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CLINICAL REVIEW

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Efficacy of different sentinel lymph node biopsy protocols in oral squamous cell carcinoma: Systematic review and meta-analysis

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Abstract

The sentinel node biopsy (SNB) is highly protocolized in other cancers, however, this is not the case for oral squamous cell carcinoma patients, hence our objective was to evaluate the different protocols published. A specific study protocol was designed and subsequently registered on PROSPERO (Ref. CRD42021279217). Twenty-three articles were included in the meta-analysis. The grouped sensitivity of the SNB was 82% (95% CI: 0.74–0.88), and the grouped specificity was 100% (95% CI: 0.99–1.00). The use of other radiotracers other than pre-operative lopamidol showed higher values of sensitivity of 82.80% (95% CI: 76.90%–87.50%; $p < 0.001$). The use of the blue dye stain showed higher sensitivity values of 85.60% (95% CI: 71.90%–93.20%), compared to sensitivity values of 77.50% when it was not used (95% CI: 69.10%–84.20%) ($p < 0.001$). Diagnostic rates are variable and they were significantly better when 99mTc was used in all its variations and accompanied by the blue dye staining.

KEYWORDS

blue dye, indocyanine green, protocols, sentinel node lymph biopsy, systematic review

1 | INTRODUCTION

The term sentinel node (SN) was coined by Gould et al.[1] in 1960 during a parotidectomy.[2] However, it was not until 1977 that the study by Cabanas et al. on a group of 90 patients with penile cancer, suggested not only that the lymph node was a metastases area, but that it could also be one of the only ones.[3]

From that point to the present, it has been evident that the patient's lymphatic condition is vital in determining the evolution of this disease. Of all of the patients suffering from oral squamous cell carcinoma (OSCC), 40%–50% present with T1–T2 classification,[4] out of which 20%–33% present with occult lymph nodes.[5,6]

In the cases of breast cancer and melanoma, the SN technique is highly implemented and protocolized[7]; however, this is not the case for OSCC patients. In order to initiate the use of the SN technique in a new territory, it is essential to first consider the pathophysiological, anatomical, and technical qualities that made the breast

tumor and melanoma ideal for its application. First, these tumors are drained by lymphatic chains that are easily accessible for physical and radiological examination, second there is sufficient distance between the point of infiltration of the tracer and the location of the sentinel lymph node, which therefore means that there is sufficient distance in time and space to allow for them to be distinguished and identified correctly, and finally these are technically accessible anatomical territories in the surgical plane.[8,9]

Taking these characteristics into account, head and neck tumors are good candidates for the application of the SN technique, given that they meet two of the aforementioned premises, as they are accessible to both exploration and extirpation. However, the third premise, in which the distance between the injection point and the sentinel lymph node is considered is not always fulfilled. This is because there is often an overlap when using imaging techniques, which can make it difficult for these to be identified with a gamma camera. In addition, these are tumors for which lymphatic drainage has traditionally been considered erratic and of discontinuous extension, and, likewise, there is a certain amount of suspicion regarding the efficacy of SLNB and its implications in terms of survival.[10,11] In addition, lesions of the oral midline and floor of the mouth can hinder drainage to the ipsilateral and contralateral areas. Another complex point is linked to the differences between the different locations within the oral cavity, therefore making it complicated for the SLNB technique to be used for gingival lesions as a result of the limited vascularization. Given its reproducibility in the different studies, the tongue seems to be the most promising location for the protocolization of this technique.

The management of T1–T2 stage OSCC patients has been the subject of considerable debate for many years, with unilateral neck dissection, a watch and see policy, and, finally, the SN technique having been considered.[4] No consensus has been reached in this regard; however, the latter appears to be the best and most promising alternative.[12] As a result, several guidelines/protocols and recommendations for this technique have already been published,[1,4,5] all of which coincide that a multidisciplinary team (nuclear medicine, radiology, maxillofacial surgery and pathological anatomy)[5,13] is an essential requirement. It is worth mentioning that in 2018, at the Eighth International Symposium on the Sentinel Node Technique, several experts in this field gathered together to give a number of scientific-evidence-based recommendations focusing on the surgical aspects. The 17 recommendations ranged from the pre-operative and intraoperative aspects of the patient, to the new technologies that can be applied with this technique.[14]

The aim of the present systematic review and meta-analysis was to evaluate the efficacy of the different sentinel lymph node biopsy protocols in the treatment of OSCC patients.

2 | MATERIAL AND METHODS

A specific study protocol was designed for the data search retrieval process. This protocol followed the PRISMA guidelines[15] and it was subsequently registered on PROSPERO (Ref. CRD42021279217). The PICO question was: Can sensitivity and specificity be affected by the different SN protocols used? P: Patients with OSCC who were subjected to the SN technique; (I: intervention) patients for which a radiotracer was used with coadjuvant techniques; (C: Comparison), patients who were treated with the SN techniques without coadjuvant techniques; (O: Observation), sensitivity and specificity of the different techniques.

2.1 | Information sources and search strategy

For this review, the search was carried out using the Rayyan QCRI program (Qatar Computing Research Institute [Data Analytics], Doha, Qatarcon). Following the PRISMA requirements, the MeSH terms used were: "Sentinel Lymph Node Biopsy," "Mouth neoplasms," "Squamous Cell Carcinoma of Head and Neck," and "Lymphatic Metastasis." For verification purposes, other keywords ("oral cancer," "oral squamous cell carcinoma," and "lymph node metastasis") were used when searching MEDLINE through PubMed, EMBASE through OVID, Web of Science, Scopus, Cochrane Library, Clinical Trials, and the five WHO regional bibliographic databases (AIM, LILACS, IMEMR, IMSEAR, WPRIM) and the Conference Proceedings Citation Index. Any potentially relevant articles that any of the authors were familiar with, as well as reference lists from the retrieved articles, were also comprehensively checked.

