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A preliminary study on sentinel lymph node biopsy: feasibility and predictive ability in oral cavity cancer

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The main factor that affects the prognosis of patients with head and neck cancer (HNC) is regional lymph node metastases. For this reason, the accurate evaluation of neck metastases is required for neck management. This study investigates the sentinel lymph node identification and the accuracy of the histopathology of the sentinel lymph node in patients with HNC. Eleven patients with histologically proven oral squamous cell carcinoma accessible to radiocolloid injection were enrolled in this study. Using both lymphoscintigraphy and a handheld gamma probe, the sentinel lymph node could be identified in all 11 patients. Subsequently, the sentinel lymph nodes and the neck dissection specimen were examined for lymph node involvement due to tumor. The histopathology of sentinel lymph nodes was consistent with the pathological N classification in all 11 patients. Furthermore, the histopathology of sentinel lymph nodes was superior to physical examination, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scan. The results of this study indicate that sentinel lymph node identification is technically feasible and predicts cervical metastases in patients with oral cavity cancer. This may be a useful diagnostic technique for identifying lymph node disease in staging lymph node dissection.

Key words: sentinel lymph node, head and neck cancer, neck dissection

INTRODUCTION

HEAD AND NECK CANCER (HNC) represents about 6% of all new cancers, and the primary cause of death in patients with HNC is uncontrolled loco-regional disease. Furthermore, survival of patients with HNC has not improved for more than 30 years, remaining at 50% to 60% at 5 years, despite advances in surgical procedures and various combinations of chemotherapeutic agents. The evidence indicates that regional lymph node metastases, the number of lymph nodes involved, location, and extranodal invasion, influence the prognosis of patients with HNC. Therefore if metastases in the regional lymph nodes are diagnosed, a neck dissection procedure should be performed. However, management of clinical N_0 neck in HNC remains controversial. Elective neck dissection, irradiation, and waiting and observing are advocated. Although there have been advances in imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), they are not sufficiently sensitive in detecting occult neck metastases. A wait-and-see approach results in a high proportion of patients subsequently developing late stage regional failure, an adverse prognostic factor. On the other hand, performing neck dissection on all patients with N_0 neck would lead to a high incidence of unnecessary surgery, which may result in functional and/or aesthetic impairment. Approximately 30% of patients with

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Table 1 Profile of patients in this study

Case	Age/Gender	Primary site	TNM classification	Histology*
1	73/M	Tongue	T3N2cM0	SCC (well)
2	68/M	Tongue	T3N0M0	SCC (well)
3	61/M	Tongue	T2N0M0	SCC (well)
4	33/M	Tongue	T2N1M0	SCC (poor)
5	36/M	Tongue	T2N1M0	SCC (mod)
6	68/M	Tongue	T2N1M0	SCC (well)
7	72/F	Tongue	T2N1M0	SCC (well)
8	74/F	Tongue	T2N1M0	SCC (mod)
9	73/F	Tongue	T2N0M0	SCC (mod)
10	65/M	Palate	T2N0M0	SCC (mod)
11	60/M	Oral floor	T2N2bM0	SCC (mod)

* SCC (well), SCC (mod) and SCC (poor), well, moderately and poorly differentiated squamous cell carcinoma

HNC with clinically N_0 neck have occult metastases in the neck, and its risk is especially high for cancers of the oral cavity, oropharynx, and hypopharynx. So far, there have been several studies on what factors are closely related to occult metastases. Tumor thickness, size, location, and vascular invasion have been reported as risk factors for cervical metastases.[1–3] Since these factors are also insufficient for evaluating neck metastases, methods with greater accuracy are required. Recently, the sentinel lymph node concept has been introduced in HNC to evaluate more precisely neck metastases following its successful application in melanoma[4] and breast cancer.[5] The concept is that pathologic evaluation of the first draining lymph node (sentinel lymph node) reflects the stage of regional nodal status, and so patients eligible for neck treatment can be selected more accurately. However, the procedures for identifying the sentinel lymph node and their success rates vary.[6–8] This study aims to 1) map the anatomical site of sentinel lymph node in HNC using radiocolloid alone and 2) determine whether the sentinel lymph node accurately predicts lymph node metastases in patients with HNC. Here we report the feasibility and predictive ability of the sentinel lymph node technique for patients with oral squamous cell carcinoma.

