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Sentinel lymph node biopsies in early stage oral and oropharyngeal carcinoma: a retrospective single-centre experience

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Abstract

The aim of this retrospective study was to analyse a consecutive series of patients with oral and oropharyngeal carcinoma who had had sentinel lymph node biopsy (SLNB) at our hospital during 2008-2017. A total of 70 patients with clinically and radiologically confirmed primary oral (n = 67) or oropharyngeal (n = 3) carcinoma, with no signs of metastatic lymph nodes preoperatively (clinically N0) were included. Patients' clinical and personal data, characteristics of the tumours, sentinel lymph node (SLN) status and outcomes were recorded. Eight patients had invaded SLN. Two patients with clear sentinel lymph node biopsies had recurrences in the cervical lymph nodes with no new primary tumour as origin. The negative predictive value (NPV) and sensitivity for SLNB were 97% and 80%, respectively. The depth of invasion was an individual predictor for cervical lymph node metastasis ($p = 0.043$). Single photo emission computed tomography (SPECT) detected fewer SLN in patients with invaded lymph nodes than in patients with clear lymph nodes ($p = 0.018$).

Our data support the use of SLNB as a minimally invasive method for staging the cervical lymph nodes among patients with cN0 oral and oropharyngeal carcinoma. Our results further confirm that greater depth of invasion is associated with cervical lymph node metastases.

Keywords: Sentinel lymph node biopsy; cervical lymph node; oral carcinoma; oropharyngeal carcinoma; neck dissection; invasion; metastasis

Introduction

Involvement of cervical lymph nodes is an important prognostic factor in early stage T1-T2N0 oral carcinoma and decreases the five-year survival considerably.[1–3] Regardless of current advanced imaging techniques, occult metastases are detected in up to 20%-30% of T1-T2N0 oral carcinomas.[2,4,5] Improved imaging techniques with contrast-enhanced computed tomography (CT) scans and magnetic resonance imaging (MRI) have been noted to increase the rate of detection of lymph node metastases.[6] The current accepted practice is to do an elective neck dissection (END) when the risk of nodal metastasis is estimated to exceed 20%.[7]

Previously, the only reliable way to detect cervical lymph node metastases in oral carcinomas was END.[8,9] However,

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neck dissection in these patients is often over-treating, as 70%-80% of patients receive no benefit from the procedure, leading to increased morbidity and decreased quality of life as a result of scarring, injury to the nerve, and sensory deficits.[10,11] Attention has therefore been focused on sentinel lymph node biopsy (SLNB) as an alternative to END, or watchful waiting. The detection rate of SLNB in oral and oropharyngeal carcinoma has been reported to be 92%-100%, the negative predictive value (NPV) 70%-100%, and the sensitivity 80%-93%. [2,4,12,13] No significant difference has been reported between survival of patients who had SLNB and END,[11] while morbidity of SLNB has been shown to be minimal.[2]

The aim of this retrospective study was to analyse a consecutive series of patients who had SLNB during a 10-year period at the Department of Otorhinolaryngology – Head and Neck Surgery and the Department of Oral and Maxillofacial Surgery at Helsinki University Hospital in Helsinki Finland.

Material and methods

Study design

We organised a retrospective cohort study to analyse the results of SLNB in patients with oral and oropharyngeal cancer. We assessed the charts of all patients who had had SLNB at the Department of Otorhinolaryngology – Head and Neck Surgery or at the Department of Oral and Maxillofacial Surgery at Helsinki University Hospital, Helsinki, Finland, between May 2008 and November 2017. The search for data was based on operative code PJA12, indicating "Excision of sentinel lymph node" as a primary or secondary surgery code. Included were patients with clinically and radiologically confirmed primary oral and oropharyngeal carcinoma, with no preoperative signs of metastatic lymph nodes (N0).

Exclusion criteria were previous radiotherapy or chemotherapy and previous malignancies. All patients (N = 70) were assessed before and after operation by a multidisciplinary Head and Neck Tumour Board. We used contrast-enhanced CT scans or MRI of the head and neck as preoperative diagnostic imaging, complemented if needed by ultrasonography with or without fine needle biopsy of the cervical lymph nodes. Patients were followed for a period of five years, consistent with the Finnish national guidelines.

The following data were recorded from the patient files: age, sex, histopathological type, size, anatomical site, depth of invasion, and pathological stage of the primary tumour, preoperative imaging, number of SLN identified, and their status and recurrences during follow up. TNM classification was assessed according to the 7th edition of the UICC, which was valid at the time of the study.[14] The end point was invaded neck nodes, which were recorded "invaded" when SLN showed invasion, or when a recurrent cervical lymph node with no new primary tumour as origin was detected during the follow-up period. The internal review board of the Head and Neck Center, Helsinki University Hospital (HUS/66/2018) approved the study.

