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CLINICAL STUDY

Sentinel lymph node radiolocalization and biopsy in oral cavity and oropharynx mucosal squamous cell carcinoma

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Abstract: *Objectives:* The aims of the study were to assess our feasibility and accuracy of sentinel lymph node radiolocalization in patients with squamous cell carcinoma of the oral cavity and oropharynx, and to determine whether the pathology of the sentinel node reflected regional disease.
Material and methods: Patients preoperatively underwent lymphoscintigraphy after peritumoral injection of a 99m Tc labeled radiocolloid. After perioperative gamma probe radiolocalization of the sentinel lymph nodes, elective neck dissection was performed. The histopathological examination of the sentinel nodes and other nodes of neck dissection specimen were compared.
Results: Detection of sentinel lymph nodes by lymphoscintigraphy was feasible in all 12 patients. Also localization with a handheld gamma probe was successful in all patients. Forty sentinel nodes and 276 non-sentinel nodes were histopathologically examined. Occult metastases were confirmed in 7 sentinel nodes (4 patients). There was no false negative sentinel lymph node in our series.
*Conclusion:*Identification of the sentinel lymph node in patients with squamous cell carcinoma of the oral cavity and oropharynx is technically feasible and accurate. This method shows to be able to predict occult metastases and select patients who would benefit from neck dissection *(Fig. 1, Tab. 2, Ref. 28).* Full Text in free PDF *www.bmj.sk.*
Key words: sentinel lymph node, lymphoscintigraphy, handheld gamma probe, occult metastasis, elective neck dissection, head and neck cancer.

The incidence of occult metastases in patients with head and neck squamous cell carcinoma is approximately 30 % (1, 2). Histopathological examination of the elective neck dissection specimen remains the gold standard in occult metastasis diagnosis (3, 4). If the incidence of occult metastases is 30%, 70% of the patients have no benefit from the elective neck dissection and these patients undergo unnecessary morbidity.

Sentinel lymph node biopsy (SLNB) has been proposed as minimally invasive, low morbidity modality able to select patients with occult metastases who will benefit from neck dissection. Consequently this method can minimize the morbidity of neck treatment in patients with clinically negative neck (5, 6, 7, 8, 9, 10).

Moreover, the sentinel lymph node biopsy reduces the number of lymph nodes that must be investigated in comparison to elective neck dissection specimen. The small number of harvested sentinel lymph nodes can be evaluated with more detailed histopathologic techniques, including step serial sectioning, immunohistochemistry, or molecular analysis. This could lead to more accurate nodal staging compared with the routine histopathologic examination with hematoxylin-eosin staining of many nodes from a neck dissection specimen (11, 12, 13, 14). Therefore the sentinel lymph node biopsy is an ever increasingly employed method for staging the clinically N0 neck (15, 16, 17).

The aim of this study was to assess our technical feasibility and accuracy of sentinel lymph node radiolocalization with preoperative lymphoscintigraphy and perioperative gamma probe localization in patients with squamous cell carcinoma of the oral cavity and oropharynx, and to evaluate whether the pathology of the sentinel nodes reflect the nodal status of the entire remaining neck.

Material and methods

From November 2006 to March 2009 a total of 12 patients with histologically confirmed squamous cell carcinoma of the oral cavity and oropharynx were enrolled in a prospective study. The primary tumor range was from T1 to T3. Primary tumor sites have to be directly accessible for peritumoral radiocolloid application in topical local anesthesia. Eleven patients were classified cN0, one patient was classified cN1. In this patient the primary tumor involved uvula and the one (contralateral) side of the neck was clinically negative. Regional lymph node status was classified as cN0 based on palpation and one of the USG or CT imaging methods. The primary tumor size and regional disease were rated according to the International Union Against Cancer (UICC), TNM classification of malignant tumors, Sixth Edition, 2002. All our patients were primarily surgically treated. All patients provided written informed consent.

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Tab. 1. Primary tumor site, size and grade of differentiation.

