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Meta-Analysis
Head and Neck Oncology

Diagnostic yield of sentinel lymph node biopsy in oral squamous cell carcinoma T1/T2-N0: systematic review and meta-analysis

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Abstract. The objective of this study was to conduct a systematic review and meta-analysis on the efficacy of sentinel lymph node biopsy (SLNB) in T1/T2-N0 oral squamous cell carcinoma (OSCC). A systematic review of the literature on SLNB until March 2019 was conducted. The review was organized according to the PRISMA protocol, considering the following PICO (population, intervention, comparison, outcome) question: What is the sensitivity of sentinel lymph node biopsy in OSCC? 'P' was patients with head and neck squamous cell carcinoma T1/2-N0; 'I' was SLNB; 'C' was neck treated with elective neck dissection and haematoxylin–eosin histopathology; 'O' was sensitivity and specificity. A meta-analysis and meta-regression were performed on the selected studies. The sensitivity of SLNB was up to 88% (95% confidence interval (CI) 72–96%) and specificity was up to 99% (95% CI 96–100%). The area under the summary receiver operating characteristic curve was 0.99 (95% CI 0.98–1.00). In the four studies where immunohistochemistry was performed, both the sensitivity and specificity were higher than in the studies without immunohistochemistry: 93% (95% CI 88–97%) and 98% (95% CI 96–100%), respectively. In conclusion, SLNB is an effective technique for treating patients with some types of stage T1/2-N0 OSCC. Some parameters such as immunohistochemistry could determine the level of diagnostic accuracy.

Key words: sentinel lymph node biopsy; mouth neoplasms; sensitivity and specificity; survival analysis; systematic review.

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The incidence of oral cancer (354,864 new cases in 2018) increases with age, and individuals of middle to advanced age develop oral cancer at a higher frequency. Oral cancer has a high mortality rate, and it accounted for 177,384 deaths worldwide in 2018[1]. The primary site of head and neck squamous cell carcinoma (HNSCC) varies considerably throughout the world. Of all the different types of malignant tumours that occur in the oral cavity, oral squamous cell carcinoma (OSCC) is the most prevalent, accounting for 90% of all cases[2].

Lymph node involvement and the presence of metastasis remain the clinical references for assessing the prognosis of oral cancer. The TNM Classification of Malignant Tumours (a globally recognized standard for classifying the extent of spread of cancer) has undergone several revisions over the years due to clinical and scientific advances. In the eighth edition of the World Health Organization (WHO) Classification of Head and Neck Tumours[3], several important parameters were updated, including tumours associated with human papillomavirus and T modifications, by taking into account the depth of invasion (DOI). In any case, regional lymph node progression remains the most important determining factor that affects the specific rate of survival for this disease, and in the case in which nodes are affected, the survival rate is reduced by up to 50%[4–6].

The treatment of patients who do not present clinical or obvious radiographic evidence of regional metastasis (N0) remains controversial. According to Weiss et al.[7], a patient with primary HNSCC and an N0 neck status should be observed if the probability of occult cervical metastasis is less than 20%. If the probability is greater than 20%, an elective neck dissection (END) is warranted. However, performing an END on N0 patients may not be the optimal procedure for assessment and diagnosis.

The sentinel lymph node (SLN) is defined as the initial node in a lymph node chain that is affected by the spread of a primary tumour, which is therefore the closest tumour to it. This means that when a cancer involves several affected nodes, the first of these will be the SLN. When a patient presents with a tumour of indefinite size (Tx) and with no apparent clinical or radiographic evidence of lymphatic involvement (N0), a sentinel lymph node biopsy (SLNB) will provide very useful information for the final stage of the tumour[8]. The advantages of performing a SLNB instead of an END include a decreased morbidity rate, a reduction in both the operative time and the duration of the postoperative hospital stay, and a more cost-effective procedure[9].

Several processes are performed in order to obtain SLNB data. The first stage is exploration of the tumour, in which various techniques are used to identify the SLN. Following this, the lymph node is extracted, and finally a biopsy is performed in order to obtain precise information[10,11]. The most commonly used diagnostic tool is Technetium 99 (Tc99), due to its easy detection and low gamma radiation[12]. This technique is very useful for showing the location of the SLN, as well as for determining the treatment area if any radiologically affected lymph nodes (Tx-N1) appear. The SLNB has been considered a standard process for the diagnosis of stage T1 or T2 OSCC since 2000; however, the first oral cancer studies in which its high metastatic detection capacity was proved were not reported until a few years later[13].

The clinical yield of SLNB has been highly variable in terms of sensitivity and specificity in the different studies, centres, and dates of completion[14–17]. Many works published worldwide have compared the great effectiveness of this technique with other more conventional, yet more aggressive techniques, such as END. The survival rate remains very low, at less than 50% after 5 years for patients with advanced stage tumours, and this is due predominantly to delayed diagnosis and distant metastasis[18]. Although several meta-analyses have been conducted in order to assess SLNB in HNSCC, the present study focused solely on oral cavity tumours. The aim of this study was to conduct a systematic review of the efficiency of SLNB in exclusively T1/T2-N0 tumours of the oral cavity and to perform a meta-analysis of the studies meeting the inclusion criteria. Secondary objectives were (1) to describe in detail the results obtained in the studies included in the systematic review, and (2) to analyse the efficacy and clinical performance of SLNB using data such as sensitivity and survival.

Methods

Protocol and eligibility criteria

A systematic review of articles published in the literature between January 1, 2000 and March 31, 2019 was conducted in the Unit of Oral Medicine, Oral Surgery and Implantology of the Faculty of Medicine and Dentistry, University of Santiago de Compostela. This systematic review was registered in PROSPERO on August 7, 2019 (reference CRD42019120157). The review was organized according to the PRISMA protocol[19], considering the following PICO (population, intervention, comparison, outcome) question: What is the sensitivity of sentinel lymph node biopsy in OSCC? 'P' was patients with head and neck squamous cell carcinoma T1/2-N0; 'I' was SLNB; 'C' was neck treated with END and haematoxylin–eosin (H&E) histopathology; 'O' was sensitivity and specificity.

