ORIGINAL ARTICLE

Sentinel Lymph Node Biopsy in Patients with Carcinoma of Oral Cavity and Oropharynx

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ABSTRACT

Mrzena L., Betka J., Stárek I., Táborská K., Kodetová D., Křížová H.: Sentinel Lymph Node Biopsy in Oral and Oropharyngeal Carcinomas

Background. The aim of our study was to assess the feasibility and accuracy of sentinel lymph node biopsy in patients with head and neck squamous cell carcinoma with clinically N0 neck.

Methods and Results. The sentinel lymph node was localised preoperatively by lymphoscintigraphy and intraoperatively by a hand-held gamma probe after peritumoral injection of a Tc99m-labeled colloidal human serum albumin. The histology of the sentinel lymph node was compared with the histology of the nodes of the elective neck dissection performed in all patients. 27 patients with oral and oropharyngeal carcinomas accessible to injection with local anaesthesia were enrolled into a prospective trial between July 1993 and December 2005. The sentinel lymph node was localised by preoperative lymphoscintigraphy in 26 of the 27 patients. Sentinel lymph node was identified perioperatively by hand-held gamma probe in 28 neck sides of 27 patients. Occult metastases were found in 4 sentinel lymph nodes in 4 cases. In one case (3.6 %) the result of sentinel lymph node biopsy was false negative. The sentinel lymph node biopsy correctly predicted the positivity and negativity of the neck in 27 of 28 cases (96.4 %).

Conclusions. Sentinel lymph node biopsy in patients with oral and oropharyngeal carcinomas is feasible and seems to predict accurately the status of the regional lymph nodes.

Key words: elective neck dissection, hand-held gamma probe, head and neck cancer, lymphoscintigraphy, sentinel lymph node. *Mr.*

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Metastases in neck nodes are the most important prognostic factor in patients with head and neck carcinomas. A combination of currently available examination methods (palpation, ultrasound, CT, MR) achieves 70 % accuracy in detection of neck metastases existence. Consequently, approximately 30 % of patients are endangered by the existence of occult metastases in neck lymph nodes (1-4). Therefore patients with head and neck carcinoma are currently being indicated for elective neck dissection, which improves patients' survival because it removes occult metastases before they manifest themselves clinically. However, a major disadvantage is that approximately 70 % of patients undergo this neck dissection unnecessarily (1, 2, 5). The only method of occult metastases detection, which may be currently established in clinical practice, is the sentinel lymph node biopsy.

Sentinel lymph node (SLN) is defined as the first draining lymph node for the specific site of primary tumour. In cases of lymphogenic spread this lymph node is the first one which is involved by metastases. All other lymph nodes are supposed to only be involved by metastases subsequently. If such lymph node can be identified and examined by histologic work-up, it is possible to decide whether it is necessary to perform elective treatment of neck lymph nodes or not (6).

SLN conception has already been proven and introduced in clinical practice in malignant melanoma and breast cancer (7-10). The first successful identification of SLN of head and neck tumours was described in 1996 by Alex and Krag (11). Several studies, which proved feasibility and accuracy of SLN biopsy in head and neck tumours, have been carried out since then. The results show that by means of this method it is possible to achieve even 95% accuracy in detection of occult metastases existence in neck lymph nodes (12-20).

Currently the SLN biopsy of examination is being investigating for patients with head and neck tumour in the Otolaryngologic clinic, Faculty of Medicine, Palacký University Olomouc, Faculty Hospital Olomouc and in the Department of Otorhinolaryngology and Head and Neck Surgery, 1st Faculty of Medicine, Charles University, Faculty Hospital Motol, Postgraduate Medical School.

The main goal of the study is to verify the feasibility and accuracy of SLN biopsy of carcinomas in oral cavity and oropharynx in our conditions; to contribute to the enlargement of knowledge of SLN biopsy; and to create conditions for participation in European multicenter study.

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PATIENTS AND METHODS

Patients with histologically confirmed squamous cell carcinoma of the oral cavity or oropharynx with staging T1-T3, N0, the primary tumour of which is accessible to peroral injection of radiocolloid in local anaesthesia, were entered into the study.

Neck metastases were excluded by negative result of clinical palpation and negative result of ultrasonography or CT examination. Previous surgical intervention or radiotherapy for head and neck tumour, gravidity, and lactation were among the excluding criteria.

