Male sex and Breslow thickness are important risk factors for recurrence of localized melanoma in Korean populations

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Background: Predicting the recurrence of localized melanoma is important; however, studies investigating risk factors for recurrence of localized melanoma are lacking in Asian populations.

Objective: To identify risk factors for recurrence of localized melanoma in Korean patients.

Methods: We retrospectively reviewed patients with cutaneous melanoma without evidence of metastasis from 2000 to 2017. Logistic and Cox regression analyses were conducted for recurrence. The average follow-up time was 46.2 months.

Results: We reviewed the data of 340 patients diagnosed with cutaneous melanoma and staged as melanoma in situ, stages I and II. Acral melanoma (70.3%, 239/340) was the predominant subtype. Ninety-two patients (27.1%) had a recurrence after primary melanoma removal (29 local recurrences, 49 regional metastases, and 28 distant metastases). Some patients had multiple types of recurrence at the same time. Male sex (P = .030) and Breslow thickness greater than 1 mm (P = .008) correlated with an increased risk of recurrence. Breslow thickness greater than 2.5 mm in males and greater than 4 mm in females showed a higher predictive value for recurrence than traditional stages IIB and IIC (hazard ratio 3.743 vs 2.972).

Limitations: This was a single-center retrospective study.

Conclusion: In patients with localized cutaneous melanoma, male sex and Breslow thickness are the most important prognostic factors for recurrence in Korean populations. Different cutoff values of Breslow thickness may better predict recurrence according to sex. (J Am Acad Dermatol 2020;83:1071-9.)

Key words: Asian melanoma; localized melanoma; melanoma; recurrence; sex disparity.

Recently total lymphadenectomy after positive results on sentinel lymph node biopsy (SLNB) has been found to be therapeutically ineffective.[1] However, SLNB is effective for predicting the prognosis of melanoma[1,2] owing to the role of regional lymph nodes as a gateway to metastasis.

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When there is no evidence of regional lymph node or any distant metastasis (DM), melanoma is classified as stage I or II according to the American Joint Committee on Cancer (AJCC) staging criteria; this is also referred as "localized" melanoma.[3]

Complete removal of the primary tumor is the treatment of choice for localized melanomas, and adjuvant systemic treatments are not recommended. However, recurrences occur even in some patients with primary localized melanomas. Recurrence is closely related to poor prognosis[4,5]; therefore, estimating recurrence is of utmost importance for predicting prognosis.

Several studies have been conducted to determine risk factors for recurrence of localized melanomas, but these studies were all from Western countries and predominantly included white patients.[4-10] Cutaneous melanomas in Asian patients show different characteristics, however, including a predominance of acral melanomas and different genetic mutation rates.[11-13] Therefore, this retrospective study aimed to identify risk factors of recurrence among patients with localized melanoma who visited a single center in Korea.

CAPSULE SUMMARY

- Predicting the recurrence of localized melanoma is important, but few studies have investigated prognostic risk factors of localized melanoma in Asians populations, in which acral melanoma is predominant.
- In localized cutaneous melanoma, male sex and Breslow thickness were the most important prognostic factors for recurrence in our Korean patient population.

METHODS

Patients

We reviewed the medical records of patients diagnosed with cutaneous malignant melanoma between 2000 and 2017 in the Dermatology Department of Severance Hospital, Yonsei University Health System, Seoul, Korea. We excluded patients with stage III or IV melanoma and those with mucosal melanoma. Only patients who visited the clinic for more than 6 months after removal of the primary melanoma were included.

For staging, we used the 8th edition of the AJCC staging system.[14] SLNB was performed in patients with tumors of Breslow thickness of 1 mm or more. In some patients who refused SLNB owing to individual preferences, systemic imaging studies such as ultrasonography, computed tomography, or positron emission tomography were performed to evaluate lymph node involvement. Primary melanoma was excised by wide excision (WE) or slow Mohs micrographic surgery (slow MMS). After complete removal, high-dose adjuvant interferon-alfa (HD IFN-α) was administrated to patients with stage IIB and IIC disease who could tolerate the treatment.