Sources

This study used the Rayyan QCRI systematic review support platform (Qatar Computing Research Institute (Data Analytics), Doha, Qatar)[20], which allows for extensive online and collaborative bibliographic searches. The keywords and medical subject heading (MeSH) terms used were: ''Sentinel Lymph Node Biopsy'', ''Oral Cancer'', ''Oral Tumour'', ''Mouth Neoplasms'' and ''Oral Squamous Cell Carcinoma''. For verification purposes, the following were electronically searched: MEDLINE (through PubMed), Embase (through OVID), Web of Science, Scopus, Cochrane Library, ClinicalTrials.gov, the five WHO regional bibliographic databases (AIM, LILACS, IMEMR, IMSEAR, WPRIM), and the Conference Proceedings Citation Index. This process was supplemented by manual searches of a series of peer-reviewed journals containing related content. Potentially relevant articles known to any of the authors were searched, and likewise, reference lists from the retrieved review articles were also exhaustively checked.

Study selection and data extraction process

The search was conducted through the Rayyan QCRI platform by three observers (MSA, MMM, and OAC); a fourth observer (MPS) was consulted in the case of any disagreement. The eligibility criteria for the retrieved studies were (1) (a) patients with HNSCC (only oral cavity), (b) patients with T1/2-N0, (c) patients managed with SLNB, (d) patients with a follow-up period of longer than 12 months; (2) articles published after 2000; (3) data on false-negatives, sensitivity, specificity, and survival. The exclusion criteria were studies including T3 tumours, case reports, letters, abstracts, systematic reviews, and texts in languages other than English. In the first round, the title and

abstract of the retrieved articles were read and any studies that met the inclusion criteria or did not provide sufficient data in order for a clear decision to be made regarding their inclusion were subsequently examined in full text. In the second round, all of the studies that were considered eligible underwent full-text screening and a final decision was made regarding their inclusion in the study.

Data were extracted using a standardized, pilot-tested form. This form included the following items: title (original title of the reviewed publication); authors (those who participated in the publication); year (year in which the article was published); sample (number of individuals who had taken part since the beginning of the study); Tx (number of patients with T1 or T2, excluding lesions with in situ carcinoma); differentiation (degree of histopathological differentiation: (a) well-differentiated, (b) moderately differentiated, or (c) undifferentiated); surgical margins (positive margins on tumour excision); neck levels (location in the neck of node(s)); removed lymph nodes (LN) (number of nodes that were removed in all of the sample); positive lymph nodes (LN+); negative lymph nodes (LN−); follow-up time (average number of months that the study patients were followed-up for); false-negatives (FN) (patients who were diagnosed with negative nodal involvement but who subsequently had involvement in at least one lymph node); positive predictive value (PPV) (the probability of having nodal involvement when the SLNB was positive); true-negatives (TN) (patients who were diagnosed with negative nodal involvement and who had no involvement); negative predictive value (NPV) (the probability that subjects with negative nodal involvement truly do not have the disease); macrometastasis (the number of nodes with at least one metastasis >2 mm); micrometastasis; isolated tumour cells; sensitivity (probability with which the SLNB is able to identify patients with some LN+); specificity (probability with which the SLNB identifies negative patients from the sample of healthy patients); death (patients who died before the end of the study); average survival (patients who were still alive at the end of the study); disease-specific survival in LN+ patients (DSSN+) (proportion of LN+ patients who were still alive at the end of the study); disease-specific survival in LN− patients (DSSN−) (proportion of LN− patients who were still alive at the end of the study); relapse (patients with recurrences in the primary tumour site or in some node); disease-free survival in SLN+ patients (DFSN+) (proportion of patients without any sign of disease with positive SLNB results); disease-free survival in SLN− patients (DFSN−) (proportion of patients without signs of disease who were LN− in the SLNB).

Risk of bias assessment, data synthesis, and analysis

The methodological quality of the included studies and the possibility of bias were assessed using the Newcastle–Ottawa scale (NOS) for cohort studies[21] and the QUADAS-2 tool, which is a tool to assess the quality of diagnostic precision studies[22]. The authors of the NOS recommend evaluating the quality of the study according to three categories: selection (four questions, maximum possible score 4 stars), comparability (one question, maximum possible score 2 stars), and outcome (three questions, maximum possible score 3 stars), giving a low quality value (1–3 stars), medium quality value (4–6 stars), or high quality value (7–9 stars). This analysis was conducted independently by two researchers (MSA and OAC), and in the case of any disagreement, a third researcher (MPS) acted as the mediator. The QUADAS-2 tool was used to