SLN was identified by preoperative lymphoscintigraphy and intraoperative use of a hand-held gamma probe. In some cases it was also combined with the use of blue dye. Less than 24 hours before the planned surgery 15-50 MBq of the radiocolloid was injected in 0,25- 2 ml of saline by a size 25F-gauge needle after topical local anaesthesia. The needle was always passed into 2-6 areas in the adjacent normal mucosa to completely surround the primary tumour with radiocolloid.

Preoperative lymphoscintigraphy was performed immediately after application of radiocolloid by means of scintillation camera with low-energy collimators. The patient was examined in supine position with hyperextended head. First the dynamic lymphoscintigraphy was performed with images obtained in 60 seconds intervals. Screening was completed as soon as the SLN was conclusively pictured. Then the static lymphoscintigraphy is performed in the anteroposterior and lateral view at the 15^{th}, 30^{th}, and 60^{th} minute after application of radiocolloid. SLN localisation was marked on the patient's skin.

Considering the fact that the two institutions are equipped with different type of hand-held gamma probe, different regimes of examination and different radiocolloids were selected.

Europrobe with a lower value of radial definition, which should work better with higher frequency of activities, is used in the Olomouc institution. Therefore the examination in the Olomouc institution was carried out in a one-day regime and the surgery was performed 3-6 hours after application the radiocolloid. Radiocolloid Nanocoll (Nycomed Amershan, Sorin, Italy) was chosen for this regime. This is a colloid solution of ^{99m}Tc-labeled albumin with small particles (approximately 80 nm), and therefore it quickly moves to SLN (15, 21–23). Gamma probe C-Trak Automatic (Care Wise Medical Products Corporation, USA) with 15-mm collimator Omniprobe EL, which achieves high values of radial definition, was used in the Prague institution. Therefore it was possible to use a two-day regime of examination, when the operation was carried out 15-20 hours after application of radiocolloid. During this regime the radiocolloid Senti-Scint (National Research Institute for Radiology and Radiohygiene, Budapest) was used. This is a colloid solution of ^{99m}Tc-labeled albumin with 200–600 nm particles, which moves slowly to SLN (15, 21–23). In addition to radiocolloid, blue dye Patent Blue V (Blue Patenté V, Laboratoire Guerbet, France), which was injected at the beginning of the operation with the same technique as the radiocolloid, was also used for SLN identification in the first 6 patients (14, 15, 21, 24). We started the operation with removal of primary tumour to reduce the quantity of radiocolloid in the area of the primary tumour, which makes SLN identification more difficult due to its radioactivity (15, 21–23).

Before the skin incision was made, the localisation of the SLN in the area of skin marks was again verified by hand-held gamma probe through the intact skin (15, 21–23). Then 5-7 cm long skin incision was performed in the area of the mark for SLN localisation so that it could be enlarged to the incision used for subsequent neck dissection. SLN was identified with hand-held gamma probe according to its radioactivity or according to its blue colour. After selective excision of SLN its radioactivity *ex situ* and radioactivity of the lymphatic bed were measured. The radioactivity in the area of the lymphatic bed should drop to the value of the background. After excision of all identified SLN the elective neck dissection was performed in all patients.

Each SLN was step sectioned and stained with hematoxyline and eosin. If no metastases were detected, the immunohistochemical staining for cytokeratin (AE1, AE3) was performed (17, 25). Subsequently all nodes in the neck dissection were examined in the same way as the SLN.

RESULTS

From July 2003 to December 2005 some 27 patients with squamous cell carcinoma of oral cavity and oropharynx were prospectively entered into the study in both institutions. The male to female ratio was 4.4 : 1 (22 male and 5 female). The mean age of patients was 56 years (range, 43 – 69).

Localisation and extent of primary tumour of all patients are stated in Table 1.

Preoperative lymphoscintigraphy was performed in all 27 patients. At least 1 SLN was identified during the lymphoscintigraphy in 26 patients. In the case of 1 patient the SLN was detected on both sides, so during the preoperative lymphoscintigraphy the SLN was detected on 27 sides of the neck in total.

Preoperatively the SLN was identified in all 27 patients – which means also in one patient with negative preoperative lymphoscintigraphy. In total the SLN was identified in 28 sides of the neck, because in the case of one patient the SLN was detected on both sides of the neck. Number and localisation of SLN in individual patients are described in Table 2. Each side of the neck is analysed as one individual case.

