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Original Research

Topographical distribution of sentinel nodes and metastases from T1–T2 oral squamous cell carcinomas

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Abstract ***Objective:*** The objective is to investigate the topographical distribution of sentinel nodes (SNs) and lymph node metastases in T1-2cN0 oral squamous cell carcinomas (OSCCs).
Methods: The study entailed a prospective enrolment of 220 patients with clinical T1-2N0 OSCCs who underwent preoperative lymphoscintigraphy (LSG) followed by gamma probe–guided sentinel lymph node biopsy (SLNB). Patients with positive SNs were treated with completion neck dissection. Excised lymph nodes were grouped into the neck level according to the international guidelines.
Results: The SN detection rate by LSG was 99.1%. Patients with midline tumours had bilateral lymphatic drainage on LSG in 15/21 (71.5%). There were 45/199 (22.6%) patients with lateralised tumours that had unexpected bilateral or contralateral drainage patterns on LSG. Fifty-five patients (25.0%) were SLNB positive, and metastases were found in 72/781 (9.2%) of the excised SNs. Metastatic involvement of neck level IV was rare and only observed in patients with anterior tongue cancer. No patients had level V involvement. Eleven patients developed isolated cervical recurrences, with no new primary tumour as origin. The SLNB procedure ensured an overall sensitivity of 83.3% and a negative predictive value of 93.3%.
Conclusion: Completion neck dissection of level I–III in SLNB-positive patients might be sufficient in most patients with OSCC except patients with anterior tongue cancer, but further studies are needed to support this potential therapeutic algorithm. Our study showed that SLNB was helpful in clarifying unexpected bilateral or contralateral metastatic

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drainage patterns. In our cohort, 8/55 patients with occult metastasis would have been missed by elective neck dissection of the ipsilateral neck.

1. Introduction

Oral squamous cell carcinoma (OSCC) is the predominant oral cavity malignancy and accounts for approximately 90% of oral cavity cancer incidents [1]. The presence of cervical lymph node metastases is the most important prognostic factor as it reduces the 5-year survival rate by 50% [2,3]. Owing to an occult metastatic rate of 20–30% in cervical lymph nodes in T1-2 OSCC, it is important to determine the lymph node status accurately. For that reason, watchful waiting is an obsolete approach, and elective neck dissection (END) has been widely accepted as the standard of care [4]. However, END is associated with long-term surgical complications and results in overtreatment of 70–80% of patients with T1-2cN0 OSCC [5,6].

Sentinel lymph node biopsy (SLNB) is used increasingly as an alternative in managing patients with T1-2cN0 staged OSCC and is the standard procedure in many institutions [7–10]. It is associated with less morbidity than END and enables precise cervical node staging [11,12]. Furthermore, SLNB renders an assessment of the individual drainage pattern and has the ability to detect aberrant drainage patterns. The sentinel node is the initial lymph node to receive drainage from a primary tumour [13]. The concept of SN mapping assumes that the drainage of metastatic cells is consistent and restricted to a limited number of cervical lymph nodes, thereby reflecting the pathological status of the lymph node basin.

The aim of the study was to make a topographical description of SNs and metastases related to the location of the primary tumour in patients with T1-T2cN0 OSCC.

2. Methods

2.1. Study population

This prospective, single-centre study enrolled consecutive patients with newly diagnosed T1-2N0 OSCC who underwent lymphoscintigraphy (LSG) and SLNB at Odense University Hospital in Denmark from November 2005 to June 2017. All patients underwent examination with neck palpation, ultrasound, tumour biopsy, *magnetic resonance imaging* and/or computed tomography (CT) for tumour-node-metastasis classification according to the national guidelines [14]. Positron-emission tomography–CT was implemented from 2013. Patients with previous radiotherapy or surgery to the neck were excluded.