We classified patients with any kind of recurrence after removal as the recurrence group. Clinical types of recurrence were subclassified as local recurrence (LR), in-transit metastasis, nodal metastasis, and DM. Classification was performed according to the type identified at the first detection of recurrence. Both in-transit metastasis and lymph node metastasis were designated as "regional metastasis" (RM). Patients with multiple types of recurrences at detection were included in both recurrence types. We analyzed the time from tumor removal to the date of the last follow-up visit or detection of recurrence, and recurrence-free survival (RFS) was calculated for each recurrence group.

Statistical analysis

Correlations between RFS and various patient and tumor factors were assessed using univariate and multivariate Cox proportional analysis. Factors significant in the univariate analysis ($P < .05$) were included in the multivariate logistic regression models. Univariate and multivariate logistic regression analysis was conducted to analyze the correlation between recurrence rate and various factors. For the analysis, cutoffs of age and tumor mitotic rate were set according to the maximum point of the Youden index. The mitotic rate is reported as number per 10 high-power fields, and 4 of 10 high-power fields was set as a cutoff point, which can be converted to 1.69/mm^2.[15] Statistical tests were performed using IBM SPSS for Windows, version 23 (IBM Corp, Armonk, NY).

RESULTS

Overall, 652 patients with a diagnosis of cutaneous malignant melanoma visited the Department of Dermatology at Severance Hospital from 2000 to 2017. Of these patients, 406 had melanoma in situ, stage I or II melanomas without evidence of nodal metastasis. After excluding 20 patients with mucosal melanoma and 46 with follow-up of less than 6 months, a final total of 340 patients were included.

Abbreviations used:

AJCC:	American Joint Committee on Cancer
DM:	distant metastasis
HD IFN-α:	high-dose adjuvant interferon-alfa
HR:	hazard ratio
LR:	local recurrence
MMS:	Mohs micrographic surgery
RFS:	recurrence-free survival
RM:	regional metastasis
SLNB:	sentinel lymph node biopsy
WE:	wide excision

Ninety-two patients (27.1%) had recurrence after primary tumor removal. The mean follow-up period for patients was 46.2 months, and the median follow-up period was 36.5 months.

On the date of first detection of recurrence, LR was detected in 25 patients, RM in 37, and DM in 18. Two patients had both local and regional metastases, 8 had both regional and distant metastases, and 2 patients had LR together with regional and distant metastases. LR (82.8%) and RMs (91.8%) were mostly detected within 3 years, but only 67.9% of DMs were detected within 3 years. The most common site of DM was the lung, and the median latency of lung metastasis was 19.7 months.

Overall demographics of the patients according to recurrence type are shown in Table I. The average patient age was 57.94 years, and women (57.4%) outnumbered men (42.6%). The acral area was the most common anatomic site (70.3%, 239/340), and acral lentiginous melanoma was the predominant histologic subtype (65.2%, 180/276). The mitotic rate was evaluated in 227 patients, and the average rate was 1.8/mm^2. *BRAF* mutation was evaluated in 71 patients, and 21 patients (29.6%) had *BRAF* mutation. *BRAF* mutation was not evaluated as a routine screening but only in patients considering systemic treatment. Among 71 evaluated patients, 50 patients had acral melanoma and 6 showed *BRAF* mutation with a mutation rate of 12% (6/50). SLNB was done in 192 patients with tumors that were mostly more than 1 mm in depth. Among these patients, 67 (34.9%) patients had tumor recurrence.

The latency of tumor recurrence after surgery is shown in Fig 1, *A*. The median latency of tumor recurrence was 16.3 months, and 81.5% of recurrences were detected within 3 years after surgery. The latency of recurrence in 239 acral melanomas is shown in Fig 1, *B*. The median latency was 18.6 months, which was not significantly different from nonacral melanomas (mean latency of 24.5 months and median latency of 11.9 months, $P = .126$, 2-sample *t* test).

The 5-year RFS was 67.3% in our patients. Patients with melanoma in situ and stage IA melanoma showed no differences in RFS, whereas those with stage IB melanoma showed a significant difference ($P = .027$). For tumor staging, patients with stage T1a disease showed no difference in RFS than patients with melanoma in situ.