In total, 70 SLN were detected preoperatively in 28 sides of neck. The average number of SLN found in one side of neck was 2.5 (range, 1-5). The mean size of sentinel lymph node was 8 mm (range, 5-15 mm).

The most frequent localisation of SLN was level II (Figure 1), where 59 SLN were identified in total (84.4 %), and where at least one SLN was found in 27 cases (96.4 %). On the contrary in level IV and in level V no SLN was found. A summary of the number of identified SLN in individual levels according to localisation of primary tumour is described in Tables 3 and 4.

In the case of the first 6 patients radiocolloid and also blue dye were used for identification of SLN. Because of the low number of the SLN identified by blue dye (Table 5) its use was abandoned in subsequent patients.

Table 1. Localisation and extent of the primary tumour in patients of the group

Localisation of the primary tumour	T1	T2	T3	Total
Floor of mouth	5	2	0	7
Tongue	4	4	1	9
Gingiva	0	1	0	1
RTM	0	2	1	3
Tonsil	4	2	0	6
Soft palate	0	1	0	1
Total	13	12	2	27

RTM – retromolar trigon

70 SLN were examined. In 4 patients the histologic work-up of SLN was positive. In all of these 4 patients only 1 SLN was positive. The positive SLN was localised in 2 cases in level II and in 2 cases in level III near to the boundary with level II.

A further 410 lymphatic nodes from 28 neck dissections were examined. In 2 cases metastases were found in neck dissection. In the first case a further 13 nodes in level II affected by metastases were detected in a patient with positive SLN localised in level II. In the second case 1 positive node was detected in neck dissection in level III in a patient with 2 negative SLN in level III and so the SLN biopsy was false-negative.

The SLN biopsy was therefore false negative in 1 (3.6 %) of 28 cases. Results of histologic work-up in patients with positive SLN or with positive node in neck dissection are described in Table 6.

Table 2. Results of sentinel lymph node biopsy and results of histopathologic examination of neck dissections in individual patients of the group

Case number (neck part)	Localisation of primary tumor	Pathological classification of primary tumor	Number of detected SLN	Number of positive SLN	Pathological classification of neck
1	Floor of mouth	T2	3	0	pN0
2	Floor of mouth	T2	3	0	pN0
3	Gingiva	T2	1	0	pN0
4	Tongue	T1	4	0	pN0
5	Floor of mouth	T1	3	0	pN0
6	Tongue	T2	3	0	pN0
7	Tongue	T3	3	**1**	**pN1**
8	Floor of mouth	T1	1	0	pN0
9	Floor of mouth	T2	1	0	pN0
10	Floor of mouth	T1	5	0	pN0
11	Soft palate	T2	3	0	pN0
12	Tongue	T1	2	0	pN0
13	Tonsil	T2	1	**1**	**pN2b**
14	Tonsil	T1	2	0	pN0
15	Tonsil	T1	4	0	pN0
16	Tonsil	T1	2	0	**pN1**
17	Tonsil	T1	4	0	pN0
18	Tonsil	T2	4	0	pN0
19	Tongue	T1	1	0	pN0
20	RTM	T3	2	0	pN0
21	Floor of mouth	T1	1	0	pN0
22	Tongue	T2	2	0	pN0
23	Tongue	T2	2	0	pN0
24	Tongue	T1	2	0	pN0
25	Floor of mouth	T1	3	**1**	**pN1**
26	Tongue	T2	4	0	pN0
27	RTM	T2	2	0	pN0
28	RTM	T2	2	**1**	**pN1**

SLN – sentinel lymph node, RTM – retromolar trigon

Table 3. Number of identified sentinel lymph nodes and number of positive sentinel lymph nodes according to neck levels

Neck areas	Number of identified SLN	Number of positive SLN
I	3	0
II	59	2
III	8	2
IV	0	0
V	0	0

SLN – sentinel lymph node

Altogether SLN biopsy was correctly negative in 23 cases, correctly positive in 4 cases and false negative in 1 case. Sensitivity of SLN biopsy was 80 %, positive predictive value 100 % and negative predictive value 95.8 %. SLN examination correctly predicted negativity or positivity of the neck nodes in 26 cases (96 %).

DISCUSSION

According to localisation of primary tumour the most suitable patients for SLN biopsy are patients with oral cavity carcinoma (15, 21, 22). The application of radiocolloid is difficult in tumors of oropharynx and in tumours of oral cavity spreading to oropharynx, where dorsal border of tumour is the limiting factor for indication for SLN biopsy.