Patient	Primary tumor	T	G
1. 49y	Oral tongue	T1	G1
2. 67y	Uvula	T1	G2
3. 56y	Palatine tonsil and soft palate	T3	G1
4. 60y	Oral tongue	T2	G2
5. 48y	Oral tongue	T2	G2
6. 56y	Palatine tonsil	T2	G2
7. 55y	Palatine tonsil	T2	G3
8. 57y	Palatine tonsil and soft palate	T2	G2
9. 71y	Anterior tonsillar pillar	T1	G2
10. 53y	Anterior tonsillar pillar	T1	G1
11. 45y	Anterior tonsillar pillar	T1	G1
12. 67y	Uvula	T2	G1

All patients were males with the mean age 57 years (from 45 to 71). The site of the primary tumor was the oral tongue in 3, palatine tonsil in 2, uvula in 2, palatine tonsil and soft palate in 2 and anterior tonsillar pillar in 3. The classification of the primary tumor was T1 in 5, T2 in 6, T3 in 1. Histologically the squamous cell carcinoma was well differentiated in 5, moderately differentiated in 6 and poorly differentiated in 1 (Tab. 1).

The day before surgery, all patients underwent lymphoscintigraphy at the Nuclear Medicine Department. From 1 to 4 radiocolloid injections, depending on the primary tumor size, were peritumorally administered under topical local anesthesia. The volume of the radiocolloid was 1.5–2 ml, with radioactivity 2 mCi (74MBq 99mTc). Radiocolloid Sentiscint (Medi-Radiopharma Ltd., Érd, Hungary), technetium 99mTc labeled colloidal human serum albumin was used in our study. More than 80% of these radiocolloid particles ranged from 100–600nm.

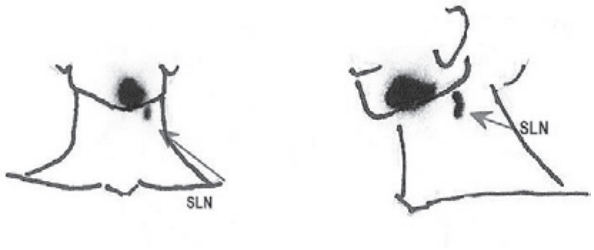

Fig. 1. Preoperative lymphoscintigraphy, anteroposterior and lateral projection. Depiction of the radiocolloid application site and 2 sentinel lymph nodes in level IIA.

After radiocolloid application the lymphatic drainage was dynamically monitored with a gamma camera (Gamma camera Siemens e.Cam, LEHR and gamma camera SOPHA MEDICAL DST, LEHR) in the anteroposterior projection for 30 minutes, or until the first appearance of the sentinel lymph node. Subsequently, static acquisition in the anteroposterior and lateral projections was performed. The time of the first sentinel lymph node appearance was noted. For determination of sentinel lymph node location, a cobalt Co57 marker was used. Location of the radioactive lymph nodes and important anatomical points in the head and neck region were marked under the gamma camera (Fig. 1).

Preoperatively under general anesthesia, in supine operating position the location of the sentinel nodes was checked through the intact skin by a handheld gamma probe (TECPROBE 2000

Tab. 2. Results of the histopathological examination, nodal staging, number and location of sentinel lymph nodes.

Patient/age	Primary tumor	T stage	Side	Number SLNs	SLNs location	SLNs histopathology	FinalN stage
1. 49y	Oral tongue	T1	Left	4	IB(2),IIA(2) ipsi	SLN1(IB) ITC	pN0(i+)(sn)
2. 67y	Uvula	T1 (cN1)	Midline /cN1-right/	3(left)	IIA	Negative (left)	pN2
3. 56y	Palatine tonsil and soft palate	T3	Midline	2(1+1)	IIA bilat	SLN1 left ITC	pN0(i+)(sn)
4. 60y	Oral tongue	T2	Left	3	IIA ipsi	Negative	pN0(i-)(sn)
5. 48y	Oral tongue	T2	Left	3	IIA ipsi	Negative	pN0(i-)(sn)
6. 56y	Palatine tonsil	T2	Right	3	IIA ipsi	SLN1,2,3 mi 3x	pN2b(mi)(sn)
7. 55y	Palatine tonsil	T2	Right	4	IIA ipsi	SLN2 mi	pN1(mi)(sn)
8. 57y	Palatine tonsil and soft palate	T2	Midline	5(2+3)	IIA(2) right IIA(3) left	SLN1 right ma SLN2 left mi	pN2c(mi)(sn)
;9. 71y	Anterior tonsillar pillar	T1	Left	3	IIA ipsi	Negative	pN0(i-)(sn)
10. 53y	Anterior tonsillar pillar	T1	Right	2	IIA ipsi	SLN1 ma	pN1(sn)
11. 45y	Anterior tonsillar pillar	T1	Right	4	IIA ipsi	Negative	pN0(i-)(sn)
12. 67y	Uvula	T2	Midline	4(1+3)	IIA(1) right IIA(2) left	Negative	pN0(i-)(sn)

