ORIGINAL ARTICLE

Risk of recurrence of nail unit melanoma after functional surgery versus amputation

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Background: Minimally invasive nail unit melanoma (NUM) can be treated with functional surgery (FS) instead of amputation.

Objective: To determine risk factors associated with recurrence in NUM.

Methods: We retrospectively reviewed patients with NUM between 2008 and 2022 at a tertiary referral center. Multivariable Cox regression models adjusted for male sex and Breslow thickness (BT) were generated. Receiver operating characteristic analysis was performed to determine optimal cut-off points of the BT for stratifying recurrence risk.

Results: We evaluated 140 NUM cases (33 amputation and 107 FS). The mean BT values were 3.14 ± 2.62 mm (amputation) and 0.70 ± 1.36 mm (FS). Recurrence occurred in 10 (30.30%) patients with amputation and 23 (21.5%) with FS. Distant disease occurred in 10 (30.30%) patients with amputation and 8 (7.48%) with FS. Male sex, greater BT, amelanotic color, ulcers, and nodules were associated with greater risk for recurrence or distant disease. A BT of 0.8 mm was deemed the optimal cut-off for stratifying recurrence risk after surgery (odds ratio, 5.32; 95% CI, 2.04-13.85).

Limitations: Small sample.

Conclusion: FS can be considered for NUM with a BT < 0.8 mm, providing an amputation-sparing benefit. However, NUM with risk factors for recurrence requires patient counselling and close follow-ups. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2022.12.039.)

Key words: Breslow thickness; distant disease; functional surgery; nail unit melanoma; recurrence; survival.

INTRODUCTION

Amputation has been widely used to treat nail unit melanoma (NUM). However, a more conservative treatment, functional surgery (FS), which considers both function and cosmesis, has been recently implemented because the resection level does not influence the outcome when histologically free margins are obtained.[1] FS mainly targets *in situ* or

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minimally invasive NUM, and a meta-analysis showed no difference in local recurrence between amputation and FS.[2]

The definition of minimal invasiveness is crucial for establishing the indication of FS. Generally, minimal invasiveness has been defined as a Breslow thickness (BT) of 0.5 mm or less based on histopathologic examination, but this value was rather arbitrary and has not been statistically quantified.

We have been performing FS for NUM with patient consent, if no bone invasion is present and a free margin is secured regardless of BT. We performed a retrospective study of patients with NUM at our institution to investigate the incidence of recurrence and distant disease in patients treated with amputation and FS and the associated factors. We also suggest an optimal cut-off value for the BT to define minimal invasiveness and criteria of FS for NUM treatment.

CAPSULE SUMMARY

- Functional surgery, rather than amputation, is a treatment option for minimally invasive nail unit melanoma, but its indication requires clarification.
- Functional surgery is suggested for nail unit melanoma without amelanotic color, nodules, and ulcers. However, nail unit melanoma with a ≥0.8-mm invasion depth shows greater recurrence risk after functional surgery.

METHODS

Study population and ethics statement

We retrospectively reviewed the medical records of patients diagnosed with NUM and treated with either amputation or FS between June 1, 2008, and March 31, 2022, at the Dermatology Department of Severance Hospital, Yonsei University Health System, Seoul, Korea. All surgical treatments were performed by dermatologic surgeons (B.H.O. and K.Y.C.). Patients who underwent surgery at other hospitals or other departments were excluded. The patients' medical records were reviewed for age, sex, tumor stage, BT, anatomical location, clinical photographs, follow-up period, local/regional/distant recurrence, and death associated with melanoma. According to the Standardized Definitions for Efficacy and Points criteria,[3,4] recurrence was defined as an occurrence of any local, regional recurrence, and death associated with melanoma during follow-up. Distant disease was defined as an occurrence of distant recurrence and death associated with melanoma. The index date was set as the day of operation for NUM.