2.2 | Eligibility criteria

All references identified from computerized databases were manually retrieved, and the studies were included if they met the following inclusion criteria: patients with OSCC who were treated using the SN technique, no time limit and N0 T1/T2 classification of tumors located in the oral cavity. With regards to the description of the technique at a preoperative and/or peri-operative level, there are 10 aspects that are considered essential in the SLNB

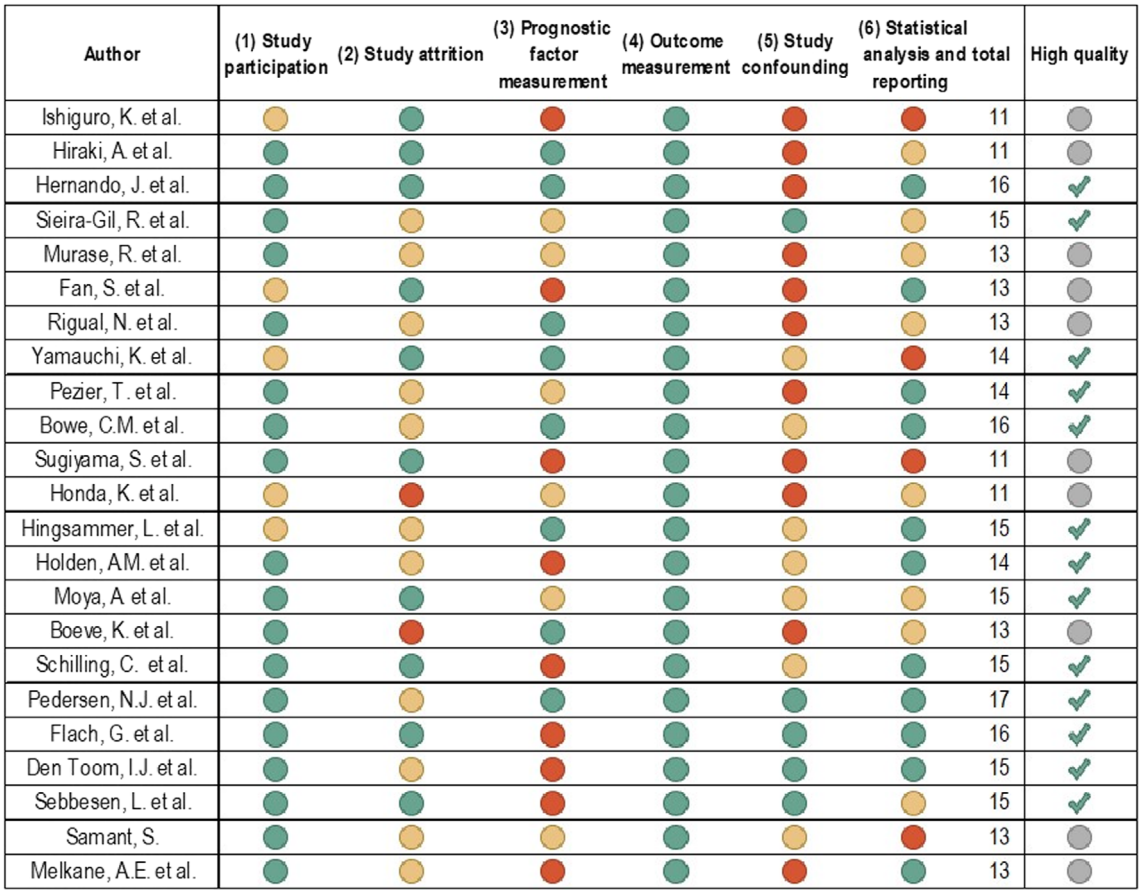

FIGURE 1 Risk of bias following the Quality in Prognosis Studies (QUIPS). Low (● = 3 points), moderate (● = 2 points), or high (● = 1 point). The studies scoring ≥14 out of 18 were considered of high methodological quality for subgroup analysis (✓) [Color figure can be viewed at wileyonlinelibrary.com]

technique: (1) number of hours before surgery, (2) use of static lymphoscintigraphy, (3) use of dynamic lymphoscintigraphy, (4) Spect/CT, (5) use of indocyanine green, (6) use of blue dye, (7) intraoperative gamma probe, (8) photodynamic probe, (9) shine-through effect, and (10) radiotracer, as a result, any studies that described at least five of the 10 aspects were included in this study.

The exclusion criteria were: any cancer that was not OSCC, T3/T4 classification, articles that were not written in English, letters to the editor, case reports, meta-analysis or reviews and articles from which the sensitivity and specificity data could not be extracted/calculated. In a second review of the articles in complete text, more exhaustive exclusion criteria were applied: protocol studies applied to the total patient sample in a non-homogeneous manner, absence of the use of a pre-operative radiotracer, absence of patient follow-up subsequent to the technique. Moreover, any articles in which a neck dissection was performed following the sentinel node technique were excluded, because of the lack of follow-up information.

2.3 | Study selection and data extraction process

The data was retrieved by two researchers (MSA and MPS) using a custom-made extraction sheet. Any discrepancies between the researchers were resolved by a third researcher (CMCP) who was blinded to the study hypothesis. The following data was recorded: year of publication, country, study type (ST: prospective and retrospective), tumor location (L: tongue or other location), sample size (N: number of patients included in the sample), pre-operative radiotracer (RAD: type of pre-surgical radiotracer), time of pre-operative injection (HBS: time of radiotracer injection before surgery), lymphography type (STL: use or non-use of static lymphoscintigraphy), (DINL: use or non-use of dynamic lymphoscintigraphy), Spect/CT (use or non-use of single photon emission computed tomography), ICG (use or non-use of the intraoperative indocyanine green), blue dye (BD: use or non-.use of the intraoperative blue dye), gamma probe (GP: use or non-use of the intraoperative gamma probe, as well as the brand, if specified), intraoperative photodynamic chamber

