早期口腔扁平上皮癌頸部リンパ節転移診断として用いたセンチネルリンパ節生検の予後

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要約：われわれは不必要な頚部郭清を施行しないことを目的として、早期口腔扁平上皮癌 N0 症例に対してセンチネルリンパ節生検法を用いて頚部リンパ節転移の有無を診断した。

（方法）2007 年から 2013 年までに当科において臨床病期がⅠ期もしくはⅡ期口腔扁平上皮癌患者 38 症例のうち 2 年以上の経過観察が可能であった 38 症例を対象とした。SLN の同定法としては、手術前日に RI を注入後シンチグラフィーにて SLN の位置と個数の目安を決定し、手術当日はガンマプローブを使用し SLN を同定摘出し、術中迅速病理診断により転移の有無を確定させた。

術後の経過観察は、CT, MRI, US, PET-CT による定期的な画像診断と視診、触診によって行われた。

（結果）SLN 同定率は 100%であった。SNB が陽性であった症例は 4/38 例（10.5%）であり根治的頚部郭清術が施行された。SNB が陰性であった症例は 34/38 例（89.5%）であり原発巣のみ切除された。局所再発を認めた症例は 6/38 症例（15.7%）であった。局所再発を認めなかった症例は 32 症例で、そのうち 4 症例に後発リンパ節転移を認めた。5 年全生存率は SNB 陽性症例で 75%、SNB 陰性症例 89.3%であった。

（結論）口腔扁平上皮癌においてセンチネルリンパ節生検は、不必要な頚部郭清を回避するのに有用である。

Abstract：Background: In early oral squamous cell carcinoma (SCC), neck dissection may be avoided by diagnosis of lymph node metastasis using sentinel lymph node (SLN) biopsy (SNB).

Methods: The subjects were 38 patients with stage I or II oral SCC and postoperative follow-up for > 2 years.  SLNs were identified by scintigraphy on the day before surgery.  During surgery, SLNs were excised and metastasis was evaluated in intraoperative frozen sections.

Results: The SLN detection rate was 100%.  Four SNB-positive cases underwent radical neck dissection and 34 SNB-negative cases underwent primary tumor resection.  Six cases had local recurrence.  Of 29 SNB-negative cases without local recurrence, 3 had secondary cervical lymph node metastasis.  Three-year overall survival rates were 75% and 89.3% in SNB-positive and SNB-negative cases, respectively.

Conclusion: The SNB contributed to avoid unnecessary neck dissection in oral SCC.

Key words：oral squamous cell carcinoma（口腔扁平上皮癌）、metastasis（転移）、prognosis（予後）、sentinel lymph node（センチネルリンパ節）
Introduction

The N status is important as a determinant of prognosis of oral squamous cell carcinoma (SCC). There are frequent reports of cases without cervical lymph node metastasis that are treated with neck dissection, but 75–80% of neck dissections performed in N0 cases are overtreatment\(^1,2\) and disorders after neck dissection may be serious and produce new morbidity\(^3\). A wait-and-see policy can be chosen, but the prognosis after secondary cervical lymph node metastasis is poorer than that after neck dissection as initial treatment. The efficacy of sentinel lymph node (SLN) biopsy (SNB) in head and neck cancer was reported about 20 years ago and may solve this dilemma\(^4-7\). Many reports show that SNB-positive patients present with cervical metastasis, but it is difficult to prove that SNB-negative patients do not have cervical lymph node metastasis\(^8\), since these patients do not undergo neck dissection. Thus, long-term follow-up of SNB-negative patients is needed to prove the absence of cervical metastatic lymph nodes through investigation of secondary cervical lymph node metastases, almost all of which occur within two years in oral SCC\(^9,10\). In this study, we describe the long-term courses of cases of stage I or II N0 oral SCC after SNB.

Patients and Methods

The subjects were 38 patients with oral SCC in clinical stage I or II treated in our department from 2007 to 2013 who underwent SNB and for whom follow-up was possible for at least 2 years. The characteristics of the patients are shown in Table 1. The clinical stage was determined on CT, MRI, palpation. \(^{99m}\)Tc phytic acid (5 mCi) was injected in four places around the primary tumor on the day before surgery. The number and positions of SLNs were detected in Radio Isotope (RI) scintigraphy performed 3 to 4 hours later for treatment planning. SLNs detected at > 18.5 MBq using a gamma probe on the day of surgery were resected and the presence of metastasis was confirmed in intraoperative frozen section analysis. In this analysis, tissue was embedded with O.C.T Compound and frozen with liquid nitrogen, followed by preparation of 5-\(\mu\)m sections with a cryostat and staining with hematoxylin and eosin. Frozen section was evaluated for serial sections (about 15–20 sections). The remaining sample was fixed in 10% buffered formalin and submitted for paraffin sections. Immunohistochemistry and special stains were not performed. Ocular inspection, palpation, and follow-up by periodic Computed Tomography (CT), Magnetic resonance imaging (MRI), Ultrasonography (US) and Positron Emission Tomography CT (PET-CT) was performed postoperatively. We diagnosed as metastatic lymph node when imaged central necrosis by CT, MRI. We diagnosed lymph node metastasis to CT, MRI and US with long diameter exceeding 10mm or more\(^11,12\) and with central necrosis image and with abnormal accumulation by PET-CT. The mean observation periods after surgery were 56 months (range, 21–96 months) for all cases and 52 months (range, 14–96 months) for survival cases. Survival curves were analyzed by the Kaplan-Meier method. The study protocol was approved by the Research Ethics Committees of University of Miyazaki Hospital (approved No, 2014-107).

