Received: 2 May 2022 | Revised: 20 July 2022 | Accepted: 10 August 2022

DOI: 10.1002/hed.27175

CLINICAL REVIEW

WILEY

Diagnostic test accuracy of sentinel lymph node biopsy in squamous cell carcinoma of the oropharynx, larynx, and hypopharynx: A systematic review and meta-analysis

Sven van den Bosch MD, PhD[1] | **Michal Czerwinski MD**[1] | **Tim Govers PhD**[2] | **Robert P. Takes MD, PhD**[3] | **Remco de Bree MD, PhD**[4] | **Abrahim Al-Mamgani MD, PhD**[5] | **Gerjon Hannink PhD**[2] | **Johannes H. A. M. Kaanders MD, PhD**[1]

[1]Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, the Netherlands

[2]Department of Operating Rooms, Radboud University Medical Center, Nijmegen, the Netherlands

[3]Department of Otolaryngology – Head and Neck Surgery, Radboud University Medical Center, Nijmegen, the Netherlands

[4]Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, the Netherlands

[5]Department of Radiation Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek, Amsterdam, the Netherlands

Correspondence
Sven van den Bosch, Department of Radiation Oncology, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands.
Email: sven.vandenbosch@radboudumc.nl

Abstract

The aim of this meta-analysis was to determine the diagnostic test accuracy of sentinel lymph node biopsy (SLNB) in patients with oropharyngeal, laryngeal, and hypopharyngeal squamous cell carcinoma (SCC). For this purpose, MEDLINE, EMBASE, and Web of Science were searched from inception to March 8, 2022. Included were studies evaluating diagnostic test accuracy of SLNB to identify cervical lymph node metastases with elective neck dissection or follow-up as reference. A bivariate generalized linear mixed model approach was used for the meta-analysis. Nineteen studies were eligible, evaluating 377 cases in total. The pooled estimates of sensitivity and negative predictive value were 0.93 (95% CI: 0.86–0.96) and 0.97 (95% CI: 0.94–0.98), respectively. The excellent accuracy of SLNB justifies a place in the diagnostic workup of patients with larynx and pharynx SCC. Randomized trials are required to demonstrate oncologic safety and benefits on treatment related morbidity and quality of life when omitting elective neck treatment based on SLNB.

KEYWORDS

hypopharynx, larynx, oropharynx, sentinel lymph node biopsy, squamous cell carcinoma

1 | INTRODUCTION

Laryngeal and pharyngeal squamous cell carcinoma (SCC) comes with a substantial risk for cervical lymph node metastases.[1] Because historically, diagnostic work-up had limited accuracy for the detection of small nodal metastases, elective irradiation of large anatomical volumes of the neck is performed routinely in the majority of patients with a clinically negative neck (cN0) receiving definitive (chemo)radiotherapy (CRT).[2,3] The aim is to eradicate metastases that stay under the diagnostic detection level (i.e., occult or microscopic metastases).

Current multimodal high-resolution imaging approaches have unprecedented accuracy in the detection of small nodal metastases.[4] As a result, the risk of having microscopic nodal metastases and also the microscopic tumor burden itself, are nowadays much lower compared to several decades before.[4] Nevertheless, elective neck irradiation (ENI) has remained largely unchanged. Therefore, RT dose and volume of ENI are nowadays likely larger than necessary to achieve control of occult disease.[4,5] An important consequence of ENI is the significant contribution to late radiation sequelae, such as dysphagia and xerostomia that negatively affect quality of life.[6,7] Depending on tumor site and T-classification, the prevalence of occult metastases ranges between 10% and 35%.[8] Therefore, the majority of patients will not benefit from ENI but do carry the burden of consequential radiation sequelae. Not surprisingly, de-escalation of both RT dose and volume of ENI are important topics in clinical research.[9–13] Obviously, the challenge is equivalent in surgically treated patients who are at risk for receiving futile elective neck dissection (END) with associated morbidity such as pain and limitations in shoulder function.[14] However, the sensitivity for detection of very small metastases with current imaging approaches is still insufficient to omit elective neck treatment in patients with a clinically negative neck.

Sentinel lymph node biopsy (SLNB) has emerged as a staging procedure that can reliably detect microscopic nodal metastases. This technique is based on the premise that metastases orderly progress with the lymphatic flow from the primary tumor to the sentinel lymph nodes (SLN) before spreading to subsequent draining lymph nodes, and that the pathologic status of the SLN accurately reflects the histology of subsequent lymph nodes.[15] Most accurate histopathological detection of metastases can be achieved with step serial sectioning and immunohistochemistry.[16] In early stage oral cavity cancers, SLNB has an important place in diagnostic workup of the neck and is decisive to perform or omit END.[17–19] For other tumor sites in the head and neck area such as the larynx and pharynx that are primarily treated with (C)RT, SLNB is not performed routinely. Analogous to oral cavity cancers, it is conceivable that SLNB can also reduce the need for elective treatment of the neck in patients treated with (C)RT. By tailoring ENI to the individual patient, guided by information provided by SLNB, unnecessary treatment-associated morbidity may be avoided. It is expected that such treatment strategy will improve quality of life without compromising oncologic outcomes.

Before such strategy can be implemented in clinical trials, data on diagnostic test accuracy of SLNB for these tumor sites is mandatory. However, studies reporting on this subject are scarce and the numbers of included subjects are small. Therefore, we performed a systematic review and meta-analysis to determine the diagnostic test accuracy of SLNB for the detection of cervical lymph node metastases in patients with oropharyngeal, laryngeal and hypopharyngeal SCC.

2 | METHODS

This review and meta-analysis of diagnostic test accuracy studies was conducted according to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy and reported following the PRISMA-DTA guidelines.[20,21] The full study protocol is available at the international prospective register of systematic reviews (PROSPERO) (registration number: CRD42021232282).

2.1 | Eligibility criteria

Included were cohort studies and randomized trials evaluating diagnostic test accuracy of SLNB using a radioactive agent and/or fluorescent dye (index test) for the detection of cervical lymph node metastases (target condition) with END or a follow-up of at least 18 months in case of a "wait and see" policy as reference standard, in an adult human population with newly diagnosed oropharyngeal, laryngeal or hypopharyngeal SCC. Exclusion criteria were: sample size <5 patients; previous oncologic treatment of the neck; clinical staging of the neck by palpation only; or when it was not possible to derive absolute numbers of observations for true positives (TP), true negatives (TN), and false negatives (FN) regarding the diagnostic test accuracy of SLNB for the tumor sites oropharynx and larynx/hypopharynx separately.