METHODS

Eleven patients with previously untreated oral squamous cell carcinoma (SCC) were enrolled in this study (Table 1). In each case, the malignancy of the primary lesion was diagnosed by histological examination; all of the tumors were SCC, 5 were well differentiated, 5 were moderately differentiated, and 1 was poorly differentiated. Staging of the neck was performed by clinical examination, CT and MRI. The criteria are based on size, shape, and firmness for the physical examination, and on size, central necrosis, and peripheral enhancement for CT and MRI. CT and MRI were evaluated by 2 radiologists. If there were positive findings on these 3 examinations, the lymph nodes were considered as clinically metastatic lymph nodes (N+). Accordingly, the neck was classified as N_0 in 4, N_1 in 5, N_{2b} in 1, and N_{2c} in 1. Moreover, 7 of 11 patients underwent fluorodeoxyglucose (FDG)-PET scan. PET scan was performed 50 minutes after intravenous injection of 5–6 MBq/kg of FDG using whole-body scanner SET 2400W (Shimadzu Co., Japan). FDG uptake in the lymph node with SUV (standardized uptake value) of >2.0 was diagnosed as positive for PET. All the patients were informed about the procedure and consent was obtained.

The methods used for the sentinel lymph node were as follows: The day before surgery, 2 m*l* of [^{99m}Tc] colloidal rhenium sulphide (NACOCIS, CIS bio international, France) with a mean particle size of 100 nm was injected in the submucosa around the tumor lesion, completely encompassing it; namely, 4 injections of equal volume (18.5 MBq/0.5 m*l*) were precisely placed at the peripheral tumor margin. On the morning of surgery, patients underwent lymphoscintigraphy imaging. The time elapsing between injection and lymphoscintigraphy imaging was approximately 13 hours. Anterior and posterior images were obtained with a gamma camera. Figure 1 shows a typical lymphoscintigraphy image identifying 3 nodes in the jugular chain (case 10). Patients were subsequently taken to the operating suite, placed under general anesthesia, and prepared for surgery. Preoperatively, the handheld gamma probe (neo 2000, Neoprobe Co., USA) was used to transcutaneously assess the sentinel lymph node. An incision for the neck dissection was made, and the subplatysmal flaps were raised. The sentinel lymph nodes were then identified with a handheld gamma probe. The identifying nodes with increased radioactivity compared to the background were dissected and individually removed. After removal, the sentinel lymph nodes were confirmed for radioactivity *ex vivo*, and anatomic location and radioactivity levels were then recorded. In this study, radioactivity to background ratio higher than 2 to 3 *in vivo* and higher than 10 *ex vivo* was defined as sentinel lymph node. After sentinel lymph node removal, the lymphatic basin was rechecked for radioactivity. Subsequently,

Table 2 Type of ND, pN classification, and No. of LNs and SLNs per case

Case	Type of ND	pN	No. of LNs examined (metastases)	No. of SLNs found (metastases)
1	Bilateral	2c	28 (7)	6 (5)
2	Bilateral	0	27 (0)	6 (0)
3	Unilateral	0	23 (0)	4 (0)
4	Bilateral	1	53 (1)	4 (1)
5	Bilateral	0	31 (0)	2 (0)
6	Unilateral	0	21 (0)	4 (0)
7	Unilateral	0	25 (0)	3 (0)
8	Bilateral	1	40 (1)	3 (1)
9	Bilateral	0	23 (0)	2 (0)
10	Unilateral	1	36 (1)	4 (1)
11	Bilateral	0	35 (0)	6 (0)
Total	—	—	342 (10)	44 (8)

ND indicates neck dissection; pN, pathologically N; LNs, lymph nodes; and SLNs, sentinel lymph nodes

Table 3 Number of sentinel lymph nodes found by lymph node level and involvement by tumor

LN level	No. of SLNs (n = 11)	pN_0 (n = 7) No. of SLNs	pN+ (n = 4) No. of SLNs (SLNs containing tumor
I	13	8	5 (3)
II	13	6	7 (3)
III	16	11	5 (2)
IV	1	1	0 (0)
V	1	1	0 (0)
Total	44	27	17 (8)

LN indicates lymph node; SLNs, sentinel lymph nodes; pN_0, pathologically N_0; and pN+, pathologically positive nodes

Table 4 Correlation with physical examination and imaging

Case	Physical examination	CT	MRI	FDG-PET	Histopathology of SLN	pN
1	+	+	+*	+	+	+
2	–	–	–	–	–	–
3	–	–	–	ND	–	–
4	+	+	+	ND	+	+
5	+	–	+	–	–	–
6	–	+	+	ND	–	–
7	–	+	+	+	–	–
8	+	+	+	+	+	+
9	–	–	–	–	–	–
10	–	–	–	+	+	+
11	+	+	+	ND	–	–

* MRI could detect only ipsilateral lymph node metastases but not contralateral.

