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REVIEW ARTICLE

# Diagnostic value of sentinel lymph node biopsy for cT1/T2N0 tongue squamous cell carcinoma: a meta-analysis

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**Abstract** The aim of this study was to systematically evaluate the diagnostic value of the sentinel lymph node biopsy (SLNB) for cT1/T2N0 tongue squamous cell carcinoma (TSCC) patients. A comprehensive and systematic literature review was performed by searching the Embase and PubMed databases for English language articles published up to December 2016. The pooled overall sentinel lymph node (SLN) detection rate, sensitivity and negative predictive value (NPV) were used to evaluate the diagnostic value of SLNB which used neck dissection or follow-up as a reference test. The $Q$ test and $I^2$ statistic were used to assess the heterogeneity across the studies. Subgroup analyses were performed in consideration of higher contribution of different clinical characteristics on the SLNB diagnostic value. Begg's linear regression and Egger's regression tests were conducted to evaluate the publication bias. Thirty-five studies (with 1084 patients) were included. The pooled SLN detection rate was 98% (95% CI 97–100%). The pooled overall sensitivity and NPV of SLNB were 0.92 (95% CI 0.88–0.95) and 0.96 (95% CI 0.94–0.97), respectively. The subgroup analyses demonstrated that higher extracted number of patients ($n \geq 30$) from the included studies achieved a more stable NPV than lower number of patients. SLNB can effectively predict the status of regional lymph nodes in cT1/T2N0 TSCC patients. With high sensitivity and NPV, SLNB can guide the treatment of SLNB-positive patients with neck dissections and those with negative SLNBs with follow-ups in order to avoid unnecessary surgical morbidity.

**Keywords** Sentinel lymph node biopsy · Tongue · Squamous cell carcinoma · Meta-analysis

## Introduction

Tongue squamous cell carcinoma (TSCC) is the most common primary malignant tumor in the head and neck. Cervical lymph node metastasis (CM) is considered as a crucial indicator for the tumor staging, treatment planning and prognostic assessment of TSCC, which could markedly impact the recurrence and survival rates [1–4]. The accurate staging of the neck is therefore vital for the management of TSCC.

To date, clinical and radiological examinations, including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography CT (PET-CT) and fine needle aspiration cytology (FNAC), have not been sufficiently sensitive in detecting occult CM in early TSCC patients. Moreover, a high incidence of occult CM (25–40%) in patients diagnosed with clinically negative neck (cN0) in early (T1/T2) TSCC was reported [5–7]. The management of cT1/T2N0 TSCC remains debatable, the majority of clinical centres preferring elective neck dissection (END) for cervical lymph node staging and occult CM removal. However, researches have shown that most patients will not benefit from END, when considering the overtreatment and surgery associated morbidity including shoulder dysfunction, pain, and contour changes [8, 9]. Therefore, some surgeons favour a wait-and-see policy, performing an

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END only when the CM is detected. Sentinel lymph node biopsy (SLNB) has been deemed as an alternative staging procedure and response to the controversy. The sentinel lymph node (SLN) is the first lymph node or lymph nodes group which receives lymphatic drainage from the primary tumor, if the SLN is metastasis-negative, the non-SLNs in the regional basin are predicted to be negative of metastases [10]. When compared to the END, the SLNB could decrease the surgery-associated morbidity and avoid an unnecessary invasive operation. An SLNB with high accuracy could be deemed better than a direct END.

A systematic meta-analysis of SLNB in head and neck squamous cell carcinoma patients demonstrated a sensitivity of 95% and negative predictive value (NPV) of 96% [11], which indicated that SLNB was a reliable indicator of the regional lymph node status. Although many studies have assessed the application of SLNB for head and neck tumors, few of these have focused on the specific region of the tongue. Many researches placed emphasis on the entire oral cavity, including tongue cancer, mouth floor cancer, oropharyngeal cancer and so on, but these cancers exhibit different characteristics and the lymphatic drainage of oral and maxillofacial tumors is multidirectional and complex, which could result in different SLNB outcomes. Therefore, we focused on the tongue subsite for a detailed and targeted evaluation. To our knowledge, this is the first meta-analysis of SLNB in patients with TSCC. To evaluate the diagnostic value of SLNB for cT1/T2N0 TSCC patients, a comprehensive and systematic review and meta-analysis of the SLN detection rate, the sensitivity and NPV of SLNB with a simultaneous END and/or follow-up as a reference test was performed.

## Materials and methods

### Study search

A systematic literature research was performed using the PubMed and Embase databases for English language articles published up to December 2016 with the following keywords: “sentinel lymph node”, “biopsy”, “tongue”, “oral”, “mouth”, “head and neck”, “cancer”, “carcinoma” and “neoplasm”. All of the studies included in this meta-analysis fit the following criteria: the subjects were human cT1/T2N0 tongue cancer patients; the full text of study was available; an absolute number of observations could be derived [true positive (TP), false positive (FP), false negative (FN) and true negative (TN)]; a concurrent END or follow-up of at least 18 months was used as the reference test at the time of SLNB.

