MANAGEMENT OF CONTRALATERAL N0 NECK IN ORAL CAVITY SQUAMOUS CELL CARCINOMA

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Accepted 23 December 2005
Published online 23 May 2006 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20423

Abstract: Background. The purpose of this study was to evaluate the incidence and predictive factors of contralateral occult lymph node metastasis in squamous cell carcinomas of the oral cavity to form a rational basis for elective contralateral neck management.

Methods. We performed a retrospective analysis of 66 patients with cancer of the N0–2 oral cavity undergoing elective neck dissection for contralaterally clinically negative necks from 1991 to 2003.

Results. Clinically negative but pathologically positive contralateral lymph nodes occurred in 11% (7 of 66). Of the 11 cases with a clinically positive ipsilateral node neck, contralateral occult lymph node metastases developed in 36% (4 of 11), in contrast with 5% (3 of 55) in the cases with clinically N0 ipsilateral necks (p < .05). Based on the clinical staging of the tumor, 8% (3 of 37) of the cases showed lymph node metastases in T2 tumors, 25% (2 of 8) in T3, and 18% (2 of 11) in T4. None of the T1 tumors (10 cases) had pathologically positive lymph nodes. The rate of contralateral occult neck metastasis was significantly higher in advanced-stage cases and those crossing the midline, compared with early-stage or unilateral lesions (p < .05).

Patients with no evidence of contralateral nodal cancer had significantly improved disease-specific survival over patients with any pathologically positive nodes (5-year disease-specific survival rate was 79% vs. 43%, p < .05).

Conclusions. The risk of contralateral occult neck involvement in the oral cavity squamous cell carcinomas above the T3 classification or those crossing the midline with unilateral metastases was high, and patients who presented with a contralateral metastatic neck had a worse prognosis than those whose disease was staged as N0. Therefore, we advocate an elective contralateral neck treatment with surgery or radiotherapy in patients with oral cavity squamous cell carcinoma with ipsilateral node metastases or tumors, or both, whose disease is greater than T3 or crossing the midline. ©2006 Wiley Periodicals, Inc. Head Neck 28: 896–901, 2006

Keywords: oral cavity squamous cell carcinoma; contralateral N0 neck; elective neck management

Squamous cell carcinoma (SCC) of the oral cavity has a high propensity for nodal metastasis in the neck, and such cervical metastasis is an important prognostic factor.1 In a retrospective study of 891 patients with oral cavity SCC, Layland et al2 reported that the disease-specific survival rate for patients with N0 disease was 58.7%, compared with 39.4% for patients with N+ disease, and that patients with nodal disease had significantly worse 5-year disease-specific survival rates than did patients with N0 disease.
In addition, the presence or absence of occult lymph nodes is 1 of the major prognostic factors for survival in patients with clinically negative cervical lymph nodes. The incidence of occult disease ranges from 21% to 42%. Numerous retrospective studies have supported the role of elective neck dissection in N0 oral cavity SCC in affecting the rate of regional recurrence, even though the procedure does not necessarily provide an absolute survival benefit. Therefore, an elective ipsilateral neck treatment is generally recommended for initial treatment in all oral cavity SCC, except for very early or superficial lesions.

However, few studies have assessed accurate histopathologic information for contralateral N0 neck, and thus no consensus has been reached about the need for elective contralateral neck treatment, despite that contralateral neck node metastasis, apart from ipsilateral neck node involvement, is also related to an extremely poor prognosis.

The purpose of this study was to evaluate the incidence of contralateral occult lymph node metastasis and analyze the factors that predict contralateral occult lymph node metastasis in oral cavity SCC to form a rational basis for elective contralateral neck management.

**MATERIALS AND METHODS**

**Patients and Tumor Characteristics.** Clinical, pathologic, and therapeutic data were reviewed from the medical records of 173 consecutive patients with newly diagnosed oral cavity SCC who were referred to the Department of Otorhinolaryngology, Yonsei University, Severance Hospital, Seoul, Korea, from January 1991 to May 2003. Of these, the cases that satisfied the following criteria were included: (1) patients with histopathologically proven SCC, (2) patients who had not previously received any treatment for head and neck tumors, (3) patients who had curative surgery as their initial treatment, and (4) patients who underwent a contralateral elective neck dissection for the clinically N0 contralateral neck. Exclusion criteria for this study included: (1) preoperative radiotherapy or neoadjuvant chemotherapy to the oral cavity region, (2) bilateral therapeutic neck dissection for clinically bilateral positive neck nodes, (3) proven distant metastasis at presentation, (4) presence of other simultaneous primary tumors at the time of admission, and (5) patients whose contralateral necks were observed without contralateral elective neck dissection for the clinically N0 contralateral neck. Consequently, the remaining 66 patients with clinically N0 contralateral neck who received prophylactic contralateral elective neck dissections were enrolled in this study.