Plus and minus signs indicate positive and negative for metastases, respectively.

SLN indicates sentinel lymph node; pN, pathologically N; and ND, not done.

radical, modified radical, or selective neck dissection was performed. The neck dissection specimen was reevaluated to confirm the removal of all sentinel lymph nodes. Then, extirpation of the primary tumor was performed. In 5 of the 11 patients, extirpation of the primary tumor was performed before neck dissection.

The sentinel lymph nodes and the neck dissection specimen were classified according to the Memorial Sloan-Kettering Cancer Center leveling system of cervical lymph nodes,[9] fixed in 10% neutral buffered formalin and after fixation were bisected through their longest axis. Subsequently, hematoxylin and eosin (H&E) staining of the sentinel lymph nodes and the neck dissection specimen were performed, and one H&E-stained section was prepared from each histologic block and examined for lymph node involvement due to tumor. After this, the histopathological status of the sentinel lymph nodes was compared with that of the remainder of the neck dissection specimen.

RESULTS

A total of 342 lymph nodes, including sentinel lymph nodes, were obtained from neck dissection specimens. Unilateral neck dissection was performed in 4 patients, and bilateral neck dissection in 7 patients. In a total of 18 neck dissections, a radical or modified radical neck dissection was performed in 13 necks, and a supraomohyoid neck dissection in 5 necks. These lymph nodes were examined histopathologically, and 10 of the 342 lymph nodes contained tumor. Seven were classified pathologically as pN_0, 3 pN_1, and 1 pN_{2c}. In all 11 patients, the sentinel lymph nodes were successfully identified and 44 sentinel lymph nodes were found in total. The mean number of sentinel lymph nodes per case was 4.0, ranging from 2 to 6 nodes. Table 2 summarizes the number of lymph nodes examined that contained tumor from the neck dissections, and that of sentinel lymph nodes identified for each case. The anatomical location of lymph nodes containing tumor was in lymph node levels I to III, which is known to be the first echelon lymph node at highest risk for early dissemination by metastatic cancer, from primary tumor in the oral cavity. Sentinel lymph nodes were identified in lymph node levels I to V, and their distribution is summarized in Table 3. Forty-two of the 44 sentinel lymph nodes (95%) were found in lymph node levels I to III. Interestingly, all of the sentinel lymph nodes from patients with pathologically positive nodes (pN+) were identified in lymph node levels I to III. None of the sentinel lymph nodes in 7 patients with pN_0 contained tumor (specificity, 100%), indicating that the sentinel lymph node technique had a negative predictive value of 100% for the absence of neck metastases. On the other hand, seventeen sentinel lymph nodes were obtained in total from the 4 patients with pN+, and 8 of 17 sentinel lymph nodes contained tumor. All of them were

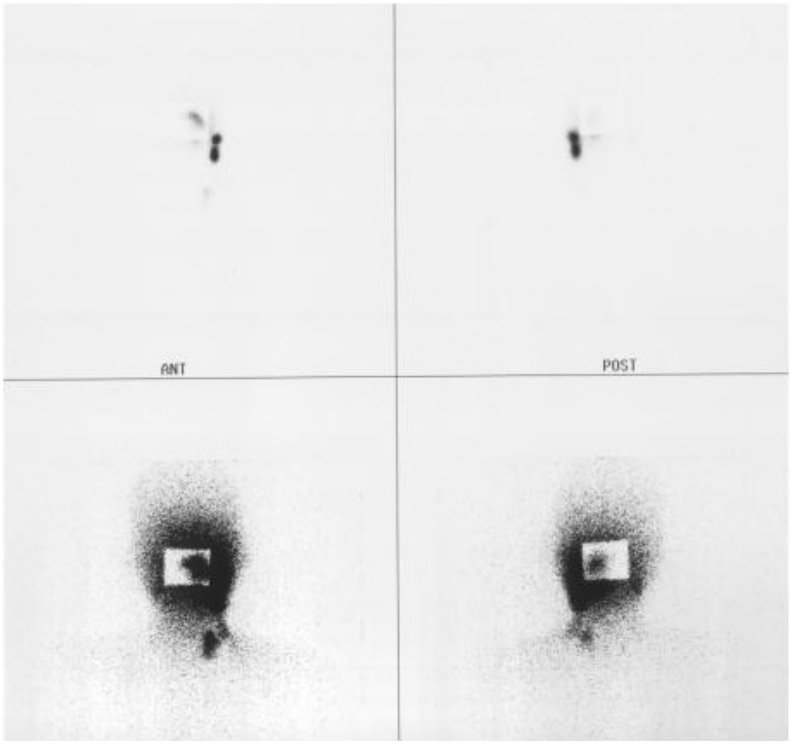

Fig. 1 Lymphoscintigraphy image identifying nodes in the jugular chain (case 10).

