The assessment of oral squamous cell carcinoma

Boeve, Koos

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CHAPTER 4

High rate of unexpected lymphatic drainage patterns and a high accuracy of the sentinel lymph node biopsy in oral cancer after previous neck treatment

Koos Boeve[1,2], Inne J. den Toom[3,4]*, Stijn van Weert[4], Elisabeth Bloemena[5,6], Adrienne H. Brouwers[7], Otto S. Hoekstra[8], Bart de Keizer[9], Bert van der Vegt[2], Stefan M. Willems[10], C. René Leemans[4], Max J.H. Witjes[1], Remco de Bree[3]*

* Both authors contributed equally to this study.

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Departments of Oral and Maxillofacial Surgery[1], Pathology & Medical Biology[2], Nuclear Medicine and Molecular Imaging[7], University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. Departments of Head and Neck Surgical Oncology[3], Nuclear Medicine[9], Pathology[10], University Medical Center Utrecht, Utrecht, The Netherlands. Departments of Otolaryngology-Head and Neck Surgery[4], Pathology[6], Radiology and Nuclear Medicine[8], Amsterdam UMC, Amsterdam, The Netherlands. Department of Oral and Maxillofacial Surgery / Oral Pathology[5], Amsterdam UMC/Academic Center for Dentistry (ACTA) Amsterdam, The Netherlands

ABSTRACT

Rationale: This study evaluates the lymphatic drainage patterns and determines the accuracy of the sentinel lymph node biopsy (SLNB) in patients diagnosed with a cT1-2N0 OSCC and a history of neck surgery or radiotherapy in three Dutch head and neck centers.

Materials and Methods: Retrospective analysis of 53 cT1-2N0 OSCC patients, who underwent SLNB between 2007 and 2016, after a history of neck surgery or radiotherapy. Ten patients had previous treatment of the neck only contralateral from the current tumour. These ten patients were not used for the analysis of lymphatic drainage patterns. The 43 patients with previous ipsilateral or bilateral treatment of the neck had a history of ipsilateral SLN extirpation (n = 9; 21%), neck dissection (n = 16; 37%), radiotherapy (n = 10; 23%), or combined neck dissection and radiotherapy (n = 8; 19%).

Results: SLNs were detected in 45 patients, resulting in an identification rate of 85% (45/53). Three patients (7%) had at least one positive SLN. One patient (1/45; 2%) was diagnosed with regional recurrence during the follow-up after a negative SLNB (sensitivity 75%, negative predictive value 98%). The first SLN was detected in level I-III in 58% of the patients, unexpected drainage patterns were observed in 30% (first SLN level IV 9% and level V 5% and contralateral neck in well-lateralized tumours 16%). In 12% no lymphatic drainage pattern was visible.

Conclusions: SLNB seems to be a reliable procedure for neck staging of cT1-2N0 OSCC patients with a previously treated neck. SLNB determines the individual lymphatic drainage patterns, enabling visualization of unexpected drainage pattern variability in 30% of these patients.

INTRODUCTION

Presence of lymphatic metastases in the neck is consistently observed as main prognostic factor in patients with oral squamous cell carcinoma (OSCC) [1-3]. Sentinel lymph node biopsy (SLNB) proved to be reliable as diagnostic staging modality for detection of occult lymph node metastases: in a large recent meta-analysis a pooled sensitivity of 87% (95% CI 85-89%), a negative predictive value of 94% (95% CI 93-95%) and an AUC of 0.98 (95% CI 0.97-0.99%) were found [4]. These meta-analysis results are based on patients with primary OSCC and a previously untreated neck. Despite the relatively common local recurrences and second primary tumours in head and neck cancer, only one study of Flach et al. reported about the accuracy of the SLNB in 22 patients with a previously treated neck [5].

