

# Sentinel lymph node biopsy for early stage tongue cancer—a 14-year single-centre experience

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L. Hingsammer, T. Seier, D. Zweifel, G. Huber, M. Rücker, M. Bredell, M. Lanzer: Sentinel lymph node biopsy for early stage tongue cancer—a 14-year single-centre experience. *Int. J. Oral Maxillofac. Surg.* 2019; 48: 437–442. © 2018 International Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.

**Abstract.** This study was performed to report the usage of sentinel lymph node biopsy (SLNB) in clinical stage I or II tongue cancer patients with cN0 necks seen over a 14-year period. Data were collected prospectively, and a retrospective analysis was performed of 41 patients with early stage oral squamous cell carcinoma of the tongue and a cN0 neck. Sentinel lymph node (SLN)-positive patients underwent elective neck dissection, whereas SLN-negative patients were kept under careful observation. Seven of the 41 (17%) patients enrolled in the study were found to have occult metastases. The patients were followed up for a mean duration of 92 months (range 60–144 months). The neck recurrence rate for SLN-positive patients was 0% and for SLN-negative patients was 3%. The authors recommend the routine use of SLNB in patients with early stage oral squamous cell carcinoma of the tongue and a cN0 neck. Furthermore, special focus should be placed on isolated tumour cells, as their presence is of high clinical relevance.

**Key words:** neck dissection; sentinel node biopsy; tongue cancer; survival rate.

Accepted for publication 5 October 2018  
Available online 30 October 2018

In 2014, approximately 55,000 people were newly diagnosed with head and neck squamous cell carcinoma (HNSCC) in the USA. This makes it the sixth most common type of cancer in the USA, and around 12,000 people die of this disease every year<sup>1</sup>. HNSCC is most frequently found in the oral cavity, and despite geographic variations, the tongue is the most commonly affected anatomical region<sup>2,3</sup>.

According to the TNM staging system, patients with early oral cavity carcinoma (stage T1 and T2) present tumours with a size <4 cm in greatest dimension, an absence of deep invasion into the adjacent tissues, and no metastatic lymph node involvement<sup>4</sup>. Involvement of the cervical lymph nodes in HNSCC has historically been a major prognostic factor, and the presence of metastatic cervical lymph

nodes decreases the 5-year survival by up to 50%. Therefore, correct staging with the detection of involved lymph nodes is of the utmost importance and is essential for treatment planning and management of the disease<sup>5,6</sup>.

Clinical examination and the use of modern imaging techniques (including ultrasound, fine needle biopsy, magnetic resonance imaging (MRI), computed to-

mography (CT), and positron emission tomography (PET)–CT are currently inadequate for the detection of occult neck metastases<sup>7</sup>. Up to 20–30% of clinically N0 patients are found to be suffering metastatic involvement of the cervical lymph nodes on examination of elective neck dissection (END) specimens<sup>8–10</sup>. Therefore many centres strive for END in T1–2 cN0 patients, although studies have shown that this includes overtreatment of up to 80% of pathologically N0 patients<sup>11,12</sup>.

In order to avoid overtreatment and to reduce the postoperative morbidity associated with END, the concept of sentinel lymph node biopsy (SLNB) with the detection of the first draining lymph nodes was introduced for patients with oral squamous cell carcinoma (OSCC)<sup>13</sup>. Although SLNB is well established and used widely in the treatment of breast carcinomas and melanomas of the skin, it remains the subject of debate whether this procedure should be used routinely in clinically and radiologically N0 necks in patients with OSCC<sup>14,15</sup>. Many studies have shown that SLNB is a safe alternative to END for the identification of occult neck metastasis in patients with early oral cavity cancer, with excellent detection rates, a sensitivity around 93%, and a negative predictive value (NPV) ranging from 88% to 100%<sup>10,16,17</sup>.

The current National Comprehensive Cancer Network guidelines for the treatment of head and neck cancers recommend SLNB as an alternative to END in T1–T2 patients for the identification of occult neck metastasis, with the advantages of reduced morbidity and improved cosmetic results, for centres with expertise in this field<sup>4,18</sup>.