Results

The positions of SLN were correctly identified by RI scintigraphy following injection of \(^{99m}\)Tc phytic acid (5 mCi) in all 38 cases, and there was no case in which SLNs could not be resected during surgery. An average of 2.6 SLNs were resected in each case (range, 1–5), giving 100 resected SLNs in total. The SLN sites were at levels I (n = 68 SLNs, 68%), II (n = 29, 29%), III (n = 2, 2%) and IV (n = 1, 1%) (Table 2). Intraoperative frozen section analysis of SNB samples and the definitive pathological diagnosis were consistent in all cases.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients (%)</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (68)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (32)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>40–87</td>
</tr>
<tr>
<td>Mean</td>
<td>68.7</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
</tr>
<tr>
<td>Tongue</td>
<td>25 (66)</td>
</tr>
<tr>
<td>Lower gingiva</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>14 (37)</td>
</tr>
<tr>
<td>II</td>
<td>24 (63)</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
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Table 1 Clinical characteristics of patients (n = 38)
Four of the 38 cases were SNB-positive (10.5%), including 2 T1 cases and 2 T2 cases. Radical neck dissection was performed in all 4 cases. In the 34 SNB-negative cases (89.5%), neck dissection was not performed and only the primary tumor was resected. Local recurrence occurred in 6 of the 38 cases (15.7%), including 1 SNB-positive case and 5 SNB-negative cases. Of these 6 patients, 3 underwent re-excision only, 2 received neck dissection and re-excision, and 1 patient received re-excision and chemotherapy with cisplatin, docetaxel, and 5-FU. The single SNB-positive case with local recurrence was among the 3 patients in whom only re-excision was performed. Death occurred in the 2 cases that underwent re-excision and neck dissection, but the other 4 patients are doing well to date.

There was no local recurrence in 32 of the 38 cases (84.3%), but 4 of these 32 cases (12.5%) showed secondary cervical lymph node metastases and cervical recurrence (Fig. 1). These cases comprised 3 T1 cases and 1 T2 case, and included one SNB-positive case. The secondary cervical lymph node metastases occurred 6, 10, 13, and 21 months after SNB, respectively and were treated by radical neck dissection (1 case), radical neck dissection and postoperative adjuvant radiotherapy (1 case), and chemoradiotherapy (2 cases).

Table 2 Location of SLNs

<table>
<thead>
<tr>
<th>Level</th>
<th>Number of lymph nodes (%)</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>68 (68)</td>
</tr>
<tr>
<td>II</td>
<td>29 (29)</td>
</tr>
<tr>
<td>III</td>
<td>2 (2)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>100 (100)</td>
</tr>
</tbody>
</table>

Of the 29 SNB-negative cases without local recurrence, 3 (10.3%) had secondary cervical lymph node metastases at primary sites of the tongue (2 cases) and the floor of the mouth (1 case). The lymph node site of secondary cervical lymph node metastases agreed with the location of the SLN in 1 case, but was mismatched in 2 cases. For prediction of secondary cervical lymph node metastases, the sensitivity of SNB was 50%, the negative predictive value (NPV) was 89.7%, the false negative rate was 10.4%.

The 3-year overall survival (OS) and disease-free survival (DFS) rates were both 75% in SNB-positive cases and were 89.3% and 93.1%, respectively, in SNB-negative cases (Fig. 2), with no significant difference between these groups.

Discussion

Neck dissection for N0 cases of early oral SCC is performed for the purpose of resection of latent lymph node metastases. However, the rate of these metastases is only about 20%, and thus 80% of patients undergo unnecessary neck dissection\(^\text{13-15}\). It is difficult to detect latent lymph node metastases in CT, MRI, US, and PET-CT\(^\text{16}\). In contrast, SNB is useful in determining whether neck dissection is necessary\(^\text{17}\), with a 100% accuracy for detection of SLNs in oral cancer and a 94% NPV in oral SCC over a follow-up period of about two years\(^\text{18}\).