2.2 | Data sources and search strategy

The electronic databases of MEDLINE, EMBASE, HTA, DARE, Cochrane, and Web of Science (Science Citation Index) were searched without applying restrictions, from inception to March 8, 2022. The search strategy was developed with input from the project team and then peer reviewed by an independent Health Sciences Librarian with expertise in systematic review searching. The search strategy included terms and synonyms for "sentinel lymph node biopsy," "squamous cell carcinoma," "head and neck neoplasm," "pharynx," "larynx," and "diagnostic test accuracy" (also see full study protocol at PROSPERO). Additionally, reference lists of included studies and relevant reviews identified through the search were screened for eligible publications.

2.3 | Study selection

The titles and abstracts yielded by the search were screened against the eligibility criteria independently by two reviewers using standardized forms. Disagreements were discussed and resolved by consensus. Unresolved disagreements were adjudicated by an independent arbitrator. Overlapping cohorts were identified based on coauthor names and affiliations, inclusion periods and the number of included subjects. For overlapping cohorts, the publication describing the largest population of interest for this review was included.

2.4 | Data extraction

The extracted data comprised characteristics with regard to the study design, population, diagnostic workup, reference standard, procedures and diagnostic outcomes of SLNB, and anatomical distribution of SLNs. All data were extracted in duplicate by two independent reviewers using standardized forms. Disagreements were discussed and resolved by consensus. To obtain 2×2 contingency tables for the evaluation of diagnostic test accuracy of SLNB, absolute numbers of TP, TN, and FN findings were extracted or calculated. Contingency tables were extracted separately for the tumor sites oropharynx and larynx/hypopharynx. Authors were contacted if the appropriate data could not be obtained from the published articles. TP was defined as the presence of metastases in SLN(s). TN was defined as the absence of metastases in SLN(s) and END specimen or the absence of regional recurrence during follow-up in case of a "wait and see policy." FN was defined as the absence of metastases in SLN(s) but presence of metastases END specimen or regional recurrence during follow-up in case of a "wait and see policy." False positive (FP) results are not possible because histopathological examination provides indisputable proof of metastases and therefore the specificity and positive predictive value (PPV) are always 1.

2.5 | Risk of bias and applicability

The methodological quality of included studies was evaluated using the Quality Assessment tool of Diagnostic Accuracy Studies (QUADAS-2).[22] Signaling questions for bias and criteria for assessment of applicability were tailored to this specific review. Signaling questions for bias regarding blinding and threshold for the domains index test and reference standard were omitted because histopathological detection of nodal metastases is considered an objective test without threshold being used. Concerns regarding applicability were rated high when patient selection and methodological procedures of SLNB in the included studies significantly diverged from current international consensus guidelines on SLNB in oral cancer.[17,18,23] For patient selection, concerns regarding applicability were rated high when ≥10% of the population had T4 tumors or a clinically positive neck. With regard to SLNB procedures, concerns regarding applicability were rated high when less than 3 peritumoral tracer injections were applied, no preoperative SLN localization was performed (planar lymphoscintigraphy or SPECT/CT), or histopathological examination of SLNs did not include both serial step sectioning and immunohistochemistry. Each included study was critically appraised by two reviewers independently and discrepancies were resolved by consensus.

2.6 | Data synthesis

Statistical analysis was carried out with R (R Foundation for Statistical Computing, Vienna, Austria). Data from 2×2 contingency tables was used to calculate pooled sensitivity, FN rate, and negative predictive value (NPV). Results are presented graphically by plotting estimates of sensitivity and NPV with their 95% confidence intervals (95% CI) in forest plots. A bivariate generalized linear mixed model approach was used for the meta-analysis in which counts of TP and TN are directly modeled.[24,25] This approach does not require the assumption that the logit sensitivity and logit specificity approximately follow normal distributions within studies, which could be seriously violated in the presence of small data counts. It also avoids corrections for zero counts. Heterogeneity was investigated visually by examining the forest plots and statistically by including covariates in the bivariate models and by conducting pre-specified subgroup and sensitivity analyses.[26] The following sources of heterogeneity were assessed: tumor site (oropharynx vs. larynx/hypopharynx), SLN localization (preoperative imaging vs. intraoperative only), reference standard (END vs. "wait and see"), and QUADAS-2 risk of bias and applicability (low vs. high). Deeks' test and funnel plots were used to explore publication bias.[27]

In addition, pooled estimates (with their corresponding 95% CI) of SLN detection rate, prevalence of contralateral SLNs and the prevalence of nodal metastases were calculated using Freeman–Tukey double arcsine transformation within a random effects model framework.[28] Heterogeneity of combined study results were assessed by I^2, and its connected chi-square test for heterogeneity, and the corresponding 95% prediction interval were calculated. Differences between the tumor sites oropharynx

and larynx/hypopharynx were tested using the Q statistic for heterogeneity.[29] The Q statistic follows a χ^2-distribution with *number of groups - 1* degrees of freedom under the null hypothesis of no heterogeneity between subgroups.

3 | RESULTS

3.1 | Study selection and characteristics of included studies

The search identified 11 687 records of which 4982 were duplicates, leaving 6705 records to screen. Based on title and abstract 6585 records were excluded. For 8 of 120 remaining records, full-text could not be retrieved, leaving 112 records for assessment of eligibility. All inclusion criteria were met in 19 articles and these were included in the analysis.[30–48] Reasons for exclusion and the flow of information through the review process are shown in Figure 1. The included studies reported the results of SLNB in a total of 377 patients with oropharyngeal ($n = 162$), laryngeal ($n = 181$), or hypopharyngeal ($n = 34$) SCC. Characteristics of study design and patient population are summarized in Table 1 and characteristics of study procedures in Table 2.