All patients were preoperatively determined to have a clinically N0 contralateral neck by physical examination and either a CT scan or MRI. The clinically N0 neck was defined as having no cervical lymph nodes palpated on physical examination and findings on imaging studies that correlated with Mancuso’s criteria for benign nodes. The stage was determined according to the guidelines from the American Joint Committee on Cancer (AJCC) (2002).

The study included 52 men and 14 women, ranging in age from 20 to 72 years (median, 53 years). The primary sites were the mobile tongue in 41 patients, the floor of the mouth in 18, the gingiva or alveolar ridge in 4, the retromolar trigone in 2, and the buccal mucosa in 1. The clinical T classifications of the primary lesions were as follows: 10 T1, 37 T2, 8 T3, and 11 T4. The number of patients with a clinical N0, N1, N2a, N2b, and N3 disease was 55, 6, 2, 3, and 0, respectively (Table 1).

**Treatment and Reconstruction of the Primary Lesion.** For resection of the primary tumor, the following surgical procedures were performed: 7 wide excisions via transoral approach, 30 via paramedian mandibulotomy, 25 via pull-through approach, 2 via visor flap, and 2 via lower cheek flap. For reconstruction of the defective areas, a forearm free flap was used in 48 cases, a pectoralis myocutaneous flap in 4 cases, a lateral thigh free flap in 3 cases, a rectus abdominis free flap in 2 cases, a fibular osseocutaneous free flap in 2 cases, a local flap in 1 case, and secondary healing in 6 cases.

**Treatment of Cervical Lymph Nodes.** Among the 11 cases in which ipsilateral cervical lymph node metastasis was suspected, radical neck dissection, modified radical neck dissection, or supraomohyoid neck dissection were performed in 4, 5, and 2 cases, respectively. For the 55 cases in which ipsilateral cervical lymph node metastasis was not suspected, supraomohyoid neck dissection was performed in 54 patients for the ipsilateral neck; there was also 1 case of modified radical neck dissection. For the all contralateral N0 necks, supraomohyoid neck dissection was performed.
**Table 1.** Clinical staging for contralateral elective neck dissection patients (n = 66).

<table>
<thead>
<tr>
<th>cT</th>
<th>N0</th>
<th>N1</th>
<th>N2a</th>
<th>N2b</th>
<th>N3</th>
<th>Total no. of patients</th>
</tr>
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<tbody>
<tr>
<td>T1</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>T2</td>
<td>29</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>T3</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>T4</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>66</td>
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</tbody>
</table>

**Postoperative Radiotherapy.** Among the 66 patients, 35, in whom pathologic multiple lymph node metastases or a positive surgical margin was observed, were selected to undergo postoperative radiotherapy, whereas the other 31 patients did not receive any further treatment. Indications of postoperative radiotherapy in this patient population were as follows: a positive resection margin (4 cases), multiple pathologic lymph nodes (15 cases), and advanced T classification (16 cases). The radiation doses were in the range of 5040 cGy to 6840 cGy, with a mean of 6248 cGy.

**Follow-up.** The follow-up period ranged from 4 to 146 months, with a mean of 44 months. Patients who were still alive were followed up for 146 months, with a mean of 44 months. Patients who were still alive were followed up for 2 years. SPSS 12.0 (SPSS Inc, Chicago, IL) was used in the statistical analysis, whereas survival rates were calculated by Kaplan–Meier and log-rank tests. The relationships between contralateral lymph node metastasis and clinical factors such as age, sex, the stage of primary lesion, and the stage of ipsilateral lymph node were analyzed by Fisher’s exact test. Statistical significance was defined by a p value of < .05.

**RESULTS**

**Pathologic Staging.** Of the 55 patients who had bilateral cN0 neck, pathologic metastasis was observed ipsilaterally in 18 cases and contralaterally in 3 cases. Among the 11 patients with a clinically positive ipsilateral neck, ipsilateral pathologic metastasis was present in 10 cases, whereas 4 showed evidence of contralateral neck metastasis. Thus, contralateral occult metastasis was noted in 11% (7 of 66) of all subjects, in 36% (4 of 11) with clinically ipsilateral neck metastasis, in 5% (3 of 55) when clinically bilateral N0, and in 21% (6 of 28) when pathologically ipsilateral neck metastasis was present. One patient without pathologically ipsilateral neck metastasis, whose primary site was the oral tongue, had contralateral neck metastasis at level I. The rate of contralateral occult neck metastasis was significantly higher when ipsilateral neck metastasis was present than when it was not (p = .002).

