Sentinel Node Biopsy for cN0 Oral Squamous Cell Carcinoma

Wu-Chia Lo1,2,3, Shan-Ying Wang4, Po-Wen Cheng2,3, Chi-Te Wang2, Li-Jen Liao2,5

1Department and Graduate Institute of Pathology, College of Medicine, National Taiwan University, Taipei, Taiwan
2Department of Otolaryngology, Far Eastern Memorial Hospital, Taipei, Taiwan
3Oriental Institute of Technology, Taipei, Taiwan
4Department of Nuclear Medicine, Far Eastern Memorial Hospital, Taipei, Taiwan
5Department of Electrical Engineering, Yuan Ze University, Taoyuan, Taiwan

Background: Sentinel node biopsy (SNB) is a potential procedure to change our current management principle of the cN0 neck in head and neck cancer. The aim of this study was to assess the long-term results of sentinel node navigation surgery (SNNS) in a tertiary medical center in Taiwan.

Methods: We conducted a primary prospective study including patients presenting with cN0 oral squamous cell carcinoma (SCC) who underwent SNB or SNNS between January 2013 and March 2014. Detailed procedures of SNB and SNNS are described, and long-term results of the recruited patients are analyzed for patients with positive and negative SNB results.

Results: One female (9%) and ten male patients (91%) were enrolled, and their ages ranged from 37 to 87 years old (mean: 54 ± 11 years) with a median follow-up of 2.3 years. Positive metastatic SNs were discovered in four patients (36%) during the operations. All of the patients with occult metastatic nodes were diagnosed with sentinel lymph node (SLN) mapping. The sensitivity was 100%, and the total operation time ranged from 60 minutes to 300 minutes (median: 120 minutes). The median operation time for negative and positive SNB was 120 min and 280 min, respectively (p < 0.01, Mann-Whitney test).

Conclusions: SNB is a reliable procedure to identify occult neck metastasis for cN0 oral SCC. However, the operation time for SNNS varies from 60 min to 300 min for negative and positive SLNs, respectively. The unpredictable operation time may hinder the intention of the surgeon to perform this procedure.

Key words: cN0 neck, oral cancer, sentinel node biopsy

Background

Malignancy is the leading cause of death in Taiwan. Oral cancer is one of the main cancers, and its incidence is increasing.1 Nodal status is the most important prognostic factor for patients with oral cancer.2 There is a high rate of occult neck metastasis for clinically negative metastatic neck (cN0) oral cancer patients; physical examination and imaging studies are not sufficiently sensitive to guide further management. Up to 20 ~ 30% of cN0 necks harbor occult neck lymph node metastasis and need delayed therapeutic neck dissection.3 Therefore, prophylactic elective neck dissection (END) is suggested for these patients.4 Sentinel node biopsy (SNB) is a potential procedure to change our current management principle of the cN0 neck in patients with head and neck cancer.5 Sentinel lymph node (SLN) assessment has been introduced extensively in melanoma and breast cancer,6,7 and SLN mapping can specifically select...
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SLNs that potentially contain metastases. The SLN is likely to be the first LN to harbor metastasis and can be used to provide information concerning the remaining nodal basin. It is usually identified by the peri-tumoral injection of a radioactive colloid or blue dye. Preoperative lymphoscintigraphy and intra-operative radionuclide detection with a gamma probe or visualization of blue coloration allows the identification of the SLN. After surgical removal of SLNs, these nodes can be studied meticulously using serial step sectioning for full histopathological assessment. The pattern of nodal metastasis is further classified as isolated tumor cells, micrometastasis (< 2 mm) and macrometastasis (≥ 2 mm).

If the SLN contains metastatic tumor cells, treatment of the neck at the same time or sometimes in a second procedure is therefore recommended. The SNB procedure might be more accurate than other imaging studies, and it is less invasive than END. Furthermore, it is associated with significantly less postoperative morbidity and better shoulder function than END.