3.2 | Risk of bias and applicability

The risk of bias and concerns regarding applicability varied among the studies (Figure S1 and Table S1, Supporting Information). Risk of bias with respect to patient selection was rated high in 2 (11%) studies because of the retrospective design and unclear in 11 (58%) prospective cohort studies because these did not explicitly report if the cohorts were consecutive. All studies were rated low risk of bias

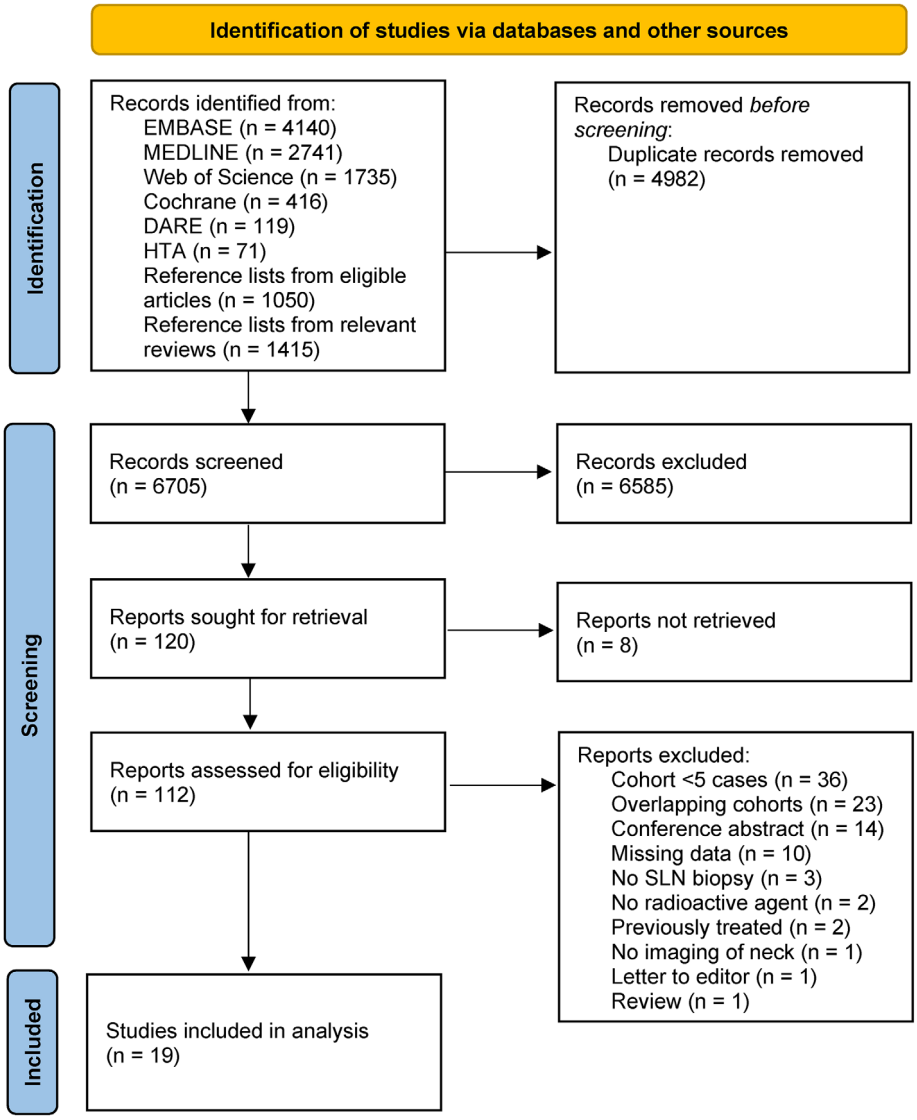


FIGURE 1 PRISMA 2020 flow diagram for systematic reviews [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of study design and patient population

		Characteristics of study design				Characteristics of patient population					
Author	**Year**	**Enrollment**	**Multicenter**	**Prospective**	**Inclusion**	**Oropharynx**	**Larynx**	**Hypopharynx**	**Total**	**T-classification**	**N-classification**
Akyildiz et al.[30]	2017	Cohort	No	No	2009–2014	0	18	0	18	1–3	0
Araki et al.[31]	2020	Cohort	Yes	Yes	2013–2015	10	4	8	22	1–2	0
Burcia et al.[32]	2010	Consecutive	No	Yes	2003–2006	16	0	0	16	1–2	0
Cizmarevic and Zargi[33]	2006	Cohort	No	Yes	2003	5	0	0	5	1–3	0
Dequanter et al.[34]	2013	Cohort	No	No	NR	11	0	0	11	1–2	0
Flach et al.[35]	2013	Cohort	No	Yes	2008–2010	0	13	0	13	3–4	0
Hoft et al.[36]	2004	Cohort	No	Yes	2000–2003	19	12	1	32	1–4	0
Hu et al.[37]	2011	Cohort	No	yes	2003–2007	0	33	12	45	1–4	0
Khadivi et al.[38]	2015	Cohort	No	Yes	2012–2014	0	10	0	10	2–3	0
Kovacs et al.[39]	2009	Consecutive	No	Yes	2000–2007	15	0	0	15	1–2	0
Lawson et al.[40]	2010	Consecutive	No	Yes	2001–2004	0	29	0	29	1–3	0
Peng et al.[41]	2015	Consecutive	No	yes	2014–2014	7	0	0	7	1–2	0
Prgomet et al.[42]	2008	Cohort	No	Yes	NR	0	15	5	20	1–3	0
Santaolalla et al.[43]	2008	Cohort	No	Yes	2002–2005	7	0	0	7	1–3	0
Schilling et al.[44]	2015	Cohort	Yes	Yes	2005–2010	10	0	0	10	1–2	0
Stefanicka et al.[45]	2010	Cohort	No	Yes	2006–2009	9	0	0	9	1–3	0–1
Stoeckli[46]	2007	Consecutive	No	Yes	2000–2006	9	0	0	9	1–2	0
Tomifuji et al.[47]	2008	Consecutive	No	Yes	2002–2004	0	16	4	20	2–4	0
Werner et al.[48]	2004	Cohort	No	Yes	NR	44	31	4	79	1–3	0

Abbreviation: NR, not reported.