Logistic and Cox regression analyses were conducted; the results are shown in Table II. The recurrence rate was significantly higher in male patients than in female patients (adjusted $P = .030$). The 8th AJCC staging system showed significant correlation with the recurrence rate and RFS (adjusted *P* values .005 and .004, respectively). Breslow thickness was related to recurrence rate and RFS with 1.0- and 2.0-mm cutoffs. Age, tumor location, histologic subtypes, type of tumor removal surgery, presence of lymphovascular invasion or tumor-infiltrating lymphocytes, and *BRAF* mutation showed no statistical relationships with the recurrence rate or RFS. The presence of ulceration and mitotic rate greater than 1.69/mm^2 was related to the recurrence rate and RFS in the univariate analysis but not after adjustment. In the subgroup analysis according to the recurrence type, male patients had significantly lower local RFS and distant RFS than female patients. Tumor stage, Clark level, and Breslow thickness greater than 2 mm were related to regional and distant RFS. A mitotic rate greater than 1.69/mm^2 was significantly related to higher distant RFS.

There was no significant difference in recurrence and RFS between patients who received adjuvant HD IFN-α treatment and those who did not (recurrence, $P = .383$; RFS $P = .509$). HD IFN-α treatment did not reduce recurrence in all recurrence types.

Recurrence according to depth was evaluated after stratification by sex (Table III). In male patients, depths 2 to 4 mm and greater than 4 mm showed similar recurrence rates, whereas female patients showed significant differences in recurrence between depths 2 to 4 mm and greater than 4 mm. The recurrence rate was calculated in additionally subdivided cutoffs of 2.5 mm and 3 mm in male patients, and the recurrence rate was significant with a 2.5-mm cutoff.

On the basis of these results, we set a new high-risk group for recurrence in males with Breslow thickness greater than 2.5 mm and in females with Breslow thickness greater than 4.0 mm. The predictive value of the new high-risk groups for recurrence was compared with that of traditional high-risk stage IIB and IIC tumors. Seventy-eight patients were included in the new high-risk group, and 42 patients among them had recurrence, whereas 88 patients were included in those with stage IIB and IIC tumors, with 42 recurrences among them. The new high-risk groups