It is well known that patients with OSCC suffer a high risk for local recurrences (10-30%) and an annual risk of 3-4% for developing second primary tumours [3,6-8]. Previous treatment of the neck most likely alters lymphatic drainage patterns. Current evidence about the drainage patterns in previously treated OSCC patients using SLNB is limited to a study by Flach et al. (n = 22) and a feasibility study by Pitman et al. (n = 5) [5,9]. Experience of alteration in lymphatic drainage patterns after previous treatment has also been reported in breast cancer and melanoma [10-15]. While gaining more and more experience with SLNB in our institutions during the last years, SLNB has been used increasingly as staging method in patients with a previously treated neck. Moreover, SLNB is valuable in assessment of the individual lymphatic drainage patterns, compensating for potential variabilities as a result of previous treatment which were reported in 67% of the cases by Flach et al [5].

However, since the study of SLNB in OSCC patients with a previously treated neck consisted of only 22 patients, more research had to be performed to confirm the findings of that study [5]. The aim of this study was to assess the accuracy of SLNB and secondly, to evaluate the lymphatic drainage patterns in a consecutive cohort of cT1-2N0 patients with a previously treated neck in three Dutch head and neck cancer centers.

METHODS

In three Dutch head and neck centers 53 patients diagnosed between 2007 and 2016 met the inclusion criteria and were retrospectively analyzed. Patients with early stage local recurrent disease or second (or even third) primary squamous cell carcinoma of the oral cavity or oropharynx with a clinically negative neck and surgical resection of the tumour combined with SLNB staging of the neck were included (cT1-2N0, following the 7th TNM staging classification, Table 1). In their history, all patients had received prior treatment

Table 1. Patient characteristics

Characteristics	No.	(%)
Total number of patients	53	(100)
Gender		
Male	29	(55)
Female	24	(45)
Age *y mean (SD)*	65	(55-75)
(range)		(44-88)
pT status (7th TNM)		
1	44	(83)
2	9	(17)
Tumour locations		
Tongue	31	(58)
FOM	9	(17)
Buccal mucosa	5	(9)
Inferior alveolar process	4	(8)
Other	4	(8)
Previous treatment or surgery ipsilateral neck		
No	10	(19)
RT alone	8	(15)
ND alone	16	(30)
ND + RT	8	(15)
CRT	2	(4)
SLNB	9	(17)
Previous treatment or surgery contralateral neck		
No	25	(47)
RT alone	9	(17)
ND alone	6	(11)
ND + RT	6	(11)
CRT	2	(4)
SLNB	5	(9)
Follow-up		
Follow-up time months, *median (IQR)*	26	(13-42)
Regional recurrence	1	(1)
Death	13	(25)
Death of local recurrence or second primary	4	(8)

Ipsilateral and contralateral side of the neck is related to the side of the local recurrence or the second primary. Abbreviations: FOM, floor of mouth; RT, radiotherapy; ND, neck dissection; CRT, chemoradiation; SLNB, sentinel lymph node biopsy

of the neck with SLNB, neck dissection, (chemo)radiotherapy or a combination of these modalities (Supplementary data 1). Twelve patients were previously included in the study by Flach et al., their follow-up was updated [5].

The SLNB procedure was described extensively before [16,17]. Briefly, patients received preoperatively injections with ^{99m}Tc-nannocolloid followed by dynamic and static lymphoscintigraphy and SPECT-CT scanning one day before surgery, intra-operatively gamma probe detection and postoperative step serial sectioning of the sentinel lymph node with additional immunohistochemical keratin staining.

As visualized in our study design (Figure 1) all 53 patients were used for analysis regarding the accuracy of the procedure and 43 patients were included for the drainage pattern analysis. Earlier studies showed the potential of bilateral drainage patterns in well-lateralized patients. Because of this potential bilateral drainage also 10 patients were included with a history of only contralateral treatment of the neck (their first tumour was contralateral of the second) whom might affect the SLNB accuracy [16,18].