2.2. Procedures

The tumour localisation was classified as lateralised to the right/left or as a midline tumour defined as touching or crossing the midline. The LSG procedure was performed according to the European joint practice guidelines [15]. On the day of surgery, the patient had four to six peritumoural injections of radiotracer (0.2 mL). 99 m Tc-labelled rhenium sulphide nanocolloid (20MBq) was used up to December 2008 and replaced with 99 m Tc-labelled albumin nanocolloid (20MBq) for the remaining period. Patients were scanned with dynamic and planar LSG, and from September 2009, single-photon emission computed tomography with CT (SPECT-CT) was added. Three specialised head and neck surgeons performed all operations. A SN was defined by a fourfold or higher radioactive count than the background activity and was excised. All counts were recorded *ex vivo*. Excised SNs were bisected in the midline and examined using the intraoperative frozen section (FS) procedure. Each section was sliced from the midline and stained with haematoxylin and eosion (H&E) and anti–pan cytokeratin antibody (CKAE1/3). If the pathologist identified metastatic disease, the procedure was continued with a completion neck dissection (CND) in level I, II, III and IV and at least one level below the level involved. Negative FS led to a formalin-fixed and paraffin-embedded procedure followed by serial step sectioning (SSS) at additional five steps with 150-μm intervals. Each section was stained with H&E and CKAE1/3. If the SSS procedure showed signs of metastatic disease, the patients were readmitted for CND. Lymph nodes obtained from the CND procedures were bisected in the midline and stained with H&E. Pathological conclusions were categorised according to the criteria by Hermanek *et al.* [16]: no signs of metastasis, mummified cells, isolated tumour cells (ITC), micrometastases at tumour deposit 0.2–2 mm or macrometastatic disease at deposit >2 mm with or without extracapsular spread. Mummified cells were considered negative for metastasis, and isolated tumour cells were considered positive for micrometastasis. Excised lymph nodes were grouped into neck levels according to the international guidelines [17]. Adjuvant postoperative radiotherapy was indicated at close or positive margins, ≥pN2 or in case of extracapsular spread.

2.3. Ethics and statistics

Data were collected on patient demographics, location of the primary tumour, recurrences and lymphatic drainage patterns. The study was approved by the Danish Health Authority (2008-58-0035) and the Danish Science Ethics Committee (24021). For comparison between groups, we used the unpaired t-test, and for categorical data, the chi-square test. GraphPad Prism 6 was used for statistical calculations.

3. Results

We included 222 patients. Two patients were excluded because LSG was unable to obtain visible lymphatic drainage. Patient characteristics and the location of the primary tumours are presented in Table 1. Dynamic and planar LSG was used to visualise SNs in 36/36 patients and LSG with SPECT-CT was used to visualise SNs in 184/186 patients. The SN detection rate by LSG was 99.1%. In the two excluded patients, where LSG visualisation failed, END was performed. One had a tumour located to the retromolar trigone (RMT) and one ipsilateral metastasis located in level II. The other patient had a tumour in the buccal mucosa (BM) with no metastases.

Among the 220 patients, 697 hotspots (median 3, range 1–9) were visualised on LSG, and 781 SNs (median 3, range 1–12) were excised. Lymphatic patterns from LSG and SLNB according to the tumour site are presented in Tables 2–3. Metastases were found in 72/781 (9.2%) SNs among 55 (25.0%) SLNB-positive patients. A detailed summary of each SLNB-positive patient and their topographical lymph node distribution are outlined in Appendix A.

Table 1
Characteristics of patients with negative and positive SLNB in oral squamous cell carcinoma.

Characteristics	Overall, n (%)	SLNB negative, n (%)	SLNB positive, n (%)
Patients	220	165 (75.0)	55 (25.0)
Gender			
Male	133 (60.5)	99 (74.4)	34 (25.6)
Female	87 (39.5)	66 (75.9)	21 (24.1)
Median age, year (range)	64.4 (30.3–93.1)	64.7 (30.3–87.3)	67.8 (31.9–93.1)
Primary tumour site			
Anterior 2/3 of tongue	113 (51.4)	76 (67.3)	37 (32.7)
Floor of mouth	68 (30.9)	57 (83.8)	11 (16.2)
Lower alveolar ridge	15 (6.8)	13 (86.7)	2 (13.3)
Upper alveolar ridge	10 (4.5)	9 (90.0)	1 (10.0)
Buccal mucosa	5 (2.3)	4 (80.0)	1 (20.0)
Retromolar trigone	9 (4.1)	6 (66.7)	3 (33.3)
pT classification			
T_1	146 (66.4)	119 (81.5)	27 (18.5)
T_2	74 (33.6)	46 (62.2)	28 (37.8)

SLNB, sentinel lymph node biopsy; pT, primary tumour.

3.1. Midline tumours

Twenty-one patients had midline tumours, and 15/21 (71.5%) had bilateral lymphatic drainage on the LSG. Fourteen of the 15 patients also showed bilateral drainage on SLNB. Two (13.3%) of these had tumours located on the floor of mouth (FOM) and metastatic disease. One had bilateral metastatic disease to one lymph node in level III, and the other had unilateral spread in level III. In midline tumours, the incidence of surgical SNs was highest in level I–II (33.8–32.4%).