With a portable detector, SLN(s) can be identified during operation. According to literature reports, SNB has a very high potential to change current management policy for the cN0 neck. There have been limited studies reported in Taiwan, and the long-term results were not described. The aim of this study was to assess the long-term results of SNB in a tertiary medical center in Taiwan.

Material and Methods

Patient selection

We conducted a primary prospective study including patients presenting with early oral squamous cell carcinoma (SCC) and who underwent SNB between January 2013 and March 2014. All of the patients were investigated and treated at the Department of Otolaryngology Head and Neck Surgery in the Far Eastern Memorial Hospital. The patients presenting with pathologically proven oral SCC and cN0 necks were eligible for the study. Patients who had previously treated head and neck malignancies were excluded.

Sentinel node navigation surgery (SNNS)

Preoperative dynamic lymphoscintigraphy

In the morning of the operation day, four sub-mucosal injections of Tc99m-labeled rhenium sulfur colloid were administered around the cancerous lesion 0.5 cm from its periphery. Two-percent xylocaine was used as local anesthesia to prevent any associated pain or discomfort before the injections. A total dosage of 60 MBq (4 × 15 MBq) was used for dynamic lymphoscintigraphy (DLS) (Fig. 1). At the time point of 60 min to 2 hrs after the injection of the radioactive colloid, DLS was performed to localize the SLN. Lymphoscintigraphy and single-photon emission computed tomography (SPECT) imaging were combined for detailed lymphatic mapping.

Intra-operative SNB surgical technique

In the operating room, a handheld gamma probe (Navigator GPS; Tyco Health care, Mansfield, MA, USA) was used to localize the SLN(s) (Fig. 2A). The skin incision was designed as part of a comprehensive ND incision. The dissection extended down to the deep cervical tissues with the guidance of a gamma probe. Important measurements included the in vivo (Fig. 2A) identification of presumed SLN and ex vivo (Fig. 2B) detection of radioactivity after nodal excision. These crucial measurements allowed us to confirm that the initially identified SLN(s) were removed and that there were no other SLN(s) remaining within the neck. The identified SLN(s) were sent for frozen pathology. If any SLN was positive for metastasis, END of levels I, II, and III were performed. After addressing the neck, the primary tumor was removed using an oral approach. In the cases of SLN(s) with negative metastasis, the neck wound was closed without further END.

Histopathological protocol and further management

The SLN(s) and entire neck dissection specimens were analyzed according to a standardized protocol. Frozen sections of all of the nodes were obtained for a timely diagnosis; next, routine analyses were performed on paraffin-embedded, formalin-fixed samples. The SLN(s) were sent for serial 150-μm step sectioning, with both hematoxylin-eosin (HE) staining and anti-cytokeratin immunohistochemistry (IHC). When a positive node was demonstrated on a frozen section, END was completed. The indication for adjuvant radiation therapy (RT) depended on the final pathological findings. The patients were followed up at our out-patient clinic, and they underwent an ultrasound examination of the neck every two months.
Fig. 1. Preoperative dynamic lymphoscintigraphy. Pre-operative fusion image of SPECT together with lymphoscintigram for case 2 showing the injection site (large white area) and SN at the left upper neck (marked with red arrows) (Table 1, Case 2).

Fig. 2. Case presentation during operation. Forty-five-year old male patient with left buccal cancer (Table 1, Case 2) with a clinical T2 lesion. No obvious palpable neck mass before the operation was noted. The sentinel node was identified with a portable gamma probe and marked over the skin pre-operatively. The SNs were identified in vivo with a portable gamma probe (A) and were confirmed ex vivo (B).
Statistical analysis

We expressed the variables as numbers (%) or means ± SD and performed the Mann-Whitney test. The survival time was measured from the beginning of the diagnosis to the date of death or last follow-up visit. The end point was classified as death or recurrence and was calculated as overall survival (OS) and disease-specific survival (DSS). We used Kaplan-Meier survival curves with log-rank tests to show different survivals between positive and negative SLN patients. Corresponding \( p \) values < 0.05 were interpreted as being statistically significant. All of the statistical analyses were accomplished using Stata software, version 12.0 (Stata Corp. LP, College Station, TX).