Table I. Demographics of 340 patients with primary localized cutaneous melanoma

Characteristic	Total (%)	Recurrence rate, n (%)	Recurrence rate, %	Local recurrence (%)	Regional metastasis (%)	Distant metastasis (%)
No. of patients	340	92	27.1	29	49	28
Mean age (y)	57.94	59.00		61.48	59.63	57.43
≥60	162 (47.7)	48 (52.2)	29.6	15 (51.7)	26 (53.1)	16 (57.1)
<60	178 (52.4)	44 (47.8)	24.7	14 (48.3)	23 (46.9)	12 (42.9)
Sex						
Male	145 (42.6)	51 (55.4)	35.2	18 (62.1)	28 (57.1)	14 (50.0)
Female	195 (57.4)	41 (44.6)	21.0	11 (37.9)	21 (42.9)	14 (50.0)
Location						
Head and neck	34 (10.0)	8 (8.7)	23.5	5 (17.2)	3 (6.1)	2 (7.1)
Trunk	28 (8.2)	9 (9.8)	32.1	2 (6.9)	4 (8.2)	5 (17.9)
Extremities	39 (11.5)	10 (10.9)	25.6	3 (10.3)	6 (12.2)	1 (3.6)
Upper extremity	16 (4.7)	6 (6.5)	37.5	3 (10.3)	2 (4.1)	1 (3.6)
Lower extremity	23 (6.8)	4 (4.3)	17.4	0 (0.0)	4 (8.2)	0 (0.0)
Acral	239 (70.3)	65 (70.7)	27.2	19 (65.5)	36 (73.5)	20 (71.4)
Hand and finger	65 (19.1)	14 (15.2)	21.5	3 (10.3)	8 (16.3)	5 (17.9)
Foot and toe	174 (51.2)	51 (55.4)	29.3	16 (55.2)	28 (57.1)	15 (53.6)
Subungual	60 (17.6)	11 (12.0)	18.3	3 (10.3)	6 (12.2)	3 (10.7)
Histologic subtype						
SSM	40 (14.5)	9 (12.9)	22.5	4 (18.2)	3 (8.1)	3 (13.6)
NM	47 (17.0)	16 (22.9)	34.0	1 (4.5)	11 (29.7)	6 (27.3)
LMM	9 (3.3)	3 (4.3)	33.3	2 (9.1)	1 (2.7)	0 (0.0)
ALM	180 (65.2)	42 (60.0)	23.3	15 (68.2)	22 (59.5)	13 (59.1)
Surgery type						
Wide excision	191 (56.7)	60 (65.2)	31.4	18 (62.1)	28 (57.1)	23 (82.1)
Slow MMS	146 (43.3)	32 (34.8)	21.9	11 (37.9)	21 (42.9)	5 (17.9)
Tumor stage						
In situ	77 (22.6)	6 (6.5)	7.8	6 (20.7)	0 (0.0)	0 (0.0)
IA	63 (18.5)	6 (6.5)	9.5	1 (3.4)	5 (10.2)	0 (0.0)
IB	57 (16.8)	19 (20.7)	33.3	7 (24.1)	10 (20.4)	6 (21.4)
IIA	55 (16.2)	19 (20.7)	34.6	2 (6.9)	10 (20.4)	9 (32.1)
IIB	50 (14.7)	22 (23.9)	44.0	6 (20.7)	13 (26.5)	6 (21.4)
IIC	38 (11.2)	20 (21.7)	52.6	7 (24.1)	11 (22.4)	7 (25.0)
Breslow thickness						
Mean thickness, mm	2.19	3.36		3.12	3.50	4.14
In situ	77 (22.6)	6 (6.5)	7.8	6 (20.7)	0 (0.0)	0 (0.0)
≤1 mm	63 (18.5)	6 (6.5)	9.5	1 (3.4)	5 (10.2)	0 (0.0)
1-2 mm	83 (24.4)	28 (30.4)	33.7	8 (27.6)	15 (30.6)	10 (35.7)
2-4 mm	54 (15.9)	22 (23.9)	40.7	6 (20.7)	11 (22.4)	9 (32.1)
>4 mm	63 (18.5)	30 (32.6)	47.6	8 (27.6)	18 (36.7)	9 (32.1)
Clark level						
I-III	131 (44.9)	14 (19.7)	10.7	7 (30.4)	7 (17.9)	2 (10.0)
IV	125 (42.8)	41 (57.7)	32.8	12 (52.2)	24 (61.5)	13 (65.5)
V	36 (12.3)	16 (22.5)	44.4	4 (17.4)	8 (20.5)	5 (25.0)
Ulceration present	93 (37.1)	39 (48.1)	41.9	12 (54.5)	22 (46.8)	9 (39.1)
LVI present	15 (5.7)	6 (8.3)	40.0	1	3	2
TIL present	104 (40.8)	29 (42.0)	27.9	7 (33.3)	17 (44.7)	10 (50.0)
Mean mitotic rate (n/mm^2)	1.8	2.2		2.0	2.1	2.5
≥1.69/mm^2	74 (32.6)	28 (47.5)	37.8	7 (36.8)	16 (47.1)	9 (60.0)
<1.69/mm^2	153 (67.4)	31 (52.5)	20.3	12 (63.2)	18 (52.9)	6 (40.0)
BRAF mutation						
Wild-type	50 (70.4)	36 (69.2)	72.0	9 (81.8)	23 (65.7)	11 (73.3)
Mutation	21 (29.6)	16 (30.8)	76.2	2 (18.2)	12 (34.3)	4 (26.7)
Adjuvant IFN-α	38 (11.2)	18 (19.6)	47.4	3 (10.3)	12 (24.5)	5 (17.9)
SLNB	192 (56.5)	67 (72.8)	34.9	18 (62.1)	38 (77.6)	19 (67.9)

ALM, Acral lentiginous melanoma; *IFN*, interferon; *LMM;* lentigo maligna melanoma; *LR;* local recurrence; *LVI*, lymphovascular invasion; *NM*, nodal melanoma; *SLNB;* sentinel lymph node biopsy; *Slow MMS*, slow Mohs micrographic surgery; *SSM*, superficial spreading melanoma; *TI*, tumor-infiltrating lymphocytes.