TABLE 1 Information obtained from the articles on the following aspects

	Y	C	ST	L	N	RAD	HBS	STL	DINL	SPECT/CT	IGC	BD
Ishiguro, K. et al.	2020	JAPAN	PROSPECTIVE	TONGUE	27	Iopamidol	24 H	NO	NO	YES	YES	NO
Hiraki, A. et al.	2016	JAPAN	RETROSPECTIVE	TONGUE /AND OTHER(S)	47	99mTc-Phytate	24 H	NO	NO	YES	NO	NO
Hernando, J. et al.	2016	SPAIN	PROSPECTIVE	TONGUE /AND OTHER(S)	32	99mTc-Nanocolloid	2 H	NO	YES	NO	NO	NO
Sieira-Gil, R. et al.	2015	SPAIN	RETROSPECTIVE	TONGUE /AND OTHER(S)	42	99mTc-Nanocolloid	24 H	YES	YES	YES	NO	NO
Murase, R. et al.	2015	JAPAN	PROSPECTIVE	TONGUE /AND OTHER(S)	16	99mTc-Tin colloid	24 H			YES	YES	NO
Fan, S. et al.	2014	CHINA	RETROSPECTIVE	TONGUE	30	99mTc-Phytate	24 H	YES	NO	NO	NO	YES
Rigual, N. et al.	2013	USA	RETROSPECTIVE	TONGUE /AND OTHER(S)	38	99mTc-Sulfur colloid				NO	NO	NO
Yamauchi, K. et al.	2011	JAPAN	PROSPECTIVE	TONGUE	11	99mTc-Phytate	24 H			YES	NO	NO
Pezier, T. et al.	2011	EUROPE	PROSPECTIVE	TONGUE /AND OTHER(S)	57	99mTc-Nanocolloid	24 H	NO	YES	NO	NO	YES
Bowe, C.M. et al.	2020	ENGLAND	PROSPECTIVE	TONGUE /AND OTHER(S)	46	99mTc-Labeled colloid tracer		NO	YES	YES	NO	YES
Sugiyama, S. et al.	2020	JAPAN	PROSPECTIVE	TONGUE /AND OTHER(S)	32	Iopamidol	24 H	NO	NO	YES	YES	NO
Honda,K. et al.	2019	JAPAN	PROSPECTIVE	TONGUE	16	Iopamidol				YES	YES	NO
Hingsammer, L. et al.	2019	GERMANY	PROSPECTIVE	TONGUE	41			NO	YES	YES	YES	NO
Holden, A.M. et al.	2019	MULTI-INSTITUTIONAL	RETROSPECTIVE	TONGUE /AND OTHER(S)	98	99mTc-Nanocolloid		YES	YES		NO	YES
Moya, A. et al.	2018	FRANCE	PROSPECTIVE	TONGUE /AND OTHER(S)	170	99mTc-Labeled rhenium sulfur colloid		YES	NO	YES	NO	NO
Boeve, K. et al.	2018	THE NETHERLANDS	PROSPECTIVE	TONGUE /AND OTHER(S)	91	99mTc-Nanocolloid	24H			YES	NO	NO
Schilling, C. et al.	2015	EUROPE	PROSPECTIVE	TONGUE /AND OTHER(S)	415	99mTc-Nanocolloid	24 h	YES	YES		NO	NO
Pedersen, N.J. et al.	2015	DENMARK	RETROSPECTIVE	TONGUE /AND OTHER(S)	253	99mTc-Nanocolloid	24 H	YES	YES	YES	NO	NO
Flach, G. et al.	2014	THE NETHERLANDS	PROSPECTIVE	TONGUE /AND OTHER(S)	62	99mTc-Nanocolloid	24 H	YES	YES	NO	NO	NO
Den Toom, I.J. et al.	2014	THE NETHERLANDS	RETROSPECTIVE	TONGUE /AND OTHER(S)	87	99mTc-Nanocolloid	24 H	YES	YES	YES	NO	YES
Sebbesen, L. et al.	2013	DENMARK	RETROSPECTIVE	TONGUE /AND OTHER(S)	53			YES	YES	YES	NO	NO
Samant, S.	2013	USA	PROSPECTIVE	TONGUE /AND OTHER(S)	32	99mTc-Sulfur colloid	8H	YES	YES	NO	NO	YES
Melkane, A.E. et al.	2012	FRANCE	PROSPECTIVE	TONGUE /AND OTHER(S)	113	99mTc-Labeled rhenium sulfur colloid	12 H	NO	YES	NO	NO	NO

	GP	PP	STE	SNB (−)	SNB (+)	GSN	PSN	PHND	NFOLLOWUP	PWHR	AFOLLOWUP
Ishiguro, K. et al.		HyperEye Medical System		22	5	41	5	5	22	3	76
Hiraki, A. et al.	Hand-held gamma detector probe	NO		36	9	99		9	36	2	43.6

(Continues)

TABLE 1 (Continued)

	GP	PP	STE	SNB (−)	SNB (+)	GSN	PSN	PHND	NFOLLOWUP	PWHR	AFOLLOWUP
Hernando, J. et al.	Europrobe	NO	The tumor first	29	3	64	3	3	29	5	48.2
Sieira-Gil, R. et al.	Sentinella S102 + Navigator; RMD Electronic	NO		34	8	130	8	3	39	2	36
Murase, R. et al.	neo2000;Century Medical, Tokyo, Japan)	PhotoDynamic Eye		14	2	35	2	2	12	0	36
Fan, S. et al.		NO		21	9	81	14	9	21	4	120
Rigual, N. et al.	Gamma probe	NO	The tumor first	33	5	76	5	5	33	2	31
Yamauchi, K. et al.	neo2000;Century Medical, Tokyo, Japan)	NO	The tumor first	9	2	40	5	2	9	0	57.0
Pezier, T. et al.	Gamma probe	NO	The tumor second	40	17	150		17	40	1	22.5
Bowe, C.M. et al.	Gamma probe	NO	The tumor second	29	17	154	24	17	29	0	19
Sugiyama, S. et al.		HyperEye Medical System		27	5			5	27	4	36
Honda,K. et al.		PhotoDynamic Eye or HyperEye Medical System	The tumor second	11	5	29	5	5	8	2	
Hingsammer, L. et al.	Gamma probe	NO	The tumor first	34	7	157	8	7	34	1	92
Holden, A.M. et al.	Gamma probe	NO		65	33			33	65	3	
Moya, A. et al.	Gamma probe	NO		109	36	215	46	97	109	7	62.4
Boeve, K. et al.	Gamma probe	NO	The tumor first	66	25	274	28	24	64	4	32
Schilling, C. et al.	Gamma probe	NO		321	94	1342		94	321	15	36
Pedersen, N.J. et al.	Gamma probe	NO	The tumor first	185	68	253	77	68	185	9	32
Flach, G. et al.	Gamma probe	NO		42	20	206		20	42	5	52.5

