
Functional surgery versus amputation for in situ or minimally invasive nail melanoma: A meta-analysis



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Background: Evidence on whether functional surgery is not inferior to amputation for the treatment of in situ or minimally invasive (Breslow thickness ≤ 0.5 mm) nail melanoma is limited.

Objective: To investigate the difference in local recurrence between the 2 interventions for in situ or minimally invasive nail melanoma using available published studies.

Methods: We performed systematic search on PubMed, Embase, Cochrane Library, trial registers, and grey literature databases from inception to June 28, 2018. We included observational studies with at least 5 patients with in situ or minimally invasive nail melanoma. Main outcome was local recurrence.

Results: The odds ratio synthesized from 5 studies including 109 patients (88 functional operations and 21 amputations) was 1.57 (95% confidence interval, 0.31-8.00).

Limitations: Small sample size and possible interstudy heterogeneity.

Conclusions: Our meta-analysis revealed no difference in local recurrence between the 2 interventions. Considering the functional deficit after amputation, conservative surgery should be the treatment of choice for in situ or minimally invasive nail melanoma. (J Am Acad Dermatol 2019;81:917-22.)

Key words: amputation; conservative surgery; functional surgery; melanoma; melanoma in situ; meta-analysis; nail disease; recurrence.

Nail melanoma (NM) is a variant of cutaneous melanoma that occurs in the nail unit of the fingers and toes.^{1,2} Amputation at various levels had been traditionally recommended as the treatment of choice for NM.³ However, recent studies have shown that functional surgery (FS) is a safe treatment modality with superior functional and cosmetic outcome compared with amputation, particularly for NM in situ (NMIS) and minimally invasive NM (MINM) (≤ 0.5 mm).⁴ We performed a meta-analysis to elucidate whether local recurrence after FS is significantly different from that after amputation in NMIS or MINM.

METHODS

Literature search

We performed a systematic search and meta-analysis based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) and MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines.^{5,6} PubMed, Embase, Cochrane Library, trial registers (www.clinicaltrials.gov), and gray literature databases (www.greynet.org, www.ntis.gov, and www.cadth.ca) were searched from inception to June 28, 2018, by 2 of the investigators (G.J. and S.I.C.) and an experienced librarian (E.-S.P.). Search terms were “(melanoma

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Drs Jo and Cho authors contributed equally to this work.

Funding sources: None.

Conflicts of interest: None disclosed.

This study was presented as a poster at the 14th European Association of Dermato-Oncology Congress and 9th World Meeting of Interdisciplinary Melanoma/Skin Cancer Centers, Barcelona, Spain, November 6-9, 2018.

Accepted for publication June 9, 2019.

Reprints not available from the authors.

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Published online June 13, 2019.

0190-9622/\$36.00

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<https://doi.org/10.1016/j.jaad.2019.06.012>

and (nail or subungual)) and (((en bloc or wide or local) and (excision)) or (total nail and excision) or ((functional or conservative) and surgery) or disarticulation or amputation) and (recurrence or metastasis or survival).” Bibliographies of articles subjected to a full-text review were checked for additional relevant studies. Only human studies reported in English were included.

Eligibility criteria

We developed our eligibility criteria before the literature search (Table I) Because there were no eligible randomized controlled trials, we selected observational studies, including case series with at least 5 patients with NMIS or MINM. The final enrolled studies included studies with 2 interventions (any kind of FS ≥2 patients and amputation at any level ≥2 patients) with a mean or median follow-up

period of >6 months. We excluded studies in which data of our interest were not extractable or studies with inappropriate designs, such as review articles.

Study selection and data extraction

Two investigators (G.J. and S.I.C.) independently screened the titles and abstracts of the retrieved articles and then assessed the full text for eligibility (Fig 1). After inclusion, the 2 investigators independently extracted data, including intervention, recurrence, disease-free time, and follow-up period. Any discrepancy was resolved through a consensus meeting with the third investigator (J.H.M.).