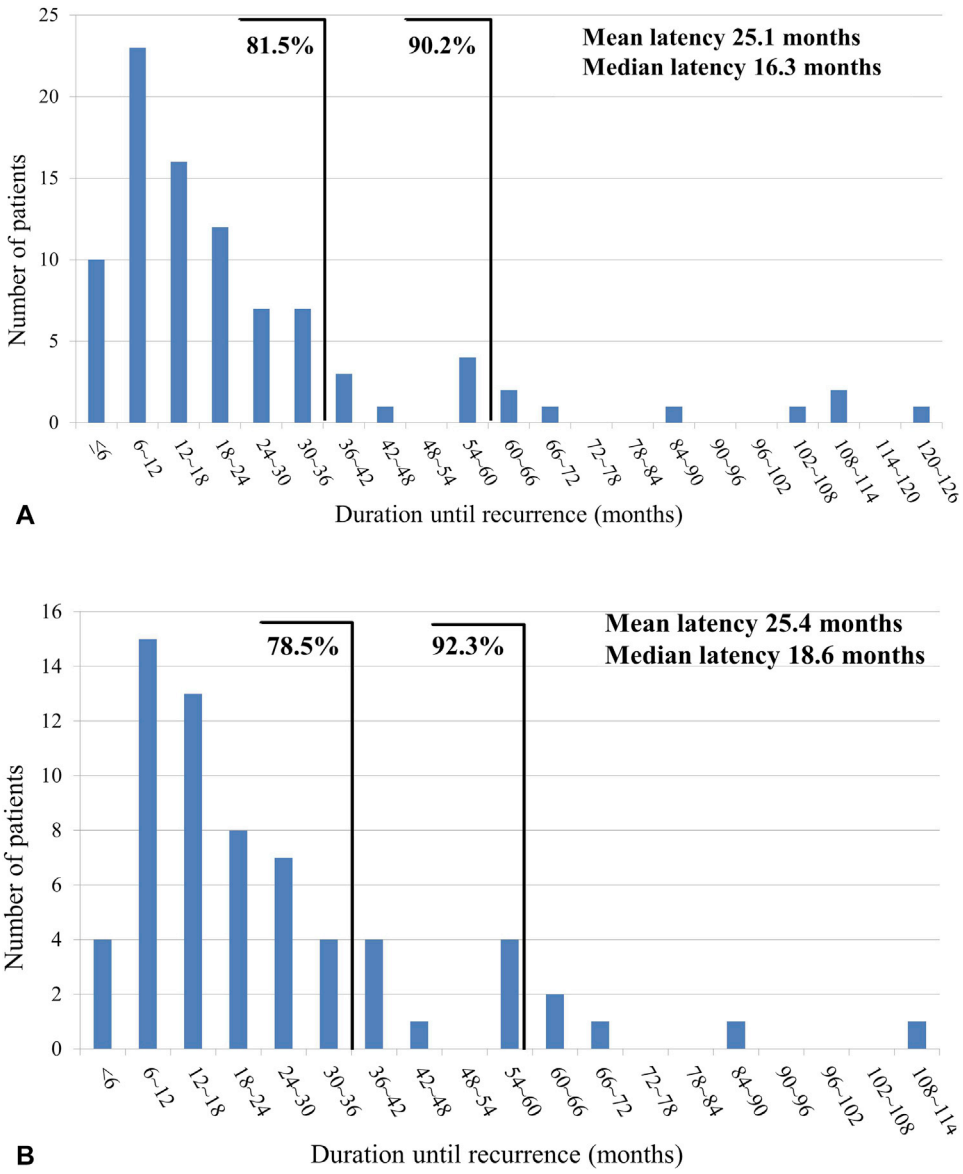

Fig 1. Latency of recurrent tumor detection after surgery (months). **A**, Recurrences in 340 patients with melanoma. **B**, Recurrences in 239 patients with acral melanoma.

showed a higher recurrence rate (53.8% vs 47.7%) and hazard ratio (HR) (3.743, 95% confidence interval 2.479-5.652 vs 2.972, 95% confidence interval 1.970-4.482). The predictive values were more powerful in the new high-risk groups with different cutoff values of Breslow thickness according to sex for all recurrence types; LR (recurrence rate, 15.4% vs 14.8%, HR 3.047 vs 2.411), RM (recurrence rate, 30.8% vs 27.3%, HR 4.081 vs 3.299, and DM (recurrence rate, 17.9% vs 14.8%, HR 4.937 vs 3.223).