Ipsi= ipsilateral, bilat= bilateral, ITC= isolated tumor cells, mi= micrometastasis, ma= macrometastasis

STRATEC, STRATEC GmbH). The first surgical step was primary tumor resection via the transoral approach. Then the radioactive lymph nodes were perioperatively identified using a handheld gamma probe. After removing the sentinel nodes the radioactivity of the nodes ex vivo was checked first and then the surgical bed. Drop of the radiation in the surgical site to background level has been expected. The counts, and the size and location of the sentinel nodes were noted. Thereafter appropriate elective selective neck dissection was performed, depending on the primary tumor site. In case of oral cavity carcinoma, levels I, IIA, IIB, III and IV (mobile tongue) were removed and in case of oropharyngeal carcinoma, levels IIA, IIB, III and IV were removed. Excided sentinel lymph nodes and the specimen from the individual levels of the neck were separately sent for histological examination. Semiserial sectioning of the lymph nodes at 200μm intervals, hematoxylin-eosin staining and imunohistochemistry with cytokeratin were performed.

Results

The sentinel lymph nodes (SLN) were identified in all 12 patients by lymphoscintigraphy. The time of the first sentinel lymph node appearance after radiocolloid application ranged from 2 to 60 minutes (mean time 12.8 minutes). The sentinel nodes in three patients with oral cavity carcinoma were depicted more quickly. The mean time in these cases was 2.5 minutes. In cases of 9 oropharyngeal carcinomas the mean time was 16.3 minutes. Detection and identification of sentinel nodes with the handheld gamma probe was available in all 12 patients, 100 %. The average number of identified sentinel nodes was 3.3 (from 2 to 5 SLN) per patient. In all patients with oropharyngeal carcinoma were sentinel nodes located in level IIA (ipsilaterally or bilaterally), but in one patient in level IIA and III. In 3 patients with carcinoma involving the midline of the pharynx, sentinel nodes were found bilaterally in level IIA. In the patient with uvular carcinoma with clinically positive metastasis in level IIA on the right side three sentinel lymph nodes in level IIA on the left side were detected. Patients with oral cavity carcinoma had identified sentinel nodes in levels IB and IIA. One patient had 2 sentinel nodes located in level IB and 2 further sentinel nodes in level IIA ipsilaterally. The remaining 2 patients with oral cavity carcinoma had sentinel nodes detected only in the level IIA (Tab. 2). There were no unexpected drainage patterns outside the levels that would not have been dissected by elective selective neck dissection. The activity counts of the sentinel lymph nodes measured ex vivo ranged from 120 – 10900 counts/s, the average 2100 counts/s per sentinel node. Overall 40 sentinel lymph nodes were excided. The size of 8 SLN has not exceed 5mm, 23 SLN ranged from 6 to 10 mm, 7 SLN from 11 to 15 mm and 2 SLN were of size more than 15mm. In 12 patients 15 selective neck dissections were performed to remove non-sentinel lymph nodes. In the patient with clinically positive one side of the neck, only the lymph nodes from contralateral neck dissection were counted. A total of 272 non-sentinel lymph nodes were removed, which means 18.4 non-sentinel lymph nodes per selective neck dissection. Nine sentinel nodes were histopathologically positive in 6 patients, but in 2 cases only isolated tumor cells (ITC) were found. In 5 sentinel lymph nodes in 3 patients micrometastases were confirmed. In one patient 3 micrometastases in 3 lymph nodes were found. In 2 sentinel nodes in 2 patients "small" macrometastases were confirmed. Here the limit of metastatic deposit exceeded 2mm for micrometastasis. Occult metastases were found in 4 patients, 33.33 %. There was no metastasis found in any of the non-sentinel lymph nodes in the whole series of 12 patients. Of 9 histopathologically positive SLN six have not exceeded the size of 10 mm (4 SLN with micrometastasis and 2 SLN with ITC only). The remaining 3 positive SLN were of size more than 10mm.