At the University Clinic of Zurich, SLNB has been used for the staging of early oral cavity cancer since 2003. This study was performed to report 14 years of experience of SLNB for the diagnosis and treatment of stage I or II tongue cancer, in patients with a clinically and radiologically node-negative neck, seen at this university clinic. Special focus was placed on patients with histologically diagnosed isolated tumour cells (ITCs) in the sentinel lymph nodes (SLN), as therapeutic guidelines are missing for these<sup>9,19</sup>. Hence, as well as reporting the long-term experience with SLNB, the study also aimed to extend knowledge regarding the prognosis and risk assessment of patients identified with ITCs on immunohistochemistry.

### Patients and methods

Ethical approval was obtained from the local ethics committee. Data were collect-

ed prospectively, and a retrospective analysis was performed of 41 patients diagnosed with cT1/T2cN0 OSCC of the tongue between 2003 and 2012 at the University Hospital of Zurich.

Patients were enrolled in the study following assessment against predefined eligibility criteria. Inclusion criteria were (1) patients operated on at the University Hospital of Zurich, (2) a follow-up period, if the patient had not died, of at least 5 years, (3) OSCC of the tongue staged cT1 or cT2, (4) no sign of neck metastasis prior to surgery (cN0), (5) signed informed consent, and (6) no simultaneous second primary at the stage of diagnosis. Exclusion criteria were (1) prior treatment including surgery, radiotherapy, and/or chemotherapy, (2) death before treatment, and (3) no informed consent for the use of data.

Clinical staging of the neck was based on palpation, neck ultrasound and/or contrast-enhanced high-resolution helical CT and/or contrast-enhanced MRI. All patients were discussed by an interdisciplinary tumour board involving specialists in otorhinolaryngology, maxillofacial surgery, oncology, radiology, and radio-oncology. The treatment plan was discussed and based on the latest recommendations of the National Comprehensive Cancer Network.

### Treatment protocol

All patients were treated following the SLNB protocol. Dynamic lymphoscintigraphy followed by single photon emission computed tomography (SPECT/CT) was performed prior to the operation. Intraoperatively, a gamma probe was used for lymph node detection and mapping. In selected patients, the additional application of indocyanine green (ICG) preoperatively served to facilitate the intraoperative detec-

tion of SLNs (Fig. 1)<sup>20</sup>. The lymph node extirpation was always performed after resection of the primary tumour in order to reduce radioactive scatter.

Excised SLNs were subject to extensive histopathological evaluation according to a standardized protocol using cytokeratin for immunohistochemistry<sup>21</sup>. In the first step, the excised lymph nodes were cut manually into slices of 2 mm. Following this, a microtome was used to generate 150- $\mu$ m-thick slices, which were then stained with haematoxylin and eosin (HE) and cytokeratin for immunohistochemistry. Lymph nodes were declared tumour-free if no occult metastasis was found using a standardized ocular device and no cytokeratin positivity was detected<sup>21</sup>.

Patients diagnosed with one or more occult metastases ( $\geq$ pN1) following histopathological examination underwent a unilateral selective neck dissection of levels I–III, or I–IV if the SLN was positive at level III. Metastases revealing positive SLNs were classified into micrometastases (0.2–2 mm) and macrometastases ( $>$ 2 mm). SLNs containing isolated tumour cells ( $<$ 0.2 mm; i+) were staged as SLN-negative<sup>19,22</sup>. In SLN-negative patients, SLNB was not followed by selective neck dissection. Further treatment of SLN-negative patients with isolated tumour cells, i.e. pN0 (i+), was discussed and determined on an individual basis.

Following surgery, all patients were enrolled in a strict follow-up regimen consisting of clinical and ultrasonography examinations, as well as MRI and CT scans. Standardized reassessment of the patients was performed every 2 months for the first 6 months, then every 3 months until 2 years, and then twice a year until at least 5 years after the operation. If disease recurrence was detected, patients were