### Data extraction

The following data were extracted from each eligible study: first author’s surname, publication year, patient enrollment, study design, cN0 diagnostics, SLN localization [lymphoscintigraphy, gamma probe, blue dye, single positron emission computed tomography (SPECT), CT and near-infrared fluorescence (NIF) imaging], histopathology [haematoxylin–eosin staining (HE), serial sectioning (SS), and immunohistochemistry (IHC)], reference test type (END and/or follow-up), age and gender distribution, T-stage, SLN detection rate, average number of SLNs harvested per patient, number of observations (TP, FP, FN and TN), regional recurrence of cervical metastasis (ROCM) and prognosis if reported.

### Statistical analysis

The sensitivity and NPV were assessed for each study. The sensitivity was calculated as the probability of a positive END or follow-up given a positive SLNB (sensitivity = TP/(TP + FN)), and the NPV referred to the probability of a negative END or follow-up after a negative SLNB (NPV = TN/(TN + FN)). The merged sensitivity and NPV were calculated using both a fixed effect model and a

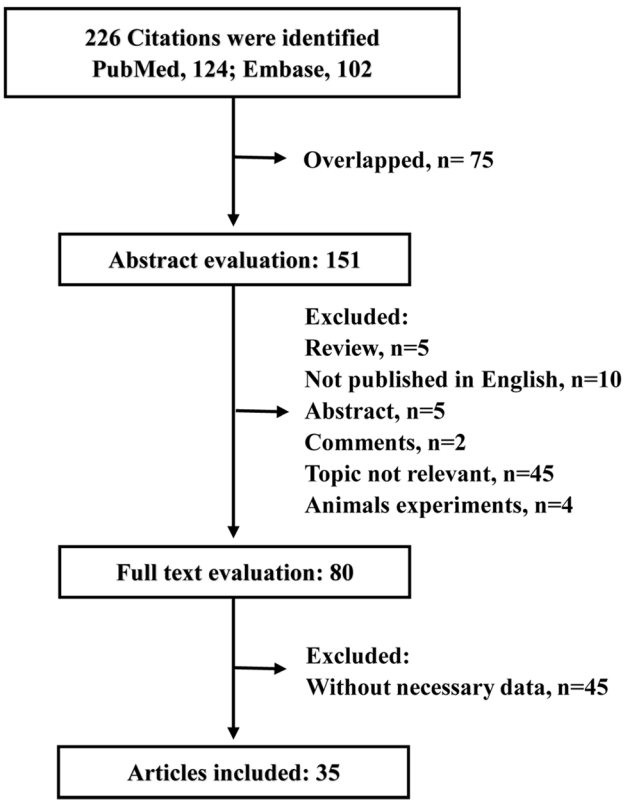


**Fig. 1** Flow diagram

**Table 1** Study characteristics

| References | Patient enrollment | Design | cN0 diagnostics | SLN localization | Histopathology | Reference test ND (type) or FU (mean/range) |
|---|---|---|---|---|---|---|
| Civantos et al. [12] | Unclear | Prospective | CT/MRI | L + G | HE + IHC + SS | ND (I–IV) |
| Matsuzuka et al. [13] | Unclear | Prospective | Clinically | L + G | HE | ND (elective) + FU (91 m) |
| Honda et al. [14] | Unclear | Prospective | Clinically/radiologically | CT + B | HE | ND (I–III or I–IV) + FU (>30 m) |
| Sagheb et al [15]. | Consecutive | Prospective | CT + US | L + G | HE | ND (I–III) +FU (18–40 m) |
| Chiesa et al. [16] | Consecutive | Prospective | Clinically | L + G | HE | ND (I–V) |
| Chung et al. [17] | Consecutive | Prospective | PE + CT + PET-CT + US-FNAC | L + G | HE + IHC + SS | ND (I–III or I–V) + FU (70 m/49–111 m) |
| Dequanter et al. [18] | Consecutive | Prospective | PE + CT/MRI | L + G | HE + IHC + SS | ND (I–V) + FU (59 m) |
| Pedersen et al. [19] | Consecutive | Retrospective | CT/MRI | L + G + SPECT/CT | HE + IHC + SS | ND (elective) + FU (unclear) |
| Schilling et al. [20] | Consecutive | Prospective | Radiologically | L + G + B | HE + IHC + SS | ND (selective/modified radical) + FU (>36 m) |
| Ramamurthy et al. [21] | Consecutive | Prospective | PE + US | B | HE + IHC + SS | ND (selective/modified radical) |
| Terada et al. [22] | Consecutive | Prospective | Clinically | L + G + SPECT | HE | ND + FU (unclear) |
| Bluemel et al. [23] | Consecutive | Prospective | PE + US + SPECT/CT/MRI | L + G + SPECT/CT | HE + IHC + SS | ND (I–V) |
| Vigili et al. [24] | Consecutive | Prospective | CT/MRI | L + G | HE + IHC | ND + FU (26.3 m/13–45 m) |
| Bilde et al. [25] | Consecutive | Prospective | PE + CT/MRI/US | L + G + SPECT/CT | HE + IHC + SS | ND + FU (unclear) |
| Yen et al. [26] | Consecutive | Prospective | Clinically | L + G | HE + IHC + SS | ND (elective) |
| Sieira-Gil et al. [27] | Consecutive | Prospective | CT/MRI | L + G + SPECT/CT | HE + IHC + SS | ND + FU (unclear) |
| Rigual et al. [28] | Consecutive | Retrospective | PE + CT | L + G | HE | ND (I–V) + FU (unclear) |