TABLE 1 (Continued)

	GP	PP	STE	SNB (−)	SNB (+)	GSN	PSN	PHND	NFOLLOWUP	PWHR	AFOLLOWUP
Den Toom, I.J. et al.	Europrobe	NO		61	26	229		26	61	2	18
Sebbesen, L. et al.	Gamma probe	NO		53	0			0	53	4	37
Samant, S.	Gamma probe	NO	The tumor second	29	3			3	29	2	36
Melkane, A.E. et al.	Gamma probe	NO		83	30			30	83	6	

Abbreviations: AFOLLOWUP, average patient follow-up; BD, blue dye; C, country; DINL, dynamic lymphoscintigraphy; GP, gamma probe intraoperative; GSN, global sentinel nodes removed, positive or negative; HBS, number of hours before surgery that the injection was given; ICG, indocyanine green; L, location; N, number of patients included; NFOLLOWUP, number of patients who were still SNB(−) in the follow-up; PHND, patients with neck dissection; PP, photodynamic probe; PSN, number of positive sentinel nodes; PWHR, patients who seen some metastases in the neck in the follow-up; RAD, radiotracer; SNB(−), number of patients with a negative sentinel lymph node biopsy result; SNB(+), number of patients with positive sentinel node; Spect/CT, single photon emission computed tomography; ST, study type; STE, shine-through effect; STL, static lymphoscintigraphy; Y, year.

(PC: use or non-use of intraoperative photodynamic chamber, as well as the brand, if specified), shine-through effect (STE: extraction of tumors before applying the SN technique, if specified), number of patients that were negative in the SN technique SNB(−), number of patients who had at least one positive sentinel node of metastases when the SN was performed, SBB(+), global sentinel nodes removed (GSN: total number of sentinel nodes removed, both positive and negative in metastases), positive sentinel nodes with metastases (PSN: number of positive sentinel nodes with metastases), patients with complete dissection (PHND: number of patients with complete dissection, both bilateral or unilateral), patients in follow-up (NFOLLOWUP: number of patients who did not undergo a dissection and who remained in the study follow-up subsequent to the SN technique), patients with relapse in the neck (PWHR: patients in the follow-up who seen some metastases in the neck during the follow-up), global follow-up (AFOLLOWUP: median follow-up of patients in months).

First, the title and abstracts of all potential records were read and the inclusion of any text with insufficient data was discussed through a full-text protocol. Subsequently, all eligible articles were fully examined, and if essential data for the review was missing or unclear, an attempt was made to contact the corresponding author of the study to resolve or clarify the problem.

2.4 | Statistical analysis

In order to assess the overall diagnostic value of sentinel lymph node biopsy protocols, the pooled sensitivity, specificity and the bivariate summary receiver operator characteristic (SROC) curve, and the area under the curve (AUC) were calculated. To analyze the heterogeneity among the studies, the Q statistical test and the I^2 were used. A p-value of <0.10 and I^2 of $>50\%$ indicates that there was heterogeneity between the studies, therefore meaning that a random-effects model would be used. To the contrary, a p-value of >0.10 and a heterogeneity of $<50\%$ indicates that there was a low heterogeneity between studies, therefore meaning that a fixed effects model would be used. The data was further analyzed using different subgroup analysis with the variables: study type (prospective/retrospective), tumor location (tongue/tongue and other[s]), radiotracer (lopamidol/99 m CT), ICG (yes/no), blue dye (no/yes), continent (Asia/Europe/United States), STE (the tumor first/the tumor second), and HBS (before 24 h/at 24 h). Results from the quantitative analysis have been presented on "forest plot" graphs. Meta-analysis was performed using the MIDAS (Meta-Analytical Integration of Diagnostic Accuracy Studies) module of STATA v16 (StataCorp, College Station, TX).

2.5 | Evaluation of quality and risk of bias

The quality of the studies was assessed using the Quality in Prognosis Studies (QUIPS).[16] This tool is comprised of six different domains: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) study confounding, and (6) statistical analysis and reporting). Each parameter could be identified by one of three attributes (i.e., low, moderate, or adequate).[16]

For each domain, the risk of bias was qualified as low (green color = 3 points), moderate (yellow = 2 points), or high (red = 1 point). Any studies that scored ≥14 out of 18 were considered to be of high methodological quality for subgroup analysis. The interrater reliability was substantial with a Kappa value equal to 0.71 (95% CI: 0.62–0.79).

3 | RESULTS

3.1 | Study selection

According to the PRISMA 2020 criteria for the systematic reviews of articles, the flow diagram of the selection has been included as Supplementary S1. In total, 449 articles were obtained from the first search. After the first review, 73.1% (331) were excluded following a partial reading of the texts in which the general criteria were applied, and the remaining articles went through to the complete reading phase. After a complete reading, 66.6% of the remaining 105 articles were excluded, therefore meaning that 35 articles made it to the third and final phase. Said articles were subjected to more exhaustive criteria, as shown in Supplementary S1, resulting in a total of 23 articles that were included in the meta-analysis.