The study protocol was approved by the Institutional Review Board of Severance Hospital in the Yonsei University Health System (approval no. 4-2022-0335) and conformed to the principles of the Declaration of Helsinki. Patient records and information were anonymized and deidentified before analysis.

Morphological phenotyping of nail unit melanoma

The morphological features were extracted by photographic evaluation of NUM (Supplementary Fig 1, available via Mendeley at https://doi.org/10.17632/w8p3cmh8vv.1). All the photographs were taken using a digital single-lens reflex camera D300 (Nikon) under the same conditions. The extent of nail involvement was described as total or partial involvement. We also noted whether the pigment had spread to the volar part, and the presence or absence of the Hutchinson sign, defined as periungual pigmentation of the nail fold or hyponychium. The presence of ulceration and nodular growth were also determined. The color of the NUM was recorded as brown, black and brown, black, or amelanotic.

Decision and procedure of surgical treatment

We performed amputation when bone invasion was evident on preoperative magnetic resonance imaging or skin biopsy. If bone invasion was not evident, FS was performed with the patient's consent regardless of BT. In FS, the entire nail unit including at least 3 to 4 mm from the nail plate and matrix was excised.[5] In the presence of the Hutchinson sign, the safety margin was calculated from the pigmentation. The deep margin was determined at the level of bone contact, and the periosteum was included as much as possible. Next, the excised tissue was pathologically reevaluated. Histopathological reexamination was subsequently performed on the tissue removed en bloc. Each specimen was initially sliced along its longitudinal axis from the proximal nail fold to the hyponychium at 2-mm intervals, and histologic examinations of 4 sequential 4-μm-thick sections were performed. Tissue staining was performed with hematoxylin and eosin, S-100 protein, human melanoma black 45 (HMB45), and Melan A.[6] Amputation was performed if melanoma was abutted or crossed the basal resection margin on the final pathological report, even after FS.

Outcomes and statistical analysis

Descriptive statistics were presented using counts and proportions or means and standard deviation as

Abbreviations used:

aHR: adjusted hazard ratio
BT: Breslow thickness
FS: functional surgery
NPV: negative predictive value
NUM: nail unit melanoma

appropriate for the variable type. The difference in clinical characteristics, including age, sex, tumor stage, morphologic characteristics, follow-up duration, recurrence, and distant disease, between patients who underwent amputation (amputation group) and those who underwent FS (FS group) were measured using standardized mean difference. The Kaplan-Meier method was used to determine survival curves for recurrence-free survival and distant disease-free survival for each group. Univariable and multivariable Cox proportional hazards analyses were used to investigate the factors associated with recurrence and distant disease in NUM after surgical treatment. The covariates included male sex and BT, previously reported as crucial risk factors for recurrence in melanoma.[7]

In addition to investigating the factors associated with recurrence and distant disease in NUM, we determined the optimal cut-off points for the BT that can stratify the risk of recurrence after surgery. To evaluate the rate of recurrence and distant disease according to the BT, patients with a follow-up period ≥3 years or patients with recurrence or distant disease were evaluated. From the receiver operating characteristic curves, each cut-off point for the BT was evaluated using the Youden index (= sensitivity + specificity-1) and negative predictive value (NPV). The potential candidates for the cut-off points were selected from 0.1 mm to 1.5 mm with a 0.1-mm increment. In addition to the Youden index, which represents an overall performance in stratifying the risk of recurrence, the NPV was used as another outcome of interest because of the life-threatening nature of recurrent diseases in melanoma. To ensure the robustness of the optimal cut-off, we performed sensitivity analysis involving only patients with a follow-up period ≥5 years.

All statistical analyses were performed using SAS version 9.4 (SAS Institute) and R version 3.6.3 (R Foundation for Statistical Computing) at a significance level of 5%.

