Neck observation versus elective neck dissection in management of clinical T1/2N0 oral squamous cell carcinoma: a retrospective study of 232 patients

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Abstract

Objective: The management of early-stage (cT1/2N0) oral squamous cell carcinoma (OSCC) remains a controversial issue. The aim of this study was to compare the clinical outcomes of neck observation (OBS) and elective neck dissection (END) in treating patients with cT1/2N0 OSCC.

Methods: A total of 232 patients with cT1/2N0 OSCC were included in this retrospective study. Of these patients, 181 were treated with END and 51 with OBS. The survival curves of 5-year overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) rates were plotted using the Kaplan-Meier method for each group, and compared using the Log-rank test.

Results: There was no significant difference in 5-year OS and DSS rates between END and OBS groups (OS: 89.0% vs 88.2%, P=0.906; DSS: 92.3% vs 92.2%, P=0.998). However, the END group had a higher 5-year RFS rate than the OBS group (90.1% vs 76.5%, P=0.009). Patients with occult metastases in OBS group (7/51) had similar 5-year OS rate (57.1% vs 64.1%, P=0.839) and DSS rate (71.4% vs 74.4%, P=0.982) to those in END group (39/181). In the regional recurrence patients, the 5-year OS rate (57.1% vs 11.1%, P=0.011) and DSS rate (71.4% vs 22.2%, P=0.022) in OBS group (7/51) were higher than those in END group (9/181).

Conclusions: The results indicated that OBS policy could obtain the same 5-year OS and DSS as END. Under close follow-up, OBS policy may be an available treatment option for patients with clinical T1/2N0 OSCC.

Keywords: Lymphatic metastasis; neck dissection; neck observation; oral squamous cell carcinoma; survival

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Introduction

Oral squamous cell carcinoma (OSCC) is the most common type of oral cancer with a high potential to metastasize even in the early stage. Though the incidence and mortality of oral cancer are not high in China, it has remained a low 5-year overall survival (OS) rate at approximately 50% for the past decades (1). According to the newest National Comprehensive Cancer Network (NCCN) Guidelines, head and neck cancer, version 1.2017, the management of early-stage OSCC (cT1/2N0) can be mainly divided into two policies: surgery and radiation therapy. However, when advocating surgery first, there is still no consensus on whether elective neck dissection (END) should be performed simultaneously with primary
The core problem leading to the argument is the existence of occult metastases, which may lead to locoregional failure and poor survival. Specifically, occult metastases are defined as lymph nodes metastases that are not detected initially by neck palpation and imaging examination, but they are detected by histological examination after neck dissection, or they are presented as delayed regional recurrence if they were untreated after OBS (4-6). However, few articles have compared the survival rates of patients with occult metastases between the END and OBS groups up to now.

Some surgeons advocate END because of the high incidence of occult metastases in patients with early-stage OSCC, ranging from 8.2% to 46.3% (7,8). However, others support OBS policy because it avoids overtreatment to those without occult metastases, and once regional recurrence is detected during follow-up, therapeutic neck dissection can also be performed in time (9-12). Nowadays, both policies have their proponents in different centers around the world.

In this retrospective study, we report our experience in the treatment of 232 patients with OSCC by comparing survival outcomes between END and OBS, as well as those of patients with occult metastases between the two treatments.

Materials and methods

Patients

This study was approved by the Ethics Committee of Institution Research of Hospital of Stomatology, Sun Yat-sen University. A total of 232 consecutive patients with clinical T1/2N0 OSCC underwent initial surgery in the Department of Oral and Maxillofacial Surgery, Hospital of Stomatology, Sun Yat-sen University, from January 2001 to June 2011. The TNM classification was established according to the Union for International Cancer Control (UICC) 2010 guidelines. The inclusion criteria were as follows: 1) the primary lesions were on tongue, buccal mucosa, floor of the mouth, or mandibular gingiva; 2) clinically N0 neck: physical examination (neck palpation) and imaging examination, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT), found no enlarged lymph node or lymph node less than 1.0 cm that was soft and movable; 3) the tumor was pathologically confirmed OSCC; and 4) the pathological results of the lymph nodes were recorded if patients received neck dissection. The exclusion criteria were as follows: 1) patients had previous head and neck treatment history (surgery, radiotherapy, or chemotherapy); or 2) patients had several kinds of systemic diseases before treatment [such as: grade III–IV cardiac function according to the New York Heart Association (NYHA) Functional Classification; stage 2–3 hypertension: higher than 160 mmHg systolic or 100 mmHg diastolic (1 mmHg = 0.133 kPa); diabetes mellitus].