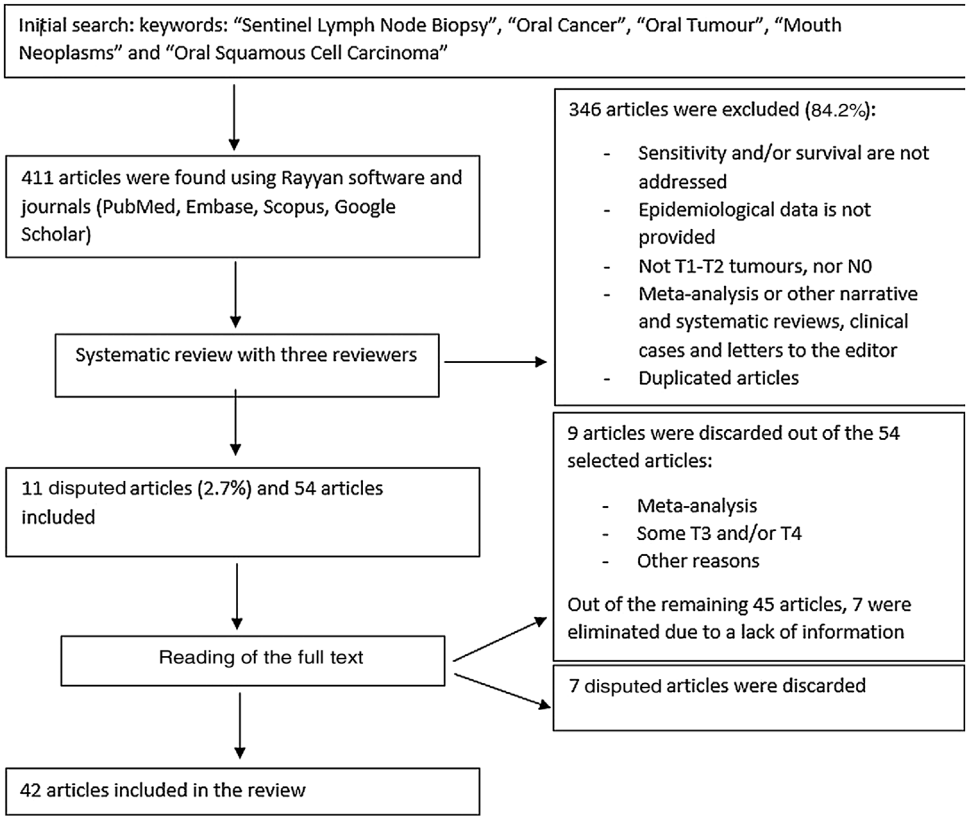

Fig. 1. Flow chart for the systematic review.

STUDY	YEAR	RISK OF BIAS				CONCERNS REGARDING APPLICABILITY			
		PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Al Dam et al. (16)	2018	HIGH	HIGH	?	?	LOW	HIGH	LOW
Riese et al. (33)	2018	LOW	LOW	LOW	?	LOW	LOW	LOW
Abdul-Razak et al. (26)	2017	LOW	LOW	LOW	?	LOW	LOW	LOW
Pedersen et al. (37)	2016	HIGH	LOW	?	LOW	LOW	HIGH	LOW
Sagheb et al. (34)	2016	HIGH	?	LOW	LOW	LOW	LOW	LOW
Chaturvedi et al. (47)	2015	LOW	?	?	?	LOW	LOW	LOW
Pezier et al.(27)	2012	LOW	LOW	LOW	?	LOW	LOW	LOW

	LOW PROBABILITY	HIGH PROBABILITY	UNCERTAIN PROBABILITY
PATIENT SELECTION	4	3	0
INDEX TEST	4	1	2
REFERENCE STANDARD	4	0	3
FLOW AND TIMING	2	0	5

	LOW PROBABILITY	HIGH PROBABILITY	UNCERTAIN PROBABILITY
PATIENT SELECTION	7	0	0
INDEX TEST	5	2	0
REFERENCE STANDARD	7	0	0

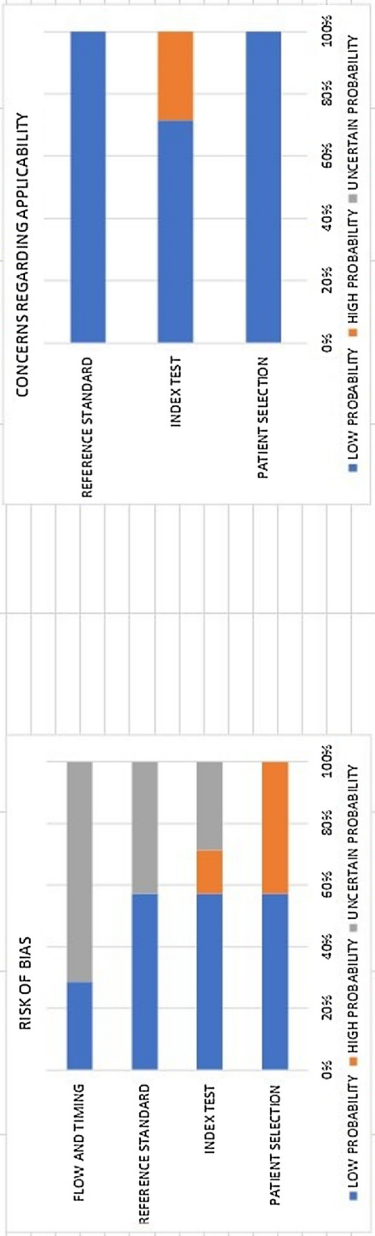

Fig. 2. Results of QUADAS-2: risk of bias and concerns regarding applicability.

assess the studies selected for meta-analysis. This tool consists of four domains: (1) patient selection, (2) index test, (3) reference test, and (4) flow and timing. Each domain is evaluated in terms of its risk of bias, and the first three domains are also evaluated in terms of their applicability.

All of the variables were collected in a database and were analysed with IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA). The variables were described using the frequency, percentage, mean, and standard deviation. For the articles that were included in the systematic review, the average data, minimum value, maximum value, standard deviation, and the total number of articles in which the information was provided were calculated.

Derived logit estimates of sensitivity, specificity, and respective variances were used to construct a hierarchical summary receiver operating characteristic (SROC) curve. The data extraction for the meta-analysis was performed by two researchers (XMM and MPS). The extracted data included the author and year of publication, and 2×2 tables for true-positives (TP), true-negatives (TN), false-positives (FP), and false-negatives (FN) in order to calculate the sensitivity and specificity.

In the meta-analysis, the data were analysed with the MIDAS module (Meta-Analytical Integration of Diagnostic Accuracy Studies) using Stata v16 software (StataCorp, College Station, TX, USA). To assess the heterogeneity among studies, the Q-statistic and I^2 value were calculated. A P-value of <0.10 and $I^2 > 50\%$ indicated considerable heterogeneity between studies, and the random-effects model was conducted; otherwise, the fixed-effects model was used. The data were further analysed using a meta-regression analysis using study covariates, stratifying the results by SLN pathology method (immunohistochemistry (IHC) or not, sectional series or not), type of reference test (neck dissection or follow-up), and study design (prospective or retrospective) in view of the greater effect of different study characteristics on the diagnostic efficacy of SLNB, and to explore the sources of between-study heterogeneity. All bilateral differences with a P-value of ≤ 0.05 were considered as significant.

