Systematic Review and Meta-Analysis

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# Sentinel lymph node biopsy in head and neck cutaneous melanomas

## A PRISMA-compliant systematic review and meta-analysis

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**Abstract**

**Background:** Head and neck melanomas (HNMs) behave differently from cutaneous melanomas in other sites, and the efficacy of sentinel lymph node biopsy (SLNB) for patients with HNMs remains controversial.

**Methods:** Studies on prognosis following SLNB were included. The prognostic role of SLNB and other potential predictors were analyzed using pooled relative risk (RR) or hazard ratio (HR).

**Results:** Pooled statistics showed that SLNB improved overall survival of HNMs patients (HR = 0.845; 95% CI: 0.725–0.986; $P = .032$). The positive status of SN was proved as a risk factor of poor prognosis in HNMs (HR = 3.416; 95% CI: 1.939–6.021; $P < .001$). SLNB did not have significant correlation with lower recurrences (RR = .794; 95% CI: 0.607–1.038; $P = .091$).

**Conclusions:** SLNB is associated with better overall survival and the SN status is a promising risk factor of poor prognosis for HNMs patients.

**Abbreviations:** CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure, CQVIP = Chongqing Weipu Information Company, HNMs = head and neck melanomas, HR = hazard ratio, NOS = Newcastle-Ottawa Scale, OS = overall survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RR = relative risk, SLNB = sentinel lymph node biopsy, SN = sentinel lymph node.

**Keywords:** head and neck melanomas (HNMs), overall survival, recurrence, sentinel lymph node biopsy (SLNB), sentinel lymph node (SN) status

### 1. Introduction

Cutaneous melanoma is rare but one of the most lethal skin cancers.[1] Approximately 15% to 35% of cutaneous melanomas occur in head and neck[2] and are termed as head and neck melanomas (HNMs). There are various evidence suggesting that HNMs behave differently from melanomas in other skin site because of the multiple drains and complex structure of this region. Patients with HNMs have higher Clark level than those with trunk or extremity melanomas.[3,4] Garbe et al found that patients with HNMs have shorter disease-free periods, significantly referring to tumor thickness ranges,[5] and lower 10-year survival rates.[3,5,6] HNMs also have worse prognosis than melanoma originating from elsewhere.[7,8]

Prophylactic removal of all regional lymph nodes in patients with clinically node-negative melanoma was performed widely before sentinel lymph node biopsy (SLNB) was developed,[9] and it suggested that elective lymph node dissection does not confer considerable survival benefit to patients with melanoma.[10] Besides, elective lymph node dissection undoubtedly increases patients' economical and mental burdens because of the high risk of complications such as wound infections, and chronic lymphedema in particular.[10,11] The use of SLNB has flourished because it is less invasive and has become a preferred alternative.

The efficiency of SLNB and sentinel lymph node (SN) status has been proved in several studies.[12–14] However, the decision to perform SLNB for patients with HNMs needs more considerations. The lower rate of SLNB detection and positivity of patients with HNMs have been reported.[15,16] Besides, a higher false negative rate of SLNB for HNMs also has been found in several researches.[16–19] In addition, the efficacy of SLNB for patients with HNMs is still the concern in term of safety and high complication rate.[20] Therefore, the efficiency of SLNB for patients with HNMs remains controversial, and we need to pay

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more attention to evaluate the prognosis benefit of SLNB for patients with HNMs.

Given the lack of studies on the efficacy of SLNB for HNMs and the small sample size of existing researches, we sought to perform a meta-analysis to determine the prognostic effect of SLNB for patients with HNMs.

## 2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21]

### 2.1. Ethical approval

This present study did not involve human subjects, so ethical approval was not necessary and informed consent was not required.

### 2.2. Search strategy

We performed a systematic search of the PubMed, Embase, Web of Science, Chinese National Knowledge Infrastructure (CNKI), Wanfang, and Chongqing Weipu Information Company (CQVIP) databases up to August 2019 using the following terms: head or neck, cutaneous melanoma, HNMs, sentinel node biopsy, SNB or SLNB. The references of related studies were also considered as potential eligible studies.

