Sentinel lymph node biopsy in T1/T2 squamous cell carcinomas of the tongue: A prospective study

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Abstract. Commonly used staging procedures often cannot predict the absence of cervical metastases (CM) in squamous cell carcinomas (SCCs) of the oral cavity. Due to the high incidence of occult CM in numerous N0 cases in the clinic, an elective neck dissection (ND) is performed. The sentinel lymph node biopsy (SNB) is a common concept in the modern surgical therapy of malignancies. The present study evaluates the applicability of this concept for T1/T2-SCC of the tongue. In a prospective clinical study, 10 consecutive patients with T1/T2-SCC of the tongue and cN0 necks, were enrolled. Following sentinel lymph node (SLN) scintigraphy, all patients underwent SNB with a γ-probe and a subsequent ND. SNB specimens were compared with histopathological assessments of surgical specimens from the ND. A total of 5 female and 5 male patients (mean age, 52 years; women, 62 years; men, 42 years), with a median follow-up time of 33.5 months (range, 10-40 months), were treated. All patients presented with detectable SLNs. In 7 cases, the SLN(s) and the residual ND were negative for CM. In 3 cases, the SLN(s) were positive without further CM in the other neck nodes. Furthermore, 1 patient showed additional CMs after 10 months in the contralateral neck and lung metastasis after 18 months, but none at the time of the initial treatment. The concept of an SNB appears to be applicable to the management of the cN0 neck in small SCC of the tongue. The role of SNB in the management of SCC requires further investigation by prospective trials with larger patient numbers.

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Introduction

Oral cancer is responsible for 200,000-350,000 cancer-associated fatalities per year worldwide and is thus ranked sixth with regard to the cause of mortality due to tumors (1,2).

Beside the time of diagnosis and the consequent size of the tumor (3), the presence of lymph node metastasis in the neck is the most important prognostic indicator (4,5). Oral SCC is disseminated preferentially by the lymphatic system and mainly the cervical lymph nodes at levels I and II are affected (6-8). The high incidence of occult cervical lymph node metastases of ~25% in N0 cases in the clinic underscores the clinical significance and the resulting therapeutic difficulties (9,10).

The commonly used staging procedures often cannot predict the absence of CM. Clinical and radiological examination have approximate false-negative and false-positive rates of 30% in the determination of CM (11). The most precise method and the gold standard for the correct N-staging is the histopathological examination of the surgical specimen following elective neck dissection (END) (12).

The management of the clinically and radiologically negative neck, particularly in patients with early oral SCC, remains a matter of debate, although the majority of centers favor END for staging of the neck and the removal of occult disease (11).

In the modern surgical treatment of melanoma or breast cancer, the presence of regional lymph node metastases is evaluated by the identification and examination of the sentinel lymph node (SLN). Radiolabeled colloid solution is injected around the primary tumor, which drains to the next lymph nodes and predominantly to the SLN, which may contain metastatic deposits of the primary tumor. The combination of pre-operative lymphoscintigraphy and the intraoperative detection of the SLN with a γ-probe allows the radioactive tracer in the lymph nodes to be precisely located during the surgery (11,13).

In the past decade, the SLN-technique has been increasingly used for other malignancies, including head and neck carcinomas. Technical developments and a gain in experience have led to a wider use of SNB, even in the complex lymphatic system of the head and neck region (14). Multiple small patient series have been published evaluating the application of SLN biopsy for head and neck cancers, with a sensitivity of at least 75% for the identification of CM (Table I) (11,15,16). But the

Table I. Epidemiological and clinical data.

Patient	Gender	Age, years	Risk factors	No. of SLNs detected during surgery	No. of CMs	Follow-up time, months	Relapse
1	Male	21	No	2	0	33	No
2	Male	28	Yes	2	0	39	No
3	Male	32	No	4	1	18	After 10 months
4	Female	33	Yes	2	0	22	No
5	Female	59	Yes	2	1	28	No
6	Male	62	Yes	3	2	40	No
7	Female	63	No	2	0	38	No
8	Male	69	Yes	2	0	40	No
9	Female	75	Yes	3	0	10	No
10	Female	82	Yes	2	0	34	No

SLN, sentinel lymph node; CM, cervical metastases.

Table II. pTNM classification following surgical therapy.

pTNM stage	Patients, n (%)
T-Stage	
pT1	8 (80)
pT2	2 (20)
N-stage	
pN0	7 (70)
pN1	2 (20)
pN2	1 (10)
M-stage	
cM0	10 (100)
Grade	
G1	4 (40)
G2	5 (50)
G3	1 (10)

pTNM, pathological tumor-node-metastasis.

majority of these studies included higher stage SCC and did not focus on a specific region and a clinical N0 neck.

