Systematic review and meta-analysis of local recurrence rates of head and neck cutaneous melanomas after wide local excision, Mohs micrographic surgery, or staged excision

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Background: Prospective trials have not compared the local recurrence rates of different excision techniques for cutaneous melanomas on the head and neck.

Objective: To determine local recurrence rates of cutaneous head and neck melanoma after wide local excision (WLE), Mohs micrographic surgery (MMS), or staged excision.

Methods: A systematic review of PubMed, EMBASE, and Web of Science identified all English case series, cohort studies, and randomized controlled trials that reported local recurrence rates after surgery for cutaneous head and neck melanoma. A meta-analysis utilizing a random effects model calculated weighted local recurrence rates and confidence intervals (CI) for each surgical technique and for subgroups of MMS and staged excision.

Results: Among 100 manuscripts with 13,998 head and neck cutaneous melanomas, 51.0% (7138) of melanomas were treated by WLE, 34.5% (4826) by MMS, and 14.5% (2034) by staged excision. Local recurrence rates were lowest for MMS (0.61%; 95% CI, 0.1%-1.4%), followed by staged excision (1.8%; 95% CI, 1.0%-2.9%) and WLE (7.8%; 95% CI, 6.4%-9.3%).

Limitations: Definitions of local recurrence varied. Surgical techniques included varying proportions of invasive melanomas. Studies had heterogeneity.

Conclusion: Systematic review and meta-analysis show lower local recurrence rates for cutaneous head and neck melanoma after treatment with MMS or staged excision compared to WLE. (J Am Acad Dermatol 2021;85:681-92.)

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INTRODUCTION

The purpose of melanoma excision is to prevent local recurrence and progression.[1,2] Local recurrence may worsen prognosis,[3,4] increase surgical costs and complexity,[5,6] and heighten patient anxiety.[7-9] The risk for local recurrence is higher after excision of cutaneous melanomas on the head and neck,[10-12] where approximately 20% of melanomas arise.[13-17]

CAPSULE SUMMARY

- Prospective trials have not compared local recurrence rates for different excision techniques used to treat cutaneous head and neck melanomas.
- Systematic review of retrospective data shows lower local recurrence rates of cutaneous head and neck melanomas after Mohs micrographic surgery or staged excision versus wide local excision.

Although wide local excision (WLE) has been the standard technique for melanoma surgery, Mohs micrographic surgery (MMS)[18] and staged excision[19] are increasingly used to treat melanomas at high risk for local recurrence.[20] MMS and staged excision aim to lower local recurrence rates by using comprehensive microscopic margin assessment to detect and remove subclinical melanoma prior to reconstruction. Subclinical melanoma is more common for both invasive and in situ melanomas on the head and neck.[21,22] In its latest guidelines for cutaneous melanoma, the National Comprehensive Cancer Network indicates that comprehensive histologic assessment of margins with MMS or staged excision should be considered "for large and/or poorly defined" in situ or minimally invasive melanomas (<0.8 mm) associated with high cumulative sun damage.[23]

Prospective randomized controlled trials have not compared local recurrence rates after WLE versus MMS or staged excision for head and neck melanomas. We hypothesized that local recurrence rates are lower after MMS or staged excision versus WLE. This systematic review and meta-analysis evaluates published local recurrence rates after WLE, MMS, or staged excision of cutaneous head and neck melanoma.

MATERIALS AND METHODS

Eligibility criteria

A priori inclusion and exclusion criteria were established to identify studies reporting local recurrence rate after surgery of cutaneous melanoma of the head and neck (Supplemental Table I; available via Mendeley at https://doi.org/10.17632/d5gkm3tk6p.1).

Inclusion criteria were published English-language case series, cohort studies, or randomized controlled trials that specified surgical technique and reported local recurrence rates for ≥10 cutaneous head and/or neck melanomas. Mucosal melanomas were excluded. Cases were also excluded if adjuvant local treatment such as radiation, electrodessication, or imiquimod was used. No restrictions were placed on tumor depth, systemic treatment use, publication date, or follow-up time. Studies were excluded if data were duplicated in another publication. Reviews, abstracts, and unpublished studies were excluded.

The primary outcome was local recurrence rate. Studies were excluded if local recurrence could not be distinguished for melanomas on the head and neck versus other locations.