Treatment

Among the 232 patients, 181 patients were treated with END and 51 patients were treated with OBS. Specifically, in the END group, local excision of primary tumor were performed simultaneously with END; reconstruction of tissue defect was also performed, if necessary. Neck specimens were examined by pathologists to identify the potential occult metastases. Postoperative radiotherapy (RT), which was scheduled within 4–6 weeks after the operation, was carried out if patients presented with pathologically positive lymph nodes. In the OBS group, patients were treated only with local excision of primary tumor and then, were observed under close follow-up.

Follow-up

For the END group, follow-up was established every 3 months for at least 2 years, and then, every 3 or 6 months later. For the OBS group, the follow-up interval was suggested to be 1–3 months for the first 3 years, and then, 3 or 6 months later. CT or MRI was performed as a routine inspection every 6 months for the OBS group and 6 months to 1 year for the END group. In the OBS group, patients with occult metastases were defined as delayed regional recurrence (apparent in the neck, detected by imaging examination or identified by pathologists after surgery) in the follow-up. If suspected regional recurrence was detected by physical or imaging examination, therapeutic neck dissection or salvage surgery on the affected side or both sides was established. In addition, RT, chemotherapy, or chemoradiotherapy were also taken into consideration.

Statistical analysis

The OS was calculated from the date of operation to the date of the last follow-up or death. Disease-specific survival
(DSS) was calculated from the date of operation to the date of last follow-up or death related to OSCC. Recurrence-free survival (RFS) was defined from the date of operation to the date of finding local, regional, or distant recurrence; LRFS for local RFS, and RRFS for regional RFS.

Statistical analysis was performed using IBM SPSS Statistics (Version 20.0; IBM Corp., New York, USA). The baseline demographic data between the END and OBS groups were compared using the Pearson Chi-square test for categorical variable. The best cut-off value was calculated using the receiver operating characteristic curve (ROC) analysis for continuous variable. The Cox multivariate regression analysis was used to adjust for confounding factors. The survival curves of OS, DSS, RFS, LRFS, and RRFS were plotted using the Kaplan-Meier method for each group, and compared using the Log-rank test. The level of significance was set at P<0.05 for two tails.

Results

General characteristics

Of the 232 patients, 181 (mean age: 57.5±12.6 years) were in the END group and 51 patients (mean age: 58.6±12.5 years) were in the OBS group. According to the ROC analysis, the best cut-off value was 55.5 years. The baseline demographic and clinical pathological characteristics showed that patients were well-matched in age, gender, alcohol/tobacco habit, site of tumor, clinical T classification, growth pattern, and histological grade between END and OBS groups (Table 1).

Clinical outcomes of END and OBS groups

This cohort of patients was followed up to January 31, 2016, with a median follow-up period of 68 (range: 5–175) months in the END group and 68 (range: 12–175) months in the OBS group. The study flow chart (Figure 1) illustrates the study population with two types of neck management from initial treatment to follow-up. During the follow-up period, tumor recurrence was significantly higher in the OBS group compared to the END group (P=0.013); 25.5% (13/51) and 11.6% (21/181) of patients in the OBS and END groups, respectively. As for regional recurrence, the incidence of 13.7% of patients (7/51) observed in the OBS group was significantly higher than that of 5.0% of patients (9/181) in the END group (P=0.029).

As shown in Figure 1, 142 (78.5%) patients in the END group were confirmed as having pathological nodal-negative diseases (pN0), while 39 (21.5%) patients in the END group were diagnosed with pathological nodal-positive diseases (pN+). Among the 142 pN0 patients in the END group, 6 (4.2%) patients, 5 (3.5%) patients, and 1 (0.7%) patient developed local recurrence, regional recurrence, and distant metastasis, respectively. Six patients (4 patients with local recurrence and 2 patients with regional recurrence) accepted salvage surgery, 2 (2/6, 33.3%) of them survived in the follow-up. Among 39 pN+ patients in END group, 4 (10.3%) patients, 4 (10.3%) patients and 1 (2.6%) patient developed local recurrence, regional recurrence, and distant metastasis, respectively. Three patients (2 patients with local recurrence and 1 patient with regional recurrence) accepted salvage surgery, but none of them survived in the follow-up. For OBS group, 6 (11.8%) patients developed local recurrence, while 7 (13.7%) patients reached regional recurrence. Nine patients (4 patients with local recurrence, 5 patients with regional recurrence) accepted salvage surgery, 6 (6/9, 66.7%) of them survived in the follow-up.