Sentinel lymph node biopsy technique

The day before operation the primary tumour was injected with Nanocoll technetium-^{99} labelled albumin (GE Healthcare) at the Department of Nuclear Medicine, Helsinki University Hospital. The SLN were identified using single-photon emission (SPE) CT 30 minutes and two hours after injection. The SLN were detected using a hand-held Neoprobe gamma detector probe at the time of operation (Neoprobe).

Histopathological examination

The SLN were sliced every 1 mm and assessed by a head and neck pathologist using a Nikon Eclipse microscope (Tokyo).

Statistical analysis

Data were analysed using GraphPad Prism version 5.00 (GraphPad Inc). The two-tailed Mann Whitney *U* test was used to assess the significance of differences in continuous variables. Fisher's exact test was used to examine the association between variables with nominal scales. Probabilities of less than 0.05 were considered significant.

Results

A total of 70 patients with oral or oropharyngeal carcinoma fulfilled the inclusion criteria (Fig. 1). Full details are given in Table 1. The mean duration of postoperative follow-up was 54 (range 14-127) months.

Detection of occult lymph node metastases

SPECT detected 213 SLN altogether (mean 3.0, range 1-8). Ipsilateral SLN were detected in all but one patient (mean 2.5 SLN, range 0-7). The patient with no evident SLN on the ipsilateral side had one SLN on the opposite side at level II and this patient had a SCC of the left lower lip. Overall, 14 patients had bilateral or contralateral SLN on SPECT (mean 2.0 SLN, range 1-5). Altogether 197 SLN were excised. The mean number of excised SLN /patient was 2.8 (range 1-11).

Of the 70 patients, eight (11%) had metastases in sentinel lymph nodes of which two were micrometastases and one showed extracapsular spread of 0.25 mm (Table 2). All SLN-positive patients had SCC.

One of the eight patients with invaded SLNB declined neck dissection and showed clinically and radiologically confirmed metastatic cervical lymph nodes six months postoperatively. This patient declined any surgery or chemotherapy and died during follow-up. One patient had a

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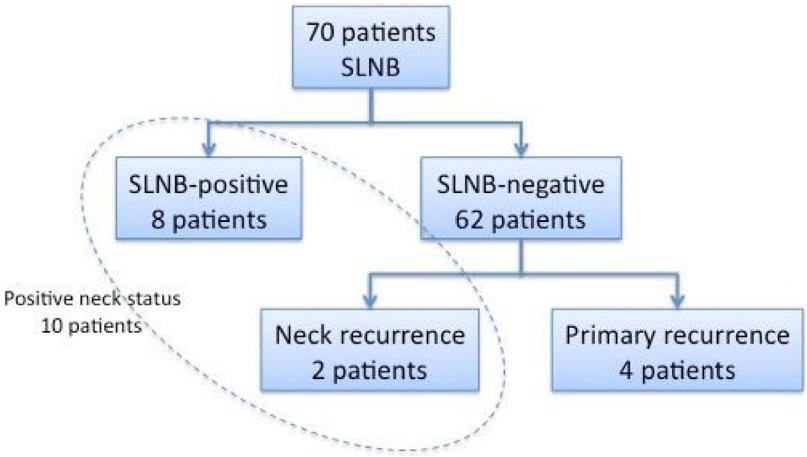

Fig. 1. Flowchart of 70 oral and oropharngeal patients having sentinel lymph node biopsy (SLNB). Eight patients had invaded nodes and two patients had neck recurrence without any new primary tumour during follow up, indicating false negatives for SLNB.

Table 1
Descriptive statistics of the 70 patients.

Variable	No. or mean (range)
Sex:	
Male	33
Female	37
Mean (range) age (years):	61 (27-91)
Histopathological type of tumour:	
SCC	68
Secretory carcinoma of salivary glands	2
Anatomical site of tumour:	
Tongue	50
Floor of the mouth	10
Lip	3
Buccal mucosa	4
Soft palate/oropharynx	2
Tonsils	1
Stage of the 68 SCC:	
T1	64
T2	3
T3	0
T4a	1
Size of tumour (mm):	
Mean (range):	9.6 (1.5-24)
1-5	17
6-10	22
11-15	13
16-20	7
21or more	2
NA	12
Depth of invasion (mm):	
Mean (range):	3.6 (1-10)

single micrometastatic SLN and the multidisciplinary Head and Neck Tumour Board recommended observation because of poor compliance. There was no sign of recurrence during five years of follow-up. The other six patients had subsequent neck dissections, in which no further metastatic lymph nodes were found. During neck dissection, the mean number of lymph nodes excised was 24 (range 18-30). None of the patients showed local or regional recurrences during follow-up. There were no significant differences between the patients with invaded or clear SLN in: age, sex, number of SLN removed, or in depth of invasion and location or size of primary tumour.