Study selection

A literature search of the PubMed, EMBASE, and Web of Science databases was conducted on November 5, 2018 using search terms detailed in Supplemental Table II (available via Mendeley at https://doi.org/10.17632/d5gkm3tk6p.1). Two investigators (PGB and JMB) independently reviewed all search results for inclusion and exclusion criteria. If investigators disagreed on article inclusion, they convened to reach consensus. Included studies were reviewed for references that were not captured in the search. Cohen's kappa was calculated to provide the level of inter-reviewer agreement.

Data extraction

Two investigators (PGB and JMB) independently extracted data from included studies. Data were recorded on Microsoft Excel (Microsoft Corp). If reviewers disagreed on data, they convened to reach consensus. A third investigator (CJM) independently verified the final references and data. All 3 investigators (PGB, JMB, and CJM) convened to resolve any disagreements.

Abbreviations used:

CI: confidence interval
IHC: immunohistochemistry
MIS: melanoma in situ
MMS: Mohs micrographic surgery
WLE: wide local excision

Data items

Extracted data included surgical technique (WLE, MMS, or staged excision), number of cutaneous head and neck melanomas, local recurrence rate, follow-up time, anatomic location, invasion status, and year(s) of surgery. Cases without follow-up information were excluded from analysis.

WLE was defined as conventional excision with microscopic margin assessment on a separate day by a dermatopathologist using formalin-fixed, paraffin-embedded breadloafed sections. MMS was defined as excision with same-day complete circumferential peripheral and deep frozen section microscopic margin assessment by the surgeon prior to reconstruction. Subcategories were: 1) MMS with immunohistochemical (IHC) stains, 2) MMS without IHC, and 3) MMS with and without IHC. The latter pertained to series that did not segregate local recurrence for patients who were treated with IHC versus without IHC.

Staged excision was defined as excision with microscopic margin assessment by the surgeon or dermatopathologist using formalin-fixed, paraffin-embedded sections prior to reconstruction. Variations of staged excision (collarette, contour, perimeter, polygon, spaghetti, square, slow-Mohs, and mapped serial excision) were grouped into 2 subcategories: 1) complete peripheral microscopic margin evaluation, defined by *en face* microscopic margin assessment of 100% of the peripheral margin or 2) partial peripheral microscopic margin evaluation, defined by breadloafed sectioning to examine a portion of the peripheral margin. The deep margin of the central tumor was typically evaluated with breadloafed vertical sections.

Invasion status, if specified, was classified as melanoma in situ (MIS) or invasive melanoma (extending deep to the epidermis). Invasive melanomas could not be stratified further due to inconsistent reporting of tumor depth and evolving staging criteria over time.

Data synthesis

Statistical analysis. The primary outcome for both MIS and invasive melanoma was overall local recurrence rate after WLE, MMS, or staged excision of cutaneous head and neck melanoma using a DerSimonion and Laird random effects model. Subgroup analysis assessed local recurrence rates after WLE, MMS, and staged excision of MIS versus invasive melanoma. For studies reporting local recurrence rates for multiple techniques, the populations for each technique were analyzed separately.

Preplanned secondary analyses assessed local recurrence rates for subcategories of MMS (with IHC, without IHC, or with and without IHC) and staged excision (complete or partial peripheral microscopic margin evaluation).

Freeman-Tukey double arcsine transformation was used because some studies had local recurrence rates at or near zero.[24] Heterogeneity of local recurrence rates across studies was evaluated using Cochran's Q statistic and I^2 index. A P value of $<.05$ was considered statistically significant heterogeneity. Forest plots and calculations were generated with Open Meta-Analyst (Brown University).

Risk of bias assessment. Risk of bias in comparative studies was assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.[25] This tool assesses studies across 7 domains of potential bias: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. In each domain of the ROBINS-I tool, assessment focused on whether results were adjusted to account for each potential source of bias. Single-arm studies were considered at high risk of bias.

RESULTS

Overview details

Figure 1 details the screening and selection process. Of 2197 abstracts reviewed, 100 manuscripts with 13,998 head and neck cutaneous melanomas published between 1972 and 2018 were included.[18,19,26-123] Cohen's kappa was 0.62. According to the ROBINS-I tool, all studies (5 comparative[39,42,54,85,92] and 95 single-arm) had high risk for bias. All included studies were either case series or cohort studies, No randomized controlled trials met the inclusion criteria. Details of each manuscript are included in Mendeley Supplemental Table III (available via Mendeley at https://doi.org/10.17632/d5gkm3tk6p.1). Table I summarizes the data for these manuscripts.