The current study was performed as a retrospective analysis in 38 cases of N0 early oral SCC to determine the efficacy of SNB for avoiding unnecessary neck dissection. The SLN detection rate was 100%. Additional treatment was provided upon recognition of recurrence and metastasis in all cases. The recurrence rate was 15.7% in follow-up of at least 2 years, which is consistent with the expected rate of recurrence in cases that did not receive adjuvant therapy such as radio-

Fig. 1 Outcomes of SNB-positive and SNB-negative patients with oral squamous cell carcinoma (SCC).
therapy, even with a closed margin. Positive rate of SNB was 10.5% (4/38 cases) is lower than the report of the past large-scale investigation\textsuperscript{18,19}, but it might be selected carefully N (+) cases diagnosed because we perform imaging studies (cystography CT, cystography MRI, US, PET-CT) more than these reports preoperatively. The positive predictive value was 100% in SNB-positive cases and radical neck dissection was performed in all these cases. Imaging studies at other institutions for preoperative diagnosis show a tendency for a moderately low SNB-positive rate because of prior diagnosis of N (+). Also, lymph node dissection in a N (+) case might cause tumor dissemination and result in a requirement for radical neck dissection in SNB-positive cases. Postoperatively, cervical recurrence at level Ⅳ was found in one SNB-positive case and this patient died due to the tumor. Secondary cervical lymph node metastases occurred in 3 of 29 SNB-negative cases without local recurrence, giving a NPV of 89.7% for SNB. Francisco et al. found a similar NPV of 94% using a similar approach\textsuperscript{20}. SLN has been most often detected at level I. However since SLN of most cases detected at both level I and Ⅱ, there was no SLN detection at inappropriate sites. Since secondary cervical lymph node metastasis in the 3 cases occurred less than two years after SNB, and thus latent lymph node metastases may originally have been present. The metastatic sites were at a SLN site found in SNB in 1 case, indicating mistaken identification of the SLN, but at other sites in 2 cases.

The primary sites of secondary cervical lymph node metastasis were the tongue in 2 cases and the floor of the mouth in 1 case. Given these sites, the presence of interpositional lymph nodes should be considered\textsuperscript{21}.

Metastasis to interpositional lymph nodes is referred to as lateral lingual lymph node metastasis of tongue cancer or submandibular lymph node metastasis of mouth floor cancer, and occurs when cervical lymph node metastasis does not go through level Ⅰ or Ⅱ\textsuperscript{22}. The 2 cases with metastasis at sites different to those detected in SNB had metastases at level Ⅲ or Ⅳ, rather than Ⅰ or Ⅱ, and may have been initially present as latent lymph node metastases to interpositional lymph nodes. Treatment of metastasis to interpositional lymph nodes in oral SCC requires a pull-through operation in simultaneous resection of the neck and primary tumor\textsuperscript{23,24}, and it is necessary to identify SLNs before resection of the primary tumor when interpositional lymph nodes are identified in SNB. However, these lymph nodes are present around the tongue and floor of the mouth, and identification is difficult due to shine through using a conventional tracer, which may explain the failure to identify these SLNs. This may be solved by inserting a lead board in the oral cavity in a scintigraphy scan, but a complete solution to shine through is still required. Thus, there is still a risk of misdiagnosis in rapid perioperative pathological diagnosis of a SLN.

Immunohistological and hematoxylin & eosin staining are usually used for diagnosis of cervical lymph node metastasis\textsuperscript{25,26}. The precision of the common perioperative pathological diagnosis is reported more than 85%\textsuperscript{27}. However, latent lymph node metastases are micrometastases that can be difficult to diagnose using intraoperative frozen section analysis. Furthermore, the precision of diagnosis falls without Immunohistochemistry. Tsujimoto et al. and Visser et al. made a metastatic diagnosis by the OSNA method using CK19 in
breast cancer\textsuperscript{28, 29}. The OSNA method using CK19 can also be used in SNB of oral SCC, but is not as accurate as pathological diagnosis\textsuperscript{30}. However, Goda et al. found improved accuracy using the OSNA method with inclusion of multiple gene expression levels, together with CK19\textsuperscript{31}. Thus, a continuing goal of pathological diagnosis is to establish a procedure that avoids overlooking micrometastasis.

In this study, we were able to avoid unnecessary neck dissection in about 90% of cases, due to SNB. Previous reports have also shown no severe problems after SNB, and these past and current findings indicate that this biopsy is effective and contributes to improvement of the quality of life of patients. We note that Leusink et al. suggested that genetic analysis of mRNA extracted from biopsy tissue of the primary tumor can be used to determine the need to perform SNB\textsuperscript{32}. Thus, selection of patients who should undergo SNB may also be possible, and this has the potential to further reduce the burden on patients.

Conflict of interest

The authors have declared no conflicts of interest.

Reference

26) Lentz, S.E., Muderspach, L.L., Felix, J.C., et al.: Identification of micrometastases in histologically negative lymph nodes