When the primary site was considered, the number of cases with contralateral occult metastasis was 4 (57%, 4 of 7) in the oral tongue, 2 (29%, 2 of 7) in the gingiva or alveolar ridge, and 1 (14%, 1 of 7) in the floor of the mouth. Sorted according to the clinical T classification of the primary lesion, the rate of contralateral occult metastasis was 8% (3 of 37) T2, 25% (2 of 8) T3, and 18% (2 of 11) T4, whereas no metastasis was observed in the 10 T1 cases (Table 2). When the site of occult metastasis was considered, the number of cases was 4 (57%, 4 of 7) in level I, 1 (14%, 1 of 7) in level II, 1 (14%, 1 of 7) in level III, and 1 (14%, 1 of 7) in level I+II.

**Correlation between Contralateral Cervical Lymph Node Metastasis and Clinical Factors.** The relationship between contralateral lymph node metastasis and several clinical factors in the 28 patients with ipsilateral pathologically positive lymph nodes was analyzed. There were no statistically significant differences in age, sex, growth type, ipsilateral lymph node with extracapsular spread, or ipsilateral multiple cervical lymph node metastasis, although the rate of contralateral occult neck metastasis was significantly higher in cases in which the primary lesion showed advanced invasion or extension across the midline, compared with early-stage or unilateral lesions (p < .05; Table 3).

**Correlation between Contralateral Cervical Lymph Node Metastasis and Survival.** Eighteen patients (27%) were seen with recurrences or metastases, of which 6 cases (9%) were local, 7 cases (11%) were in the neck, 2 cases (3%) were distant metastasis, 1 patient (2%) had local recurrence and distant metastasis, and 2 patients (3%) had neck and distant metastasis. Of the 9 neck recurrences, 8 were found in the ipsilateral neck and 1 in the

<table>
<thead>
<tr>
<th>T classification</th>
<th>No. of cases</th>
<th>No. of patients with N+ (%)</th>
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</thead>
<tbody>
<tr>
<td>T1</td>
<td>10</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>T2</td>
<td>37</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>T4</td>
<td>11</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>7 (11%)</td>
</tr>
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bilateral neck. Therefore, the ipsilateral regional recurrence rate was 14% (9 of 66), and the contralateral regional recurrence rate was 2% (1 of 66). Of the 9 cases of ipsilateral neck recurrence, except for 1 case, the ipsilateral neck recurrence occurred at the dissected area. One case recurred in the outside field, level IV and V (Table 4). Salvage treatment was attempted in 6 patients. The remaining 3 patients were not considered candidates for salvage treatment. Five of the 6 patients who attempted salvage treatment were treated with radical neck dissection with or without postoperative radiation therapy. The remaining 1 patient received chemotherapy and radiation therapy for his recurrences; 7 patients died of the disease, 1 died from other causes, and 1 survived with no evidence of the disease.

In the 35 patients who received adjuvant radiotherapy, the local control rate was 83% (29 of 35), the ipsilateral regional control rate was 83% (29 of 35), and the contralateral regional control rate was 100%. The overall 5-year survival rate and disease-specific survival rate for patients who received adjuvant radiotherapy were 80% and 87%, respectively.

In the 31 patients who did not receive adjuvant radiotherapy, the local control rate was 97% (30 of 31), the ipsilateral regional control rate was 90% (28 of 31), and the contralateral regional control rate was 97% (30 of 31). The overall 5-year survival rate and disease-specific survival rate for patients who did not receive adjuvant radiotherapy were 80% and 87%, respectively.

The final outcomes of all 66 patients were as follows: 15 patients died of the disease, 2 died from other causes, and 49 survived with no evidence of the disease. The overall 5-year survival rate and disease-specific survival rate for all patients treated with elective contralateral lymph node dissection were 70% and 75%, respectively.

Among the 7 patients with contralateral occult metastasis, 4 (57%) died of the disease, and the mean length of the time until death was 9 months. Among these 4 patients, 2 had distant metastasis (1 case to the lung and the other case to the spine), and 2 had recurrences at the primary site without nodal recurrence. Three patients survived with no evidence of the disease after postoperative radiotherapy. As calculated by the Kaplan–Meier method, the overall 5-year survival rate and disease-specific survival rate were both 43% in the 7 cases with contralateral metastasis and were significantly lower than for the 59 metastasis-free subjects, whose rates were 74% and 79%, respectively (p = .0192, p = .0079; Figure 1).