Of the 100 manuscripts selected, 28% (28) provided a definition for local recurrence. Definitions varied from recurrence "in the scar" (n = 1)[18]; "within or adjacent to the scar" (n = 3)[96,97,101]; within "2 cm"

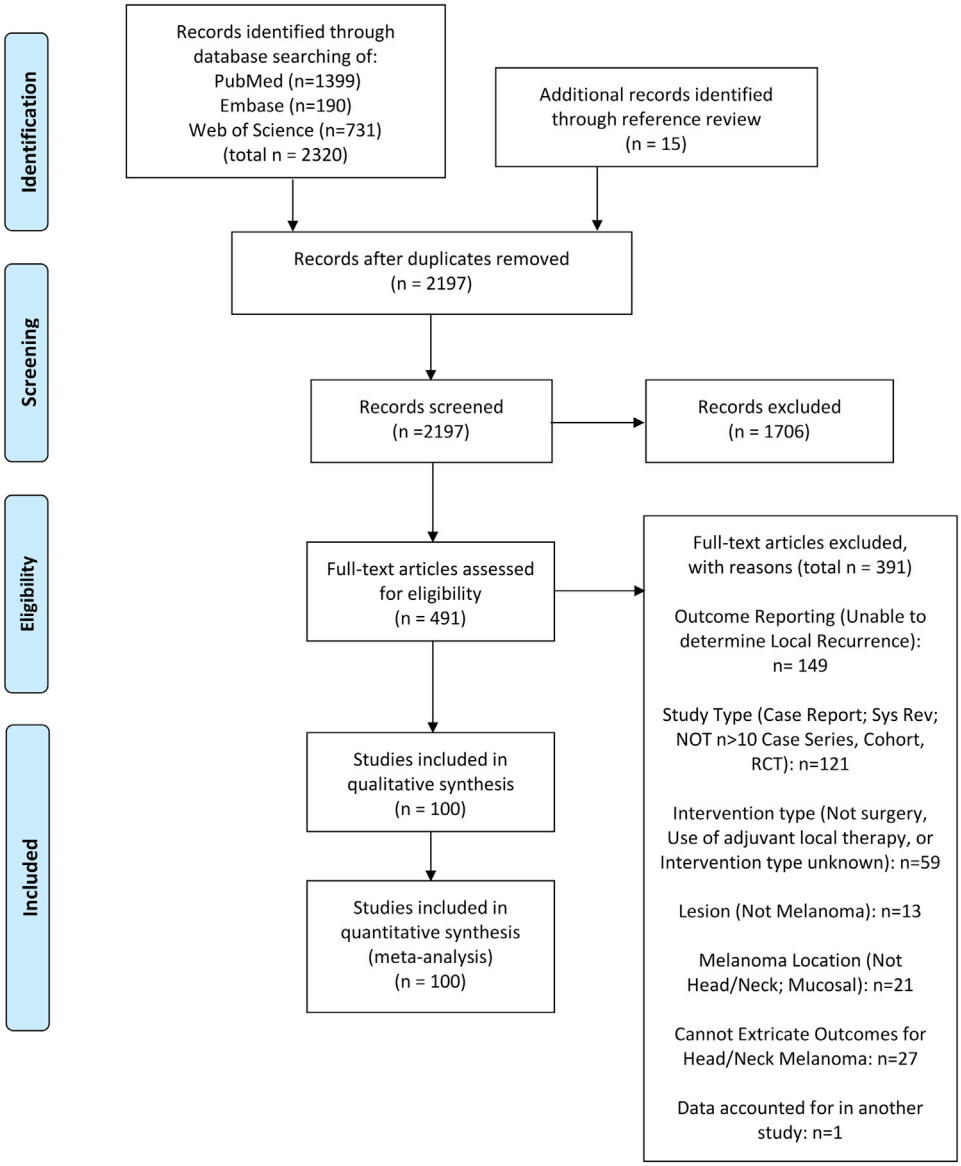

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of the search process.

(n = 7),[39,49,63,69,99,104,112] "3 cm" (n = 1),[71] or "5 cm" (n = 4) of the scar[28,38,64,102]; "at the primary/original site" (n = 8)[40,41,46,48,59,66,73,89]; or "recurrence that was not nodal/regional or distal" (n = 4).[58,61,65,67] Details for local recurrence definitions by surgical technique are available in Supplemental Table IV (available via Mendeley at https://doi.org/10.17632/d5gkm3tk6p.1).