TABLE 2 Characteristics of study procedures

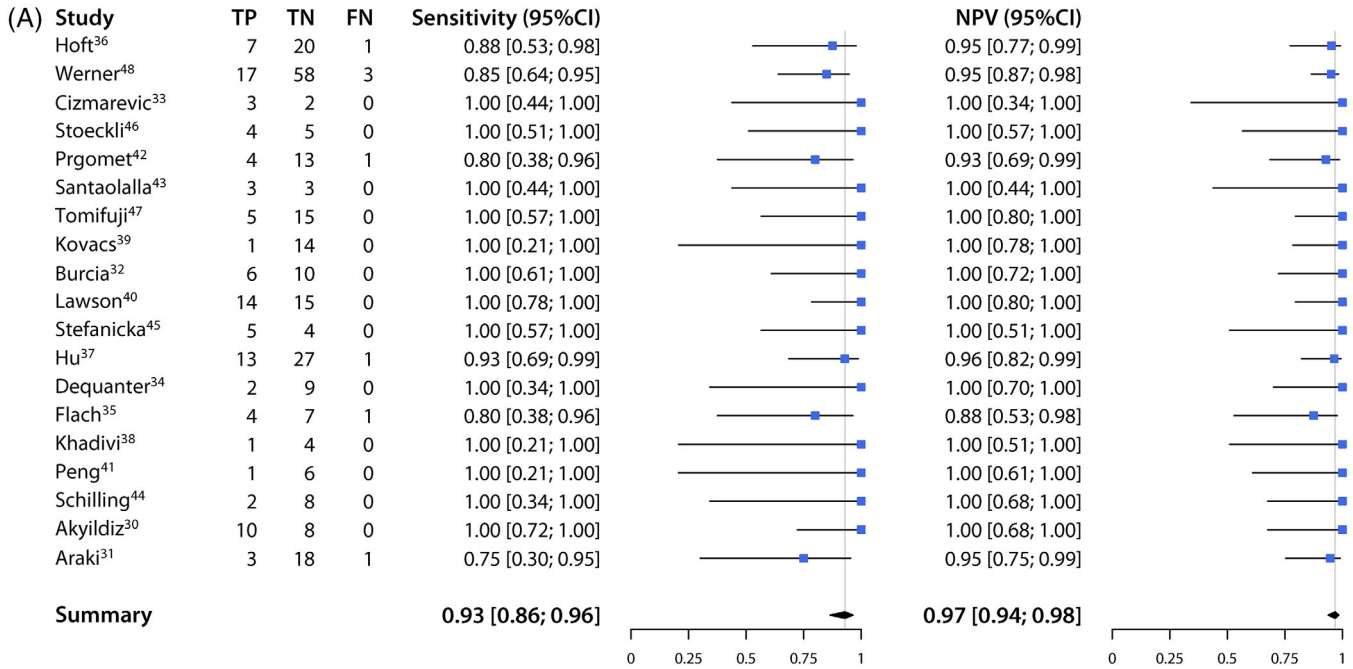
Author	Year	Clinical evaluation of the neck	Procedures of sentinel lymph node biopsy		Histopathological evaluation of sentinel node(s)		Reference standard
			Tracer injection	Imaging	Step-serial sectioning	Staining	
Akyildiz et al.[30]	2017	CT/MRI, US	Pre-epiglottic	L, G	Yes (100 μm)	HE, IHC	END
Araki et al.[31]	2020	CT/MRI	PT 4x	FLUO	No (1 section per 2 mm blocks)	HE, IHC	FU (≥24 M)
Burcia et al.[32]	2010	CT	PT 3-4x	L, G	Yes (250 μm)	HE, IHC	END
Cizmarevic and Zargi[33]	2006	CT, US	PT 4x	L, G	Yes (100–150 μm)	HE, IHC	END
Dequanter et al.[34]	2013	CT/MRI	PT	G	No (2 sections per 2.5 mm blocks)	HE, IHC	FU (median 59 M)
Flach et al.[35]	2013	CT/MRI, US-FNAC	PT 4x	G	Yes (150 μm)	HE, IHC	END
Hoft et al.[36]	2004	US-FNAC	PT 4x	L, G	No (3 sections per 2 mm blocks)	HE, IHC	END
Hu et al.[37]	2011	CT/MRI	PT 3-4x	L, SPECT, G	Yes (not specified)	HE, IHC	END
Khadivi et al.[38]	2015	CT	PT 4x	G	Yes (not specified)	HE	END
Kovacs et al.[39]	2009	CT, US	PT 2-8x	L, G	Yes (150 μm)	HE, IHC	FU (mean 80 M)
Lawson et al.[40]	2010	CT	PT 4x	G	Yes (150 μm)	HE, IHC	END
Peng et al.[41]	2015	CT/MRI	PT 4x	FLUO	NR	NR	END
Prgomet et al.[42]	2008	CT, US	PT 3-4x	L, G	NR	HE	END
Santaolalla et al.[43]	2008	CT	PT 4x	L, G	Yes (150 μm)	HE, IHC	END
Schilling et al.[44]	2015	CT/MRI, US-FNAC	PT 4x	L, G	Yes (150 μm)	HE, IHC	FU (≥36 M)
Stefanicka et al.[45]	2010	CT, US	PT 1-4x	L, G	Yes (200 μm)	HE, IHC	END
Stoeckli[46]	2007	CT/MRI, US-FNAC	PT 4x	L, SPECT, G	Yes (150 μm)	HE, IHC	END / FU (mean 19 M)
Tomifuji et al.[47]	2008	CT, US	PT 3-4x	L, G	Yes (not specified)	HE, IHC	END
Werner et al.[48]	2004	CT, US	PT 4x	G	No (1 mm slices)	HE, IHC	END

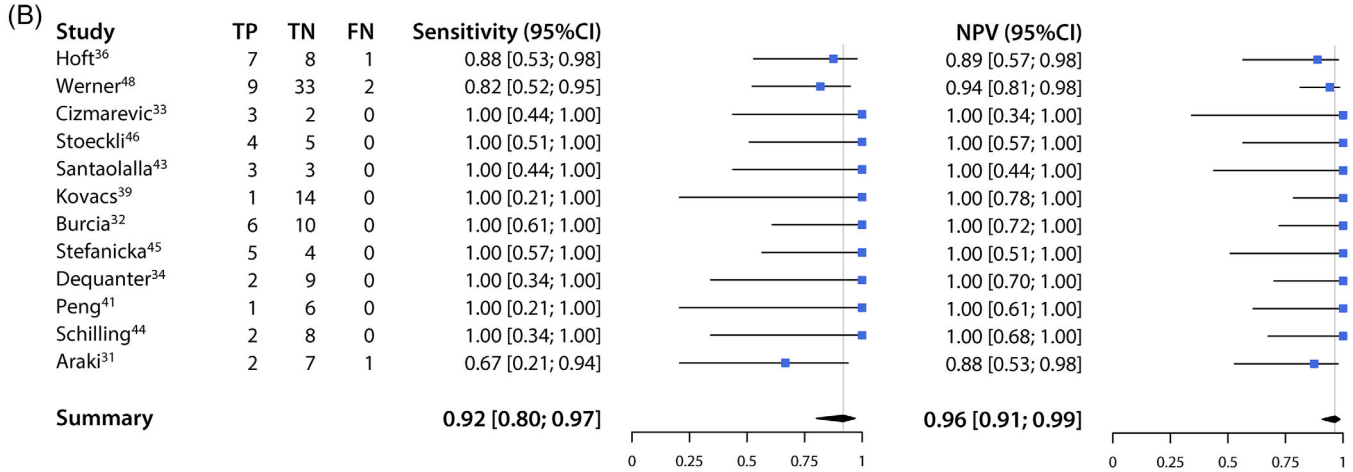
Abbreviations: CT, computed tomography; END, elective neck dissection; FLUO, fluorescence; FNAC, fine needle aspirated cytology; FU, follow-up; G, gamma-probe; HE, hematoxylin and eosin; IHC, immunohistochemistry; L, planar lymphoscintigraphy; MRI, magnetic resonance imaging; NR, not reported; PT, peritumoral; SPECT, single photon-emission computed tomography; US, ultrasound.

with respect to the index test and reference standard. Risk of bias with respect to flow and timing was rated high in 3 (16%) studies because not all patients were included in the final analysis. There were concerns regarding applicability of results in 12 (63%) studies because patient selection or study procedures significantly diverged from international consensus guidelines on SLNB.