Results

Between June 2013 and March 2014, the study group consisted of a total of eleven consecutive newly diagnosed oral cavity patients. One female patient (9%) and ten male patients (91%) were enrolled, and their ages ranged from 37 to 87 years old (mean: 54 ± 11 years). The primary sites were the tongue in six cases, the cheek mucosa in three cases, the lower lip in one case and the lower gum in one case. No obvious palpable neck mass was identified in any of the patients before surgery. In addition, no definite metastatic lymphadenopathy was noted upon MRI or CT examination.

Result of sentinel node navigation surgery

DLS was performed on all of the patients. The first node exhibiting radioactivity based on the Tc99-sulfur radioactive colloid was identified as an SLN. One to three SLNs with a mean of two nodes per patient were removed. At least one SLN was identified in all of the patients (100%). All of the sentinel nodes were located at level I ~ level III. Table 1 summarizes the demographic data and SLN distribution of these eleven cases. The SLNs were located at level I in three cases, level II in seven cases and level III in one case. Positive metastatic SNs were discovered in four patients (36%) during the operations. In these four positive metastatic SLN patients, formal END (level I, II & III) was performed. The positive SNLs were located at level I in one case and level II in three cases, and the cases were upstaged to the nodal positive stage after surgery. Post-operative concurrent chemoradiotherapy of the neck was administered in three of these four patients. However, two patients (cases 2 and 3) had lung metastasis six to ten months after surgery. In the remaining seven patients, only an SNB procedure was performed on the neck. All of the patients with occult metastatic nodes were diagnosed with SLN mapping. Therefore, the sensitivity was 100%.

Sentinel node biopsy wounds are much smaller than those of elective neck dissection (Fig. 3), and the patients had less neck soreness and no arm weakness complications. However, the total operation time ranged from 60 min to 300 min (median: 120 min). The median operation time for negative and positive SLNs were 120 min and 280 min, respectively (\( p < 0.01; \) Mann-Whitney test).

Long-term results of recruited patients

The follow-up time ranged from one year to 3.5 years with a median of 2.3 years. Table 1 shows that there were four cases with SLN metastasis, and specimens from the four elective neck dissections revealed only one additional metastatic LN (case 3). A total of seven positive SLNs was identified by pathological reports (Table 1), and six of the seven SLNs exhibited extra-capsular spread. Two regional recurrences (cases 6 and 11) occurred one year later. Both of them had positive SLNs and received selective neck dissection at that time. One (case 6) of the two patients refused post-operative radiotherapy, and he died three years later. The other patient (case 11) received post-operative concurrent chemo-radiotherapy. However, rapid neck out-field recurrence occurred. He received salvage neck dissection and is still alive today. In this case, whole LNs including SLNs were rechecked by a pathologist (Dr. Juang J.-Y.), and no obvious micrometastases were identified in the other sixteen nodes at the time of initial neck dissection.

Two patients (cases 2 and 3) had distant lung metastasis approximately one year after the operation; they were both positive for SLN metastasis, and both patients died without local or regional recurrence. SLN-positive patients had significantly poorer disease-specific survival than SLN negative patients (\( p = 0.02 \)) (Fig. 4), but there was no significant difference (\( p = 0.21 \)) in overall survival.

Discussion

SLNs are the first lymph nodes to receive drain-
<table>
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<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
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<th>Side of ND</th>
<th>cT</th>
<th>SNL</th>
<th>SNR</th>
<th>SN+</th>
<th>Pathology</th>
<th>PNI</th>
<th>LVI</th>
<th>Death</th>
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<td>–</td>
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<tr>
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<td>M</td>
<td>Buccal</td>
<td>L</td>
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<td>0</td>
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<td>(0/8)</td>
<td>+</td>
<td>+</td>
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<td>0</td>
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<td>L</td>
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<td>3</td>
<td>0</td>
<td>3†</td>
<td>(1/24)</td>
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</table>

Abbreviations: ND: neck dissection; SNL: SN over left neck; SNR: SN over right neck; SN+: positive metastatic SN; L: left; B: bilateral; OP: operation; PNI: perineural invasion; LVI: lymphovascular invasion.