Unfortunately, 12 (12/21, 57.1%) recurrent patients (4 patients with local recurrence, 6 patients with regional recurrence, and 2 patients with distant metastases) in the END group were in poor physical condition or in low intentions to accept surgery. Unlike the recurrent cases in the END group, only 4 (4/13, 30.8%) patients (2 patients with local recurrence and 2 patients with regional recurrence) in the OBS group gave up surgery (Figure 1).

Comparison of survival rates between END and OBS groups

For adjusting for confounding factors, the balanced variables from Table 1 showed no significant survival differences according to the Cox multivariate regression analysis, except surgery treatment for 5-year RFS rate (P=0.012, HR=0.329, 95% CI: 0.153–0.707). It was specifically shown that END could decrease the risk of recurrence to 0.329 compared with OBS (Table 2).

The 5-year OS, DSS, RFS, LRFS and RRFS rates between END and OBS groups were 89.0% vs. 88.2%, 92.3% vs. 92.2%, 90.1% vs. 76.5%, 96.1% vs. 90.2%, and 95.0% vs. 86.3%, respectively (Figure 2). Significantly lower 5-year RFS and RRFS rates could be seen in the END group than the OBS group (Log-rank, P=0.009 and P=0.028, respectively), while no statistical difference was
found in the 5-year OS (P=0.906), DSS (P=0.998), and LRFS (P=0.081) rates.

The survival rates of cT1 and cT2 patients between the END and OBS groups are shown in Table 3. For cT1 patients, the 5-year OS, DSS, RFS, LRFS, and RRFS rates had no significant differences between the two groups. Similar findings were also investigated for cT2 patients.

For patients with occult metastases, comparisons of the 5-year OS and DSS rates between the two groups are shown in Table 4. A total of 46 patients (46/232, 19.8%)
had occult metastases, including 7 patients (delayed regional recurrence) in the OBS group (7/51, 13.7%) and 39 patients (pN+) in the END group (39/181, 21.5%). Among these patients, no significant difference was observed in the incidence of occult metastases between the two groups (P=0.216). Moreover, the 5-year OS rate (57.1% vs. 64.1%, P=0.839) and DSS rate (71.4% vs. 74.4%, P=0.982) also showed no significant difference.

Table 4 presents the 5-year OS and DSS rates of the recurrent patients including 21 patients in END group and 13 in OBS group. Results demonstrated no significant difference in the local recurrence rate (11.8% vs. 5.5%, P=0.120), 5-year OS rate (50.0% vs. 30.0%, P=0.488), and 5-year DSS rate (66.7% vs. 50.0%, P=0.488) between the two groups. However, for the regional recurrence patients, the 5-year OS (57.1% vs. 11.1%, P=0.011) and DSS (71.4% vs. 22.2%, P=0.022) rates in the OBS group (7/51, 13.7%) were higher than those in the END group (9/181, 5.0%).

Discussion

According to the newest NCCN guidelines, OBS and END are the two main surgery treatment policies for patients with early-stage OSCC. However, which of them is more effective still remains a controversial issue. This study analyzed the survival outcomes of patients with clinical T1/2N0 OSCC treated with OBS or END. We showed that OBS-treated patients obtained similar 5-year OS, DSS, and LRFS rates, but lower 5-year RFS and RRFS rates when compared with the END-treated patients. It was worthy to note that patients with regional recurrence...
Table 2 Cox multivariate survival analysis of clinicopathological variables