3.3 | Diagnostic test accuracy

The forest plots in Figure 2 show the number of TP, FN, and TN observations, and the sensitivity and NPV of each included study. For the whole group, the pooled estimate of the sensitivity of SLNB was 0.93 (95% CI: 0.86–0.96) and for the NPV this was 0.97 (95% CI: 0.94–0.98) (Figure 2A).





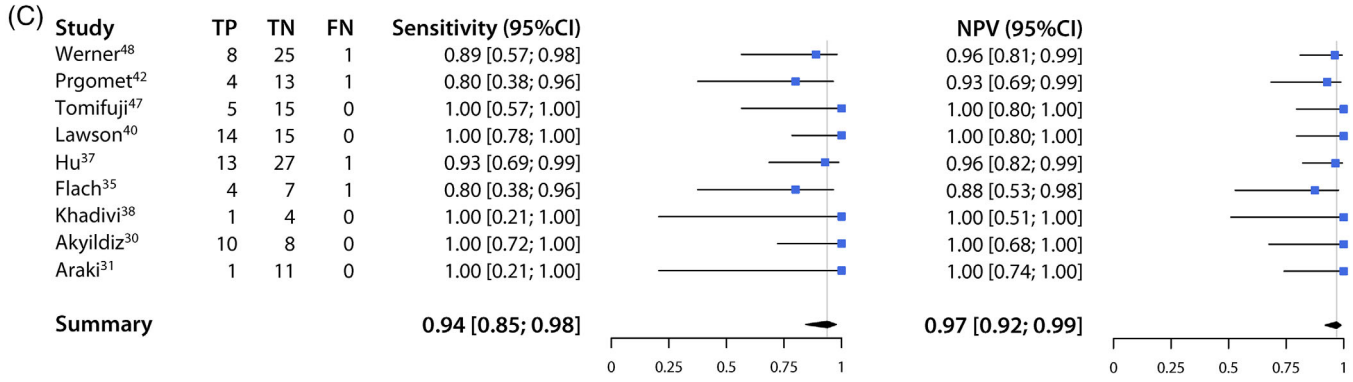


FIGURE 2 Forest plots of sensitivity and negative predictive value for all (A) tumor sites (oropharynx, larynx, and hypopharynx), and the tumor sites (B) oropharynx and (C) larynx and hypopharynx. CI, confidence interval; FN, false negative; TN, true negative; TP, true positive [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Additional analyses

Subgroup analyses on tumor site demonstrated a pooled estimate of the sensitivity of SLNB of 0.92 (95% CI: 0.80–0.97) and a NPV of 0.96 (95% CI: 0.91–0.99) for oropharyngeal tumors (Figure 2B) and 0.94 (95% CI: 0.85–0.98) and 0.97 (95% CI: 0.92–0.99) for laryngeal/hypopharyngeal tumors, respectively (Figure 2C).

Sensitivity analyses were performed to investigate heterogeneity in diagnostic test accuracy (Figure 3). For studies with low risk for bias (QUADAS-2), the pooled estimate of the sensitivity of SLNB was 0.93 (95% CI: 0.85–0.96), for the NPV this was 0.97 (95% CI: 0.93–0.98). For studies with low concerns for applicability (QUADAS-2), this was 0.95 (95% CI: 0.81–0.99) and 0.97 (95% CI: 0.89–0.99), respectively. For studies that performed preoperative SLN localization (planar lymphoscintigraphy or SPECT/CT), sensitivity was 0.95 (95% CI: 0.87–0.99) and NPV was 0.98 (95% CI: 0.93–0.99). A "wait and see" policy was used as reference standard in 4 studies. For these studies, sensitivity was 0.90 (95% CI: 0.53–0.99) and NPV was 0.98 (95% CI: 0.88–1.00).

Publication bias is unlikely, because Deek's funnel plot was relatively symmetrical with respect to the regression line and having a nonsignificant asymmetry test ($p = 0.16$) (Figure S2).

3.5 | Results of sentinel lymph node biopsy

For the whole group, the pooled SLN detection rate was 0.98 (95% CI: 0.94–1.0) (reported in 19/19 studies in 377 patients). A total of 810 SLNs were identified and

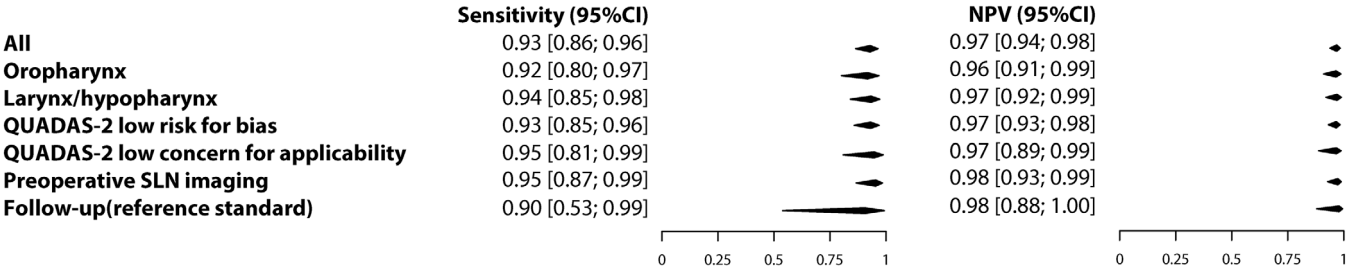


FIGURE 3 Pooled estimates of sensitivity and negative predictive value of all studies, subgroups and sensitivity analysis. CI, confidence interval; NPV, negative predictive value; SLN, sentinel lymph node