DISCUSSION

Male sex and Breslow thickness were associated with the recurrence of localized cutaneous melanoma in our population of Korean patients. Tumor thickness affected prognosis differently according to the patient' sex. To date there are no studies investigating the prognostic factors of localized melanomas in Asian populations. However, tumor stage, Breslow thickness, and ulceration were commonly indicated as poor prognostic factors for disease-free survival in studies investigating the prognosis of melanoma in Asian patients.[13,16-19]

In Western countries, several studies have investigated risk factors for recurrence of localized melanomas. Egger et al.[6] and Adler et al.[10] studied patients with SLNB-negative status, and Laks et al.[8] and Lyth et al.[9] examined patients with stage I and II

Table II. Correlation between recurrence and various factors

			Total recurrence*		Local recurrence	Regional metastasis	Distant metastasis
	Recurrence rate (%)	*P* value (adjusted)†	5-year RFS (%)	*P* value (adjusted)‡	*P* value (adjusted)§	*P* value (adjusted)¶	*P* value (adjusted)‖
Total	27.1		67.3				
Age ≥ 60 y	29.6	.309	63.0	.258 (.676)	.552 (.811)	.342 (.630)	.256 (.759)
Male (vs female)	35.2	.004** (.030*)	58.1	.007** (.057)	.027* (.029*)	.022* (.161)	.224 (.018*)
Location							
Head and neck	23.5	.626	76.5	.418	.302	.336	.468
Trunk	32.1	.528	68.3	.831	.700	.859	.187
Extremity	25.6	.832	75.5	.606	.732	.867	.155
Acral	27.2	.930	63.3	.434	.826	.387	.451
Subungual	18.3	.097	78.0	.189	.632	.330	.359
Histologic type							
SSM	22.5	.653	74.4	.449	.883	.248	.667
NM	34.0	.136	64.0	.099	.201	.051 (.889)	.135
LMM	33.3	.579	77.8	.834	.273	.998	.611
ALM	23.3	.290	67.1	.449	.666	.792	.578
Wide excision (vs Slow MMS)	31.4	.049* (.098)	67.4	.894	.752	.274	.136
Tumor stage		<.001** (.005**)		<.001** (.004**)	.020* (.058)	<.001** (.021*)	<.001** (.025*)
In situ	7.8	(ref)	92.8	(ref)	(ref)		
IA	9.5	.716	88.6	.960	.093	(ref)	
IB	33.3	<.001**	66.8	.009**	.650	.117	(ref)
IIA	34.6	<.001**	61.6	.002**	.605	.061	.228
IIB	44.0	<.001**	44.2	<.001**	.974	.005**	.382
IIC	52.6	<.001**	42.6	<.001**	.031*	.003**	.133
T stage		<.001** (.001**)		<.001** (.001**)	.024* (.029*)	<.001** (.001**)	<.001** (.018*)
In situ	7.8	(ref)	92.8	(ref)	(ref)		
1a	5.7	.693	94.1	.505	.254	(ref)	
1b	14.3	.323	81.3	.555	.979	.142	
2a	33.3	<.001**	62.6	.009**	.663	.071	(ref)
2b	34.6	.002**	52.1	.010*	.447	.068	.495
3a	34.5	.002**	61.0	.002**	.971	.053	.174
3b	41.4	<.001**	44.5	.001**	.345	.033*	.378
4a	47.6	<.001**	45.0	.001**	.984	.011*	.579
4b	52.6	<.001**	42.7	.001**	.031*	.011*	.131
Breslow thickness		<.001** (.451)		.001** (.098)	.010* (.122)	<.001** (.197)	<.001** (.034*)
≥0.8 mm	37.2	<.001** (.059)	56.2	.001** (.064)	.225	<.001** (.143)	.023* (.978)
≥1.0 mm	40.0	<.001** (.008**)	53.8	.001** (0.014*)	.035* (.082)	<.001** (.068)	.001** (.958)
≥2.0 mm	44.4	<.001** (.008**)	47.5	.001** (.005**)	.069	<.001** (.021*)	.001** (.009**)
Clark level		<.001** (.013*)		.001** (.014*)	.088	<.001** (.047*)	.001** (.027*)
Ulceration	41.9	.013* (.335)	49.3	.004** (.332)	.042* (.257)	.048* (.148)	.378
LVI	40.0	.261	65.5	.713	.597	.915	.715
TIL	27.9	.649	66.4	.830	.254	.624	.754
Mitotic rate (≥1.69/mm^2)	37.8	.004** (.075)	55.8	.005** (.132)	.516	.042* (.438)	.015* (.049*)
BRAF mutation	76.2	.750	32.7	.730	.341	.886	.551

