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High sensitivity and negative predictive value of sentinel lymph node biopsy in a retrospective early stage oral cavity cancer cohort in the Northern Netherlands

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Objectives: In cT1-2N0, oral squamous cell carcinoma (OSCC) occult metastases are detected in 23%-37% of cases. Sentinel lymph node biopsy (SLNB) was introduced in head and neck cancer as a minimally invasive alternative for an elective neck dissection in neck staging. Meta-analyses of SLNB accuracy show heterogeneity in the existing studies for reference standards, imaging techniques and pathological examination. The aim of this study was to assess the sensitivity and negative predictive value (NPV) of the SLNB in detecting occult metastases in cT1-2N0 OSCC in a well-defined cohort.

Design: Retrospective study. The SLNB procedure consisted of lymphoscintigraphy, SPECT/CT-scanning and gamma probe detection. Routine follow-up was the reference standard for the SLNB negative neck. Histopathological examination of sentinel lymph nodes (SLN) consisted of step serial sectioning, haematoxylin-eosin and cytokeratin AE1/3 staining.

Setting: Two comprehensive oncology centres.

Participants: A total of 91 consecutive patients with primary cT1-2N0 OSCC treated by primary resection and neck staging by SLNB procedure between 2008 and 2016.

Main outcome measures: Sensitivity and negative predictive value.

Results: In all cases, SLNs were harvested. A total of 25 (27%) patients had tumour-positive SLNs. The median follow-up was 32 months (range 2-104). Four patients were diagnosed with an isolated regional recurrence in the SLNB negative neck side resulting in an 85% sensitivity and a 94% NPV.

Conclusion: In our cohort, the SLNB detected occult metastases in early OSCC with 85% sensitivity and 94% NPV. This supports that SLNB is a reliable procedure for surgical staging of the neck in case of oral cT1-2N0 SCC.

1 | INTRODUCTION

Regional metastases occur in 23%-37% of the early stage (cT1-2N0) oral squamous cell carcinomas (OSCC).[1-3] Lymph node status is an important prognostic factor for outcome and treatment decision-making of head and neck cancer.[1-8] However, not all metastases are clinically detectable with the current diagnostic modalities.[9-11] Occult metastases are conventionally treated by removal of the lymph nodes by elective neck dissection (END) after research showed higher rates of overall and disease-specific survival compared to a watchful waiting strategy.[12] However, an END has disadvantages: it leads to overtreatment in 63%-77% of the cases and has a risk of postoperative comorbidity (eg shoulder pain, reduced limb movement).[13] Therefore, there is a need for a better neck staging modality.

The sentinel lymph node biopsy (SLNB) was introduced in oral cavity cancer as a less invasive lymph node staging technique after successful implementation in melanoma and breast cancer.[5] The limited number of lymph nodes (LN) with the SLNB enables a more meticulous pathological examination incorporating step serial sectioning (SSS) and additional immunohistochemistry (IHC).[14] Recently, Liu and Wang reported a meta-analysis of 3566 early stage OSCC patients from 66 studies with a pooled sensitivity of 87% and negative predictive value (NPV) of 94% for SLNB in detecting occult metastasis.[15] However, many of these studies consist of small cohorts and differ in reference treatment, SLNB localisation technique (eg use of gamma probe, blue dye or single photon emission CT (SPECT-CT)) and pathological work-up (with or without IHC or SSS). Furthermore, several studies provide incomplete clinico-pathological information. This heterogeneity and lack of complete data underline the need for more studies using complete and homogeneous cohorts. The aim of this study was to determine the sensitivity and NPV of the SLNB in detecting occult metastases in a large, well-defined cohort. For this purpose, we used a retrospective cT1-2N0 OSCC cohort of 91 patients all treated by primary surgical resection, neck staging with the SLNB procedure and routine follow-up as reference standard for the SLNB negative neck.

Keypoints

- The sentinel lymph node biopsy detected occult metastases in our cN0 cohort with an 85% sensitivity and a 94% negative predictive value.
- No additional metastases were seen in the neck dissection lymph nodes of patients with micrometastases or isolated tumor cells in the sentinel lymph nodes.
- The sentinel lymph node biopsy reveals unexpected lymphatic drainage patterns and therefore prevents patients for undertreatment of the neck.