### 2.3. Inclusion and exclusion criteria

Studies were included if they: (I) recruited patients with head or neck cutaneous melanoma; (II) investigated the association between SLNB and local recurrence, distant metastasis, or overall survival; (III) were published in English or Chinese. Studies were excluded if they: (I) were case reports, letters, reviews, or conference abstracts; (II) had insufficient data for meta-analysis; (III) performed SLNB on all included patients. Moreover, for studies with overlapping patient populations, we selected the study with the larger sample size to avoid duplication.

### 2.4. Quality assessment

The quality of each non-randomized study was assessed using the Newcastle-Ottawa Scale (NOS).[22] The NOS consists of 3 items with a maximum of 9 stars: selection, a maximum of 4 stars; comparability, 2 stars; and the ascertainment of either the exposure or outcome of interest, 3 stars. Studies with a NOS score of $\geq 5$ were considered high quality.

### 2.5. Data extraction

Two reviewers (ZYY, LCQ) reviewed the 5 eligible articles independently and extracted the data with a standard extraction table. The 2 reviewers reached agreement after discussion, and the following essential information was retrieved: the first author's last name, publication year, country of origin, ethnicity of patients, SLNB rate, SN status, and survival data with the corresponding variability.

### 2.6. Statistical analysis

We used the relative risk (RR) or hazard ratio (HR) and 95% confidence intervals (95% CI) to assess the survival benefit of SLNB in patients with HNMs; $P < .05$ was considered statistically significant. If the RR or HR were not reported explicitly, Kaplan–Meier curves were retrieved according to the method of Parmar.[21] Statistical heterogeneity was assessed with the chi square-based $I^2$ test and $Q$ statistic test. $I^2 < 50\%$ and pH $> 0.10$ indicated acceptable heterogeneity, following which a fixed effect model was used. Otherwise, there was significant heterogeneity, and a random effect model was used. Sensitivity and publication bias analyses were also performed by excluded each study sequentially. All calculations were performed using STATA version 12.0 (Stata Corporation, College Station, TX) and Review Manager V.5.3 (The Cochrane Collaboration, Software Update, Oxford, UK)

## 3. Results

### 3.1. Literature search and study characteristics

We eventually identified 5 studies[23–27] involving 7217 patients from an initial 4168 studies. Our systematic literature selection process was summarized in a flow chart (Fig. 1). All included papers obtained a mean NOS score of 6.4 (range, 5–8) referring to high quality of research, and the baseline information of eligible articles was also listed in Table 1.

### 3.2. Association between SLNB and overall survival of HNMs

All 5 studies including 3168 patients with HNMs accepted SLNB were included in the generation of the outcome and the heterogeneity of these included articles was acceptable (pH = 0.302; $I^2 = 17.60\%$). Our pooled statistics showed that SLNB was associated with a significant better overall survival in patients with HNMs (HR = 0.845; 95% CI: 0.725–0.986; $P = .032$). The result was shown in Figure 2 and Table 2.

### 3.3. Relationship between SLNB and recurrence as well as other clinical pathological characteristics of HNMs

There were total 3 studies[23–25] evaluating the correlation between SLNB and recurrences. According to the result of our meta-analysis (Fig. 3A, Table 2), we found there is a trend that SLNB might decrease the total recurrences of patients with HNMs (RR = 0.794; 95% CI: 0.607–1.038; $P = .091$; pH = 0.793; $I^2 = 0.00\%$). We further analyzed the effect of SLNB on satellite/intransit metastases, regional lymph node metastases as well as distant metastases respectively. No significant differences were found for satellite/intransit ($P = .876$; Table 2; Fig. 3B), regional lymph node metastases ($P = .185$; Table 2; Fig. 3C), or distant metastases ($P = .117$; Table 2; Fig. 3D).

We further investigated the other clinical pathological characteristics for patients with HNMs (Table 3), and our pooled results showed that ulceration indicated poorer outcome of patients with HNMs (HR = 2.399; 95% CI: 1.475–3.902; $P < .001$; pH = 0.247; $I^2 = 25.30\%$) (Fig. 4A). Besides, the positive status of SN was also proved to be a risk factor of poor prognosis in HNMs (HR = 3.416; 95% CI: 1.939–6.021; $P < .001$; pH = 0.539; $I^2 = 0.00\%$) (Fig. 4B).