found in lymph node levels I to III. The sentinel lymph nodes were the only pathologically positive nodes in 3 of 4 patients with pN+. None of the 11 patients was metastatic disease detected pathologically in the skip levels. In only 1 case, 2 non-sentinel lymph nodes contained tumor in addition to pathologically positive sentinel lymph nodes. This case (case 1) was a patient with a T3 tongue tumor undergoing bilateral neck dissections with palpable lymphadenopathy in the bilateral submandibular region. There was extensive tumor in these palpable lymph nodes. These results suggest that complete replacement by tumor obstructs and changes the lymphatic flow. Even in this case, however, there were no positive lymph nodes in the levels lower than the sentinel lymph nodes.

For staging of the neck, physical examination, CT, MRI and PET were performed, and each patient's stage was assigned by the surgeon according to the TNM staging system before surgery. As shown in Table 4, the physical examination, CT and MRI were carried out in all 11 patients. Five patients were considered to have positive nodes as a result of physical examination, and 4 of the patients proved to have pathologically positive nodes. In the CT and MRI findings, the lymph nodes were considered malignant in 6 and 7 patients, respectively. Pathological examination revealed 3 false positive results and 1 false negative result in CT, 4 false positive and 1 false negative result in MRI, respectively. In case 1, MRI detected only ipsilateral lymph node metastases but not contralateral lymph node metastases. In addition, 7 patients underwent an FDG-PET scan. Interestingly, one pathologically positive node (case 10) was only detected by FDG-PET, but not by the physical examination, CT or MRI. However, FDG-PET still had 1 false positive result (case 7). Thus, these imaging studies were inaccurate in identifying lymph node disease for performing staging lymph node dissection. In contrast, the histopathology of sentinel lymph nodes was consistent with the pathological N classification. Namely, the sentinel lymph node correctly predicted positivity or negativity in all 11 patients.

DISCUSSION

The main factor that affects the prognosis of patients with HNC is regional lymph node metastases. Therefore, accurate evaluation of regional nodal status is essential. However, approximately 30% of patients with clinically N_0 neck have occult metastases of the neck. Since physical examination and imaging techniques are thus unreliable in detecting neck metastases, the sentinel lymph node concept has been introduced. This study demonstrates that the sentinel lymph node concept is a feasible approach in HNC. To date, sentinel lymph node biopsy for head and neck cutaneous melanoma can be performed with a high success rate similar to non-head and neck sites, and is gaining popularity.[10,11] However lymphatic flow related to HNC is different from that to cutaneous head and neck melanoma. In general, lymphatic mapping in HNC is the most difficult because the primary sites are

close to or overlap the lymphatic basin. Moreover, the sentinel lymph nodes are so small that they are difficult to identify. In fact, a number of studies have failed to identify sentinel lymph nodes in HNC. Two materials, blue dye and radiocolloid, have been used to detect sentinel lymph node.[12] The lymphatic mapping technique with blue dye alone has often been unsuccessful as has been reported.[6,12] On the other hand, studies using radiocolloids have very successfully detected sentinel lymph nodes.[13–15] Regarding radiocolloids, several colloids are available whose ability to remain in lymph nodes depends on particle size.[13,16,17] So far, human serum albumin and sulfur colloid have been chosen for use in most studies.[18] In this study, we selected a ^{99m}Tc labeled-rhenium colloid as a radiocolloid, whose particle size is around 100 nm. The radiocolloid was injected around the tumor on the day before surgery, and subsequently lymphoscintigraphy was performed on the day of surgery. The lymphoscintigraphy showed the approximate location of the sentinel lymph nodes (Fig. 1). Subsequent intraoperative use of a handheld gamma probe was useful in identifying the sentinel lymph nodes in all patients. Thus, a combination of preoperative lymphoscintigraphy and the intraoperative use of a handheld gamma probe was successful in identifying the sentinel lymph nodes in a similar way to studies on other groups.[19,20]