2 | PATIENTS AND METHODS

2.1 | Ethical consideration

Sentinel lymph node biopsy was part of standard treatment and data were retrospectively gathered from existing data sources; therefore, no approval from the hospital research ethics board was required according to the Dutch ethical regulations.[16,17]

2.2 | Patients and setting

Patients treated at the Oral & Maxillofacial Surgery or Otorhinolaryngology/Head & Neck Surgery departments of the University Medical Center Groningen (UMCG) (n = 83) or the Oral & Maxillofacial Surgery department of the Medical Center Leeuwarden (MCL) (n = 8) between October 2008 and December 2016 were used for analysis. Detailed information about the patient selection and the SLNB procedure are added to this manuscript as Appendix S1.

Briefly, inclusion criteria were as follows: clinically T1-2 and N0 staged OSCC (7th TNM classification); primary treatment by surgical resection and neck staging by SLNB. Clinico-pathological data of the 91 (100%) patients were retrospectively collected from the digital patients files (Table 1). Cases with a positive SNLB underwent a modified radical neck dissection (MRND) during a second surgery. Routine follow-up of the neck was used as reference standard in the SLNB negative patients and consisted of physical examination that was followed by ultrasound fine needle aspiration cytology (USFNAC) in case of enlarged (>1 cm) or otherwise suspicious lymph nodes.

2.3 | Study procedure

The SLNB procedure was described in detail before and was mostly the same in both centres.[18] Lymphoscintigraphy and SPECT/CT scans were made 1 day before surgery. Intraoperatively, SLNs were harvested after gamma probe assisted localisation.[18] SLNs were histopathologically examined by SSS with an interval of 500 μm and additional pan-cytokeratin antibody (AE 1/3) immunohistochemistry staining. Additional lymph nodes (non-SLNs) were harvested if they blocked the SLN or formed a conglomerate with the SLN.

2.4 | Statistical analysis

IBM SPSS Statistics 23 (Statistical Package for the Social Sciences, Inc., Chicago, IL, USA) was used for analysis. Categorical data are presented as number (n) and their percentages (%). Associations between categorical data were tested with the Fisher's exact or Chi-squared test. Continuous data were tested using the Student's *t* test or the Mann-Whitney *U* test for normally or skewed distributed data, respectively. False negative SLNB patients were defined as patients with isolated regional recurrence in the SLNB negative neck side and were used to calculate the sensitivity and negative predictive value. Significant differences were defined as a *P*-value ≤.05.

TABLE 1 Patient and tumour demographic characteristics

Demographic characteristics	Overall, n (%)	Histopathological status of SLNB		*P* value
		pN0, n (%)	pN+, n (%)	
Total	91 (100)	66 (100)	25 (100)	NA
Sex				
Male	43 (48)	32 (48)	11 (44)	.815
Female	48 (52)	34 (52)	14 (56)	
Age at first treatment, y				
Median (IQR)	62 (56-70)	61 (56-71)	64 (57-69)	.996
Tumour location n (%)				
Tongue	52 (57)	35 (53)	17 (68)	.111[a]
FOM	27 (30)	23 (35)	4 (16)	
Cheek mucosa	8 (9)	5 (8)	3 (12)	
Upper gum	3 (3)	2 (3)	1 (4)	
Lower gum	1 (1)	1 (2)	0 (0)	
cT classification				
cT1	66 (73)	51 (77)	15 (60)	.119
cT2	25 (27)	15 (23)	10 (40)	
pT classification				
pT1	73 (80)	57 (86)	16 (64)	.036
pT2	18 (20)	9 (14)	9 (36)	
SLNB side				
Ipsilateral	57 (63)	40 (61)	17 (68)	.701
Contralateral	1 (1)	1 (2)	0 (0)	
Both sides	33 (36)	25 (38)	8 (32)	
Number of SLNs per patient				
Median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)	.585
Tumour infiltration depth				
<4.59 mm	59 (65)	46 (70)	13 (52)	.142
≥4.59 mm	32 (35)	20 (30)	12 (48)	
Perineural invasion				
Yes	6 (7)	3 (5)	3 (12)	.340
No	85 (93)	63 (95)	22 (88)	
Lymphovascular invasion				
Yes	9 (10)	6 (9)	3 (12)	.702
No	82 (90)	60 (91)	22 (88)	
Tumour border configuration				
Pushing	54 (59)	45 (68)	9 (36)	.008
Infiltrative	37 (41)	21 (32)	16 (64)	
Differentiation grade				
Well	29 (32)	21 (32)	8 (32)	1.000
Moderate	62 (68)	45 (68)	17 (68)	
Follow-up data				
Time in months median (IQR)	32 (21-47)	37 (22-49)	25 (19-33)	.014
Total range	2-104			
Recurrence				
Local/2nd primary	9 (10)	5 (8)	4 (16)	[b]
Isolated regional rec.	5 (5)	2 (3)	3 (12)	
Dead				
Dead of disease	3 (3)	0 (0)	3 (12)	[b]
Dead not of disease	7 (8)	6 (9)	1 (4)	