### 3.4. Sensitivity and publication bias analyses

Sensitivity analysis was carried out by excluding each study sequentially, which used to evaluate whether the prognosis

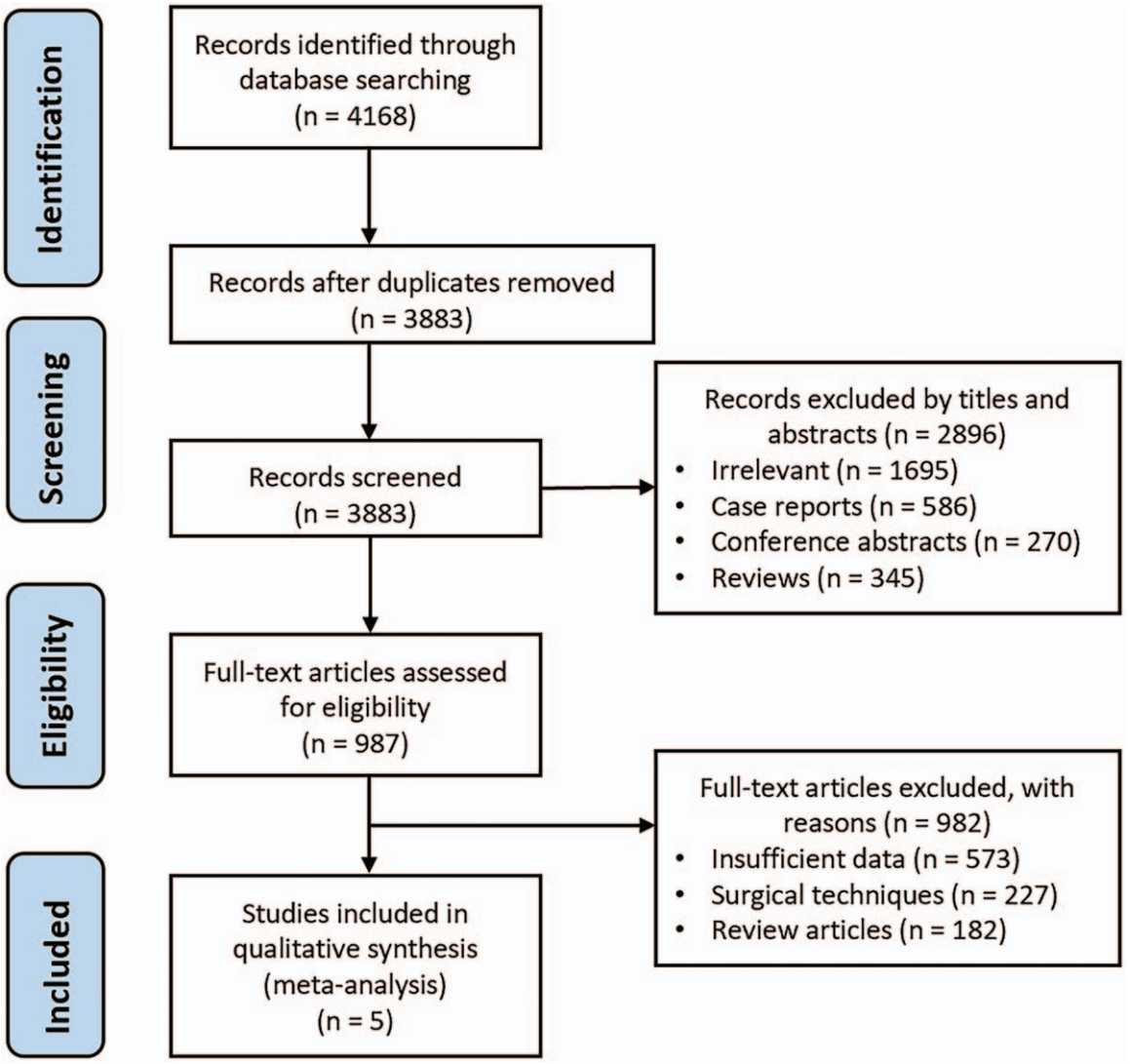


**Figure 1.** PRISMA flow chart of literature selection. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Table 1**

**Baseline information of included articles.**

| First author | Publication year (study period) | Source | Ethnicity | Number of patients (patients with SLNB) | Type of study | Significant prognostic factors | Type of analysis | NOS |
|---|---|---|---|---|---|---|---|---|
| Sperry | 2014 (2004–2011) | Surveillance Epidemiology and End Results database, Bethesda, USA | Caucasian | 5102 (2551) | Retrospective | SLNB | Multivariate | 6 |
| Ruskin | 2016 (2002–2012) | Peter MacCallum Cancer Centre, Melbourne, Australia | Australoid | 108 (59) | Retrospective | SLNB, the status of SN, gender, Breslow thickness, ulceration | Univariate | 6 |