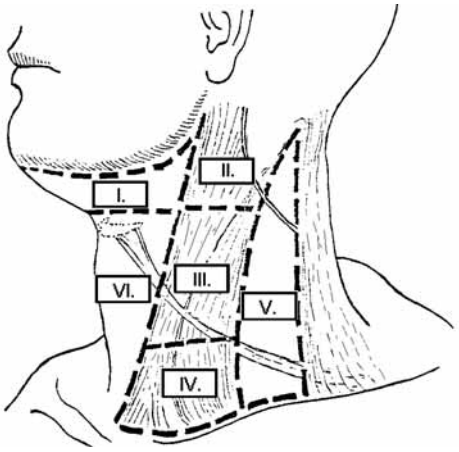

Figure 1. Neck levels (28)

SLN biopsy is indicated especially in patients with the primary tumour, which is suitable for removal, by transoral approach (T1-T2). These patients represented 92 % of our group.

In patients with advanced tumours (T3-T4) the necessary surgery procedure is so extensive that the elective neck dissection does not significantly increase postoperative morbidity. Therefore there is not reason for indication of SLN biopsy (12, 15, and 17). Only 2 patients with advanced primary tumour (T3) localised near to the midline were entered into the study with the aim to exclude lymphatic drainage to contralateral nodes and necessity to perform the bilateral elective neck dissection (15, 21, 22).

Primary tumour reached to the close proximity of midline in 7

Table 4. Localisation of sentinel lymph node according to localisation of primary tumour

Localisation of primary tumor:	level I	level II	level III	level IV	level V
Floor of mouth	2	16	2	0	0
Tongue	1	18	4	0	0
Gingiva	0	1	0	0	0
RTM	0	6	0	0	0
Tonsil	0	15	2	0	0
Soft palate	0	3	0	0	0
Total	3	59	8	0	0

Table 5. Comparison of sentinel node identification results by radiocolloid and blue dye:

Case number (neck part)	Radioactive and blue	Only radioactive	Only blue	Results of histologic work-up of SLN
1	0	3	0	neg.
2	0	3	0	neg.
3	1	3	0	neg.
4	0	3	0	neg.
5	0	3	0	neg.
6	1	0	0	neg.
7	2	0	0	neg.
Total	4	15	0	

SLN – sentinel lymph node

Table 6. Number, localisation and histopathological status of sentinel lymph nodes and lymph nodes in neck dissections in patients with positive sentinel or nonsentinel node

Case	Localisation of primary tumor	Number of SLN	Localisation of SLN according to neck levels	Number of positive SLN	Localisation of positive SLN	Number of positive nodes in neck dissection	Localisation of positive nodes in neck dissection
1	Tongue	3	II, II, III	1	III	0	–
2	Tonsil	1	II	1	II	13	II
3	Tonsil	2	II, II	0	–	1	III
4	Floor of mouth	3	I, I, III	1	III	0	–
5	RTM	2	II, II	1	II	0	–

SLN – sentinel lymph node, RTM – retromolar trigon

patients. Only in 1 patient with floor of mouth carcinoma (T2) spreading 2 cm across the midline was the SLN identified bilaterally. In the other patients the primary tumour did not significantly spread across the midline.

An absolutely essential precondition for correct indication of SLN biopsy is exclusion of neck metastases. More extensive involvement of lymphatic node by metastases may lead to blockage of lymphatic drainage through the SLN. In this case the injected radiocolloid can not reach the SLN and accumulates in lymph nodes through which the lymphatic drainage does not pass normally from the area of primary tumour. The examination result may be false negative (15, 21, 22). Therefore in addition to clinical palpation an ultrasound examination was performed in all patients and CT or MR was performed in patients with lymph node diameters from 10 mm to 15 mm on the ultrasound examination.

A frequently discussed question is the significance blue dye for SLN indication. Blue dye and radiocolloid have different pharmacokinetic and pharmacodynamic properties, therefore the achieved results differ as well (7, 11, 13, 14, 22, 24). For the 6 patients in this study examined by both methods only 4 SLN (21%) of the total number of 19 SLN were radioactive and blue, and no SLN was identified only according to the blue colouring. Though in some studies better results were achieved by means of blue dye and its use was considered useful (15, 17, 21, and 26), most authors agree that the percentage of SLN identified by means of blue dye is lower and that only rarely is it possible to identify SLN solely by means of blue dye (14, 15, and 21). Another disadvantage of using blue dye is the fact that blue staining of tissue around the tumour makes correct determination of the tumour edges during the resection more difficult (7, 11, 13, and 22). Therefore for other patients in the study the use of blue dye was abandoned.