Table I. Characteristics of patients with nail unit melanoma

Characteristic	Value (count [%] or mean ± SD)		SMD
	Amputation (*n* = 33)	Functional Surgery (*n* = 107)	
Age, y	63.9 ± 14.0	56.5 ± 5.2	0.485
<60, *n* (%)	13 (39.4)	56 (52.4)	−0.259
≥60, *n* (%)	20 (60.6)	51 (47.6)	0.259
Sex, *n* (%)			
Female	18 (54.6)	57 (53.3)	0.026
Male	15 (45.4)	50 (46.7)	−0.026
Breslow thickness, mm	3.1 ± 2.6	0.7 ± 1.4	1.795
<1.0, *n* (%)	5 (15.2)	84 (78.5)	−1.542
≥1.0, *n* (%)	28 (84.8)	23 (21.5)	1.542
T stage, *n* (%)			
Tis	2 (6.1)	68 (63.6)	−1.195
IA	2 (6.1)	12 (11.2)	−0.163
IB	5 (15.2)	10 (9.4)	0.196
IIA	4 (12.1)	8 (7.5)	0.177
IIB	10 (30.3)	3 (2.8)	1.666
IIC	2 (6.1)	2 (1.9)	0.310
IIIA	1 (3.0)	3 (2.8)	0.014
IIIB	4 (12.1)	1 (0.9)	1.163
IIIC	2 (6.1)	0 (0.00)	0.511
IIID	1 (3.)	0 (0.00)	0.360
Location, *n* (%)			
Fingernail	23 (69.70)	71 (66.4)	0.071
Toenail	10 (30.30)	36 (33.6)	−0.071
Color, *n* (%)			
Black	0 (0.00)	18 (16.8)	−0.450
Black and brown	16 (48.5)	61 (57.0)	−0.172
Brown	13 (39.4)	20 (18.7)	0.531
Amelanotic	4 (12.1)	8 (7.5)	0.177
Volar involvement, *n* (%)	20 (60.6)	31 (29.0)	0.697
Total nail involvement, *n* (%)	19 (57.6)	43 (40.2)	0.355
Hutchinson sign, *n* (%)	31 (93.9)	79 (73.8)	0.458
Ulcer, *n* (%)	15 (45.5)	12 (11.2)	1.085
Nodule, *n* (%)	21 (63.6)	22 (20.6)	1.066
Follow-up, years	4.0 ± 3.2	3.8 ± 2.6	0.065
Recurrence, *n* (%)	10 (30.3)	23 (21.5)	0.214
Distant disease, *n* (%)	10 (30.3)	8 (7.5)	0.868

SMD, Standardized mean difference.

RESULTS

Study population and baseline characteristics

A total of 140 patients with NUM were included from the study period. Among them, 33 had amputation and 107 had FS. The demographic and clinical characteristics of the patients are summarized in Table I. The mean BT of NUM was 3.14 ± 2.62 mm