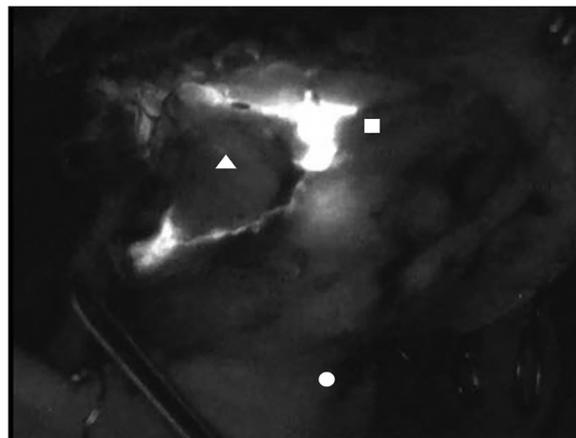


Fig. 1. Visualization of lymphatic vessels using indocyanine green<sup>20</sup>. Submandibular gland; ■ digastric muscle; ● cricoid cartilage.

treated individually according to the disease stage. Any newly detected ipsilateral lymph node metastasis during follow-up indicated false-negative results of SLNB. Hence, the NPV and false-negative rate of SLNB were calculated. Furthermore, disease-free survival (DFS), overall survival (OS), and disease-specific survival (DSS) rates were evaluated for the 41 patients enrolled in the study.

### Statistical analysis

GraphPad Prism 6.0 software (GraphPad Software Inc., La Jolla, CA, USA) was used for the statistical analysis. The patient profiles were compared by  $\chi^2$  test, Fisher's exact test, or Mann-Whitney *U*-test. The NPV of SLNB was calculated by dividing the number of true-negative cases by the number of true- and false-negative cases. A *P*-value of <0.05 was considered statistically significant. DFS, OS, and DSS were analyzed by Kaplan-Meier statistics. The log rank test was used to compare survival rates between subgroups (SLN-positive, SLN-negative). Univariate analysis was used to determine the influence of patient and tumour-specific characteristics on OS, DSS, and DFS rates.

### Results

A total of 41 patients were included in the study, of which 13 (32%) were female and 28 (68%) were male; their median age was 57 years (range 29–83 years). Twelve (29%) patients were staged as cT2 and 29 (71%) as cT1 according to the Union for International Cancer Control criteria. The primary was located on the right border of the tongue in 49% of cases ( $n = 20$ ), on the left border in 49% ( $n = 20$ ), and in the centre of the tongue in 2% ( $n = 1$ ).

Fifty-eight percent ( $n = 7$ ) of cT2 tumours were staged pT2, 42% ( $n = 5$ ) of cT2 cases were down-staged to pT1, and 10% ( $n = 3$ ) of cT1 patients were up-staged to pT2 after histopathological examination of the resected tumour. Thus the positive predictive value for clinical staging was 80%. Patient demographic data and tumour-related data are presented in Table 1.

For all patients (100%,  $n = 41$ ), the SLNs could be detected preoperatively by lymphoscintigraphy and SPECT/CT, and the intraoperative detection rate of these hot spots was also 100% using the gamma probe. In total, 157 SLNs were resected from the 41 patients. The locations of the excised SLNs are shown in Table 2.

Table 1. Demographic and tumour-related patient data.

Characteristic	Overall		SLN-negative patients		SLN-positive patients	
	n	(%)	n	(%)	n	(%)
Patients, <i>n</i> (%)	41	(100%)	34	(83%)	7	(17%)
Sex, <i>n</i> (%)						
Male	28	(68%)	23	(68%)	5	(71%)
Female	13	(32%)	11	(32%)	2	(29%)
Age (years), median (range)	57	(29–83)	59	(29–83)	56	(34–67)
Smokers, <i>n</i> (%)	26	(63%)	20	(59%)	6	(86%)
Alcohol drinking habit, <i>n</i> (%)	12	(29%)	9	(26%)	3	(43%)
T classification, <i>n</i> (%)						
cT1	29	(71%)	25	(74%)	4	(57%)
cT2	12	(29%)	9	(26%)	3	(43%)
pT1	31	(76%)	24	(71%)	7	(100%)
pT2	10	(24%)	10	(29%)	0	(0%)
G classification, <i>n</i> (%)						
G1	7	(17%)	7	(20%)	0	(0%)
G2	26	(63%)	21	(62%)	5	(71%)
G3	8	(20%)	6	(18%)	2	(29%)

SLN, sentinel lymph node.