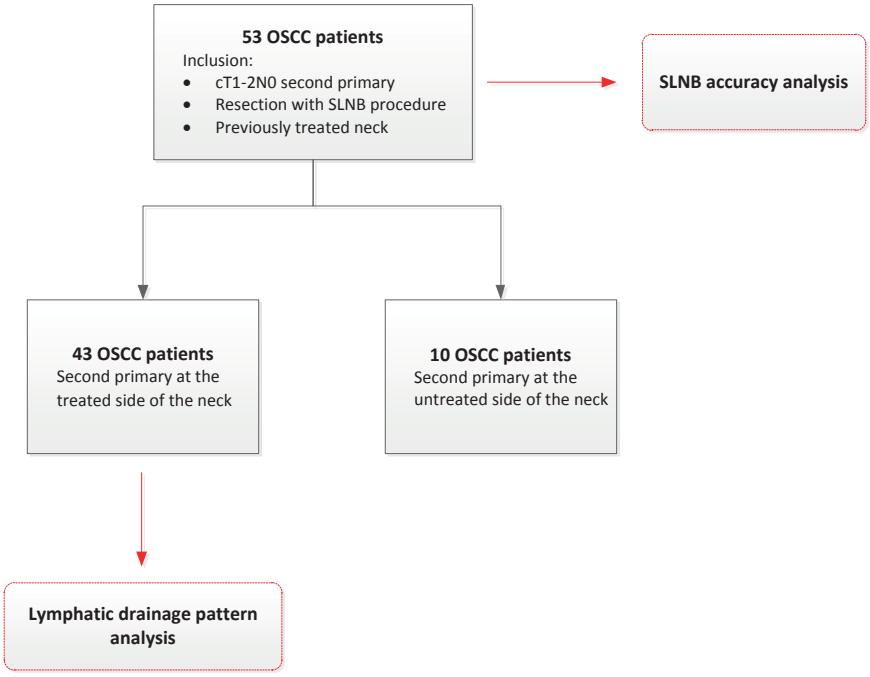


Figure 1: Study design. All 53 patients were used for the SLNB accuracy analysis, only the 43 patients with a history of neck treatment at the ipsi- or bilateral side were used for the analysis of altered lymphatic drainage patterns.

In OSCC lymphatic drainage is at least expected in level I-III at the ipsilateral side of the neck [18]. With the second aim to detect unexpected drainage patterns, only 43 patients with previous treatment of the ipsilateral side of the neck were used for lymphatic drainage pattern analysis.

In this study, definition of lateralization of the neck is related to the site of the local recurrence or second primary tumour.

Ethical consideration

Due to the retrospective design no approval was required from the hospital research ethics board of our centers according to the Dutch ethical regulations. SLNB was part of the standard management of these patients and patient information regarding clinical and pathological characteristics and follow-up was retrospectively collected from electronic patient files.

RESULTS

The data of 53 patients, 29 male (55%) and 24 female (45%) were used for analysis. Mean age was 65 years. Tongue was the most affected tumour location (59%), followed by floor of mouth. Forty-four patients (83%) were diagnosed with a pathologically T1 tumour and 9 patients (17%) with a T2 tumour. These and other characteristics are summarized in Table 1. Characteristics per patient are given in Supplementary data 1.

SLNB accuracy

Fifty-three patients were used for the SLNB accuracy analysis. Neck dissection, with or without postoperative radiotherapy, was seen most as previous treatment in both the ipsilateral and contralateral neck compared to the local recurrence or second primary side (Table 1). Thirteen patients (25%) died during follow-up of which four (8%) died as a result of the local recurrence or second primary tumour in the oral cavity (disease specific death: median 26 months, IQR 13-42 months).

No SLNs were visualized by lymphoscintigraphy in 7 of these 53 patients resulting in an 87% imaging detection rate. In one patient no SLNs were detected intraoperatively, despite preoperative visualization. In two patients with bilateral drainage on lymphoscintigraphy the SLNs were not detected in one neck side intraoperatively, but were harvested in the other side of the neck, resulting in a surgical detection rate of 93% (43/46, Supplementary data 1). In total, at least one SLN was harvested in 85% of the patients (45/53). Three patients had a positive SLN, respectively in the ipsilateral neck with a history of a SLNB, in the

ipsilateral neck without a history of pretreatment and in the ipsilateral neck with a history of chemoradiation therapy. In the first two patients, no additional metastases were detected after harvesting respectively 21 and 17 lymph nodes in the completed neck dissection specimens. Because of the history of chemoradiation and the metastasis size (ITC), the last patient received watchful waiting instead of a neck dissection. These 3 patients did not show regional disease during follow-up.