| Keski-Santti et al. [29] | Consecutive | Prospective | PE + CT/MRI | L + G + B | HE + IHC + SS | ND (I–IV) + FU (21 m/12–42 m) |
| Flach et al. [30] | Consecutive | Prospective | US-FNAC | L + G + B | HE + IHC + SS | ND + FU (unclear) |
| Hasegawa et al. [31] | Consecutive | Prospective | Clinically | G | Unclear | ND + FU (unclear) |
| Burns et al. [32] | Consecutive | Prospective | CT/MRI | L + G + B | HE + IHC | ND + FU (unclear) |
| Frerich et al. [33] | Consecutive | Prospective | Clinically | G | HE + IHC + SS | ND (I–V) + FU (unclear) |
| Fan et al. [34] | Consecutive | Retrospective | Clinically/radiologically | L + G + B | HE | ND (I–V) + FU (>120 m) |
| Rigual et al. [35] | Consecutive | Prospective | PE + CT | L + G + B | HE | ND (I–III or I–IV or I–V) + FU |
| Stoeckli et al. [36] | Consecutive | Prospective | PE + CT | L + G + B | HE + IHC + SS | ND + FU (unclear) |
| Jeong et al. [37] | Consecutive | Prospective | CT/MRI | L + G | HE + IHC + SS | ND (I–III or I–IV) |
| Hoft et al. [38] | Consecutive | Prospective | US + US-FNAC | L + G | HE + IHC + SS | ND (selective) |
| Stoeckli et al. [39] | Consecutive | Prospective | PE + CT | L + G | HE + IHC + SS | ND + FU (unclear) |
| Peng et al. [40] | Consecutive | Prospective | PE + CT/MRI | B + NIF | HE | ND (selective/modified radical) |
| Taylor et al. [41] | Consecutive | Prospective | Clinically | L + G | Unclear | ND |
| Yamauchi et al. [42] | Consecutive | Prospective | CT + MRI + US | L + G | HE + SS | ND + FU (37.1 ± 17.0 m) |
| Kaya et al. [43] | Consecutive | Retrospective | PE + US + CT | L + G | HE + IHC | ND (I–III or I–IV or I–V) + FU |

**Table 1** (continued)

| References | Patient enrollment | Design | cN0 diagnostics | SLN localization | Histopathology | Reference test ND (type) or FU (mean/range) |
|---|---|---|---|---|---|---|
| Tartaglione et al. [44] | Consecutive | Prospective | US + CT | L + G | HE + IHC | ND (selective) + FU (unclear) |
| Nakamura et al. [45] | Consecutive | Prospective | Clinically | L + G + NIF | Unclear | ND + FU (unclear) |
| van der Vorst et al. [46] | Consecutive | Prospective | Clinically/radiologically | NIF | HE | ND (I–IV) |

*US* ultrasonography, *PE* physical examination, *PET-CT* positron emission tomography-CT, *US-FNAC* ultrasonography-guided fine needle aspiration cytology, *NIF* near-infrared fluorescence camera, *L* lymphoscintigraphy, *G* gamma probe, *B* blue dye, *SPECT* single positron emission computed tomography, *HE* hematoxylin and eosin staining, *IHC* immunohistochemistry, *SS* serial sectioning, *ND* neck dissection, *FU* follow-up, *m* months

random effects model. The effect of heterogeneity was quantified using $I^2 = 100\% \times (Q\text{-df})/Q$. A significant $I^2$ statistic ($I^2 > 50\%$) or $Q$ statistic ($P < 0.10$) indicated heterogeneity across the studies, then the random effects model was used for the meta-analysis, otherwise, the fixed effect model was chosen. The asymmetry of the funnel plot was calculated using Begg's linear regression and Egger's regression tests for the evaluation of publication bias. The statistical analyses were carried out using the meta package in the R statistical software (version 3.3.2 http://cran.r-project.org/).