3.2. Lateralised tumours

Of 199 patients with lateralised tumours, 154 (77.4%) patients showed only ipsilateral drainage patterns on LSG and SLNB. Metastatic disease was found in 33/154 (21.4%). Bilateral patterns were detected in 41/199 (20.6%) patients. Metastatic disease was identified in 17/41 (41.5%) patients. Ten of these had metastatic ipsilateral SNs, while four patients, one with FOM tumour and three with anterior tongue (AT) tumours, had metastatic SNs exclusively on the contralateral side in level I–III. The last three patients, all with AT tumours, showed bilateral metastatic SNs in level II–III on the ipsilateral side and in level I, II and IV on the contralateral side. Exclusive contralateral drainage was found in 4/199 (2.0%) patients with AT tumours, one of whom had a metastatic SN in level II.

Most resected SNs were seen in level II (37.6%) followed by level I (27.8%) and III (25.0%). Eight percent were located in level IV, but only AT tumours showed metastases in this level. On SLNB, one AT patient had an ipsilateral metastasis in level I and a discontinuous spread of a single metastasis in level IV. Similarly, one AT patient had a positive ipsilateral SN in level I and a contralateral positive SN in level IV. In a single SLNB-positive patient with a lateralised AT tumour, we detected an ipsilateral metastatic SN on FS and a suspicious metastatic non-SN with no radioactive count. Both were found in level I.

The distribution of metastases found by SLNB and CND are shown in Table 4. Metastatic disease was identified by the FS in 39/55 (70.9%) SLNB-positive patients. The location of SNs detected by LSG procedure correlated with the location of positive SNs during surgery in 57/72 (79.2%) SNs. Fourteen (19.4%) positive SNs were in the adjacent neck level, and only one (1.4%) was found two levels away.

3.3. Completion neck dissection

Because of high age and a synchronous oesophageal cancer, 2/55 SLNB-positive patients did not undergo

Table 2
Distribution of SNs found by LSG and SLNB in OSCC patients with midline tumours.

Location	Level I LSG/SLNB SN (%)		Level II LSG/SLNB SN (%)		Level III LSG/SLNB SN (%)		Level IV LSG/SLNB SN (%)		Level V LSG/SLNB SN (%)		Total LSG/SLNB SN (%)		Bilat drainage, cases (%)
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	
FOM	6/10	8/4	12/7	7/3	6/10	5/6	2/2	1/2	1/0	1/0	27/29	22/14	9 (60.0)
Ant. tongue	–	2/1	1/2	2/2	–	1/1	–	–	–	2/0	1/2	7/4	1 (6.7)
BM	1/2	–	–	–	–	–	–	–	–	–	1/2	–	0 (0.0)
LAR	4/2	2/2	1/2	1/2	1/1	–	–	–	–	–	6/5	3/4	3 (20.0)
UAR	3/2	1/1	1/4	1/1	0/1	0/1	–	–	1/0	–	4/7	2/3	2 (13.3)
Total	14/16 (36.5/33.8)	13/8	15/15 (35.1/32.4)	11/8	7/12 (17.6/28.2)	6/8	2/2 (4.0/5.6)	1/2	2/0 (6.8/0.0)	3/0	40/45 (54.1/63.4)	34/26 (45.9/36.6)	15 (100.0)

FOM, floor of mouth; Ant., anterior; BM, buccal mucosa; RMT, retromolar trigone; LAR, lower alveolar ridge; UAR, upper alveolar ridge; LSG, lymphoscintigraphy; SLNB, sentinel lymph node biopsy; SN, sentinel node.

CND, respectively. In total, 1211 lymph nodes were excised from 53 patients, and nine (0.7%) lymph nodes among eight (15.1%) patients showed further metastatic disease. All had lateralised tumours: six AT tumours and one FOM and RMT tumour. Additional ipsilateral metastases were found at the same level localisation as on the LSG and SLNB in 4/8 patients (level I–II). Discordance between the location given by LSG, SLNB and CND was found in the remaining four patients: in two AT patients, one ipsilateral metastasis was found in level IV, where nearest hotspots on LSG and positive SNs were found in level II and III, respectively. One AT and one FOM patient had ipsilateral metastases in level I, where adjacent hotspots and positive SNs were in level II.