One patient (2%) was diagnosed with regional recurrence without local disease in level II at the ipsilateral side of the neck after 7 months of follow-up. This patient had a second primary tumour located in the buccal mucosa and only negative SLNs were found in level I at the contralateral side. This patient was previously treated with a MRND at the ipsilateral side of the neck for the first primary tumour, followed by postoperative chemoradiation at both sides of the neck. This patient was still alive after 19 months of follow-up after the regional recurrence was surgically removed and postoperatively irradiated.

One regional recurrence resulted in a 75% sensitivity with a 95% CI of 22-98% (3 of 4 true positive) and 98% NPV with a 95% CI of 88-100% (42 of 43 true negative) of the SLNB in patients with a previously treated neck.

If we restrict the accuracy analysis to patients with a history of neck dissection and/or radiotherapy in the ipsilateral neck, one out of 34 patients showed a positive SLN and one patient showed regional recurrence after a negative SLNB, resulting in a 50% sensitivity (1 of 2 true positive) with a 95% CI of 3-97% and a NPV of 97% (32 of 33 true negative) with a 95% CI of 82-100%.

Lymphatic drainage patterns

In 38 of the 43 patients with a second primary or local recurrence at the previously treated neck side SLNs were detected, resulting in an 88% identification rate. The five patients without detectable SLNs had in common a history of radiotherapy of the neck (Supplementary data 1). Since lymphatic drainage is expected generally in levels I-III for OSCC, in 30% (13/43) patients unexpected drainage was found. Of these 13 patients, four patients showed SLNs located ipsilaterally in level IV as closest located SLN, in two patients this closest location was ipsilaterally in level V. Seven patients had only SLNs located contralateral from the side of the well-lateralized local recurrence or second primary tumour (Supplementary data 1). Besides a lower identification rate, unexpected drainage was more common in patients with a history of neck irradiation compared to patients with a history of a SLNB and comparable to patients with a previous neck dissection, respectively 40% versus 11% and 38%. However the highest unexpected drainage was found after a history of neck dissection combined with postoperative radiotherapy (88%). Localization of harvested SLNs per patient and

per different prior treatment are given in Supplementary data 2. Some SLNs were found in earlier dissected neck levels. For example, eight of the 13 patients with a history of a selective supraomohyoid neck dissection had SLNs located in level I-III, also three of the seven patients with a history of a MRND had SLNs located in level II-IV (Supplementary data 2).

If we restrict the drainage pattern analysis to patients with a history of treatment of the ipsilateral neck, unexpected drainage patterns were found in 12 (35%) of the 34 patients and no drainage to any side of the neck was found in 5 patients (12%).

DISCUSSION

This study demonstrates that SLNB in a previously treated neck can be performed with a high accuracy (sensitivity 75%, NPV 98%). In this study unexpected lymphatic drainage patterns were found in 30% of the patients and no drainage was found in 12% of the patients.

SLNB in early stage OSCC has been frequently described in literature during the last decade with high sensitivity rates and negative predictive values [4]. SLNB was initially implemented in our institutions for patients with primary OSCC without previous treatment of the neck. However, after gaining more experience with SLNB, this staging technique was also extended to patients with a previously treated neck [5]. As a result of the previous treatment, lymphatic drainage patterns could be disrupted resulting in aberrant drainage patterns compared to primary OSCC. Lack of knowledge about these aberrant drainage patterns resulted in missing a standard neck staging and standard elective neck dissection in previously treated patients. Flach et al. showed in a study of 22 patients that the SLNB could be useful in previously treated patients with a high sensitivity and negative predictive value for neck staging and especially for assessment of the individual lymphatic drainage patterns after previous treatment [5].

As mentioned in the introduction, only one feasibility study and the above mentioned study of Flach et al. are published for SLNB in patients with a pretreated neck [5,9]. However, interesting studies in a variety of tumour types have been published regarding SLNB in recurrent or second primary tumours. In a recent meta-analysis of aberrant lymphatic drainage in recurrent breast cancer an 59.6% intraoperatively SLN identification rate was found [10]. The authors concluded that SLNB in these patients avoided unnecessary axillary lymph node dissection and provide targeted localized surgery [10]. Similarly, in recurrent vulvar cancer the SLNB procedure seemed feasible, although the authors stated that the

procedure appears technically more challenging compared to initial surgery. In a cohort of 27 patients, SLNs were found in two groins at unpredicted localizations and four lateral tumours showed bilateral SLNs [19]. Beasley et al. reported about the feasibility of SLNB in recurrent melanoma (107 patients) and also found in 24% of the patients additional sites of SLNs compared to the first SLNB procedure [15].