Results

A flow diagram of the article selection process is given in Fig. 1. A total of 411 articles were identified in the first search. After the first review, which was performed by three evaluators, 346 articles

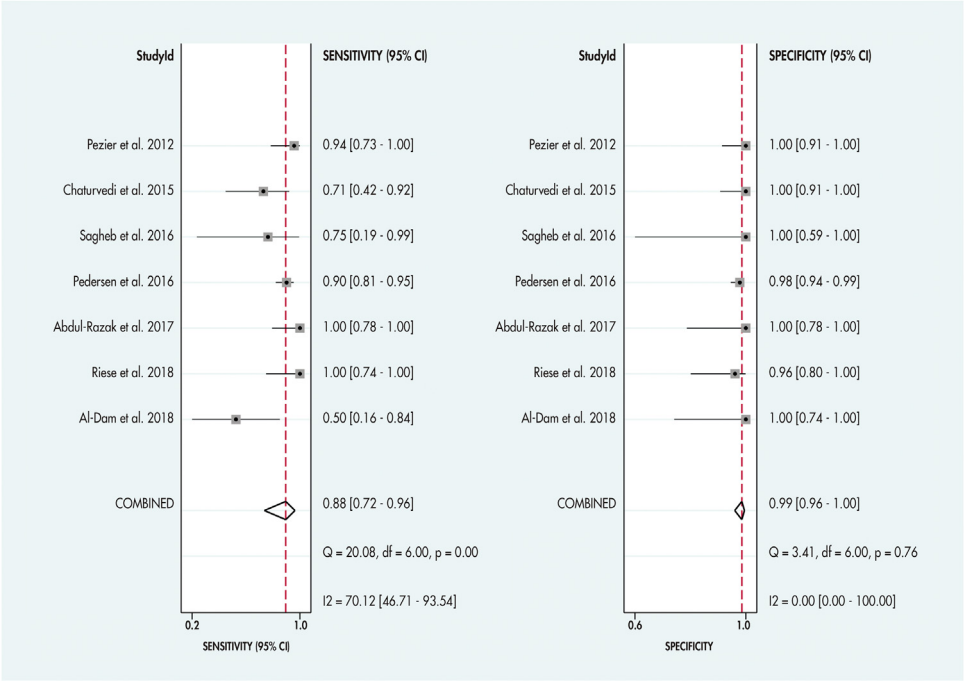

Fig. 3. Forest plots of pooled sensitivity and specificity.

(84.2%) were excluded, and 54 included articles (13.1%) and 11 disputed articles (2.7%) were obtained. After reading the full texts, nine of the initially accepted articles and seven of the disputed articles were discarded, resulting in a final total of 42 included articles (10.2%)[14–17,23–60]. In the quality assessment of included articles according to the NOS scale, one (2.4%) was rated as low quality, 21 (50%) as medium quality, and 20 (47.6%) as high quality (Supplementary Material Table S1).

The quality assessment of the articles included in the meta-analysis ($n = 7$) according to the QUADAS-2 tool is shown in Fig. 2. The graph in Fig. 2 shows that all of the included studies were of moderately high quality. The risk of bias with regards to patient selection was high in three (42.9%) of the studies, mostly due to their retrospective nature, without a consecutive or random sample enrolment of patients. The risk of bias regarding the index test was unclear in two (28.6%) studies, high in one (14.3%) study, and low in four (57.1%) studies. In contrast, the reference standard was unclear in three (42.9%) of the studies. For risk of bias in flow and timing, five (71.4%) of the studies were considered to be of unclear risk. There was less concern regarding the applicability of the studies. There were no concerns about applicability regarding patient selection and the reference test in seven (100%) of the studies, while only two (28.6%) studies showed a high risk because of the index test.

Tables S2 and S3 in the **Supplementary Material** report all of the study variables in the articles that were selected for systematic review.

A total of seven studies with 457 patients were included in the meta-analysis[16,26,27,33,34,37,47]. The eligibility of the articles was determined by the data provided in each article. In order for an article to be included, it had to report at least three of the four indexes: true-positives, true-negatives, false-negatives, and false-positives, as well as the sensitivity and specificity values.

The pooled sensitivity of SLNB was 88% (95% confidence interval (CI) 72–96%) and the pooled specificity was 99% (95% CI 96–100%) (Fig. 3). The area under the SROC curve (AUC) was 0.99 (95% CI 0.98–1.00) (Fig. 4). The PPV was 0.98 (95% CI 0.97–0.99) and the NPV was 0.88 (95% CI 0.87–0.89) (Fig. 5). Sensi-

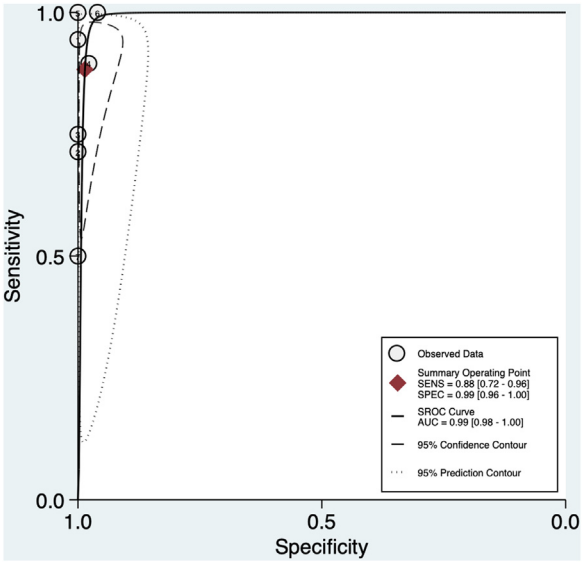

Fig. 4. Summary receiver operating characteristic (SROC) curve.