## Results

### Characteristics of the studies

A total of 226 studies were identified. After assessing the studies' titles and abstracts, 80 studies were selected for potentially relevant full text. In total, 35 studies met the criteria and were included in this meta-analysis [12–46]. A summary of the study results is shown in Fig. 1.

In total, 1084 patients were considered in this meta-analysis. The study characteristics and population characteristics are listed in Tables 1 and 2. The involved studies were published between 2000 and 2016. In all included studies, most patients (1077/1084, 99.4%) had at least one SLN identified, so that an SLNB could be performed. The overall SLN detection rate was 98% (95% CI 97–100%). The average number of SLNs harvested per patient and the number of observations (TP, FP, FN and TN) in each study are listed in Table 2. The sample sizes of the studies varied between 3 and 256. There was wide variation in the numbers of patients extracted from each series, 25 studies extracted less than 30 patients with TSCC, and ten studies contained 30 patients or more, the NPV of which was lower ($P < 0.05$). There were multiple SLN detection methods, including radionuclide tracer technique, dye tracer technique, SPECT, CT and NIF imaging. Twenty studies used a single mode to identify the SLNs, while 15 studies performed dual mode imaging for the SLN detection, there was no difference in the sensitivity and NPV of the two groups. Moreover, the different combinations of pathology methods also showed no difference in sensitivity and NPV (Table 3).

The summary of the reported regional ROCMs and the prognoses are listed in Table 4. There is no statistical difference between the recurrence rates of SLNB positive and negative groups ($P = 0.528$). Moreover, there is no statistical difference between the ND group and follow-up group in SLNB-negative patients with ROCM ($P = 0.071$). The reported salvage rates of SLNB-positive patients and SLNB-negative patients with ROCM also showed no statistical difference ($P = 0.129$).

### Overall sensitivity and NPV of SLNB

The forest plots in Figs. 2 and 3 show the number of TP, FN, TN and the overall sensitivity and NPV of the SLNB of all included studies. A fixed effect model was used due to no significant heterogeneity (sensitivity, $P = 0.91$, $I^2 = 0\%$; NPV, $P = 1.00$, $I^2 = 0\%$) was observed. The pooled overall sensitivity and NPV of the SLNB were 0.92 (95% CI 0.88–0.95) and 0.96 (95% CI 0.94–0.97) respectively.

### Evaluation of publication bias

Based on the funnel plot of the sensitivity and NPV assessed using Begg's linear regression and Egger's regression tests, no obvious publication bias was observed in this meta-analysis (Fig. 4, sensitivity: $P = 0.6592$, NPV: $P = 0.5752$).

## Discussion

In this meta-analysis, most patients had at least one SLN identification which allowed for an SLNB to be performed.