Risk of bias and quality assessment

Comparative studies were assessed using the risk of bias assessment tool for nonrandomized studies (RoBANS).⁷ We rated studies

CAPSULE SUMMARY

- Nail melanoma should be treated by complete surgical excision.
- Our meta-analysis showed no significant difference in local recurrence between functional surgery and amputation for in situ or minimally invasive nail melanoma; therefore, functional surgery should be the first treatment for in situ or minimally invasive nail melanoma.

Table I. Inclusion and exclusion criteria: participants, interventions, comparators, outcomes, time, setting, and study designs (PICOTS-SD)

Parameters	Inclusion criteria	Exclusion criteria
Participants	Studies with at least 5 participants with a diagnosis of nail unit melanoma in situ or minimally invasive melanoma (Breslow thickness ≤0.5 mm) based on histopathologic examination.	<ol style="list-style-type: none"> 1. Studies without participants with melanoma in situ or minimally invasive melanoma of the nail unit diagnosed with histopathologic examination. 2. Data of nail unit melanoma in studies were presented only as a part of the whole data, such as acral lentiginous melanoma or nail disease, but could not be separated from the whole data.
Interventions	Articles including both interventions (any functional surgery ≥2 cases and digital amputation at any level ≥2 cases).	<ol style="list-style-type: none"> 1. No clear description of the surgical procedures. 2. Participants without previous treatment or any combination treatment could not be separated from the whole data.
Comparators	All studies dealing with both interventions	None
Outcomes	Any recurrence	<ol style="list-style-type: none"> 1. Studies without information about any recurrence. 2. Outcomes based on stage and surgical method could not be separated from the whole data.
Time	Mean or median follow-up period >6 months	Mean or median follow-up period ≤6 months
Setting	Any setting	No exclusion criteria
Study designs	Any study design	Review articles, economic evaluations, editorials, opinion pieces, abstract only, or meeting reports

Abbreviations used:

CI:	confidence intervals
FS:	functional surgery
MINM:	minimally invasive nail melanoma
NM:	nail melanoma
NMIS:	nail melanoma in situ
OR:	odds ratio
RoBANS:	Risk of Bias Assessment tool for Non-randomized Studies

Statistical analysis

We calculated the effect sizes as odds ratios (ORs) with 95% confidence intervals (CIs) between FS and amputation for comparative studies. Statistical heterogeneity was calculated using I^2 statistics. We used a random-effects model because there could be heterogeneity in surgical methods. The meta-analysis was performed using R 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) statistical software. Subgroup analyses were performed for NMIS patients only. Publication bias was assessed using the Egger regression test.

as follows: no “high,” low risk of bias; 1 “high,” moderate risk of bias; 2 “high,” high risk of bias; and ≥ 3 “high,” extremely high risk of bias.