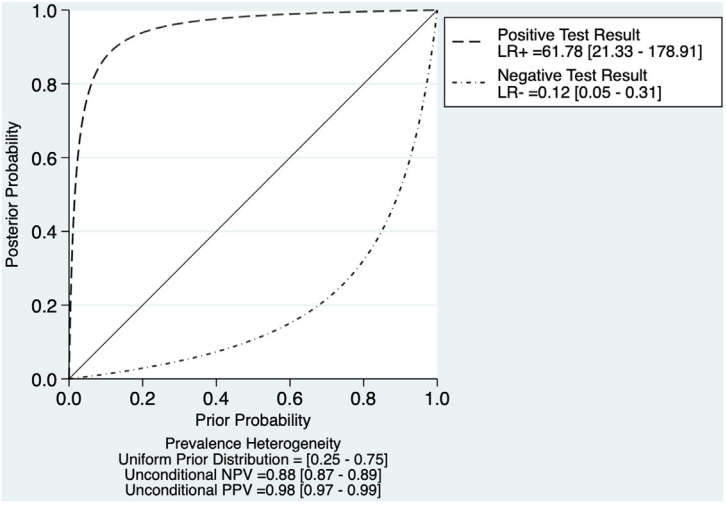

Fig. 5. Probability modifying plot.

tivity was the only parameter that showed an I^2 >50%, therefore suggesting considerable heterogeneity. By performing a leave-one-out meta-analysis, it was observed that by eliminating the work of Al-Dam et al.[16], the heterogeneity of the meta-analysis for sensitivity dropped to 0.49 (95% CI 0.01–0.96), giving a sensitivity value of 91% (95% CI 79–96%).

The meta-regression analysis showed that the IHC covariate was the most important source of heterogeneity. A subgroup analysis was performed to assess differences in diagnostic accuracy using the IHC covariate. In the four studies where IHC was performed, both the sensitivity and specificity were high: 93% (95% CI 88–97%) and 98% (95% CI 96–100%), respectively. However, in the three studies where IHC was not performed, the sensitivity was low, although the specificity was high: 65% (95% CI 47–84%) and 100% (95% CI 100–100%), respectively. The other covariates did not show statistically significant differences (Table 1).

Discussion

The SLNB is a key factor in the patient's prognosis. On the one hand, performing a lymph node dissection in order to remove all of the lymphatic chains in the neck is not necessary, therefore reducing patient morbidity[61], and on the other hand, as a relatively new technique, the SLNB produces very effective results in certain cancers such as breast cancer and melanoma[62]. This technique was extrapolated for use in oral cancer; however it produced different results, as shown in the articles that were included in this systematic review.

With regard to sensitivity, the diagnostic capacity of the SLNB in sick patients will be appreciated, i.e. a very sensitive test will be very effective. In this meta-analysis, the average sensitivity reached 88%, however it varied from 50% to 100%, therefore yielding mixed results. The studies by Hernando et al.[14] and Al-Dam et al.[16] both obtained a sensitivity of 50% in a sample of 73 and 20 patients, respectively, and these data suggest that the SLNB should not be proposed as a routine technique. On the other hand, several articles reported a sensitivity of 100% for SLNB, including Christensen et al.[15] and Burcia et al.[17], with a sample of 51 and 50 patients, respectively, obtaining no false-negatives. On the other hand, Schilling et al.[40] obtained a sensitivity of 86% with a considerable sample size of 415 patients, demonstrating results very close to those attained in this review.

The average survival should be the key factor when deciding whether to use END or SLNB in patients with T1/T2-N0 tumours. Previous results have been diverse depending on the type of survival studied. Therefore, in this review, data on average survival, DSSN+, DSSN−, DFSN+, and DFSN− were variable, especially when considering that in cases of LN+ patients the result was lower. The lowest survival rate was recorded in the work of Moya-Plana et al.[30], who reported an average survival of 77.3% in a total sample of 229 patients. This is in contrast to other articles, which reported survival reaching 100%, such as the studies by Stoeckli et al.[32] and Heuveling et al.[59]. Terada et al.[57] reported a DSSN+ of just 57.1%, a result differing considerably from the mean DSSN− of 96.60%. Hernando et al.[14] obtained a DSSN− of 86%, and despite being the article with the lowest DSSN− percentage, they demonstrated that when a patient is diagnosed by means of SLNB and the results are negative, the patient's prognosis improves considerably. The DFSN+ data differed from the data obtained by Broglie et al.[48] in which only 73% of subjects with positive SLNB results were disease-free, far from the 92% achieved in the study by Schilling et al.[40]. For the DFSN−, the results varied from Flach et al. (72.0%)[39], but were lower than the 97.2% obtained by Ionna et al.[55].

Approximately 20–30% of primary OSCCs have some occult nodal metastasis, which can be identified by SLNB or END. Nodal dissection is a much more aggressive technique; however, it is very effective in controlling metastasis in N1 patients, although it has a greater impact on patients in comparison with more conservative techniques such as SLNB. Nodal dissection often leads to the overtreatment of patients, resulting in postoperative consequences, with the most frequent being decreased functionality at the shoulder level, lymphedema, and postoperative scars[9]. As has already been demonstrated,

Table 1. Meta-regression analysis of the different identified covariates.

Parameter	Category	Studies, *n*	Sensitivity (95% CI)	*P*-value	Specificity (95% CI)	*P*-value
Study design	Retrospective	2	86% (62–100%)	0.94	98% (95–100%)	0.23
	Prospective	5	91% (78–100%)		100% (98–100%)	
IHC/serial section	Yes	4	93% (88–97%)	0.19	98% (96–100%)	<0.001
	No	3	65% (47–84%)		100% (100–100%)	
Reference test	Follow-up	2	92% (81–100%)	0.41	98% (96–100%)	0.88
	END	5	86% (70–100%)		99% (97–100%)	

CI, confidence interval; IHC, immunohistochemistry; END, elective neck dissection.

SLNB produces more than acceptable clinical results, with a reduction in the aforementioned consequences. Hernando et al.[14] compared the different complications that occur following both SLNB procedures and nodal dissection of the neck. Their results showed greater pain, less shoulder mobility, greater scarring, and more neck haemorrhages when the latter was performed. In the study by Govers et al.[63], quality of life was evaluated in different groups: under surveillance, SLNB, supraomohyoid neck dissection, and modified radical dissection. The quality of life of patients who underwent the SLNB procedure was higher, and likewise they experienced less discomfort than those who underwent dissection, especially modified radical dissection.