TABLE 3 Tumor site specific results of sentinel lymph node biopsy

	Oropharynx	Larynx and hypopharynx	*p*-value
No. of patients	162 (reported in 12 studies)	215 (reported in 10 studies)	NA
Pooled detection rate of SLNs	1.0 (95% CI: 0.96–1.0)	0.96 (95% CI: 0.87–1.0)	0.37
Mean number of SLNs per patient	2.2 (264/117) (reported in 9/12 studies in 117 patients with 264 SLN)	2.7 (546/201) (reported in 10/10 studies in 201 patients with 546 SLN)	NA
Pooled prevalence of contralateral SLN	0.16 (95% CI: 0.06–0.29) (reported in 8/12 studies in 107 patients)	0.35 (95% CI: 0.19–0.52) (reported in 7/10 studies in 159 patients)	0.09
Anatomical neck levels of SLN	Level I in 5% (12/258) Level II in 69% (181/258) Level III in 22% (56/258) Level IV in 2% (5/258) Level V in 1% (3/258) Level VI in 1% (1/258) (reported in 9/12 studies in 115 patients with 258 SLNs)	Level I in 1% (2/276) Level II in 48% (131/276) Level III in 41% (114/276) Level IV in 7% (18/276) Level V in 1% (2/276) Level VI in 3% (9/276) (reported in 7/10 studies in 113 patients with 276 SLNs)	NA
No. of patients with nodal metastases	49 of which 45 were detected by SLNB and 4 with END/FU (with negative SLNB)	64 of which 60 were detected by SLNB and 4 with END/FU (with negative SLNB)	NA
Pooled prevalence of nodal metastases	0.29 (95% CI: 0.18–0.41)	0.30 (95% CI: 0.20–0.41)	0.93

Abbreviations: END, elective neck dissection; FU, follow-up; NA, not applicable; SLN, sentinel lymph node.

excised with a mean number of SLNs per patient of 2.6 (810/310) (reported in 16/19 studies in 310 patients). The pooled prevalence of contralateral SLNs was 0.26 (95% CI: 0.15–0.38) (reported in 13/19 studies in 266 patients). A higher prevalence of contralateral SLNs was observed for laryngeal/hypopharyngeal SCC (0.35, 95% CI: 0.19–0.52) compared to oropharyngeal SCC (0.16, 95% CI: 0.05–0.29), but the difference did not reach statistical significance ($p = 0.09$). The pooled prevalence of clinically occult nodal metastases was 0.29 (95% CI: 0.22–0.37) and were detected by SLNB ($n = 105$) or END/FU (with negative SLNB) ($n = 8$). The prevalence of clinically occult metastases was not different between laryngeal/hypopharyngeal SCC (0.30, 95% CI: 0.20–0.41) and oropharyngeal SCC (0.29, 95% CI: 0.18–0.41) ($p = 0.93$). Forest plots of pooled data are shown in Figure S3. Tumor site specific results of SLNB and the anatomical distribution of SLNs are shown in Table 3.

4 | DISCUSSION

The principal finding of this systematic review and meta-analysis is that the diagnostic test accuracy of SLNB for the detection of cervical lymph node metastases in patients with oropharyngeal, laryngeal and hypopharyngeal SCC is excellent. The procedure appears to be applicable in these tumor sites, because in 98% of the patients at least 1 SLN could be detected and surgically removed for histopathological examination. Subgroup analysis demonstrated no relevant differences in diagnostic test accuracy between the tumor sites oropharynx and larynx/hypopharynx. As expected, the anatomical distribution of SLNs demonstrate high concordance with the historical data on the distribution of clinically manifest cervical lymph node metastases in head and neck SCC as reported by Lindberg et al. in 1973.[49] For oropharyngeal SCC, the majority of SLNs was seen in neck level II (69%), mostly with unilateral SLNs only (84%). For laryngeal/hypopharyngeal SCC, most SLNs were seen in neck level II (48%) and III (41%) with more frequent bilateral SLNs (35%).

Among tumors arising from the mucosal surface of the upper aerodigestive tract, the oral cavity is the only tumor site where SLNB is a validated alternative to END and is routinely applied by experienced surgical teams in clinical practice.[17–19] Literature on the diagnostic test accuracy for SLNB in patients with oral cavity cancers demonstrates a high concordance with the results of the current study. A meta-analysis of 66 studies including 3566 patients with oral cancer demonstrated a pooled sensitivity of 0.87 and a NPV of 0.94.[50] In the current study, this was 0.93 and 0.97, respectively.

In both the present study and the aforementioned oral cavity cancer meta-analysis, clinically occult metastases were identified in approximately 30% of the patients.[50] This emphasizes that the detection of very small lymph node metastases with current diagnostic imaging approaches is still insufficient to omit elective neck treatment.[4] It is for this reason that ENI is performed routinely in patients primarily treated with (C)RT for cN0 oropharyngeal, laryngeal, and hypopharyngeal SCC.[2,3] The consequence is that 70% of the patients do not benefit from ENI but may potentially suffer from its associated permanent long-term side effects that can negatively affect quality of life.[6,7] It is conceivable that SLNB can also be implemented as a diagnostic procedure in patients primarily treated with (C)RT for cN0 laryngeal and pharyngeal SCC to individually tailor ENI. This approach is expected to avoid futile ENI and its associated morbidity in the majority of patients, aiming to improve the patients' long-term well-being without compromising oncologic safety. However, until now, this concept has only been sparsely explored by radiation oncologists. First studies on selective ENI guided by SLN mapping with SPECT/CT (without biopsy of SLNs) demonstrate feasibility of the concept with high gains in toxicity and quality of life.[11–13] Based on the results of this meta-analysis, a randomized controlled trial evaluating the safety and efficacy of SLNB guided selective ENI in patients with cN0 laryngeal and pharyngeal SCC treated with (C)RT is planned (PRIMO-trial, clinicaltrials.gov identifier: NCT05333523).

The quality of included studies was assessed using the QUADAS-2 tool. Concerns for applicability were rated high when patient selection or methodological procedures of SLNB significantly diverged from international consensus guidelines on SLNB in oral cancer.[17,18] Note that these guidelines date from 2019, while the majority of the studies (14/19) accrued patients before 2010. Sensitivity analysis demonstrated that studies with low concerns for applicability and studies that performed preoperative SLN localization with planar lymphoscintigraphy or SPECT/CT had the most favorable combination of sensitivity (0.95) and NPV (0.98). Studies that performed preoperative SLN localization yielded higher number of SLNs per patient (2.8 vs. 2.3). Preoperative SLN imaging is highly recommended in current guidelines.[17,18]

Implementation of the SLNB technique in larynx and pharynx tumors in routine clinical practice faces a number of challenges. Among these are the logistics for peritumoral tracer injection, interdisciplinary coordination of procedures, avoiding increased time-to-treatment interval and paucity of local expertise. Recent development of transnasal flexible digital video laryngoscopes with a

working channel now enable that a variety of surgical procedures can be performed in the outpatient clinic under topical anesthesia instead of the operating room under general anesthesia.[51,52] Among these procedures are tumor biopsies and peritumoral tracer injection for SLNB. This approach has been shown to significantly decrease diagnostic workup time and the risk of general anesthesia can be avoided.[53] Two of the included studies in this meta-analysis performed flexible endoscopic peritumoral tracer injection under topical anesthesia for laryngeal/hypopharyngeal tumors and demonstrate excellent sensitivity (≥0.93) and NPV (≥0.96).[37,47] Not surprisingly, flexible endoscopic peritumoral tracer injection is increasingly being utilized in ongoing clinical trials (clinicaltrials.gov identifiers: NCT02572661, NCT03968679, NCT04068636, NCT05333523).