**Table 2** Population characteristics

| References | *N* | Age, median (range) or mean ± SD, year | Gender distribution (M/F) | T staging (T1/T2) | Detection rate | No. of SLNs (mean) | TP | FP | FN | TN |
|---|---|---|---|---|---|---|---|---|---|---|
| Civantos et al. [12] | 95 | Unclear | Unclear | Unclear | 95/95 (100%) | Unclear | 28 | 0 | 3 | 64 |
| Matsuzuka et al. [13] | 29 | 66 (31–82) | 15/14 | 14/15 | 29/29 (100%) | 3.1 | 6 | 0 | 2 | 21 |
| Honda et al. [14] | 31 | 64 (33–91) | 17/14 | 14/17 | 28/31 (90.3%) | 1.8 | 4 | 0 | 1 | 23 |
| Sagheb et al. [15] | 10 | 52 (21–82) | 5/5 | 8/2 | 10/10 (100%) | 2.4 | 3 | 0 | 0 | 7 |
| Chiesa et al. [16] | 11 | 50 (22–69) | 7/4 | 6/5 | 8/11 (72.7%) | 1.9 | 2 | 0 | 0 | 6 |
| Chung et al. [17] | 61 | 49.3 ± 10.3 | 25/36 | 39/22 | 61/61 (100%) | 2.2 | 12 | 0 | 5 | 44 |
| Dequanter et al. [18] | 8 | 61.5 ± 7.6 | Unclear | 1/7 | 8/8 (100%) | 1.8 | 4 | 0 | 0 | 4 |
| Pedersen et al. [19] | 106 | Unclear | Unclear | Unclear | 106/106 (100%) | 3.0 | 39 | 0 | 2 | 65 |
| Schilling et al. [20] | 256 | Unclear | Unclear | Unclear | 256/256 (100%) | 3.2 | 67 | 0 | 12 | 177 |
| Ramamurthy et al. [21] | 18 | Unclear | Unclear | Unclear | 18/18 (100%) | Unclear | 4 | 0 | 0 | 14 |
| Terada et al. [22] | 38 | Unclear | Unclear | 22/16 | 38/38 (100%) | Unclear | 6 | 0 | 3 | 29 |
| Bluemel et al. [23] | 10 | 58.6 (41.0–74.0) | Unclear | 7/3 | 10/10 (100%) | 2.3 | 3 | 0 | 0 | 7 |
| Vigili et al. [24] | 11 | Unclear | Unclear | 1/10 | 11/11 (100%) | 2.3 | 5 | 0 | 0 | 6 |
| Bilde et al. [25] | 26 | Unclear | Unclear | Unclear | 26/26 (100%) | 4.0 | 6 | 0 | 0 | 20 |
| Yen et al. [26] | 6 | 50 (39–65) | 6/0 | 4/2 | 6/6 (100%) | 2.1 | 2 | 0 | 0 | 4 |
| Sieira-Gil et al. [27] | 22 | 63 (38–90) | 12/10 | 16/6 | 22/22 (100%) | 3.4 | 4 | 0 | 0 | 18 |
| Rigual et al. [28] | 22 | Unclear | Unclear | Unclear | 22/22 (100%) | Unclear | 4 | 0 | 1 | 17 |
| Keski-Santti et al. [29] | 11 | Unclear | Unclear | 11/0 | 11/11 (100%) | Unclear | 2 | 0 | 0 | 9 |
| Flach et al. [30] | 33 | Unclear | Unclear | Unclear | 33/33 (100%) | Unclear | 10 | 0 | 1 | 22 |
| Hasegawa et al. [31] | 61 | Unclear | Unclear | Unclear | 60/61 (98.4%) | Unclear | 9 | 0 | 3 | 48 |
| Burns et al. [32] | 6 | Unclear | Unclear | 1/5 | 6/6 (100%) | 1.2 | 2 | 0 | 0 | 4 |
| Frerich et al. [33] | 14 | Unclear | Unclear | Unclear | 14/14 (100%) | 2.5 | 4 | 0 | 1 | 9 |
| Fan et al. [34] | 30 | 48 (27 ± 75) | 21/9 | 17/13 | 30/30 (100%) | 2.7 | 9 | 0 | 1 | 20 |
| Rigual et al. [35] | 13 | Unclear | Unclear | 0/13 | 13/13 (100%) | Unclear | 7 | 0 | 1 | 5 |
| Stoeckli et al. [36] | 13 | Unclear | Unclear | 2/11 | 13/13 (100%) | Unclear | 3 | 0 | 0 | 10 |
| Jeong et al. [37] | 19 | 53 (35–68) | 14/5 | 12/7 | 19/19 (100%) | 2.6 | 6 | 0 | 0 | 13 |
| Hoft et al. [38] | 10 | Unclear | Unclear | 3/7 | 10/10 (100%) | 4.9 | 5 | 0 | 0 | 5 |
| Stoeckli et al. [39] | 49 | 61 (34–87) | 28/21 | 22/27 | 49/49 (100%) | 1.6 | 17 | 0 | 1 | 31 |
| Peng et al. [40] | 12 | 63 (50–77) | 3/9 | 8/4 | 12/12 (100%) | 3.6 | 2 | 0 | 0 | 10 |
| Taylor et al. [41] | 3 | Unclear | Unclear | Unclear | 3/3 (100%) | 2.0 | 1 | 0 | 0 | 2 |
| Yamauchi et al. [42] | 11 | 62.3 ± 15.0 | 9/2 | 2/9 | 11/11 (100%) | 1.5 | 2 | 0 | 1 | 8 |
| Kaya et al. [43] | 7 | 59 (28–76) | 3/4 | 2/5 | 7/7 (100%) | 3.4 | 5 | 0 | 0 | 2 |
| Tartaglione et al. [44] | 12 | 68 (28–78) | 7/5 | 6/6 | 12/12 (100%) | 2.4 | 5 | 0 | 0 | 7 |
| Nakamura et al. [45] | 13 | 63 (50–840) | 11/2 | 5/8 | 13/13 (100%) | 3.2 | 2 | 0 | 1 | 10 |
| van der Vorst et al. [46] | 7 | 59.5 (33 ± 73) | Unclear | Unclear | 7/7 (100%) | 1.7 | 2 | 0 | 1 | 4 |

*TP* true positive, *FP* false positive, *FN* false negative, *TN* true negative

In the present study, 20 researches used lymphoscintigraphy and a gamma probe with radionuclide as a single mode imaging for SLN identification and 15 researches used a dual mode imaging mostly with a combination of radionuclide imaging and CT imaging, or with radionuclide imaging and blue dye technique to identify the SLN, indicating that radionuclide imaging was the main method for SLN detection for early TSCC patients. The overall SLN detection rate was 98% (95% CI 97–100%), and most included studies (32/35) showed a detection rate of 100%. Although some researchers used CT, blue dye, and NIF imaging for the SLN detection, NIF imaging requires special equipment, blue dye could only identify SLNs intraoperatively, whereas CT is commonly used in hospitals. Preoperative CT lymphography and intraoperative black-staining of the SLN with gold nanoparticles agents have been successfully performed to identify SLNs of TSCC in animal mode with a detection rate of 100% [47, 48]. Although the publication bias evaluation demonstrated that there was no obvious bias in the studies and the *P* values of the heterogeneity tests were both