There are a number of factors that determine the variability in the diagnostic performance values of SLNB: work centre, type of tumour sample (head and neck cancer or only OSCC from the oral cavity), follow-up period, date of publication of the study, and the performance of serial SLN cuts with or without IHC. According to Liu et al.[64], the subgroup analysis based on IHC indicated that H&E staining combined with IHC was significantly more sensitive than the results obtained when H&E staining was performed on its own, with a sensitivity of 88% (95% CI 86–90%) versus 77% (95% CI 68–85%). Furthermore, the early publication subgroup (2000 to 2008) had a better combined sensitivity than the late publication subgroup (2009 to 2016): 92% (95% CI 87–95%) versus 86% (95% CI 83–88%). The present study confirmed similar results, obtaining better results in the IHC subgroup.

In conclusion, SLNB has emerged as a relatively novel technique for determining nodal involvement in certain cancers such as oral cancer. With the information provided by this review, sentinel node biopsy appears to be an effective technique for treating patients with OSCC in stage T1/2-N0. SLNB reached a sensitivity of 88% and a specificity of 99% in the meta-analysis. Some parameters such as IHC could determine the level of diagnostic accuracy.

Competing interests

There are no competing interests.

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Ethical approval

This article is exempt from approval by the ethics committee.

Patient consent

Not applicable.

Statement to confirm

All the authors have viewed and agreed to the submission

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijom.2021.01.020.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68**:394–424.
2. Mupparapu M, Shanti RM. Evaluation and staging of oral cancer. *Dent Clin North Am* 2018;**62**:47–58.
3. Huang SH, O'Sullivan B. Overview of the 8th edition TNM Classification for Head and Neck Cancer. *Curr Treat Options Oncol* 2017;**18**:40.
4. Sopik V, Sun P, Narod SA. Predictors of time to death after distant recurrence in breast cancer patients. *Breast Cancer Res Treat* 2019;**173**:465–74.
5. Suen JY, Goepfert H. Standardization of neck dissection nomenclature. *Head Neck Surg* 1987;**10**:75–7.
6. Som PM, Curtin HD, Mancuso AA. An imaging-based classification for the cervical nodes designed as an adjunct to recent clinically based nodal classifications. *Arch Otolaryngol Head Neck Surg* 1999;**125**:388–96.
7. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. *Arch Otolaryngol Head Neck Surg* 1994;**120**:699–702.
8. Mehta V, Nathan CA. What is the role of sentinel lymph node biopsy in early-stage oral cavity carcinoma? *Laryngoscope* 2016;**126**:9–10.
9. Murer K, Huber GF, Haile SR, Stoeckli SJ. Comparison of morbidity between sentinel node biopsy and elective neck dissection for treatment of the N0 neck in patients with oral squamous cell carcinoma. *Head Neck* 2011;**33**:1260–4.
10. Moncayo VM, Alazraki AL, Alazraki NP, Aarsvold JN. Sentinel lymph node biopsy procedures. *Semin Nucl Med* 2017;**47**:595–617.
11. Guo J, Yang H, Wang S, Cao Y, Liu M, Xie F, Liu P, Zhou B, Tong F, Cheng L, Liu H, Wang S. Comparison of sentinel lymph node biopsy guided by indocyanine green, blue dye, and their combination in breast cancer patients: a prospective cohort study. *World J Surg Oncol* 2017;**15**:196–7.
12. Surasi DS, O'Malley J, Bhambhvani P. 99mTc-Tilmanocept: a novel molecular agent for lymphatic mapping and sentinel lymph node localization. *J Nucl Med Technol* 2015;**43**:87–91.
13. Sharma D, Koshy G, Grover S, Sharma B. Sentinel lymph node biopsy: a new approach in the management of head and neck cancers. *Sultan Qaboos Univ Med J* 2017;**17**:e3–10.
14. Hernando J, Villarreal P, Álvarez-Marcos F, García-Consuegra L, Gallego L, Junquera L. Sentinel node biopsy versus elective neck dissection. Which is more cost-effective? A prospective observational study. *J Craniomaxillofac Surg* 2016;**44**:550–6.
15. Christensen A, Bilde A, Therkildsen MH, Mortensen J, Charabi B, Kirkegaard J, Specht L, von Buchwald C. The prevalence of occult metastases in nonsentinel lymph nodes after step-serial sectioning and immunohistochemistry in cN0 oral squamous cell carcinoma. *Laryngoscope* 2011;**121**:294–8.
16. Al-Dam A, Precht C, Barbe A, Kohlmeier C, Hanken H, Wikner J, Schön G, Heiland M, Assaf AT. Sensitivity and specificity of sentinel lymph node biopsy in patients with oral squamous cell carcinomas using indocyanine green fluorescence imaging. *J Craniomaxillofac Surg* 2018;**46**:1379–84.
17. Burcia V, Costes V, Faillie JL, Gardiner Q, de Verbizier D, Cartier C, Jouzdani E, Crampette L, Guerrier B, Garrel R. Neck restaging with sentinel node biopsy in T1–T2N0 oral and oropharyngeal cancer: why and how? *Otolaryngol Head Neck Surg* 2010;**142**:592–7.e1.
18. Ding D, Stokes W, Eguchi M, Hararah M, Sumner W, Amini A, Goddard J, Somerset H, Bradley C, McDermott J, Raben D, Karam SD. Association between lymph node ratio and recurrence and survival outcomes in patients with oral cavity cancer. *JAMA Otolaryngol Head Neck Surg* 2019;**145**:53–61.
19. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700.
20. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev* 2016;**5**:210.
21. Wells G, Shea B, O'Connell DL, Peterson J, Welch V, Losos M, Tugwell P. *The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in*