Comparison of population characteristics

Among the 13,998 cases reviewed, the most common technique was WLE (60 references, 51.0% [7138] of cases),[26-85] followed by MMS (22 references, 34.5% [4826] of cases),[18,39,42,54,85-102] and staged excision (23 references, 14.5% [2034] of cases).[19,92,103-123]

The proportion of invasive melanomas was higher in the WLE group (96% [5734 of 5955 cases]) compared to MMS (30% [926 of 3080 cases]) or SE (27% [416 of 1539 cases]). The weighted mean follow-up time was longest for staged excision (66.5 months), followed by WLE (52.8 months) and MMS (46.9 months).

Subcategories of MMS and staged excision

Studies for MMS varied in their use of IHC. Of the 4826 cases treated using MMS, 50.0% (2411) were treated with IHC,[18,93-98] 15.2% (732) without

Table I. Summary results of meta-analysis showing data and local recurrence rates by technique and invasion status

Technique	Articles n	Mean follow-up (months)[†]	Overall n	Overall LR % (95% CI)	Overall I^2 %	MIS n	MIS LR % (95% CI)	MIS I^2 %	Invasive n	Invasive LR % (95% CI)	Invasive I^2 %
WLE	60	52.8	7138	7.81 (6.4-9.3)	72.1*	141	3.28 (0.0-10.2)	10.3	4255	7.65 (5.8-9.7)	70.2*
MMS	22	46.9	4826	0.61 (0.1-1.4)	68.9*	2154	0.74 (0.3-1.4)	32.9	926	0.61 (0.0-1.9)	28.5
Without IHC	10	41.3	732	3.37 (0.5-7.7)	74.8*	274	1.64 (0.2-3.8)	0.0	155	2.90 (0.4-6.8)	0.0
With IHC	7	38.2	2411	0.49 (0.2-0.9)	7.0	733	0.78 (0.2-1.7)	0.0	235	0.37 (0.0-2.1)	0.0
With and without IHC	5	60.5	1683	0.20 (0.0-1.2)	64.0*	1147	0.57 (0.0-1.5)	44.7	536	0.17 (0.0-2.2)	56.0
Staged excision	23	66.5	2034	1.84 (1.0-2.9)	20.0	1097	1.36 (0.3-2.8)	21.4	402	1.08 (0.0-4.0)	12.0
Complete[¶]	20	70.5	1786	1.68 (0.8-2.8)	18.0	1052	1.36 (0.2-3.1)	26.8	381	1.56 (0.0-5.5)	20.0
Partial	3	40.8	248	3.09 (0.3-7.8)	48.5	45	2.20 (n/a)[‡]	n/a[‡]	21	0 (n/a)[‡]	n/a[‡]
Total	100[§]	52.9	13,998	—[‖]	—[‖]	3392	—[‖]	—[‖]	5583	—[‖]	—[‖]

CI, Confidence interval; *IHC*, immunohistochemistry; *LR*, local recurrence rate; *MIS*, melanoma in situ; *MMS*, Mohs micrographic surgery; *n/a*, not applicable; *Partial*, partial peripheral microscopic assessment of margins; *WLE*, wide local excision.

*Statistically significant for $P < .05$.

[†]The mean follow-up was weighted by number of cases in each article reporting a mean follow-up time.

[‡]Contained only 1 study, so confidence interval could not be calculated.

[§]5 articles reported cases treated with techniques from more than 1 category.

[‖]The population sizes for MIS and invasive melanoma do not add up to the overall population size because it was not possible to distinguish local recurrence rates between MIS and invasive melanomas in some studies with mixed populations.

[¶]Complete peripheral microscopic assessment of margins.

IHC,[39,42,54,86-92] and 34.9% (1683) with or without IHC.[85,99-102] Among the 2034 cases treated with staged excision, 87.8% (1786) were evaluated with complete,[19,103-121] and 12.2% (248) with partial, peripheral microscopic margins.[92,122,123]

Overall local recurrence rates

Overall local recurrence rate was lowest for MMS (0.61% [95% CI, 0.1%-1.4%]), followed by staged excision (1.8% [95% CI, 1.0%-2.9%]) and WLE (7.8% [95% CI, 6.4%-9.3%]). Summary data are provided in Table I and forest plots are seen in Figs 2 to 4.