Table 4. Regional recurrence in all patients (n = 66).

<table>
<thead>
<tr>
<th>Neck level</th>
<th>Ipsilateral neck</th>
<th>Contralateral neck</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>3</td>
<td>1*</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>I+II</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>I+II+III</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>IV+V</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>9 (14%)</td>
<td>1 (2%)</td>
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</table>

*One case of bilateral neck recurrence.
†One case of recurrence outside of the dissection field.

DISCUSSION

Nodal metastasis is the most influential factor in the prognosis of oral cavity SCC.1 In the oral cavity, the incidence of occult nodal disease varies broadly with the tumor site and stage.7 However, the relatively high incidence of occult cervical metastases is generally acknowledged.12,13 Although the importance of treatment of the neck in patients with clinically palpable lymph nodes is beyond doubt, elective treatment of the clinically negative
The disease-free survival rate at 3.5 years for the group with elective neck treatment was 72%, versus 49% in the patients who had resection of the primary alone. In a retrospective study of patients with stage I and II SCC of the oral tongue, Yuen et al reported that elective neck dissection significantly reduced the regional recurrence rate to 9% and also significantly reduced the regional recurrence–related mortality to 3%. Elective neck dissection also increased the 5-year disease-free actuarial survival rate to 86% as compared with 55% for “watchful waiting” in the surgical treatment of patients with early oral tongue carcinoma. Therefore, it is a well-accepted fact that ipsilateral elective neck dissection should be performed in the oral cavity SCC.

Oral cavity SCC has a high incidence of cervical micrometastases and frequently metastasizes bilaterally because of the rich lymphatics in the submucosal plexus, which freely communicate across the midline. The presence of contralateral lymph nodes has been reported previously as indicating a poor prognosis. In a study of 1069 patients in whom cervical dissection was performed for the treatment of oral and oropharyngeal carcinoma, Spiro et al reported that the 5-year survival rate in patients with ipsilateral nodal metastasis was 28%, but this rate decreased significantly to 8% in cases of bilateral metastasis, which emphasizes the prognostic importance of contralateral cervical lymph node metastasis. However, there have been few reports on occult metastasis and treatment of the contralateral N0 neck in oral cavity SCC.

In our study, the overall rate of occult contralateral metastasis in oral cavity SCC was 11% (7 of 66), and the rate was 21% (6 of 28) in cases of ipsilateral pathologic metastasis. The rate of overall survival or disease-specific survival decreased dramatically when there was occult contralateral nodal metastasis (p < .05).

In their study of factors influencing contralateral lymph node metastasis from oral carcinoma, Kowalski et al showed that the clinical stage, a tumor crossing the midline, and floor of the mouth involvement were the most important predictors of contralateral metastasis. Kurita et al reported that patients with advanced tumors, multi-involvement of the ipsilateral neck nodes, or a higher degree of histopathologic grading were at a higher risk for contralateral lymph node metastasis.

In our study, the rate of contralateral occult neck metastasis was significantly higher in patients in whom the ipsilateral lymph node involvement
was presented and when the primary lesion showed advanced invasion or extension across the midline, compared with early-stage or unilateral lesions (p < .05). However, there were no statistically significant differences in age, sex, growth type, ipsilateral lymph node with extracapsular spread, or ipsilateral multiple cervical lymph node metastasis. Moreover, our results may be more precise than previous studies in contralateral occult metastasis, because the population enrolled in this study was restricted to clinically contralateral N0 necks.

Our study showed that the patients who received adjuvant radiotherapy had a lower locoregional control and survival rate compared with those who did not receive adjuvant radiotherapy. However, this is attributed to the fact that the patients who received adjuvant radiotherapy were those who had an advanced-stage disease or worse prognosis, which would have affected the locoregional control and survival rate. Consequently, we consider it inappropriate to compare the local control rate between those patients who did receive adjuvant radiotherapy and those who did not.

In conclusion, in this study of 66 patients in whom elective dissection of the contralateral neck was performed, the rate of occult contralateral neck metastasis was found to be 21% when ipsilateral metastasis was present. There was a statistically significant increase in contralateral lymph node metastasis when the stage of the primary lesion was greater than T3 or was presented across the midline, and the rate of survival was reduced when contralateral metastasis was present. Therefore, elective contralateral neck management with surgery or radiotherapy is suggested in the treatment of oral cavity SCC patients with ipsilateral node metastasis and/or those with tumors either greater than stage T3 or crossing the midline.

REFERENCES