*Demonstrated case; †extracapsular spread.
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age from a primary tumor. If SLNs are negative, then the other lymph nodes are thought to be free of cancer. SLN mapping can help us to detect microscopic disease before it becomes clinically apparent. In the scenario of occult metastasis in lymph nodes, it can be detected by SLN mapping and treated before delayed regional recurrence after obvious metastatic transformation.

The name SNNS was first reported by Yamauchi et al. (2012) and referred to patients who underwent neck dissection only if SLNs were positive for metastasis. Otherwise, the patients received watchful waiting management to the neck. SNNS has become the standard procedure for cT1/2N0 oropharyngeal SCC in their institution.

Perineural invasion (PNI) or lymphovascular invasion (LVI) was reported as aggressive determinants for neck lymph node metastasis. We also found these pathologic parameters were related to neck lymph metastasis (Table 1). Three in the four positive SLNs patients (75%) revealed positive LVI and none in the seven negative SNLs showed positive LVI ($p < 0.01$, Fisher exact test). Two in the four positive SLNs patients (50%) revealed positive PNI and two in the seven negative SLNs patients (29%) showed positive PNI ($p > 0.05$). The extracapsular spread of positive lymph nodes is an important prognostic factor. In the present study, six of the seven positive SLNs had extracapsular spread. This is one major reason why prophylactic neck dissection has an advantage over watchful waiting in terms of regional control. For SNNS, most positive metastatic nodes could be identified, and END would be performed subsequently; however, in most patients with negative SNLs, unnecessary neck dissection can be avoided.

In our study, all of the patients with occult metastatic node were diagnosed with SLN mapping. Therefore, the sensitivity was 100%. According to Weiss et al.’s suggestion, if the NPV is approximately 80%, indicating that the probability of occult cervical metastasis is less than 20%, a watchful waiting management approach is favored. Thus, SNNS seems highly feasible in clinical practice.

The SNNS offers another type of staging method for cN0 patients. The disease-specific survival in SLN-positive patients was much poorer than that in SLN-negative patients. SNNS can reduce the incidence of adverse events resulting from functional and cosmetic morbidities associated with routine neck dissection. However, the operation time varied from 60 min for negative SLN and 300 min for positive SLN. The unpredictable operation time may hinder the intention of the surgeon to perform SNNS. Hiraki et al. proposed only performing the sentinel node biopsy procedure for cN0 neck without prophylactic neck dissection. The survival was also better without neck dissection than for the watchful waiting group. On average, 2.1 SLNs were removed, and the time required to remove one SLN was 9.2 minutes. Only one of the four ENDs (72 lymph nodes) had positive metastasis.

Fig. 3. Post-operative view of the SNNS is shown, a small scar approximately 3 cm after sentinel node biopsy was identified.

Fig. 4. SLN-positive patients (SNB meta+) had significantly poorer disease-specific survival than SLN negative patients (SNB-; $p = 0.02$).
in our patients. Sentinel node biopsy without END may be an alternative to SNNS.

Our study still has some limitations. First, the case number is limited. Second, the follow-up time is not sufficiently long. Third, two T3 lesions were included, which may lead to poor survival in our recruited patients. Fourth, we did not have a patient with mouth floor cancer, which was reported to be more technically demanding. 19

Conclusions

SNB is a reliable procedure to identify occult neck metastasis for cN0 oral SCC. However, the operation time for SNNS varies from 60 min to 300 min for negative and positive SLNs. The unpredictable operation time may hinder the intention of the surgeon to perform this procedure.

Acknowledgment

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References