FOM, floor of mouth; IQR, interquartile range; NA, not applicable; pN0, SLNs negative for metastases; pN+, SLNs positive for metastases; Rec, recurrence; SLNB, sentinel lymph node biopsy.

[a]Tongue vs floor of mouth, other subgroups too small to analyse.

[b]Group too small to analyse.

3 | RESULTS

Sentinel lymph nodes were identified in all 91 cases (100%). In total, 274 SLNs were harvested with a median of 3 (range 1-11) per patient. The results of the SLN procedures are summarised in Table 1. In all patients, at least one SLN was intraoperatively detected. However, in 4 patients (4%), additional hotspots were noticed besides the harvested SLNs on the SPECT-CT without intraoperative detectable radioactive LNs. In 1 of these 4 patients, the harvested SLN was positive and the neck was treated by MRND in a second operation. The other 3 patients were isolated regional recurrence (IRR) free after 10, 11 and 47 months of routine follow-up. In 1 patient with a ventral floor of mouth tumour, only a contralateral SLN was identified. The other patients had ipsilateral (n = 57, 63%) or bilateral (n = 33, 36%) located SLNs.

Positive SLNs were found in 25 (27%) patients. In 1 patient with a 1 mm metastasis in the SLN routine follow-up was chosen instead of a MRND. This patient was still recurrence free after 23 months. In none of the patients with micrometastases or ITCs in the SLN, additional metastases were found in the MRND specimen (Figure 1, Table 2, $P = .024$). Also, none of the 57 non-SLNs harvested during the SLNB were positive. Finally, skip metastases were not seen: all patients with positive SLNs had at least one positive SLN in level I-III. Infiltrative tumour border configuration ($P = .008$) and pT2 tumour stage ($P = .036$) showed an association with lymph node status (Table 1).

3.1 | Follow-up and regional recurrence

Overall the median FU was 32 months (IQR 21-47, Range 2-104, Table 1). All patients with a follow-up <10 months died. In total, 8 (9%) patients of this cohort died. Three patients died of disease, two 10 months and one 21 months after the initial treatment.