3.4. SLNB failure and diagnostic performance

In the study period, 9/165 (5.5%) SLNB-negative patients developed isolated cervical metastases, with no new primary tumour as origin. Among SLNB-positive patients, two AT patients developed regional neck recurrence in undissected locations not found by the LSG or SLNB procedure. These 11 patients were considered SLNB failures because of missed disease by the SLNB procedure and underwent neck dissection when diagnosed with recurrences. The excision of the primary tumour was with clear margins in all 11 cases. A summary of each SLNB failure patient and their topographical lymph node distribution are outlined in Appendix B. The median follow-up time was 30.4 months (range 2.99–110.9 months), and the median time for cervical recurrence was 7.35 months (range 2.99–12.5 months). Of the nine SLNB-negative patients, eight had a lateralised primary tumour site, and recurrences were found at the ipsilateral side of the SLNB intervention in each case. The ninth patient had a primary tumour crossing the midline of the BM in the upper labial mucosa, and the recurrence was found in level I at the contralateral side, where no hotspots had been detected on LSG. Our SLNB procedure had a sensitivity of 83.3% (95% CI: 71.7–90.9) and an negative predictive value (NPV) of 93.3% (95% CI: 88.8–96.9). Sensitivity and NPV for AT and FOM patients were 88.1% and 93.4% and 78.6% and 94.7%, respectively.

4. Discussion

The SLNB procedure is based on the unique lymphatic drainage pattern of each individual patient, and the applicability and accuracy of SLNB have been validated by numerous studies. In the latest and largest meta-analysis investigating the diagnostic efficacy of SLNB in early OSCC, Liu *et al.* [18] reported a pooled sensitivity of 87% and an NPV of 94%. A study by Broglie *et al.* [2] reported a false-negative rate of 6% with an NPV of 96%, and the European Multicenter Trial revealed an NPV of 95%. Both are comparable to our results (NPV 93.3%) [8]. It is important to notice that these results are equivalent to the regional recurrence rate after END in neck node–negative T1-2cN0 OSCC patients reported by previous literature and implies that SLNB is an excellent alternative to END [19,20]. The study by Hernando *et al.* [5] comparing SLNB and END reported a false-negative rate of 17% in the END group and 10.3% in the SLNB group.

The patterns of metastases in neck dissection specimens have been assessed by several large-scale studies evaluating the site of nodal metastases [21–24]. A significant drawback in these previous studies is the lack of thorough histopathologic examination, which is not common practice in routine END specimens. This study contributes to a more profound description of the lymphatic drainage pattern with more accurate data on spread of smaller deposits of ITC or micrometastases. A similar smaller study conducted by Stoeckli *et al.* [10] revealed lymph drainage to SNs that would not have been dissected by routine END in 9/70 (13%) patients, including six with contralateral SNs. By comparison, the SENT study and Flach *et al.* [25] reported 12% and 13% contralateral drainage from well-lateralised tumours, respectively, while midline tumours showed 60% bilateral drainage [8].

Table 3
Distribution of SNs found by LSG and SLNB in OSCC patients with lateralised tumours.

Location	Level I LSG/SLNB n (%)		Level II LSG/SLNB n (%)		Level III LSG/SLNB n (%)		Level IV LSG/SLNB n (%)		Level V LSG/SLNB n (%)		Total LSG/SLNB n (%)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
FOM	30/50	12/15	52/51	9/9	35/39	8/11	11/15	1/1	2/1	0/1	130/156	30/37
Ant. tongue	65/81	13/8	127/161	22/20	92/110	16/12/1	40/35	3/5	13/7	0/2	337/394	54/47
BM	6/10	–	3/3	–	–	–	–	–	1/0	–	10/13	–
RMT	5/10	–	13/8	–	2/3	–	–	–	3/0	–	23/21	–
LAR	7/11	–	7/8	–	3/2	–	2/1	–	–	–	19/22	–
UAR	8/8	2/5	6/7	1/0	1/0	2/1	–	–	1/0	–	16/15	5/6
Total	121/170 (23.7/27.8)	27/28	208/238 (38.5/37.6)	32/29	133/154 (25.5/25.0)	26/24	53/51 (9.1/8.0)	4/6	20/8 (3.2/1.6)	0/3	535/621 (85.7/87.3)	89/90 (14.3/12.7)

FOM, floor of mouth; Ant., anterior; BM, buccal mucosa; RMT, retromolar trigone; LAR, lower alveolar ridge; UAR, upper alveolar ridge; LSG, lymphoscintigraphy; SLNB, sentinel lymph node biopsy.

Table 4
Distribution of metastases in SNs and from SLNB-assisted CND in patients with OSCC.