meta-analyses. Ottawa Hospital Research Institute; 2014.
22. Ciapponi A. QUADAS-2: instrumento para la evaluación de la calidad de estudios de precisión diagnóstica. [QUADAS-2: an instrument for the evaluation of the quality of diagnostic precision studies]. *EVIDENCIA – Actualizaciæn PrÃctica Ambulatoria* 2015;**18**:22–6.
23. Hiraki A, Fukuma D, Nagata M, Shiraishi S, Kawahara K, Matsuoka Y, Nakagawa Y, Yoshida R, Tanaka T, Yoshitake Y, Shinohara M, Yamashita Y, Nakayama H. Sentinel lymph node biopsy reduces the incidence of secondary neck metastasis in patients with oral squamous cell carcinoma. *Mol Clin Oncol* 2016;**5**:57–60.
24. Alkureishi LW, Ross GL, Shoaib T, Soutar DS, Robertson AG, Thompson R, Hunter KD, Sorensen JA, Thomsen J, Krogdahl A, Alvarez J, Barbier L, Santamaria J, Poli T, Sesenna E, Kovács AF, Grünwald F, Barzan L, Sulfaro S, Alberti F. Sentinel node biopsy in head and neck squamous cell cancer: 5-year follow-up of a European multicenter trial. *Ann Surg Oncol* 2010;**17**:2459–64.
25. Gallegos-Hernández JF, Hernández-Hernández DM, Flores-Díaz R, Sierra-Santiesteban I, Pichardo-Romero P, Arias-Ceballos H, Minauro-Muñoz G, Alvarado-Cabrero I. The number of sentinel nodes identified as prognostic factor in oral epidermoid cancer. *Oral Oncol* 2005;**41**:947–52.
26. Abdul-Razak M, Chung H, Wong E, Palme C, Veness M, Farlow D, Coleman H, Morgan G. Sentinel lymph node biopsy for early oral cancers: Westmead Hospital experience. *ANZ J Surg* 2017;**87**:65–9.
27. Pezier T, Nixon IJ, Gurney B, Schilling C, Hussain K, Lyons AJ, Oakley R, Simo R, Jeannon JP, McGurk M. Sentinel lymph node biopsy for T1/T2 oral cavity squamous cell carcinoma—a prospective case series. *Ann Surg Oncol* 2012;**19**:3528–33.
28. van der Linden N, Flach GB, de Bree R, Uyl-de Groot CA. Cost-utility of sentinel lymph node biopsy in cT1–T2N0 oral cancer. *Oral Oncol* 2016;**53**:20–6.
29. Holden AM, Sharma D, Schilling C, Gnanasegaran G, Odell EW, Sassoon I, McGurk M. Biopsy of the sentinel lymph node in oral squamous cell carcinoma: analysis of error in 100 consecutive cases. *Br J Oral Maxillofac Surg* 2018;**56**:615–20.
30. Moya-Plana A, Aupérin A, Guerlain J, Gorphe P, Casiraghi O, Mamelle G, Melkane A, Lumbroso J, Janot F, Temam S. Sentinel node biopsy in early oral squamous cell carcinomas: long-term follow-up and nodal failure analysis. *Oral Oncol* 2018;**82**:187–94.
31. Boeve K, Schepman KP, Schuuring E, Roodenburg JLN, Halmos GB, van Dijk BAC, Boorsma RAC, de Visscher JGAM, Brouwers AH, van der Vegt B, Witjes MJH. High sensitivity and negative predictive value of sentinel lymph node biopsy in a retrospective early stage oral cavity cancer cohort in the Northern Netherlands. *Clin Otolaryngol* 2018. Mar 25.
32. Stoeckli SJ, Huebner T, Huber GF, Broglie MA. Technique for reliable sentinel node biopsy in squamous cell carcinomas of the floor of mouth. *Head Neck* 2016;**38**:1367–72.
33. Riese CGU, Karstadt JA, Schramm A, Güleryüz S, Dressel G, Lorenz KJ, Klemenz B, Sailer A, Seitz S, Wilde F. Validity of sentinel node biopsy in early oral and oropharyngeal carcinoma. *J Craniomaxillofac Surg* 2018;**46**:1748–52.
34. Sagheb K, Sagheb K, Rahimi-Nedjat R, Taylor K, Al-Nawas B, Walter C. Sentinel lymph node biopsy in T1/T2 squamous cell carcinomas of the tongue: a prospective study. *Oncol Lett* 2016;**11**:600–4.
35. Mehta V, Nathan C. What is the role of sentinel lymph node biopsy in early-stage oral cavity carcinoma? *Laryngoscope* 2016;**126**:9–10.
36. Chung MK, Lee GJ, Choi N, Cho J, Jeong H, Baek C. Comparative study of sentinel lymph node biopsy in clinically N0 oral tongue squamous cell carcinoma: long-term oncologic outcomes between validation and application phases. *Oral Oncol* 2015;**51**:914–20.
37. Pedersen NJ, Jensen DH, Hedbäck N, Frendø M, Kiss K, Lelkaitis G, Mortensen J, Christensen A, Specht L, von Buchwald C. Staging of early lymph node metastases with the sentinel lymph node technique and predictive factors in T1/T2 oral cavity cancer: a retrospective single-center study. *Head Neck* 2016;**38**(Suppl 1):1033.
38. Ramamurthy R, Kottayasamy Seenivasagam R, Shanmugam S, Palanivelu K. A prospective study on sentinel lymph node biopsy in early oral cancers using methylene blue dye alone. *Indian J Surg Oncol* 2014;**5**:178–83.
39. Flach GB, Bloemena E, Klop WM, van Es RJ, Schepman KP, Hoekstra OS, Castelijns JA, Leemans CR, de Bree R. Sentinel lymph node biopsy in clinically N0 T1–T2 staged oral cancer: the Dutch multicenter trial. *Oral Oncol* 2014;**50**:1020–4.
40. Schilling C, Stoeckli SJ, Haerle SK, Broglie MA, Huber GF, Sorensen JA, Bakholdt V, Krogdahl A, von Buchwald C, Bilde A, Sebbesen LR, Odell E, Gurney B, O'Doherty M, de Bree R, Bloemena E, Flach GB, Villarreal PM, Fresno Forcelledo MF, Junquera Gutiérrez LM, Amézaga JA, Barbier L, Santamaría-Zuazua J, Moreira A, Jacome M, Vigili MG, Rahimi S, Tartaglione G, Lawson G, Nollevaux MC, Grandi C, Donner D, Bragantini E, Dequanter D, Lothaire P, Poli T, Silini EM, Sesenna E, Dolivet G, Mastronicola R, Leroux A, Sassoon I, Sloan P, McGurk M. Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. *Eur J Cancer* 2015;**51**:2777–84.
41. Sabaté-Llobera A, Benítez-Segura A, Marí A, Arranz C, Bajén MT, Maymó-Garrido S, Martín-Comín J. Lymphoscintigraphy in oral squamous cell carcinoma sentinel node biopsy and its role in the surgical planning. *Clin Nucl Med* 2014;**39**:142.
42. Samant S. Sentinel node biopsy as an alternative to elective neck dissection for staging of early oral carcinoma. *Head Neck* 2014;**36**:241–6.
43. Den Toom IJ, Heuveling DA, Flach GB, van Weert S, Karagozoglu KH, van Schie A, Bloemena E, Leemans CR, de Bree R. Sentinel node biopsy for early-stage oral cavity cancer: the VU University Medical Center experience. *Head Neck* 2015;**37**:573–8.
44. Bell RB, Markiewicz MR, Dierks EJ, Gregoire CE, Rader A. Thin serial step sectioning of sentinel lymph node biopsy specimen may not be necessary to accurately stage the neck in oral squamous cell carcinoma. *J Oral Maxillofac Surg* 2013;**71**:1268–77.
45. 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.
46. Rigual N, Loree T, Frustino J, Jayaprakash V, Cohan D, Sullivan M, Kuriakose MA. Sentinel node biopsy in lieu of neck dissection for staging oral cancer. *JAMA Otolaryngol Head Neck Surg* 2013;**139**:779–82.
47. Chaturvedi P, Datta S, Arya S, Rangarajan V, Kane SV, Nair D, Nair S, Chaukar DA, Pai PS, Pantvaidya G, Deshmukh AD, Agrawal A, D'Cruz AK. Prospective study of ultrasound-guided fine-needle aspiration cytology and sentinel node biopsy in the staging of clinically negative T1 and T2 oral cancer. *Head Neck* 2015;**37**:1504–8.
48. Broglie MA, Haerle SK, Huber GF, Haile SR, Stoeckli SJ. Occult metastases detected by sentinel node biopsy in patients with early oral and oropharyngeal squamous cell carcinomas: impact on survival. *Head Neck* 2013;**35**:660–6.
49. Melkane AE, Mamelle G, Wycisk G, Temam S, Janot F, Casiraghi O, Lumbroso J. Sentinel node biopsy in early oral squamous cell carcinomas: a 10-year experience. *Laryngoscope* 2012;**122**:1782–8.
50. Yamauchi K, Fujioka Y, Kohno N. Sentinel node navigation surgery versus observation as a management strategy for early tongue carcinoma. *Head Neck* 2012;**34**:568–72.
51. Broglie MA, Haile SR, Stoeckli SJ. Long-term experience in sentinel node biopsy for early oral and oropharyngeal squamous cell carcinoma. *Ann Surg Oncol* 2011;**18**:2732–8.
52. Chone CT, Aniteli MB, Magalhães RS, Freitas LL, Altemani A, Ramos CD, Etchebehere E, Crespo AN. Impact of immunohistochemistry in sentinel lymph node biopsy in head and neck cancer. *Eur Arch Otorhinolaryngol* 2013;**270**:313–7.
53. Civantos FJ, Zitsch RP, Schuller DE, Agrawal A, Smith RB, Nason R, Petruzelli G, Gourin CG, Wong RJ, Ferris RL, El Naggar A, Ridge JA, Paniello RC, Owzar K, McCall L, Chepeha DB, Yarbrough WG, Myers JN.