Although it is difficult to compare different tumour types, a trend towards a lower identification rate of SLNs compared to untreated patients was observed in present and all above mentioned studies. The most common explanation is the damage of lymphatic pathways due to prior treatment and a more difficult technical procedure to harvest SLNs in previously treated nodal basins. In untreated OSCC identification rates of 97-98% have been reported, while in this study a rate of 85% was found [16,17,20,21]. All patients without harvested SLNs had radiotherapy in history, sometimes combined with surgery. This lower identification rate was not observed in patients with a prior SLNB procedure, possibly reflecting that SLNB ensures less damage to lymphatic vessels compared to radiotherapy. Furthermore, despite the lower identification rate in previously treated patients no lower NPV of the SLNB for neck staging was found in this study. This might indicate that lymphatic drainage patterns in these patients are not only aberrant, but may even be absent. Nonetheless, this study included only three patients with positive SLNs and one patient with a regional recurrence after a negative SLNB procedure. Due to the low number of SLN positive patients and regional recurrences, it might be prematurely to conclude that SLNB is a reliable procedure in previously treated patients. This is also reflected in a sensitivity rate with a wide 95% CI. However, the high NPV of 98% with a 95% CI of 88-100% strongly suggest that SLNB is a promising procedure for these pretreated patients, but its reliability needs further investigation.

Although surgery of the lymphatic drainage patterns is part of the SLNB procedure, the procedure is strictly not part of the treatment but belongs to the diagnostic modalities for neck staging. Therefore subanalysis of patients with a history of neck treatment (neck dissection and/or radiotherapy) are presented in the results regarding the accuracy of the SLNB procedure and lymphatic drainage patterns. These figures indicate that in OSCC patients who had undergone more extensive treatment of the neck (i.e. neck dissection and/or radiotherapy) lymphatic drainage follow more frequently an unexpected pattern or was absent (35% vs 30%). Due to the low number of lymph node metastases (2 and 3) the sensitivity of SLNB (50% and 75%) could not sensibly be compared.

Unexpected drainage pathways are generally reported in all tumour types, including our study. These findings strengthen the value of SLNB in assessing the individual lymphatic drainage pattern. In patients who received already prior treatment (e.g. radiotherapy) it

is perhaps even more important to select the actual lymph nodes at risk for metastasis, considering the fact that treatment options are limited due to their prior therapy. In this study an overall unexpected drainage pattern was found in 30% of the patients, which was most frequently found after prior radiotherapy (40%) and especially when this was preceded by a neck dissection (88%). In early stage OSCC patients with an untreated neck unexpected drainage patterns were reported in up to 16% in a large multicenter trial [22].

Even though it is well possible to determine individual drainage patterns with the SLNB, one of the disadvantages is to perform an additional neck dissection during a second surgical procedure in case of a positive SLNB procedure. Although improvements a recent review concluded that still no other modality (e.g., ultrasound, CT, MRI and PET-CT) is accurate enough to detect occult metastasis preoperatively in a clinically negative neck reliably [23]. Moreover, posttreatment effects and the high rate of unexpected drainage in pretreated patients might affect the sensitivity of these modalities in detecting occult metastasis.