The sentinel node biopsy upstaged one patient from cN0 to pN1(mi)(sn), one patient from cN0 to pN1(sn), one patient from cN0 to pN2b(mi)(sn), and one patient from cN0 to pN2c(mi)(sn). Two patients with isolated tumor cells were upstaged from cN0 to pN0(i+)(sn) (Tab. 2).

In all patients sentinel lymph nodes were detected, and only sentinel nodes were histopathologically positive, which means 100 % sensitivity. In case of negative SLN (6 patients), also the remaining non-sentinel lymph nodes were negative, which means negative predictive value of 100 %.

Discussion

The sentinel node concept states that tumor will spread from the primary site to a single node or group nodes, termed sentinel nodes, before progressing to remainder of the lymph node basin. Sentinel lymph node (SLN) is defined as the first lymph node to receive lymphatic drainage from a primary tumor. There might be more than one SLN for a specific tumor. If lymphatic spread occurs, the sentinel lymph nodes are the first involved. Other nodes should be involved only subsequently. Histopathological evaluation of SLNs then allows accurate prediction of the disease status of the rest of the basin (14, 16, 18, 19).

Accurate radiocolloid injection surrounding the tumor is the basic requirement for correct sentinel lymph node detection (6, 20, 21). The radiocolloid has to adequately reflect lymphatic mapping of the primary tumor. Incorrect radiocolloid application causes, the responsive lymphatic basin not to be depicted, and the identified first node will not be really sentinel. The selection of the radiocolloid in sentinel lymph node radiolocalization is also important. In our work radiocolloid Sentiscint with particle size 100 – 600 nm was injected. The sentinel lymph node detection was successful in all our patients. Because of the high density of the lymphatic vessels in patients with oral and oropharyngeal carcinoma, sentinel lymph node depictions were relatively fast. Mean time was 12.8 minutes, and in patients with oral carcinomas only 2.5 minutes. In a group of 19 patients with oral and oropharyngeal carcinomas after radiocolloid Nanocoll injection, Stoeckli et al (5) reports, that the mean time of sentinel lymph node appearance was 9 minutes (time range, from 3 to 20 minutes). The radiocolloid volume of 1.5–2 ml was sufficient for complete application to surround the tumor

in our series. In total dose of 74MBq (2mCi) 99Tc radioactivity of radiolabeled lymph node ex vivo was in the range 120- 10900 counts/s. Stárek et al (22) measured the sentinel lymph node radioactivity from 200 to 1700 counts/s. after application of 50 MBq Nanocoll. The lower thresholds of the measured radioactivity are still adequate for gamma probe sentinel lymph node detection, since this is still more than three times the counts of the background.

Sentinel lymph nodes in our series were localized in levels IB, IIA and III by lymphoscintigraphy, and perioperatively with a handheld gamma probe. In patients with oropharyngeal carcinomas sentinel nodes were found in the level IIA and in only one patient in the levels IIA and III. In carcinomas close to the midline or over the midline, sentinel nodes were identified bilaterally in level IIA. Despite the fact that SLNB did not reveal drainage to levels that would not have been dissected by elective neck dissection, the advantage of SLNB is assessment of individual lymphatic drainage patterns of each primary tumor (13). In both levels IB and IIA lymph nodes may be too close to the primary tumor, especially level IB in patients with floor of mouth and mobile tongue carcinomas. Despite resection of the primary tumor, the remaining radioactivity from the radiocolloid application site is still considerable. It was possible to measure lymph node radioactivity with changing of gamma probe angle. In this situation it is very important to verify lymph node radioactivity ex vivo. In the patient with carcinoma of the uvula with clinically positive lymph node on one side of the neck, we detected sentinel lymph nodes in the contralateral side. Although metastasis can change the lymphatic flow, the negative finding of the contralateral sentinel node in this case may be beneficial, because patient does not need to undergo elective neck dissection on the contralateral side. Patient can also be saved from higher morbidity of bilateral neck dissections. Despite the sentinel lymph node biopsy is indicated especially for patients with clinically negative necks with intact lymphatic drainage pathways, in case of tumors close to the midline and lymph node metastasis on one side only, this method is useful in the decision to perform bilateral neck dissections (6, 7, 23). This attitude corresponds with currently accepted indications for SLNB in early oral/oropharyngeal squamous cell carcinomas (14, 16).