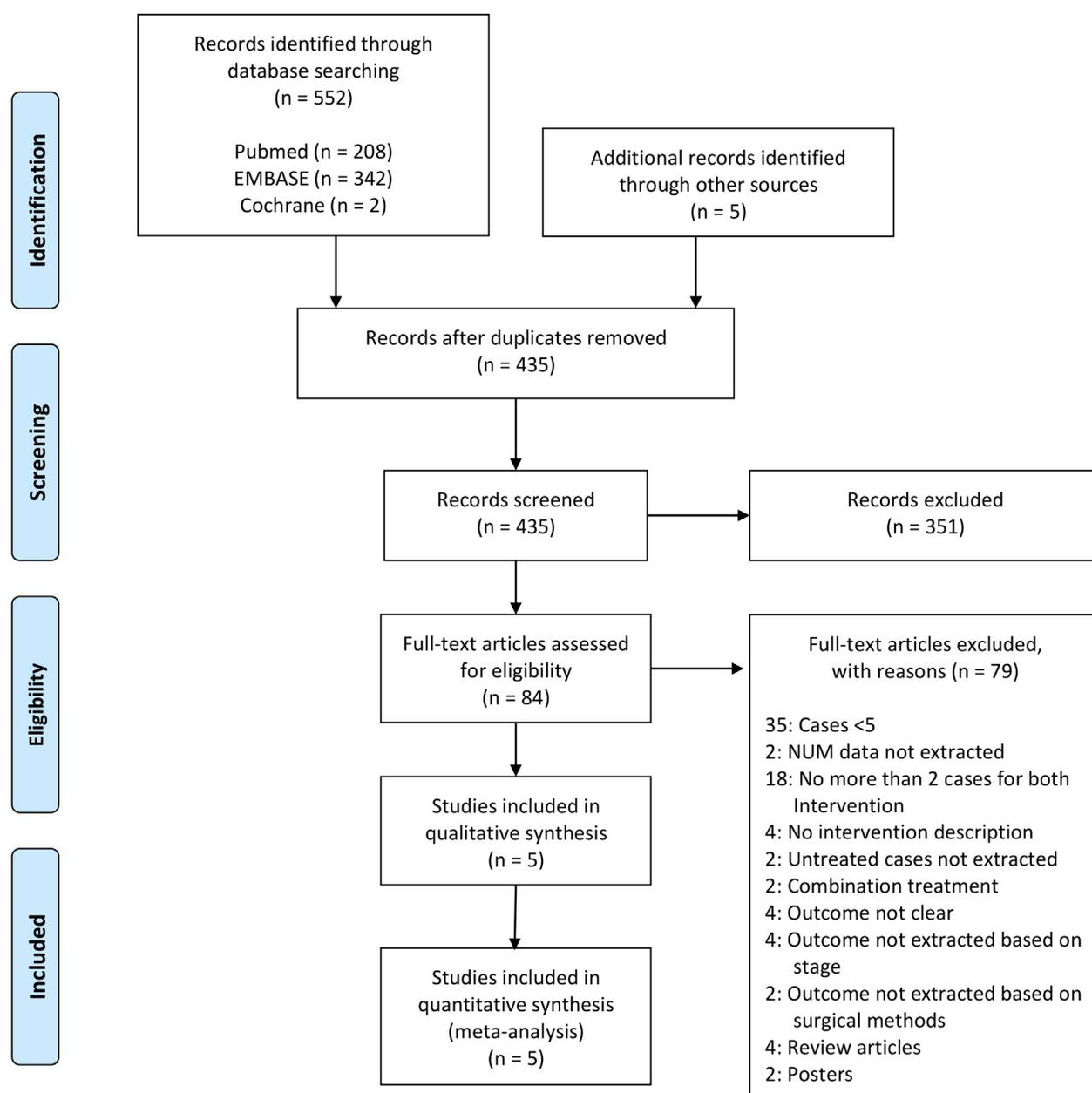


Fig 1. Flow diagram (search date: June 28, 2018).

Table II. Characteristics of included studies

Study	Year, setting	NMIS/MINM	Age	Sex	Digit	Intervention	Margin or level of amputation	Evolution	Local recurrences	Death	Follow-up
			Mean (range), y	F/M	Finger/toe						Mean (range), mo
High et al ⁸	2004, United States	7 NMIS	56 (34-87)	5/2	5/2	4 MMS only	NS	1 AMH at 5 mo → partial DA	1/4	0	24 (10-38)
						3 MMS → partial DA	Partial DA	...	0/3	0	
Cohen et al ⁹	2008, United States	8 NMIS, 1 MINM (40 others)	NS	NS	NS	4 EBENU	1 cm in 1 MINM, 5 mm in 2, wide in 3, 3 mm in 1	1 in situ at 18 mo → DA	1/4	NS	NS
						2 Amp at initial treatment, 3 EBENU → margin (+) → Amp	NS in 3, DA in 2	1 in situ at NS → WLE & SG	1/5	NS	
Park et al ¹⁰	2016, Korea	18 NMIS	48 (27-64)	10/8	13/5	16 EBENU with/without free flap	NS	...	0/14*	0	16 (2-51)
Goettmann et al ¹¹	2018, France	63 NMIS	51 (20-86)	44/19	52/11	2 DA	DA	...	0/2	0	120 (3-273)
						56 EBENU with SIH, FTSG, or flap	5 mm	1 in situ at 24 mo → DA	2/56	0	
Montagner et al ¹²	2018, Brazil	13 NMIS, 1 MINM (7 others)	47 (5-81)	7/7	6/8	7 DA	DA	...	0/7	0	79 (26-175)
						10 EBENU with SIH	5 mm	1 in situ at 11 mo → EBENU	2/10	0	
						4 DA	DA	...	0/4	0	