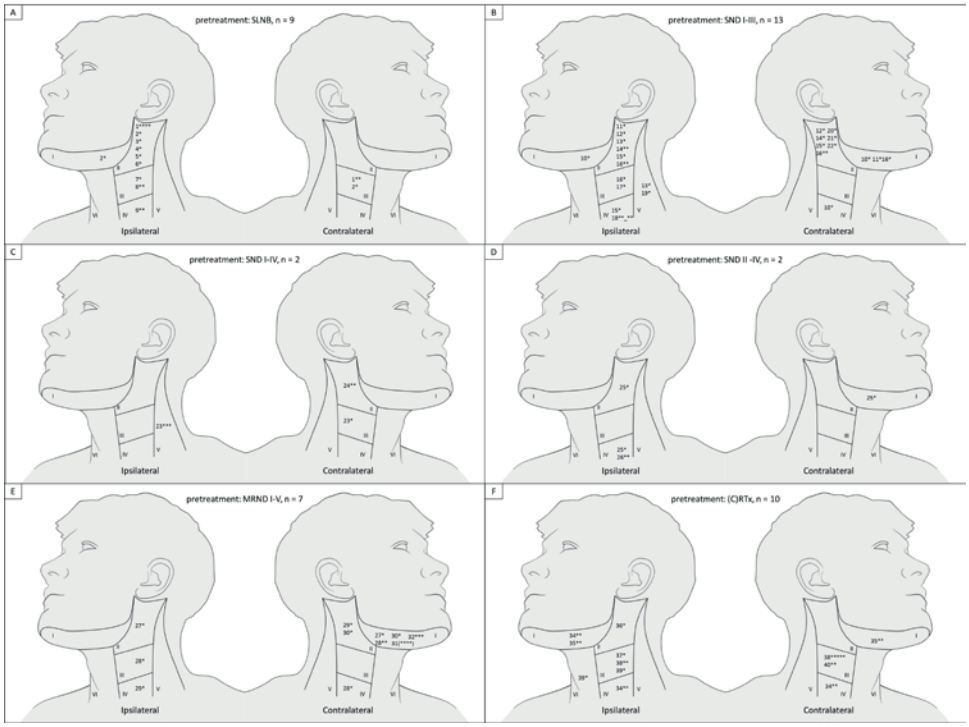
A limitation of the accuracy analysis is the low number of metastasis and regional recurrences in our cohort. A possible explanation for these low numbers compared to untreated patients (with an often reported risk of nodal metastases of approximately 25-30%) could be our close follow-up scheme after treatment of their first tumour. Patients in follow-up are potentially earlier diagnosed with recurrent or second primary OSCC, which might cause a relatively high number of early T1 tumours in this cohort. Despite these limitations, this study showed that metastasis appear in early stage local recurrences and second primary tumours. Currently, no guidelines about neck treatment are available for cT1-2N0 OSCC patients with a previously treated neck. In untreated OSCC prognosis was better after an elective neck dissection (of the standard lymph node levels at risk for metastasis) compared to a 'wait and see' policy [24]. Because of the aberrant drainage patterns, we advocate to use the SLNB also in patients with early stage second primaries or local recurrences to select patients who might benefit from treatment of the neck . However, more extensive research is needed to confirm that this strategy actually improves the prognosis of these patients.

CONCLUSION

SLNB seems to be a reliable procedure for neck staging of cT1-2N0 OSCC patients with a previously treated neck. Moreover, SLNB determines the individual lymphatic drainage patterns, enabling visualization of drainage pattern variability in 30% of these patients.

SUPPLEMENTARY DATA

Supplementary data 1 is available on the following pages.



Supplementary data 2. Locations of the SLNs divided by history of the neck.
_: in total 12 removed LNs in one conglomerate (Figure B, ipsilateral level IV).
(****): four LNs removed without activity on gamma probe (figure E, contralateral level I)
Supplementary data 2 is in a higher resolution available at: https://www.sciencedirect.com/science/article/pii/S1368837519301423?via%3Dihub

Supplementary data 1. Individual patient characteristics with their previous treatment.