| Leiter | 2015 (1991–2012) | University Hospital of Tübingen, Tübingen, Germany | Caucasian | 477 (259) | Retrospective | SLNB, the status of SN | Multivariate | 7 |
| Koskivuo | 2009 (1983–2006) | Turku University Hospital, Turku, Finland | Caucasian | 146 (22) | Retrospective | SLNB, gender, Breslow thickness, ulceration | Univariate | 5 |
| Uslu | 2017 (1976–2017) | Central Malignant Melanoma Registry of Tübingen University, Tübingen, Germany | Caucasian | 1384 (277) | Retrospective | SLNB | Multivariate | 8 |

NOS = New-castle Ottawa scale, SLNB = sentinel lymph node biopsy, SN = sentinel lymph node.

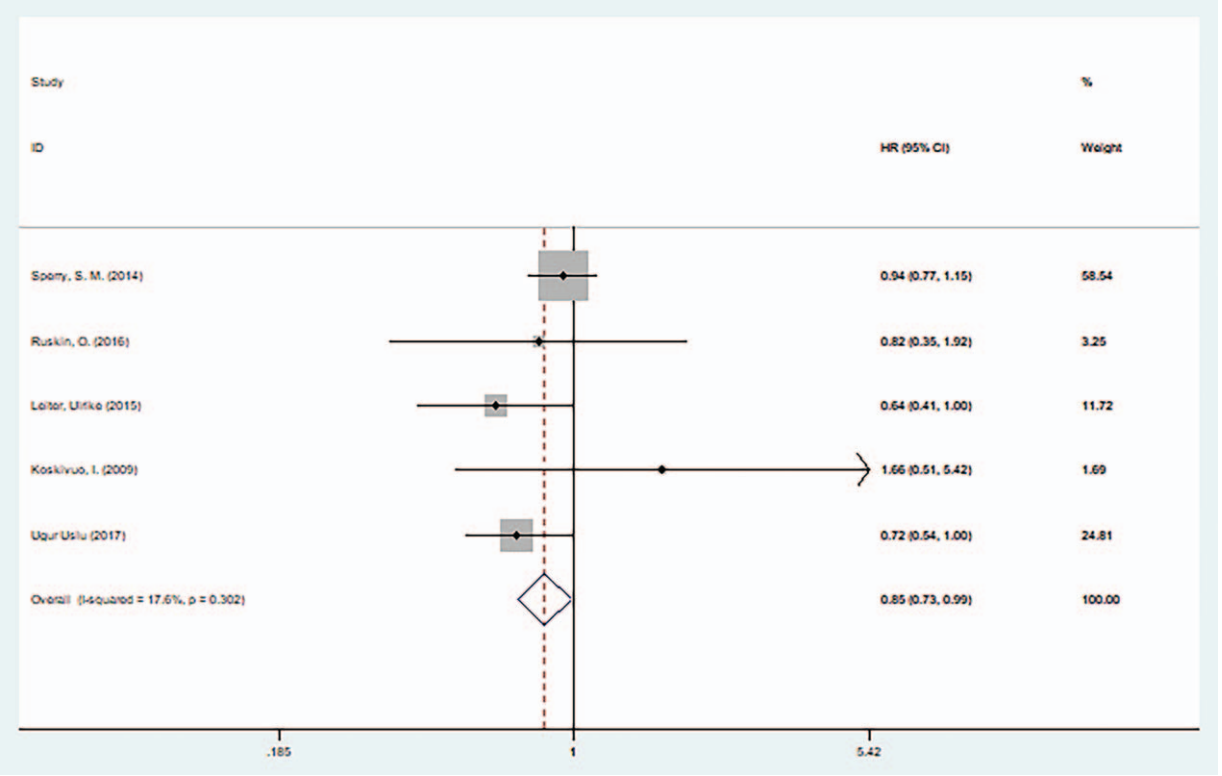


**Figure 2.** Forest plot of role of HR and its 95% CI of SLNB on overall survival of patients with HNMs. For each study, the estimate of HR was plotted with squares, and the size of the square reflects the weight of the study in the meta-analysis. The horizontal line crossing the square represents the 95% CI. The diamond represents the summary HR and 95% CI. CI = confidence interval, HNMs = head and neck melanomas, HR = hazard ratio, SLNB = sentinel lymph node biopsy.