AMH, Atypical melanocytic hyperplasia; Amp, amputation; DA, distal amputation; EBENU, en bloc excision of the nail unit; F, female; FS, functional surgery; FTSG, full-thickness skin graft; inv, invasive; M, male; MINM, minimally invasive nail melanoma; MMS, Mohs micrographic surgery; NMIS, nail melanoma in situ; NS, not specified or not extractable; PAF, paronychia advancement flap; SG, skin graft; SIH, secondary intention healing; SLNB, sentinel lymph node biopsy; WLE, wide local excision.

*Patients with no follow-up information were excluded.

Table III. Risk of bias reported for each domain using the Risk of Bias Assessment tool for Nonrandomized Studies (RoBANS)

Study	Study design	1. Selection of participants	2. Confounding variables	3. Measurement of exposure	4. Blinding of outcome	5. Incomplete outcome data	6. Selective reporting
High et al ⁸	Retrospective review*	Low	Low [†]	Low	Low	Low	Low
Cohen et al ⁹	Retrospective review*	Low	High	Low	Low	Low	Low
Park et al ¹⁰	Retrospective case-control study	Low	Low [†]	Low	Low	Low	Low
Montagner et al ¹²	Retrospective review*	Low	Low [†]	Low	Low	Low	Low
Goettmann et al ¹¹	Retrospective review*	Low	High	Low	Low	Low	Low

*Studies with a design other than a case-control study were assessed using the RoBANS tool for retrospective cohort studies.

[†]Rated as low because recurrence and confounding variables were described.

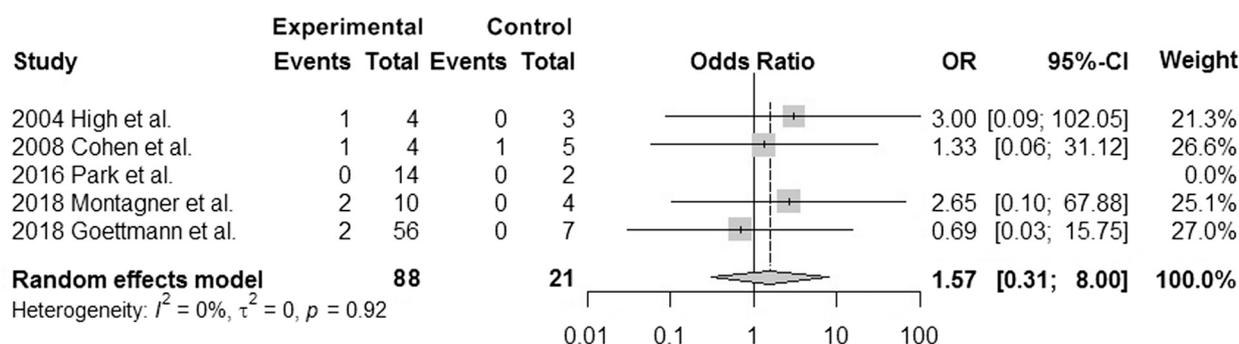


Fig 2. Forest plot shows the odds ratios (OR) of local recurrence. A random-effects model was used to compare the ORs between functional surgery and amputation. The *solid squares* indicate the mean difference and are proportional to the weights used in the meta-analysis. The *horizontal lines* represent the 95% confidence interval (CI). The *solid vertical line* indicates no effect. The *dashed line* indicates the summary measure, with the associated *diamond* indicating the weighted mean difference and the *lateral tips* of the diamond indicating the associated 95% CIs.