Seven lymph nodes with ITCs (i+) were identified in six patients, reflecting 4% of the overall excised SLNs (7/157). Thus, six patients were staged pN0 (i+), as tumour cells were only verifiable on immunohistochemistry. In accordance with the literature, these SLNs were not defined as occult metastases<sup>19,22</sup>. However, following the recommendations of the interdisciplinary tumour board, two patients staged pN0 (i+) underwent selective neck dissection. No selective neck dissection was performed in the other four patients. The decision regarding selective neck dissection was based on histological features, including perineural or vascular invasion and multiple tumour cell clusters. Following selective neck dissection, no further lymph node revealed tumour cells in these patients.

Seven patients, i.e. 17% of the study population, were diagnosed with occult metastases of the neck, revealing one or more positive SLNs ( $\geq$ pN1) after SLNB. Overall, eight of 157 resected SLNs were histopathologically staged as positive (5%) (Table 3). Thus, two positive SLNs were detected in one patient. Consequently, these seven SLN-positive patients underwent unilateral selective neck dissections. Following selective neck dissection, a mean of 26 (standard deviation 9) lymph nodes were excised. However, no further positive lymph node (0/184) was detected following selective neck dissection in any case.

On average, the eight harvested tumour cell-positive SLNs had a diameter of 14 mm (standard deviation 6 mm). Histopathological evaluation confirmed micrometastases in four and macrometastases in four. Additionally, extracapsular spread was identified in one case and perineural invasion in another. The patient with extracapsular spread underwent radiother-

apy following surgery. However, the same patient suffered from a second primary located in the hypopharynx 16 months following tumour resection and died 6 months after detection of this second primary. The patient diagnosed with perineural invasion of tumour cells underwent chemoradiotherapy. At clinical follow-up at 66 months, the patient was healthy and without any signs of tumour recurrence. All other SLNB-positive and negative patients ( $n = 39$ ) received no radio- and/or chemotherapy.

During a mean observation time of 92 months (standard deviation 28; range 60–144 months), 11 patients died; eight of these patients did not reach the 5-year follow-up. Seven patients died of causes unrelated to any oncological disease, two died due to a second primary (pancreas and hypopharynx), and in two patients the tongue cancer and its associated consequences were identified as the cause of death. Thus, at 5 years the OS was 80% (33/41) and the DSS was 95% (39/41). Tumour recurrence or progression was observed in two patients (2/41, 5%), revealing a 5-year DFS of 95% (39/41).

One of the patients suffering from a relapse had a negative SLN (1/34, 3%) and one patient had a positive SLN (1/7, 14%) at tumour resection surgery. In the SLN-negative patient, a metastasis of the

Table 2. Distribution of excised sentinel lymph nodes.

Location of SLN	SLN, <i>n</i> (%)
Level I	17 (11%)
Level II	90 (57%)
Level III	44 (28%)
Level IV	6 (4%)
Total	157 (100%)

SLN, sentinel lymph node.

Table 3. Related findings in SLN-positive patients.

Patient	Age (years)	SLN biopsy <sup>a</sup>	Selective neck dissection <sup>b</sup>	Level of positive SLN	Size of SLN (mm)
1	34	1/4	0/42	III	21
2	64	1/2	0/24	II	10
3	35	1/4	0/24	II	23
4	40	1/3	0/34	II	17
5	55	2/6	0/18	II and II	5 and 9
6	62	1/5	0/18	II	12
7	66	1/4	0/24	II	15
Total	Mean ± SD 51 ± 14	8/28	0/184	II: 7 III: 1	Mean ± SD 14 ± 6

SD, standard deviation; SLN, sentinel lymph node.

<sup>a</sup>Sentinel lymph node biopsy: positive sentinel lymph nodes/resected sentinel lymph nodes.