Sentinel lymph node biopsy accurately stages the regional lymph nodes for T1–T2 oral squamous cell carcinomas: results of a prospective multi-institutional trial. *J Clin Oncol* 2010;**28**:1395–400.
54. Thomsen JB, Sørensen JA, Grupe P, Krogdahl A. Sentinel lymph node biopsy in oral cancer: validation of technique and clinical implications of added oblique planar lymphoscintigraphy and/or tomography. *Acta Radiol* 2005;**46**:569–75.
55. Ionna F, Chiesa F, Longo F, Manola M, Villano S, Calabrese L, Lastoria S, Mozzillo N. Prognostic value of sentinel node in oral cancer. *Tumori* 2002;**88**:18.
56. Stoeckli SJ, Steinert H, Pfaltz M, Schmid S. Is there a role for positron emission tomography with 18F-fluorodeoxyglucose in the initial staging of nodal negative oral and oropharyngeal squamous cell carcinoma. *Head Neck* 2002;**24**:345–9.
57. Terada A, Hasegawa Y, Yatabe Y, Hanai N, Ozawa T, Hirakawa H, Maruo T, Kawakita D, Mikami S, Suzuki A, Miyazaki T, Nakashima T. Follow-up after intraoperative sentinel node biopsy of N0 neck oral cancer patients. *Eur Arch Otorhinolaryngol* 2011;**268**:429–35.
58. Rigual N, Douglas W, Lamonica D, Wiseman S, Cheney R, Hicks Jr W, Loree T. Sentinel lymph node biopsy: a rational approach for staging T2N0 oral cancer. *Laryngoscope* 2005;**115**:2217–20.
59. Heuveling DA, van Weert S, Karagozoglu KH, de Bree R. Evaluation of the use of freehand SPECT for sentinel node biopsy in early stage oral carcinoma. *Oral Oncol* 2015;**51**:287–90.
60. Thomsen JB, Sørensen JA, Grupe P, Karstoft J, Krogdahl A. Staging N0 oral cancer: lymphoscintigraphy and conventional imaging. *Acta Radiol* 2005;**46**:492–6.
61. Cramer JD, Sridharan S, Ferris RL, Duvvuri U, Samant S. Sentinel lymph node biopsy versus elective neck dissection for stage I to II oral cavity cancer. *Laryngoscope* 2019;**129**:162–9.
62. Vidal-Sicart S, Vilalta Solsona A, Alonso Vargas MI. Sentinel node in melanoma and breast cancer. Current considerations. *Rev Esp Med Nucl Imagen Mol* 2015;**34**:30–44.
63. Govers TM, Schreuder WH, Klop WM, Grutters JP, Rovers MM, Merkx MA, Takes RP. Quality of life after different procedures for regional control in oral cancer patients: cross-sectional survey. *Clin Otolaryngol* 2016;**41**:228–33.
64. 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**. e0170322.

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