| Variables                   | 5-year OS (%) | P   | 5-year DSS (%)   | P   | 5-year RFS (%) | P   |
|-----------------------------|---------------|-----|------------------|-----|----------------|-----|
|                             | HR (95% CI)   |     | HR (95% CI)      |     | HR (95% CI)   |     |
| Age (year)                  |               |     |                  |     |                |     |
| <55.5                       | Reference     | 0.404 | Reference        | 0.134 | Reference     | 0.793 |
| ≥55.5                       | 1.533         | (0.634–3.709) | 3.016 | (0.942–9.653) | 1.307 | (0.597–2.861) |
| Gender                      |               |     |                  |     |                |     |
| Female                      | Reference     | 0.841 | Reference        | 0.499 | Reference     | 0.093 |
| Male                        | 0.975         | (0.409–2.324) | 0.742 | (0.245–2.254) | 0.476 | (0.194–1.166) |
| Tobacco                     |               |     |                  |     |                |     |
| No                          | Reference     | 0.556 | Reference        | 0.864 | Reference     | 0.733 |
| Yes                         | 0.681         | (0.154–3.007) | 1.282 | (0.247–6.667) | 0.777 | (0.195–3.088) |
| Alcohol                     |               |     |                  |     |                |     |
| No                          | Reference     | 0.694 | Reference        | 0.870 | Reference     | 0.844 |
| Yes                         | 0.664         | (0.065–6.730) | 0.793 | (0.072–8.737) | 1.284 | (0.208–7.941) |
| Site of tumor               |               |     |                  |     |                |     |
| Tongue                      | Reference     | 0.237 | Reference        | 0.526 | Reference     | 0.315 |
| Buccal mucosa               | 0.577         | (0.128–2.599) | 0.979 | (0.021–9.108) | 0.487 | (0.110–2.159) |
| Mandibular gingival         | 2.092         | (0.642–6.818) | 1.550 | (0.414–5.807) | 1.116 | (0.311–4.009) |
| Floor of the mouth          | 1.585         | (0.452–5.557) | 1.265 | (0.267–6.000) | 1.821 | (0.602–5.504) |
| Clinical T classification   |               |     |                  |     |                |     |
| cT1                         | Reference     | 0.995 | Reference        | 0.513 | Reference     | 0.635 |
| cT2                         | 1.152         | (0.491–2.704) | 1.723 | (0.602–4.931) | 1.392 | (0.614–3.157) |
| Growth pattern              |               |     |                  |     |                |     |
| Ulcerative                  | Reference     | 0.250 | Reference        | 0.885 | Reference     | 0.538 |
| Infiltrative                | 0.690         | (0.270–1.759) | 1.228 | (0.383–3.938) | 0.949 | (0.393–2.290) |
| Exophytic                   | 0.476         | (0.164–1.378) | 0.807 | (0.217–2.997) | 0.733 | (0.274–1.956) |
| Histological grade          |               |     |                  |     |                |     |
| Well                        | Reference     | 0.608 | Reference        | 0.341 | Reference     | 0.884 |
| Moderately/poorly           | 1.349         | (0.293–6.212) | 1.173 | (0.143–9.661) | 1.743 | (0.485–6.272) |
| Not sure                    | 0.510         | (0.172–1.510) | 0.305 | (0.067–1.375) | 0.527 | (0.194–1.431) |
| Surgery treatment           |               |     |                  |     |                |     |
| OBS                         | Reference     | 0.967 | Reference        | 0.916 | Reference     | 0.012 |
| END                         | 0.906         | (0.354–2.315) | 0.785 | (0.245–2.512) | 0.329 | (0.153–0.707) |

OS, overall survival; DSS, disease-specific survival; RFS, relapse-free survival; HR, hazard ratio; 95% CI, 95% confidence interval.
in the OBS group had higher 5-year OS and DSS rates than those in the END group. Moreover, patients with occult metastases in the OBS group achieved similar 5-year OS and DSS rates with those in the END group.

As far as we know, only five prospective studies have compared the survival outcomes between patients treated with END and OBS (13-17). In 1994, Kligerman et al. (15) demonstrated that patients who underwent END had a significantly higher 3-year disease-free survival rate than those who received OBS. Vandenbrouk et al. (14), Fakih et al. (13), and Yuen et al. (16) reported that there was no significant difference in OS between the two treatments, which is consistent with our study results. However, all these four prospective studies lacked adequate samples to detect a meaningful difference (3). Hence, in another prospectively randomized clinical trial with a large sample size from India, D’Cruz et al. (17) enrolled 500 patients with early-stage OSCC in their study and found that the

Table 3 Comparisons of 5-year survival rates between END and OBS groups in cT1 and cT2 patients

| Survival rate | cT1 (%) | P   | cT2 (%) | P   |
|---------------|---------|-----|---------|-----|
| END           | OBS     |     | END     | OBS |
| 5-year OS     | 87.1    | 92.0| 0.511   | 90.1| 84.6| 0.639 |
| 5-year DSS    | 94.3    | 92.0| 0.731   | 91.0| 92.3| 0.814 |
| 5-year RFS    | 90.0    | 76.0| 0.078   | 90.1| 76.9| 0.055 |
| 5-year LRFS   | 95.7    | 88.0| 0.186   | 96.4| 92.3| 0.372 |
| 5-year RRFS   | 97.1    | 88.0| 0.078   | 93.7| 84.6| 0.116 |

END, elective neck dissection; OBS, neck observation; OS, overall survival; DSS, disease-specific survival; RFS, recurrence-free survival; LRFS, local RFS; RRFS, regional RFS.
END group had higher 3-year OS and disease-free survival rates than the OBS group, which was different from our findings. This difference might result from their inadequate 5-year follow-up, regional differences, diet structure, or other influencing factors (8). In our study, although END had a good control on regional recurrence, it did not influence the 5-year OS and DSS rates.