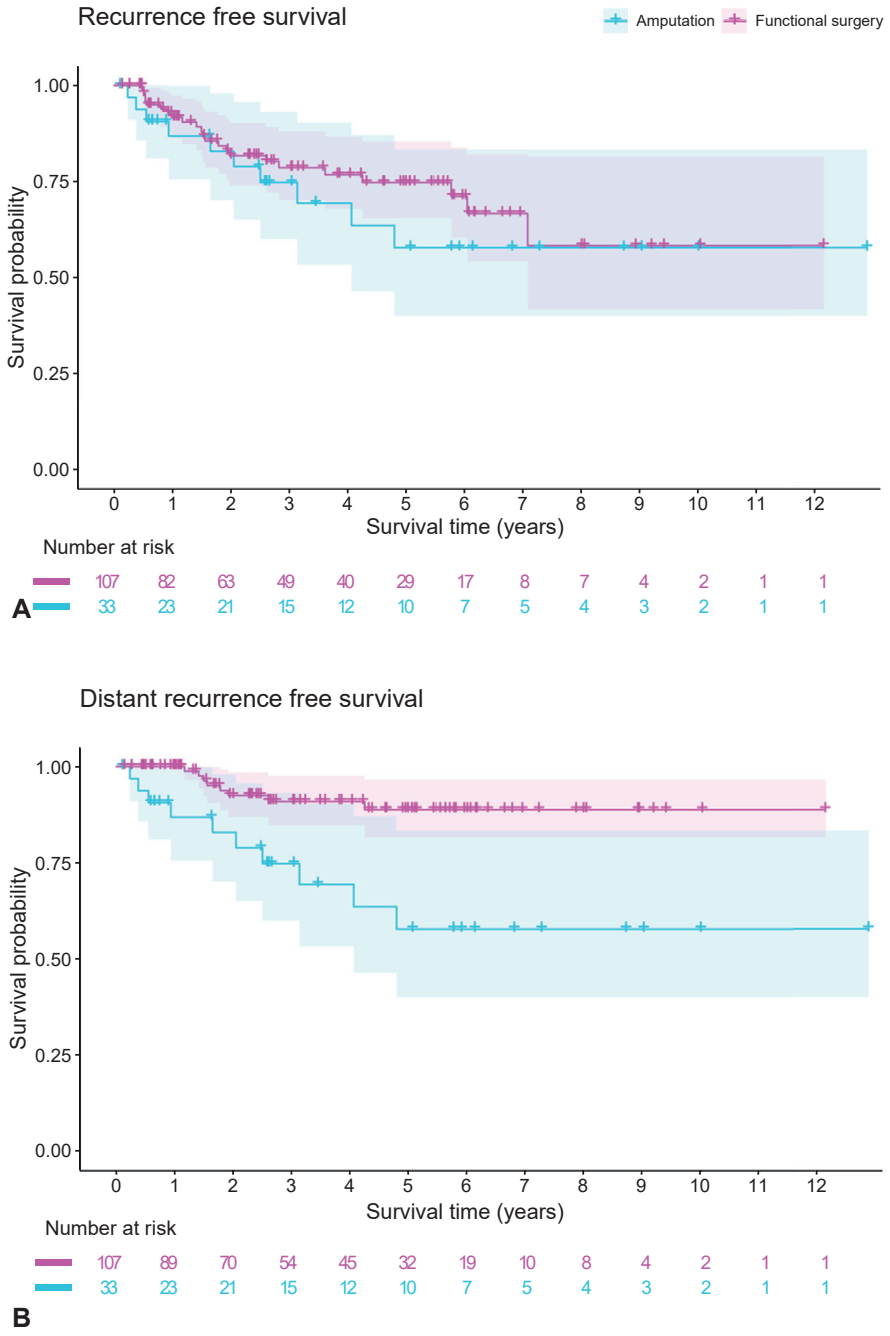

Fig 1. Probability of recurrence free survival and distant disease free survival after surgical treatment for nail unit melanoma. The Kaplan–Meier plot shows the probability of (**A**) recurrence free survival and (**B**) distant recurrence free survival in patients who underwent amputation and functional surgery for nail unit melanoma over 12 years.

for the amputation group (range: *in situ* to 11.0 mm), a value markedly greater than that of the FS group at 0.70 ± 1.36 mm (range: *in situ* to 5.0 mm). Patients in the amputation group were more likely to be older and have higher rates of volar involvement, total nail involvement, the Hutchinson sign, ulcers, and nodules than those in the FS group.

Recurrence and distant disease during study period

The mean follow-up period was 3.97 ± 3.19 years for the amputation group and 3.80 ± 2.62 years for the FS group. A Kaplan–Meier plot for recurrence and distant disease is presented in Fig 1. Recurrence was reported in 10 (30.30%) patients in the

Table II. Factors associated with recurrence and distant disease in nail unit melanoma