Recurrences

Two patients (3%), both with negative SLNB and T1 tumours, had recurrence in the cervical lymph nodes with no new primary tumour as origin (Table 3), and four patients had local recurrences of their primary tumours. The mean time to primary-site recurrence was 16.3 (range 3-36) months. The mean time for neck recurrence was 21 (range 17-25) months. The mean size of the primary tumour in patients with neck recurrence was 8.5 (range 8-9) mm, mean depth of invasion of primary tumour was 4.3 (range 3-5.5) mm, and mean number of SLN removed was 1.5 (range 1-2). The NPV, the false negative rate, and sensitivity for SLNB were 97%, 20% and 80%, respectively.

Predictive factors for cervical lymph node metastasis

There was a significant association between cervical lymph node metastasis and depth of invasion ($p = 0.043$). Mean depth of invasion was significantly greater among patients with cervical lymph node metastasis (including SLN-invaded and those with neck recurrence - true positives and false negatives, $n = 10$) compared with patients with no lymph node metastases (mean 4.6 (range 2.1-8) mm and 3.4 (range 1-10) mm, respectively, $p=0.043$). The mean number of SLN detected in SPECT/CT in patients with invaded lymph nodes was significantly lower than that in patients with no metastases (mean 1.8 (range 1-4) and mean 3.3 (range 1-8), respectively; $p = 0.018$). However, we found no association between the numbers of SLN harvested.

There were also no significant associations in the diameter or location of the primary tumour, stage of tumour, or age or

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Table 2
Eight patients had positive sentinel lymph node biopsies.

Age	Gender	Location of the tumour	CT/MRI	Depth of invasion	Size of tumour	No. of positive/excised SLNs	Neck dissection level
64	female	Lateral side of tongue	CT	4.2 mm	11mm	1/4 (LII)	LI-IV dx
39	male	Lateral side of tongue	MRI	2.5mm	6 mm	1/1 (micrometastasis)	I, IIa, III dx
59	female	Base of tongue	MRI	7mm	15mm	1/1	*
73	female	Floor of mouth	MRI	2.5mm	14 mm	1/2	L I-IV dx
66	female	Upper surface of tongue	MRI	8 mm	20 mm	1/2 (micrometastasis)	Observation**
63	female	Floor of mouth	CT	5mm	4 mm	1/2 (LI and LIII)	LI-V dx
37	male	Lateral side of tongue	CT	2.1mm	10 mm	1/3 (extracapsular growth)	LI-III sin
58	female	Posterior part of tongue	CT	6 mm	14 mm	1/11 (LIIa) (micrometastasis)	LI-III sin

* declined neck dissection, metastases in the right side of the neck 6 months postoperatively.
** the multidisciplinary Head and Neck Cancer Board recommended observation due to lack of compliance.

Table 3
Descriptive details on patients with neck recurrence. The patients had negative SLNs.

Site of recurrence	Age	Gender	Location of tumour	Size of primary tumour	Depth of invasion	Closest resection margin	No. of positive /excised SLNs	Time until recurrence	Treatment*
Ipsilateral	36	F	Tongue, lateral	8 mm	5,5mm	1mm	0/1	25 months	Neck dissection (1/7)
Ipsilateral	76	M	Tongue, lateral	9mm	3mm	3mm	0/2	17 months	Neck dissection (3/43)

* Number of positive/harvested lymph nodes provided.

sex of the patient between the patients with invaded and clear lymph nodes (Table 4).

Discussion

There is still uncertainty over the best line of treatment for patients with clinically N0 oral and oropharyngeal disease. The guidelines in different clinics vary, and the evidence provided by different studies is heterogeneous. Some evidence favours END plus clinical follow up.[3,15–18] Recently, Hutchison et al showed in the selective neck dissection (SEND) trial that END results in a lower risk of death and recurrence than observation.[16] However, END resulted in more damage to the facial and neck nerves. This emphasises the need for a better staging option in early stage carcinoma of the oral cavity with no evident cervical lymph node metastases. The Sentinel European Node Trial (SENT) showed that SNB is a reliable and safe technique for staging clinically N0 neck in patients with T1 and T2 oral cancer.[2] Our results contribute to the pool of publications about SLNB in patients with oral and oropharyngeal carcinoma.