Clinical T stage and occult metastases were the significant tumor-related predictive factors for performing END (2). Ganly et al. (18) found that patients with cT2 OSCC treated with OBS had lower 5-year OS and DSS rates than those treated with END, but similar results were not found for cT1 patients; thus, they concluded that neck dissection should be performed in cT2 patients. However, Flach et al. (19) observed 234 patients with early-stage OSCC using ultrasound guided fine needle aspiration cytology followed by OBS. This study found that these patients had similar survival outcomes as those treated with END. Currently, some studies still considered that cT2 patients should receive END because of the high occult metastases and poor survival outcomes (7,8,20). In our study, since patients treated with OBS could have a close follow-up and receive therapeutic neck dissection in time, we found similar survival rates in cT1 and cT2 patients between the OBS and END groups. Thus, in our opinion, both cT1 and cT2 patients could be treated with OBS policy under close follow-up.

The incidence of occult metastases in cNO OSCC varied in different studies (7-11,18-20). Since 1994, the probability of 20% for occult metastases was recognized as the common threshold value for performing END (21). In 2009, a study demonstrated that OBS policy was recommended when the risk was lower than 44% (22). In our study, the incidence of occult metastases was 19.8%, which indicated that OBS policy may be appropriate for patients with early-stage OSCC. In a further investigation, we explored the 5-year OS and DSS rates of patients with proven nodal metastases, and results showed no significant differences between the OBS group and END group. This was consistent with a study performed by Flach et al. (19), which demonstrated that patients treated with OBS and presented with delayed metastases had similar 5-year OS and DSS rates to those treated with END and presented with proven metastases. Some other researches also indicated that END turned out to be unnecessary and was an overtreatment method, as after comparing the two policies in patients with occult metastases, similar OS and DSS rates were observed (16,23). Moreover, END could cause a number of complications, such as shoulder disability and scarring (9,12). To avoid overtreatment, sentinel lymph node biopsy (SLNB) had been introduced in clinical treatment. Compared to conditional examinations, SLNB could improve the detection of potential nodes and reduce recurrence rate (24,25). However, there was still no accurate technique for the detection of all the occult nodes in neck (26).

Regional recurrence had been the most common cause of failure in early-stage oral cancer. Multiple studies indicated that patients with early-stage OSCC treated with OBS had a higher rate of regional failure than END (7,8,17,20). In a retrospective study, Liu et al. (12) found that the 5-year DSS rate of cN0 patients with proven neck metastases would decrease by 35% when compared with patients with proven negative results for neck metastases. However, there was still lack of data on the survival outcomes of patients with neck recurrence between the END and OBS groups (8). In our study though, the OBS group had a higher rate of regional recurrence than the END group, and the 5-year OS and DSS rates in the OBS group were higher than those in the END group. This indicates that the patients with delayed metastases in the OBS group could achieve even longer survival time since patients in the OBS group were under closer follow-up and it was easier to perform active interventions in these patients.

Some limitations can be noticed in this retrospective study, which may lead to selection bias for the patients included in the END or OBS group. Firstly, there were unbalanced sample sizes between the two study groups. For
this reason, the Cox multivariate regression analysis was used to adjust for potential confounding factors. Secondly, tumor thickness or depth of invasion was not recorded or analyzed. In patients with cN0 OSCC, depth of invasion has been considered in future versions of the AJCC TNM staging system according to high incidence of occult metastasis (27,28). Thirdly, considering the economic status or emotional reasons of the patients in developing countries, including China, END is more extensively used than OBS. Considering the possible selection bias mentioned above, observed better 5-year OS and DSS in the OBS group may be based on patients with low-risk potential to metastasis (such as smaller T size, smaller tumor thickness or other clinical variables). However, selection bias cannot be eliminated in the retrospective study, which urges us to carry out multicenter prospective randomized cohort study in the future.

**Conclusions**

Our study demonstrates that OBS could obtain similar 5-year OS and DSS rates as END. Moreover, in the regional recurrence patients, OBS can result in higher 5-year OS and DSS rates than END. Even though END can provide effective neck recurrence control, END still needs close follow-up and active interventions as OBS. Under close follow-up, OBS policy may be an available treatment option for patients with clinical T1/2N0 OSCC.

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**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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