Within MMS subcategories, the local recurrence rate was 0.49% for MMS with IHC (95% CI, 0.18%-0.91%), 0.20% for MMS with and without IHC (95% CI, 0%-1.18%), and 3.37% for MMS without IHC (95% CI, 0.54%-7.72%). Table I and Mendeley Supplemental Figs 1 to 3 (available via Mendeley at https://doi.org/10.17632/d5gkm3tk6p.1) illustrate these data. Within staged excision subcategories, the local recurrence rate was 1.7% (95% CI, 0.79%-2.8%) for complete peripheral margin assessment versus 3.1% (95% CI, 0.32%-7.8%) for partial peripheral margin assessment. Table I and Supplemental Figs 4 and 5 (available via Mendeley at https://doi.org/10.17632/d5gkm3tk6p.1) illustrate these data.

For overall local recurrence rates, heterogeneity was significant for studies with WLE (I^2 = 72.1%, $P < .0001$) and MMS [all subgroups combined] (I^2 = 68.9%, $P < .0001$) and nonsignificant for staged excision (I^2 = 20.0%, P = .1933). For MMS subgroups, heterogeneity was significant for MMS without IHC (I^2 = 74.8%, P = .0004) and MMS with and without IHC (I^2 = 64.0%, P = .025) but was not significant for MMS with IHC (I^2 = 6.96%, P = .37).

Local recurrence rates by invasion status

Invasion status was available for 75.5% (10,574) of the 13,998 melanomas studied, of which 66.9% (7076 of 10,574) were invasive. It was not possible to distinguish local recurrence rates between MIS and invasive melanomas in some studies with mixed populations. However, local recurrence rates could be determined for 96.9% (3392) of 3498 MIS and 78.9% (5583) of 7076 invasive melanomas.

For invasive melanomas, local recurrence rates could be determined for 4255 cases treated with WLE; 926 treated with MMS; and 402 treated with staged excision. For these invasive melanomas, the local recurrence rate was lowest for MMS (0.61% [95% CI, 0%-1.85%]), followed by staged excision (1.08% [95% CI, 0%-4.04%]) and WLE (7.65% [95% CI, 5.83%-9.65%]). Table I provides summary data and Supplemental Figs 6 to 8 (available via Mendeley at https://doi.org/10.17632/d5gkm3tk6p.1) provide forest plots.

For MIS, local recurrence rates could be determined for 141 cases treated with WLE, 2154 treated with MMS, and 1097 treated with staged excision. For these MIS cases, the local recurrence rate was lowest