3.2 | Risk of bias

The quality of the articles included in the meta-analysis ($n = 23$) were assessed according to the QUIPS tool, the results of which are included in Figure 1. Thirteen of the articles were considered to be of high methodological quality. With regards to the (1) study participation, (2) study attrition, and (4) outcome measurement parameters, most of the articles were classified as low to moderate risk of bias, except two articles that were classified as being of high risk of bias in terms of the study attrition parameter. On the other hand, the (3) prognostic factor measurement, (5) study confounding, and (6) statistical analysis and reporting parameters were more conflictive, with a total of 9, 11, and 4 articles classified as being of high risk of bias, respectively.

3.3 | Synthesis of the qualitative and quantitative analysis

3.3.1 | Qualitative analysis

Table 1 shows the data retrieval from the proceedings conducted in the different studies, both in pre-operative and intraoperative terms, as well as the characteristics that were obtained both in the post-operative and follow-up.

The final sample is comprised of a total of 1352 patients SNB (−) in follow-up, with an average follow-up time of 45.5 months and a range of 18–120 months. A total of 6.2% relapses in the neck were found during the follow-up.

Out of the 23[1,17–38] articles, 15 were prospective[1,18,19,21,24–28,30–32,34,37,38] and eight were retrospective.[18,20,22,23,29,33,35,36] All of the articles considered tumors on the tongue, as well as other locations in the oral cavity.

With regards to the lymphography (static or dynamic) and the pre-operative Spect/ct, it was observed that the studies reported a very disparate use, with the heterogeneity making it impossible to unify the data retrieval. The most commonly used radiotracer for performing the SNB was 99mTc ($N = 18$), followed by the Iopamiron ($N = 3$); and two other studies also used a radiotracer but without specifying its name. Likewise, in 13 of the studies, the radiotracer was injected 24 hours prior to the surgical

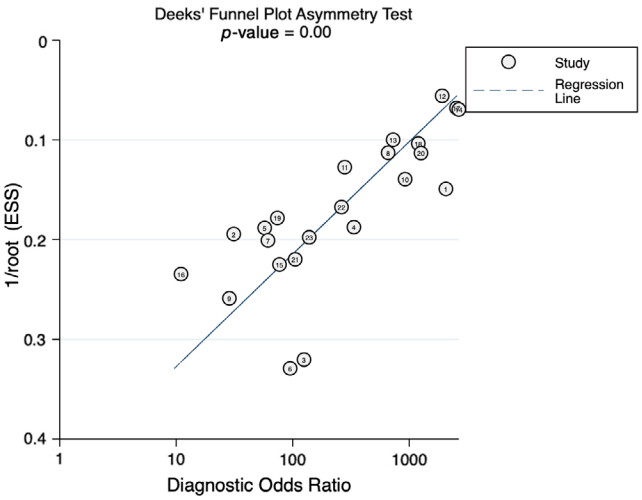

FIGURE 2 Deeks' funnel plot asymmetry test for the diagnostic odds ratio (DOR). The vertical axis displays the inverse of the square root of the effective sample size (1/root[ESS]). The horizontal axis displays the ratio DOR [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Subgroup analysis of different variables

	Parameter	Category	Studies, *n*	% (CI)	Meta-analysis *p*-value	Heterogeneity I^2	Heterogeneity *p*-value	Subgroup analysis *p*-value
Sensitivity	Study type	Prospective	15	79.60% (70.90%–86.30%)	<0.001	53.74%	0.007	0.974
		Retrospective	8	78.90% (65.30%–88.20%)	<0.001	56.60	0.024	
	Tumor location	Tongue	5	70.00% (54.50%–82.00%)	0.013	0.0%	0.855	0.195
		Tongue and other(s)	18	81.10% (73.60%–86.80%)	<0.001	57.91	0.001	
	Radiotracer	Iopamidol	3	60.90% (41.70%–77.30%)	0.263	0.0%	0.839	**0.021***
		99 m TC	18	82.80% (76.90%–87.50%)	<0.001	45.14%	0.02	
	ICG	Yes	5	66.50% (49.90%–79.90%)	0.052	0.0%	0.710	0.083
		No	18	81.60% (74.60%–87.00%)	<0.001	54.90%	0.003	
	Blue dye	No	17	77.50% (69.10%–84.10%)	<0.001	55.52%	0.003	0.245
		Yes	6	85.60% (71.90%–93.20%)	<0.001	49.63%	0.077	
	Continent	Asia	7	67.8% (54.6%–78.7%)	0.009	0.0%	0.897	**0.005***
		Europe	14	84.0% (77.0%–89.2%)	<0.001	57.26%	0.004	
		United States	2	64.1% (37.3%–84.3%)	0.300	0.0%	0.688	
	STE	The tumor first	5	85.0% (77.5%–90.3%)	<0.001	0.0%	0.726	0.489
		The tumor second	4	82.1% (56.0%–94.3%)	0.02	50.76%	0.107	
	HBS	Before 24 h	3	63.9% (32.4%–86.7%)	0.393	69.70%	0.037	0.132
		At 24 h	13	81.0% (74.5%–86.2%)	<0.001	28.61	0.157	
Specificity	Study type	Prospective	15	98.5% (97.0%–99.3%)	<0.001	0.0%	0.957	0.631
		Retrospective	8	98.9% (97.2%–99.6%)	<0.001	0.0%	0.996	
	Tumor location	Tongue	5	96.8% (89.4%–99.1%)	<0.001	0.0%	0.940	0.099
		Tongue and other(s)	18	99.0% (98.0%–99.5%)	<0.001	0.0%	0.998	
	Radiotracer	Iopamidol	3	96.7% (85.1%–99.3%)	<0.001	0.0%	0.796	0.212
		99 m TC	18	98.9% (97.8%–99.4%)	<0.001	0.0%	0.991	
	ICG	Yes	5	97.1% (90.5%–99.2%)	<0.001	0.0%	0.944	0.146
		No	18	98.9% (98.0%–99.4%)	<0.001	0.0%	0.996	
	Blue dye	No	17	98.7% (97.5%–99.3%)	<0.001	0.0%	0.959	0.883
		Yes	6	98.6% (95.8%–99.6%)	<0.001	0.0%	0.989	
	Continent	Asia	7	96.9% (91.5%–98.9%)	<0.001	0.0%	0.988	0.116
		Europe	14	99.2% (98.3%–99.6%)	<0.001	0.0%	0.999	