Distribution of radiocolloid through the lymphatic system and its accumulation in nodes depends on the size of particles of the colloid solution. In our study we selected Senti-Scint with large particles for 19 patients who were examined in two-day regime and

Nanocoll with small particles for 8 patients who were examined in one-day regime (15, 21, and 22).

SLN identification in both regimes and with both radiocolloids was entirely feasible, and comparable results were achieved. The advantage of the two-day regime is the lower level of radioactivity during the operation and subsequently also lower radiation dose to the surgical staff. Its disadvantage is the subsequent partial transfer of radioactivity from SLN to second- and third- and subsequent echelon nodes, which was however compensated by the use of radiocolloid with larger particles, so SLN was easily identifiable in all patients.

Based on our experience, we consider the preoperative lymphoscintigraphy to be an essential part of SLN identification. It helps to localise correctly the SLN located in clinically unpredictable sites and prevent incorrect determination of SLN in cases of quick distribution of radiocolloid to second echelon nodes (15, 21, and 22).

On preoperative lymphoscintigraphy SLN localisation was correctly determined in 26 cases (92.8 %). In 2 cases the SLN was localised high in level I and II in a small distance from the primary tumour and its radiation was overlapped by radiation of the primary injection site, which was not possible to eliminate sufficiently even by shading lead plates or software masking. Therefore it is recommended to explore level I and upper part of level II by hand-held gamma probe in all cases in which the primary tumour is located close to cervical lymph nodes for instance in the floor of mouth (12, 13, 15, 17, and 21).

The number of SLN detected on the preoperative lymphoscintigraphy was lower than the number of SLN identified during surgery, because in 17 cases a group of several (2-4) radioactive lymph nodes were localised so close to each other that they were not discernible by the gamma camera.

Almost 84 % of identified SLN were localised in level II. Level II was the most frequent location of SLN in carcinomas of all sites as in similar studies (15, 21, and 22). The number of SLN in all neck levels in carcinomas of all sites of oral cavity and oropharynx is described in Table 4. Whilst some authors have found SLN rarely also in level IV (15, 21, 26), no SLN was identified in levels IV or V in this study.

The success rate of SLN identification in patients with head and neck carcinoma ranges between 90 and 100 % (12, 15, 16, 21, and 22). In this study SLN was identified in all 27 patients (100 %).

Histologic work-up of SLN is technically very challenging, because even small groups of viable tumour cells must be identified. Therefore serial step sectioning of the SLN and imunohistochemical examination are inevitable. 4 nodes in 4 patients were positive out of 70 examined SLNs. In two cases there were metastases detected by routine histologic work-up. In 2 cases micrometastases smaller than 2 mm were detected by histologic work-up with step serial sectioning (27). No positive result was detected by immunohistochemical examination.

Thus positive SLN was detected in 4 cases (14.3 %) out of 28 neck sides. In other published studies on the oral and oropharyngeal carcinoma the occurrence of positive SLN ranged from 16 to 54 % (12, 15, 21, and 22). We explain the slightly lower occurrence of metastases in SLN with the predominance of patients with early carcinoma and the strict criteria for enrolment of patients into the study, because patients were entered into several studies based on negative palpation examination and no sonographic examination, CT or MR of neck were performed.

The low occurrence (3.6 %) of false-negative SLN biopsies manifests the correct identification of SLN. The goal of the study was to manage the SLN biopsy to the extent that occurrence of these false-negative results is not higher than 5 %, which is considered by many authors to be the principal precondition for the introduction of SLN biopsy to routine practice (15, 26).

CONCLUSION

Results of the study show that the SLN biopsy in the carcinoma of oral cavity and oropharynx is accurately feasible and adequately predict the presence of occult metastases.

The results should be proved by a multicenter study with sufficient number of patients and with long-term follow-up. In the future the SLN biopsy may a role of selection criterion weather to perform elective neck dissections in clinical practice.

Abbreviations

CT – computer tomography,
MR – magnetic resonance,
SLNB – sentinel lymph node biopsy,
SLN – sentinel lymph node,

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