Location	Level I SN/CND n (%)		Level II SN/CND n (%)		Level III SN/CND n (%)		Level IV SN/CND n (%)		Level V SN/CND n (%)		Total SN/CND n (%)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
FOM	3/1	1/0	4/0	–	1+3[a]/0	–	–	–	–	–	11/1	1
Ant. tongue	12/3	3/1	23/1	2/0	8/0	1/0	2/2	1/0	–	–	45/6	7/1
BM	2/0	–	–	–	–	–	–	–	–	–	2/0	–
RMT	2/1	–	1/0	–	–	–	–	–	–	–	3/1	–
LAR	2/0	–	–	–	–	–	–	–	–	–	2/0	–
UAR	1/0	–	–	–	–	–	–	–	–	–	1/0	–
Total	22/5 (36.1/66.7)	4/1	28/1 (41.7/11.1)	2/0	12/0 (18.1/0.0)	1/0	2/2 (4.2/22.2)	1/0	– (–/–)	–	64/8 (88.9/88.9)	8/1 (11.1/11.1)

FOM, floor of mouth; Ant., anterior; BM, buccal mucosa; RMT, retromolar trigone; LAR, lower alveolar ridge; UAR, upper alveolar ridge; SN, sentinel node; CND, completion neck dissection.
[a] Two SLNB-positive FOM patients with a midline tumour had three metastases in level III.

A study by Ganly *et al.* [20] found that 40% of regional recurrences occurred on the undissected contralateral side in their patients with T1-T2N0 oral tongue cancer who underwent END. This supports the strength of SLNB in assessing the individual drainage pattern. Our results are in line with previously published data on regional lymphatic metastases in patients with OSCC, all pointing out that most occult metastases are located in neck level I–III [2,10,21]. Farmer *et al.* [26] made a similar trial, investigating the lymphatic drainage pattern for 140 patients with T1-2N0 oral cavity cancer; their results demonstrated a minimal metastatic distribution to level IV in 2% of their cases. We found no studies reporting metastatic activity in neck level V for the T1-2N0 OSCC.

In our study, only tongue tumours demonstrated metastatic distribution to level IV. Our incidences of metastatic spread to level IV in patients with tongue cancer are similar to other studies [2,10,27]. Unfortunately, previous studies did not report if metastatic SNs in level IV were encountered by LSG, which we only found in two of our patients with metastases in this level. This could indicate that CND should be extended to level IV in positive AT patients, even if LSG does not detect hotspots in this region.

Among FOM tumours, we found metastatic SNs in level I–III. The study by Melkane *et al.* [9] detected one metastasis in level IV in 1/67 patients. A topic of interest in many studies has been the reduced SN detection rate of FOM tumours. As reported by Civantos *et al.* [28], the false-negative rate of FOM tumours was significantly higher compared with other oral cancers and could be explained by the close proximity between the SNs and the primary tumour [7]. With SLNB-positive FOM patients, only one had additional metastatic activity during CND. However, 3/11 (27.3%) SLNB failures had tumours located in the FOM, resulting in a lower sensitivity. Alkureishi *et al.* [29] found many of their failures in FOM tumours to have recurrence in level I and suggested a combination of SLNB and dissection of level I to improve the sensitivity. We began to routinely perform a level I exploration and resect the lymph node anterior to the submandibular gland and often the gland itself in FOM patients.

There are still limitations to the SLNB technique and its accuracy in identifying occult metastases near the tumour and injection site due to high background radioactivity. Recently published literature by Christensen *et al.* [31] investigated an optimised approach by adding infrared fluorescence imaging to the SLNB procedure, and Agrawal *et al.* [30] evaluated the use of the radiopharmaceutical 99 m Tc-Tilmanocept. Both studies reported a favourable benefit of their techniques. These approaches could result in a higher detection rate and sensitivity for SN identification. A limitation in our study is that lymph nodes from the CND specimen were not examined by use of SSS histopathologic evaluation. Thus, small metastatic deposits such as micrometastases and ITC could be missed. However, metastatic activity outside of the SNs is reportedly low [32,33].

5. Conclusion

To our knowledge, this is one of the largest single-centre cohort studies focussed on the lymphatic drainage patterns of LSG and SLNB in early OSCC. Only AT cancers revealed metastases in level IV, which could suggest that additional dissection of level IV in patients with positive tongue cancer might be advisable, but further studies are needed to support this potential therapeutic algorithm. The development of the SLNB procedure is ongoing, and our study has shown a pronounced benefit of the SLNB procedure in the clarification of unexpected bilateral or contralateral metastatic spread. In our cohort, 8/55 (14.5%) patients with occult metastasis would have been missed by conservative END treatment of the ipsilateral neck.

Conflict of interest statement

None declared.

Appendix A and B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.10.021.

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