In our study the prevalence of occult lymph node metastases consisting of both patients with invaded SLN (n = 8) and patients with later cervical lymph node metastases (considered as false negative SLNB, n = 2) was 14%, which is slightly lower than that reported by other groups (20%-30%).[2,4,5] Previous studies of SLNB at our hospital reported occult metastases in 27% of patients during 2000-2001[19] and 22% during 2002-2005.[20]

Two patients had recurrence of cervical lymph nodes, both of whom had clear SLNB and neither had local recurrence. They were therefore regarded as false negative for SLNB. The negative predictive value for SLNB in our series of patients was 97%, which is in line with several other studies.[2,12,13] Previous studies regarding SLNB at our institute reported negative predictive values of 92%[19] and 94%.[20] However, despite a low number of occult metastases, the sensitivity of SLNB in our patients was 80%, which is slightly lower than that reported by other groups (88%-93%), and highlights the need for further improvement in our protocol.[2,4,13] However, if END had been done for all the patients it would have lead to over-treatment of 60 (86%) of our 70 patients, leading to increased cost and morbidity. A large proportion of our patients had early stage carcinoma with small primary tumours and the alternative for SLNB or END would have been observation. However, it has been shown that observation and therapeutic neck dissection decrease the overall and disease-free survival, compared with END alone, in this group of patients.[3]

There is no standard for the histopathological sectioning of SLNB samples, though sectioning at 150 μm intervals has been recommended.[21,22] However, a study by Jefferson et al did not report any missed micrometastases in samples that had been primarily sectioned at 2 to 3 mm when re-examining them at 150 μm intervals.[23] Fine sectioning increases the cost of the histopathological analyses and the additional benefit it would bring is uncertain. We use sectioning at 1 mm intervals. Several groups use sectioning at 2 to 3 mm intervals with negative predictive values as good as 94%.[24] Further studies are required to provide suffi-

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Table 4
Associations between positive and negative neck status and the different patient variables. *P*-value provided when statistically significant.

Variable	Positive neck (n = 10)	Negative neck (n = 60)	*p*-value
Age (mean and range)	57 years (36-76)	61.5 years (27-91)	ns
Gender			
Female (n = 37)	7	30	ns
Male (n = 33)	3	30	
Location of primary tumour			
Tongue (n = 50)	8	42	
Floor of mouth (n = 10)	2	8	
Buccal (n = 4)		4	
Lip (n = 3)		3	
Soft palate/oropharynx (n = 2)		2	
Tonsillae (n = 1)		1	ns
Size of primary tumour (mean and range)	10.8 mm (4-20 mm)	9.2 mm (1.5-24 mm)	ns
Depth of invasion (mean and range)	4.6 mm (2.1-8 mm)	3.4 mm (1-10 mm)	.043*
Number of SLNs detected in SPECT/CT (mean and range)	1.8 (1-4)	3.3 (1-8)	.018*
Number of harvested SLNs (mean and range)	2.2 (1-5)	3.0 (1-11)	ns

cient evidence regarding the optimal sectioning of SLNB samples.

Increasing depth of invasion has been shown to decrease the prognosis of oral SCC.[25,26] A study by Ganly et al reported the depth of invasion of 4 mm or more as the only predictor for neck recurrence in patients with SCC of the tongue with ipsilateral neck dissections.[27] Similarly, in a study by Pedersen et al, depth of invasion of 4 mm or more was reported to be an independent predictive factor for the presence of metastases in oral cavity cancer.[4] According to the updated 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging manual depth of invasion is a significant prognostic factor, and primary tumours formerly categorised as T1 are now staged T2 in the presence of invasion 5 mm beyond the basement membrane.[28]

Several studies have highlighted the lesser ability of the SLN technique to identify lymph node metastases in tumours of the floor of the mouth.[4,21] The proximity of level I lymph nodes to the primary tumour has been proposed as contributing to the difficulty, because of a shine-through effect. Of floor of the mouth-tumours located in the midline, up to 93% have showed SLN bilaterally at level I.[29] Altogether, a 40% probability of nodal metastases even at a depth of invasion of 2 - 4 mm has been proposed in tumours of the floor of the mouth.[26] It has therefore been proposed that level I should be explored in all such tumours. [29]

Most of the patients in our cohort were classified according to the UICC 7th edition, which was valid at the time of the study period (May 2008 and November 2017). According to this classification the treatment recommendation of the national guideline for T2 tumours was END, which explains the small number of T2 tumours in our study. Currently, with increased experience, we offer SLNB for T2 tumours, particularly for those of the tongue and buccal mucosa.

Conclusion

In conclusion, SLNB is justified as a minimally invasive approach for assessing the status of cervical lymph nodes in early stage oral carcinoma with no evident cervical lymph node metastases.

Ethics statement/confirmation of patients' permission

The internal review board of the Head and Neck Center, Helsinki University Hospital (HUS/66/2018) approved the study. Patient permission was not obtained.

Conflict of interest

None.

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