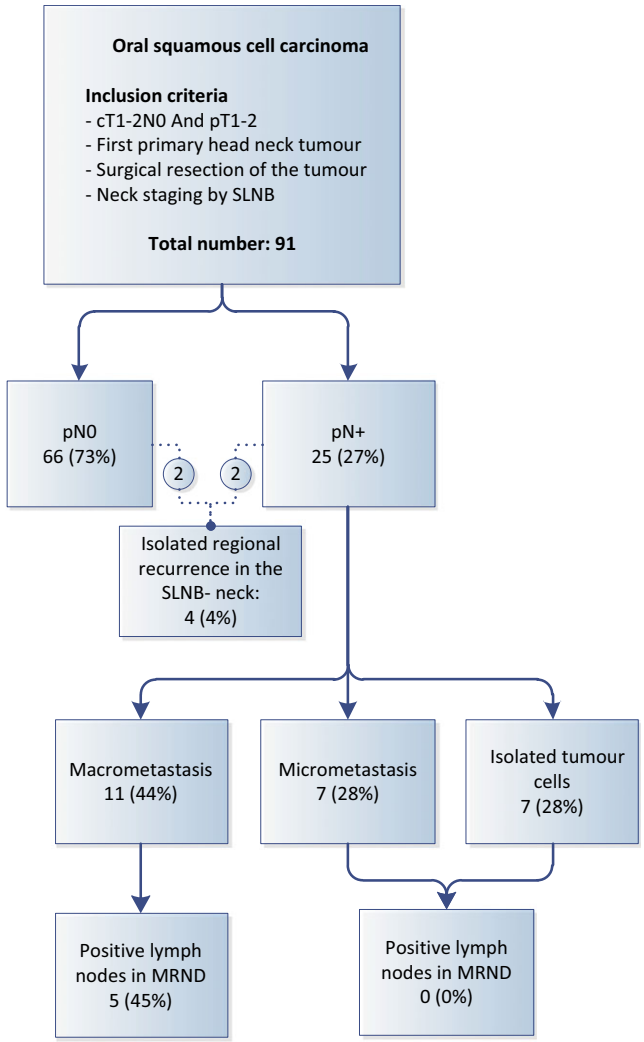

FIGURE 1 Flow chart of the UMCG and MCL cT1-2N0 oral squamous cell carcinoma cohort. In total, 91 patients were used for analysis. A total of 25 patients had metastasis positive SLNB. Two patients with pN0 and 2 patients with pN+ SLNB neck status were diagnosed with isolated regional recurrence in the SLNB negative neck side. MRND, modified radical neck dissection; pN0, All SLNs negative for metastasis; pN+, at least one SLN positive for metastasis; SLNB, sentinel lymph node biopsy

TABLE 2 Association between SLN metastasis size and additional metastases in modified radical neck dissection lymph nodes

		HKD lymph node status		
SLN status	**n (%)**	**pN-, n (%)**	**pN+, n (%)**	***P* value**
Isolated tumour cells	7 (29)	7 (37)	0 (0)	.024
Micrometastases	6 (25)	6 (32)	0 (0)	
Macrometastases	11 (46)	6 (32)	5 (100)	

MRND, modified radical neck dissection; pN0, SLNs negative for metastases; pN+, SLNs positive for metastases; SLN, sentinel lymph node.

Local recurrence and second primary tumours, with or without regional recurrence, were seen in 9 (10%) cases. Isolated regional recurrence was detected in 5 (5%) patients. One of these patients had IRR after a positive SLN and subsequent neck dissection at that neck side. The other 4 patients were diagnosed with IRR after 4, 6, 9 and 19 months. Their tumour, treatment and recurrence characteristics are shown in Table 3. The first patient had a positive ipsilateral SLN and was 4 months later diagnosed with level I and level II IRRs at the contralateral side. Revision of the SPECT-CT images and the conventional CT images of the IRR did not reveal new insights. The second patient had ipsilateral negative SLNs and was diagnosed with level Ib and level IV IRRs after 9 months. Revision of the SPECT-CT images of this patient showed a lymph node with a diameter of 7 mm without radioactivity just at the inside of the mandibular angle in level Ib. This lymph node was most likely not resected during the SLNB procedure and could be the same as the IRR lymph node. The third patient had a positive contralateral SLN. IRR occurred on the ipsilateral side, which was SLNB negative and was therefore not treated by MRND. Revision of the lymphoscintigraphy images revealed a low signal in level Ib at the ipsilateral side, what might be a missed SLN. The fourth patient had a negative SLN in level II and was diagnosed with IRR in level Ib, both ipsilateral. Revision of the SPECT/CT scan showed a LN within the radioactive hotspot of the floor of mouth tumour of this patient. Most likely, this is the same LN in which the IRR was diagnosed (Figure 2).

Due to the four IRRs, the SLNB detected occult metastases with 85% sensitivity and 94% NPV.

4 | DISCUSSION

4.1 | Synopsis of key findings

In our retrospective cohort of 91 patients treated for cT1-2N0 OSCC, 4 patients developed isolated regional recurrence on the side of a negative SLNB. This resulted in 85% sensitivity and 94% negative predictive value.

4.2 | Comparison to previous studies

The sensitivity and NPV are in agreement with the results of other studies with routine follow-up as a reference: sensitivity range 80%-94% and NPV range 88%-97.5% (number of patients 59-415).[1,6-8,19] A recent meta-analysis also showed comparable results: sensitivity 87%, NPV 94%.[15] The slightly higher NPV of this cohort compared to these meta-analyses can be explained by the relative short follow-up of some patients in our cohort. Two of the 66 patients (3%) with routine follow-up after a negative SLNB were diagnosed with IRR. This percentage is much lower than the conventional 20% change of having IRR from Weis et al[20], which is generally used in literature as threshold to choose between watchful waiting and END. The low percentage IRR indicates the accurate selection of cT1-2N0 patients for neck dissection or routine follow-up by performing a SLNB.