**Table 3** Subgroup analyses of different study characteristics

| Subgroup | *n* | Sensitivity (95% CIs) | *P* value | NPV (95% CIs) | *P* value |
|---|---|---|---|---|---|
| No. of patients | | | 0.0779 | | 0.0457 |
| ≥30 | 10 | 0.90 (0.86–0.94) | | 0.95 (0.93–0.97) | |
| <30 | 25 | 0.96 (0.90–1.00) | | 0.98 (0.96–1.00) | |
| Pathological method | | | 0.1760 | | 0.7269 |
| HE | 10 | 0.85 (0.76–0.95) | | 0.95 (0.91–0.99) | |
| HE + IHC | 4 | 1.00 (0.88–1.00) | | 1.00 (0.89–1.00) | |
| HE + IHC + SS | 17 | 0.92 (0.89–0.96) | | 0.96 (0.95–0.98) | |
| Identification method | | | 0.7829 | | 0.7721 |
| Single mode | 20 | 0.92 (0.87–0.97) | | 0.96 (0.93–0.98) | |
| Dual mode | 15 | 0.91 (0.87–0.95) | | 0.96 (0.94–0.98) | |

*HE* hematoxylin and eosin staining, *IHC* immunohistochemistry, *SS* serial sectioning, *NPV* negative predictive value

**Table 4** Summary of the reported regional recurrences of cervical metastases

| | Study author | *n* | ND | No. of ROCM | ROCM site (recurrence time) | Recurrence rate | Prognosis | Salvaged rate |
|---|---|---|---|---|---|---|---|---|
| SLNB (+) | Sagheb | 3 | I–III | 1 | 1 con IV (10 m) | 3.01% (10/332) | NR | 33.3% (2/6) |
| | Vigili | 5 | I–III | 2 | 1 ipsi, 1 con | | 1 DOD, 1 DOO | |
| | Terada | 6 | NR | 4 | 2 ipsi, 1 con, 1 ipsi + con | | 2 DOD, 2S | |
| | Fan | 9 | I–V | 3 | 3 ipsi: I (8 m), III (6 m), III + IV (24 m) | | NR | |
| SLNB (−) | Matsuzuka | 2 | NR | 0 | – | Total recurrence rate | NR | 77.0% (10/13) |
| | | 21 | – | 2 | NR | 2.28% (17/745) | 2S | $P = 0.129$ |
| | Honda | 13 | I–III | 0 | – | 3.01 vs 2.28%, | NR | |
| | | 11 | – | 1 | NR | $P = 0.528$ | NR | |
| | Chung | 15 | I–III | 1 | 1 ipsi (7 m) | Recurrence rate with ND | 1 DOD | |
| | | 34 | – | 4 | NR | 0.83% (2/242) | 1 DOO, 3S | |
| | Terada | 32 | – | 5 | NR | Recurrence rate with FU | 1 DOO, 4S | |
| | Fan | 21 | – | 1 | I + II (7 m) | 2.98% (15/503), | NR | |
| | Stoeckli | 32 | – | 1 | NR | 0.83 vs 2.98%, | NR | |
| | Yamauchi | 9 | I–IV | 1 | III (6 m) | $P = 0.071$ | NR | |
| | Nakamura | 11 | – | 1 | NR | | 1S | |

*ND* neck dissection, *FU* follow-up, *NR* not reported, *ROCM* recurrence of cervical metastases, *con* contralateral, *ipsi* ipsilateral, *DOD* died of disease, *DOO* died of others, *S* salvaged

>0.10, the subgroup analyses of certain study characteristics were also conducted to analyze potential subgroup differences. The pooled sensitivity and NPV between single mode imaging and dual mode imaging showed no statistical difference, indicating that all used detection methods efficiently identified the SLN which was in favor of a precise SLNB procedure. Liu's meta-analysis of early oral cancer demonstrated that SLN pathological evaluation with IHC achieved a higher sensitivity than without IHC [49], but in the present study, there were no statistical differences in the sensitivity and NPV of different combinations of pathology methods. Although the difference was not significant statistically, the pooled sensitivity and NPV of pathological assessment with IHC and/or SS were higher than with HE staining only. The SS and IHC could detect the missing micrometastases to decrease FN and improve the NPV, as Sagheb [15] reported that the NPV could be improved from 0.94 to 0.96 with the addition of SS and IHC, so the additional SS and IHC were optional for the HE staining. There were only ten studies with an extracted patient number over 30, but the included patients accounted for 70.1% of all patients (760/1084), so the pooled NPV calculation was more stable and much closer to the overall pooled NPV.

