the small numbers of recurrent IM trunk/extremity tumors, a single outlier with wide amelanotic extensions resulted in impracticably large surgical margins.

Cost

The overall average cost per tumor treated with MMS was $1336.60 (range, $729.00-$3260.76). Tumors located on the trunk/extremity averaged $1100.89 (range, $729.00-$2707.36), with 18.1% healing by second intent, 65.1% reconstructed with side-to-side closures, 13.9% with adjacent tissue flap,

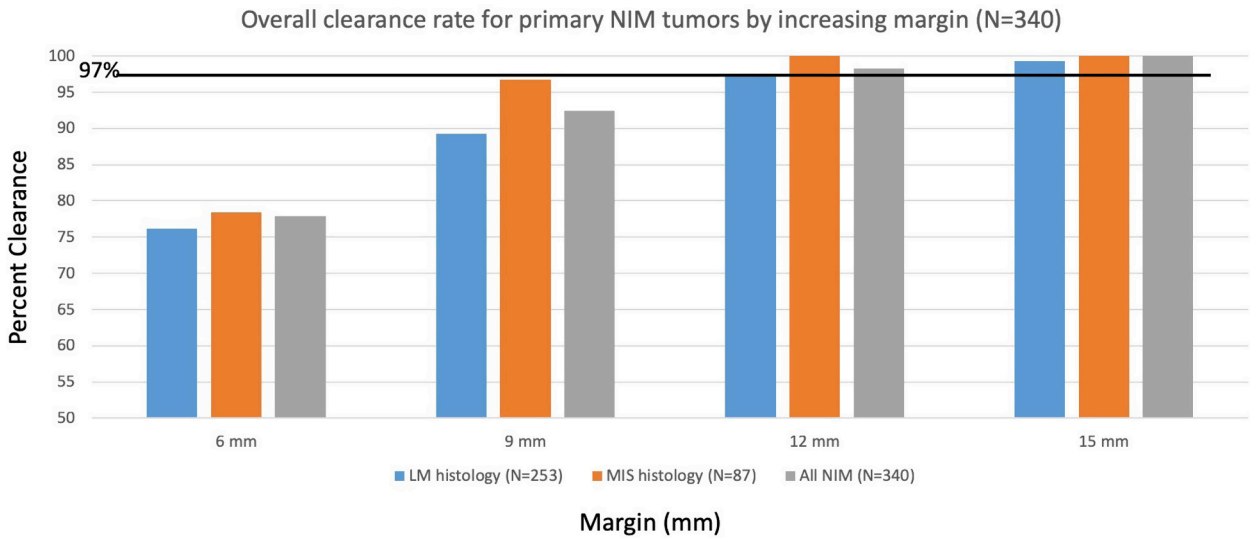

Fig 1. Overall clearance rate for primary noninvasive melanomas (*NIM*) by increasing margin (N = 340). *LM*, Lentigo maligna; *MIS*, melanoma in situ.

and 3% with full-thickness skin grafts. Tumors on the head/neck averaged $1459.22 (range, $771.93-$3260.76), with 9.2% healing by second intent, 31.4% repaired with side-to-side closures, 37.2% with adjacent tissue flap, 17.2% with full-thickness skin grafts, and the remaining 5% repaired with an interpolation or pedicle flap. In all, 57.1% of defects were allowed to heal by second intent or were reconstructed primarily with a side-to-side closure.

DISCUSSION

Stronger evidence is needed to support surgical margins in the treatment of melanoma, particularly on the head, neck, hands, and feet. Current guidelines for excision margins are based on randomized controlled trials, but these trials only compared a wide margin against a wider margin, and in each trial, the more narrow margin was just as effective as the wider margin.[10,17-22] Furthermore, these studies were limited to melanomas on the trunk and proximal extremities, leaving a significant void in the need for margin evidence on the head and neck. This study fills that void and provides evidence-based guidelines for routine excision margins based on the objective measurement of subclinical extension of melanoma beyond the clinically observed border.

To develop these guidelines, we chose to use historically derived recurrence rates of 3%[18,21] after wide-margin surgery and evaluated our data to calculate what margin of normal-looking skin around the clinical border of a melanoma would be necessary to completely remove melanomas 97% of the time. We recognize that there are outlier melanomas with very wide subclinical extensions and that a goal of complete removal 100% of the time would require unreasonable margins for a guideline. Thus, we chose 97% to match a commonly currently accepted recurrence rate seen on the trunk and proximal extremities.