5 | LIMITATIONS

A limitation of this study is a potential risk for bias in 13 of the 19 studies (QUADAS-2). While 17 of the studies were prospective, only 6 explicitly stated that consecutive patient cohorts were recruited. For the other 11 studies, it could not be determined with certainty if there was selection of patients that underwent SLNB. Three studies scored high risk for bias because patients were excluded from analysis.

Another potential source of bias is that 10 papers (227 cases) that were potentially eligible for inclusion had to be excluded because insufficient data were available to create 2×2 contingency tables. Efforts were made to retrieve missing data by contacting the authors. Only two responded, but the data were no longer available. Because these excluded studies comprised mixed patient cohorts also including oral cavity cancers, it could not be established if the results in patients with laryngeal and pharyngeal tumor sites substantially differed from those included in the current meta-analysis.

6 | CONCLUSIONS

This systematic review and meta-analysis demonstrates a high sensitivity and NPV of SLNB for the detection of cervical lymph node metastases in patients with oropharyngeal, laryngeal, and hypopharyngeal SCC, justifying a place in the diagnostic workup. Results from randomized controlled clinical trials are required to demonstrate oncologic safety and benefits on treatment related morbidity and quality of life when omitting elective neck treatment based on SLNB in these patients.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Sven van den Bosch https://orcid.org/0000-0002-0675-1847
Robert P. Takes https://orcid.org/0000-0003-4784-0499
Remco de Bree https://orcid.org/0000-0001-7128-5814
Abrahim Al-Mamgani https://orcid.org/0000-0003-0748-6640

REFERENCES

1. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. *N Engl J Med*. 1993;328(3):184-194.
2. Machiels JP, Rene Leemans C, Golusinski W, et al. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(11):1462-1475.
3. Gregoire V, Ang K, Budach W, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol*. 2014;110(1):172-181.
4. van den Bosch S, Vogel WV, Raaijmakers CP, et al. Implications of improved diagnostic imaging of small nodal metastases in head and neck cancer: radiotherapy target volume transformation and dose de-escalation. *Radiother Oncol*. 2018;128(3):472-478.
5. Kaanders J, van den Bosch S, Dijkema T, Al-Mamgani A, Raaijmakers CPJ, Vogel WV. Advances in cancer imaging require renewed radiotherapy dose and target volume concepts. *Radiother Oncol*. 2020;148:140-142.
6. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol*. 2008;26(22):3770-3776.
7. Ramaekers BL, Joore MA, Grutters JP, et al. The impact of late treatment-toxicity on generic health-related quality of life in head and neck cancer patients after radiotherapy. *Oral Oncol*. 2011;47(8):768-774.
8. Pillsbury HC 3rd, Clark M. A rationale for therapy of the N0 neck. *Laryngoscope*. 1997;107(10):1294-1315.
9. van den Bosch S, Dijkema T, Kunze-Busch MC, et al. Uniform FDG-PET guided GRAdient dose prEscription to reduce late radiation toxicity (UPGRADE-RT): study protocol for a randomized clinical trial with dose reduction to the elective neck in head and neck squamous cell carcinoma. *BMC Cancer*. 2017;17(1):208.
10. Deschuymer S, Nevens D, Duprez F, et al. Randomized clinical trial on reduction of radiotherapy dose to the elective neck in head and neck squamous cell carcinoma; update of the long-term tumor outcome. *Radiother Oncol*. 2020;143:24-29.
11. de Veij Mestdagh PD, Walraven I, Vogel WV, et al. SPECT/CT-guided elective nodal irradiation for head and neck cancer is