False negativity was defined as patients with IRR in an earlier SLNB negative neck side, regardless of a positive SLNB on the other side of the neck. Four (4%) patients in our cohort were diagnosed with IRR in a SLNB negative side of the neck, which is comparable

TABLE 3 Characteristics of the 4 patients with isolated regional recurrence

	Patients with isolated regional recurrence			
Variables	**1**	**2**	**3**	**4**
Tumour	Tongue	Cheek mucosa	Tongue	FOM
pT classification	1	1	2	2
Infiltration depth (mm)	8	5.0	3.7	2.7
Border growth	Pushing	Infiltrative	Infiltrative	Infiltrative
Resection margins	Free	Free	Free	Free
Perineural growth or Lympho-/angioinvasion	Yes, both	No	No	No
Differentiation grade	Good	Moderate	Moderate	Moderate
Reresection	Yes	No	No	No
Postoperative radiotherapy	Tumour & Neck	No	No	No
SLNB side	Ipsilateral	Ipsilateral	Both	Both
Positive SLN side	Ipsilateral	NA	Contralateral	NA
MRND side	Ipsilateral	NA	Contralateral	NA
Regional recurrence side	Contralateral	Ipsilateral	Ipsilateral	Ipsilateral
Number of SLNs recurrence side	NA	3	1	1
Number of positive SLNs recurrence side	NA	0	0	0
SLN level recurrence side	NA	Level II	Level II	Level II
Recurrence level	Level I + II	Level Ib + IV	Level Ib, II, IV	Level Ib
Number of LNs (positive/total)	2/44 (ENE+)	6/41	4/46	NA[a]
Maximum diameter regional recurrence metastasis (mm)	25	12	15	13[a]
Time between 1st treatment and rec. (mo)	4	9.2	5.5	19
Total follow-up (mo)	27	36	9	25
Dead of disease	NA	NA	Yes	NA

ENE, extranodal extension; MRND, modified radical neck dissection; NA, not applicable; SLNB, sentinel lymph node biopsy.
[a]The isolated regional recurrence of patient 4 was not operatively removed; therefore, only clinical data were available.

with other studies.[6,8] Retrospectively, the reason for missing these regional metastases remains unclear; shine-through phenomenon and aberrant lymphatic drainage due to metastatic tumour in the SLNs might be involved. Another possible explanation might be micrometastases in lymph nodes, other than the SLN (skip metastases).

Other studies reported a lower sensitivity of the SLNB procedure in FOM tumours compared to other oral cavity subsites due to the shine-through phenomenon.[7,8,21,22] One patient in this study had a FOM with an IRR resulting in an 80% sensitivity and a 96% NPV for FOM tumours. Retrospectively, this SLNB was overlooked because of this shine-through phenomenon (Figure 2). To overcome shine-through and subsequent regional recurrences, Stoeckli et al[23] proposed a surgical technique with dissection of all the LNs in level I irrespective of the location of the SLNs. Van den Berg et al[24] combined the SLNB procedure with radio and fluorescence guidance and found this combination especially helpful in detecting SLNs located close to the primary tumour. Our data support the findings of the

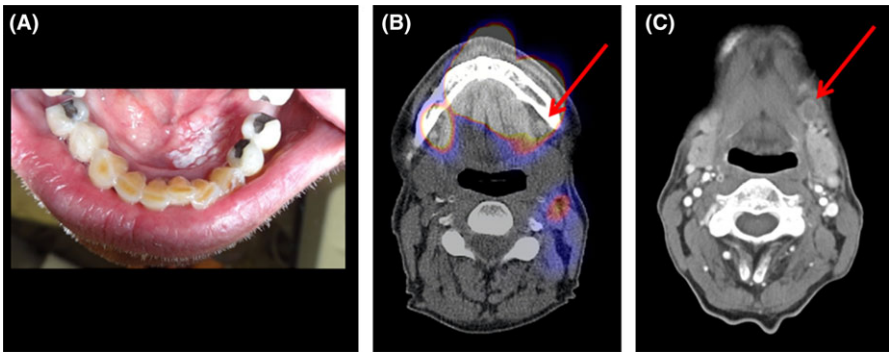

FIGURE 2 Shine-through phenomenon example. Patient with floor of mouth tumour on the left side closes the midline (A), with a lymph node within the tumour hotspot (B) and an isolated regional recurrence after 19 mo (C)

previously mentioned studies[23,24] that patients with primary tumours adjacent to level I could benefit from additional techniques besides the SLNB procedure alone.