The guidelines for the treatment of melanoma published by the American Academy of Dermatology[23] acknowledge the importance of complete tumor removal. These guidelines state, "The primary goal of surgical excision of melanoma is to achieve histologically negative margins and prevent local recurrence because of persistent disease."

The tendency for melanoma to grow with clinically invisible, amelanotic extensions is well documented[24,25] and reinforces the benefit of comprehensive margin evaluation. The precision of MMS with MART-1 is ideally suited to accomplish histologically negative margin verification, especially when treating melanoma on cosmetically or functionally demanding locations such as the head, neck, hands, feet, and genitalia, where surgeons frequently opt for subcentimeter margins.[8,25-28]

Recurrence rates for melanoma treated with SSE are reported to be 1% to 20% for tumors on the trunk/extremities[20-22,29-31] and 5% to 28% for head/neck tumors.[32-36] In contrast, local recurrence rates for melanoma treated with MMS with MART-1 are frequently superior, occurring at rates of 0.2% to 0.49%.[3,5,7] The importance of preventing recurrent disease is to avoid not only additional surgery but also the risk of subsequent tumor progression.[37] Highlighting this risk, Debloom et al[38] noted that

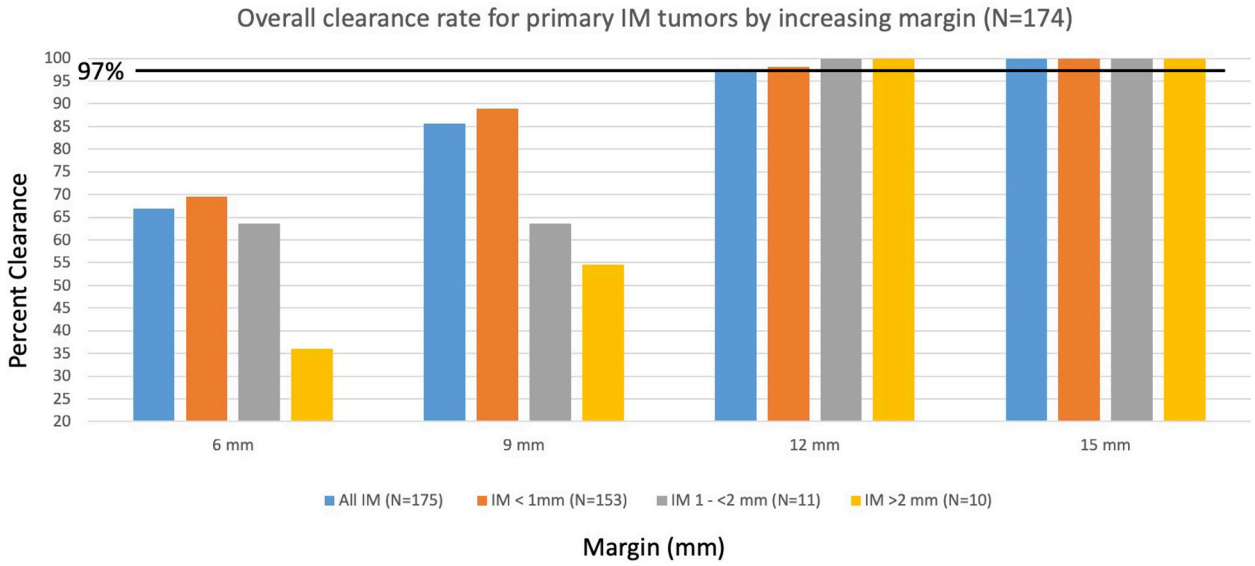

Fig 2. Overall clearance rate for all primary invasive melanomas (*IM*) by increasing margin (n = 174).