(Continues)

TABLE 2 (Continued)

Parameter	Category	Studies, *n*	% (CI)	Meta-analysis *p*-value	Heterogeneity I^2	Heterogeneity *p*-value	Subgroup analysis *p*-value
	United States	2	98.3% (89.1%–99.8%)	<0.001	0.0%	0.946	
STE	The tumor first	5	98.8% (95.9%–99.7%)	<0.001	0.0%	0.698	0.510
	The tumor second	4	97.8% (91.4%–99.4%)	<0.001	0.0%	0.819	
HBS	Before 24 h	3	98.7% (93.7%–99.7%)	<0.001	0.0%	0.820	0.933
	At 24 h	13	98.8% (97.5%–99.4%)	<0.001	0.0%	0.942	

Note: * and bold indicates significant statistical differences.
Abbreviations: CI, confidence interval; HBS, time of radiotracer injection before surgery; ICG, indocyanine green; STE, extraction of tumors before applying the SN technique.

procedure. It was observed that in all the studies in which lopamiron was used, a gamma probe was not used to detect the SN intraoperatively.

In addition to the radiotracer, other fluorescent substances were injected intraoperatively, such as ICG in 21.7% ($n = 5$) of the studies, and blue dye staining in 26.08% of the studies ($n = 6$). The two stains were never combined in the same protocol. Lastly, it must be highlighted that in four out of the five studies, the type of photodynamic chamber that was used together with the ICG was specified (see Table 1).

Surgically, six studies took into account the importance of the shine-through effect, first removing the tumor to prevent it from impeding the visualization of the SN.

3.3.2 | Quantitative analysis

The grouped sensitivity of the SNB was 82% (95% CI: 0.74–0.88), and the grouped specificity was 100% (95% CI: 0.99–1.00), with an area under the ROC curve of 100 (95% CI: 0.99–1.00). A high risk of bias was identified in the different studies using the Deeks' funnel plot asymmetry test ($p < 0.001$) (Figure 2).

Subgroup analysis was performed for type of study, tumor location, radiotracer, ICG and blue dye, continent, STE and HBS (Table 2). No differences were found in relation to the specificity.

With regards to the radiotracer marker, the use of radiotracers other than pre-operative lopamidol (99mTc-Sulfur colloid, 99mTc-labeled rhenium sulfur colloid, 99mTc-Tin colloid, 99mTc-Phytate, 99mTc-labeled colloid tracer, 99mTc-Nanocolloid) presented higher values of sensitivity of 82.80% (95% CI: 76.90%–87.50%; $p = 0.021 < 0.001$) and low heterogeneity for lopamidol ($I^2 = 0\%$, $p = 0.839$) (Figure 3). In relation to the continent where the study was performed, the studies conducted in Europe attained the highest sensitivity with 84.0% (95% CI: 77.0%–89.2%), compared to those conducted in the United States or Asia, however there was a high heterogeneity ($I^2 = 57.26\%$, $p = 0.004$) (Figure 4).

With regards to the other two most interesting parameters, no statistically significant differences were recorded when ICG was used as coadjuvant ($p = 0.083$), although higher sensitivity values were recorded when it was not used, 81.60% (95% CI: 74.60%–87.00%) with a heterogeneity of $I^2 > 50\%$ (Figure 5). Lastly, the use of the blue dye stain presented higher sensitivity values of 85.60% (95% CI: 71.90%–93.20%), compared to the sensitivity values of 77.50% when it was not used (95% CI: 69.10%–84.20%), however no significant differences were determined ($p = 0.245$) and high heterogeneity was determined ($I^2 = 52.76\%$, $p = 0.002$) (Figure 6).

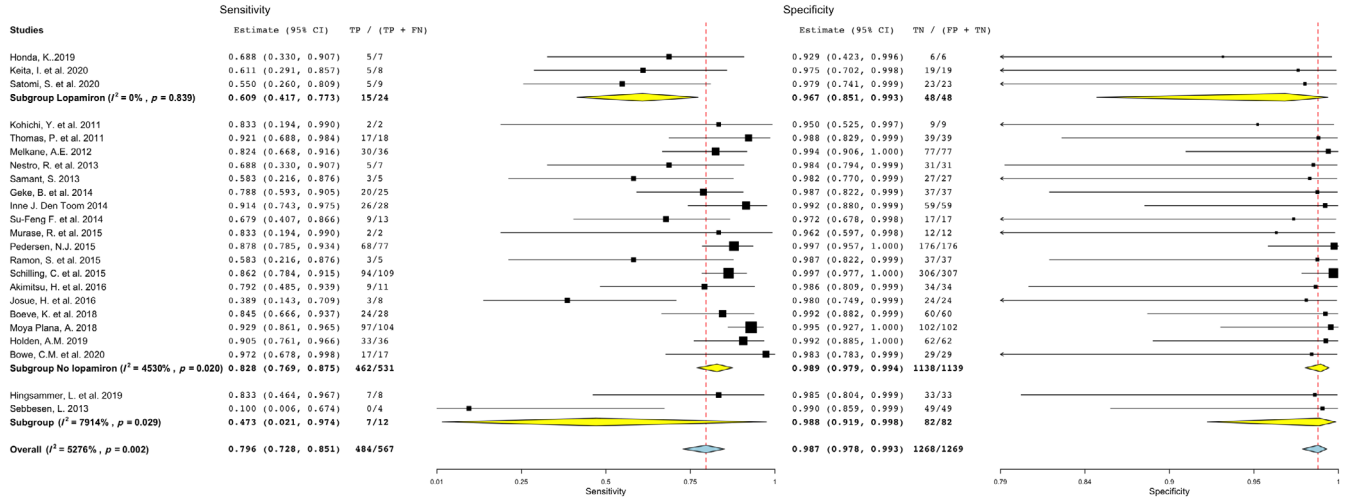

FIGURE 3 Forest plot for radiotracer marker (use of lopamiron). FN, false negatives; TN, true negatives; TP, true positives [Color figure can be viewed at wileyonlinelibrary.com]