outcomes were driven by any specific study and showed a stable result ($P = .859$) (Fig. 5). The funnel plot was validated to assess the presence of publication bias qualitatively, and no significant publication bias among all of identified articles was observed (Fig. 6).

## 4. Discussion

It is known that HNMs behave differently from cutaneous melanomas in other sites due to the unpredictable lymphatic drainage patterns of the head and neck region.[3–6,14,16,28] Patients with HNMs usually have worse survival rate, lower rate

**Table 2**

**Pooled results of the effect of SLNB.**

| | n | Heterogeneity ($I^2$, pH) | Model | Effect size | 95% CI | *P* value |
|---|---|---|---|---|---|---|
| First Recurrence* | 3 | | | | | |
| Satellite/intransit metastases | 2 | | | | | |
| Nodal observation | | | | 1 | | |
| SLNB | | 0%, 0.557 | Fixed | 0.957 | 0.551–1.661 | .876 |
| Regional lymph node metastases | 2 | | | | | |
| Nodal observation | | | | 1 | | |
| SLNB | | 0%, 0.457 | Fixed | 0.733 | 0.463–1.161 | .185 |
| Distant metastases | 2 | | | | | |
| Nodal observation | | 0%, 0.549 | Fixed | 1 | 0.402–1.106 | .117 |
| SLNB | 3 | | | 0.667 | | |
| All recurrences | | 0%, 0.793 | Fixed | | 0.607–1.038 | .091 |
| Nodal observation | | | | 1 | | |
| SLNB | | | | 0.794 | | |
| Overall survival | 5 | | | | | |
| Nodal observation | | | | 1 | | |
| SLNB | | 17.6%, 0.302 | Fixed | 0.845 | 0.725–0.986 | .032 |

95% CI = 95% confidence interval, n = number of included studies, SLNB = sentinel lymph node biopsy.
* Patients with satellite/intransit metastases, regional lymph node metastases and distant metastases.