	Recurrence				Distant disease			
	Crude model		Sex, BT-adjusted model		Crude model		Sex, BT-adjusted model	
Characteristic	HR	(95% CI)	aHR	(95% CI)	HR	(95% CI)	aHR	(95% CI)
Age (y)	1.01	(0.99-1.04)	1.01	(0.99-1.03)	1.01	(0.98-1.04)	1.00	(0.97-1.03)
<60, *n* (%)		(ref)		(ref)		(ref)		(ref)
≥60, *n* (%)	1.55	(0.78-3.10)	1.44	(0.71-2.92)	1.11	(0.44-2.79)	1.05	(0.41-2.70)
Sex, *n* (%)								
Female		(ref)		(ref)		(ref)		(ref)
Male	1.73	(0.87-3.44)	1.77	(0.89-3.53)	2.86	(1.07-7.63)	2.85	(1.07-7.61)
Breslow thickness (mm)	1.20	(1.07-1.35)	1.04	(0.87-1.25)	1.27	(1.11-1.47)	1.06	(0.86-1.32)
<1.0, *n* (%)		(ref)		(ref)		(ref)		(ref)
≥1.0, *n* (%)	3.87	(1.87-7.99)	3.91	(1.89-8.08)	6.53	(2.15-19.84)	6.50	(2.14-19.76)
T stage, *n* (%)								
Tis		(ref)		(ref)		(ref)		(ref)
I	1.74	(0.60-5.03)	1.59	(0.39-6.40)	1.18	(0.10-13.01)	2.24	(0.18-27.65)
II	4.97	(2.08-11.89)	2.71	(0.51-14.29)	14.56	(3.23-68.72)	32.60	(2.81-378.39)
III	4.54	(1.48-13.93)	2.69	(0.50-14.62)	14.28	(2.61-78.10)	27.65	(3.15-242.33)
Location, *n* (%)								
Fingernail		(ref)		(ref)		(ref)		(ref)
Toenail	1.69	(0.84-3.37)	1.28	(0.63-2.60)	2.38	(0.94-6.00)	1.83	(0.71-4.68)
Color, *n* (%)								
Black		(ref)		(ref)		(ref)		(ref)
Black and brown	1.96	(0.45-8.63)	1.72	(0.39-7.71)	1.04	(0.12-9.27)	0.95	(0.10-8.69)
Brown	2.68	(0.59-12.24)	1.77	(0.38-8.22)	4.95	(0.63-39.13)	3.04	(0.38-24.49)
Amelanotic	7.83	(1.62-37.82)	5.69	(1.16-27.84)	6.72	(0.75-60.17)	3.52	(0.38-32.45)
Volar involvement, *n* (%)	4.87	(2.43-9.74)	0.89	(0.43-1.81)	1.45	(0.57-3.69)	0.99	(0.39-2.55)
Total nail involvement, *n* (%)	1.27	(0.64-2.51)	1.02	(0.50-2.09)	1.56	(0.61-3.94)	1.26	(0.47-3.34)
Hutchinson sign, *n* (%)	0.82	(0.37-1.81)	0.70	(0.31-1.61)	1.08	(0.36-3.29)	1.18	(0.38-3.70)
Ulcer, *n* (%)	4.87	(2.43-9.74)	2.76	(1.20-6.37)	10.47	(3.93-27.94)	5.49	(1.56-19.36)
Nodule, *n* (%)	2.49	(1.26-4.93)	1.29	(0.60-2.80)	8.19	(2.69-24.88)	4.05	(1.14-14.45)
Type of surgery								
Amputation		(ref)		(ref)		(ref)		(ref)
Functional surgery	0.74	(0.35-1.56)	1.67	(0.74-3.77)	0.23	(0.09-0.58)	0.45	(0.16-1.28)

aHR, Adjusted hazard ratio; *BT*, Breslow thickness; *HR*, hazard ratio.

amputation group and 23 (21.5%) patients in the FS group, with a 5-year recurrence-free survival of 57.9% (95% CI, 40.2%-83.4%) and 74.8% (95% CI, 65.5%-85.4%), respectively. Distant disease was reported in 10 (30.30%) patients in the amputation group and 8 (7.48%) patients in the FS group, with a 5-year distant disease-free survival of 57.9% (95% CI, 40.2%-83.4%) and 88.8% (95% CI, 81.6%-96.7%), respectively.