The status of the regional lymph nodes is an important prognostic indicator and can be used to assess the need for

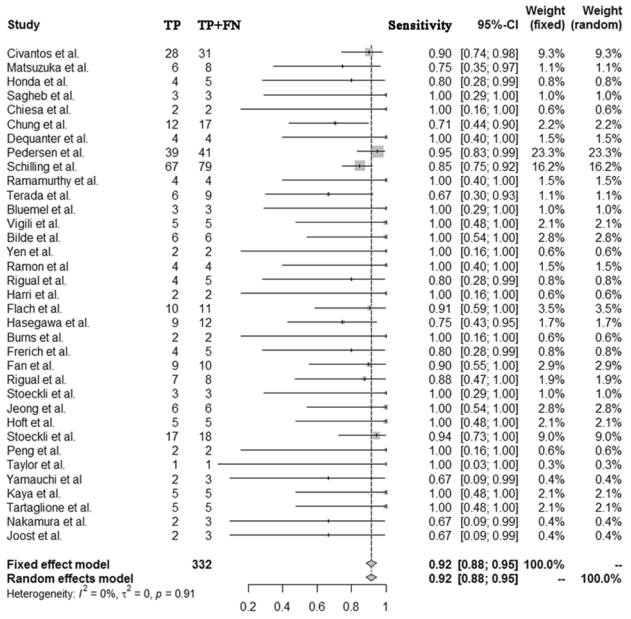


**Fig. 2** Forest plot of the sensitivity

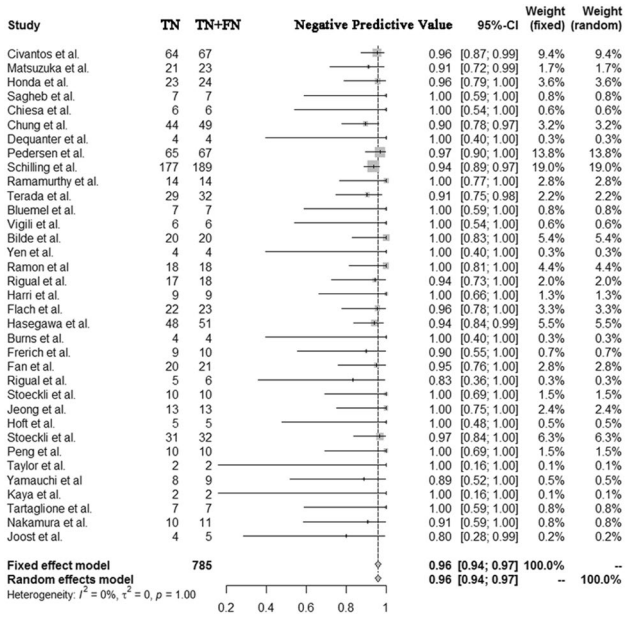


**Fig. 3** Forest plot of the negative predictive value

adjuvant treatment. Therefore, the determination of a positive regional lymph nodes status is of great importance.

There were 1084 patients with TSCC included in the meta-analysis, and 1077 of them underwent an SLNB followed by an END or a long-term follow-up. A positive SLNB was verified by confirming occult metastasis in intraoperative SLN specimens with histopathology in 27.1% patients (292/1077). Overall, the pooled sensitivity and NPV of SLNB was 0.92 which compares favourably with the 0.95 found by Thompson in a meta-analysis of head and neck squamous cell carcinoma [11].

In total, there were 40 FNs observed in this meta-analysis. Many mechanisms could lead to an FN, including uneven contrast agent injections (radionuclide or iopamidol), resulting in an obscure radioactive signal of SLN with primary tumor, unclear imaging or even no imaging of SLN; also lymphatic flow system obstructions caused by carcinoma cells, leading to the redirection or interruption of lymphatic drainage from the primary tumor to the SLN [50, 51]. In this meta-analysis, some studies reported the SLNs levels, which showed that most SLNs were detected in the common upper neck level I–III and a few in the lower neck level IV–V. It was reported that the detection of SLN in level IV was very rare (1%) [52], thus the majority removed levels I–III after a positive SLNB. However, attention should be paid to some skipped metastases in level IV–V in TSCC [15, 22, 24, 53]. In four studies, ten ROCMs were reported and four patients had contralateral metastases. In the SLNB-negative patients, 17 ROCMs were reported in eight studies. The recurrence rates in SLNB-positive and SLNB negative patients were similar, 3.01 and 2.28% respectively, though the statistical difference was not significant, but only ten studies reported on ROCMs, so the recurrence might be underestimated. Considering the fact that TSCC is prone to CM and skipped metastases existence, the SLNB-positive finding indicated a greater possibility of other potential lymph node metastases, so a selective ND of level I–III might not be enough and the lower neck level IV–V should be included. In the reported recurrent SLNB-negative patients, two were confirmed by ENDs and 15 were confirmed by follow-ups, the reference test with ND and follow-up showed no statistical difference in the calculation of sensitivity and NPV of each group ($P = 0.071$), so for the SLNB-negative patients, END and follow-up are both optional. However, when compared to END, follow-up is less invasive and the patients would have a second chance to be salvaged by surgery if recurrences occur, which benefits the patients with free of invasive surgery and operative morbidity. The reported salvage rates of the SLNB-positive and SLNB-negative recurrent patients were 33.3 and 77.0% with no statistical difference ($P = 0.129$), but the reported sample size of recurrence was small, so the salvage rate might also be underestimated.