oncologically safe and less toxic: a potentially practice-changing approach. *Radiother Oncol*. 2020;147:56-63.
12. de Veij Mestdagh PD, Schreuder WH, Vogel WV, et al. Mapping of sentinel lymph node drainage using SPECT/CT to tailor elective nodal irradiation in head and neck cancer patients (SUSPECT-2): a single-center prospective trial. *BMC Cancer*. 2019;19(1):1110.
13. Longton E, Lawson G, Bihin B, et al. Individualized prophylactic neck irradiation in patients with cN0 head and neck cancer based on sentinel lymph node(s) identification: definitive results of a prospective phase 1-2 study. *Int J Radiat Oncol Biol Phys*. 2020;107(4):652-661.
14. Gane EM, Michaleff ZA, Cottrell MA, et al. Prevalence, incidence, and risk factors for shoulder and neck dysfunction after neck dissection: a systematic review. *Eur J Surg Oncol*. 2017;43(7):1199-1218.
15. Ross G. Rationale for sentinel node biopsy to stage N0 head and neck squamous-cell carcinoma. *Cancer Biother Radiopharm*. 2004;19(3):273-284.
16. Rinaldo A, Devaney KO, Ferlito A. Immunohistochemical studies in the identification of lymph node micrometastases in patients with squamous cell carcinoma of the head and neck. *ORL J Otorhinolaryngol Relat Spec*. 2004;66(1):38-41.
17. Schilling C, Stoeckli SJ, Vigili MG, et al. Surgical consensus guidelines on sentinel node biopsy (SNB) in patients with oral cancer. *Head Neck*. 2019;41(8):2655-2664.
18. Giammarile F, Schilling C, Gnanasegaran G, et al. The EANM practical guidelines for sentinel lymph node localisation in oral cavity squamous cell carcinoma. *Eur J Nucl Med Mol Imaging*. 2019;46(3):623-637.
19. Gupta T, Maheshwari G, Kannan S, Nair S, Chaturvedi P, Agarwal JP. Systematic review and meta-analysis of randomized controlled trials comparing elective neck dissection versus sentinel lymph node biopsy in early-stage clinically node-negative oral and/or oropharyngeal squamous cell carcinoma: evidence-base for practice and implications for research. *Oral Oncol*. 2022;124:105642.
20. Deeks JJ, Bossuyt PM, Gatsonis C, eds. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0*. The Cochrane Collaboration; 2013. http://srdta.cochrane.org
21. McInnes MDF, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. *Jama*. 2018;319(4):388-396.
22. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536.
23. Sloan P. Head and neck sentinel lymph node biopsy: current state of the art. *Head Neck Pathol*. 2009;3(3):231-237.
24. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. *J Clin Epidemiol*. 2006;59(12):1331-1332. author reply 1332–1333.
25. Ma X, Nie L, Cole SR, Chu H. Statistical methods for multivariate meta-analysis of diagnostic tests: an overview and tutorial. *Stat Methods Med Res*. 2016;25(4):1596-1619.
26. Takwoingi Y, Riley RD, Deeks JJ. Meta-analysis of diagnostic accuracy studies in mental health. *Evid Based Ment Health*. 2015;18(4):103-109.
27. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol*. 2005;58(9):882-893.
28. Miller JJ. The inverse of the Freeman–Tukey double arcsine transformation. *Am Stat*. 1978;32(4):138.
29. Schwarzer G, Carpenter JR, Rücker G. Meta-analysis with R. *Use R!*. Springer; 2015.
30. Akyildiz S, Kaya I, Ozturk K, Turhal G, Yavuzer A. Effectiveness of sentinel lymph node biopsy with pre-epiglottic Tc99 injection. *B-Ent*. 2017;13(3):205-210.
31. Araki K, Tomifuji M, Shiotani A, et al. Minimally invasive surgery for laryngopharyngeal cancer: multicenter feasibility study of a combination strategy involving transoral surgery and real-time indocyanine green fluorescence-navigated sentinel node navigation surgery. *Head Neck J Sci Spec Head Neck*. 2020;42(2):254-261.
32. Burcia V, Costes V, Faillie JL, et al. Neck restaging with sentinel node biopsy in T1-T2N0 oral and oropharyngeal cancer: why and how? *Otolaryngol Head Neck Surg*. 2010;142(4):592-597.
33. Cizmarevic B, Zargi M. Sentinel lymph node in oral and oropharyngeal epithelial tumors. *Wien Klin Wochenschr*. 2006;118(3–4):114-119.
34. Dequanter D, Shahla M, Paulus P, Lothaire P. Long term results of sentinel lymph node biopsy in early oral squamous cell carcinoma. *Onco Targets Ther*. 2013;6:799-802.
35. Flach GB, Bloemena E, van Schie A, et al. Sentinel node identification in laryngeal cancer: feasible in primary cancer with previously untreated neck. *Oral Oncol*. 2013;49(2):165-168.
36. Hoft S, Maune S, Muhle C, et al. Sentinel lymph-node biopsy in head and neck cancer. *Br J Cancer*. 2004;91(1):124-128.
37. Hu G, Zhong S, Xiao Q, Li Z, Hong S. Radiolocalization of sentinel lymph nodes in clinically N0 laryngeal and hypopharyngeal cancers. *Ann Otol Rhinol Laryngol*. 2011;120(5):345-350.
38. Khadivi E, Daghighi M, Khazaeni K, Dabbagh Kakhki VR, Zarifmahmoudi L, Sadeghi R. Intra-operative lymphatic mapping and sentinel node biopsy in laryngeal carcinoma: preliminary results. *Iran J Otorhinolaryngol*. 2015;27(81):285-291.
39. Kovacs AF, Stefenelli U, Seitz O, et al. Positive sentinel lymph nodes are a negative prognostic factor for survival in T1-2 oral/oropharyngeal cancer—a long-term study on 103 patients. *Ann Surg Oncol*. 2009;16(2):233-239.
40. Lawson G, Matar N, Nollevaux MC, et al. Reliability of sentinel node technique in the treatment of N0 supraglottic laryngeal cancer. *Laryngoscope*. 2010;120(11):2213-2217.
41. Peng H, Wang SJ, Niu X, Yang X, Chi C, Zhang G. Sentinel node biopsy using indocyanine green in oral/oropharyngeal cancer. *World J Surg Oncol*. 2015;13:278.
42. Prgomet D, Huic D, Mutvar A, Rakusic Z, Bilic M, Katic V. Sentinel lymphadenectomy in squamous cell carcinoma of the pharynx and larynx. *Lijec Vjesn*. 2008;130(3–4):58-61.
43. Santaolalla F, Sanchez JM, Ereno C, et al. Non-sentinel node tumor invasion in oropharyngeal and oral cancer: risk of misdiagnosis of metastasis. *Acta Otolaryngol*. 2008;128(10):1159-1164.
44. Schilling C, Stoeckli SJ, Haerle SK, et al. Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. *Eur J Cancer*. 2015;51(18):2777-2784.

45. Stefanicka P, Profant M, Duchaj B, et al. Sentinel lymph node radiolocalization and biopsy in oral cavity and oropharynx mucosal squamous cell carcinoma. *Bratisl Lek Listy*. 2010;111(11):590-594.
46. Stoeckli SJ. Sentinel node biopsy for oral and oropharyngeal squamous cell carcinoma of the head and neck. *Laryngoscope*. 2007;117(9):1539-1551.
47. Tomifuji M, Shiotani A, Fujii H, et al. Sentinel node concept in clinically n0 laryngeal and hypopharyngeal cancer. *Ann Surg Oncol*. 2008;15(9):2568-2575.
48. Werner JA, Dunne AA, Ramaswamy A, et al. The sentinel node concept in head and neck cancer: solution for the controversies in the N0 neck? *Head Neck*. 2004;26(7):603-611.
49. Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer*. 1972;29(6):1446-1449.
50. Liu M, Wang SJ, Yang X, Peng H. Diagnostic efficacy of sentinel lymph node biopsy in early oral squamous cell carcinoma: a meta-analysis of 66 studies. *PLoS One*. 2017;12(1):e0170322.
51. Wellenstein DJ, Schutte HW, Takes RP, et al. Office-based procedures for the diagnosis and treatment of laryngeal pathology. *J Voice*. 2018;32(4):502-513.
52. Wellenstein DJ, van der Wal RAB, Schutte HW, et al. Topical anesthesia for endoscopic office-based procedures of the upper aerodigestive tract. *J Voice*. 2019;33(5):732-746.
53. Schutte HW, Takes RP, Slootweg PJ, et al. Digital video laryngoscopy and flexible endoscopic biopsies as an alternative diagnostic workup in laryngopharyngeal cancer: a prospective clinical study. *Ann Otol Rhinol Laryngol*. 2018;127(11):770-776.

How to cite this article: van den Bosch S, Czerwinski M, Govers T, et al. Diagnostic test accuracy of sentinel lymph node biopsy in squamous cell carcinoma of the oropharynx, larynx, and hypopharynx: A systematic review and meta-analysis. *Head & Neck*. 2022;44(11): 2621-2632. doi:10.1002/hed.27175