Number	Sex	Age	cT (7th)	cN (7th)	pT (7th)	pN (7th)	Tumor location	Tumor side	History ipsilateral
1	Male	67	1	0	1	0	Tongue	Left	SLNB
2	Female	61	1	0	1	0	Floor of mouth	Midline	SLNB
3	Female	71	1	0	1	0	Tongue	Right	SLNB
4	Female	49	1	0	1	0	Tongue	Left	SLNB
5	Female	44	1	0	1	0	Tongue	Right	SLNB
6	Male	55	1	0	1	1	Tongue	Right	SLNB
7	Female	71	1	0	1	0	Floor of mouth	Right	SLNB
8	Female	59	1	0	1	0	Tongue	Left	SLNB
9	Male	73	1	0	1	0	Tongue	Left	SLNB
10	Male	59	1	0	2	0	Tongue	Left	Selective ND I-III
11	Male	50	1	0	1	0	Tongue	Left	Selective ND I-III
12	Female	88	2	0	2	0	Hard palate	Midline	Selective ND I-III
13	Female	49	1	0	1	0	Tongue	Left	Selective ND I-III
14	Female	82	1	0	1	0	Buccal mucosa	Left	Selective ND I-III
15	Male	75	1	0	1	0	Buccal mucosa	Left	Selective ND I-III
16	Female	76	1	0	2	0	Inferior alveolar process	Left	Selective ND I-III
17	Male	74	1	0	1	0	Tongue	Left	Selective ND I-III
18	Male	71	1	0	1	0	Tongue	Right	Selective ND I-III
19	Female	51	1	0	1	0	Buccal mucosa	Right	Selective ND I-III
20	Male	78	1	0	2	0	Tongue	Right	Selective ND I-III
21	Male	72	1	0	2	0	Floor of mouth	Left	Selective ND I-III + RT
22	Female	63	2	0	1	0	Tongue	Right	Selective ND I-III + RT
23	Female	51	2	0	2	0	Tongue	Left	Selective ND I-IV
24	Female	68	1	0	1	0	Tongue	Left	Selective ND I-IV
25	Male	51	1	0	1	0	Tongue	Left	Selective ND II-IV
26	Male	57	1	0	1	0	Floor of mouth	Right	Selective ND II-IV
27	Female	73	2	0	1	0	Inferior alveolar process	Left	MRND
28	Male	60	1	0	1	0	Tongue	Left	MRND + RT
29	Female	59	1	0	1	0	Tongue	Right	MRND + RT
30	Male	68	1	0	1	0	Tongue	Right	MRND + RT
31	Female	67	2	0	2	0	Buccal mucosa	Right	MRND + CRT
32	Male	71	2	0	1	0	Tongue	Right	MRND + RT
33	Male	66	1	0	1	0	Tongue	Left	MRND + RT
34	Male	58	1	0	1	0	Floor of mouth	Left	RT alone
35	Female	69	1	0	1	0	Floor of mouth	Right	RT alone
36	Female	60	1	0	1	0	Tongue	Left	RT alone
37	Male	74	1	0	1	0	Tongue	Right	RT alone
38	Female	62	1	0	1	0	Uvula	Left	RT alone
39	Male	80	1	0	1	1	Tongue	Right	CRT
40	Female	60	1	0	1	0	Tongue	Right	RT alone
41	Male	69	1	0	1	0	Floor of mouth	Paramedian	RT alone
42	Male	58	1	0	1	0	Buccal mucosa	Right	RT alone
43	Male	57	1	0	1	0	Floor of mouth	Right	CRT
44	Male	76	1	0	1	0	Tongue	Right	No treatment
45	Male	61	2	0	1	1	Floor of mouth	Left	No treatment
46	Male	70	2	0	2	0	Retromolar trigone	Left	No treatment
47	Male	81	1	0	1	0	Tongue	Right	No treatment
48	Male	49	1	0	1	0	Tongue	Left	No treatment
49	Female	66	1	0	1	0	Tongue	Left	No treatment
50	Male	57	1	0	1	0	Tongue	Left	No treatment
51	Male	52	1	0	1	0	Pharyngeal arch	Right	No treatment
52	Female	60	1	0	1	0	Inferior alveolar process	Left	No treatment
53	Female	71	1	0	2	0	Inferior alveolar process	Right	No treatment

Abbreviations: 7th, 7th TNM classification; RT, radiotherapy; CRT, chemoradiotherapy; ND, neck dissection; MRND, modified radical neck dissection; SLNB, sentinel lymph node biopsy; FoM, floor of mouth; MFH, Malignant Fibrous Histiocytoma; CIS, Carcinoma in situ.