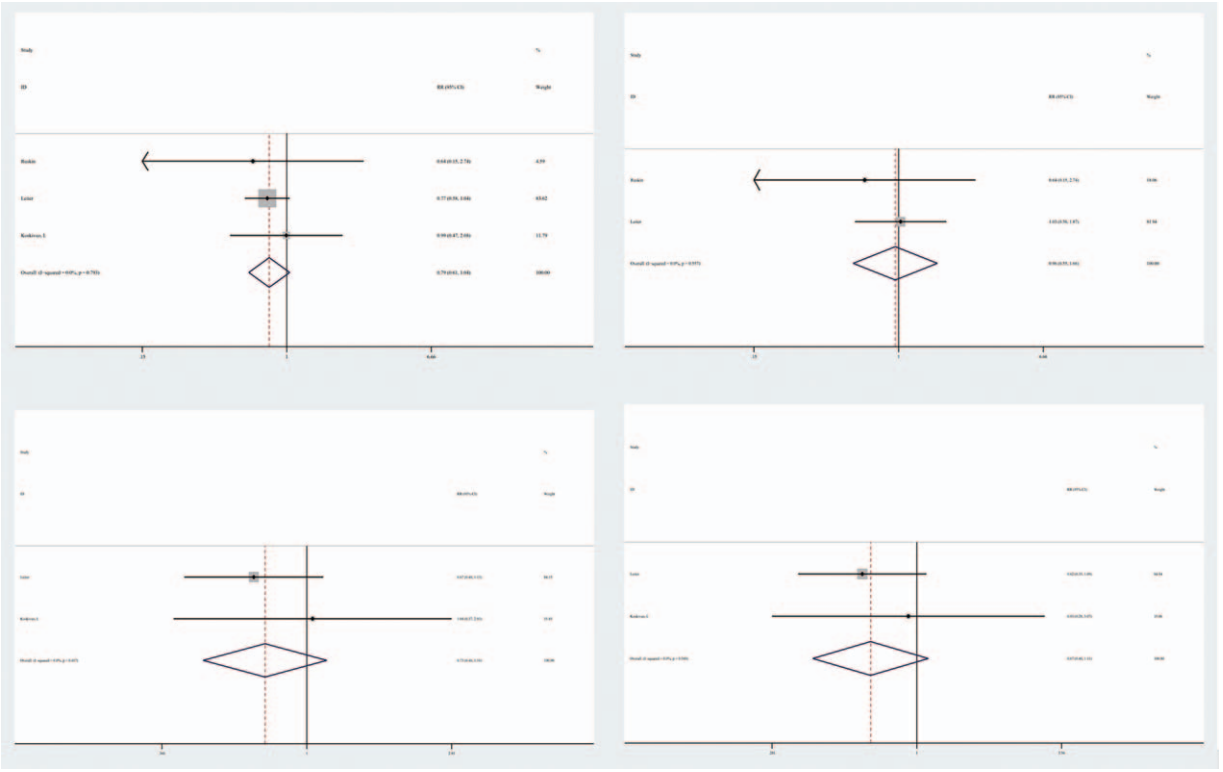

**Figure 3.** Forest plot of role of RR and its 95% CI of SLNB on total recurrence (A), satellite/transit metastases (B), regional lymph node metastases (C) and distant metastases (D) of patients with HNMs. For each study, the estimate of RR was plotted with squares, and the size of the square reflects the weight of the study in the meta-analysis. The horizontal line crossing the square represents the 95% CI. The diamond represents the summary RR and 95% CI. CI = confidence interval, HNMs = head and neck melanomas, RR = relative risk, SLNB = sentinel lymph node biopsy.

of SLNB positivity, and higher SLNB false negative rate.[4,16,28] However, The objective evaluation of SLNB on patients with HNMs is still a giant challenge because there are insufficient studies on HNMs, as well as scanty data to illustrate the survival benefit of SLNB to patients with HNMs. Meta-analysis as a scientific statistical analysis can concentrate limited data for systematic evaluation, which finally yield a relatively objective result.[29,30] Therefore, meta-analysis may solve the above-mentioned problem and we did not find other meta-analyses on this subject even upon completing the present study.

In our study, we brought into 5 studies to evaluate the prognostic information of SLNB on patients with HNMs. The included patients underwent SLNB from 2002 to 2011, which mostly ensured that the impact of SLNB was contemporaneous and stable. According to the outcomes of our present meta-analysis, SLNB was benefit to patients with HNMs mainly on improving patients' overall survival (HR = 0.845; $P = .032$), and this is in line with the current mainstream findings of SLNB[12,19] and most of our included articles.[24–27] The study by Koskivuo et al, as the only one included article showing the difference conclusion from the others, represented the HR of 1.66, which might be severely affected by the small sample size (n = 146).[23] Even so, our heterogeneity and sensitivity analyses have ensured the stability and reliability of our study (pH = 0.302; $I^2 = 17.60\%$).

A total of 3 studies[23–25] evaluated the correlation between SLNB and recurrences. Although SLNB did not decrease total recurrences of patients with HNMs statistically, our pooled results showed there is a trend that SLNB might reduce total recurrences of patients with HNMs (RR = 0.794; 95% CI: 0.607–1.038; $P = .091$; pH = 0.793; $I^2 = 0.00\%$). With the increase of sample size, we believe the trend would be more prominent. As

**Table 3**

**Pooled results of prognostic factors.**

| Prognostic factors | n | Heterogeneity ($I^2$, pH) | Model | HR | 95% CI | *P* value |
|---|---|---|---|---|---|---|
| SN status | 2 | | | | | |
| Negative | | | | 1 | | |
| Positive | | 25.3%, 0.247 | Fixed | 2.399 | 1.475–3.902 | <.001 |
| Ulceration | 2 | | | | | |
| Absent | | | | 1 | | |
| Present | | 0%, 0.539 | Fixed | 3.416 | 1.939–6.021 | <.001 |

95% CI = 95% confidence interval, HR = hazard ratio, n = number of included studies, SN = sentinel lymph node.