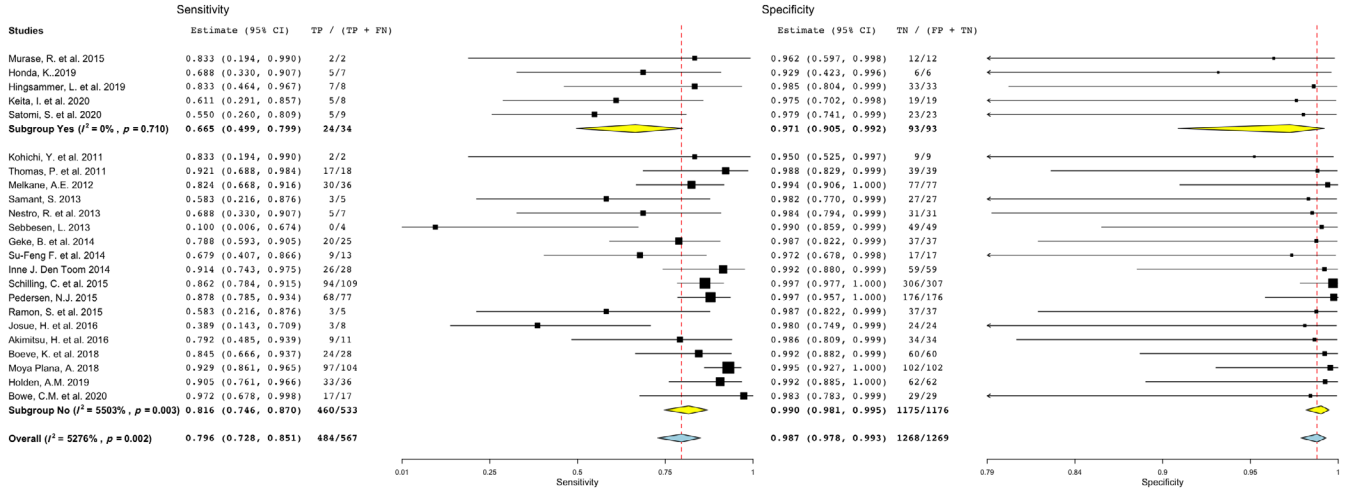

FIGURE 4 Forest plot for the continent of origin: Europe, United States, and Asia. FN, false negatives; TN, true negatives; TP, true positives [Color figure can be viewed at wileyonlinelibrary.com]

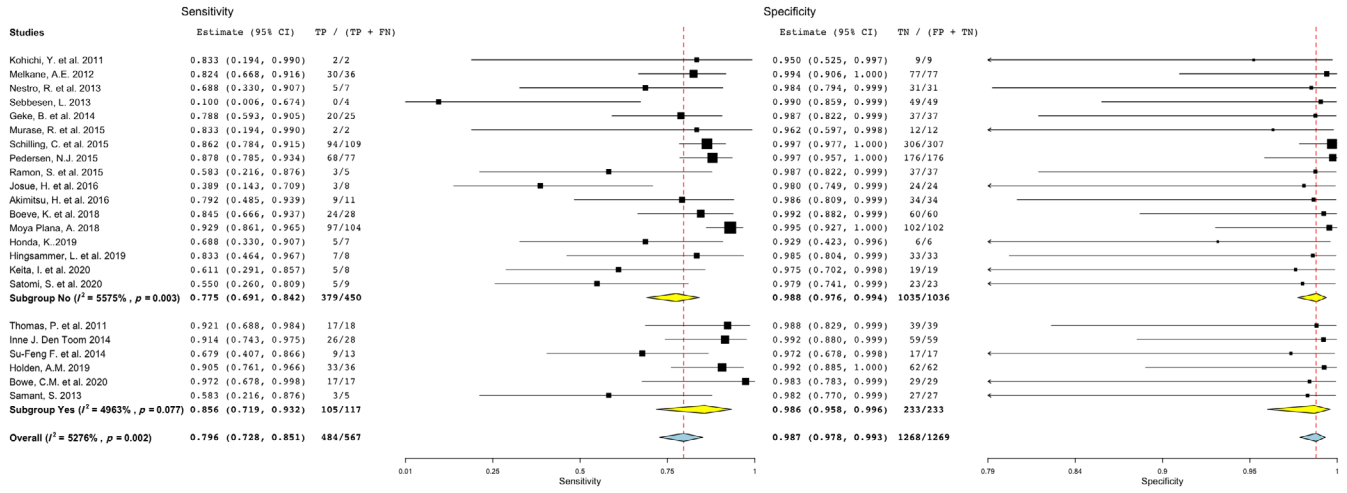

FIGURE 5 Forest plot for the use of ICG (use or non-use of the intraoperative indocyanine green). FN, false negatives; TN, true negatives; TP, true positives [Color figure can be viewed at wileyonlinelibrary.com]