<sup>b</sup>Selective neck dissection: positive lymph nodes/resected lymph nodes.

neck was identified at level IIb ipsilateral to the primary tumour location at 24 months after surgery. This patient was staged pN0 (i+) after SLNB. A selective neck dissection was performed following the detection of the metastasis. However, the patient died due to tumour progression 17 months later. In the SLN-positive patient, a metastasis in the upper lobe of the lung was detected 5 months following the operation. The patient died 12 months later. Thus, the neck recurrence rate for SLN-negative patients was 3% (1/34). Dividing these patients into pN0 (i-) and pN0 (i+) depending on the identification of ITCs, 0% (0/27) of pN0 (i-) patients and 14% (1/7) of pN0 (i+) patients developed a neck metastasis ( $P = 0.200$ ). SLN-positive patients showed a neck recurrence rate of 0% (0/7). Therefore, SLNB was true-negative in 33 cases and false-negative in one case, resulting in a negative predictive value of 97%.

5-year OS, DSS, and DFS rates for SLN-positive patients ( $n = 7$ ) were 71%, 86%, and 86%, respectively, and for SLN-negative patients ( $n = 34$ ) were 82%, 96%, and 97%, respectively (Fig. 2). There was no statistically significant difference between the two groups regarding neck recurrence ( $P = 0.509$ ), OS ( $P = 0.482$ ), DSS ( $P = 0.208$ ), or DFS ( $P = 0.182$ ).

On univariate regression analysis, patient-specific characteristics including age, sex, smoking habit, alcohol drinking habit, tumour stage, and tumour grade did not show an influence on OS, DSS, or DFS rates.

## Discussion

The results of this study reveal SLNB to be an appropriate procedure for staging and treating early stage OSCC including an unsuspecting neck (N0). The benefits of SLNB compared to END in stage I and II OSCC have already been demonstrated in

prior studies, contradicting former recommendations<sup>8,9</sup>. SLNB is reported to spare about 60–80% of patients from unnecessary neck dissection<sup>9</sup>.

Although preoperative tumour staging was based on a thorough clinical examination combined with adequate imaging, occult lymph node metastases were detected in seven patients, accounting for about 17% of the study population. This finding is comparable to previously reported rates of up to 30% for maxillary OSCCs<sup>9</sup>. The extensive histopathological examination following the SLNB protocol is one of the great benefits of the SLNB method<sup>8,9</sup>. SLNB is reported to be suitable for the detection of minimal disease as well as the path of lymphatic tumour drainage<sup>9</sup>. In the present study, preoperative tumour staging was based on non-invasive radiographic imaging, including ultrasonography and/or MRI and/or CT. However, a meta-analysis found ultrasonography-guided fine needle aspiration cytology to be the most accurate imaging modality for the detection of cervical lymph node metastases when compared to ultrasonography alone, MRI, and CT<sup>23</sup>.

Recently SLNB was evaluated in a prospective multicentre phase II trial. This previous study highlighted the advantages of SLNB compared to END, especially for diagnostic concerns, and even in T3

OSCC<sup>24</sup>. The potential of SLNB to detect metastasis missed on clinical, radiological, and routine histological examinations is of great interest, as postoperative adjuvant therapy regimes differ according to neck stage<sup>18</sup>. The evaluation of SLNs in the present study followed an established protocol including serial sectioning and anti-cytokeratin 22 immunohistochemistry<sup>25</sup>. Consequently, it took considerable time to obtain definitive histological results.

A notable downside of SLNB is the fact that it is not possible to determine whether or not to perform a selective neck dissection intraoperatively. Although intraoperative frozen sectioning is considered to provide a solution in this regard to some extent, the extensive workup described is more sensitive for the detection of occult metastases<sup>21,24</sup>.

All patients presented with detectable SLNs. Approximately four SLNs were detected in and excised from each patient using the intraoperative gamma probe. According to the literature, the detection of SLNs is more consistent in tongue cancer than in other carcinomas such as floor of the mouth cancer<sup>26,27</sup>. Since only tongue carcinomas were investigated in this study, this issue could not be addressed. However, as the rate of detection of SLNs in this cohort of 41 patients