Table III. Histologic clearance rate of 97% based on preoperative size*

Preoperative size	No.	6 mm, No. (%)	9 mm, No. (%)	12 mm, No. (%)	15 mm, No. (%)	21 mm, No. (%)
Primary melanoma†						
<1.0 cm						
NIM	77	67 (87)	**76 (99)**	77 (100)		
IM	45	34 (76)	**43 (96)**	45 (100)		
1.0-1.99 cm						
NIM	180	148 (82)	168 (93)	**179 (99)**	180 (100)	
IM	83	51 (61)	69 (83)	**82 (99)**	83 (100)	
>2.0 cm						
NIM	83	40 (48)	70 (84)	79 (95)	**83 (100)**	
IM	46	32 (70)	37 (80)	42 (91)	**46 (100)**	
Recurrent melanoma‡						
<1 cm						
NIM	5	3 (60)	4 (80)	**5 (100)**		
IM	0	…	…	…		
1.0-1.99 cm						
NIM	10	7 (70)	8 (80)	9 (90)	9 (90)	**10 (100)**
IM	6	4 (66.7)	4 (66.7)	4 (66.7)	5 (83.3)	**6 (100)**
>2.0 cm						
NIM	22	8 (36.3)	15 (68.2)	18 (81.8)	20 (90.9)	21 (95.5)
IM	5	1 (20)	1 (20)	1 (20)	2 (40)	4 (80)

IM, Invasive melanoma; *NIM*, noninvasive melanoma.
*Values in bold denote margin where histologically negative margins were achieved in ~97% of tumors.
†Primary NIM, n = 340; primary IM, n = 174.
‡Recurrent NIM, n = 37; recurrent IM, n = 11.

nearly 23% of marginally recurrent primary MISs studied demonstrated an invasive component to a mean depth of 0.94 mm. The same study demonstrated that 33% of marginally recurrent IMs also became more invasive, increasing from a mean Breslow depth of 1.53 mm to 2.83 mm at the time of recurrence.[38]

In our cohort, subclinical spread of more than 5 to 6 mm occurred in 153 of 562 of tumors (27%). Melanomas likely to exhibit subclinical spread were located on the head/neck, recurrent, larger than 1 cm in diameter, or occurred in patients aged 60 years or older. These findings were remarkably similar between the NIM and IM subsets and are consistent with

prior studies linking similar clinical factors with greater peripheral subclinical tumor spread.[39-41]

The fiscal advantage of MMS is inextricably linked to performance in the outpatient setting and the bundling of component costs of Mohs excision, pathology preparation, and interpretation. Economy is further achieved with same day closure, multiple surgery reimbursement reduction, and expected lesser cost of reconstruction for the 77% of NIM cases and 69% of thin <1 mm IM cleared with 6-mm margins. The use of MMS paired with MART-1, followed by immediate reconstruction, resulted in a mean cost of $1336.60 per tumor for our entire cohort.

Although outpatient costs of MMS and SSE are comparable,[42-44] the cost of SSE in a hospital operating room. A case-matched comparison of the actual cost of melanoma and nonmelanoma tumors treated in the outpatient vs operating room setting determined a median cost difference of $9578 per tumor in favor of office-based surgery. Notably, in the outpatient setting, the median cost was $1745 per tumor, and when accounting for wide local excision of melanoma or MIS in the outpatient setting, this reduced to $1272 per tumor.[45] A plastic surgery prospective cohort study of 534 cutaneous melanomas (38% MIS and 62% IM mean Breslow depth of 1.02 mm) treated with SSE in the operating room setting with immediate reconstruction averaged $22,528 per tumor, increasing to $35,641 when reconstruction was delayed to confirm clear margins.[46] These data emphasize the value of MMS for melanoma on a cost basis alone in both the outpatient and operating room setting, and combined with the lower marginal recurrence rate, the value of MMS is compounded.

CONCLUSION

To our knowledge, this is the first-ever prospective multicenter study of MMS using frozen sections paired with MART-1 immunostaining for melanoma and represents an important step in refining and affirming information from previously published studies from single institutions on the utility of MMS for melanoma. Its prospective nature and numerous contributors from diverse facilities and geographic locations provides strong support for the value of immediate, complete margin evaluation with same-day reconstruction of tumor-free margins.

Our study shows that clinically apparent margins are often not representative of the true tumor margin, histologically. When 97% histologic tumor clearance is used as a standard, 10-mm to 12-mm margins are required for primary tumors (NIM and IM) on the trunk/extremity and head/neck, respectively. Tumor characteristics such as location, size, recurrence, and patient age older than 60 years are important factors in anticipating melanomas with extensions beyond guideline-recommended margins and illustrate characteristics where MMS would be an appropriate first-line treatment and, arguably, should be included in the patient's informed consent at the time of diagnosis.

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