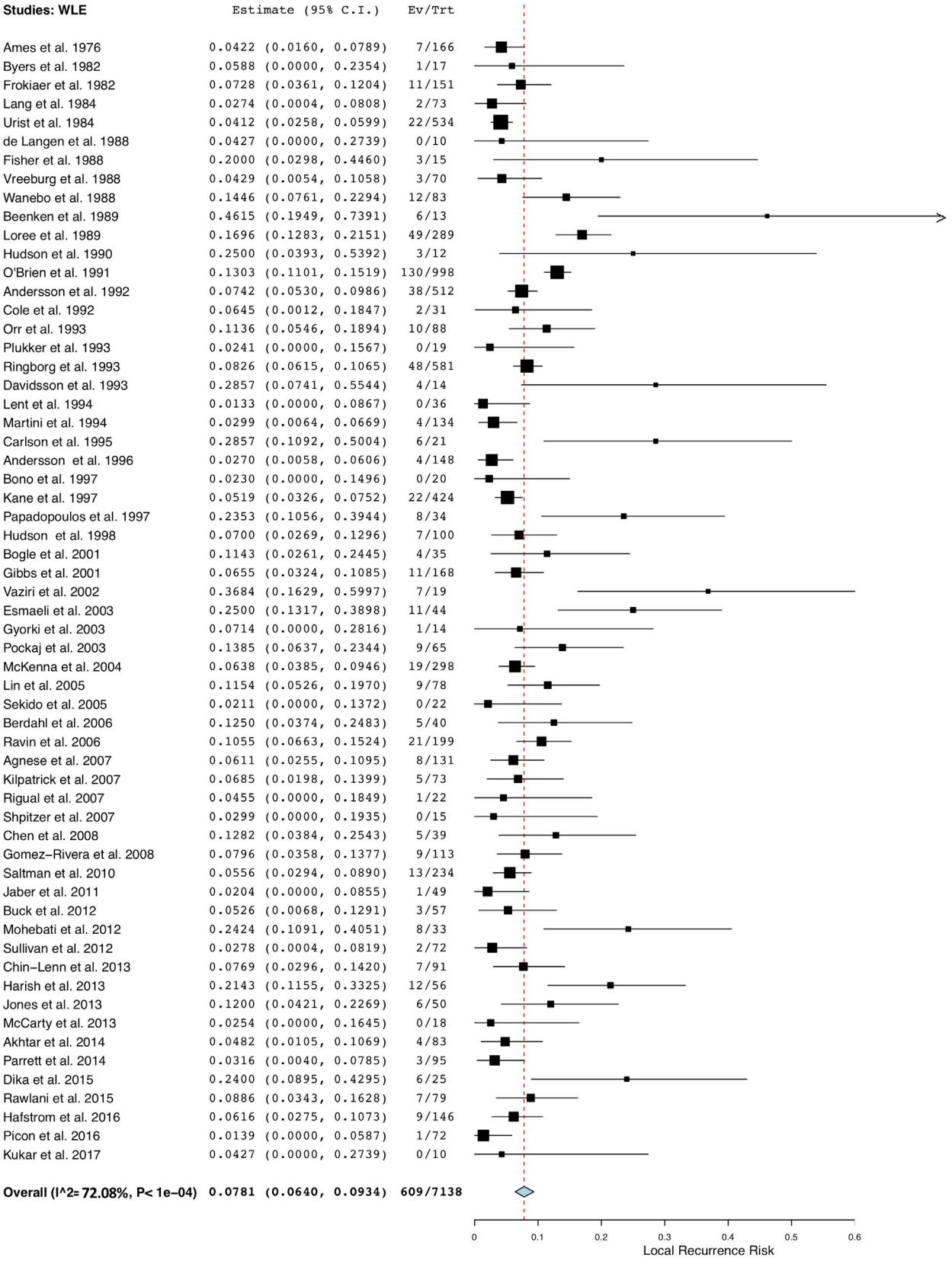

Fig 2. Forest plots of studies of WLE. *WLE*, Wide local excision.[26-85]