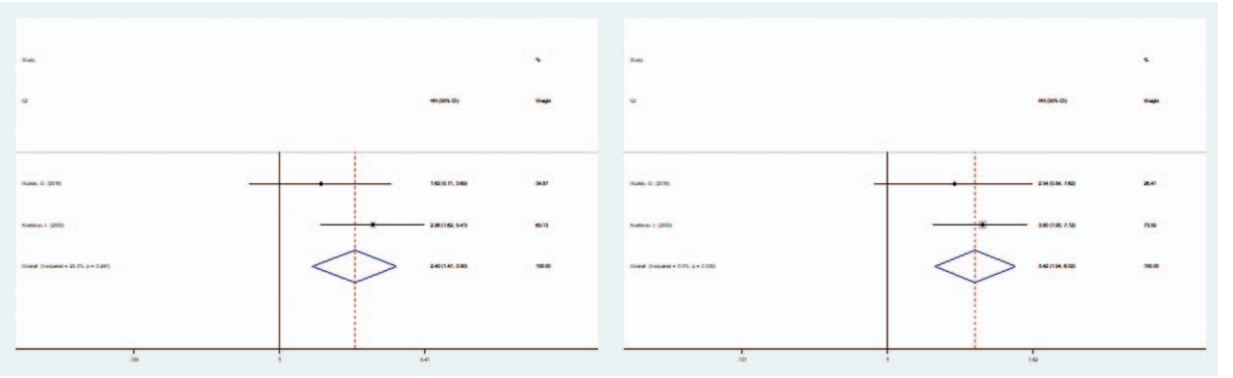

**Figure 4.** Forest plot of prognostic role of ulceration (A) and SN status (B) of patients with HNMs. For each study, the estimate of HR was plotted with squares, and the size of the square reflects the weight of the study in the meta-analysis. The horizontal line crossing the square represents the 95% CI. The diamond represents the summary HR and 95% CI. CI = confidence interval, HNMs = head and neck melanomas, HR = hazard ratio, SN = sentinel lymph node.

for the effect of SLNB on satellite/intransit metastases (RR = 0.794; 95% CI: 0.607–1.038; $P = .091$; pH = 0.793; $I^2 = 0.00\%$), regional lymph node metastases (RR = 0.794; 95% CI: 0.607–1.038; $P = .091$; pH = 0.793; $I^2 = 0.00\%$) and distant metastases (RR = 0.794; 95% CI: 0.607–1.038; $P = .091$; pH = 0.793; $I^2 = 0.00\%$), no significant difference was found. We speculated these outcomes above were affected by the sample size to a large extent according to the gap of sample size between overall survival and recurrences analyses (7217 patients vs 702 patients) in our study. Besides, it is worth noting that SLNB did not improve recurrences statistically, but improve the overall survival for patients with HNMs according to our pooled results. The higher false negative rate and lower detection rate of SLNB for patients with HNMs[15–18] might explain this difference.

Despite a plenty of researchers have confirmed that ulceration is the acknowledged predictor of cutaneous melanoma[31–33] and the SN status is the most powerful prognostic factor in early-stage melanoma,[13,34,35] it should be noted that most of these studies excluded patients with HNMs. According to our analysis, ulceration was a strong prognostic factor of HNMs (HR = 2.399; 95% CI: 1.475–3.902; $P < .001$; pH = 0.247; $I^2 = 25.30\%$). Besides, SN status might work as a significant predictor in HNMs in our pooled results (HR = 3.416; 95% CI: 1.939–6.021; $P < .001$; pH = 0.539; $I^2 = 0.00\%$). Even though the stability of above analyses were acceptable, the number of included studies was not ideal (each analysis only included 2 articles). In the future, large-scale randomized studies are still needed to prove the prognostic role of SN status with an accurate critical value in HNMs.