RESULTS

Literature search and study characteristics

The search process is detailed in Fig 1. Finally, 5 studies with 109 patients were included (Table II).⁸⁻¹² The risks of bias of the 5 studies are reported in Table III.

Meta-analysis of comparative studies between FS and amputation

The meta-analysis of 5 studies with 109 patients (88 FS and 21 amputations) revealed that the synthesized OR was 1.57 (95% CI, 0.31-8.00) (Fig 2).⁸⁻¹² There was no statistical heterogeneity ($I^2 = 0\%$). The risk of publication bias estimated using the Egger regression test was not significant ($P = .478$). Subgroup analysis including NMIS only (107 patients) showed an OR of 1.81 (95% CI, 0.35-9.31) without heterogeneity ($I^2 = 0\%$).

DISCUSSION

The ideal surgical method for NM has been controversial for several decades. In 1965, Das

Gupta and Brasfield¹³ reported a 25-year review of 34 cases of NM at a single center. All of the patients were treated using different forms of amputation. Among them, 3 patients who were treated with a conservative form (phalangeal) of amputation experienced recurrence within 18 months and did not survive for 5 years. However, 7 of 8 patients with major amputation (metacarpo- or metatarsophalangeal amputation) survived for ≥ 5 years. Although the results of the study were limited by the small sample size and lack of detailed data such as Breslow thickness, the authors suggested that any type of conservative amputation is not suitable for NM. They emphasized that NM requires adequate amputation. Traditionally, the surgical management of NM has been amputation of the involved digit.³

In 2003, Moehrle et al¹⁴ showed that FS did not differ from distal phalanx amputation in recurrence and survival in 62 patients with stage I or II melanoma. Thereafter, FS has been widely used, particularly for NMIS or MINM, and relevant data have been published.^{4,11} To date, however, there has



Fig 3. Nail melanoma in situ. **A**, Total melanonychia with subtle Hutchinson sign on the hyponychium. **B**, View 24 months after functional surgery. Reconstruction was performed using a full-thickness skin graft.

been no randomized controlled trial. All possible evidence is based on observational studies, some of which are studies including both interventions. Most of the previous studies were investigations of patients with heterogeneous prognostic factors, such as lymph node metastasis or Breslow thickness. Therefore, it is difficult to determine the difference in prognosis according to the interventions.³

We intended to elucidate the impact of FS and amputation on the prognosis of NMIS or MINM. Because lymph node status or Breslow thickness are variables that may have greater impact than interventions, we limited the participants to patients with NMIS or MINM who were recently considered to be appropriate candidates for FS. Our meta-analysis investigating 5 studies with 109 patients revealed no statistically significant difference in postoperative local recurrence between FS and amputation (OR, 1.57; 95% CI, 0.31-8.00). In addition, we could not find metastasis or mortality cases due to NMIS or MINM from the included studies. From these findings, it seems that FS should be the treatment of choice for NMIS or MINM (Fig 3).

Limitations

Our study has some limitations. First, this study did not include controlled trials. We analyzed only retrospective observational studies.

Second, 5 studies were included; therefore, the power was low when the OR was synthesized.

Third, the follow-up duration of the enrolled studies was short (minimum 6 months), and we did not include single-treatment series.

Fourth, in some aspects, FS is more complicated than amputation due to the unique nail anatomy and the subsequent intricacies in obtaining clear surgical margins. Therefore, this may limit the wide application of FS to surgeons without sufficient experience.

Despite these limitations, given that NMIS or MINM are rare conditions for which no controlled trial has been performed, this study provides meaningful information for physicians who treat patients with melanoma.

CONCLUSION

Our meta-analysis revealed that there is no significant difference in the recurrence rate between FS and amputation. Therefore, conservative surgery is recommended as the first-line treatment option to avoid severe functional deficit after amputation. To produce more solid evidence on this topic, future data with more observational studies with large sample size or randomized controlled trials are necessary.

We thank Eun-Sun Park for support with the literature search.

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