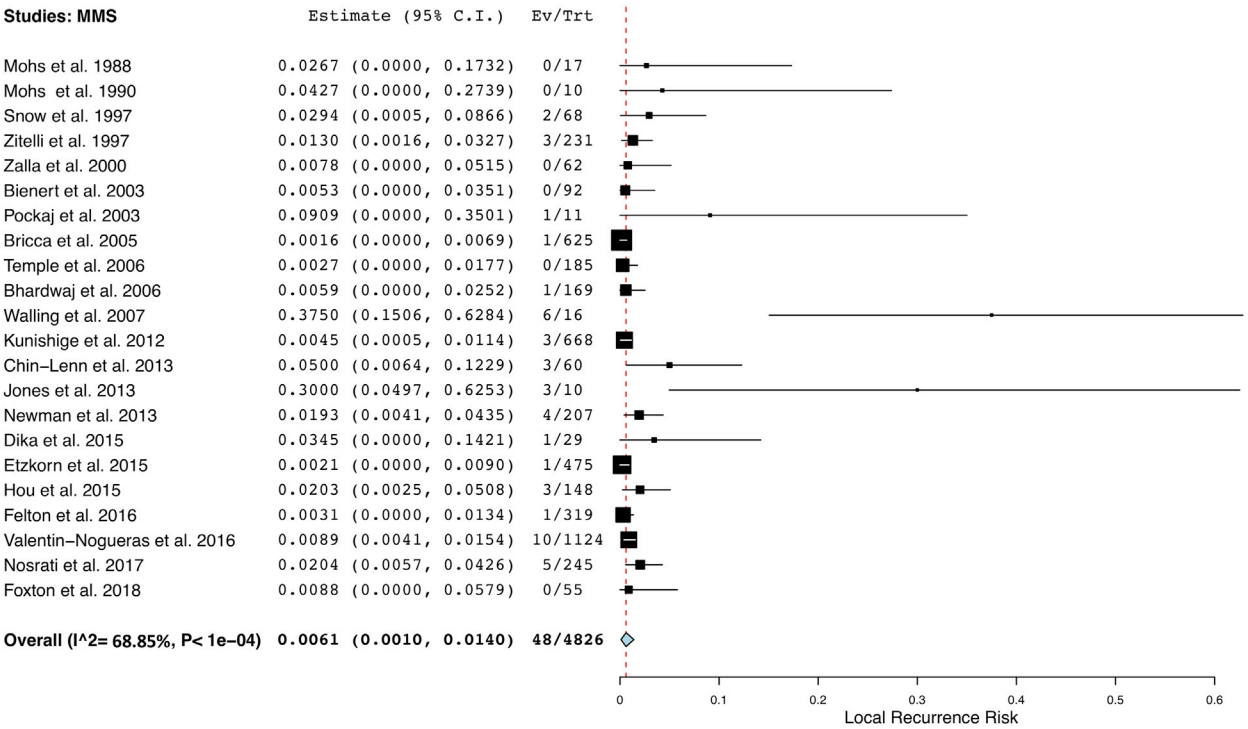

Fig 3. Forest plots of studies of MMS, including studies with, without, and with and without IHC.[18,39,42,54,85-102] *IHC*, Immunohistochemistry; *MMS*, Mohs micrographic surgery.

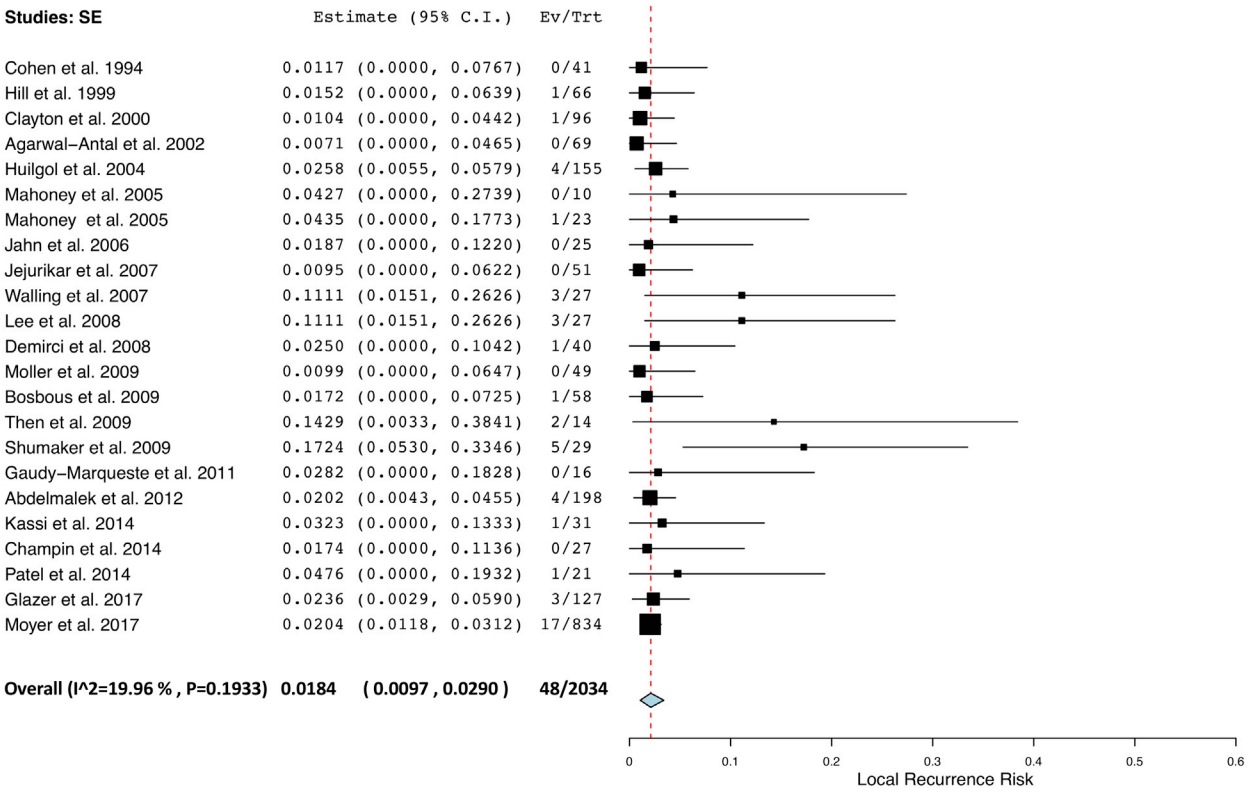

Fig 4. Forest plots of studies of SE, including studies with complete and partial peripheral margin assessment.[19,92,103-123] *SE*, Staged excision.

for MMS (0.74% [95% CI, 0.25%-1.42%]) followed by staged excision (1.30% [95% CI, 0.27%-2.83%]) and WLE (3.28% [95% CI, 0%-10.17%]). Table I provides summary data and Supplemental Figs 9 to 11 (available via Mendeley at https://doi.org/10.17632/d5gkm3tk6p.1) provide forest plots.