History contralateral	Lymphatic drainage patterns	SLNB postitive	Head neck oncology history
No treatment	Ipsi and contralateral	No	T1N0 Tongue
No treatment	Ipsi and contralateral	No	T1N0 FoM
SLNB	Ipsilateral	No	TT2N0 Tongue
No treatment	Ipsilateral	No	T1N0 FoM
No treatment	Ipsilateral	No	T1N0 Tongue
MRND	Ipsilateral	Yes, micro	T1N1 FoM
SLNB	Ipsilateral	No	T1N0 FoM
SLNB	Ipsilateral	No	T2N1 Tongue
No treatment	Ipsilateral	No	T1N0 Tongue
No treatment	Ipsi and contralateral	No	(1) T1N0 Buccal mucosa, (2) T1N0 FoM
No treatment	Ipsi and contralateral	No	T1N0 Tongue
No treatment	Ipsi and contralateral	No	T4N0 Superior alveolar process
No treatment	Ipsilateral	No	T1N2b Tongue
No treatment	Ipsi and contralateral	No	(1) T2N0 Inferior alveolar process, (2) T1Nx Buccal mucosa
No treatment	Ipsi and contralateral	No	T2N0 Buccal mucosa
No treatment	Ipsi and contralateral	No	T1N0 Inferior alveolar process
No treatment	Ipsilateral	No	T1N0 Tongue
No treatment	Ipsi and contralateral	No	T1N0 Tongue
Selective ND I-III	Ipsilateral	No	(1) T4aN0 Buccal mocusa, (2) T1N0 Tongue
No treatment	Contralateral	No	T1N0 Tongue
No treatment	Contralateral	No	(1) Retromolar trigone, (2) T2N0 Buccal mucosa
No treatment	Contralateral	No	T2N1 Tongue
No treatment	Ipsi and contralateral	No	T2N1 Tongue
No treatment	Contralateral	No	T1N2b Tongue
Selective II-IV	Ipsi and contralateral	No	(1) MFH grade 2, (2) T2N2b Hypopharynx
MRND	Ipsilateral	No	T2N0 Tonsil
No treatment	Ipsi and contralateral	No	Tongue
No treatment	Ipsi and contralateral	No	T2N0 Tongue
RT alone	Ipsi and contralateral	No	T2N2b Tongue
No treatment	Contralateral	No	T2N2b Hypopharynx
CRT	Contralateral	No	(1) T1N0 Buccal mucosa, (2) T2N0 Inferior alveolar process
Selective ND I-IV + RT	Contralateral	No	Larynx
Selective ND I-IV + RT	No	NA	T4N1 Larynx
RT alone	Ipsi and contralateral	No	T1N1 Supraglottic larynx
RT alone	Ipsi and contralateral	No	T2N0 Supraglotic larynx
RT alone	Ipsilateral	No	T2N0 Glottic larynx
RT alone	Ipsilateral	No	T4N0 Larynx
RT alone	Ipsi and contralateral	No	T3N0 Uvula
No treatment	Ipsilateral	Yes, itc	(1) T4N1 Tongue, (2) T1Nx Tongue
No treatment	Contralateral	No	T1N0 Oropharynx
RT alone	No	NA	T2N1 Tongue
No treatment	No	NA	Myxofibrosarcoma maxillary sinus
CRT	No	NA	(1) T3N0 Supraglottic larynx, (2)T1N0 FoM
MRND	Ipsilateral	No	T1N0 Tongue
RT alone	Ipsi and contralateral	Yes, macro	T4aN1 Larynx
RT alone	Ipsilateral	No	(1) T2N0 Soft palate, (2) CIS FoM
SLNB	Ipsilateral	No	T2N0 Tongue
SLNB	Ipsilateral	No	T1N0 Tongue
MRND + RT	No	NA	T2N2b Tongue
MRND + RT	No	NA	T2N0 Tongue
MRND + RT	Ipsilateral	No	T2N3 Tonsil
MRND	Contralateral	No	T1N1 Inferior alveolar process
Selective ND I-III + RT	No	NA	T2N0 Tongue

Supplementary data 1 is a higher resolution available at: https://www.sciencedirect.com/science/article/pii/S1368837519301423?via%3Dihub

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