The aim of the present study was to analyze and evaluate the applicability of the SLN concept for T1/T2 SCC of the tongue with a clinical N0 situation.

Patients and methods

Patients. Between 2010 and 2012, 10 patients with SCC of the tongue were selected from the Department of Oral and Maxillofacial of the University Medical Center (Johannes Gutenberg-University of Mainz, Mainz, Germany) to take part in the study. The criteria for inclusion were: SCC of the tongue, a tumor size <T3 and a clinical N0 situation. All tumors were classified and staged according to the 2003 tumor-node-metastasis (TNM) staging system of the Union for International Cancer Control, and special attention was paid to the CM (17).

The study protocol was approved by the internal institutional review board and informed consent was obtained from all the patients involved in the study. Computed tomography and ultrasonography of the head and neck region were performed on all patients prior to the treatment.

Treatment. All patients received peritumorous injections of technetium-99m-labeled colloidal human serum albumin (0.2 ml; 50 MBq) in an attempt to completely surround the tumor in its deep and lateral aspects. Injection was performed 1 day prior to surgery. The pre-operative lymphoscintigraphy was performed 30 min after the injection. Static images were accomplished in lateral and antero-posterior projections, and the radioactive lymph nodes were marked on the skin and controlled by B-mode sonography.

Beside the resection of the tongue tumor, all patients received an END at levels I-III. Using a hand-held γ-probe (Gamma Finder® II, World Of Medicine USA, Inc., Orlando, Florida, USA), the SLN was identified *in vivo* and dissected separately. Next, the remaining neck was re-evaluated for the absence of radioactivity. All lymph nodes with radioactivity were dissected and considered as SLNs. Afterwards, the proposed END was performed. The SLNs and all neck specimens from the subsequent END were sent for histopathological examination.

Results

The cohort consisted of 5 (50%) female and 5 (50%) male patients, with an average age of 52 years and a range of 21-82 years (female: Mean, 62 years; range, 33-82 years; male: Mean, 42 years; range, 21-69 years). The majority of the patients (70%) showed a risk profile regarding smoking and alcohol consumption (Table I).

SCC was evenly spread in the tongue without a preference for a side, however, 70% was located in the front and middle section of the tongue (Fig. 1).

The pathological TNM stage of the patients is shown in Table II; 80% of the patients presented with a T1 tumor and 20% with a T2 tumor. No distant metastases were detected

Table III. Published sensitivity rates for SLN biopsy.

First author (ref.)	Year	No. of patients with oral SCC /no. of patients	Cancer	T-Stage	No. of detected CM by SLN/no. of all CM	Sensitivity, %
Hyde *et al* (38)	2003	19/19	Oral cancer	1-4	3/4	75
Gallegos *et al* (33)	2005	48/48	Oral cancer	1-2	13/17	77
Frerich *et al* (39)	2007	28/40	Oropharyngeal cancer	1-2	8/10	80
Chone *et al* (11)	2008	24/35	Oropharyngeal cancer	1-3	9/11	82
Werner *et al* (30)	2004	11/90	Oropharyngeal cancer	1-3	20/23	87
Civantos *et al* (23)	2010	140/140	Oral cancer	1-2	34/40	90
Tschopp *et al* (40)	2005	25/31	Oropharyngeal cancer	1-3	14/15	93
Shoaib *et al* (41)	2001	37/37	Oral cancer	1-4	16/17	94
Ionna *et al* (42)	2002	40/40	Oral cancer	1-2	4/4	100
Höft *et al* (43)	2004	22/50	Oropharyngeal cancer	1-4	12/12	100
Bilde *et al* (44)	2008	51/51	Oral cancer	1-2	11/11	100
Current study	2015	10/10	Oral cancer	1-2	4/5	80

SLN, sentinel lymph node; CM, cervical metastases; T, tumor.

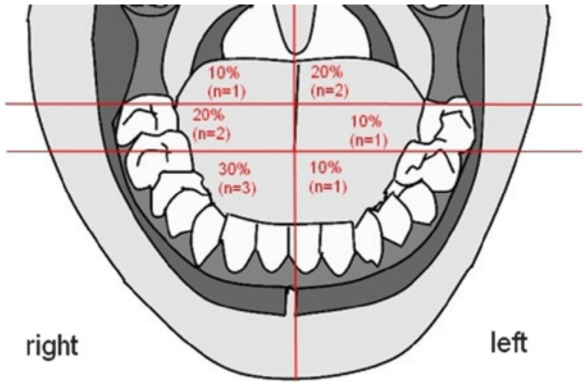

Figure 1. Classification and distribution of the primary tumor location.