ALM, Acral lentiginous melanoma; *LMM*, lentigo maligna melanoma; *LVI*, lymphovascular invasion; *NM*, nodal melanoma; *ref*, reference value; *RFS*, recurrence-free survival; *Slow MMS*, slow Mohs micrographic surgery; *SSM*, superficial spreading melanoma; *TIL*, tumor-infiltrating lymphocytes.

Logistic regression analysis was conducted for the recurrence rate and Cox regression analysis was conducted for recurrence-free survival.

*For *P* value < .05 and ** for *P* value 0.01.

†Adjusted for age, sex, surgery type (wide excision or MMS), Breslow thickness, ulceration, and mitotic rate (≥1.69/mm^2). Tumor stage was adjusted for factors except for thickness and ulceration, and Clark level was adjusted except for thickness.

‡Adjusted for age, sex, Breslow thickness, ulceration, and mitotic rate (≥1.69/mm^2). Tumor stage was adjusted for factors except for thickness and ulceration, and Clark level was adjusted except for thickness.

§Adjusted for age, sex, Breslow thickness, and ulceration.

¶Adjusted for age, sex, histologic subtype (NM), Breslow thickness, ulceration, and mitotic rate.

‖Adjusted for age, sex, Breslow thickness, and mitotic rate.

Table III. Correlation between depth and recurrence according to sex

	Total	Recurrence group (recurrence rate, %)	5-year RFS (%)	*P* value	Hazard ratio (95% confidence interval)
Male	145	51 (35.2)			
In situ	31	3 (9.7)	93.2	(ref)	
≤1 mm	25	5 (20.0)	76.2	.457	1.727 (0.410-7.284)
1-2 mm	36	16 (44.4)	46.5	.028	4.009 (1.164-13.812)
2-4 mm	28	14 (50.0)	46.6	.004	6.396 (1.837-22.272)
2-2.5	9	2 (22.22)	49.9	.011	4.962 (1.436-17.146)
2.5-3	8	5 (62.5)	30.0	.004	8.281 (1.972-34.772)
3-4	11	7 (63.64)	29.1	.001	9.858 (2.538-38.291)
>4 mm	25	13 (52.0)	38.4	.004	6.191 (1.763-21.739)
Female	195	41 (21.0)			
In situ	46	3 (6.5)	92.8	(ref)	
≤1 mm	38	1 (2.6)	96.9	.319	0.316 (0.033-3.044)
1-2 mm	47	12 (25.5)	70.8	.093	2.974 (0.833-10.622)
2-4 mm	30	8 (26.7)	60.9	.042	3.972 (1.051-15.012)
>4 mm	34	17 (50.0)	47.4	.001	7.681 (2.243-26.300)

ref, Reference value; *RFS,* recurrence-free survival; *y,* year.

melanoma.[8,9] In general, age, tumor thickness, and presence of ulceration were common risk factors for recurrence of localized melanomas.

In our study, recurrence of localized melanoma showed no relevance to age or the presence of ulceration, but it was associated with the patient's sex. In studies investigating overall survival in patients with melanoma, male patients had a poorer prognosis than female patients.[20,21] Despite many reports of sexual imbalance in prognosis, the biologic pathophysiology of sex differences is not completely understood.[21,22] Behavioral factors, including higher smoking rates, lower awareness of skin condition, and greater sun exposure among males, are suspected.[21,22] In addition to environmental factors, disparities with respect to gene mutations and sex hormones are suspected factors in sex differences.[23] Although there are no differences in the mutations of major causative genes in melanoma, including *BRAF* and *c-kit*,[12,24,25] males have a greater burden of missense mutations in metastatic melanomas.[26] Estrogen and androgen receptors are proven to be present on melanoma cells,[27,28] and sex hormones also affect immune microenvironments.[23] Although previous studies investigating risk factors for recurrence of localized melanomas could not prove male sex as a risk factor, we showed that sex was an important risk factor for predicting recurrence, even in localized melanomas.