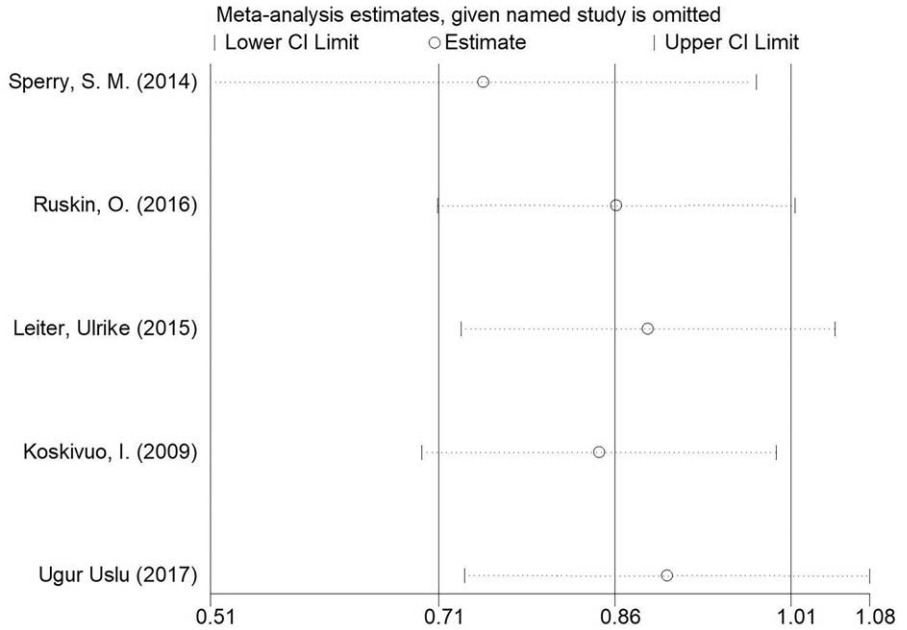


**Figure 5.** Sensitivity analysis of overall survival. For each study, the circle represents the summary hazard ratio (HR) when excluded this study. The horizontal line crossing the circle represents the 95% confidence interval (CI). The short vertical at the ends of horizontal line represents the lower and upper limit of 95% CI, respectively.

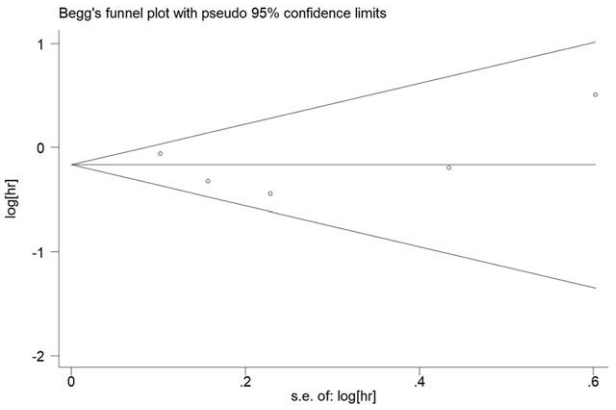


**Figure 6.** Funnel plot of the included studies evaluated the effect of SLNB on patients of HNMs. HNMs = head and neck melanomas, SLNB = sentinel lymph node biopsy.

## 5. Conclusion

This meta-analysis indicates that SLNB is benefit to patients with HNMs mainly on improving patients' overall survival and has shown a trend to reduce recurrences. Besides, ulceration and SN status might work as the significant predictors of HNMs.

## Author contributions

**Conceptualization:** Yingyi Zhang, Yange Zhang, Xuewen Xu.
**Data curation:** Yingyi Zhang, Yuyang Xu.
**Formal analysis:** Chuanqi Liu.
**Funding acquisition:** Yingyi Zhang, Yuyang Xu.
**Investigation:** Chuanqi Liu.
**Methodology:** Chuanqi Liu, Zihuai Wang, Yange Zhang, Yuyang Xu, Xuewen Xu.
**Project administration:** Chuanqi Liu, Zihuai Wang, Yange Zhang.
**Resources:** Yingyi Zhang, Chuanqi Liu, Zihuai Wang, Guonian Zhu.
**Software:** Zihuai Wang, Guonian Zhu.
**Supervision:** Chuanqi Liu, Zihuai Wang, Guonian Zhu.
**Validation:** Zihuai Wang, Guonian Zhu, Xuewen Xu.
**Visualization:** Zihuai Wang, Guonian Zhu, Yange Zhang, Xuewen Xu.
**Writing – original draft:** Yingyi Zhang.
**Writing – review & editing:** Yingyi Zhang, Yange Zhang, Xuewen Xu.

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