In subgroup analyses of MIS or invasive melanoma (Table I), heterogeneity was not significant for any surgical technique, except for WLE of invasive melanomas (I^2 = 70.2, $P < .0001$).

Local recurrence in comparative studies

Five studies compared 2 techniques. Four articles (n = 341 patients) compared local recurrence rates after WLE versus MMS (3 articles without IHC and 1 article with and without IHC). Secondary analysis of these 4 articles (Supplemental Fig 12 available via Mendeley at https://doi.org/10.17632/d5gkm3tk6p.1) showed that the local recurrence rate was lower for MMS, with a pooled odds ratio of 0.70 (95% CI, 0.20-2.49) and heterogeneity was nonsignificant (I^2 = 50.15%, P = .11).[39,42,54,85] However, the difference in local recurrence rates for these comparative studies was not statistically significant (P = .5801). Three of these 4 articles reported lower local recurrence rates after MMS and 1 reported a higher local recurrence rate after MMS, but this latter article exclusively evaluated ear melanomas and only 10 were treated with MMS (without IHC).[54] Analysis of MMS versus SE could not be performed, as only 1 study compared these techniques.[92]

DISCUSSION

This systematic review and meta-analysis compiles the largest data set for head and neck melanomas treated with WLE, MMS, or staged excision. These retrospective data show lower overall local recurrence rates with nonoverlapping CIs after treatment of cutaneous head and neck melanoma with MMS or staged excision compared to WLE. Subgroup analyses for MIS and invasive melanoma also show lower local recurrence rates after MMS or staged excision versus WLE. These retrospective data are important because current guidelines for WLE of melanoma are based on 6 randomized controlled trials[124-129] (n = 4231 randomized cases), which included only 27 (<1%) head and neck melanomas.[130] Until prospective data are available, meta-analysis of available data provides the best method to make rational, evidence-based treatment decisions.

This study has limitations and results should be interpreted with caution. One limitation is that the WLE cohort had a higher percentage of invasive melanomas compared to MMS or staged excision, and it was not possible to determine tumor stage or Breslow depth for all of the invasive melanomas. The WLE cohort may have had deeper melanomas that could have contributed to more local recurrences. However, the impact of tumor stage on local recurrence is uncertain. Whereas some studies show that higher stage melanomas have an increased risk for true local[10] and local satellite/in-transit recurrence,[131,132] others show no correlation between tumor stage and local recurrence.[12,19] In this analysis, local recurrence rate was lower after MMS or staged excision versus WLE for head and neck melanomas, whether evaluating MIS or invasive melanomas together or in subgroups (Table I).

Another limitation was missing or nonuniform definitions for local recurrence. The majority of studies in the 100 articles reviewed did not specify criteria for local recurrence; among the 28 that did specify criteria, definitions for local recurrence varied. Some definitions of local recurrence could include both true local recurrences and local satellite/in-transit recurrences. However, it is unlikely that local satellite/in-transit recurrences would account for meaningful differences in local recurrence rates because localized intralymphatic metastasis occur with a low overall rate of 16%[131] and with an even lower rate of 2%-11% as the site of first recurrence.[131-134] In addition, local satellite/in-transit recurrences are less common for melanomas arising on the head and neck versus the extremities.[131,134]

Another limitation was study heterogeneity, but our random effects model and subgroup analyses help minimize the effect of heterogeneity on the results. Although overall analysis showed significant heterogeneity for MMS and WLE, subgroup analysis for MIS and invasive melanomas showed nonsignificant heterogeneity for all techniques except WLE of invasive melanomas (I^2 = 70.2%, $P < .0001$). Overall local recurrence rates were inconsistent after WLE, ranging from 0 to 46%, and exceeded 5% in two thirds (40) of 60 WLE studies (Fig 2). Staged excision and MMS, particularly when performed with IHC, have lower heterogeneity and less variable local recurrence rates, possibly because microscopic margin-directed excisions are less dependent on clinical judgment.

CONCLUSION

In the absence of prospective comparative studies, meta-analysis of case series provides the best available evidence to compare surgical techniques[135-137] and to guide current practice. Although retrospective data have limitations, this systematic review and meta-analysis demonstrates lower local recurrence rates for cutaneous head and neck

melanoma after treatment with MMS or staged excision, compared to WLE.

Conflicts of interest

None disclosed.

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