Furthermore, we showed that even the thickness for predicting recurrence can be different according to sex. We identified new criteria for the high-risk group (for males, thickness >2.5 mm; for females, thickness >4.0 mm) using thickness and sex rather than tumor ulceration; these criteria had higher predictive power in localized melanoma than the traditional high-risk groups of stage IIB and IIC disease.

Recently the overall survival in patients with malignant melanoma has become greatly extended because of newly developed drugs, including *BRAF* inhibitors, *MEK* inhibitors, and immune checkpoint inhibitors. However, these new treatments are indicated for patients with advanced melanoma, and there are only a few trials of preventive systemic treatments for localized melanomas. Identifying high-risk groups in localized melanoma is important for determining candidate adjuvant treatments. Thus our new criteria for high-risk groups need to be verified in a larger multicenter or population-based study.

In our study, Breslow thickness of 1 mm was also a significant cutoff for a higher recurrence rate compared with melanoma in situ. Patients with stage IB disease showed a significantly higher recurrence, whereas those with stage IA disease showed no difference compared with those with melanoma in situ. When subdivided according to tumor stage, those with stage 2a disease showed a significant difference from those with stage 1b disease, which is classified as 1-mm depth. The AJCC 8th edition staging system was changed to include stage T1b in stage Ia; our result supports this change in stage regrouping.

Although acral melanoma is known to have different biologic characteristics compared with nonacral melanomas—such as independency to sun exposure and low rate of *BRAF* mutations[12,13,17]—acral melanoma was not a significant risk factor for recurrence, and the latency of tumor recurrence showed no difference between acral and nonacral melanomas in our study.

A tumor mitotic rate higher than 1.69/mm^2 was predictive for DM in our study. Previous reports contend that tumors with a mitotic rate higher than 1/mm^2 have a higher risk of metastasis than those with a mitotic rate of 0/mm^2. Some studies demonstrated that tumor mitotic rate is a more powerful prognostic factor in localized melanoma than ulceration[29,30]; our study results also showed that a mitotic rate higher than 1.69/mm^2 is a more predictive factor for recurrence than ulceration. Our study results support the role of the tumor mitotic rate in evaluating the prognosis in localized melanoma.

The median latency of recurrence was 16.3 months, and most recurrences were detected within 3 years after surgery in our study. In previous literature reports, the median time until recurrence varies from 16.0 to 39.5 months.[4-7,9,10] Variable follow-up intervals among health care centers might be a cause of the large variance in time until recurrence. Medical accessibility to tertiary health care centers is convenient in Korea, which allows patients with suspected recurrence to visit their dermatologist immediately. Owing to these factors, the median time to recurrence in our patients was quite accurate, which implies that more intensified screening for recurrence, including screening for lung metastasis, should be conducted in patient subsets within 2 years after surgery. Moreover, at least 3 years of close follow-up is needed as most recurrences are detected within 3 years after surgery.

Slow MMS showed no prognostic inferiority with respect to WE in our study. Seventy percent of our patients had melanoma on an acral location where sparing tissue is functionally important. More tissue can be spared and distal digits can be preserved using slow MMS, leading to better quality of life for patients. Considering the functional benefit and no prognostic inferiority of slow MMS comparison with WE, we recommend slow MMS for the removal of melanomas, especially acral melanomas.

This study has several limitations. This was a retrospective study, and the methods of surgery, follow-up interval, and HD IFN-α treatment were not controlled. The number of patients was relatively small compared with that of population-based studies. Therefore, further prospective or larger nationwide studies among Asian patients with melanoma are needed to validate our results.

CONCLUSION

Male sex and Breslow thickness were the most important prognostic factors for recurrence of localized cutaneous melanoma in a Korean population. Moreover, different cutoff values of Breslow thickness according to sex (males, 2.5 mm; females, 4 mm) may be applied for better prognostic predictability in patients with melanoma.

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