Von Buchwald et al. explained that the main difficulties with sentinel node biopsy were related to shine-through and radioactivity scatter.[18] Higher radioactivity from the injection sites often makes identification of sentinel lymph nodes difficult, particularly in level I of the neck. In several studies, therefore, primary tumor extirpation was performed before sentinel lymph node biopsy and/or neck dissection to avoid radioactive interference.[8,21] Shoaib et al. recommended the use of sterilized lead plates for isolating radioactivity from lymph nodes.[12] In our study, the primary tumor and neck specimen was resected separately and simultaneously in 7 and 4 patients, respectively. In the former 7 cases, primary tumor extirpation was performed before neck dissection in 5 patients (cases 3, 7–9 and 11). This procedure was not necessary to identify sentinel lymph node in the other 2 patients (cases 6 and 10). In the latter 4 patients (cases 1, 2, 4 and 5), although primary tumor was removed with a neck dissection specimen en bloc because of the following reconstructive surgery, even their sentinel lymph nodes could be successfully identified. Thus, we could detect sentinel lymph nodes successfully in all patients using both lymphoscintigraphy and the handheld gamma probe. The sentinel node location was predicted approximately by lymphoscintigraphy, and careful direction of the handheld gamma probe was useful in identifying sentinel lymph nodes. Our results suggest that sentinel lymph node identification using radiocolloid is a reliable technique in oral cancer.

In this study, patients with clinical N+ were also enrolled. The inclusion of patients with clinical N+ may be called into question. However, several studies have reported sentinel node biopsy in patients with clinical N+.[12,20] When metastases from a primary tumor are present in the ipsilateral nodes, the management of clinically negative contralateral lymph nodes is another problem similar to management of clinical N_0 neck. Barzan et al. reported sentinel nodes from clinically negative contralateral lymph nodes in patients with clinical N+.[20] Actually, the sentinel lymph nodes were identified in the contralateral lymph nodes in two patients with clinical N+, one of whom had metastatic nodal disease. In 3 of 4 patients with pN+, the sentinel lymph nodes were the only lymph nodes that contained tumor. This result may be a reflection of tumor spread from the sentinel lymph node to a second echelon lymph node at the regional lymph node level draining a specific primary site. In the other 1 patient with bilateral cervical lymphadenopathy classified pN_{2c}, 2 non-sentinel lymph nodes in levels I and II also contained tumor. In this patient, 2 sentinel lymph nodes were involved and were extensively replaced by tumor. Interestingly, these sentinel lymph nodes were located further upstream than the non-sentinel lymph nodes containing tumor. This may be explained by obstruction of lymphatic flow. Thus, sentinel lymph node biopsy in N+ neck may predict the true lymphatic drainage diverted by tumor involvement. This is another possible clinical application of the sentinel lymph node concept.

Most patients with HNC require radiographic evaluation of the nodes for diagnosis. To date, imaging techniques including CT, MRI and PET have been used to evaluate the staging of neck disease. However, their accuracy has been limited. We performed staging of the neck with physical examination, CT, and MRI. In addition, we also estimated the utility of PET in 7 of 11 patients. The correlation between physical examination, these imaging techniques, and the histopathology of the sentinel lymph node was investigated. There were 3 false positive and 1 false negative, and 4 false positive and 1 false negative in CT and MRI, respectively. One false positive was found in PET, a relative new technology, which has been reported as significantly more sensitive than MRI. Civantos et al. have also demonstrated that PET scan is not helpful in detecting occult cervical lymph metastases.[21] In contrast, the histopathology of sentinel lymph nodes was completely consistent with the pathological N classification. Similarly, several studies have demonstrated that sentinel lymph node biopsy is a better diagnostic technique to stage neck disease compared to CT, MRI and PET.[21,22] Thus, our results confirmed the accuracy of sentinel lymph node biopsy for staging neck disease.

In conclusion, sentinel node localization is technically feasible and is predictive of cervical metastasis in patients with oral cavity cancer. The application of the sentinel lymph node concept to managing the neck may be a new

diagnostic technique for improving the prognosis as well as QOL. The results of this study indicate that neck dissection in patients with N_0 neck, which is determined by sentinel lymph node biopsy, can be omitted even if physical examination or imaging is positive for lymph node metastases. This study is currently continuing to provide a large enough sample to determine if this technique provides sufficient specificity and predictive value to determine the presence of neck metastases.

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