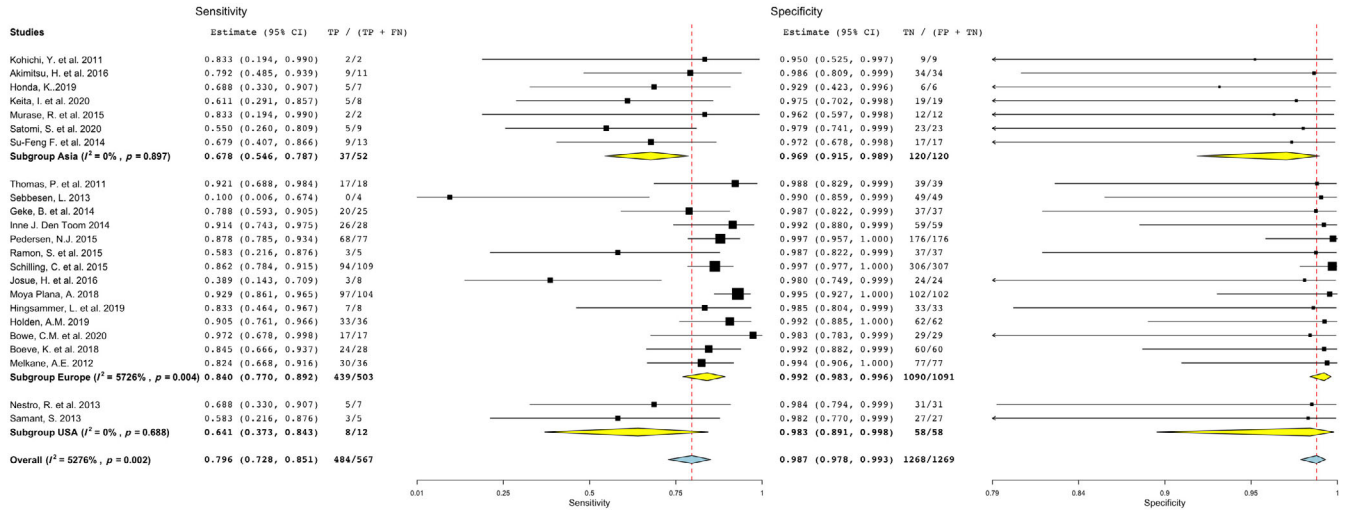

FIGURE 6 Forest plot for the use of blue dye (use or non-use of the intraoperative blue dye). FN, false negatives; TN, true negatives; TP, true positives [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

According to the different SNB guidelines, it is a technique in which multiple tests, both diagnostic and surgical are performed, with the involvement of different medical disciplines (maxillofacial surgery, radiology, nuclear medicine, and pathological anatomy).[4,5,39] The multidisciplinary nature of this technique is the main justification for the limitations of this technique.

Establishing a correct lymphatic diagnosis and presurgical preparation using lymphography (dynamic and/or static) and SPEC/CT[4] appear to be mandatory. Determining a pattern proved to be a very complex task in this study due to the high heterogeneity of the reported data. Specifically, the EANM guidelines[5] indicate that a dynamic lymphography is required after the radiotracer injection.[5] On the other hand, it is worth mentioning that Rutger et al.[40] carried out a systematic review in which they assessed different techniques (MR lymphography, CT lymphography, PET lymphoscintigraphy, and contrast-enhanced lymphosonography) to locate the sentinel nodes pre-operatively, however, they were unable to conclude whether said techniques were more effective than lymphography and SPECT/CT.

Second, the radiotracer seemed to be an important factor for studying this technique. The 99mTC was the most used radiotracer in the studies, and the *VIII International Symposium on the Sentinel Node Technique*,[14] as well as other guidelines and reviews[4,13] have indicated that it should be the radiotracer of choice. The sensitivity in our study was 82.80%, which is significantly higher than the sensitivity obtained by lopamidol, which was 60.9%. However, all the studies ($n = 3$) that used lopamidol were conducted outside of Europe, specifically in Japan, and we did not find any guidelines recommending its usage. The subgroup analysis showed differences in sensitivity between the different countries, with the United States and Asia presenting the lowest results, nonetheless, these results must be considered with caution due to the limited number of cases in some countries and the high global heterogeneity.

Likewise, in the aforementioned VIII Symposium, the use of ICG was recommended as a coadjuvant at 99Tc, advising against it being used on its own. Statistically significant differences were not found in the present meta-analysis. However, it is worth pointing out that in three[17,26,27] out of the five studies[17,21,26–28] in which it was used as coadjuvant, Iopamiron 300 was injected as a radiotracer, although as previously observed, it is not the radiotracer of choice. Likewise, a gamma probe was not used to detect the radiotracer in any of the three studies, with a photodynamic chamber used instead, which could explain the inferior results obtained.

The gamma probe, which is used to locate the "nodal hot spots" that emit gamma radiation obtained through the radiotracer[14] was the method of choice in all the papers included in the meta-analysis, except for the three[17,26,27] mentioned previously. The results were very different to the ones obtained with the photodynamic chamber, which is highly sensitive to the fluorescence of the ICG.[21]

On the other hand, the sensitivity when using blue dye was greater than when it was not used, with a sensitivity of 85.60% compared to 77.50%, and it was always used in conjunction with the 99mTc, however, these differences were not statistically significant. De bree et al.[13] stated that this stain is not used in most of the protocols because the ICG's properties are superior. Likewise, Schilling et al.[14] stated that the blue dye reaches the node quickly, but that it is not retained, meaning that it could

stain adjacent structures. In the present meta-analysis, better rates were obtained when using it than when not using it, and it is important to highlight the main limitation, which is that it cannot be compared to ICG since the same protocols were not used and that is a determining factor.

Lastly, it was observed that only a few articles reported the shine-through effect,[19,23,24,28,31,33] in which the tumor was removed first, in fact, some of the articles even stated that the tumor was removed after performing the SNB,[1,25,27,36] therefore, this phenomenon may be included among the main recommendations of the protocol, limiting its efficacy to the technique.[14] The results achieved were similar between both subgroups and no statistically significant differences were found.

5 | CONCLUSIONS

The grouped sensitivity to the SNB was 82% and the specificity was 100%. These diagnostic rates are variable and they were significantly better when 99mTc was used in all its variations. More studies with rigorous and homogeneous protocols, which study the effect of coadjuvant staining in the diagnostic yield of SNB are needed.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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