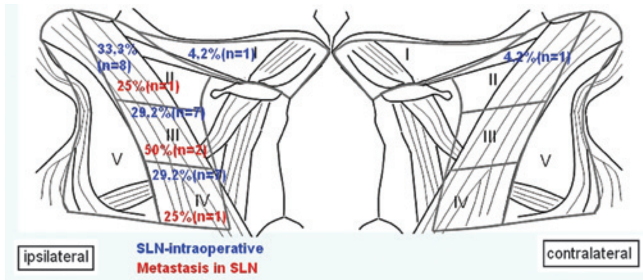

Figure 2. Distribution of the sentinel lymph nodes (SLNs) detected during the surgery (blue) and distribution of the cervical metastases following pathological examination according to the neck level (red).

following primary staging. The majority of the patients (90%) presented with a tumor of grade G1-G2.

In all patients, SLN could be detected intraoperatively. On average, 2.4 SLNs per patient were found. Fig. 2 shows the distribution of SLNs and CMs at the neck level. A total of 2 SLNs were found in 7 patients, 3 SLNs in 2 patients and 1 SLN in 1 patient were detected. In 7 cases, the SLNs and the residual neck dissection were negative for cervical lymph node metastasis.

In total, 30% (n=3) of the patients exhibited lymph node metastases, which were detected by the SLN biopsy, without further CM in the other neck nodes. One patient exhibited skip metastasis; the patient presented with a CM in a SLN at level IV, which had bypassed the common upper neck level I-III.

Additional CMs were developed in 1 patient after 10 months in the contralateral neck, with lung metastasis after 18 months.

The median follow-up time for the patients was 32 months (range, 8-39 months). During the follow-up, none of the other 9 patients experienced local or cervical recurrence.

If the case with the contralateral CM recurrence after 10 months is defined as a false-negative result, then the sensitivity and specificity of the SLN biopsy in the patient group were 75% (3/4 patients with CM were detected) and 100% (6/6 patient without CN were detected), respectively, and the false negative rate was 25%.

Discussion

The demographic data of the present SCC patients, with a mean age of 52 years and the high presence of risk factors, are comparable with the international literature (15-20). SCC was

evenly spread in the tongue and was identical to the distribution pattern in the literature (21).

The management of patients with early oral SCC with a clinically negative neck remains controversial. The majority of clinics prefer the END instead of a wait-and-see strategy due to the high rate of occult metastases. However, 70-80% of this patient group are ultimately pN0 and are theoretically overtreated with a selective neck dissection (SND) (22,23). Although an SND is less invasive than a modified radical dissection, measurable morbidity does exist, including shoulder dysfunction, contour changes, pain and lower lip paresis (24-27). Although the SND has proven reliability and worldwide acceptance, it is an extended surgery compared with the SLN biopsy, meaning a longer surgical time, higher costs and greater morbidity. Functional outcome and post-operative complications following an SLN biopsy are also significantly better than after an SND (28,29).

The concept of an SLN biopsy provides the possibility of accurate pathological cervical node staging, whilst minimizing the invasiveness of the procedure and its associated morbidity. In addition, pre-operative lymphoscintigraphy and intraoperative detection with a hand-held γ-probe have the additional advantage of identifying aberrant drainage pathways (22,23). In the present study, a contralateral SLN could be detected in 1 patient and a CM was found at level IV, which had bypassed the common upper neck level I-III (skip metastasis).

The SLN biopsy has the benefit of concentrating only on the relevant nodes for pathological examination. This selection allows a more in-depth evaluation of the small number of sentinel nodes, using step serial sections and immunohistochemistry (22,30,31). However, if there are multiple SLNS at different levels, the number of SLNs that should be removed for the examination remains unknown. The majority of studies recommend the removal of at least 2-3 SLNs to reduce the possibility of false-negative results (32-34). In the present study, an average of 2.4 SLNs were detected per patient.

There are a number of studies focusing on the use of SLN in SCC (Table III) (11,15,16,26,33,36,38-44). But only few studies do have a homogenous clientele with only small tumors and a clinical N0 neck in which the SLN is of importance. In addition the majority of these studies did not focus on a specific region (oral cavity vs. oropharynx). The sensitivity of the SLN biopsy for head and neck cancer varies in the literature between 75 and 100%.

The sensitivity of the SLN biopsy for head and neck cancer varies in the literature between 75 and 100%. This has to be compared with the rate of regional recurrence after SND, which is recorded as between 6-30% in the literature (35-37). In the present patient group, the sensitivity of the SLN biopsy was 75% when defining the contralateral CM recurrence after 10 months in 1 patient as a false-negative result.

Although further studies are necessary to confirm the results, patients with cN0 and early-stage oral SCC may benefit from an SLN biopsy by avoiding the morbidity of a neck dissection.

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