In our series of 40 excided sentinel lymph nodes 31 (77.5 %) were of size up to 10mm (8 SLN to 5mm, 23 SLN from 6 to 10mm). Four metastases were found in lymph nodes of size up to 10mm. This data supports the criticism that perioperative selection of a lymph node based on macroscopic appearance, which will be sent to frozen-section, is inadequate. Starek et al (22) found 83.9 % sentinel lymph nodes of size up to 10mm (59.7 % SLN of size to 5mm). Stoeckli et al. (5) reported that the mean size of the sentinel lymph nodes was 12mm (from 5 to 20mm). The average number of excided sentinel lymph nodes in our work was 3.3 (from 2 to 5 SLN) per patient. In comparison with Shoaib et al (6) and Starek et al (22), they found the mean number of 2.2 (0 to 6 SLN) and 3.1 SLN per patient. Of 9 histopathoogically positive sentinel nodes, all were among the three hottest nodes. This finding is in concordance with the results of other studies, that three hottest SLNs suffices to predict the neck status (10, 13, 24, 25). Werner et al (10) reported, that histological results of SN1-SN3 reflected the correct stage of metastatic disease in 97 %. If only the lymph node with the highest tracer activity had been excided, 39 % of cancer-positive neck would have been missed.

Only detailed histopathological examination of the sentinel lymph nodes can reflect the status of the regional lymph nodes (16, 26, 27, 28). We performed semiserial sectioning of the sentinel lymph nodes at 200μm intervals with hematoxylin-eosin staining, and the imunohistochemical stain method for cytokeratin. With this method, apart from micrometastases we can reveal also isolated tumor cells. The regional disease was upgraded by the sentinel lymph node biopsy to pN+ in four patients, pN1(mi)(sn), pN2b(mi)(sn), pN2c(mi)(sn) a pN1(sn). Another two patients with isolated tumor cells were subsequently classified as pN0(i+)(sn).

In all 12 patients we were able to identify sentinel lymph nodes by lymphoscintigraphy and perioperatively with the gamma probe. The sentinel lymph node identification accuracy in our small group of patients was 100 %. Our initial good results were achieved by a strict selection of our patients for this method. All our selected patients had primary tumors well accessible for accurate radiocolloid injection.

From the clinical exploitation point of view, sensitivity and negative predictive value of negative SLN are the most important parameters of this method. In our study the only identified sentinel lymph nodes were histopathologically positive. In cases where metastases were not found in remaining lymph nodes of the neck dissection specimen, the sentinel lymph nodes were negative. False negative sentinel lymph nodes were not found. This represents sensitivity and negative predictive value of 100 %.

Due to quality assurance, it is recommended that centers should perform at least 10 cases of SLNB assisted elective neck dissection (END) before using SLNB alone as a staging tool (15). Successful validation against the standard of reference neck dissection with negative predictive value of 100% is encouraging for us and it leads to the introduction of SLNB to our observational clinical practice, when elective neck dissection will be performed only in case of positive SLNB.

Conclusion

Identification of the sentinel lymph node in patients with squamous cell carcinoma of the oral cavity and oropharynx is technically feasible and accurate. High rate of identification and sensitivity of the sentinel lymph node biopsy turn out to be able to detect occult metastases. High accuracy of SLNB and the negative predictive value for negative SLNB in our study in conjunction with the results of other studies proves high reliability of this technique. Therefore SLNB can select patients, who will benefit from elective neck dissection. In patients with N0 neck and negative sentinel lymph node elective neck dissection can be abandoned and morbidity, cost, and time of treatment could be decreased.

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