To date, for the late stage (T3/T4) tongue cancer with cN0 neck, the management of patients has reached a consensus that modified radical neck dissection or END should be performed, but for the early stage (T1/T2), it still remains controversial. Some surgeons refer to direct END of level I–III without SLNB, but so far there is insufficient evidence to prove that the curative effect of early cN0 TSCC patients with END is better than without surgery. As our study reported that the pooled NPV of SLNB was 0.95, which indicated that if the early TSCC patients had a negative

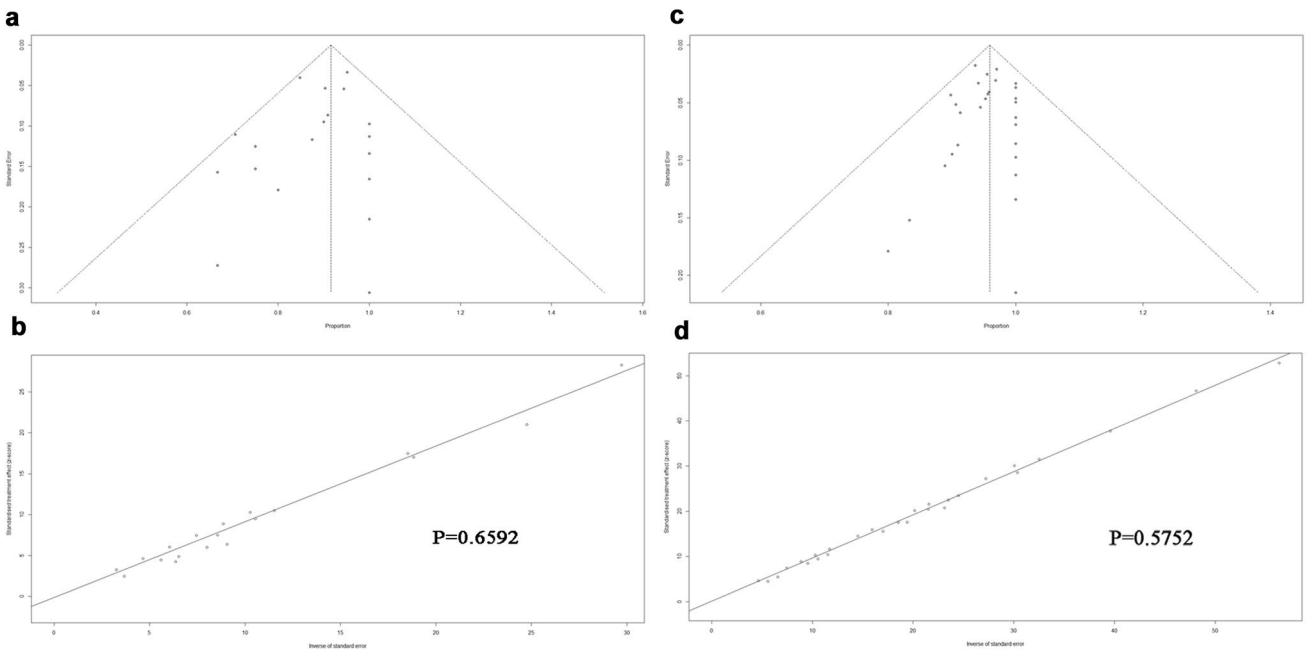


**Fig. 4** Begg's linear regression of sensitivity (**a**) and NPV (**c**), Egger's regression test of sensitivity (**b**, $P = 0.6592$) and NPV (**d**, $P = 0.5752$)

SLNB, the subsequent ENDs or follow-ups were very likely to be negative too. In the present study, 95% of patients (745/785) were TNs and these patients could have an option of watchful waiting instead of END, avoiding overtreatment.

The strength of our meta-analysis is that we emphasized the specific tongue subsite, providing a detailed and targeted evaluation of SLNB for early neck-negative TSCC patients. In conclusion, SLNB could effectively predict the status of regional lymph nodes in cT1/T2N0 TSCC patients. Certainly, further studies with larger sample sizes are needed, and cancers of other head and neck subsites should also be studied.

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**Compliance with ethical standards**

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**Conflict of interest** Author Yue Yang declares that she has no conflict of interest. Author Jian Zhou declares that he has no conflict of interest. Author Haitao Wu declares that he has no conflict of interest.

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