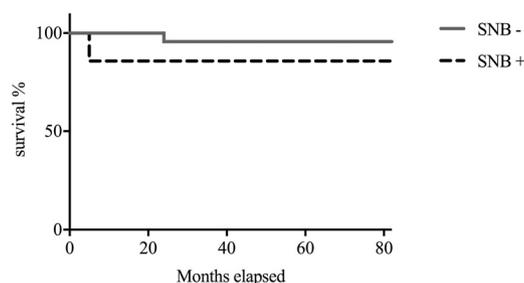


Fig. 2. Kaplan–Meier curve illustrating disease-free survival (DFS) over a mean follow-up period of 92 months. Sentinel lymph node-negative (SLN-) and sentinel lymph node-positive (SLN+) patients revealed a DFS of 97% and 86%, respectively ( $P = 0.182$ ).

was 100%, no problem was experienced. In certain situations, high tracer uptake around the floor of the mouth might prevent the detection of SLNs at level I due to the proximity of the tumour and lymph nodes<sup>28</sup>. This appearance has been described previously as the 'shine through' phenomenon, but is not evident in early tongue cancer<sup>9,17</sup>.

Recently, Miura et al. investigated the rate of false-negative results of SLNB in OSCC, performing SLNB and consecutive END<sup>24</sup>. In two of 57 patients, including patients with advanced tumour stages, additional occult metastases were found after END, revealing a NPV of 91% for the SLNB method<sup>24</sup>. Throughout follow-up in the present study, only one patient showed a lymph node recurrence. Since only ITCs were identified in the harvested SLNs, this patient was staged as SLN-negative. However, due to unpromising histological features, including multiple tumour cell clusters and evident perineural as well as lymph node invasion, the decision was made to perform a neck dissection. Thus, from a therapeutic point of view, this patient was not considered as having a false-negative result on SLNB, whereas from a diagnostic point of view the patient was.

The topic of ITCs is rarely dealt with in the current literature. In the present study, seven SLNs were staged as SLN-negative although ITCs were detected, in accordance with the classification of prior studies<sup>19,22</sup>. This is also congruent with recommendations regarding the therapeutic approach to ITCs and micrometastases<sup>29</sup>. However there are reports of SLNs with evident ITCs being classified as SLN-positive and treated in the same way as micrometastases<sup>9</sup>. Thus it appears that no clear guidelines regarding the management of ITCs have yet been established. Hence, the treatment strategies for the patients identified with ITCs in the present study were determined individually by an interdisciplinary tumour board. The authors consider that the presence of even small tumour cell deposits, only detectable through the extensive workup of the SLNB protocol, has an important impact on tumour control<sup>19</sup>. Further clinical studies investigating pN0 (i+) staged patients are greatly required to highlight this consideration and establish clinical practice guidelines for these cases.

Goto et al. discovered late cervical metastases in 17% of patients with stage I or II tongue cancer treated by local tumour excision alone, not performing SLNB or END<sup>30</sup>. In contrast to this, only one patient

in the present study cohort developed late cervical metastasis, demonstrating the oncological benefit of the SLNB approach.

As shown in previous investigations, this study showed a better outcome for SLN-negative patients as compared to SLN-positive patients<sup>9,10,19</sup>. DSS is reported to be significantly shortened if lymph node metastasis is detected on SLNB<sup>19</sup>. However, although a trend was found in this regard, no significant difference in DSS was observed within the patient cohort in this study. As well as the clinical benefits of SLNB, this is considered to be the most favourable diagnostic strategy over a 5- or 10-year time horizon regarding the cost-utility<sup>31</sup>. Compared to ultrasound-guided fine needle aspiration cytology and END, SLNB results in the highest number of additional quality-adjusted life years for the smallest additional costs<sup>31</sup>.

In conclusion, we consider SLNB as a reliable staging and appropriate treatment option for patients with early stage OSCC of the tongue and initial clinical N0 staging. Furthermore, we support the findings of previous studies indicating SLNB to be a reliable procedure to determine the appropriate levels for neck dissection<sup>9,24</sup>. Although ITCs appeared to represent a potential risk factor for the development of late cervical metastasis in this study, more evidence is needed for a better understanding of the clinical relevance of ITCs and its potential influence on treatment strategies.

### Funding

The study was not funded.

### Competing interests

The authors have declared that no competing interests exist.

### Ethical approval

Ethical approval was obtained from the local ethics committee of Zurich (KEK-ZH-Nr. 2013-0298).

### Patient consent

Signed consent was obtained from all patients included in the study.

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