Factors associated with recurrence and distant disease

Univariable and multivariable Cox proportional hazards models were generated to investigate the factors associated with recurrence in NUM (Table II and Supplementary Tables 1 and 2, available via Mendeley at https://doi.org/10.17632/w8p3cmh8vv.1). For recurrence, a greater BT (≥1.0 mm) (sex and BT-adjusted hazard ratio [aHR], 3.91; 95% CI, 1.89-8.08), higher T stage, amelanotic color (aHR, 5.69; 95% CI, 1.16-27.84), and ulcers (aHR, 2.76; 95% CI, 1.20-6.37) were associated with a greater risk. For distant disease, male sex (aHR, 2.85; 95% CI, 1.07-7.61), greater BT (≥1.0 mm) (aHR, 6.50; 95% CI, 2.14-19.76), higher T stage, ulcers (aHR, 5.49; 95% CI, 1.56-19.36), and nodules (aHR, 4.05; 95% CI, 1.14-14.45) were associated with a greater risk.

Thresholding of the Breslow thickness for stratifying the risk of disease recurrence

A total of 89 patients with either more than 3 years of follow-up, recurrence, or distant disease were selected. Recurrence and distant disease according to the BT are shown in Table III, with the receiver operating characteristic curves and the performance metrics summarized in Supplementary Fig 2, available via Mendeley at https://doi.org/10.17632/w8p3cmh8vv.1 and Supplementary Table III,

Table III. Recurrence and distant disease according to the Breslow thickness in nail unit melanoma

	Recurrence		Distant disease		Surgical strategy			
Threshold for Breslow thickness	Youden index	Negative predictive value (%)	Youden index	Negative predictive value (%)	Functional surgery, *n* (%)		Amputation sparing*, *n* (%)	
≥0.1 mm	0.256	90.9	0.308	84.8	33	(37.1)	−9	(−21.4)
≥0.2 mm	0.284	91.4	0.292	82.9	35	(39.3)	−7	(−16.7)
≥0.3 mm	0.298	91.7	0.308	83.3	36	(40.4)	−6	(−14.3)
≥0.4 mm	0.215	87.5	0.276	80.0	40	(44.9)	−2	(−4.8)
≥0.5 mm	0.174	85.7	0.259	78.6	42	(47.2)	Reference	
≥0.6 mm	0.202	86.4	0.293	79.5	44	(49.4)	2	(4.8)
≥0.7 mm	0.230	87.0	0.327	80.4	46	(51.7)	4	(9.5)
≥0.8 mm	0.287	88.0	0.395	82.0	50	(61.2)	8	(19.0)
≥0.9 mm	0.231	86.3	0.362	80.4	51	(57.3)	9	(21.4)
≥1.0 mm	0.259	86.8	0.345	79.2	53	(59.6)	11	(26.2)
≥1.1 mm	0.162	83.9	0.295	76.8	56	(62.9)	14	(33.3)
≥1.2 mm	0.176	84.2	0.312	77.2	57	(64.0)	15	(35.7)
≥1.3 mm	0.176	84.2	0.312	77.2	57	(64.0)	15	(35.7)
≥1.4 mm	0.190	84.5	0.329	77.6	58	(65.2)	16	(38.1)
≥1.5 mm	0.190	84.5	0.329	77.6	58	(65.2)	16	(38.1)

*The number of amputations that can be spared if functional surgery is performed for cases with invasion less than the corresponding cut-off of Breslow thickness. The empirical threshold of Breslow thickness of 0.5 mm is set as a reference.