The upstaging rate in this study (27%) is in agreement with the literature; 23%-37%.[1,2,7,8] We found no additional metastasis in the MRND lymph nodes after a SLNB positive for ITCs or micrometastases. Recently, den Toom et al reported that the ratio of positive vs negative SLNs and the size of the tumour in the SLN possibly could be predictive factors for non-SLN metastasis in SLN positive patients. However, their analysis was underpowered due to the use of the ITC, micro- and macrometastasis classification in just a few SLNB studies.[25] No additional metastasis in ITC or micrometastasis SLN positive patients could be the reason why Liu and Wang et al[15] concluded in their meta-analysis that SSS is not necessary for SLN assessment. Despite the lack of impact of the SSS on the IRR rate, in agreement with den Toom and our data presented in this paper, SLN metastasis size might be used to select patients for routine follow-up instead of MRND.[8] Besides the SSS itself, also the step interval size could be discussed. After the second international conference on SLNB, intervals of 150 μm were recommended.[26] As was reported earlier for breast cancer, Jefferson et al suggested that SSS intervals of 2 mm are thin enough to detect micrometastasis.[27,28] In this study, intervals of 500 μm were used, because our head and neck SCC protocol was adapted from our vulvar SCC SLNB protocol. This is a protocol we have much experience with and has shown to provide accurate staging of vulvar SCC in our centre.[29-31] Besides this, the accuracy we found is comparable to that of most head and neck SLNB studies.[15] Moreover, the ITC, micro- and macrometastasis ratio is comparable with other studies, indicating that we did not miss ITCs using this protocol. We therefore assume that this protocol has not influenced our results. However, we propose to continue SSS and classification of SLN metastasis size according to Hermanek, until well powered studies have defined the clinical impact of the SLN metastasis size.[32] Afterwards, further research is needed to reach consensus about minimal interval thickness for SSS to detect these metastases with clinical impact.

Thirty-three patients had SLNs on both sides of the neck, also in cases with lateralised border of tongue tumours. Moreover, 1 patient did not show ipsilateral lymphatic drainage patterns, but instead showed a negative contralateral SLN. This patient did not develop IRR at either side within 34 months follow-up. These 34 (37%) patients showed the advantage of detecting unexpected drainage patterns with the SLNB procedure and were thereby prevented from undertreatment.

Despite the good accuracy of the SLNB procedure, improvements might be made for the clinical negative neck. For example, in our centres, the use of blue dye has been abandoned, because it blurred surgical tumour resection margins preoperatively. A disadvantage of the SLNB procedure is the second operation for the MRND after a positive SLNB. Especially in frail elderly or patients with multiple comorbidities, a second operation with general anaesthesia is undesirable due to a higher complication and mortality chance.[33] Moreover, in all positive cases, scar tissue makes the neck dissection surgery more challenging in the SLN levels. To avoid repeat surgery, the possibility of intraoperatively staging of SLNs with frozen sections has been studied.[34] However, frozen sections have a substantial false negative rate; therefore, frozen sections of the SLNs are not applied in our centres. Also, a substantial amount of the SLN is lost for the FFPE sections and thereby increasing the risk of missing ITCs and micrometastases.[34]

In an ideal situation, patients at high risk of lymph node metastases are preoperatively selected for MRND or watchful waiting. In the current study, an infiltrative tumour border configuration or a pT2 tumour was significantly associated with more regional metastases. Our research group reported earlier infiltration depth and lymphovascular invasion as independent predictors for nodal status in pT1-2N0 and N-status determination by routine HKD and watchful waiting.[35] These markers are not associated with positive lymph nodes in this study. The lack of significance could be explained by the difference in patient selection between the mentioned study by Melchers (cN0 and cN+) and this study (cN0).[35] Therefore, the SLNB procedure is still more accurate in detecting occult metastasis in cT1-2N0 OSCC than the current clinical and pathological markers. In addition, it would be interesting to study the prognostic value of OSCC lymph node status associated biological markers such as WISP1, RAB25 or EpCAM in cT1-2N0 OSCC SLNB staged patients.[36-38]

4.3 | Study limitations

Limitation of this study is that the SLNB procedure was not part of the standard workflow for cT1-2N0 OSCC patients in the first years after introduction. If we analyse the accuracy without the 6 patients from this period, the sensitivity and NPV are still 85% and 94% respectively.

5 | CONCLUSION

In this retrospective well-defined cohort consisting of 91 patients, we showed that the sentinel lymph node biopsy is an accurate diagnostic technique in detecting occult metastases in cT1-2N0 OSCC and is a safe and reliable alternative to an END or watchful waiting.

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CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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