available via Mendeley at https://doi.org/10.17632/w8p3cmh8vv.1. From among the various cut-off points, 0.8 mm was determined as the cut off value in which the risk of recurrence was stratified using the greatest Youden index and a NPV of 88.0%, as NUM with a BT greater than 0.8 mm were associated with greater odds of recurrence (odds ratio, 3.26; 95% CI, 1.10-9.70). In addition, amputation could have been spared in 19.0% of cases, where the reference cut-off value was set at a BT of 0.5 mm, if FS had been performed for all cases with a BT of 0.8 mm or less without any loss in the Youden index and NPV. It was also found that a cut-off value of 0.8 mm was optimal to stratify the risk of distant disease (odds ratio, 5.32; 95% CI, 2.04-13.85). Sensitivity analyses on 69 patients with either over 5 years of follow-up, recurrence, or distant disease was performed (Supplementary Table IV, available via Mendeley at https://doi.org/10.17632/w8p3cmh8vv.1), in which the finding was consistent with that of the original analysis.

DISCUSSION

Proposing an appropriate surgical method for NUM has been controversial for several decades. Traditionally, amputation of the involved digit has been chosen. However, in 1992, Park et al first reported no recurrence in 7 patients after local excision without amputation, although the BT of the patients had not been reported, suggesting a paradigm shift toward less extensive resections.[8,9] Since then, FS without amputation has been performed primarily for NUM *in situ*,[10-14] emphasizing close clinical follow-up because of a reported case of recurrence of NUM *in situ*.[11,15] In a report targeting thicker NUM, Rayatt et al[16] performed FS to excise up to the periosteum or peritendon level for patients with 0.9- to 4-mm BT. Recurrence was found in the patient with 4-mm BT, but none in the patients with 0.9-, 1.5-, and 3.0-mm BT during the 77- to 118-month follow-up period. Other authors have reported no recurrence during the follow-up period after FS, Cohen et al[17] in patients with 0.2- and 0.6-mm BT, Smock et al[18] in a patient with 1.2-mm BT, and Sureda et al[19] in patients with 0.2- and 0.15-mm BT. Regarding prognosis, one study reported no difference in recurrence between FS and amputation in patients with 1- to 2-mm BT. However, to date, no controlled studies have been found on the effectiveness of FS for thick melanomas. In addition, the data supporting FS of thick melanomas are less robust because many retrospective studies defaulted to digital amputation for thicker melanomas.[20]

We tried to present a cut-off value of BT for performing FS in a range that does not affect the prognosis in terms of recurrence and distant disease. Among various thresholds for BT, 0.8 mm was found to be an optimal cut-off point for stratifying the risk of recurrence and distant disease in NUM. In addition, when 0.8 mm was used as a criterion for determining the surgical strategy, instead of 0.5 mm, amputation could be spared without losing the Youden index and NPV.

This study also found that male sex, greater BT, higher T stage, an amelanotic color, ulcers, and nodules were associated with a greater risk of

recurrence or distant disease in NUM. Our results provide a basis for predicting tumor progression clinically. Previous reports have suggested that volar involvement is associated with a poor prognosis,[21] but this association was not significant in our analysis. However, our results were consistent with previously identified poor prognosis factors of acral melanoma such as ulcers,[22] amelanotic color,[23,24] male sex,[7] and greater T stage.[7] In the case of nodular melanoma, a high hazard ratio was shown even after BT adjustment, presumably because the weight of the nodule itself acts as mechanical stress and affects the surrounding lymphatic vessels.

This study is limited by its retrospective nature and insufficient sample size to draw statistical conclusions from. Specifically, the sample size limited the ability to adjust for several confounders associated with melanoma recurrence. Therefore, the lack of confounding control may have yielded potentially biased estimates. In addition, the operator-dependent nature of FS may affect recurrence and survival outcomes. However, this study presents a cut-off value for performing FS that can help determine the surgical method and predict patient prognosis, which had rarely been studied before.

In conclusion, FS can be considered as a treatment for NUM with a BT of less than 0.8 mm, providing an amputation-sparing benefit. However, in the case of NUM with risk factors for recurrence, such as amelanotic color, ulcers, or nodules, patient counselling and a close follow-up are required.

Conflicts of interest

None disclosed.

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